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Schwartz's Reagent-Mediated Regiospecific Synthesis of 2,3-Disubstituted Indoles from Isatins

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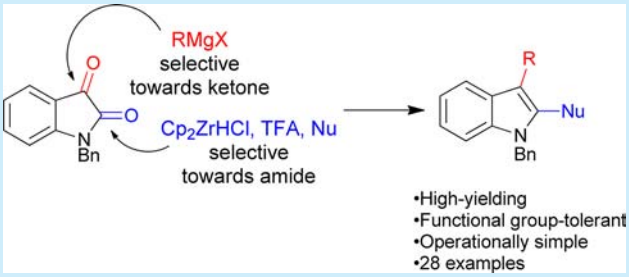
Supporting Information

ABSTRACT: An expeditious, functional group-tolerant synthesis of indoles from isatins is described. Isatins are treated with Grignard reagents to yield oxindoles. These, in turn, are reduced with Schwartz's reagent and subjected to nucleophile addition and dehydration to yield 2,3-disubstituted indoles regiospecifically. This represents a divergent approach to the synthesis of these medicinally and synthetically important compounds.



Indoles are one of the most enduring motifs in organic chemistry. They form the core of a myriad of natural products and occur in a number of medicinally relevant compounds.[1] Their importance is expressed in the wealth of methods for their synthesis developed over the years.[2] One of the most commonly used methods is the classic Fisher indole synthesis.[3] More recently, a number of transition-metal-mediated methods have appeared, the most well-known of which is the Larock indole synthesis.[4]

Despite the rich methodology available for their synthesis, the chemistry of indoles is not free of challenges. Among them, especially pronounced is the question of regioselectivity in the synthesis of 2,3-disubstituted indoles.

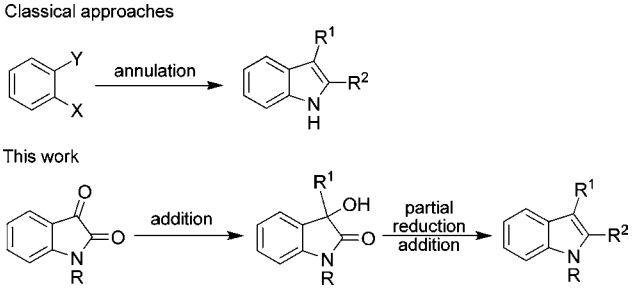
The majority of known methods are most suitable for the synthesis of 2- or 3-monosubstituted indoles. This is problematic, as 2,3-disubstituted indoles are compounds of marked importance.[5]

As most known strategies for the synthesis of indoles involve the annulation of the azacycle to an existing aromatic ring (Scheme 1), a possibility of differently annulated regioisomers arises. Addressing this issue is a priority in modern methods of indole synthesis.

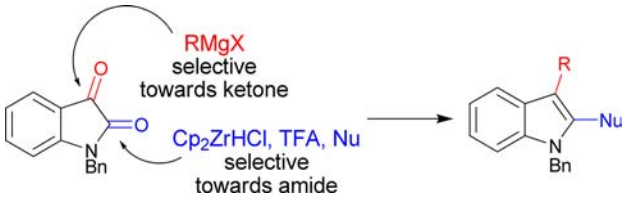
We envisioned an alternative approach to the regioselective synthesis of 2,3-disubstituted indoles that involved the differential activation of the two carbonyl groups present in the isatin molecule (Scheme 2). Isatins are an ideal substrate for the synthesis of indoles owing to their ready availability.[6,7] We expected that the ketone group would undergo ready substitution by a number of nucleophiles, leaving the amide carbonyl to be manipulated in the next step.

The unique chemistry of Schwartz's reagent, allowing for the selective activation of amide carbonyls,[8] prompted us to employ this reagent in the second step of the synthesis to form a reactive iminium moiety which would allow the addition of a range of nucleophiles not available in previous work.[7] We expected the partial reduction and addition to proceed in a one-pot manner,

Scheme 1. Different Approaches to the Synthesis of Indoles



Scheme 2. Selective Activation of Isatin Carbonyls



with subsequent dehydration to the indole proceeding spontaneously under the acidic conditions employed. The anticipated reaction pathway is shown in Scheme 3. The amide carbonyl group undergoes reduction with Schwartz's reagent. The resulting zirconium complex is decomposed by the action of added TFA. The addition of the nucleophile yields a hydroxyamine, which is then dehydrated in the acidic conditions employed.

To test our hypothesis, we synthesized a series of oxindoles containing different functional groups from *N*-benzylisatin (Scheme 4). We employed modified literature conditions[9] and

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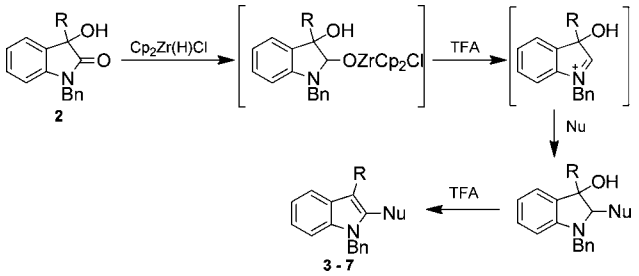
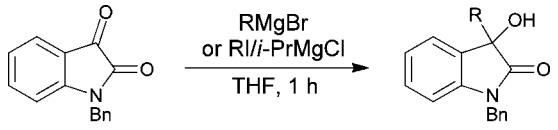
Scheme 3. Anticipated Reaction Pathway



Scheme 4. Synthesis of Oxindoles from *N*-Benzylisatin



2a R = Me
2b R = Ph
2c R = 4-$MeOC_6H_4$
2d R = 4-$EtO_2CC_6H_4$
2e R = 4-CNC_6H_4
2f R = 4-$NO_2C_6H_4$

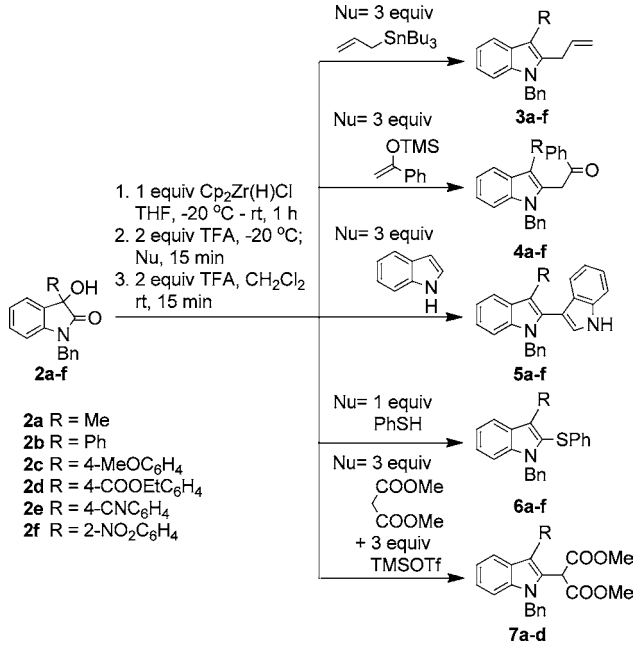
used magnesium−iodine exchange[10] to obtain the Grignard reagents necessary. The 3-substituted oxindoles were produced in good yields.

We then subjected the synthesized oxindoles to reduction with Schwartz's reagent using a modified literature procedure.[8c] As it turned out, using more than 1 equiv of the reductant did not improve the yield. We discovered that cooling the reaction mixture prior to the addition of Schwartz's reagent avoided over-reduction of the sensitive functionalities. Preformed Schwartz's reagent was employed as using a reagent generated in situ led to over-reduction to 2-unsubstituted indoles.

Next, we subjected the reduced substrates to the addition of the nucleophile in the same pot. The addition of allyltributylstannane, acetophenone enol TMS ether, and indole proceeded smoothly. In the case of thiophenol it was necessary to use only 1 equiv of the nucleophile. Otherwise, extensive over-reduction to a 3-monosubstituted indole occurred. Amines were unreactive; neither pyrrolidine nor *p*-anisidine gave the expected product. We are currently working on addressing this issue. The reaction with dimethyl malonate did not proceed under the standard conditions, but we were able to obtain the expected effect by the addition of an excess of TMSOTf. We suspect that this is due to the additional activation of the nucleophile by the formation of a ketene acetal in situ. Contrary to our expectations, we normally isolated a mixture of the target indole and the product of addition which did not dehydrate spontaneously. We found that simple treatment of the crude reaction mixture with excess TFA in CH_2Cl_2 effected dehydration, converting the mixture into the desired indole only (Scheme 5). The product was normally obtained in good to excellent yield (Table 1).

Only when the nitro-substituted oxindole was subjected to the reaction with thiophenol did we isolate low amounts of the desired indole, probably due to over-reduction of the nitro group by the thiol reagent. In the case of other functional groups the yields stayed uniformly high. We also did not observe the desired product in the reactions of dimethyl malonate with the arylnitro-

Scheme 5. Synthesis of Indoles from Oxindoles



2a R = Me
2b R = Ph
2c R = 4-$MeOC_6H_4$
2d R = 4-$COOEtC_6H_4$
2e R = 4-CNC_6H_4
2f R = 2-$NO_2C_6H_4$

Table 1. Yields of Indoles

substrate	product yield (%)				
2a	**3a**, 99	**4a**, 82	**5a**, 80	**6a**, 49	**7a**, 51
2b	**3b**, 99	**4b**, 82	**5b**, 70	**6b**, 84	**7b**, 55
2c	**3c**, 75	**4c**, 78	**5c**, 73	**6c**, 67	**7c**, 35[a]
2d	**3d**, 84	**4d**, 57	**5d**, 69	**6d**, 41	**7d**, 59
2e	**3e**, 75	**4e**, 73	**5e**, 49	**6e**, 67	*b*
2f	**3f**, 65	**4f**, 67	**5f**, 49	**6f**, 12[a]	*b*

[a]These products could not be isolated in pure form; yield is estimated from NMR. [b]No expected product was isolated.

and -cyano-substituted substrates. This is probably due to the more forcing conditions required in the reactions with this nucleophile. The same probably accounts for the poor yield when employing the electrophile bearing the acid-sensitive methoxy group. We believe that these limitations might be overcome by careful optimization of the reaction conditions. In the case where TMSCN was employed as the nucleophile, we observed quite a different reaction outcome. Instead of obtaining the desired indole, we isolated a compound to which we ascribe the tetrahydroquinoline structure **8**. We suspect that this is due to the decomposition of zirconocene by cyanide anion with the release of cyclopentadiene, which reacts with the nascent iminium salt in the manner of a Povarov reaction[11]−fragmentation cascade (Scheme 6). We believe that the observed unusual *anti* stereochemistry stems from the minimization of steric hindrance in the bicyclic intermediate. This represents a new approach to the diastereoselective synthesis of highly substituted tetrahydroquinolines.[12] We are currently in the process of investigating the scope of this transformation.

The results show that the method employed is regiospecific in contrast to classical methods that rely on constructing the five-membered azacycle from scratch. The excellent functional group tolerance of this method allows the introduction of varied substituents to the product structure, allaying the limitations of previous methods, i.e., especially the work of Lu et al.[7] In comparison to that methodology, the present method allows for sensitive functionalities to be introduced in the addition step

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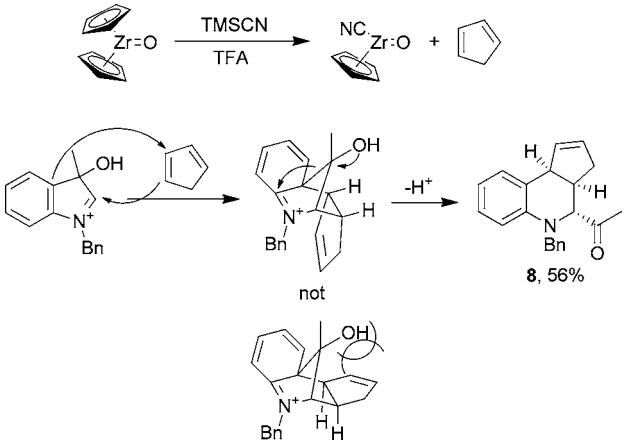
Scheme 6. Mechanism of Rearrangement to Tetrahydroquinoline



(Scheme 4) while preserving them in the next synthetic steps. This represents a marked departure from the previous work, where mainly hydrocarbon-substituted indoles could be obtained. The intermediacy of an iminium cation enables the use of a wider array of nucleophiles than only Grignard reagents, which have been used under rather forcing conditions.[7] The method described is carried out in a straightforward and rapid fashion, permitting the synthesis of large libraries of compounds in a timely manner. A diverse set of nucleophiles can be employed, including C- and S-nucleophiles, which leads to greater diversification of the products.

In summary, we have developed an expeditious method of synthesizing 2,3-disubstituted indoles from commercially available isatins regiospecifically. The methodology is characterized by high functional group tolerance and employs the readily available Schwartz's reagent as the reducing agent. It opens up an attractive route to a variety of 2,3-disubstituted indoles and has the potential to aid in the synthesis of pharmacologically and synthetically relevant indole derivatives. We have also described a new diastereoselective synthesis of highly substituted tetrahydroquinolines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03449.

Detailed synthetic procedures, characterization, and ^{1}H and ^{13}C spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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■ REFERENCES

(1) (a) Sharma, V.; Kumar, P.; Pathak, D. *J. Heterocycl. Chem.* **2010**, *47*, 491. (b) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. *Molecules* **2013**, *18*, 6620. (c) Zhang, M.-Z.; Chen, Q.; Yang, G.-F. *Eur. J. Med. Chem.* **2015**, *89*, 421. (d) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. *Nat. Prod. Rep.* **2013**, *30*, 694. (e) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489.

(2) (a) Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195. (b) Inman, M.; Moody, C. J. *Chem. Sci.* **2013**, *4*, 29. (c) Vicente, R. *Org. Biomol. Chem.* **2011**, *9*, 6469. (d) Gribble, G. W. *J. Chem. Soc. Perkin 1* **2000**, 1045. (e) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, PR215. (f) Bartoli, G.; Dalpozzo, R.; Nardi, M. *Chem. Soc. Rev.* **2014**, *43*, 4728.

(3) (a) Robinson, B. *Chem. Rev.* **1963**, *63*, 373. (b) Robinson, B. *Chem. Rev.* **1969**, *69*, 227. (c) Robinson, B. *The Fischer Indole Synthesis*; Wiley, 1982.

(4) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (c) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644.

(5) (a) Alex, K.; Schwarz, N.; Khedkar, V.; Sayyed, I. A.; Tillack, A.; Michalik, D.; Holenz, J.; Díaz, J. L.; Beller, M. *Org. Biomol. Chem.* **2008**, *6*, 1802. (b) Arcadi, A.; Cacchi, S.; Carnicelli, V.; Marinelli, F. *Tetrahedron* **1994**, *50*, 437. (c) Pawlak, J. M.; Khau, V. V.; Hutchison, D. R.; Martinelli, M. J. *J. Org. Chem.* **1996**, *61*, 9055. (d) Krüger (née Alex), K.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2153.

(6) (a) Silva, J. F. M. da; Garden, S. J.; Pinto, A. C. *J. Braz. Chem. Soc.* **2001**, *12*, 273. (b) Garden, S. J.; da Silva, R. B.; Pinto, A. C. *Tetrahedron* **2002**, *58*, 8399.

(7) Dou, X.; Yao, W.; Wen, S.; Lu, Y. *Chem. Commun.* **2014**, *50*, 9469.

(8) (a) Spletstoser, J. T.; White, J. M.; Tunoori, A. R.; Georg, G. I. *J. Am. Chem. Soc.* **2007**, *129*, 3408. (b) Schedler, D. J. A.; Li, J.; Ganem, B. *J. Org. Chem.* **1996**, *61*, 4115. (c) Oda, Y.; Sato, T.; Chida, N. *Org. Lett.* **2012**, *14*, 950. (d) Nakajima, M.; Oda, Y.; Wada, T.; Minamikawa, R.; Shirokane, K.; Sato, T.; Chida, N. *Chem. - Eur. J.* **2014**, *20*, 17565.

(9) Connolly, T. J.; Durst, T. *Can. J. Chem.* **1997**, *75*, 542.

(10) (a) Jensen, A. E.; Dohle, W.; Sapountzis, I.; Lindsay, D. M.; Vu, V. A.; Knochel, P. *Synthesis* **2002**, *2002*, 565. (b) Calí, P.; Begtrup, M. *Synthesis* **2002**, *2002*, 63. (c) Sapountzis, I.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 1610.

(11) (a) Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656. (b) Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721. (c) Fochi, M.; Caruana, L.; Bernardi, L. *Synthesis* **2014**, *46*, 135.

(12) Sridharan, V.; Suryavanshi, P. A.; Menéndez, J. C. *Chem. Rev.* **2011**, *111*, 7157.

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Palladium-Catalyzed Tandem Regioselective Oxidative Coupling from Indoles and Maleimides: One-Pot Synthesis of Indolopyrrolocarbazoles and Related Indolylmaleimides

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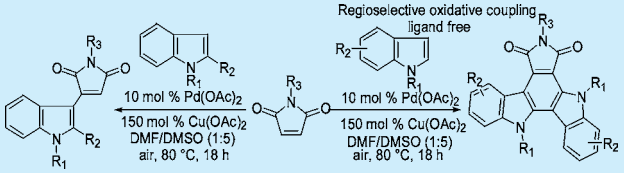
Supporting Information

ABSTRACT: An efficient Pd(II)-catalyzed approach for the direct synthesis of indolo[3,2-*a*]pyrrolo[3,4-*c*]carbazole-6,8-diones has been developed from both free and protected (NH) indoles and maleimides via a regioselective tandem oxidative coupling reaction. The yields are moderate to excellent. In addition, 2-substituted indoles are suitable substrates in this protocol, leading to the formation of indolylmaleimides. The present methodology provides a concise route to highly functionalized indolopyrrolocarbazole derivatives.

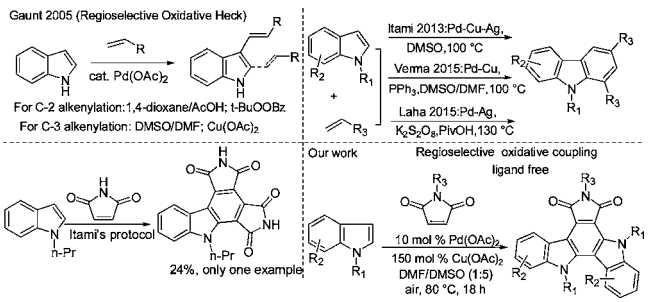


The indolocarbazole nucleus is incorporated in a wide range of natural products,[1] pharmaceuticals,[2] photorefractive materials, and organic dyes.[3] Staurosporine was the first discovered indolocarbazole from *Actinomyces*. A variety of indolocarbazole analogues have since been isolated and confirmed.[1] Most of them have shown to be effective protein kinase inhibitors, offering tremendous promise in anticancer activity. However, staurosporine has significant specificity to kinases in the human body.[4] Previous researchers modified the structure of staurosporine to obtain novel skeletons, such as indolylmaleimides and indolopyrrolocarbazoles.[5] However, almost all of the indolopyrrolocarbazoles isolated from nature are indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles; little attention has been paid to its isomers, such as indolo[3,2-*a*]pyrrolo[3,4-*c*]carbazole-6,8-dione.[6] Fonseca et al. reported the indolo[3,2-*a*]pyrrolo[3,4-*c*]carbazole-6,8-dione in the synthesis of arcyriaflavin-A with low yield.[6a] Subsequently, Bergman and Janosik finished the synthesis from indole[6b] and 2,3′-biindolyl,[6c] respectively. The yields were still unsatisfactory (<26%). Derivatives were obtained as byproducts in the synthesis of indolylsuccinimides with 1−2% yield.[6d,e] Thus, an efficient synthetic methodology is highly desirable for this process.

Palladium-catalyzed oxidative cross-coupling reactions have drawn much interest due to their C−C bond formations via direct C−H functionalization.[7−16] Indeed, they have been widely utilized in the synthesis of heterocycles through oxidative cross-coupling of alkenes with arenes[8] or heteroarenes,[9] acrylates with vinyl carboxylates,[10] 2-oxazolones with olefins,[11] heteroarenes with alkynes,[12] and arenes with arenes.[13]

Gaunt et al. reported indole alkenylation in a formal C−H/C−H coupling fashion in 2005, elegantly achieving C-2- or C-3-selective introduction of various alkenyl groups to indoles.[14a] In recent years, research topics on Pd-catalyzed intermolecular alkenylation of indoles or pyrrole via C−H functionalization have been reported continuously.[15,16] Itami et al. demonstrated the formation of carbazoles from N-protected indoles via a Diels−Alder reaction using trimetallic and bimetallic systems of Pd−Cu−Ag.[16a] Most carbazole syntheses are successful with N-protected indoles and remain challenging with a free (NH) indole. Notably, during the preparation of this paper, a Pd-catalyzed alkenylation of indoles and subsequent conversion to the 1,3-disubstituted carbazoles appeared.[16b] A tandem approach to functionlized carbazoles from indoles with alkenes via two successive regioselctive oxidative Heck reactions followed by thermal electrocyclization was also developed (Scheme 1).[16c]

Scheme 1. Synthesis of Carbazoles from Indoles



Nevertheless, a literature survey revealed that the synthesis of both indolopyrrolocarbazoles and indolylmaleimides via oxidative Heck reactions has not been reported. In our continued research program directed toward the synthesis of indolylsuccinimides and related indolylmaleimides in this area,[17] and intrigued

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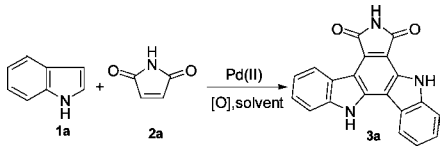
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst[b] (mol %)	oxidant (equiv)	solvent	temp (°C)/time (h)	yield[d] (%)
1	$Pd(OAc)_2$/10	$Cu(OAc)_2$/1.5	DMSO	80/18	56
2	$Pd(OAc)_2$/10	Ag_2CO_3/1.5	DMSO	80/24	17
3	$Pd(OAc)_2$/10	$AgNO_3$/1.5	DMSO	80/24	15
4	$Pd(OAc)_2$/10	DDQ/1.5	DMSO	80/24	0
5	$Pd(OAc)_2$/10	O_2	DMSO	80/24	0
6	$Pd(OAc)_2$/10	$Cu(OAc)_2$/0.5	DMSO	80/36	13
7	$Pd(OAc)_2$/10	$Cu(OAc)_2$/1.5	DMF	80/18	34
8	$Pd(OAc)_2$/10	$Cu(OAc)_2$/1.5	dioxane	80/24	trace
9	$Pd(OAc)_2$/10	$Cu(OAc)_2$/1.5	DMF/DMSO[c]	80/18	75
10	$Pd(OAc)_2$/10	$Cu(OAc)_2$/1.5	DMF/DMSO[c]	rt/120	27
11	$Pd(OAc)_2$/10	$Cu(OAc)_2$/1.5	DMF/DMSO[c]	120/18	58
12[b]	$Pd(OAc)_2$/10	$Cu(OAc)_2$/1.5	DMF/DMSO[c]	80/18	16
13	$Pd(OAc)_2$/10	$Cu(OAc)_2$/1.5	AcOH/DMSO[c]	80/18	25
14	$PdCl_2$/15	$Cu(OAc)_2$/1.5	DMF/DMSO[c]	80/18	62

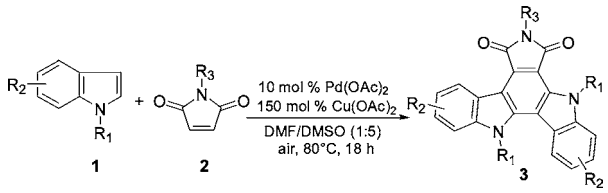
[a]Reactions were performed using indole **1a** (1.5 mmol), maleimide **2a** (0.75 mmol), catalyst, and oxidant in 3 mL of solvent. [b]Indole **1a** (0.75 mmol) and maleimide **2a** (1.5 mmol) were used. [c]v/v = 1:5. [d]Isolated yield based on maleimide.

by the advantages of using direct Pd-catalyzed C−H functionalization for C−C bond formation, we envisioned that free or protected (NH) indoles could be linked with the C=C bond of maleimides via oxidative Heck reactions. Herein, we report the direct synthesis of indolo[3,2-*a*]pyrrolo[3,4-*c*]carbazole-6,8-diones and 3-(2-substituted indol-3-yl)maleimides via Pd-catalyzed regioselective tandem cross-coupling reactions.

Initially, we began our study with indole **1a** and maleimide **2a** to screen the reaction conditions in the presence of 10 mol % of $Pd(OAc)_2$ as the catalyst and 150 mol % of $Cu(OAc)_2$ as the oxidant (Table 1). Compound indolo[3,2-*a*]-pyrrolo-[3,4-*c*]-carbazole-6,8-dione **3a** was obtained in 56% yield in DMSO at 80 °C (Table 1, entry 1). Product **3a** was fully characterized by spectrum analysis, which was identical to the data reported in the literature.[6a,b] Next, to improve the yield, our research plan was returned to screen various oxidants and solvents to get the optimal reaction conditions (Table 1). Unfortunately, poor results were obtained when oxidants such as Ag_2CO_3 and $AgNO_3$ were used (Table 1, entries 2 and 3). DDQ and O_2 barely worked as oxidant (Table 1, entries 4 and 5). Decreasing the dosage of $Cu(OAc)_2$ gave a poor yield of product **3a** around 13% (Table 1, entry 6). The reaction did not work well using DMF and dioxane as solvent (Table 1, entries 7 and 8). The process afforded **3a** in 75% yield using a mixture of DMF/DMSO (v/v, 1/5) as solvent (Table 1, entry 9). The reaction could work at room temperature for a long time and gave a low yield (27%, Table 1, entry 10). However, increasing the temperature to 120 °C, the reaction became complex, and the yield decreased to 58% due to the partial polymerization of maleimides (Table 1, entry 11). When the ratio of indole to maleimide was decreased to 1:2, only **3a** was collected in 16% yield (Table 1, entry 12). Our results indicated 2 equiv of indoles and 1 equiv of maleimide took part in the formation of the indolo[3,2-*a*]pyrrolo[3,4-*c*]carbazole-6,8-dione annulations even if a large excess maleimide was used. Protonic acid did not work well as cosolvent (Table 1, entry 13). $PdCl_2$ as catalyst did not improve the results (Table 1, entry 14). The above result demonstrated that $Pd(OAc)_2/Cu(OAc)_2$ is a more effective catalyst/oxidant in this reaction. It should be noted that without any catalyst, the reaction did not generate the desired product at all.

With the optimal reaction conditions in hand, the scope of various indoles **1** and maleimides **2** was explored to probe the general protocol (Table 2). Maleimide **1a** reacted with indoles to form the target products **3a**−**3d** in 55−85% yields. Both free and protected (NH) indoles could work well in this protocol (Table 2, entry 3). The substituent group in the indole moiety played an important role in reaction yield. That is, an electron-rich indole (e.g., 5-methoxylindole) had an excellent yield (Table 2, entries 2, 5, and 8), and an electron-deficient indole (e.g., 5-chloroindole) gave a moderate yield (Table 2, entry 4). The

Table 2. Substrate Scope for the Synthesis of Indolopyrrolocarbazoles (3)[a]



entry	**1** R_1, R_2	**2** R_3	**3**, yield[b] (%)
1	H, H	H	**3a**, 75
2	H, 5-OCH_3	H	**3b**, 81
3	CH_3, H	H	**3c**, 60
4	H, 5-Cl	H	**3d**, 55
5	H, 5-OCH_3	CH_3	**3e**, 82
6	H, H	CH_3	**3f**, 73
7	H, H	Ph	**3g**, 80
8	H, 5-OCH_3	Ph	**3h**, 85
9	H, 5-OBn	Ph	**3i**, 78
10	H, 7-CH_3	Ph	**3j**, 83
11	H, H	Bn	**3k**, 63

[a]Reactions were performed using indoles **1** (1.5 mmol) and maleimides **2** (0.75 mmol). [b]Isolated yield.

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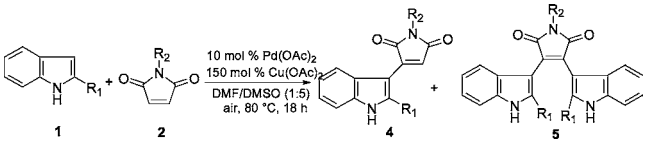
substituent from (NH) maleimides showed no obvious impact on yields (Table 2, entries 1, 6, 7, and 11). As we know, this is the first two reported indole molecules that can react with one maleimide molecule to produce the indolo[3,2-*a*]pyrrolo[3,4-*c*]carbazole-6,8-diones involving in C-3/C-2 alkenylation for indoles.

Subsequently, we turned our attention to investigating the reaction of 2-substituent indoles with maleimides. First, the maleimides were reacted with 2-substituted indoles to form 3-indolylmaleimide products **4a**−**4e** in 77−88% yields using the protocol (Table 3). When 2-methylindole and maleimide were

Table 3. Synthesis of Indolylmaleimides[a]



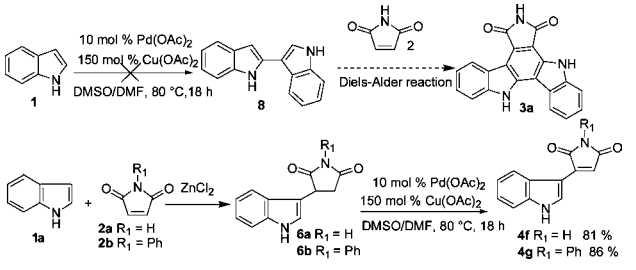
entry	1 R_1	2 R_2	4, 5 yield[b] (%)
1	CH_3	H	**4a**, 85; **5a**, 5[c]
			4a, 43; **5a**, 31[c,d]
2	$COOC_2H_5$	H	**4b**, 77
3	CH_3	CH_3	**4c**, 83
4	CH_3	Ph	**4d**, 88
5	CH_3	Bn	**4e**, 80

[a]Reactions were performed using indoles **1** (0.75 mmol) and maleimides **2** (0.75 mmol). [b]Isolated yield. [c]1.5 mmol of indole **1** was used. [d]In DMSO.

treated in ratio of 2:1 in this protocol, **4a** was obtained in 85% yield and **5a** was formed around 5% yield (Table 3, entry 1). Interestingly, when DMSO was used as the solvent, **4a** was obtained in 43% yield, and bisindolylmaleimide **5a** was isolated in 31% yield (Table 3, entry 1). It seemed that DMF could prevent the formation of bisindolylmaleimide in a cosolvent. Thus, when the ratio of indole to maleimide was decreased to 1:1, indolylmaleimides **4** were obtained in moderate to excellent yields in cosolvent conditions (Table 3, entries 2−5).

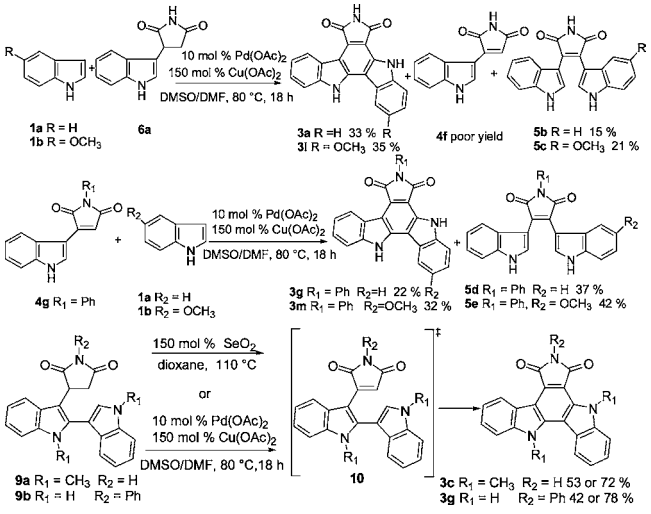
To understand the sequence of the reaction and identify the possible reaction intermediates, additional experiments were carried out. First, 2,3′-biindolyl **8** could not be obtained when indole **1a** solely reacted under the optimized conditions (Scheme 2). It was not subjected to Diels−Alder reaction with maleimides

Scheme 2. Indole and Indolylsuccinimide Experiments

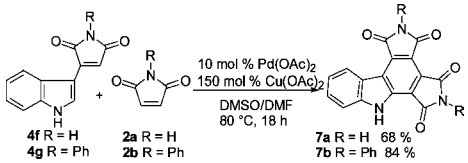


to provide indolopyrrolocarbazoles.[18] 3-Indolylsuccinimide **6a** and **6b**, obtained from indole and maleimides catalyzed by $ZnCl_2$,[17b] could be well oxidized in the Pd-catalyzed protocol, leading to the formation of 3-indolylmaleimides **4f** and **4g** in 81 and 86%, respectively (Scheme 2). Indeed, the reactions of indoles **1a** and **1b** with 3-indolylsuccinimide **6a** were conducted (Scheme 3). Besides product **4f** with a poor yield, both indolopyrrolocarbazoles (**3a**, **3l**) and bisindolylmaleimides (**5b**, **5c**) could be obtained. Similarly, indolopyrrolocarbazoles (**3g**, **3m**) were prepared from indolylmaleimides and indoles via the Pd-catalyzed protocol in 22 and 32% yields, accompanied by bisindolylmaleimides (**5d**, **5e**) with 37 and 42% yields. In addition, 2,3′-biindolylsuccinimides **9** were synthesized and subjected to oxidative dehydrogenation by SeO_2. Products **3** were obtained around 50% yield instead of compounds **10**.[19] We suppose that compounds **10** could be formed and quickly undergo thermal electrocyclization to provide indolopyrrolocarbazoles **3**. Compounds **9** were also performed in Pd-catalyzed protocol to give products **3** in about 75% yield (Scheme 3). Finally, we conducted the reactions of indolylmaleimides with maleimides in the protocol (Scheme 4). The dipyrrolocarbazo-

Scheme 3. Indolylsuccinimide and Indolylmaleimide Experiments



Scheme 4. Diels−Alder Reactions



letetraones **7a** and **7b** were obtained in 68 and 84% yields, respectively. It explains the fact that Pd-catalyzed alkenylation occurs initially at the C-3-positon of indole. However, we had used 1 equiv of indole to react with 2 equiv of maleimide via the Pd-catalyzed protocol, leading to **3a** in a yield of 16%. **7a** was not observed (Table 1, entry 12), which may be because C−H functionalization occurs rather than the Diels−Alder reaction.

These results indicate (i) the second C−H activation starts as soon as the *β*-hydride elimination of the first oxidative Heck reaction; (ii) the second C−H activation occurs exclusively on the indole fraction; (iii) thermal electrocyclization occurs after the second oxidative Heck reaction.

Based on above evidence, the plausible pathway is proposed in Scheme 5. DMSO could prevent the precipitation of Pd^0 with its Pd coordination ability in the reaction.[14a,20] The desired products **3** were synthesized directly from indoles and maleimides via regioselective double successive oxidative Heck

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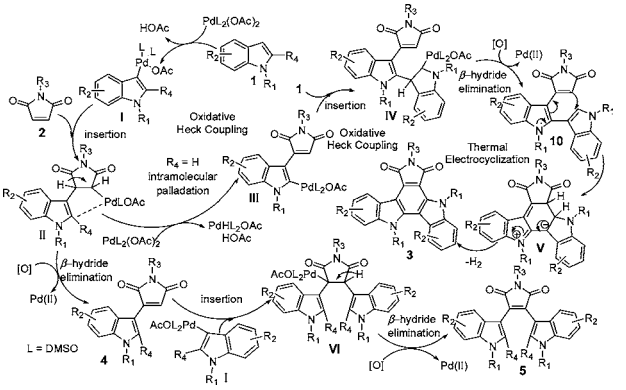
Scheme 5. Plausible Mechanism for the Synthesis of Indolopyrrolocarbazoles and Indolylmaleimides



reactions and thermal electrocyclization. The first oxidative coupling reaction took place via regioselective C-3 palladation (**I**), maleimide insertion (**II**), and β-hydride elimination to form compounds **4** ($R_4 \neq H$). Simultaneously, the following fast intramolecular regioselective C-2 palladation of **II** ($R_4 = H$) was performed, and the reduced Pd(0) complex was oxidized by $Cu(OAc)_2$ to generate Pd(II). The intermediates **10** were formed via the second oxidative coupling reaction (III−IV). Finally, the intermediate **10** undergo thermal induced intramolecular ring closure to provide products **3**. When 2-substituent indoles were used in this protocol, compounds **4** were produced and subjected to the second oxidative coupling reaction to provide compounds **5**.

In summary, an efficient Pd(II)-catalyzed protocol for the direct synthesis of indolopyrrolocarbazoles from both free and protected (NH) indoles and maleimides via a regioselective oxidative cross-coupling reaction has been successfully developed. This approach is different from the usual Pd-catalyzed regioselective C-2,C-3 alkenylation of indole and will lead to further indolopyrrolocarbazole synthesis. In addition, 2-substituent indoles are suitable for this protocol, leading to the formation of indolylmaleimides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02944.

Experimental details, characterization data of all compounds, and copies of ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Sanchez, C.; Mendez, C.; Salas, J. A. *Nat. Prod. Rep.* **2006**, *23*, 1007. (b) Shaaban, K. A.; Elshahawi, S. I.; Wang, X.; Horn, J.; Kharel, M. K.; Leggas, M.; Thorson, J. S. *J. Nat. Prod.* **2015**, *78*, 1723. (c) Fu, P.; Zhuang, Y.; Wang, Y.; Liu, P.; Qi, X.; Gu, K.; Zhang, D.; Zhu, W. *Org. Lett.* **2012**, *14*, 6194. (d) Zhang, W.; Ma, L.; Li, S.; Liu, Z.; Chen, Y.; Zhang, H.; Zhang, G.; Zhang, Q.; Tian, X.; Yuan, C.; Zhang, S.; Zhang, W.; Zhang, C. *J. Nat. Prod.* **2014**, *77*, 1887.

(2) (a) Animati, F.; Berettoni, M.; Bigioni, M.; Binaschi, M.; Cipollone, A.; Irrissuto, C.; Nardelli, F.; Olivieri, L. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5013. (b) Panesar, H. K.; Solano, J.; Minehan, T. G. *Org. Biomol. Chem.* **2015**, *13*, 2879. (c) Sherer, C.; Snape, T.J. *Eur. J. Med. Chem.* **2015**, *97*, 552. (d) Deslandes, S.; Chassaing, S.; Delfourne, E. *Mar. Drugs* **2009**, *7*, 754.

(3) (a) Lai, C. C.; Huang, M. J.; Chou, H. H.; Liao, C. Y.; Rajamalli, P.; Cheng, C. H. *Adv. Funct. Mater.* **2015**, *25*, 5548. (b) Chen, Q.; Zhang, L.; Ebrahim, S.; Soliman, M.; Zhang, C.; Qiao, Q. *Polymer* **2013**, *54*, 223. (c) Park, K. S.; Salunkhe, S. M.; Lim, I.; Cho, C. G.; Han, S. H.; Sung, M. M. *Adv. Mater.* **2013**, *25*, 3351.

(4) (a) Bush, J. A.; Long, B. H.; Catino, J. J.; Bradner, W. T. *J. Antibiot.* **1987**, *40*, 668. (b) Nakano, H.; Omura, S. *J. Antibiot.* **2009**, *62*, 17.

(5) (a) Nakazono, M.; Obayashi, K.; Oshikawa, Y.; Tani, K.; Suenaga, G.; Ando, Y.; Nanbu, S.; Kuwano, R. *J. Photochem. Photobiol., A* **2014**, *289*, 39. (b) Lin, Z.; Lin, Y. D.; Wu, C. Y.; Chow, P. T.; Sun, C. H.; Chow, T. J. *Macromolecules* **2010**, *43*, 5925. (c) Delarue-Cochin, S.; McCort-Tranchepain, I. *Org. Biomol. Chem.* **2009**, *7*, 706. (d) Zhao, S. Y.; Shao, Z. Y.; Qin, W. M.; Zhang, D. Q. *Chin. J. Org. Chem.* **2008**, *28*, 1676.

(6) (a) Fonseca, A. P.; Lobo, A. M.; Prabhakar, S. *Tetrahedron Lett.* **1995**, *36*, 2689. (b) Bergman, J.; Desarbre, E.; Koch, E. *Tetrahedron* **1999**, *55*, 2363. (c) Janosik, T.; Bergman, J. *Tetrahedron* **1999**, *55*, 2371. (d) Henon, H.; Messaoudi, S.; Hugon, B.; Anizon, F.; Pfeiffer, B.; Prudhomme, M. *Tetrahedron* **2005**, *61*, 5599. (e) Henon, H.; Anizon, F.; Golsteyn, R. M.; Leonce, S.; Hofmann, R.; Pfeiffer, B.; Prudhomme, M. *Bioorg. Med. Chem.* **2006**, *14*, 3825.

(7) (a) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (b) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315.

(8) Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6144.

(9) Zhang, Y.; Li, Z.; Liu, Z. Q. *Org. Lett.* **2012**, *14*, 226.

(10) Hatamoto, Y.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2004**, *6*, 4623.

(11) Lu, Z.; Luo, F.; Wang, L.; Zhu, G. *J. Org. Chem.* **2013**, *78*, 10894.

(12) Yamashita, M.; Horiguchi, H.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 7481.

(13) Jiao, L. Y.; Smirnov, P.; Oestreich, M. *Org. Lett.* **2014**, *16*, 6020.

(14) (a) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125. (b) Garcia-Rubia, A.; Arrayas, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 6511. (c) Chen, W. L.; Gao, Y. R.; Mao, S.; Zhang, Y. L.; Wang, Y. F.; Wang, Y. Q. *Org. Lett.* **2012**, *14*, 5920. (d) Garcia-Rubia, A.; Urones, B.; Gomez Arrayas, R.; Carretero, J. C. *Chem. - Eur. J.* **2010**, *16*, 9676. (e) Young, P. C.; Hadfield, M. S.; Arrowsmith, L.; Macleod, K. M.; Mudd, R. J.; Jordan-Hore, J. A.; Lee, A.L. *Org. Lett.* **2012**, *14*, 898.

(15) Guo, T.; Jiang, Q.; Yu, Z. *Org. Chem. Front.* **2015**, *2*, 1361.

(16) (a) Ozaki, K.; Zhang, H.; Ito, H.; Lei, A.; Itami, K. *Chem. Sci.* **2013**, *4*, 3416. (b) Verma, A. K.; Danodia, A. K.; Saunthwal, R. K.; Patel, M.; Choudhary, D. *Org. Lett.* **2015**, *17*, 3658. (c) Laha, J. K.; Dayal, N. *Org. Lett.* **2015**, *17*, 4742.

(17) (a) Zhao, S. Y.; Yang, Y. W.; Zhang, H. Q.; Yue, Y.; Fan, M. *Arch. Pharmacal Res.* **2011**, *34*, 519. (b) An, Y. L.; Shao, Z. Y.; Cheng, J.; Zhao, S. Y. *Synthesis* **2013**, *45*, 2719. (c) An, Y. L.; Deng, Y. X.; Zhang, W.; Zhao, S. Y. *Synthesis* **2015**, *47*, 1581.

(18) (a) Liang, Z.; Zhao, J.; Zhang, Y. H. *J. Org. Chem.* **2010**, *75*, 170. (b) Dupeyre, G.; Lemoine, P.; Ainseba, N.; Michel, S.; Cachet, X. *Org. Biomol. Chem.* **2011**, *9*, 7780.

(19) The details can be viewed in the Supporting Information.

(20) (a) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766. (b) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346.

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Organic LETTERS

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An Aza-Diels–Alder Approach to Crowded Benzoquinolines

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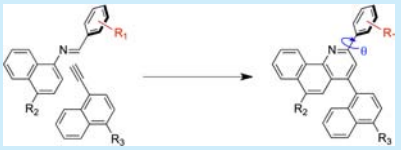
Supporting Information

ABSTRACT: Graphene nanoribbons (GNRs) are promising candidate materials for the next generation of nanoscale electronics. Described herein is the synthesis of 2,4,6-substituted benzoquinolines, which constitute building blocks for nitrogen-doped GNRs. The presented facile and modular aza-Diels–Alder chemistry accommodates the installation of diverse functionalities at the crowded benzoquinolines' 2 positions. Given the general utility of the benzoquinoline motif, these findings hold relevance not only for carbon-based electronics but also for a range of chemical disciplines.



Graphene nanoribbons (GNRs), which are narrow strips of sp^2-hybridized carbon, are viewed as promising materials for the next generation of nanoscale electronics.[1−5] Thus, much effort has been devoted to the bottom-up, solution-phase synthesis of atomically well-defined all-carbon GNRs.[6−15] However, only a handful of studies have focused on the synthesis of nitrogen-containing GNRs in solution.[14,15] This lack of precedent in the literature is quite surprising, given the known utility of substitutional doping for tuning the electrical properties of carbon-based electronic materials.[16−18] Within this context, our group has proposed the construction of nitrogen-doped N = 7 armchair GNRs via the cyclodehydrogenation of polybenzoquinoline precursors comprised of 4,6-linked benzoquinoline subunits (Figure 1). We have

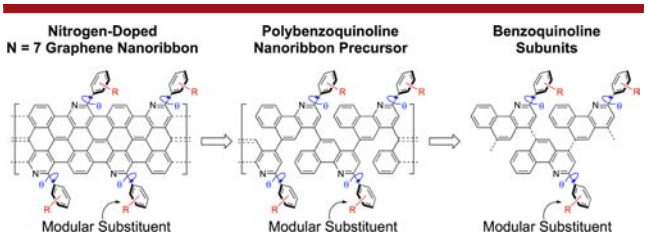


Figure 1. Illustration of the construction of a nitrogen-doped N = 7 GNR (left) from a polybenzoquinoline precursor (middle) comprised of benzoquinoline subunits (right). The aryl groups at the 2 positions of the benzoquinolines, which would influence the electronic properties of the proposed GNR, can possess different substituents and dihedral angles.

recently used the aza-Diels–Alder (Povarov) reaction[19−26] to synthesize the envisioned oligobenzoquinoline and polybenzoquinoline precursors, in a rare demonstration of this reaction's applicability for the construction of the benzoquinoline motif.[27] However, in the previous work, we did not investigate the scope of our methodology, optimize the reaction conditions for high yields, or demonstrate the installation of varying chemical functionalities at the benzoquinolines' 2 positions (corresponding to edge locations in the proposed GNRs).[27] Moreover, we did not systematically evaluate both the emergent spectroscopic and electronic properties of the synthesized constructs.[27] Indeed, due to the sensitivity of the properties of GNRs to edge modification,[1−5] such studies are of paramount importance for eventually controlling the electrical functionality of the proposed graphitic materials.

Herein, we describe an aza-Diels–Alder route to crowded benzoquinolines, which constitute building blocks for nitrogen-doped N = 7 armchair GNRs. We first optimized general aza-Diels–Alder reaction conditions for the synthesis of a 2,4,6-substituted benzoquinoline model compound. We next demonstrated the scope of this chemistry by preparing a number of analogous benzoquinolines featuring electron withdrawing, electron donating, sterically congested, or branched alkyl functionalities at their 2 positions (all in good yield). We, in turn, studied these compounds with ultraviolet–visible (UV–vis) spectroscopy. We subsequently used density functional theory calculations (DFT) to gain insight into the factors dictating the compounds' spectroscopic and electronic properties. Overall, the reported findings established an effective route to crowded benzoquinolines and provided insight that is valuable for the ultimate rational design and bottom-up preparation of nitrogen-doped GNRs.

We began our studies by optimizing the conditions for the synthesis of 2,4,6-substituted benzoquinoline **3a** via the Lewis acid-promoted Povarov reaction (Table 1).[26,27] Thus, we first prepared aldimine precursor **1a** from commercially available starting materials (4-bromonaphthylamine and octyl benzaldehyde) through a known literature protocol.[26,27] To furnish **3a**, we screened a variety of Lewis acid promoters for the cycloaddition of naphthyl alkyne **2** to aldimine **1a** (Table 1); here, we included the sacrificial oxidant chloranil[28] to ensure that **3a** was fully aromatized. Although several Lewis acids

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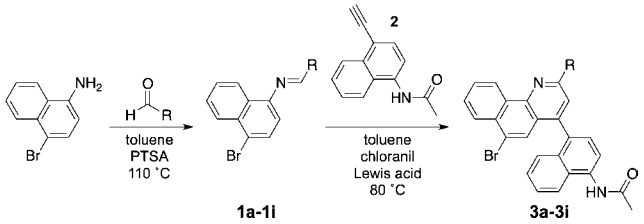
Table 1. Synthesis of 2,4,6-Substituted Benzoquinolines 3a–3i



entry	compound[a]	Lewis acid	R	yield[b] (%)
1	3a	$AlCl_3$		0
2	3a	$SnCl_2$		33
3	3a	$Y(OTf)_3$		38
4	3a	$FeCl_3$		53
5	3a	AgOTf		67
6	3a	$ZnCl_2$		75
7	3a	$BF_3{\cdot}OEt_2$		83
8	3b	$BF_3{\cdot}OEt_2$		83
9	3c	$BF_3{\cdot}OEt_2$		82
10	3d	$BF_3{\cdot}OEt_2$		76
11	3e	$BF_3{\cdot}OEt_2$		76
12	3f	$BF_3{\cdot}OEt_2$		75
13	3g	$BF_3{\cdot}OEt_2$		70
14	3h	$BF_3{\cdot}OEt_2$		68
15	3i	$BF_3{\cdot}OEt_2$		68

[a]Reaction conditions: *N*-(4-ethynylnaphthalen-1-yl)acetamide (1.0 equiv), aldimine (1.1 equiv), chloranil (1.2 equiv), Lewis acid (1.5 equiv), toluene, 80 °C, under an inert atmosphere overnight. [b]Isolated yield calculated on the basis of the alkyne.

(entries 2 to 4 in Table 1) resulted in modest yields for **3a**, we obtained good yields and regioselectivity for AgOTf (67%), $ZnCl_2$ (75%), and $BF_3{\cdot}OEt_2$ (83%) (entries 5 to 7 in Table 1). Based on our observations, we selected $BF_3{\cdot}OEt_2$ as the most promising Lewis acid for the subsequent experiments.

Having determined the optimal conditions for the regioselective synthesis of benzoquinoline **3a** in high yield, we examined the scope of our reaction for the installation of different substituents at this molecule's 2 position. We therefore used different commercially available aldehyde derivatives to prepare distinct aldimines **1b–1i**. We coupled each of these aldimines with alkyne **2** to furnish regioisomerically pure 2,4,6-substituted benzoquinolines **3b–3i**, as confirmed by ^1H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy (see Supporting Information Figures S1 to S38). Notably, our reaction conditions readily enabled the preparation of benzoquinolines featuring both electron withdrawing (entries 8, 9, 10, and 12 in Table 1) and electron donating (entry 15 in Table 1) groups in good yields of >67%. Moreover, the protocol was capable of accommodating sterically hindered aldimines featuring ortho substituents on their pendant phenyl rings (entries 8 and 13 in Table 1), with no deleterious effects on the yields. Finally, we discovered that our conditions even permitted branched aliphatic chains (entry 14 in Table 1). Together, the above observations underscored the general applicability of our method for the production of benzoquinolines featuring varied functionalities at their 2 positions.

We proceeded to evaluate the conformations of our aldimines and benzoquinolines. For this purpose, we determined the solid-state structure of **1a** via X-ray crystallography techniques and compared it to the previously reported structure of benzoquinoline **3e** (Figure 2).[27] For

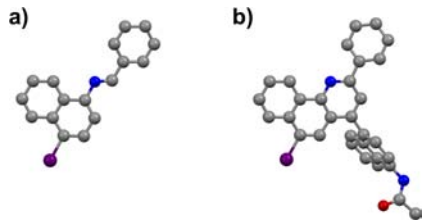


Figure 2. X-ray crystal structures of (a) aldimine **1a** and (b) benzoquinoline **3e**. For both crystal structures, the carbon, nitrogen, oxygen, and bromine atoms are indicated in gray, blue, red, and purple, respectively. Note that the hydrogen atoms in (a) and (b), as well as the octyl chain in (a), have been omitted for clarity.

aldimine **1a**, we noted that the pendant phenyl ring was nearly in plane with the naphthyl system (Figure 2a). Thus, the π-conjugation along the imine backbone appeared to be maintained, likely stabilizing this molecule. For benzoquinoline **3e**, we noted that the pendant phenyl ring and the benzoquinoline core were also close to coplanar, with their slight dihedral angle of ~15° presumably resulting from crowding of the neighboring hydrogens (Figure 2b). This analysis provided insight into the possible influence of steric interactions on the geometry of our compounds.

We next investigated the electronic properties of benzoquinolines **3a–3i** with UV–vis spectroscopy. As a specific example, the spectrum measured for compound **3e** featured absorption peaks with maxima at 223, 241, 289, 311, 349, and 367 nm (Figure 3 and Supporting Information Figure S39). This spectrum also differed somewhat from the one obtained for the benzoquinoline core due to the red shift and presence of

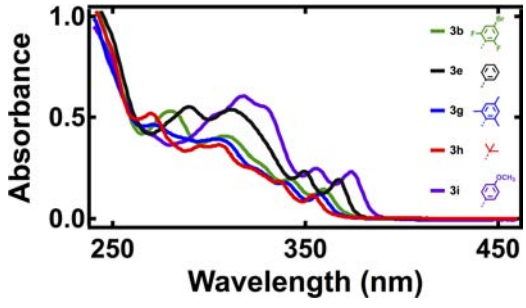


Figure 3. UV–vis absorbance spectra obtained for benzoquinoline model compounds **3b** (green line), **3e** (black line), **3g** (blue line), **3h** (red line), and **3i** (purple line). Note that the spectra of **3b** and **3g** are blue-shifted with respect to **3e** and resemble the spectrum of **3h**.

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distinctive peaks (Supporting Information Figure S39); the difference could be readily rationalized by considering the aromatic substituents and expanded π-conjugated system of **3e** (relative to the unsubstituted benzoquinoline). In general, the spectra of our crowded benzoquinolines all exhibited clusters of peaks at 220−300 nm and 300−375 nm but were blue- or red-shifted with respect to one another, as illustrated for compounds **3b**, **3e**, **3g**, **3h**, and **3i** (Figure 3 and Supporting Information Figure S39).

When analyzing our molecules' spectroscopic properties, we were somewhat surprised to find that the spectra of congested compounds **3b** and **3g** were both substantially blue-shifted with respect to that of compound **3e**, and even generally resembled the spectrum of compound **3h** (Figure 3). Here, based on our analysis of the solid state structure of **3e** (Figure 2b), we hypothesized that steric interactions between the benzoquinoline core and the 2,6 substituents of the pendant phenyl rings of **3b** and **3g** increased the dihedral angle between the two aromatic systems, twisting them far out of coplanarity. This effect would decouple the benzoquinoline core and phenyl rings, leading to a reduction in the overall size of the π-conjugated framework for **3b** and **3g** and, thus, to the observed blue shifts in the spectra.

To provide theoretical validation for our hypothesis, we performed DFT calculations for all of the 2,4,6-substituted benzoquinolines. As illustrative examples, Figure 4 shows the chemical structures and corresponding HOMO and LUMO isosurface plots for compounds **3b**, **3e**, **3g**, **3h**, and **3i**. First, we found that the orientation of the naphthyl substituent relative to the benzoquinoline core was similar for these molecules, with a typical dihedral angle of ∼74°. This observation indicated that the naphthyl moiety probably played a minor role in the blue shift observed for **3b** and **3g**. In addition, we found that the dihedral angle between the pendant phenyl ring and benzoquinoline core for **3b**, **3e**, **3g**, and **3i** could be roughly correlated with the localization of the HOMO (Figure 4). Indeed, this molecular orbital was more likely to encompass the pendant phenyl ring for compounds **3e** and **3i**, than for compounds **3b** and **3g**. Moreover, the HOMO and LUMO orbitals of compound **3g** resembled those of compound **3h**, indicating that the pendant phenyl of **3g** was electronically decoupled from its benzoquinoline core (Figure 4). Overall, this analysis suggested that steric effects play a prominent role in dictating the electronic properties of our compounds.

In summary, we have expanded the scope of our previously established methodology and synthesized a library of crowded 2,4,6-substituted benzoquinolines. The presented findings hold significance for several reasons. First, this study constitutes a rare example (few previous reports exist)[21−25,27] of the construction of substituted benzoquinolines via the aza-Diels−Alder reaction. Second, the scalable, straightforward, and mild chemistry accommodates the installation of diverse chemical functionalities at the 2 position, including electron donating, electron withdrawing, sterically hindered, and branched alkyl moieties, all in good yields of >67%. Third, the spectroscopic measurements and theoretical calculations indicate that the electronic structures of the substituted benzoquinolines are dictated by an interplay of electronic and steric factors; this constitutes important information for the eventual rational design of GNRs from such building blocks. Finally, given the known utility of the quinoline and benzoquinoline motifs,[29−32] our observations are likely to prove valuable for a wide range of chemical disciplines.

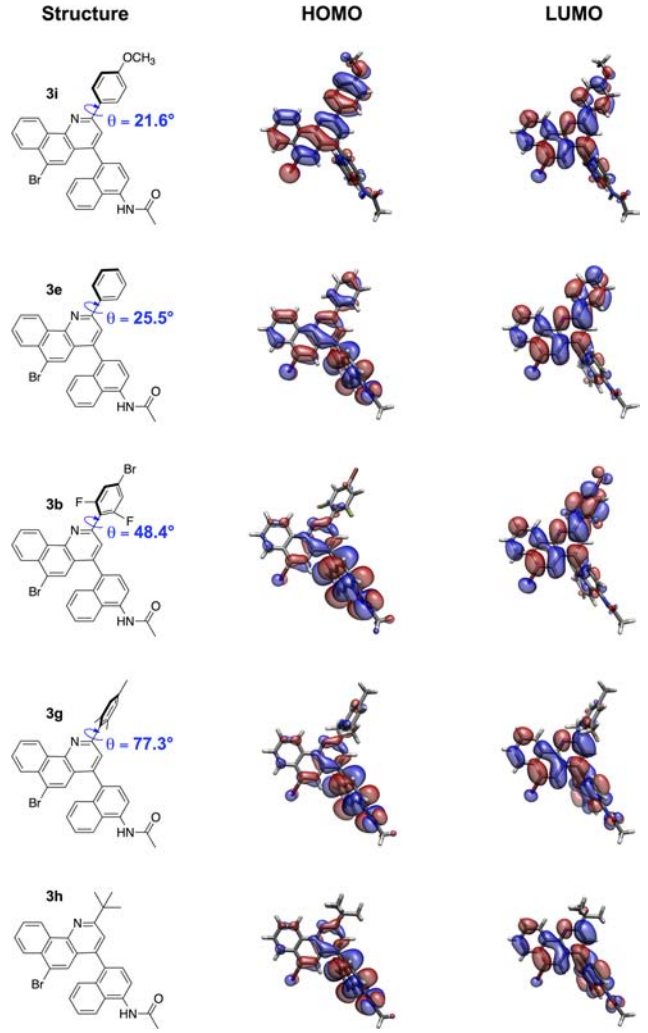

Figure 4. Left: The chemical structures of benzoquinolines **3i**, **3e**, **3b**, **3g**, and **3h**. The dihedral angles associated with the phenyl ring at the 2 position are indicated for **3i**, **3e**, **3b**, and **3g**. Middle: The HOMO obtained for each benzoquinoline. Right: The LUMO obtained for each benzoquinoline.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02939.

Crystallographic data for **1a** (CIF)
Crystallographic data for **3e** (CIF)
Detailed experimental procedures for all synthesis and purification steps, the density functional theory calculations protocol, the characterization data for all of the presented compounds, and the X-ray data for compounds **1a** and **3e** (PDF)

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Author Contributions

§A.M. and D.J.D. contributed equally.

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Notes

The authors declare no competing financial interest.

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We thank Dr. Irina A. Gorodetskaya (University of California, Irvine) and Prof. David Van Vranken (University of California, Irvine) for enlightening discussions. This work was supported by the Office of Naval Research (N000141210491, N000141310650, and N000141512680). Computer modeling was performed on the University of California, Irvine Greenplanet cluster, which is supported by NSF Grant CHE-0840513.

■ REFERENCES

(1) Castro Neto, A. H.; Guinea, F.; Peres, N. M. R.; Novoselov, K. S.; Geim, A. K. *Rev. Mod. Phys.* **2009**, *81*, 109−162.
(2) Chen, L.; Hernandez, Y.; Feng, X.; Müllen, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 7640−7654.
(3) Narita, A.; Feng, X.; Müllen, K. *Chem. Rec.* **2015**, *15*, 295−309.
(4) Shen, H.; Shi, Y.; Wang, X. *Synth. Met. In Press*, **2015**, DOI: 10.1016/j.synthmet.2015.07.010.
(5) Narita, A.; Wang, X.-Y.; Feng, X.; Müllen, K. *Chem. Soc. Rev.* **2015**, *44*, 6616−6643.
(6) Yang, X.; Dou, X.; Rouhanipour, A.; Zhi, L.; Räder, H. J.; Müllen, K. *J. Am. Chem. Soc.* **2008**, *130*, 4216−4217.
(7) Dössel, L.; Gherghel, L.; Feng, X.; Müllen, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2540−2543; *Angew. Chem.* **2011**, *123*, 2588−2591.
(8) Schwab, M. G.; Narita, A.; Hernandez, Y.; Balandina, T.; Mali, K. S.; De Feyter, S.; Feng, X.; Müllen, K. *J. Am. Chem. Soc.* **2012**, *134*, 18169−18172.
(9) Tan, Y.-Z.; Yang, B.; Parvez, K.; Narita, A.; Osella, S.; Beljonne, D.; Feng, X.; Müllen, K. *Nat. Commun.* **2013**, *4*, 2646.
(10) Kim, K. T.; Jung, J. W.; Jo, W. H. *Carbon* **2013**, *63*, 202−209.
(11) Narita, A.; Feng, X.; Hernandez, Y.; Jensen, S. A.; Bonn, M.; Yang, H.; Verzhbitskiy, I. A.; Casiraghi, C.; Hansen, M. R.; Koch, A. H. R.; Fytas, G.; Ivasenko, O.; Li, B.; Mali, K. S.; Balandina, T.; Mahesh, S.; De Feyter, S.; Müllen, K. *Nat. Chem.* **2013**, *6*, 126−132.
(12) Narita, A.; Verzhbitskiy, I. A.; Frederickx, W.; Mali, K. S.; Jensen, S. A.; Hansen, M. R.; Bonn, M.; De Feyter, S.; Casiraghi, C.; Feng, X.; Müllen, K. *ACS Nano* **2014**, *8*, 11622−11630.
(13) Vo, T. H.; Shekhirev, M.; Kunkel, D. A.; Morton, M. D.; Berglund, E.; Kong, L.; Wilson, P. M.; Dowben, P. A.; Enders, A.; Sinitskii, A. *Nat. Commun.* **2014**, *5*, 3189.
(14) Kim, K. T.; Lee, J. W.; Jo, W. H. *Macromol. Chem. Phys.* **2013**, *214*, 2768−2773.
(15) Vo, T. H.; Shekhirev, M.; Kunkel, D. A.; Orange, F.; Guinel, M. J.-F.; Enders, A.; Sinitskii, A. *Chem. Commun.* **2014**, *50*, 4172−4174.
(16) Araujo, P. T.; Terrones, M.; Dresselhaus, M. S. *Mater. Today* **2012**, *15*, 98−109.
(17) Lv, R.; Terrones, M. *Mater. Lett.* **2012**, *78*, 209−218.
(18) Wang, H.; Maiyalagan, T.; Wang, X. *ACS Catal.* **2012**, *2*, 781−794.
(19) Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656−670.
(20) Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721−2750.
(21) Zhang, Y.; Li, P.; Wang, L. *J. Heterocycl. Chem.* **2011**, *48*, 153−157.
(22) Yao, C.; Qin, B.; Zhang, H.; Lu, J.; Wang, D.; Tu, S. *RSC Adv.* **2012**, *2*, 3759−3764.
(23) Suresh, R.; Muthusubramanian, S.; Senthilkumaran, R.; Manickam, G. *J. Org. Chem.* **2012**, *77*, 1468−1476.
(24) Sarmah, M. M.; Bhuyan, D.; Prajapati, D. *Synlett* **2013**, *24*, 2245−2248.
(25) Maiti, G.; Karmakar, R.; Kayal, U. *Tetrahedron Lett.* **2013**, *54*, 2920−2923.
(26) Dibble, D. J.; Umerani, M. J.; Mazaheripour, A.; Park, Y. S.; Ziller, J. W.; Gorodetsky, A. A. *Macromolecules* **2015**, *48*, 557−561.
(27) Dibble, D. J.; Park, Y. S.; Mazaheripour, A.; Umerani, M. J.; Ziller, J. W.; Gorodetsky, A. A. *Angew. Chem., Int. Ed.* **2015**, *54*, 5883−5887.
(28) Buckle, D. R. Chloranil. *e-EROS Encyclopedia of Reagents for Organic Synthesis*; Wiley: Hoboken, NJ, 2001; DOI:10.1002/047084289X.
(29) Kimyonok, A.; Wang, X.-Y.; Weck, M. *J. Macromol. Sci., Polym. Rev.* **2006**, *46*, 47−77.
(30) Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. *Chem. Rev.* **2010**, *110*, 824−889.
(31) Solomon, V. R.; Lee, H. *Curr. Med. Chem.* **2011**, *18*, 1488−1508.
(32) Prachayasittikul, V.; Prachayasittikul, S.; Ruchirawat, S.; Prachayasittikul, V. *Drug Des., Dev. Ther.* **2013**, *7*, 1157−1178.

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Organic LETTERS

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Enantioselective Cyclopropanation with α-Alkyl-α-diazoesters Catalyzed by Chiral Oxazaborolidinium Ion: Total Synthesis of (+)-Hamavellone B

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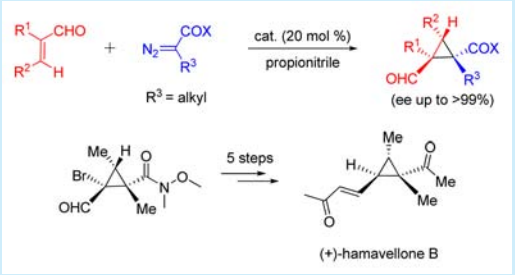
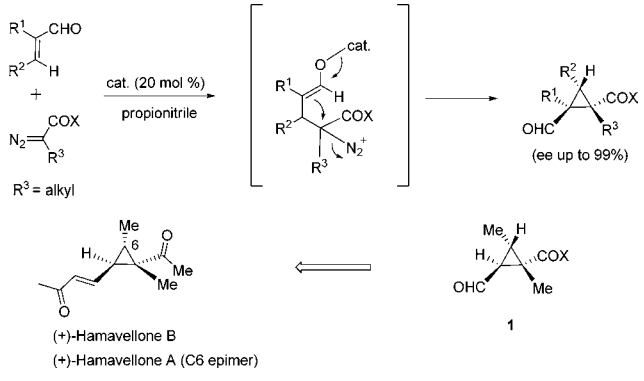
Supporting Information

ABSTRACT: Chiral oxazaborolidinium ion-catalyzed asymmetric cyclopropanation of α- or α,β-substituted acroleins with α-alkyl-α-diazoesters has been developed. With this methodology, chiral functionalized cyclopropanes containing a quaternary stereogenic center were obtained with high to excellent enantioselectivities (up to >99% ee). The synthetic utility of optically enriched functionalized cyclopropane was demonstrated in the first total synthesis of (+)-hamavellone B, which establishes the absolute configuration of natural (+)-hamavellone B.



Substituted cyclopropane is an important structural motif that is essential for biological activity and is found in a wide variety of natural products and medicinal agents.[1] During the past two decades, various catalytic systems have been developed for highly diastereo- and enantioselective cyclopropanation reactions.[2] Among them, catalytic cyclopropanation of diazo reagents and alkenes is a useful method for constructing chiral cyclopropane derivatives. Transition-metal-catalyzed cyclopropanation of alkenes[3] with various types of diazo compounds has been developed to result in stereocontrolled cyclopropane derivatives. In a complementary approach, a Lewis acid catalyzed Michael-initiated ring-closure (MIRC) reaction using diazo compounds as ylides proceeds with electron-deficient olefins, such as α,β-unsaturated carbonyl compounds (Scheme 1).[4] This method provides optically active dicarbonyl cyclopropane compounds, which were found to be important synthetic intermediates for various applications.[5]

Scheme 1. Enantioselective Synthesis of Hamavellone B



Our group reported the first example of highly enantiocontrolled catalytic cyclopropanation using α-aryl-α-diazoester as an ylide (Scheme 1, R^3 = Ar, X = O-*t*-Bu).[4d] The oxazaborolidinium ion catalyzed MIRC reaction provided highly functionalized cyclopropanes in high yields with excellent enantioselectivities. Extension of this methodology to include α-alkyl-α-diazoesters[6] is particularly attractive because this reaction forms cyclopropanes with a quaternary stereogenic carbon center bearing all alkyl groups. We envisaged enantioselective MIRC reactions with α-methyl-α-diazoesters to provide a key intermediate **1**, which has all requisite stereocenters and functional groups for synthesis of natural hamavellone B. In this paper, we report the first case of highly stereoselective catalytic cyclopropanation with α-alkyl-α-diazoester as an ylide. The synthetic utility of optically enriched functionalized cyclopropane was demonstrated in the first total synthesis of (+)-hamavellone B,[7] which also establishes the absolute configuration of natural hamavellone B.

Stereoselective cyclopropanation between α-bromoacrolein and α-benzyl diazoester was first examined in the presence of 20 mol % of oxazaborolidinium ion **2a** activated by triflic imide (Table 1, entry 1). When the reaction was performed at −78 °C in CH_2Cl_2, the desired chiral cyclopropane **3a** was formed in 48% yield, 43% ee, and with a 7:1 of *trans*/*cis* ratio[8] via the MIRC pathway (Table 1, path a). Simultaneously, 40% of diazo carbon-inserted product[9] **4** was formed as a side product via 1,2-hydride shift (path b). Use of the polar solvent propionitrile led to an increased ratio of the desired product in 83% ee with excellent trans selectivity (>20:1) (Table 1, entry 2). With propionitrile as solvent, the effect of changing boracycle catalyst

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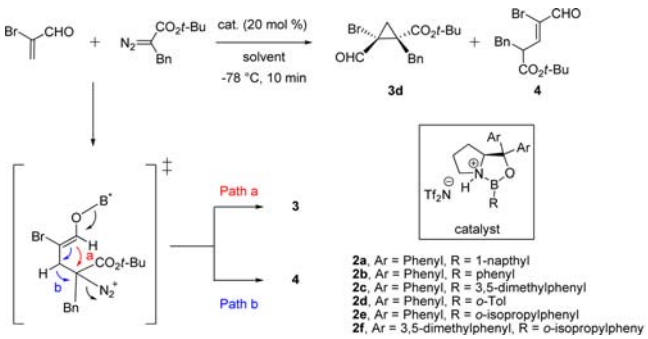
Table 1. Optimization of Asymmetric Cyclopropanation of α-Bromoacrolein with α-Benzyl-α-diazoester[a]



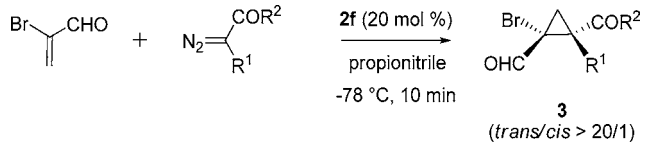
entry	solvent	cat.	3d, yield[b] (%)	3d, ee[c] (%)	*trans*/*cis*[d]
1	CH_2Cl_2	**2a**	48	43	7:1
2	CH_3CH_2CN	**2a**	47	83	>20:1
3	CH_3CH_2CN	**2b**	41	77	>20:1
4	CH_3CH_2CN	**2c**	47	81	16:1
5	CH_3CH_2CN	**2d**	52	85	>20:1
6	CH_3CH_2CN	**2e**	57	98	>20:1
7	CH_3CH_2CN	**2f**	66	99	>20:1

[a]Reaction of α-alkyl-α-diazoester (0.24 mmol) with α-bromoacrolein (0.34 mmol) was performed in the presence of **2** (20 mol %) in 1.0 mL of propionitrile at −78 °C for 10 min. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Determined by ^{1}H NMR analysis of crude product.

substituents was then investigated. The catalyst system with a 3,5-dimethylphenyl Ar substituent and 2-isopropylphenyl R substituent gave the best result (Table 1, entries 3−7). The yield of **2f** improved to 66% in 99% ee with virtually complete *trans*-diastereoselectivity (>20:1) (Table 1, entry 7).

With the optimized reaction conditions for asymmetric cyclopropanation, this synthetic method was evaluated using a range of α-alkyl-α-diazocarbonyl compounds (Table 2).

Table 2. Asymmetric Cyclopropanation of α-Bromoacrolein with α-Alkyl-α-diazocarbonyl Compounds[a]



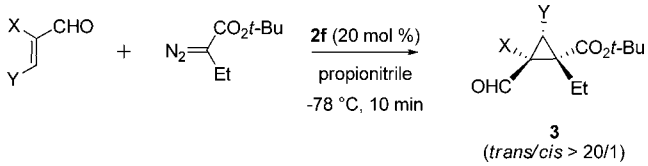
entry	3	R^1	R^2	yield[b] (%)	ee[c] (%)
1	**3a**	Me	O-*t*-Bu	50	99
2	**3b**	Et	O-*t*-Bu	76	>99
3	**3c**	*n*-Hex	O-*t*-Bu	62	>99
4	**3d**	CH_2Ph	O-*t*-Bu	66	99
5	**3e**	Propargyl	O-*t*-Bu	50	91
6	**3f**	allyl	O-*t*-Bu	55	91
7	**3g**	Et	OCH_2Ph	60	92
8	**3h**	Et	OEt	56	99
9	**3i**	Me	NMe(OMe)	51	>99
10	**3j**	CH_2Ph	NMe(OMe)	70	>99

[a]Reaction of α-alkyl-α-diazoester (0.24 mmol) with α-bromoacrolein (0.34 mmol) was performed in the presence of **2f** (20 mol %) in 1.0 mL of propionitrile at −78 °C for 10 min. [b]Isolated yield. About 30% of diazo carbon-inserted product was formed as a major side product. [c]Determined by chiral HPLC analysis.

As shown in Table 2, chiral oxazaborolidinium ion **2f** was applied to a reasonable range of olefinic substrates to provide corresponding cyclopropanes in fairly good yields with excellent enantioselectivities (Table 2, entries 1−6). Considering the other possible reaction pathways, such as 1,2-hydride shift (Table 1, path b),[4c,9] 2-pyrazoline formation,[10] and the Roskamp reaction,[11] the yield of cyclopropanation products is remarkable. Different alkyl α-diazoesters, such as benzyls or ethyls, were good substrates for this catalytic system to provide the corresponding cyclopropanes with lower enantioselectivities (Table 2, entry 7 and 8). Next, α-alkyl-α-diazo *N*-methoxy-*N*-methylamide (Weinreb amide) was applied to these catalytic conditions because the Weinreb amide group has many advantages in terms of facile transformation to ketones or aldehydes. Notably, replacement of the ester group of the diazo compound with the Weinreb amide group afforded optically pure chiral cyclopropanes in moderate to good yields (Table 2, entries 9 and 10).

To further investigate the substrate scope of the present catalytic system, catalytic asymmetric cyclopropanation reaction was performed with a range of α- or α,β-substituted acroleins and α-ethyl-α-diazoester (Table 3). Regardless of the electronic

Table 3. Asymmetric Cyclopropanation of α- or α,β-Substituted Acroleins with α-Ethyl-α-diazoester[a]



entry	3	X	Y	yield[b] (%)	ee[c] (%)
1	**3b**	Br	H	76	>99
2	**3k**	Cl	H	57	>99
3	**3l**	I	H	53	>99
4	**3m**	CH_3	H	45	99
5	**3n**	$(CH_2)_4CH_3$	H	50	86
6	**3o**	CH_2Ph	H	51	95
7	**3p**	Br	Me	75	>99
8[d]	**3q**	Br	Me	52	>99

[a]Reaction of α-ethyl-α-diazoester (0.24 mmol) with α- or α,β-substituted acroleins (0.34 mmol) was performed in the presence of **2f** (20 mol %) in 1.0 mL of propionitrile at −78 °C for 10 min. [b]Isolated yield. About 30% of diazo carbon-inserted product was formed as a major side product. [c]Determined by chiral HPLC analysis. [d]α-Methyl-α-diazo Weinreb amide was used instead of α-diazoester. The reaction time was 1 h.

or steric properties of substituents on the α-position of acroleins, highly optically active cyclopropanes **3** were obtained (Table 3, entries 1−6). Among the α-halogen substituents, α-bromoacrolein was the best substrate to give bromocyclopropanes[12] in good yield with complete control of enantio- and diastereoselectivity (Table 3, entries 1−3).

Encouraged by the good results of α-bromoacrolein, a catalytic asymmetric cyclopropanation of (*Z*)-α-bromo-β-methylacrolein was attempted to obtain highly functionalized chiral cyclopropanes containing three stereogenic centers, including two adjacent quaternary centers. All three chiral centers of controlled cyclopropane were obtained in 66% yield with an optically pure form (Table 3, entry 7). Under the optimized conditions, cyclopropanation with α-methyl-α-diazo Weinreb amide provided corresponding cyclopropane **3q** with

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excellent enantio- and diastereoselectivity, although in moderate yield (Table 3, entry 8). Absolute configurations were assigned on the basis of the structure of **3p**, which was confirmed unambiguously by X-ray crystallographic study after transformation to the corresponding carboxylic acid **3r** with a dimethyl acetal group (Figure 1).

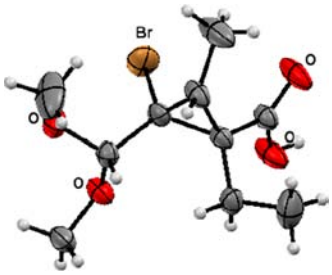
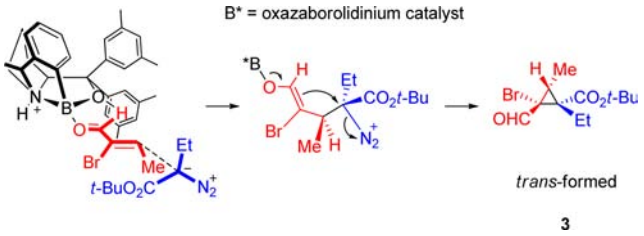


Figure 1. Single-crystal X-ray structure of **3r**.

The observed stereochemistry for the enantioselective cyclopropanation reaction with oxazaborolidinium ion catalyst **2f** is explained by the transition-state model shown in Scheme 2, which is the same as was previously postulated for the enantioselective cyclopropanation reaction with α-aryl-α-diazoester.[4d]

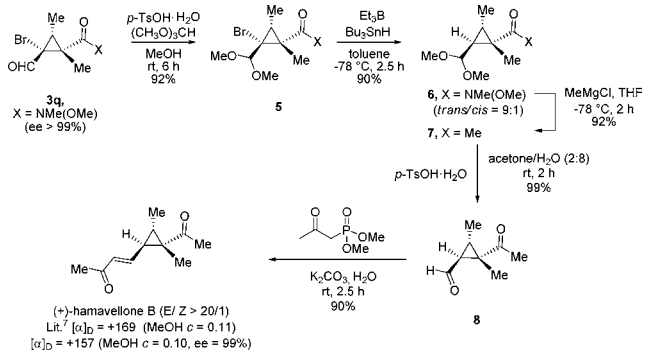
Scheme 2. Proposed Mechanism for Stereoselective Cyclopropanation between (*Z*)-α-Bromo-β-methylacrolein and α-Ethyl-α-diazoester



Having established the scope of the synthetic methodology, we then turned our attention to the first total synthesis of hamavellone B, which was isolated from the soil fungus *Hamigera avellanea* by Isaka and co-workers in 2008.[7] Hamavellone B exhibits antimalarial and anticancer activities. To date, there has been no reported synthesis of hamavellone B, and its absolute structure has not been determined.

Optically pure cyclopropane **3q**, a key intermediate for hamavellone B, was successfully synthesized with catalyst **2f** (Table 3, entry 8) (Scheme 3). After conversion of aldehyde to dimethyl acetal **5** for aldehyde protection, various radical reduction conditions for debromination were attempted. However, most of the attempted reactions resulted in decomposition of starting cyclopropane **5**. Fortunately, the use of Et_3B as a radical initiator at low temperature afforded the desired product **6** in 90% isolated yield of trans isomer. After the Weinreb amide group was converted to methyl ketone **7** with methylmagnesium chloride in 92% yield, deprotection of the dimethyl acetal group under aqueous acidic conditions provided the desired aldehyde **8** in 99% yield. Finally, Horner–Wadsworth–Emmons reaction of **8** with dimethyl 2-oxopropylphosphonate using K_2CO_3 as a base afforded (+)-hamavellone B in 90% yield. The physical data (NMR and optical rotation) of synthetic hamavellone B were in agreement with

Scheme 3. Stereoselective Synthesis of the Natural Product Hamavellone B



the reported data. Its structure determined from spectroscopic analysis indicates that the absolute structure of natural hamavellone B is a (1*S*,2*S*,3*S*)-configuration.[13]

In summary, the first case of highly enantioselective catalytic MIRC cyclopropanation using α-alkyl-α-diazoester has been developed. This method gives highly functionalized cyclopropanes containing quaternary stereogenic centers in which excellent enantioselectivity (up to >99% ee) and virtually complete trans-diastereoselectivity were achieved. Moreover, this methodology was successfully applied to the first total synthesis of (+)-hamavellone B and determination of the absolute structure of natural hamavellone B.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02970.

Experimental procedures and full analytical data (PDF)
X-ray crystallographic data for **3r** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Liu, H. W.; Walsh, C. T. *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; John Wiley: New York, 1997; p 959. (b) Nishii, Y.; Maruyama, N.; Wakasugi, K.; Tanabe, Y. *Bioorg. Med. Chem.* **2001**, *9*, 33. (c) Csuk, R.; Schabel, M. J.; von Scholz, T. *Tetrahedron: Asymmetry* **1996**, *7*, 3505. (d) Ravi Kumar, J. S.; Roy, S.; Datta, A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 513. (e) Zhang, X.; Hodgetts, K.; Rachwal, S.; Zhao, H.; Wasley, J. W. F.; Craven, K.;

DOI: 10.1021/acs.orglett.5b02970
Org. Lett. 2016, 18, 160–163

Brodbeck, R.; Kieltyka, A.; Hoffman, D.; Bacolod, M. D.; Girard, B.; Tran, J.; Thurkauf, A. *J. Med. Chem.* **2000**, *43*, 3923. (f) Mohapatra, D. K.; Datta, A. *J. Org. Chem.* **1998**, *63*, 642.

(2) Selected reviews: (a) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Synthesis* **2014**, *46*, 979. (b) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (c) Pellissier, H. *Tetrahedron* **2008**, *64*, 7041.

(3) For selected examples of transition-metal-catalyzed asymmetric cyclopropanation, see: (a) Zhu, S.; Perman, J. A.; Zhang, X. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8460. (b) Fantauzzi, S.; Gallo, E.; Rose, E.; Raoul, N.; Caselli, A.; Issa, S.; Ragaini, F.; Cenini, S. *Organometallics* **2008**, *27*, 6143. (c) Özüduru, G.; Schubach, T.; Boysen, M. M. K. *Org. Lett.* **2012**, *14*, 4990. (d) Lindsay, V. N. G.; Lin, W.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 16383. (e) Lindsay, V. N. G.; Fiset, D.; Gritsch, P. J.; Azzi, S.; Charette, A. B. *J. Am. Chem. Soc.* **2013**, *135*, 1463. (f) Qin, C.; Boyarskikh, V.; Hansen, J. H.; Hardcastle, K. I.; Musaev, D. G.; Davies, H. M. L. *J. Am. Chem. Soc.* **2011**, *133*, 19198. (g) Ito, J.-i.; Ujiie, S.; Nishiyama, H. *Chem. - Eur. J.* **2010**, *16*, 4986. (h) Suematsu, H.; Kanchiku, S.; Uchida, T.; Katsuki, T. *J. Am. Chem. Soc.* **2008**, *130*, 10327.

(4) For selected examples of MIRC reaction using diazo compounds, see: (a) Doyle, M. P.; Buhro, W. E.; Dellaria, J. F., Jr. *Tetrahedron Lett.* **1979**, *20*, 4429. (b) Branstetter, B.; Hossain, M. M. *Tetrahedron Lett.* **2006**, *47*, 221. (c) Hashimoto, T.; Naganawa, Y.; Kano, T.; Maruoka, K. *Chem. Commun.* **2007**, 5143. (d) Gao, L.; Hwang, G.-S.; Ryu, D. H. *J. Am. Chem. Soc.* **2011**, *133*, 20708.

(5) (a) Trost, B. M.; Dirat, O.; Gunzner, J. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 841. (b) Zhang, M.-X.; Eaton, P. E. *Angew. Chem., Int. Ed.* **2002**, *41*, 2169. (c) Miller, J. A.; Hennessy, E. J.; Marshall, W. J.; Scialdone, M. A.; Nguyen, S. T. *J. Org. Chem.* **2003**, *68*, 7884. (d) Sørensen, U. S.; Bleisch, T. J.; Kingston, A. E.; Wright, R. A.; Johnson, B. G.; Schoepp, D. D.; Ornstein, P. L. *Bioorg. Med. Chem.* **2003**, *11*, 197. (e) Pokorski, J. K.; Myers, M. C.; Appella, D. H. *Tetrahedron Lett.* **2005**, *46*, 915.

(6) Successful applications of α-alkyl-α-diazoesters have been recently realized in Rh(II)-catalyzed reactions; see: (a) Goto, T.; Takeda, K.; Anada, M.; Ando, K.; Hashimoto, S. *Tetrahedron Lett.* **2011**, *52*, 4200. (b) DeAngelis, A.; Dmitrenko, O.; Yap, G. P. A.; Fox, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 7230. (c) Panne, P.; DeAngelis, A.; Fox, J. M. *Org. Lett.* **2008**, *10*, 2987.

(7) Isaka, M.; Chinthanom, P.; Veeranondha, S.; Supothina, S.; Luangsa-ard, J. J. *Tetrahedron* **2008**, *64*, 11028.

(8) The *trans* geometry means the ester and aldehyde groups are directed trans to each other in the cyclopropane.

(9) (a) Lee, S. I.; Kang, B. C.; Hwang, G.-S.; Ryu, D. H. *Org. Lett.* **2013**, *15*, 1428. (b) Lee, S. I.; Hwang, G.-S.; Ryu, D. H. *J. Am. Chem. Soc.* **2013**, *135*, 7126.

(10) (a) Gao, L.; Hwang, G.-S.; Lee, M. Y.; Ryu, D. H. *Chem. Commun.* **2009**, 5460. (b) Lee, S. I.; Kim, K. E.; Hwang, G.-S.; Ryu, D. H. *Org. Biomol. Chem.* **2015**, *13*, 2745. (c) Sibi, M. P.; Stanley, L. M.; Soeta, T. *Org. Lett.* **2007**, *9*, 1553. (d) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2174.

(11) (a) Gao, L.; Kang, B. C.; Hwang, G.-S.; Ryu, D. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 8322. (b) Kang, B. C.; Nam, D. G.; Hwang, G.-S.; Ryu, D. H. *Org. Lett.* **2015**, *17*, 4810. (c) Shin, S. H.; Baek, E. H.; Hwang, G.-S.; Ryu, D. H. *Org. Lett.* **2015**, *17*, 4746. (d) Li, W.; Wang, J.; Hu, X.; Shen, K.; Wang, W.; Chu, Y.; Lin, L.; Liu, X.; Feng, X. *J. Am. Chem. Soc.* **2010**, *132*, 8532.

(12) For the synthetic application of halocyclopropanes, see: (a) Hohn, E.; Pietruszka, J. *Adv. Synth. Catal.* **2004**, *346*, 863. (b) Beaulieu, L.-P. B.; Zimmer, L. E.; Gagnon, A.; Charette, A. B. *Chem. - Eur. J.* **2012**, *18*, 14784. (c) Baird, M. S.; Fitton, H. L.; Clegg, W.; McCamley, A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 321. (d) Sheshenev, A. E.; Baird, M. S.; Croft, A. K.; Starikova, Z. A.; Shashkov, A. S.; Zhuze, A. L.; Bolesov, I. G. *Tetrahedron Lett.* **2006**, *47*, 2839. (e) Tverezovsky, V. V.; Baird, M. S.; Bolesov, I. G. *Tetrahedron* **1997**, *53*, 14773.

(13) Conversion of **1** (X = O-*t*-Bu) and **3q** to diol provided same product, and (−)-hamavellone B was synthesized with *ent*-**2f** catalyst; see the Supporting Information.

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Organic LETTERS

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Boc-SPPS: Compatible Linker for the Synthesis of Peptide *o*-Aminoanilides

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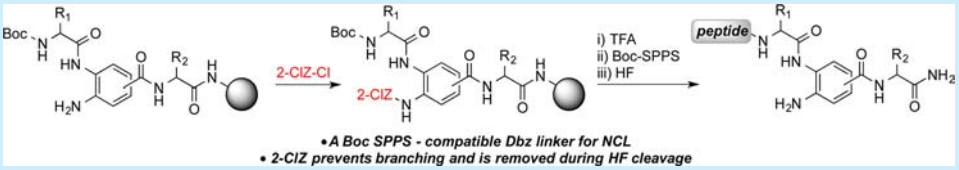
Supporting Information



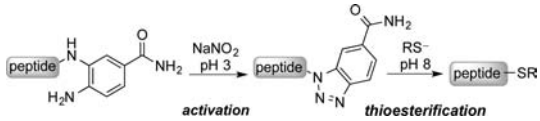
ABSTRACT: A protection strategy is described for the efficient synthesis of peptide *o*-aminoanilides using *in situ* neutralization protocols for Boc-SPPS. On-resin protection of Boc-protected aminoacyl *o*-aminoanilides is achieved with 2-chlorobenzyl chloroformate. Activation through a peptidyl-benzotriazole intermediate allows for facile conversion to peptide-thioesters for use in native chemical ligation. In addition to providing a robust alternative to established thioester resins, as a latent thioester, the peptide *o*-aminoanilide has broad utility in convergent ligation strategies.

The chemical synthesis of proteins allows for complete control over their covalent structure and enables the introduction of various natural and unnatural modifications with atomic precision.[1,2] Additionally, chemical synthesis enables the preparation of mirror-image proteins and proteins with non-natural architectures.[3−5] Native chemical ligation (NCL) is a versatile method that is commonly used in chemical protein synthesis for the chemoselective ligation of unprotected peptide fragments in solution.[6] NCL proceeds through the selective but reversible reaction between a peptide with an N-terminal cysteine and a peptide-thioester. As a result, the generation of C-terminal thioester peptides is critical for the implementation of NCL and related synthetic approaches.

Peptide thioesters can be synthesized directly by solid phase peptide synthesis (SPPS) using the Boc/Bzl protection strategy.[7,8] Peptide-thioester[9] and peptide-thioacid[10] linkers have been used in the synthesis of a wide range of protein molecules;[11] however, the sensitivity of the thioester moiety to nucleophiles requires the use of partially protected peptide intermediates. For instance, His(Dnp) and Trp(For) cannot be removed in the presence of the thioester and typically remain protected following HF cleavage.[12] Similarly, the use of the Fmoc group for orthogonal side chain protection is limited due to the nucleophilic nature of piperidine.[13] A base stable linker that could be converted to a thioester following chain elongation would provide a general solution to these synthetic limitations.

The 3,4-diaminobenzoyl (Dbz) group has been developed as a linker for the Fmoc-SPPS of thioester peptides.[14,15] Following chain elongation, the linker can be treated with nitrophenyl-chloroformate to generate an *N*-acylbenzimadazolinone (Nbz) intermediate[16,17] that can be readily converted into a thioester peptide.[14] Alternatively, *o*-aminoanilide peptides can be obtained by cleaving the Dbz linker without modification. Subsequent treatment of the unprotected peptide with sodium nitrite yields an acyl benzotriazole (Bt) intermediate[18−20] that can be intercepted by a thiol to generate C-terminal thioester peptides[21] (Scheme 1) in an analogous manner to the transfer active ester approach of Ramage.[22,23] The utility of acylbenzotriazole peptides has been extensively explored by Katrizky and applied to the synthesis of peptide thioesters.[24,25]

Scheme 1. Peptide-Dbz Conversion to Peptide-Thioester via Acylbenzotriazole Intermediate[21]



The Dbz linker was originally developed for Fmoc-SPPS protocols using neutral to acidic coupling conditions.[15] In our hands, the Dbz linker is not suitable for the synthesis of long peptides using the in situ neutralization protocols for Boc SPPS, pioneered by Schnölzer et al.,[8] since the use of excess base to neutralize residual TFA leads to branched intermediates[26] (Scheme 2, top). In order to facilitate a more robust route for peptide *o*-aminoanilides by Boc-SPPS, we have developed a solid phase Dbz protection strategy that is compatible with basic *in situ* neutralization coupling protocols (Scheme 2, bottom).

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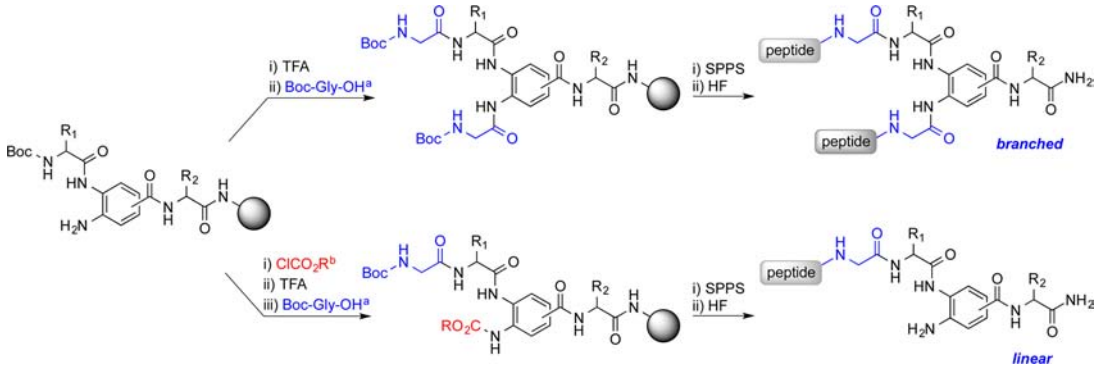
Scheme 2. Use of the Dbz Linker in SPPS Using Boc *in Situ* Neutralization with and without a Free Amine



[a]Conditions: Boc-Gly-OH (5 equiv), HATU (5 equiv), DIEA (7.5 equiv), DMF (0.4 M), 15 min, 23 °C. [b]10% (v/v) $ClCO_2R/CH_2Cl_2$ (10 equiv), 16 h, 23 °C.

To illustrate the limitations of the first generation Dbz linker, a model glycine rich peptide Phe-Gly_5-Dbz-Lys-NH_2 was synthesized using excess base during coupling.[26,15] We recommend incorporating a Lys residue at the C-terminus (ultimately part of the leaving group) to maintain the known acid lability of α-amino acids from MBHA resin[27] and also to provide improved handling and ionization properties. The peptide was synthesized using a common variant of the Boc *in situ* neutralization protocol, which employs excess base (5 equiv of amino acid, 5 equiv of HATU, 7.5 equiv of DIEA).[8] As may have been expected, without prior protection of the free aromatic amine, a high degree of branched peptides **1a**−**1d** was obtained, while minimal amounts (>10%) of the desired product **2** were observed (Figure 1).

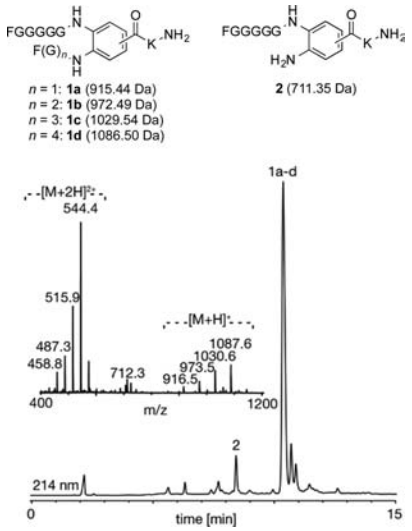


Figure 1. Synthesis of FGGGGG-Dbz-K-NH_2 using the Boc in situ neutralization protocol without Dbz protection. Observed masses of branched peptides: **1a**, 915.5 ± 0.1 Da; **1b**, 972.5 ± 0.1 Da; **1c**, 1029.7 ± 0.1 Da; **1d**, 1086.6 ± 0.2 Da. Calculated monoisotopic masses: **1a**, 915.44 Da; **1b**, 972.49 Da; **1c**, 1029.54 Da; **1d**, 1086.50 Da.

To avoid the formation of branched side products, carbamate protection of the Dbz linker has been demonstrated.[26] To obtain Dbz-peptides after cleavage, a protecting group that is TFA stable and HF labile was evaluated. The 2-ClZ group, which is commonly used for Lys side chain protection, was expected to have these properties. However, because 2-ClZ-anilides are HF-labile, we sought to validate our approach with the analogous HF-stable ethyl carbamate. Boc-Gly-Dbz-resin was treated with 10% (v/v) ethyl chloroformate in DCM for 16 h before a polyglycine model peptide was synthesized. The protected chloroformate was then cleaved by HF to yield **3**. Analysis of the crude reaction by MS showed that only negligible amounts of branched peptide were detected, with the main mass corresponding to that of the desired product (calculated, 783.4 Da; observed, 783.5 ± 0.1 Da) (Figure 2).

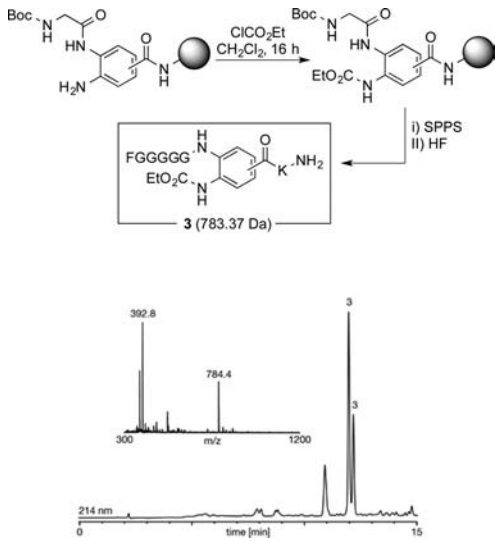


Figure 2. Use of ethyl chloroformate protected Dbz for the synthesis of a linear polyglycine peptide. Observed mass of **3**, 783.5 ± 0.1 Da; calculated monoisotopic mass, 783.4 Da.

Based on the results from the HF stable ethyl carbamate, the HF labile 2-ClZ was installed by treatment of Boc-Gly-Dbz-resin with 2-chlorobenzyl chloroformate, and the desired non-branched model peptide **2** was formed as the main synthetic product (Figure 3). The clean product obtained from 2-ClZ protected Dbz is in stark contrast to that obtained from the Dbz linker and suggests that carbamate protection could be a general solution for the synthesis of *o*-aminoanilide thioester precursor peptides by means of Boc in situ neutralization SPPS.

In order to demonstrate the broader applicability of this approach, we synthesized peptide sequences of practical relevance. The most common His protecting group for thioester peptides is dinitrophenyl (Dnp).[7,28] The alternative His(Bom)

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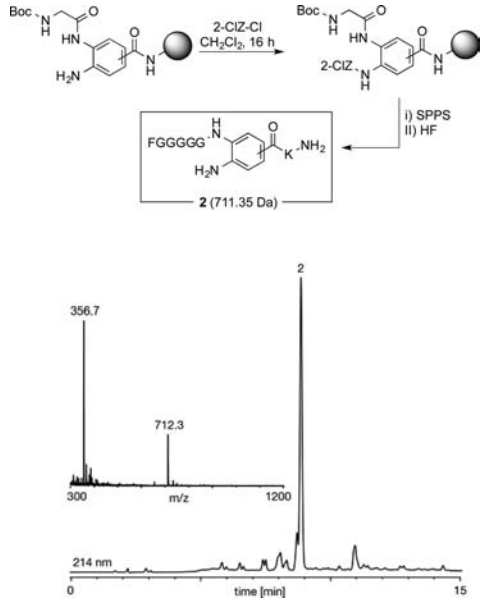


Figure 3. Use of 2-ClZ protected Dbz for the synthesis of a linear polyglycine peptide. Observed mass of **2**, 711.3 ± 0.1 Da; calculated monoisotopic mass, 711.35 Da.

releases formaldehyde and is therefore not commonly used in peptides for NCL.[29] Because on-resin Dnp deprotection is not compatible with thioester linkers, this side chain protecting group remains on the peptide until ligation.[7] Tryptophan is frequently used without any side chain protection for the same reason, or alternatively, the formyl group is removed post-ligation.[30] Therefore, we synthesized peptide **4** (WHGGG-Dbz-K), using Boc-Trp(For)-OH and Boc-His(Dnp)-OH. Peptide cleavage off the resin was successfully performed before and after deprotection to generate partially protected peptide **4a** or fully unprotected peptide **4b** (Figures S1 and S2). This illustrates that the Dbz thioester precursor enables the standard usage of both of these amino acids in the synthesis of *o*-aminoanilide peptides because the linker is stable to on-resin deprotection of His(Dnp) (20% (v/v) *β*-mercaptoethanol, 10% (v/v) DIEA in DMF, 23 °C) and Trp(For) (10% (v/v) piperidine in DMF, 0 °C).[8,12]

Biotin or other side chain modifications during Boc SPPS are commonly introduced through the incorporation of Boc-Lys(Fmoc)-OH.[31] This approach utilizes the robust deprotection and orthogonality of the Fmoc protecting group. The stability of the *o*-aminoanilide linker to piperidine should enable the routine use of Boc-Lys(Fmoc)-OH (Scheme 3). Indeed, we were pleased to find that FK(Biotin)GGG-Dbz-K (**5**) could be obtained using our protocol (Figure S3). HPLC and MS analysis showed that this biotinylated model peptide was obtained in high purity (calculated, 951.14 Da; observed, 951.6 Da ± 0.1 Da). As this is a general approach for Lys side chain modifications, it is not limited to biotinylation and could be applied to other modifications (dyes, fluorescent probes, etc.) or for the synthesis of branched peptide[32] or dendrimer thioesters.[33,34]

Hepcidin is a regulator of iron metabolism,[35] containing eight cysteines that are oxidized in the native conformation.[36] We sought to synthesize this peptide with a site for side chain modification at residue 12 using side chain Fmoc protection and NCL. The peptide DTHFPICIFCCK(N^{ϵ}-biotin)-Dbz-K-NH_2 (**6**) was prepared on MBHA resin,[27] cleaved with HF, and purified by HPLC (Figure 4). Activation to the peptidyl-

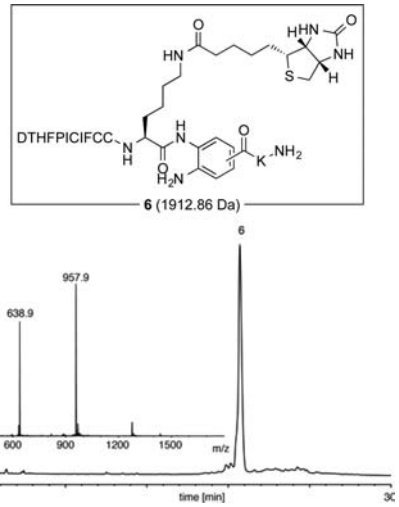
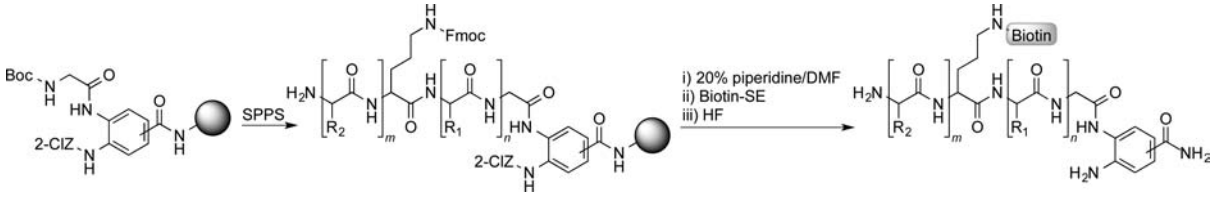


Figure 4. HPLC and MS traces of DTHFPICIFCCK(N^{ϵ}-biotin)-Dbz-K-NH_2 (**6**).

benzotriazole was achieved by incubation of 10 mM peptide in 6 M GuHCl, 100 mM NaH_2PO_4, 50 mM sodium nitrite, final pH 3, at −15 °C, for 5 min. Direct conversion to the thioester proceeded upon adding one volume of 200 mM Mesna in 6 M GuHCl and 200 mM Na_2HPO_4 (pH 8) adjusted to a final pH of 7, for 5 min, 23 °C.[21] The peptide thioester **7** was purified immediately by preparative HPLC (53% recovered yield, Figure S4). DTHFPICIFCCK(N^{ϵ}-Biotin)-Mesna (**7**) was then ligated with the N-terminal peptide CCHRSKCGMCCKT (**8**) in 6 M GuHCl, 200 mM phosphate buffer (final pH 7) and 100 mM mercaptophenylacetic acid.[37] After 2 h, the peptides were fully reduced by the addition of 10 equiv TCEP and the product (**9**) was purified by HPLC, 80% conversion based on limiting peptide **7** (Figure 5).

Finally, to demonstrate the utility of this approach in the synthesis of longer peptides, a 27 amino acid fragment of the SH2 domain (**10**) was prepared on a 0.1 mmol scale to yield 405 mg of peptide resin, representing 76% of the expected weight gain (Figure S5). The resin was cleaved to yield 245 mg of crude

Scheme 3. Strategy for the Use of Boc-Lys(Fmoc)-OH in the Synthesis of Biotinylated *o*-Aminoanilide Peptides, Demonstrating the Compatibility of Fmoc-Protective Groups with Boc-SPPS



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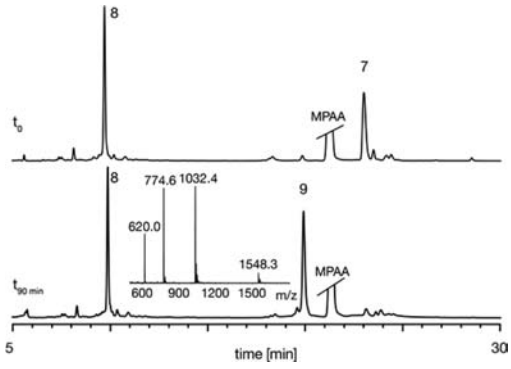

Figure 5. HPLC traces of the ligation between thioester peptide **7** and Cys-peptide **8** at 0 and 90 min. MS of purified ligation product **9** is also shown.

peptide **10**, 74% recovered yield, suggesting that the linker does not reduce the loading of the resin and is stable to Boc-SPPS.

In summary, a solid phase protection strategy has been developed that allows for the synthesis of thioester precursor *o*-aminoanilide peptides. The strategy is compatible with Boc *in situ* neutralization chemistry and nucleophile-labile protecting groups, and we expect that the standard linkers and resins previously developed for Boc-SPPS can also be used. Moreover, the resulting *o*-aminoanilide peptides are compatible with convergent ligation strategies[30] and allow for N to C terminal sequential peptide ligation.[21,38] The 2-ClZ-Dbz linker enables efficient synthesis of highly reactive aryl thioesters that can be used directly for NCL or of highly stable alkyl thioesters that can be stored long-term.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and HPLC and MS data of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Beligere, G. S.; Dawson, P. E. *J. Am. Chem. Soc.* **2000**, *122*, 12079−12082.
(2) Adhikary, R.; Zimmermann, J.; Liu, J.; Forrest, R. P.; Janicki, T. D.; Dawson, P. E.; Corcelli, S. A.; Romesberg, F. E. *J. Am. Chem. Soc.* **2014**, *136*, 13474−13477.
(3) Milton, R. C.; Milton, S. C.; Kent, S. B. *Science* **1992**, *256*, 1445−1448.
(4) Weinstock, M. T.; Jacobsen, M. T.; Kay, M. S. *Proc. Natl. Acad. Sci. U. S. A.* **2014**, *111*, 11679−11684.
(5) Mandal, K.; Uppalapati, M.; Ault-Riche, D.; Kenney, J.; Lowitz, J.; Sidhu, S. S.; Kent, S. B. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 14779−14784.
(6) Dawson, P. E.; Muir, T. W.; Clark-Lewis, I.; Kent, S. B. *Science* **1994**, *266*, 776−779.
(7) Hackeng, T. M.; Griffin, J. H.; Dawson, P. E. *Proc. Natl. Acad. Sci. U. S. A.* **1999**, *96*, 10068−10073.
(8) Schnolzer, M.; Alewood, P.; Jones, A.; Alewood, D.; Kent, S. B. *Int. J. Pept. Protein Res.* **1992**, *40*, 180−193.
(9) Hojo, H.; Aimoto, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 111−117.
(10) Blake, J.; Yamashiro, D.; Ramasharma, K.; Li, C. H. *Int. J. Pept. Protein Res.* **1986**, *28*, 468−476.
(11) Kent, S. B. *Chem. Soc. Rev.* **2009**, *38*, 338−351.
(12) Muttenthaler, M.; Albericio, F.; Dawson, P. E. *Nat. Protoc.* **2015**, *10*, 1067−1083.
(13) Li, X. Q.; Kawakami, T.; Aimoto, S. *Tetrahedron Lett.* **1998**, *39*, 8669−8672.
(14) Blanco-Canosa, J. B.; Dawson, P. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 6851−6855.
(15) Blanco-Canosa, J. B.; Nardone, B.; Albericio, F.; Dawson, P. E. *J. Am. Chem. Soc.* **2015**, *137*, 7197−7209.
(16) Pascal, R.; Chauvey, D.; Sola, R. *Tetrahedron Lett.* **1994**, *35*, 6291−6294.
(17) Sola, R.; Saguer, P.; David, M. L.; Pascal, R. *J. Chem. Soc., Chem. Commun.* **1993**, 1786−1788.
(18) Ladenburg, A. *Ber. Dtsch. Chem. Ges.* **1876**, *9*, 219−223.
(19) Katritzky, A. R.; Ji, F. B.; Fan, W. Q.; Beretta, P.; Bertoldi, M. *J. Heterocycl. Chem.* **1992**, *29*, 1519−1523.
(20) Plummer, B. F.; Russell, S. J.; Reese, W. G.; Watson, W. H.; Krawiec, M. *J. Org. Chem.* **1991**, *56*, 3219−3223.
(21) Wang, J. X.; Fang, G. M.; He, Y.; Qu, D. L.; Yu, M.; Hong, Z. Y.; Liu, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 2194−2198.
(22) Wang, P.; Layfield, R.; Landon, M.; Mayer, R. J.; Ramage, R. *Tetrahedron Lett.* **1998**, *39*, 8711−8714.
(23) Wang, P.; Shaw, K. T.; Whigham, B.; Ramage, R. *Tetrahedron Lett.* **1998**, *39*, 8719−8720.
(24) Katritzky, A. R.; Shestopalov, A. A.; Suzuki, K. *Synthesis* **2004**, *2004*, 1806−1813.
(25) Avan, I.; Hall, C. D.; Katritzky, A. R. *Chem. Soc. Rev.* **2014**, *43*, 3575−3594.
(26) Mahto, S. K.; Howard, C. J.; Shimko, J. C.; Ottesen, J. J. *ChemBioChem* **2011**, *12*, 2488−2494.
(27) Matsueda, G. R.; Stewart, J. M. *Peptides* **1981**, *2*, 45−50.
(28) Hackeng, T. M.; Mounier, C. M.; Bon, C.; Dawson, P. E.; Griffin, J. H.; Kent, S. B. *Proc. Natl. Acad. Sci. U. S. A.* **1997**, *94*, 7845−7850.
(29) Dawson, P. E. *Methods Enzymol.* **1997**, *287*, 34−45.
(30) Durek, T.; Torbeev, V. Y.; Kent, S. B. *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 4846−4851.
(31) Albericio, F.; Nicolas, E.; Rizo, J.; Ruizgayo, M.; Pedroso, E.; Giralt, E. *Synthesis* **1990**, *1990*, 119−122.
(32) Tam, J. P. *Proc. Natl. Acad. Sci. U. S. A.* **1988**, *85*, 5409−5413.
(33) Wan, J.; Huang, J. X.; Vetter, I.; Mobli, M.; Lawson, J.; Tae, H. S.; Abraham, N.; Paul, B.; Cooper, M. A.; Adams, D. J.; Lewis, R. J.; Alewood, P. F. *J. Am. Chem. Soc.* **2015**, *137*, 3209−3212.
(34) Lempens, E. H.; van Baal, I.; van Dongen, J. L.; Hackeng, T. M.; Merkx, M.; Meijer, E. W. *Chem. - Eur. J.* **2009**, *15*, 8760−8767.
(35) Nemeth, E.; Ganz, T. *Annu. Rev. Nutr.* **2006**, *26*, 323−342.
(36) Clark, R. J.; Tan, C. C.; Preza, G. C.; Nemeth, E.; Ganz, T.; Craik, D. J. *Chem. Biol.* **2011**, *18*, 336−343.
(37) Johnson, E. C.; Kent, S. B. *J. Am. Chem. Soc.* **2006**, *128*, 6640−6646.
(38) Canne, L. E.; Botti, P.; Simon, R. J.; Chen, Y. J.; Dennis, E. A.; Kent, S. B. H. *J. Am. Chem. Soc.* **1999**, *121*, 8720−8727.

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Organic LETTERS

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Guajavadimer A, a Dimeric Caryophyllene-Derived Meroterpenoid with a New Carbon Skeleton from the Leaves of *Psidium guajava*

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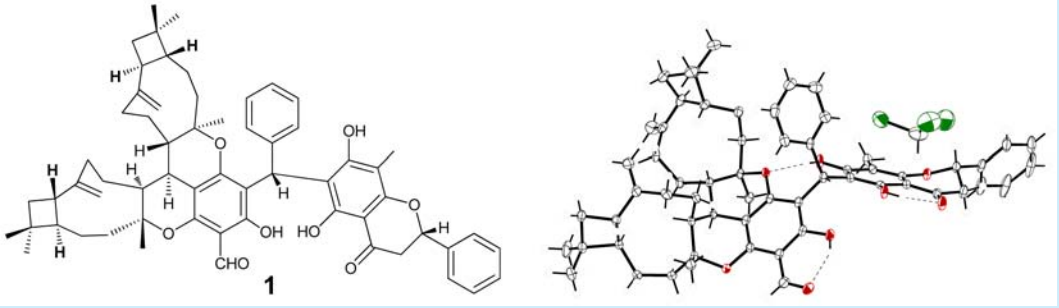
Supporting Information



ABSTRACT: Guajavadimer A (**1**), a dimeric sesquiterpene-based meroterpenoid which possessed an unprecedented two caryophyllenes, a benzylphlorogulcinol, and a flavonone-fused complicated stereochemical skeleton, was isolated from the leaves of *Psidium guajava* L. Its structure and absolute configuration were elucidated on the basis of spectroscopic data and X-ray crystallography. Guajavadimer A (**1**) showed moderate hepatoprotective activity against *N*-acetyl-*p*-aminophenol (APAP)-induced toxicity in HepG2 cells.

Myrtacea is a rich source of sesquiterpene-based meroterpenoids.[1] Some of these compounds exhibited significant biological activities such as cytotoxicity against the HL-60[1a] and HepG2[3a,b] cell lines and an inhibitory effect on PTPIB (protein tyrosine phosphatase 1B).[2b] Their structural diversity and biological activities have attracted interest from both natural products and synthetic chemists. A typical example was the isolation and biosysnthesis of caryophyllene-derived meroterpenoids guajadial and psidial A, which were isolated from *Psidium guajava*. L.[2] *P. guajava* is a fruit tree wildly distributed throughout the tropics and subtropics areas. Its leaves are used in folk medicine as antidiabetes, hepatoprotective, antioxidant, hemostatic, and anti-inflammatory agents.[4a] The aqueous extract of the leaves has been marketed to treat type II diabetes in China.[4b] Chemical investigations on the leaves of *P. guajava* led to the isolation of several sesquiterpene- and monoterpene-based meroterpenoids with unprecedented skeletons.[2,3] Our previous chemical studies on the ethanol extract of *P. guajava* resulted in the isolation of three unique meroterpenoids with an inhibitory effect on PTPIB.[2b] In a continuing study on meroterpenoids, a dimeric caryophyllene-derived meroterpenoid guajavadimier A (**1**) was obtained from the same sample. Although more than 10 sesquiterpene-based meroterpenoids have been isolated, guajavadimier A (**1**) represents the most complex dimeric sesquiterpene-based meroterpenoids identified so far. Herein, we describe the isolation, structural elucidation, bioactivity, and plausible biogenesis of guajavadimer A (**1**, Figure 1).

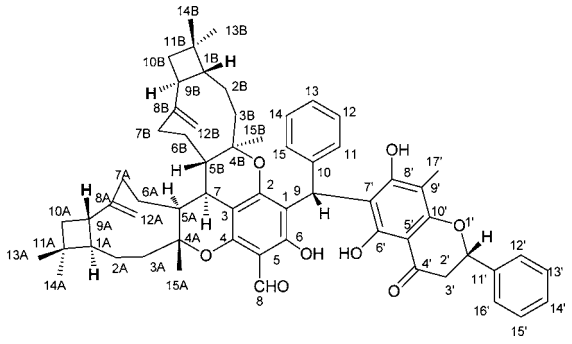


Figure 1. Chemical structure of compound **1**.

Compound **1** was obtained as a colorless crystal (in MeOH: $CHCl_3$). Its molecular formula $C_{61}H_{70}O_8$ was determined by HRESI (−) MS at *m*/*z*: 929.4977 $[M - H]^-$ (cal. 929.4998) and revealed 27 degrees of unsaturation. The IR spectrum displayed absorption bands for hydroxyls (at 3280 cm^{-1}), aldehyde (at 2938 cm^{-1}), and conjugated carbonyl (at 1628 cm^{-1}) functionalities. The ^1H NMR spectrum of **1** (Table 1) showed signals of two phenolic hydroxyls at δ_H 12.83 and 12.71 (both were hydrogen bonded to carbonyl group); an aldehyde at δ_H 10.0; two monosubstituted benzene rings at δ_H 7.45 (2H, d, *J* = 7.2 Hz), 7.42 (2H, t, *J* = 7.2 Hz), 7.39 (1H, t, *J* = 7.2 Hz),

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Table 1. NMR Data of 1 (in $CDCl_3$, δ Values in ppm, J Values in Hz)[a]

no.	^{13}C	^{1}H	no.	^{13}C	^{1}H
1	108.8		1A	56.2	1.67 (m)
2	157.3		2A	27.1	1.64 (m)
3	106.1				1.70[b]
4	159.3		3A	41.1	1.97 (2H, m)
5	106.8		4A	88.6	
6	159.6		5A	39.0	2.20 (m)
7	35.7	2.27 (m)	6A	21.8	1.30, 1.12 (m)
8	191.3	10.00 (s)	7A	36.5	2.41, 1.89 (m)
9	32.7	6.62 (s)	8A	150.7	
10	140.3		9A	47.4	2.40 (dd, 18.0, 10.8)
11	127.0	7.09 (d, 7.2)			
12	128.4	7.26 (t, 7.2)	10A	36.9	1.68 (dd, 18.0, 10.8)
13	126.0	7.20 (t, 7.2)			
14	128.4	7.26 (t, 7.2)			1.84 (t, 10.8)
15	127.0	7.09 (d, 7.2)	11A	33.1	
6OH		12.71 (s)	12A	113.7	5.03, 4.89 (s)
2′	78.3	5.55 (dd, 12.6, 3.0)	13A	21.1	1.03 (s)
			14A	30.2	1.02 (s)
3′	43.4	2.86 (dd, 16.8, 3.0)	15A	24.6	1.50 (s)
			1B	50.8	2.04 (m)
		2.99 (dd, 16.8, 12.6)	2B	29.7	1.27 (m), 1.70[b]
			3B	35.4	1.40 (m), 2.27[b]
4′	195.7				
5′	102.2		4B	84.7	
6′	160.1		5B	35.1	1.74 (m)
7′	107.2		6B	25.4	1.08, 1.29 (m)
8′	163.3		7B	33.7	2.39, 2.18 (m)
9′	104.1		8B	153.3	
10′	158.2		9B	41.2	2.44 (dd, 10.2, 18.3)
11′	139.8				
12′	125.8	7.45 (d, 7.2)	10B	37.3	1.56 (t, 10.2)
13′	128.7	7.42 (t, 7.2)			1.67 (dd, 10.2, 18.3)
14′	128.4	7.39 (t, 7.2)			
15′	128.7	7.42 (t, 7.2)	11B	34.0	
16′	125.8	7.45 (d, 7.2)	12B	111.8	4.81, 4.79 (s)
17′	8.1	2.04	13B	31.2	1.05 (s)
6′OH		12.83 (s)	14B	22.2	0.97 (s)
			15B	21.3	1.02 (s)

[a]Data were recorded on Bruker AV-600 spectrometer. [b]Overlapped with other signals.

7.26 (2H, t, J = 7.2 Hz), 7.20 (2H, t, J = 7.2 Hz) and 7.09 (2H, d, 7.2 Hz); and a singlet at δ_H 6.62; an oxygenic methane at δ_H 5.55 (1H, dd, J = 12.6, 3.0 Hz); a methylene at δ_H 2.99 (1H, dd, J = 16.8, 12.6 Hz) and δ_H 2.86 (1H, dd, J = 16.8, 3.0 Hz); two olefinic exomethylenes at δ_H 5.03, 4.89, 4.81, and 4.79 (each 1H, s); a vinyl methyl singlet at δ_H 2.04; and six aliphatic methyl singlets at δ_H 0.97,1.02, 1.03, 1.03, 1.05, and 1.48. Analysis of the ^{13}C NMR data (Table 1) with the aid of DEPT experiments revealed the presence of 61 carbon resonances, including seven methyls, 24 aromatic carbons, four olefinic carbons, two carbonyls, 10 methylenes, and 10 methines, which were consistent with the signals observed in the ^{1}H NMR spectrum and revealed four benzene rings in **1**. The aforementioned NMR spectroscopic data, molecular formula, and the existence of sesquiterpenoid-based meroterpenoids in this plant[2] suggested that **1** was probably a dimeric sesquiterpenoid-based meroterpenoid. The dimeric feature and functional linkage of **1** were further corroborated by the 1D and 2D NMR observations.

Comparison of the ^{1}H and ^{13}C NMR data of **1** with those of caryophyllene, psidial A,[2a] and guajadial[2b] indicated the presence of two caryophyllene moieties, which was further confirmed by $^{1}H-^{1}H$ COSY, 1D-TOCSY, and HMBC spectra (Figure 2). The $^{1}H-^{1}H$ COSY data of **1** showed cross signals for the H-1A/H-9A H-10A, H-5A/H-6A/H-7A, and H-1A/H-

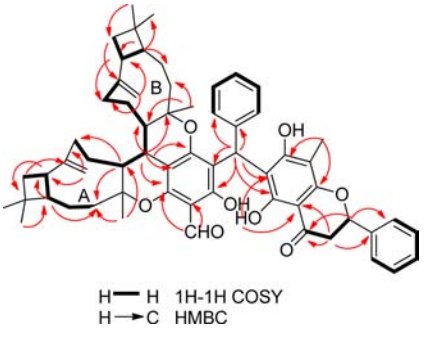

Figure 2. Key $^{1}H-^{1}H$ COSY and HMBC correlations of **1**.

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2A/H-3A coupling systems. In the HMBC spectrum, the correlations of H-12A/C-8A, C-9A, and C-7A; H-1A/C-3A, C-9A, and C-11A; H-5A/C-3A, and C-7A, and H-15A/C-3A, C-4A, and C-5A indicated the presence of a caryophyllene (A) moiety. Another caryophyllene (B) moiety also determined by $^{1}H-^{1}H$ COSY and HMBC correlations (Figure 2). Similarly, an aldehyde benzylphlorogulcinol moiety was established by the key HMBC correlations of H-7/C-2, C-3, and C-4; H-8/C-1, C-4, and C-5; H-9/C-1, C-2, C-10, and C-11; and H-11/C-9. The two caryophyllenes A and B were finally linked via the tertiary C-7 of benzylphlorogulcinol by the key HMBC correlations of H-7/C-5A, C-15A, C-4B, C-15B, and C-5B, which furnished two additional dihydrobenzopyran rings. The ROESY correlationS of H-9/H-15A and H-14B suggested the position of caryophyllene A was in the lower of structure (Figure 3).

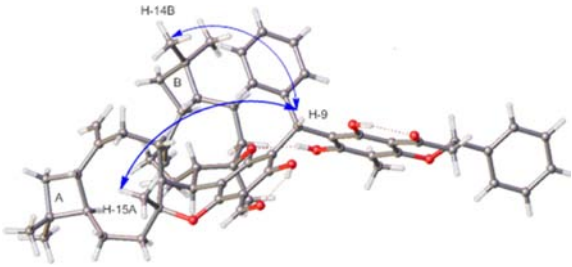


Figure 3. Key ROESY correlations of **1**.

Furthermore, the presence of three proton signals at δ_H 5.55, 2.99, and 2.86 in the ^{1}H NMR spectrum and carbon signals at δ_C 195.7, 163.3, 160.1, 158.2, 128.7(2C), 128.4, 125.8 (2C), 107.2, 104.1, 102.2, 78.3, and 43.4 in the ^{13}C NMR spectrum revealed a flavonone part in **1**.[5a,b] The HMBC correlations (Figure 2) of H-2′/C-3′, C-11′, and C-12′(16′); H-3′/C-2′, and C-4′; H-12′/C-2′, and C-11′; and 17′-CH_3/ C-8′, C-9′, and C-10′ further confirmed the presence of a 6′,8′-dihydroxy-9′-methylflavonone. The relative configuration of C-2′ and C-3′ was elucidated by the examination of its coupling constant.[7] Moreover, the HMBC correlations between H-9 and C-7′, C-8′ were observed and suggested that the flavonone moiety was connected at C-9. Thus, the basic planar structure of **1** was therefore determined.

Considering compound **1** is a novel dimeric sesquiterpene-based meroterpenoid possessing such a unique and complex skeleton, X-ray diffraction was necessary to confirm its structure and absolute configuration. Fortunately, a single crystal of **1** was successfully obtained from a mixture of $CHCl_3$: MeOH (1:1), and X-ray crystallographic analysis was carried out by using the anomalous dispersion of Cu Kα radiation (Figure 4). The absolute configuration of **1** was unambiguously determined as depicted in Figure 1 by refinement of the Flack parameter [0.013(15)].[6,10]

Guajavadimer A (**1**) represented the first example of dimeric meroterpenoids with two caryophyllene moieties fused with a 3.5-diformylbenzylphloroglucinol and a flavonone. This skeleton is unprecedented among known natural products. Scheme 1 showed a plausible biogenetic pathway for guajavadimer A (**1**). In this pathway, caryophyllene (**4**), 3.5-dimethyl-2,4,6,-trihydroxybenzophenone (**2**), and 5, 7-dihydroxy-8-methylflavonone (**3**) were considered as the biosynthetic precursors of **1**. Compound **2** could be oxidized to generate **A**,[3a] which was attacked by nucleophilic flavonone (**3**) to form the key

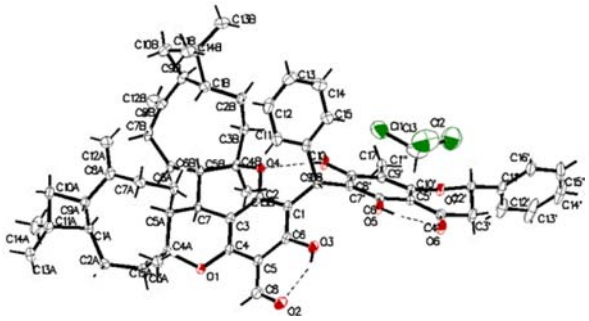
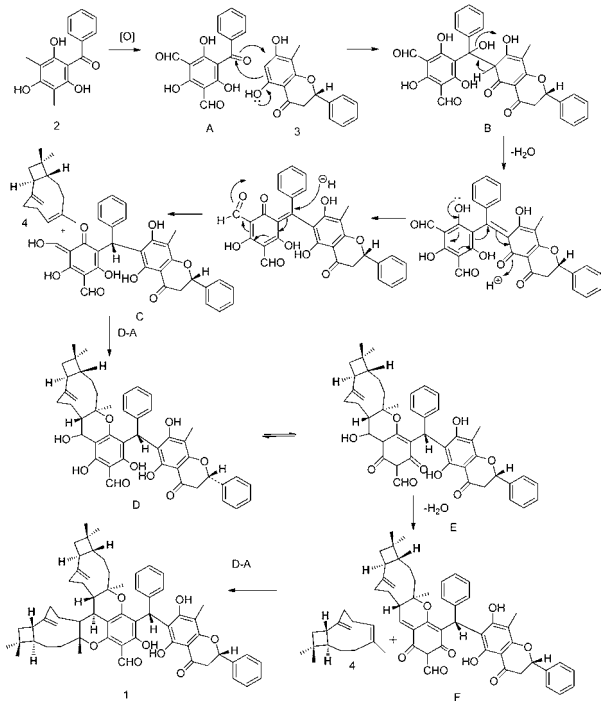


Figure 4. X-ray crystal structure of **1**.

Scheme 1. Hypothetical biogenetic pathway of 1



intermediate **B**. Intermediate **B** was readily transformed into the key semiquinone **C**, which after a hetero-Diels–Alder reaction produced intermediate **D**.[7] Similarly, intermediate **D** underwent an intramolecular transform and a hetero-Diels–Alder reaction with caryophyllene to yield **1**.

Guajavadimer A (**1**) was evaluated in vitro for its hepatoprotective activity against *N*-acetyl-*p*-aminophenol (APAP)-induced toxicity in HepG2 (human hepatocellular liver carcinoma cell line) cell, using the hepatoprotective activity drug bicyclol as the positive control,[8] and moderate hepatoprotective activity was observed. The cell survival rate of **1** is 67.84% at 10 μM when added into the resuscitated HePG2 cells with APAP for incubating 48h. Guajavadimer A (**1**) was also measured for an inhibitory effect on PTP1B, but it showed a negative result at 10 μM.[9]

In conclusion, guajavadimer A (**1**) represents the most complex structure of meroterpenoids unique in its complicated stereochemical skeleton fused with two caryophyllenes, a benzylphloroglucinol, and a flavonone. In addition, the dimerization mechanism of the two caryophyllene fragments through the carbonyl of 3.5-diformylphloroglucinol, which leads to the formation of two dihydrobenzopyran rings, is also unprecedented. Bioactivity screening of guajavadimer A (**1**) was

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carried out in some models, guajavadimer A (**1**) exhibited moderate hepatoprotective activity against *N*-acetyl-*p*-aminophenol (APAP)-induced toxicity in HepG2 cells. The findings presented here will attract both chemists and biologists to pursue further investigations with synthetic efforts and in-depth biological studies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03117.

X-ray crystallographic data for **1** (CIF)
Experimental section, MS, and 1D and 2D NMR spectra of compound **1** (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected examples, see: (a) Li, Y.; Niu, S. B.; Sun, B. D.; Liu, S. C.; Liu, X. Z.; Che, Y. S. *Org. Lett.* **2010**, *12*, 3144−3147. (b) Yin, S.; Xue, J. J.; Fan, C. Q.; Miao, Z. H.; Ding, J.; Yue, J. M. *Org. Lett.* **2007**, *9*, 5549−5552. (c) Kozuka, M.; Sawada, T.; Kasahara, F.; Mizuta, E.; Amano, T.; Komiya, T.; Goto, M. *Chem. Pharm. Bull.* **1982**, *30*, 1952−1963. (d) Kozuka, M.; Sawada, T.; Mizuta, E.; Kasahara, F.; Amano, T.; Komiya, T.; Goto, M. *Chem. Pharm. Bull.* **1982**, *30*, 1964−1973. (e) Nishizawa, M.; Emura, M.; Kan, Y.; Yamada, H.; Ogawa, K.; Hamanaka, N. *Tetrahedron Lett.* **1992**, *33*, 2983−2986.

(2) (a) Yang, X. L.; Hsieh, K. L.; Liu, J. K. *Org. Lett.* **2007**, *9*, 5135−5138. (b) Fu, H. Z.; Luo, Y. M.; Li, C. J.; Yang, J. Z.; Zhang, D. M. *Org. Lett.* **2010**, *12*, 656−659.

(3) (a) Shao, M.; Wang, Y.; Liu, Z.; Zhang, D. M.; Cao, H. H.; Jiang, R. W.; Fan, C. L.; Zhang, X. Q.; Chen, H. R.; Yao, X. S.; Ye, W. C. *Org. Lett.* **2010**, *12*, 5040−5043. (b) Shao, M.; Wang, Y.; Jian, Y. Q.; Huang, X. J.; Zhang, D. M.; Tang, Q. F.; Jiang, R. W.; Sun, X. G.; Lv, Z. P.; Zhang, X. Q.; Ye, W. C. *Org. Lett.* **2012**, *14*, 5262−5265. (c) Gao, Y.; Wang, G. Q.; Wei, K.; Hai, P.; Wang, F.; Liu, J. K. *Org. Lett.* **2012**, *14*, 5936−5939. (d) Gao, Y.; Li, G. T.; Li, Y.; Hai, P.; Wang, F.; Liu, J. K. *Nat. Prod. Bioprospect.* **2013**, *3*, 14−19.

(4) (a) Gutierrez, R. M. P.; Mitchell, S.; Solis, R. V. *J. Ethnopharmacol.* **2008**, *117*, 1−27. (b) Ma, S.; Cui, R. J.; Guo, S. F. *Journal of Mudanjiang Medical college* **2007**, *28*, 20−22.

(5) (a) Jayaprakasam, B.; Damu, A. G.; Gunasekar, D.; Blond, A.; Bodo, B. *Phytochemistry* **1999**, *52*, 935−937. (b) Basnet, P.; Kadota, S.; Shimizu, M.; Xu, H. X.; Namba, T. *Chem. Pharm. Bull.* **1993**, *41*, 1790−1795. (c) Wollenweber, E.; Wehde, R.; Doerr; Lang, M. G.; Stevens, J. F. *Phytochemistry* **2000**, *55*, 965−970.

(6) (a) Jin, Z.; Mashuta, M. S.; Stolowich, N. J.; Vaisberg, A. J.; Stivers, N. S.; Bates, P. J.; Lewis, W. H.; Hammond, G. B. *Org. Lett.* **2012**, *14*, 1230−1233. (b) Liang, C. Q.; Shi, Y. M.; Luo, R. H.; Li, X. Y.; Gao, Z. H.; Li, X. N.; Yang, L. M.; Shang, S. Z.; Li, Y.; Zheng, Y. T.; Zhang, H. B.; Xiao, W. L.; Sun, H. D. *Org. Lett.* **2012**, *14*, 6362−6365. (c) Xu, J. B.; Zhang, H.; Gan, L. S.; Han, Y. S.; Wainberg, M. A.; Yue, J. M. *J. Am. Chem. Soc.* **2014**, *136*, 7631−7633.

(7) Lawrence, A. L.; Adlington, R. M.; Baldwin, J. E.; Lee, V.; Kershaw, J. A.; Thompson, A. L. *Org. Lett.* **2010**, *12*, 1676−1679.

(8) Hao, Z. Y.; Liang, D.; Luo, H.; Liu, Y. F.; Ni, G.; Zhang, Q. J.; Li, L.; Si, Y. K.; Sun, H.; Chen, R. Y.; Yu, D. Q. *J. Nat. Prod.* **2012**, *75*, 1083−1089.

(9) Ma, Y. M.; Liu, Q.; Li, J.; Tian, J. Y.; Zhang, X. L.; Xiao, Z. Y.; Ye, F. *Mol. Cell. Biochem.* **2011**, *357*, 65−72.

(10) Guajavadimer A (**1**): $C_{61}H_{70}O_8 \cdot CHCl_3$, M = 1050.54, orthorhombic system, space group $P2_12_12_1$, crystal dimensions 0.50 × 0.45 × 0.40 mm, Cu Kα radiation, a = 10.343(4) Å, b = 17.047 (8) Å, c = 30.567 (13) Å, V = 5389.8 (4) Å3, Z = 4, ρ_{calcd} = 1.295 g·cm^{-3}. The total number of independent reflections measured was 19407, of which 10218 were observed ($|F|^2 \geq 2\sigma|F|^2$). The final indices were R1 = 0.0480, wR2 = 0.1283 ($w = 1/\sigma|F|^2$), S = 1.034. Flack parameter 0.013 (15). CCDC deposition no. 1430940.

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Synthesis and Crystal Structure of Highly Strained [4]Cyclofluorene: Green-Emitting Fluorophore

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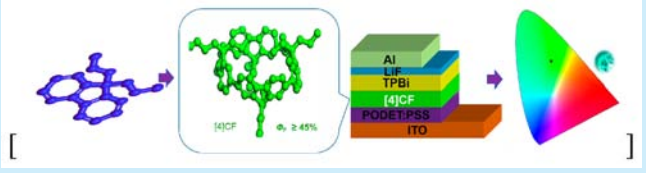
Supporting Information

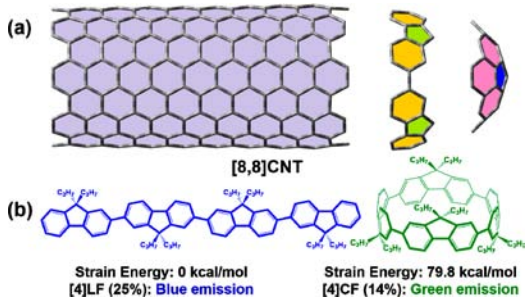
ABSTRACT: [4]Cyclo-9,9-dipropyl-2,7-fluorene ([4]CF) with the strain energy of 79.8 kcal/mol is synthesized in high quantum yield. Impressively, hoop-shaped [4]CF exhibits a green fluorescence emission around 512 nm offering a new explanation for the green band (g-band) in polyfluorenes. The solution-processed [4]CF-based organic light emitting diode (OLED) has also been fabricated with the a stronger green band emission. Strained semiconductors offer a promising approach to fabricating multifunctional optoelectronic materials in organic electronics and biomedicine.



Hoop-shaped cycloparaphenylenes (CPPs) and related π-conjugated molecules have attracted considerable attention from synthetic chemists and theoreticians owing to their aesthetic structure.[1] These strained molecules not only are used as elegant segments for nanotechnology,[2] host−guest molecules for supramolecular systems,[3] ligands for metal coordination,[4] and asymmetric inducer for catalysis chemistry[5] but also exhibit novel size-dependent photophysical properties.[6] Therefore, these series of molecules with radial p orbitals provide likely state-of-the-art strained semiconductor models to tune π-channels and optoelectronic properties in organic electronics. However, the low fluorescence quantum yield (Φ_F) of strained molecules with the high strain energy (>70 kcal/mol) restricts their application in OLEDs and organic lasers.[1e,6b,7]

Different from the π-conjugated segments above, fluorene exhibits inherent larger exciton binding energies and excellent charge delocalization, enabling it to be an important building block in the molecular design of the light-emitting materials with high quantum yield.[8] In this regard, fluorene-based strained molecules could achieve both merits of CPPs and fluorene-based emitters with high-efficiency feature, different from fluorene-based macrocycles[9] with the same luminescence behaviors resembling linear oligofluorenes. Furthermore, it is noted that strained [n]cyclofluorenes ([n]CF) would offer a series of unprecedented models to obtain insight into the contribution of out-of-plane bending conformations to green band emission in polyfluorenes. In addition, [4]cyclo-2,7-fluorene is the key junction fragment to connect ring parts with bow-shaped end-caps in armchair CNTs (Scheme 1a). However, there are few

Scheme 1. (a) [4]CF Unit in CNT is Shown in Color; (b) Chemical Structure of [4]CF and [4]LF



reports on fully fluorene-based [n]CF.[10] Herein, hoop-shaped [4]cyclo-9,9-dipropyl-2,7-fluorene ([4]CF, strain energy = 79.8 kcal/mol) as an example of strained semiconductors has been synthesized through another low toxicity method (Scheme 1).[1h,i] The molecular structure of [4]CF has been first validated by X-ray crystallographic analysis. Contrary to the deep blue emission of controlled linear quaterfluorene ([4]LF), the [4]CF gives rise to stronger green emissions around 512 nm in the solution, film, and crystal state. Finally, the preliminary [4]CF-based nondoped OLED has been fabricated by solution-processed procedures.

[4]CF can be synthesized according to the literature of CPPs which have been synthesized by four methods, such as Bertozzi

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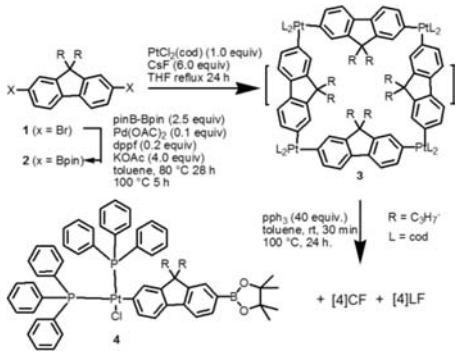
and Jasti's synthesis,[1a,e,11] Itami's synthesis,[12] Yamago's synthesis,[1h,i,13] and Ni^0-mediated Stepien synthesis.[11] In this work, Yamago's method was chosen to prepare [4]CF via two steps utilizing a ligand exchange reaction and reductive elimination strategy.[1h,i] The detailed synthetic route of the [4]CF is fully outlined in Scheme 2. Besides, a propyl group was

Scheme 2. Synthetic Routes of [4]CF and [4]LF



introduced as one of the alkyl groups at the 9-site of the fluorene segments to obtain suitable solubility. First, diboronic ester **2** was synthesized from dibromide **1** under Pd catalysis with a yield of 90%. **2** was heated with 1 equiv of $PtCl_2$(cod) (cod = 1,5-cyclooctadiene) and CsF in a refluxing tetrahydrofuran (THF) to give an intermediate of square shape tetranuclear Pt-complex **3** with the yield of 85%. Then the Pt-complex was treated with 40 equiv of PPh_3 in toluene at 100 °C for 24 h to afford [4]CF. The strain energy of [4]CF was estimated to be ~79.8 kcal/mol (Scheme S1), higher than that of [8]CPP (72.2 kcal/mol).[14] Considering this point, the overall yield of [4]CF from the commercially available and inexpensive starting material **1** was reasonably high (14%). Besides, the linear quaterfluorene ([4]LF) can be obtained as a byproduct with an overall yield of 25%. Another yellow solid byproduct **4** was isolated. The structure of **4** was determined by using single-crystal X-ray analysis (Figure S10).[15] Interestingly, [4]CF exhibits better solubility than CPPs in common organic solvents, such as cyclohexane, dichloromethane (CH_2Cl_2), chloroform ($CHCl_3$), THF, and toluene, which is important for application in solution-processed devices.

The ^{1}HNMR spectra of [4]CF, [4]LF, and the corresponding monomer **1** in $CDCl_3$ are shown in Figure 1. Two aromatic protons (H^b and H^c) are much further downfield (~7.57 and 7.51 ppm) than is observed in monomer **1**. However, the proton

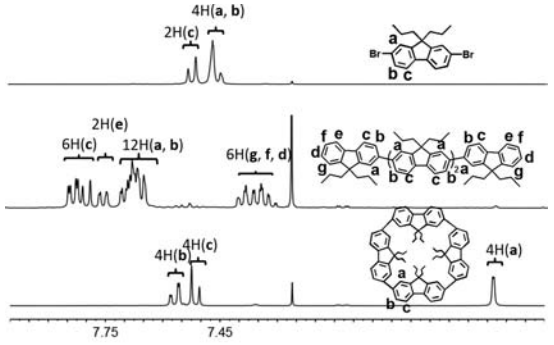


Figure 1. ^{1}H NMR spectra of [4]CF, [4]LF, and corresponding monomer in $CDCl_3$.

signal of H^a (~6.73 ppm) is shifted upfield by 0.71 ppm compared with that in dibromide **1**. Due to long-range coupling between Ha and Hb, the proton signal of Hb is split further into four peaks. [4]CF has been fully characterized by ^{13}C NMR and high resolution (HR) mass spectrometry (MS) (see Supporting Information).

Single crystals of [4]CF suitable for X-ray analysis are obtained by the slow evaporation of THF solution at rt (Figure 2).

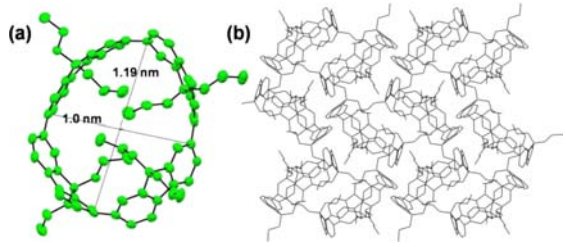


Figure 2. (a) X-ray diffraction crystallography of [4]CF. (b) Herringbone packing alignment of [4]CF.

Structure characterization by X-ray analysis reveals that [4]CF crystallizes in an achiral space group $Pna2_1$ at rt, which belongs to 10 polar point groups with the potential ferroelectric property,[16] different from most reported [*n*]CPPs with the achiral space groups. Hoop-shaped [4]CF has an ellipsoidal cavity whose minor axes are 19% shorter than the major axes. This large deformation is probably due to steric hindrance associated with the propyl group. And, the average fluorenyl-fluorenyl dihedral angle for [4]CF is 34.60° lower than the calculated 38.90°. Compared to other fluorene-based semiconductors, the most arresting feature of [4]CF is out-of-plane distortion. The average distance between the 2 and 7 site (6.65 Å) in the fluorene is shorter than that in normal fluorene (6.80−6.90 Å).[17] The tertiary carbons in each molecule are displaced out of the fluorene plane by an average of 28.93°. The bend angle (θ) of 57.86° is also calculated according to the previous works.[18] To our knowledge, this conformation has the largest bend angle in fluorene systems. Besides, from the position of the H^a in the molecules, the upfield-shifted signals of H^a are probably due to the magnetic field produced by the ring currents of the fluorenyl π-system (Figure S9).[11] The analysis of the crystal packing structure indicates that the [4]CF can be self-organized into a herringbone formation in the presence of the CH···π and $\pi-\pi$ contacts from the *c* axis (Figure S11) and the tubular alignment from the *b* axis (Figure 2b). Impressively, the orientation of major axis helps to distinguish the array of the enantiomers in the crystal packing, which is probably induced by strain (Figure S12).[19]

The absorption and photoluminescence (PL) spectra of [4]CF in solution, and film are illustrated in Figure 3a. [4]CF in diluted solution exhibits a green color and has the maximum absorption at 349 nm (λ_{abs1}) and a shoulder-like absorption band at 398 nm (λ_{abs2}) with weak oscillator strength. [4]CF shows green photoluminescence with the emission maxima at 512 nm and two shoulder peaks at 396 and 416 nm. The UV absorption and PL spectra of [4]CF in toluene, $CHCl_3$, and DCE are similar to those in THF solution and film (Figure S14, Table S1). In addition, the concentration-dependent PL spectra of [4]CF in 1,2-bichloroethane (DCE) solution, normalized through the blue peak, are shown in Figure S15. The maximum emission at 512 nm is slightly changed with decreasing concentration from 10^{-4} to 10^{-9} M. The green index φ ($\varphi = I_{green}/I_{blue}$) increases

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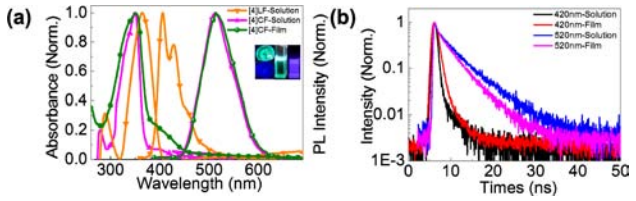

Figure 3. Optical properties of [4]CF and [4]LF. (a) UV and PL spectra of [4]CF and [4]LF in THF solution (10^{-5} M) and spin-coated film from $CHCl_3$. (b)Transient decay spectra of [4]CF in THF solution (10^{-5} M) and spin-coated film from $CHCl_3$.

with the concentration from 10^{-9} to 10^{-4} M. The shape of the PL spectrum of [4]CF in the crystal state is identical to that of other states (Figure S18). However, the emissions around 512 nm are not observed in the PL spectra of [4]LF in various states (Figure S19–S20).

To gain insight into the optical properties of [4]CF, time-dependent DFT calculations are carried out at the B3LYP/6–31G(d) level. According to calculation results (Scheme S2), the strongest absorption λ_{abs1} at 349 nm can be assigned to a combination of HOMO → LUMO+1 (2) and HOMO−1 (2) → LUMO excitations. A weaker absorption λ_{abs2} at 398 nm can be described as the forbidden transition involving HOMO and LUMO. Two emission bands at 396 and 416 nm for [4]CF can be assigned to the 0–0, 0–1 intrachain transitions.[20] And the maximum emission at 512 nm is assigned to the transition corresponding to the HOMO–LUMO energy with the oscillator strength (f) of 0.000. The structural relaxation from the Franck–Condon state[6b] or the self-trapping of the lowest excitonic state due to electron–phonon coupling[21] may induce the forbidden transition.

The quantum yield for [4]CF in solution and spin-coated film are estimated to be 0.45 and 0.48 (Figure 3b, Table S2), respectively, similar to [4]CFR.[10] The values are higher than that of other hoop-shaped molecules with a similar ring size, such as [8]CPP (0.08[6b] or 0.10[7]) and [4]cyclo-2,7-pyrenylene ([4]CPY) (0.05).[4a] Further, the decay times of the blue emission band are found to be biexponential decay with lifetimes of 0.70 (80.81%) and 3.17 (19.19%) ns for [4]CF, 0.60 (79.22%) and 2.00 (20.78%) ns for [4]LF, respectively (Figure S21, Table S2). The decay time of the green emission for [4]CF exhibits single-exponential decay (1A*) in dilute THF (7.7 ns) solution and film (10.4 ns) suggesting that only a single fluorescent species. In this regard, it is effectively concluded that the green emission at 512 nm is the intrinsic emitting property of [4]CF rather than the intra- and intermolecular charge-transfer induced by photo, interchain ketone-based excimers or fluorenone defects. Our result strongly indicated that the distorted conformation or entanglement chains of the fluorene segment probably induce green emission, resulting in the poor spectral stability in wide-band gap blue light-emitting polyfluorenes.[8] The bending mode of chain would be the third mechanism of g-band formation after ketone and aggregates/excimers.

The oxidation curve is found to be reversible for [4]CF, indicating the stable radical cation intermediates. [4]CF has a lower half-wave oxidation potential of 0.61 eV (vs the ferrocene/ferrocenium couple) than [4]LF (0.88 eV) (Figures S22–23). The HOMO and LUMO energy levels of [4]CF are estimated to be about −5.35 and −2.35 eV from the above-mentioned experiments, respectively. The energy gap of [4]CF is calculated about 3.0 eV. Finally, the preliminary OLED using the [4]CF spin-coated film from $CHCl_3$ as an active layer has been fabricated with a configuration of ITO/PODET:PSS (60 nm)/[4]CF (60 nm)/TPBi (40 nm)/LiF (1.2 nm)/Al (80 nm) (Figures S24–S25). And the electroluminescent (EL) spectra show the green emission at 508 nm with CIE coordinates of (0.25, 0.52) at the 5.38 V (turn-on voltage), similar to the corresponding PL spectra, suggesting single molecular emission in the film states (Figure 4). And OLED exhibits the maximum

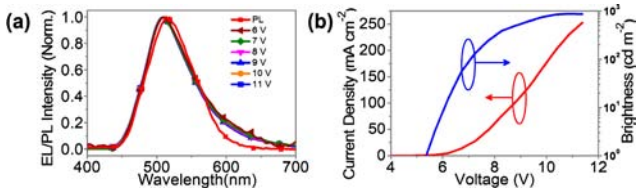

Figure 4. (a) Normalized EL spectra of devices at 6–11 V. (b) Current density–voltage–luminance characteristics of devices.

brightness of 878 cd/cm^2 at 10 V with a maximum luminescent efficiency of 0.83 cd/A, which is the first OLED via fluorene-based strained semiconductor used as the emissive material.

In conclusion, a fully fluorene-based strained semiconductor ([4]CF, strain energy = 79.8 kcal/mol) has been designed and synthesized successfully. Dramatically different from linear [4]LF, [4]CF showed a green emission at 512 nm with high-efficiency $\Phi_F \geq 45\%$. The bending conformation with a hoop shape not only became a tool for modulating the photoelectric properties of [4]CF but also offered an alternative explanation of the origin of the g-band in polyfluorenes for the first time. Furthermore, an OLED of a fluorene-based strained semiconductor has been fabricated via solution processing with a stronger green emission of 508 nm and CIE coordinates of (0.25, 0.52). Steric strain will be a potential tool to design multifunctional ferroelectric semiconductors for a wide range of memory applications in the future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03038.

Experimental details, compound characterization, and NMR spectra for all compounds (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Jasti, R.; Bhattacharjee, J.; Neaton, J. B.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2008**, *130*, 17646−17647. (b) Omachi, H.; Segawa, Y.; Itami, K. *Acc. Chem. Res.* **2012**, *45*, 1378−1389. (c) Yamago, S.; Kayahara, E.; Iwamoto, T. *Chem. Rec.* **2014**, *14*, 84−100. (d) Lewis, S. E. *Chem. Soc. Rev.* **2015**, *44*, 2221−2304. (e) Golder, M. R.; Jasti, R. *Acc. Chem. Res.* **2015**, *48*, 557−566. (f) Darzi, E. R.; Jasti, R. *Chem. Soc. Rev.* **2015**, *44*, 6401−6410. (g) Yagi, A.; Segawa, Y.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 2962−2965. (h) Hitosugi, S.; Nakanishi, W.; Yamasaki, T.; Isobe, H. *Nat. Commun.* **2011**, *2*, 492. (i) Hitosugi, S.; Yamasaki, T.; Isobe, H. *J. Am. Chem. Soc.* **2012**, *134*, 12442−12445. (j) Iwamoto, T.; Kayahara, E.; Yasuda, N.; Suzuki, T.; Yamago, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 6430−6434. (k) Ito, H.; Mitamura, Y.; Segawa, Y.; Itami, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 159−163. (l) Mysliwiec, D.; Kondratowicz, M.; Lis, T.; Chmielewski, P. J.; Stepien, M. *J. Am. Chem. Soc.* **2015**, *137*, 1643−1649. (m) Patel, V. K.; Kayahara, E.; Yamago, S. *Chem. - Eur. J.* **2015**, *21*, 5742−5749. (n) Kayahara, E.; Patel, V. K.; Xia, J.; Jasti, R.; Yamago, S. *Synlett* **2015**, *26*, 1615. (o) Wong, B. M. *J. Phys. Chem. C* **2009**, *113*, 21921−21927.

(2) Omachi, H.; Nakayama, T.; Takahashi, E.; Segawa, Y.; Itami, K. *Nat. Chem.* **2013**, *5*, 572−576.

(3) (a) Iwamoto, T.; Watanabe, Y.; Sadahiro, T.; Haino, T.; Yamago, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 8342−8344. (b) Iwamoto, T.; Watanabe, Y.; Takaya, H.; Haino, T.; Yasuda, N.; Yamago, S. *Chem. - Eur. J.* **2013**, *19*, 14061−14068. (c) Sato, S.; Yamasaki, T.; Isobe, H. *Proc. Natl. Acad. Sci. U. S. A.* **2014**, *111*, 8374−8379. (d) Hitosugi, S.; Ohkubo, K.; Iizuka, R.; Kawashima, Y.; Nakamura, K.; Sato, S.; Kono, H.; Fukuzumi, S.; Isobe, H. *Org. Lett.* **2014**, *16*, 3352−3355. (e) Iwamoto, T.; Slanina, Z.; Mizorogi, N.; Guo, J.; Akasaka, T.; Nagase, S.; Takaya, H.; Yasuda, N.; Kato, T.; Yamago, S. *Chem. - Eur. J.* **2014**, *20*, 14403−14409. (f) Ueno, H.; Nishihara, T.; Segawa, Y.; Itami, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 3707−3711.

(4) (a) Zabula, A. V.; Filatov, A. S.; Xia, J.; Jasti, R.; Petrukhina, M. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 5033−5036. (b) Kubota, N.; Segawa, Y.; Itami, K. *J. Am. Chem. Soc.* **2015**, *137*, 1356−1361. (c) Kayahara, E.; Patel, V. K.; Mercier, A.; Kündig, E. P.; Yamago, S. *Angew. Chem., Int. Ed.* **2015**, Early view.

(5) Hitosugi, S.; Matsumoto, A.; Kaimori, Y.; Iizuka, R.; Soai, K.; Isobe, H. *Org. Lett.* **2014**, *16*, 645−647.

(6) (a) Iwamoto, T.; Watanabe, Y.; Sakamoto, Y.; Suzuki, T.; Yamago, S. *J. Am. Chem. Soc.* **2011**, *133*, 8354−8361. (b) Fujitsuka, M.; Cho, D. W.; Iwamoto, T.; Yamago, S.; Majima, T. *Phys. Chem. Chem. Phys.* **2012**, *14*, 14585−14588. (c) Segawa, Y.; Fukazawa, A.; Matsuura, S.; Omachi, H.; Yamaguchi, S.; Irle, S.; Itami, K. *Org. Biomol. Chem.* **2012**, *10*, 5979−5984. (d) Chen, H.; Golder, M. R.; Wang, F.; Jasti, R.; Swan, A. K. *Carbon* **2014**, *67*, 203−213. (e) Alvarez, M. P.; Burrezo, P. M.; Kertesz, M.; Iwamoto, T.; Yamago, S.; Xia, J.; Jasti, R.; Navarrete, J. T. L.; Taravillo, M.; Baonza, V. G. *Angew. Chem.* **2014**, *126*, 7153. (f) Chen, H.; Golder, M. R.; Wang, F.; Doorn, S. K.; Jasti, R.; Tretiak, S.; Swan, A. K. *J. Phys. Chem. C* **2015**, *119*, 2879−2887.

(7) Darzi, E. R.; Sisto, T. J.; Jasti, R. *J. Org. Chem.* **2012**, *77*, 6624−6628.

(8) (a) Xie, L. H.; Yin, C. R.; Lai, W. Y.; Fan, Q. L.; Huang, W. *Prog. Polym. Sci.* **2012**, *37*, 1192−1264. (b) Wang, L.; Zhang, G.-W.; Ou, C.-J.; Xie, L.-H.; Lin, J.-Y.; Liu, Y.-Y.; Huang, W. *Org. Lett.* **2014**, *16*, 1748−1751.

(9) (a) Simon, S. C.; Schmaltz, B.; Rouhanipour, A.; Raeder, H. J.; Muellen, K. *Adv. Mater.* **2009**, *21*, 83−85. (b) Fomina, N.; Hogen-Esch, T. E. *Macromolecules* **2008**, *41*, 3765−3768.

(10) Kayahara, E.; Rui, Q.; Kojima, M.; Iwamoto, T.; Suzuki, T.; Yamago, S. *Chem. - Eur. J.* **2015**, *21*, 18939.

(11) Evans, P. J.; Darzi, E. R.; Jasti, R. *Nat. Chem.* **2014**, *6*, 404−408.

(12) Takaba, H.; Omachi, H.; Yamamoto, Y.; Bouffard, J.; Itami, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 6112−6116.

(13) Yamago, S.; Watanabe, Y.; Iwamoto, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 757−759.

(14) Segawa, Y.; Omachi, H.; Itami, K. *Org. Lett.* **2010**, *12*, 2262−2265.

(15) CCDC 1031897 (**4**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information.

(16) Zhang, W.; Ye, H. Y.; Xiong, R. G. *Coord. Chem. Rev.* **2009**, *253*, 2980−2997.

(17) (a) Song, Y.; Xu, W.; Zhu, D. *Tetrahedron Lett.* **2010**, *51*, 4894−4897. (b) Xie, L. H.; Hou, X. Y.; Hua, Y. R.; Huang, Y. Q.; Zhao, B.-M.; Liu, F.; Peng, B.; Wei, W.; Huang, W. *Org. Lett.* **2007**, *9*, 1619−1622.

(18) Bodwell, G. J.; Fleming, J. J.; Miller, D. O. *Tetrahedron* **2001**, *57*, 3577−3585.

(19) Hitosugi, S.; Nakanishi, W.; Isobe, H. *Chem. - Asian J.* **2012**, *7*, 1550−1552.

(20) Fukuda, M.; Sawada, K.; Yoshino, K. *J. Polym. Sci., Part A: Polym. Chem.* **1993**, *31*, 2465−2471.

(21) Adamska, L.; Nayyar, I.; Chen, H.; Swan, A. K.; Oldani, N.; Fernandez-Alberti, S.; Golder, M. R.; Jasti, R.; Doorn, S. K.; Tretiak, S. *Nano Lett.* **2014**, *14*, 6539.

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Organic LETTERS

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Catalytic and Atom-Economic Intermolecular Amidoselenenylation of Alkenes

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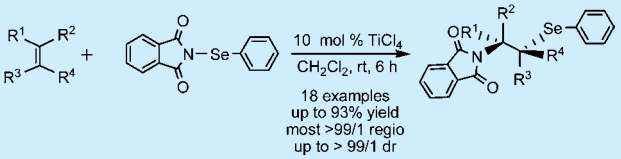
Supporting Information

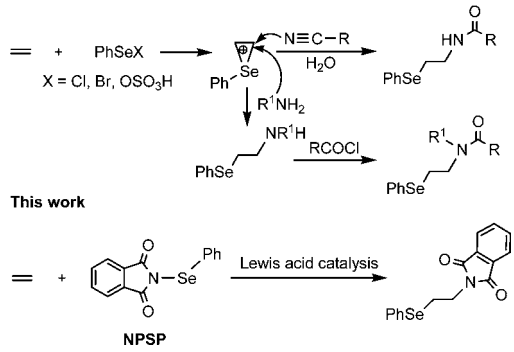
ABSTRACT: A method for the simple, efficient, and atom-economic amidoselenenylation of simple alkenes under mild conditions using $TiCl_4$ as a catalyst and *N*-(phenylseleno)-phthalimide as both a nitrogen and selenium source was developed. A broad range of olefins can be applied to afford vicinal amidoselenides in good yield and with high regioselectivity and diastereoselectivity.



As basic structural moieties, amides widely exist in bioactive natural products and pharmaceuticals.[1] Therefore, the efficient incorporation of an amido group into organic molecules has drawn much attention. Organoselenium compounds continue to be extensively studied because of their recognized biological activities.[2] The antioxidant properties and mimetic activity of some selenoenzymes such as thioredoxin reductases (TrxRs), selenophosphate synthetase, and selenoprotein P, in addition to the well-known glutathione peroxidase (GPx), which contains a selenocysteine residue at the active site, are well-established, making these compounds interesting synthetic targets.[3] Organoselenium compounds have been widely used as versatile reagents in organic synthesis, playing an important role in a wide range of transformations.[4] We speculated that if both the selenium atom and amido group can be simultaneously installed into the carbon−carbon double bond, a variety of vicinal amidoselenides could be easily accessed from simple alkenes, which we expect would provide efficient access to selenocysteine.

The selenofunctionalization of olefins using electrophilic organoselenium reagents represents an important method for the rapid introduction of vicinal functional groups, often with the concomitant formation of stereocenters.[5] Typically, the amidoselenenylation of olefins occurs via nucleophilic attack to a seleniranium intermediate with organonitrile as a nucleophile in the presence of water and trifluoromethanesulfonic acid (Scheme 1).[6] The reaction proceeds in poor yield on styrene and electron-rich olefins. In these cases, better yields were achieved by starting from the corresponding hydroxyselenylating or methoxyselenylating agent. Similar reactions have been conducted using different nitriles, affording the corresponding selenoamides.[7] Another approach to selenoamides is the acylation of the amino group in aminoselenides with a suitable acid chloride (Scheme 1).[8] Although *N*-(phenylseleno)-phthalimide (NPSP) is odorless and can provide a convenient source of electrophilic selenium, realizing the amidoselenenylation of olefins by using NPSP as a nitrogen and selenium source remains a substantial challenge because of the poor

Scheme 1. Synthesis of Vicinal Amidoselenides by an Intermolecular Addition Reaction of Alkenes and Organoselenide



nucleophilicity of the phthalimide counteranion, where good nucleophilicity is a prerequisite for a highly electrophilic seleniranium ion. Unfortunately, successful examples of such atom-economic processes are quite rare. Córsova reported the organocatalytic aminosulfenylation of α,β-unsaturated aldehydes; they obtained only one amidoselenenylation product by treating cinnamic aldehyde with *N*-(phenylseleno)succinimide, whereas they obtained both *syn*- and *trans*-diastereomers via the Michael addition mechanism.[9] However, the amidoselenenylation of styrene and electron-rich olefins has not been reported. On the basis of our research interests in the Lewis acid-catalyzed selenofunctionalization of olefins,[10] we herein disclose a Lewis acid-catalyzed intermolecular amidoselenenylation of alkenes with NPSP as both a nitrogen and selenium source under mild conditions and with high regioselectivity and diastereoselectivity.

Initially, (*E*)-β-methylstyrene (**1a**) was chosen as a model substrate with *N*-(phenylseleno)phthalimide[11] as both the

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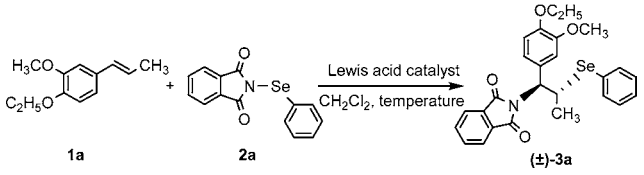
nitrogen/selenium source; this reaction was rather sluggish in the absence of catalyst, even under reflux conditions (Table 1, entries 1 and 2). An investigation using a series of Lewis acids and Brønsted acids identified TMSOTf and $TiCl_4$ as active catalysts. In the presence of 10 mol % of TMSOTf, the reaction proceeded smoothly at −78 °C for 2 h and then −20 °C for 4 h to afford the desired product in 75% yield (Table 1, entry 11). With an increase of temperature, the yield of product **3a** decreased, whereas *β*-hydroxyalkyl phenyl selenide, the product of the hydroxyselenenylation of an alkene, gradually became the main product. $TiCl_4$ (10 mol %) is a better catalyst, and the reaction was completed at room temperature in 6 h to afford a 93% yield of the desired product **3a**; no *β*-hydroxyalkyl phenyl selenide was observed in the product (Table 1, entry 16). In this case, the catalyst loading was reduced to 5 mol % to afford product **3a** in 80% yield (Table 1, entry 19). The yield of product **3a** did not increase with the increase of the amount of the catalyst (Table 1, entry 20 and 21).

Table 1. Optimization of the Intermolecular Amidoselenenylation of (*E*)-*β*-Methylstyrene (1a) and *N*-(Phenylseleno)phthalimide[a]

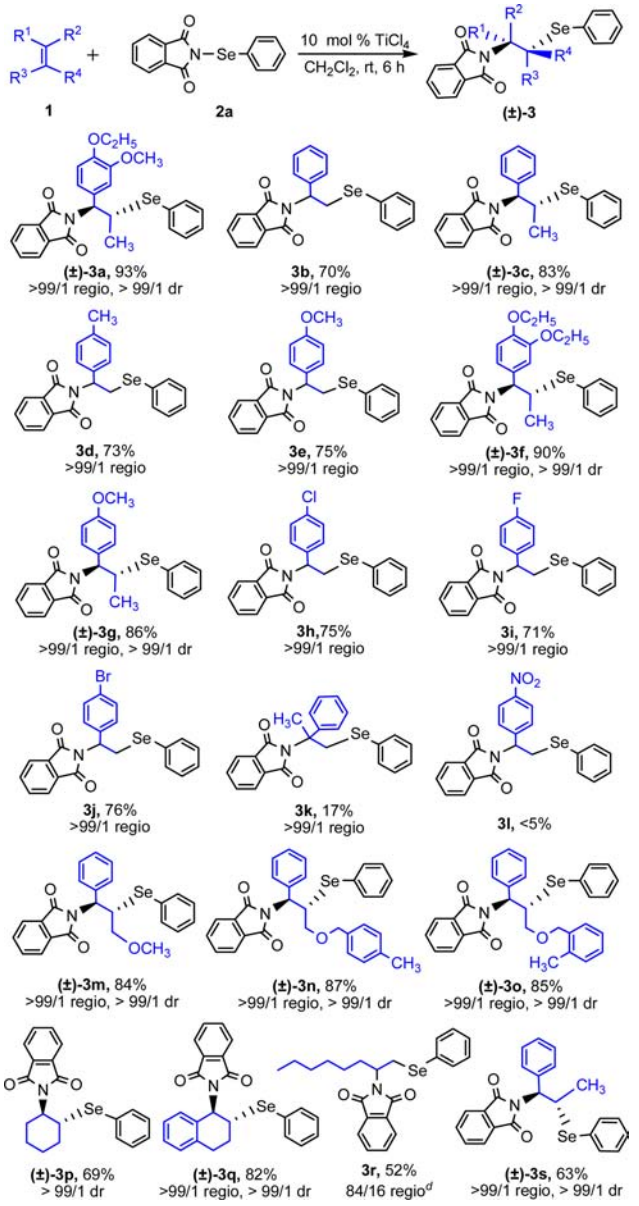


entry	catalyst	amt of catalyst (mol %)	temp (°C)	yield[b] (%)
1	none		rt	0
2	none		−78	0
3	TsOH	10	rt	0
4	$PhSO_3H$	10	rt	0
5	TFA	10	rt	0
6	$AlCl_3$	10	rt	0
7	$AgBF_4$	10	rt	0
8	$FeCl_3$	10	rt	0
9	$ZnCl_2$	10	rt	0
10	$SnCl_4$	10	rt	13
11	TMSOTf	10	−78 to −20	75
12	TMSOTf	10	−40	58
13	TMSOTf	10	−20	37
14	TMSOTf	10	0	20
15	TMSOTf	10	rt	15
16	$TiCl_4$	10	rt	93
17	$TiCl_4$	10	0	24
18	$TiCl_4$	10	−78	0
19	$TiCl_4$	5	rt	80
20	$TiCl_4$	20	rt	92
21	$TiCl_4$	40	rt	88

[a]The general reaction was carried out on a 0.5 mmol scale in 5 mL of CH_2Cl_2 for 6 h; the molar ratio of **1a**/**2a** was 1/1.10. [b]Isolated yield.

With the optimized conditions in hand, we next expanded the substrate scope; the results are shown in Scheme 2. In general, the reactions all proceeded smoothly to give products in good yields and with high regioselectivity. Styrene and styrene-bearing electron-withdrawing chloro, fluoro, and bromo substituents and electron-donating methyl, *p*-methoxyl, 3,5-diethoxyl, and 3-methoxyl-5-ethoxyl substituents gave good yields with 99% regioselectivity (Scheme 2, **3b,d,e,h−j**); by contrast, the strongly electron-withdrawing *p*-nitro substituent gave less than 5% yield (Scheme 2, **3l**). (*E*)-*β*-Methyl-, (*Z*)-*β*-methyl-, (*E*)-*β*-methoxymethyl-, and (*E*)-*β*-benzyloxymethylstyrenes gave good yields with 99% regioselectivity and diastereoselectivity (Scheme 2, **3a,c,f,g,m−o,s**), whereas *α*-methylstyrene gave 17% yield with 99% regioselectivity (Scheme 2, **3k**). These results indicate that the attack of the nucleophilic nitrogen at the episelenonium ion was governed by the steric effect of the substituent in the *α*-position of styrene, whereas substituents in the *β*-position promoted the amidoselenenylation of alkenes. In addition, both *E*- and *Z*-alkenes gave good results (Scheme 2, **3c,s**). Furthermore, Markovnikov-type adducts were obtained with good yields by

Scheme 2. Scope of the Intermolecular Amidoselenenylation of Alkenes and *N*-Phenylselenophthalimide[a−c]



[a]The general reaction was carried out on a 0.5 mmol scale in 5 mL of CH_2Cl_2; the molar ratio of **1**/**2a** was 1/1.10. [b]Isolated yield. [c]The value of dr was determined by ^1H NMR. [d]The reaction gave 52% yield of 2-(1-phenylseleno-2-octyl)-1*H*-isoindole-1,3(2*H*)-dione (**3r**) and 10% yield of 2-(2-phenylseleno-1-octyl)-1*H*-isoindole-1,3(2*H*)-dione (**3r′**).

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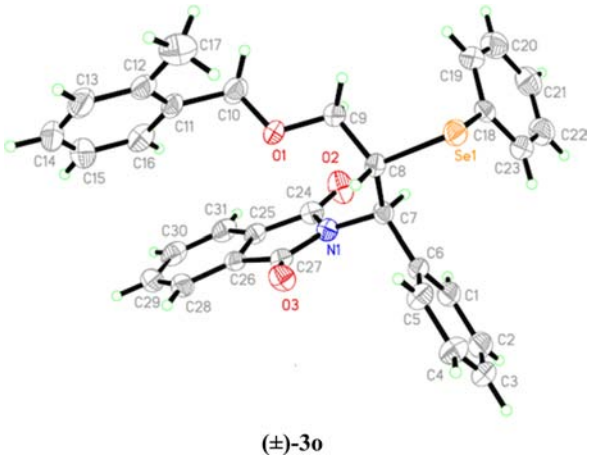
the highly regioselective amidoselenenylation of styrenes, and *trans*-type adducts were obtained regioselectively and diastereoselectively by amidoselenenylation of *β*-methylstyrenes and 1,2-dihydronaphthalene (Scheme 2, **3a,c,f,g,m−o,q,s**). The reaction also occurred smoothly with simple cyclic alkenes such as cyclohexene to give products with high diastereoselectivity (Scheme 2, **3p**). The relative stereochemistry of the reaction was indicated by the structural analysis of the crystal structure of **3o** (Figure 1). Long-chain alkenes such as 1-

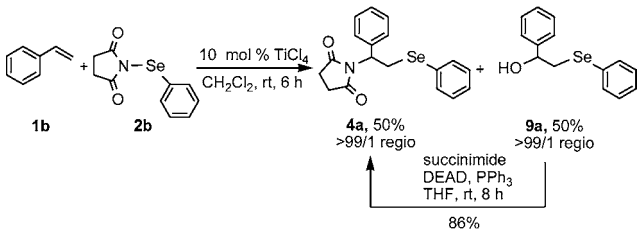


(±)-3o

Figure 1. ORTEP of the molecular structure of compound (±)-**3o**.

octylene, however, afforded adducts **3r** and **3r′** with low regioselectivity (Scheme 2, **3r**). According to the HMBC

Scheme 3. Intermolecular Amidoselenenylation of Alkenes and *N*-Phenylselenosuccinimide[a,b]



[a]The general reaction was carried out on a 0.5 mmol scale in 5 mL of CH_2Cl_2; the molar ratio of **1b**/**2b** was 1/1.10. [b]Isolated yield.

spectra of **3r**, the correlations of δ_C (168.6) and δ_H (7.75, 7.68, 4.41), and the correlation of δ_C (129.1) and δ_H (7.10, 3.68, 3.17), together with the ^{1}H NMR, ^{13}C NMR, and HSQC spectra, the following structure of compound **3r** can be deduced (Figure 2).

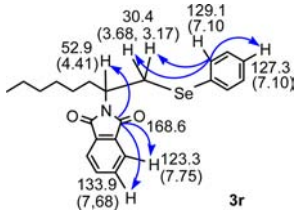
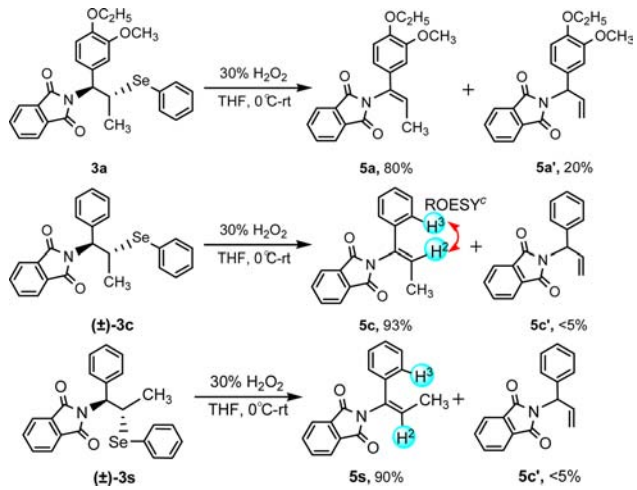


Figure 2. Long-range coupling correlations of carbon atoms (δ_C 168.6, 129.1) and the related hydrogen atoms in compound **3r**.

The reaction was next investigated in terms of another *N*-(phenylseleno)imide reagent, *N*-(phenylseleno)succinimide (NPSS) **2b**, resulting in 50% yield of amidoselenenylation product **4a** and 50% yield of hydroxyselenenylation product **9a**, both with 99% regioselectivity (Scheme 3). Treatment of other alkenes with NPSS mainly afforded hydroxyselenenylation products because the amidoselenenylation reactions were quenched with aqueous $NaHCO_3$ solution. However, the hydroxyselenylation product **9a** was treated with diethyl azodicarboxylate (DEAD) and triphenyl phosphine in THF at room temperature for 8 h to afford the desired product **4a** in 86% yield.

The regioselectivity of the products of the amidoselenenylation of alkenes was verified by the treatment of compounds **3a**, **3c**, and **3s** with 30% H_2O_2 aqueous solution in THF at 0 °C for 1.5 h and then at room temperature for 30 min to 3 h to afford **5a**, **5a′**, **5c**, and **5s** via a selenoxide *syn*-elimination reaction (Scheme 4). According to the ROESY spectrum of **5c**,

Scheme 4. Selenoxide *syn*-Elimination of Compound 3a, 3c, and 3s[a,b]



[a]The general reaction was carried out on a 0.2 mmol scale in 8 mL of THF, in the presence of H_2O_2 aqueous solution (0.5 mL). [b]Isolated yield. [c]The correlation of δH^3 (7.32) and δH^2 (6.51) in the ROESY spectrum of **5c**.

the correlation of δ_H (7.32) and δ_H (6.51), together with the ^{1}H NMR, and ^{13}C NMR spectra, the structure of **5c** was verified to be (*Z*)-2-[1-phenyl-1-propenyl]-1*H*-isoindole-1,3(2*H*)-dione, whereas the structure of **5s** was verified to be (*E*)-2-[1-phenyl-1-propenyl]-1*H*-isoindole-1,3(2*H*)-dione. Therefore, the reaction of (*E*)-*β*-methylstyphene (**1a**) produces (1*S*,2*S*) and (1*R*,2*R*) adducts (±)-**3c**, and the reaction of (*Z*)-*β*-methylstyphene (**1s**) produces (1*S*,2*R*) and (1*R*,2*S*) adducts (±)-**3s** (Scheme 4).

Mechanistically, the amidoselenenylation reaction is proposed to occur via the typical episelenonium ion intermediate **8** (Scheme 5). In this scenario, $TiCl_4$ may promote the formation of a three-membered-ring seleniranium ion with high electrophilicity by chelation to the amide carbonyl group (**6**); most importantly, the in situ generated phthalimide anion (**7**) would have sufficient solubility and nucleophilicity to participate in nucleophilic attack in situ because of its benzo-conjugate nature. The observation of *trans*-type adducts supports the proposed mechanism. In addition, the amidoselenenylation

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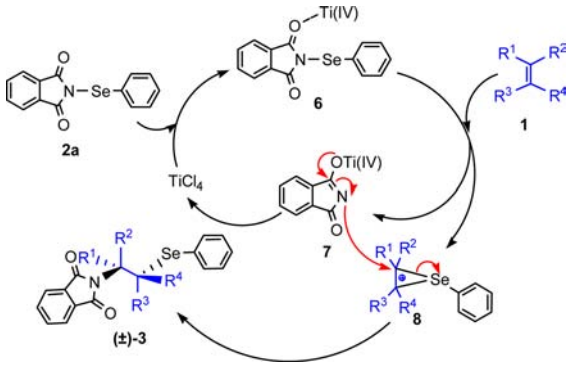
Scheme 5. Proposed Mechanism for the Intermolecular Amidoselenenylation of Alkenes and *N*-(Phenylseleno)phthalimide[a,b]



reaction at room temperature affords the thermodynamically more stable Markovnikov adducts.

In conclusion, we have developed a catalytic, simple, efficient, atom-economic, and regioselective and diastereoselective amidoselenenylation reaction of electron-rich alkenes using *N*-(phenylseleno)phthalimide as both a nitrogen and selenium source. The use of phthalimide-type electrophilic selenium reagents is also synthetically appealing because such an *N*-protection moiety can be readily removed for subsequent transformations. Investigations of the enantioselective amidoselenenylation reaction are currently ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03157.

Experimental procedures and ^{1}H NMR and ^{13}C NMR spectral data for compounds **3**, **4a**, **5a**, **5a′**, **5c**, **5s**, and **9a**, HSQC and HMBC spectral data for compound **3r**, crystal data of compound **3o**, and ROESY spectra for compounds **5c** and **5s** (PDF)

X-ray data for **3o** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Gao, K.; Ma, D. W.; Cheng, Y.; Tian, X. R.; Lu, Y. Y.; Du, X. Y.; Tang, H. F.; Chen, J. Z. *J. Agric. Food Chem.* **2015**, *63*, 1067. (b) Castral, T. C.; Matos, A. P.; Monteiro, J. L. *J. Agric. Food Chem.* **2011**, *59*, 4822. (c) Kang, S.; Kim, R. Y.; Seo, M. J.; Lee, S. *J. Med. Chem.* **2014**, *57*, 5293. (d) Brown, D. G.; Bernstein, P. R.; Griffin, A. *J. Med. Chem.* **2014**, *57*, 733. (e) Healy, A. R.; Vinale, F.; Lorito, M.; Westwood, N. J. *Org. Lett.* **2015**, *17*, 692. (f) Yu, Y.; Guo, H.; Zhang, Q.; Duan, L.; Ding, Y.; Liao, R. J.; Lei, C.; Shen, B.; Liu, W. *J. Am. Chem. Soc.* **2010**, *132*, 16324.

(2) (a) Klayman, D. L.; Günter, H. H. *Organoselenium Compounds: Their Chemistry and Biology*; Wiley: New York, 1973. (b) Gai, B. M.; Bortolatto, C. F.; Brüning, C. A.; Zborowski, V. A.; Stein, A. L.; Zeni, G.; Nogueira, C. W. *Neuropharmacology* **2014**, *79*, 580. (c) Hort, M. A.; Straliotto, M. R.; Netto, P. M.; da Rocha, J. B. T.; de Bem, A. F.; Ribeiro-do-Valle, R. M. *J. Cardiovasc. Pharmacol.* **2011**, *58*, 91. (d) Nogueira, C. W.; Zeni, G.; Rocha, J. B. T. *Chem. Rev.* **2004**, *104*, 6255. (e) Back, T. G.; Moussa, Z. *J. Am. Chem. Soc.* **2002**, *124*, 12104. (f) Piovan, L.; Alves, M. F. M.; Juliano, L.; Bromme, D.; Cunha, R. L. O. R.; Andrade, L. H. *J. Braz. Chem. Soc.* **2010**, *21*, 2108. (g) Ibrahim, M.; Prigol, M.; Hassan, W.; Nogueira, C. W.; Rocha, J. B. T. *Cell Biochem. Funct.* **2010**, *28*, 258. (h) Borges, V. C.; Dadalt, G.; Savegnago, L.; Moro, A. V.; Rocha, J. B. T.; Nogueira, C. W. *Toxicol. In Vitro* **2007**, *21*, 387. (i) De Silva, V.; Woznichak, M. M.; Burns, K. L.; Grant, K. B.; May, S. W. *J. Am. Chem. Soc.* **2004**, *126*, 2409. (j) Glaser, V.; Moritz, B.; Schmitz, A.; Dafre, A. L.; Nazari, E. M.; Rauh Muller, Y. M.; Feksa, L.; Straliottoa, M. R.; de Bem Andreza, F.; Farina, M. *Chem.-Biol. Interact.* **2013**, *206*, 18. (k) Seng, H.-L.; Tiekink, E. R. T. *Appl. Organomet. Chem.* **2012**, *26*, 655.

(3) (a) Nascimento, V.; Alberto, E. E.; Tondo, D. W.; Dambrowski, D.; Detty, M. R.; Nome, F.; Braga, A. L. *J. Am. Chem. Soc.* **2012**, *134*, 138. (b) Sarma, B. K.; Mugesh, G. *J. Am. Chem. Soc.* **2005**, *127*, 11477. (c) Roy, G.; Nethaji, M.; Mugesh, G. *J. Am. Chem. Soc.* **2004**, *126*, 2712. (d) Flohé, L.; Günzler, E. A.; Schock, H. H. *FEBS Lett.* **1973**, *32*, 132. (e) Shamberger, R. J. *Biochemistry of Selenium*; Plenum Press: New York, 1983. (f) Mugesh, G.; Du Mont, W. W.; Sies, H. *Chem. Rev.* **2001**, *101*, 2125.

(4) (a) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Organic Chemistry Series; Pergamon: Oxford, U.K., 1986. (b) Freudendahl, D. M.; Santoro, S.; Shahzad, S. A.; Santi, C.; Wirth, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 8409. (c) Derek, W. J.; Risto, L. *Selenium and Tellurium Chemistry: From Small Molecules to Biomolecules and Materials*; Springer-Verlag: Berlin, 2011.

(5) (a) Wirth, T. *Organoselenium Chemistry: Synthesis and Reactions*; Wiley-VCH: Weinheim, 2012. (b) Conner, E. S.; Crocker, K. E.; Fernando, R. G.; Fronczek, F. R.; Stanley, G. G.; Ragains, J. R. *Org. Lett.* **2013**, *15*, 5558. (c) Denmark, S. E.; Kalyani, D.; Collins, W. R. *J. Am. Chem. Soc.* **2010**, *132*, 15752.

(6) Toshimitsu, A.; Aoai, T.; Uemura, S.; Okano, M. *J. Chem. Soc., Chem. Commun.* **1980**, 1041.

(7) (a) Toshimitsu, A.; Aoai, T.; Owada, H.; Uemura, S.; Okano, M. *J. Org. Chem.* **1981**, *46*, 4727. (b) Toshimitsu, A.; Hayashi, G.; Terao, K.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 343. (c) Tiecco, M.; Testaferri, L.; Santi, C.; Tomassini, C.; Marini, F.; Bagnoli, L.; Temperini, A. *Tetrahedron: Asymmetry* **2002**, *13*, 429. (d) Toshimitsu, A.; Nakano, K.; Mukai, T.; Tamao, K. *J. Am. Chem. Soc.* **1996**, *118*, 2756.

(8) Tiecco, M.; Testaferri, L.; Santi, C.; Tomassini, C.; Marini, F.; Bagnoli, L.; Temperini, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3131.

(9) Zhao, G. L.; Rios, R.; Vesely, J.; Eriksson, L.; Córdova, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8468.

(10) (a) Tang, E.; Cheng, B. Z. *Synlett* **2011**, 707. (b) Tang, E.; Li, W. *Synlett* **2012**, *23*, 907. (c) Huang, X.; Tang, E.; Xu, W. M.; Cao, J. *J. Comb. Chem.* **2005**, *7*, 802. (d) Xu, W. M.; Xu; Huang, X.; Tang, E. *J. Comb. Chem.* **2005**, *7*, 726. (e) Tang, E.; Huang, X.; Xu, W. M. *Tetrahedron* **2004**, *60*, 9963. (f) Tang, E.; Mao, D. S.; Li, W.; Gao, Z. Y.; Yao, P. F. *Heterocycles* **2012**, *85*, 667. (g) Tang, E.; Li, W.; Gao, Z. Y.; Gu, X. *Chin. Chem. Lett.* **2012**, *23*, 631.

(11) Nicolaou, K. C.; Petasis, N. A.; Claremon, D. A. *Tetrahedron* **1985**, *41*, 4835.

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Organic LETTERS

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Copper-Catalyzed Coupling of Oxime Acetates with Isothiocyanates: A Strategy for 2-Aminothiazoles

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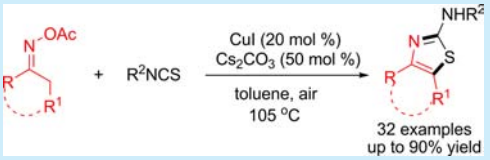
School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, P. R. China

Supporting Information

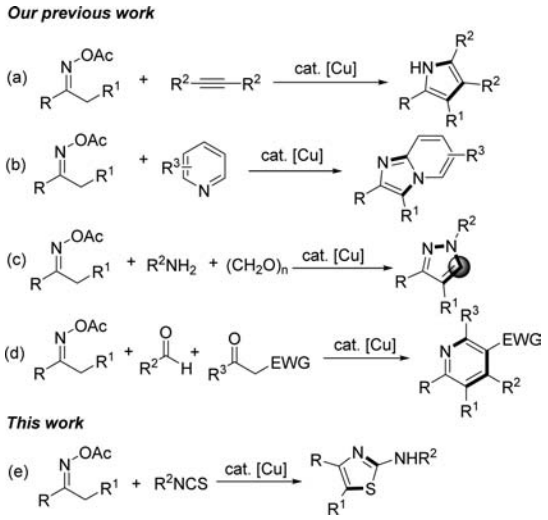
ABSTRACT: A new strategy for 2-aminothiazoles is developed via the copper-catalyzed coupling of oxime acetates with isothiocyanates. Various 4-substituted and 4,5-disubstituted 2-aminothiazoles were formed smoothly under mild reaction conditions. This process involved copper-catalyzed N−O bond cleavage, activation of vinyl sp^2 C−H bonds, and C−S/C−N bond formations. It is noteworthy that the oxime acetates were used not only as a substrate but also as a single oxidant.



In the past few decades, transition-metal-catalyzed oxidation reactions have been a good method for carbon−carbon and carbon−heteroatom bond formations.[1] However, the use of the external oxidants makes these reactions suffer from harsh reaction conditions, poor functional group tolerance, and the waste of the reduced external oxidant. To solve this problem, attention has shifted to the internal oxidants.[2] The reactions which utilize internal oxidants are redox-neutral and do not require external oxidants. While the N−N,[3] N−S,[4] and N−O[5−7] bonds were all used as internal oxidants, the N−O bond is the most common. Narasaka et al. seminally studied palladium-catalyzed intramolecular Heck-type cyclization of oxime derivatives, and other groups recently reported palladium-catalyzed C−H functionalizations which use the N−O bond as the internal oxidant.[5] In addition, the N−O bond cleavage was also used as the oxidant in ruthenium- and rhodium-catalyzed reactions.[6,7] These reactions utilizing internal oxidants have many advantages, such as mild reaction conditions, high selectivity, and good functional group tolerance. Thus, it is meaningful and desirable to apply internal oxidants in more transition-metal-catalyzed oxidation coupling reactions.

The 2-aminothiazole motif has been widely used in medicinal chemistry.[8] Until now, one of the most common methods for the synthesis of 2-aminothiazoles has been the Hantzsch reaction, which uses α-halocarbonyl compounds to couple with thioureas.[9] Recently, reactions directly starting from ketones and thioureas have been also reported for synthesis of 2-aminothiazole.[10] However, they suffer from harsh reaction conditions, poor functional group tolerance, or limited starting materials. Therefore, it is desirable and challenging to develop more green reagents and new routes for 2-aminothiazoles. An oxime ester, which comes from the esterification of oxime, is cheap and readily available.[11] In recent years, we and other groups have found that oxime esters were good synthons for nitrogen-bearing heterocyclic compounds in the presence of a copper catalyst,[12,13] and oxime esters were used not only as substrates but also as oxidants. We have developed a series of methods for the synthesis of *N*-heterocycle compounds such as pyrroles, imidazo[1,2-*a*]pyridines, pyrazoles, and pyridines via copper-catalyzed coupling reactions with oxime esters as the substrates (Scheme 1a−d).[12] Herein, we report a novel method for 2-aminothiazoles via the copper-catalyzed oxidative coupling of oxime acetates with isothiocyanates using N−O bonds as the internal oxidant; thus, there is no need for additional oxidants (Scheme 1e).

Scheme 1. Our Previous Work and This Work



At the start of our studies, we used acetophenone oxime acetate (**1a**) and phenyl isothiocyanate (**2a**) as models to screen bases, copper salts, and solvents, and the results are summarized in Table 1. Initial attempts were performed with a catalytic amount of CuI, K_2CO_3 as base, and toluene as solvent under an air atmosphere. We were excited that the unpredicted product *N*,4-diphenylthiazol-2-amine (**3aa**) was obtained in

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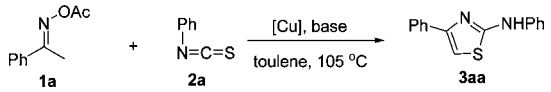
Table 1. Optimization of Reaction Conditions[a]



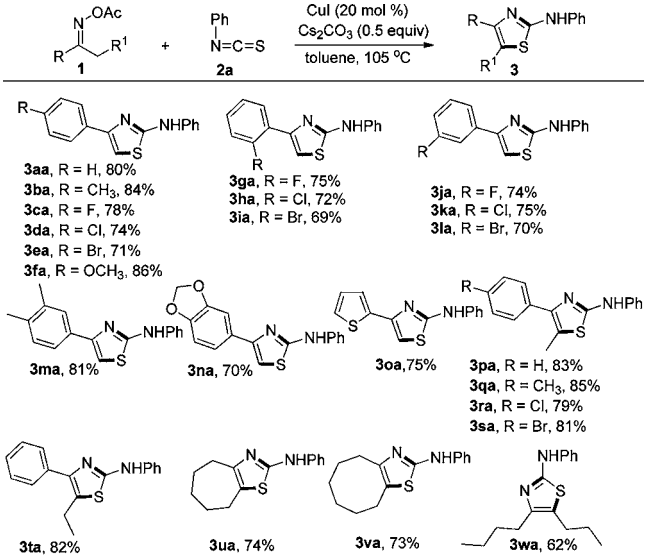
entry	[Cu]	base	solvent	yield[b](%)
1	CuI	K_2CO_3	toluene	14
2	CuI	Na_2SO_3	toluene	23
3	CuI	$NaHSO_3$	toluene	13
4	CuI	KO^{t}Bu	toluene	43
5	CuI	DBu	toluene	15
6	**CuI**	**Cs_2CO_3**	**toluene**	**84 (80)**
7	CuI	–	toluene	n.d.
8	–	Cs_2CO_3	toluene	n.d.
9	CuCl	Cs_2CO_3	toluene	42
10	CuBr	Cs_2CO_3	toluene	79
11	$CuCl_2$	Cs_2CO_3	toluene	12
12	$CuBr_2$	Cs_2CO_3	toluene	14
13	$Cu(OAc)_2$	Cs_2CO_3	toluene	69
14	$Cu(OTf)_2$	Cs_2CO_3	toluene	67
15	CuI	Cs_2CO_3	DMSO	n.d.
16	CuI	Cs_2CO_3	DMF	n.d.
17	CuI	Cs_2CO_3	1,4-dioxane	48
18[c]	CuI	Cs_2CO_3	toluene	82

[a]Reaction conditions: unless otherwise noted, all reactions were performed with **1a** (0.5 mmol), **2a** (0.5 mmol), base (0.25 mmol), and [Cu] (20 mol %), in toluene (3 mL) at 105 °C under air for 8 h. [b]Determined by GC and dodecane as internal standard. Number in parentheses is yield of isolated product. [c]Under N_2 atmosphere.

14% GC yield (Table 1, entry 1). Various bases, such as Na_2SO_3, $NaHSO_3$, KO^{t}Bu, DBU, and Cs_2CO_3, were examined (entries 2–6). To our delight, Cs_2CO_3 gave a satisfactory yield (84% GC yield and 80% isolated yield). Without a base or catalyst, there was no product detected (entries 7–8). Different copper salts such as CuCl, CuBr, $CuCl_2$, $CuBr_2$, $Cu(OAc)_2$, and $Cu(OTf)_2$ could also catalyze this reaction (entries 9–14). When we used DMSO and DMF as solvents, the desired product was not detected and acetophenone oxime acetate was found to be decomposed into acetophenone oxime and acetophenone (entries 15–16). However, we could obtain a moderate yield when using 1,4-dioxane as solvent (entry 17). When the reaction was performed under a N_2 atmosphere, the result was the same as that under an air atmosphere (entry 18). In order to simplify the operation, we elected to carry out our process under an air atmosphere. Thus, the optimal catalytic system for this copper-catalyzed oxidative coupling reaction was as follows: **1a** (0.5 mmol), **2a** (0.5 mmol), CuI (20 mol %), and Cs_2CO_3 (0.25 mmol) in toluene (3 mL) at 105 °C under air for 8 h.

With the optimized reaction conditions in hand, the generality of this copper-catalyzed oxidative coupling of oxime acetates with isothiocyanates was examined. The scope of the oxime acetates was first explored by the adoption of phenyl isothiocyanate as the coupling partner, and the results are summarized in Scheme 2. Both electron-rich (H, **1a**; CH_3, **1b**; OMe, **1f**) and electron-poor (halogen, **1c–e**) *para*-substituted acetophenone oxime acetates participated well in this reaction, and the desired products were formed in good yields. In addition, the substrates with a fluoro, chloro, bromo group at the *meta*- or *ortho*-position could also react smoothly to afford the corresponding products with good to excellent yields (**3ga–3la**). In general, acetophenone oxime acetates with

Scheme 2. Cu(I)-Catalyzed Synthesis of 2-Aminothiazoles from Various Oxime Acetates and Phenyl Isothiocyanate[a]



[a]The reactions were carried out at 105 °C using **1** (0.5 mmol), **2a** (0.5 mmol), CuI (20 mol %), and Cs_2CO_3 (0.25 mmol) in toluene (3 mL) under air for 8 h. Yields refer to the isolated yields.

an electron-donating group showed higher reactivity than those with an electron-withdrawing group. Unfortunately, a strong electron-withdrawing group such as nitro was not applicable in this transformation. It is worth noting that the disubstituted acetophenone oxime acetates were a suitable substrate, and the corresponding products were formed in 81% and 70% yields, respectively (**3ma**, **3na**). Notably, a heteroaryl-bearing oxime acetate was also compatible for this transformation and transferred to the corresponding product in 75% yield (**3oa**). More importantly, the strategy was also available for the construction of 4,5-disubstituted 2-aminothiazoles in good yields (**3pa–3wa**).

Next, the scope of isothiocyanates was examined for this reaction (Scheme 3). For various *para*-substituted phenyl isothiocyanates with electron-donating or -withdrawing substituents on the aromatic ring, the reactions proceeded smoothly to afford the desired products **3ab–3af** in good yields. When 3-methylphenyl isothiocyanate was used, product **3ag** was isolated in 77% yield. It is worth mentioning that the annulation reaction could be expanded to alkyl and benzyl isothiocyanates, and the corresponding products could be formed in 90%, 73%, and 85% yields, respectively (**3ah–3aj**).

To gain more insight into the reaction mechanism, we added the radical scavenger TEMPO or BHT to our standard reaction [eqs 1 and 2]. When TEMPO was added, the reaction system was very complex and no product was detected. In addition, acetophenone was obtained in 18% yield and acetophenone oxime acetate was recovered in 11% yield [eq 1]. When BHT was added, the conditions were similar to the case with TEMPO; acetophenone was obtained in 10% yield and acetophenone oxime acetate was recovered in 35% yield [eq 2]. When phenyl isocyanate was added to the reaction, the corresponding product **4** was not detected [eq 3].

Based on previous works on copper-catalyzed transformation of oxime esters and our control experiment, a possible mechanism is proposed in Scheme 4.[12−16] First, iminium radical **A** was produced via reduction by Cu^{I}.[12−14] The free-

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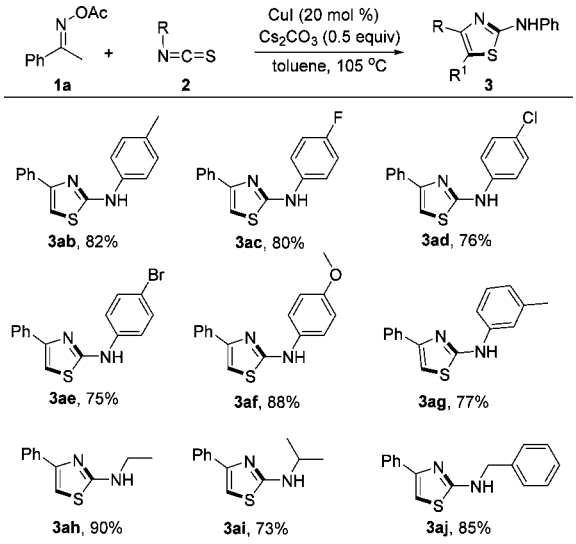
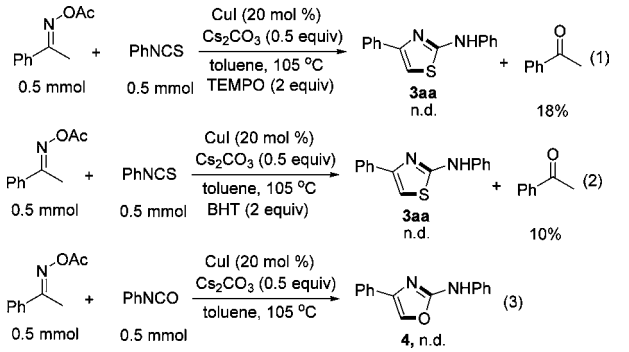
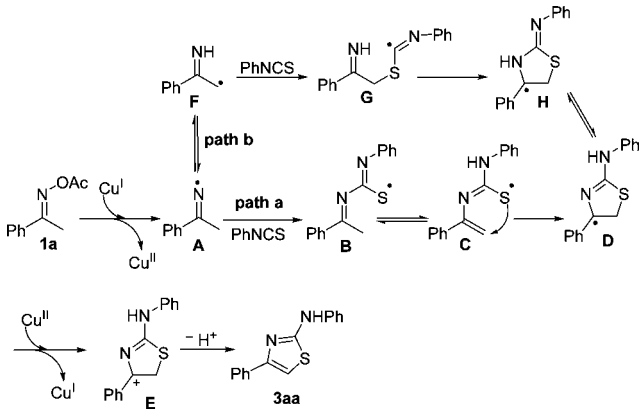
Scheme 3. Cu(I)-Catalyzed Synthesis of 2-Aminothiazoles from Acetophenone Oxime Acetate and Various Isothiocyanates[a]



[a]The reactions were carried out at 105 °C using **1a** (0.5 mmol), **2** (0.5 mmol), CuI (20 mol %), and Cs_2CO_3 (0.25 mmol) in toluene (3 mL) under air for 8 h. Yields refer to the isolated yields.



Scheme 4. Possible Catalytic Cycle



radical addition of iminium radical **A** to phenyl isothiocyanate formed the intermediate **B**, which isomerized to intermediate **C**. Subsequently, intramolecular free-radical addition occurs to construct a new C−S bond to afford intermediate **D** (path a).[15] It is also possible that the intermediate **D** is generated by addition of carbon radical **F** to the sulfur atom of phenyl isothiocyanate, followed by intramolecular radical cyclization and isomerization (path b).[16] Subsequently, the intermediate **D** was oxidized by Cu^{II} to give the intermediate **E**. Finally, the desired product **3aa** was obtained by deprotonation and the resulting acid was neutralized by the base.

In summary, an efficient and external-oxidant-free 2-aminothiazole synthesis from copper-catalyzed oxidative coupling of oxime acetates with isothiocyanates has been developed. Importantly, the reaction was accomplished through N−O bond cleavage, and new C−S/C−N bond formations, along with the activation of vinyl sp^2 C−H bonds under mild conditions. Various 4- and 4,5-substituted 2-aminothiazoles were formed in good yields. Further studies on this topic are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03188.

Typical experimental procedure and characterization for all products (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews on transition-metal-catalyzed oxidation reactions, see: (a) Wu, W.; Jiang, H. *Acc. Chem. Res.* **2012**, *45*, 1736. (b) Hirano, K.; Miura, M. *Chem. Commun.* **2012**, *48*, 10704. (c) Le Bras, J. L.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170. (d) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381. (e) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (f) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (g) Sarhan, A. A. O.; Bolm, C. *Chem. Soc. Rev.* **2009**, *38*, 2730. (h) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062. (i) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215.

(2) (a) Huang, H.; Ji, X.; Wu, W.; Jiang, H. *Chem. Soc. Rev.* **2015**, *44*, 1155. (b) Patureau, F. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1977.

(3) For selected examples of the N−N bond as an internal oxidant: (a) Zheng, L.; Hua, R. *Chem. - Eur. J.* **2014**, *20*, 2352. (b) Zhao, D.; Shi, Z.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 12426. (c) Liu, B.; Song, C.; Sun, C.; Zhou, S.; Zhu, J. *J. Am. Chem. Soc.* **2013**, *135*, 16625. (d) Wang, C.; Huang, Y. *Org. Lett.* **2013**, *15*, 5294. (e) Zhang, Z.; Jiang, H.; Huang, Y. *Org. Lett.* **2014**, *16*, 5976.

(4) For selected examples of the N−S bond as an internal oxidant: Zhang, Q.-R.; Huang, J.-R.; Zhang, W.; Dong, L. *Org. Lett.* **2014**, *16*, 1684.

(5) For the N−O bond as an internal oxidant in Pd-catalyzed reactions, see: (a) Kitamura, M.; Zaman, S.; Narasaka, K. *Synlett* **2001**, *2001*, 974. (b) Kitamura, M.; Chiba, S.; Saku, O.; Narasaka, K. *Chem. Lett.* **2002**, 606. (c) Wu, J.; Cui, X.; Chen, L.; Jiang, G.; Wu, Y. *J. Am. Chem. Soc.* **2009**, *131*, 13888. (d) Hong, W. P.; Iosub, A. V.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 13664. (e) Gerfaud, T.; Neuville, L.; Zhu,

DOI: 10.1021/acs.orglett.5b03188
Org. Lett. 2016, 18, 180−183

J. *Angew. Chem., Int. Ed.* **2009**, *48*, 572. (f) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676. (g) Zhang, Z.-W.; Lin, A.; Yang, J. *J. Org. Chem.* **2014**, *79*, 7041. (h) Xu, Y.; Hu, W.; Tang, X.; Zhao, J.; Wu, W.; Jiang, H. *Chem. Commun.* **2015**, *51*, 6843.

(6) For the N−O bond as an internal oxidant in Ru-catalyzed reactions, see: (a) Kornhaaß, C.; Li, J.; Ackermann, L. *J. Org. Chem.* **2012**, *77*, 9190. (b) Chinnagolla, R. K.; Pimparkar, S.; Jeganmohan, M. *Org. Lett.* **2012**, *14*, 3032. (c) Li, B.; Ma, J.; Wang, N.; Feng, H.; Xu, S.; Wang, B. *Org. Lett.* **2012**, *14*, 736. (d) Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548. (e) Li, B.; Feng, H.; Xu, S.; Wang, B. *Chem. - Eur. J.* **2011**, *17*, 12573.

(7) For the N−O bond as an internal oxidant in Rh-catalyzed reactions, see: (a) Hyster, T. K. *Science* **2012**, *338*, 500. (b) Ye, B.; Cramer, N. *Science* **2012**, *338*, 504. (c) Zhang, X.; Chen, D.; Zhao, M.; Zhao, J.; Jia, A.; Li, X. *Adv. Synth. Catal.* **2011**, *353*, 719. (d) Wang, H.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 7318. (e) Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2014**, *136*, 2735. (f) Huang, X.; Huang, J.; Du, C.; Zhang, X.; Song, F.; You, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12970. (g) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449. (h) Hu, F.; Xia, Y.; Ye, F.; Liu, Z.; Ma, C.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 1364. (i) Liu, G.; Shen, Y.; Zhou, Z.; Lu, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 6033.

(8) (a) Gentles, R. G.; Grant-Young, K.; Hu, S.; Huang, Y.; Poss, M. A.; Andres, C.; Fiedler, T.; Knox, R.; Lodge, N.; Weaver, C. D.; Harden, D. G. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5316. (b) Zhao, M.; Yin, J.; Huffman, M. A.; McNamara, J. M. *Tetrahedron* **2006**, *62*, 1110. (c) Heng, S.; Gryncel, K. R.; Kantrowitz, E. R. *Bioorg. Med. Chem.* **2009**, *17*, 3916. (d) Gallardo-Godoy, A.; Gever, J.; Fife, K. L.; Silber, B. M.; Prusiner, S. B.; Renslo, A. R. *J. Med. Chem.* **2011**, *54*, 1010.

(9) (a) Potewar, T. M.; Ingale, S. A.; Srinivasan, K. V. *Tetrahedron* **2008**, *64*, 5019. (b) El Kazzouli, S.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Tetrahedron Lett.* **2002**, *43*, 3193. (c) Narender, M.; Reddy, M. S.; Sridhar, R.; Nageswar, Y. V. D.; Rao, K. R. *Tetrahedron Lett.* **2005**, *46*, 5953. (d) Kabalka, G. W.; Mereddy, A. R. *Tetrahedron Lett.* **2006**, *47*, 5171. (e) Kearney, P. C.; Fernandez, M.; Flygare, J. A. *J. Org. Chem.* **1998**, *63*, 196.

(10) (a) Yin, G.; Ma, J.; Shi, H.; Tao, Q. *Heterocycles* **2012**, *85*, 1941. (b) Zhao, J.; Xu, J.; Chen, J.; He, M.; Wang, X. *Tetrahedron* **2015**, *71*, 539.

(11) (a) Too, P. C.; Wang, Y.-F.; Chiba, S. *Org. Lett.* **2010**, *12*, 5688. (b) Neufeldt, S. R.; Sanford, M. S. *Org. Lett.* **2010**, *12*, 532.

(12) (a) Tang, X.; Huang, L.; Qi, C.; Wu, W.; Jiang, H. *Chem. Commun.* **2013**, *49*, 9597. (b) Huang, H.; Ji, X.; Tang, X.; Zhang, M.; Li, X.; Jiang, H. *Org. Lett.* **2013**, *15*, 6254. (c) Tang, X.; Huang, L.; Yang, J.; Xu, Y.; Wu, W.; Jiang, H. *Chem. Commun.* **2014**, *50*, 14793. (d) Jiang, H.; Yang, J.; Tang, X.; Li, J.; Wu, W. *J. Org. Chem.* **2015**, *80*, 8763.

(13) (a) Ran, L.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Green Chem.* **2014**, *16*, 112. (b) Wu, Q.; Zhang, Y.; Cui, S. *Org. Lett.* **2014**, *16*, 1350. (c) Wei, Y.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 3756. (d) Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918.

(14) Tang, X.; Huang, L.; Xu, Y.; Yang, J.; Wu, W.; Jiang, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 4205.

(15) (a) Wang, H.; Wang, L.; Shang, J.; Li, X.; Wang, H.; Gui, J.; Lei, A. *Chem. Commun.* **2012**, *48*, 76. (b) Lo, W.-S.; Hu, W.-P.; Lo, H.-P.; Chen, C.-Y.; Kao, C.-L.; Vandavasi, J. K.; Wang, J.-J. *Org. Lett.* **2010**, *12*, 5570. (c) Zhang, G.; Liu, C.; Yi, H.; Meng, Q.; Bian, C.; Chen, H.; Jian, J.-X.; Wu, L.-Z.; Lei, A. *J. Am. Chem. Soc.* **2015**, *137*, 9273. (d) Zhou, S.-F.; Pan, X.-Q; Zhou, Z.-H.; Shoberu, A.; Zhang, P.-Z.; Zou, J.-P. *J. Org. Chem.* **2015**, *80*, 5348.

(16) Leardini, R.; Nanni, D.; Pareschi, P.; Tundo, A.; Zanardi, G. *J. Org. Chem.* **1997**, *62*, 8394.

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Organic LETTERS

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C_{70} as a Photocatalyst for Oxidation of Secondary Benzylamines to Imines

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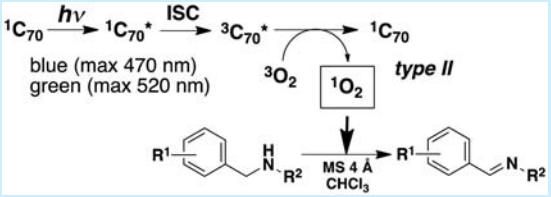
Supporting Information

ABSTRACT: Photosensitive C_{70} was used for the catalytic oxidation of benzylamines to the corresponding imines. The advantages of using C_{70} compared to C_{60} or other commonly used photosensitizers such as tetraphenylporphyrin (TPP) are (1) faster reaction rates, especially under lower energy of light sources, (2) clean reactions with simple workup without chromatography, and (3) lower catalyst loadings. The reactions were suitable for various benzylamine derivatives. Subsequent nucleophilic additions to the imines were successfully carried out on substituted products. Quenching experiments in the presence of DABCO and benzoquinone implicate the involvement of the singlet oxygen ($^1O_2$) and the superoxide radical anion ($O_2^{\bullet-}$) as important reactive species in the oxidation.



The remarkable photosensitivity of fullerenes such as C_{60} and C_{70} has been widely known for decades and has been applied in photovoltaic materials and photodynamic therapy (PDT) agents. In the case of the former, the electron-donating or -accepting properties of fullerenes, which can be induced by photoirradiation, is utilized. In the case of the latter, photo-induced generation of reactive oxygen species (ROSs) such as $^1O_2$[1,2] and $O_2^{\bullet-}$[3] produced, respectively, via energy transfer (type II reaction) and electron transfer (type I reaction) is a key phenomenon. Importantly, the quantum yields of both type I and II reactions are quantitiative,[4] and therefore, many PDT studies using fullerenes were reported, influenced by an initial report on photo DNA-cleavage with C_{60}[5] using water-soluble fullerene materials.[6] Alternatively, the use of fullerenes as organic reagents such as a catalyst for oxidation has been studied for decades. These studies include the oxidation of olefins,[7] phenols,[8] and sulfides.[9]

Imines are important intermediates in the synthesis of bioactive compounds,[10] and there is a high demand for useful synthetic methods for the production of imines.[11−13] Reported methods for the conversion of amines to imines include the use of (1) stoichiometric oxidants such as *N-tert*-butylphenylsulfinimidoyl chloride[14] and *o*-iodoxybenzoic acid (IBX)[15,16] and (2) metal catalysts in the presence of oxidants[10,17−23] or molecular oxygen.[17,24−26] Quinone- and catechol-based aerobic oxidations of amines were also found to be efficient.[27−29] These methods provide sufficient yields but often require harsh reaction conditions, stoichiometric oxidizing reagents, or other additives.

Recently, the use of photosensitizers has emerged as a promising method for the conversion of amines to imines. Photocatalysts such as organic dyes[30,31] and transition-metal complexes[30,32,33] have been explored for various organic transformations. Specifically, recent reports on the oxidation of amines using $^1O_2$ generated from photosensitizers such as porphyrin derivatives[34−36] and gold catalysts have received a great attention.[37] Che and co-workers used tetraphenylporphyrin (TPP) as a catalyst for the photooxidation of amines to imines, which were directly subjected to a subsequent Ugi reaction.[34] The same group also reported an organogold(III) complex for the oxidation of benzylamines to imines, including the oxidative cyanation of tertiary amines.[37] König and co-workers used porphycene in photooxidation reactions of primary and secondary amines to provide the corresponding imines and aldehydes.[35] Recent work by Seeberger and co-workers described the photooxidation of amines and subsequent nucleophilic addition with TPP using continuous-flow photoreactor techniques.[36,38]

In this study, we used C_{60} and C_{70} as photocatalysts for the oxidation of benzylamines to imines. Although the price of fullerenes is now comparable to other photosensitizers such as TPP, the application of fullerenes for such a reaction has not been previously explored. While the initial trials with C_{60} were not as efficient when compared to the commonly used photosensitizer TPP, the use of C_{70} provided a very effective reaction even with lower catalyst loadings. In addition, under lower light energy (blue LED), nucleophilic addition to the imines can be successfully carried out in the same reaction flask to provide a substitution at the benzylic position. Due to the low solubility of C_{70}, the workup of the reactions is very simple and requires only the removal of C_{70} by precipitation to provide imines as a single product. The reaction was successfully applied to various benzylamines as substrates.

As an initial trial for the oxidation of benzylamines to imines, 1,2,3,4-tetrahydroisoquinoline **1** was used as a substrate in the presence of C_{60} (99.95%, MTR Ltd.) as a photocatalyst under white light irradiation by a tungsten lamp. The reaction rates were compared in the several different solvents as listed in Table

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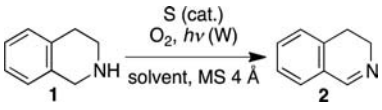
Table 1. Photoinduced Oxidation of Amine 1 in the Presence of Photosensitizer (C_{60}, TPP or C_{70}) and under White Light Irradiation[a]



run	catalyst S	catalyst mol %	O_2[b]	light[c]	solvents	reaction time ($t_{1/2}$) [h][d]	NMR yield [%][e]
1	C_{60}	1.0	satd.	+	$CHCl_3$	7 (3.5)	>99
2	C_{60}	1.0	satd.	+	CH_2Cl_2	13 (6.3)	>99
3	C_{60}	1.0	satd.	+	THF	28 (15)	>99
4	C_{60}	1.0	satd.	+	CH_3CN	>40 (N.D.)	<10
5	C_{60}	0.1	satd.	+	$CHCl_3$	21 (11)	>99
6	C_{60}	0.05	satd.	+	$CHCl_3$	>53 (44)	56
7	C_{60}	0.01	satd.	+	$CHCl_3$	>53 (N.D.)	20
8	C_{60}	0.1	satd.	–(Δ)[f]	$CHCl_3$	>19 (N.D.)	N.R.
9	C_{60}	0.1	air	+	$CHCl_3$	>19 (18)	53
10	–	–	satd.	+	$CHCl_3$	>19 (N.D.)	<6
11	C_{60}-adduct[g]	0.1	satd.	+	$CHCl_3$	15(7)	>99
12	TPP	0.1	satd.	+	$CHCl_3$	5 (2.4)	>99
13	C_{70}	0.1	satd.	+	$CHCl_3$	5 (2.4)	>99
14	C_{70}	0.05	satd.	+	$CHCl_3$	8.5 (4.2)	>99
15	C_{70}	0.01	satd.	+	$CHCl_3$	28 (13)	>99

[a]Amine **1** (50 mg, 0.38 mmol) was subjected in the reaction with 5 mL of solvent. [b]Satd: oxygen was saturated by bubbling (about 11.5 mM of O_2 in $CHCl_3$). Air: reaction mixture was exposed to the air by using an open flask (about 2.1 mM of O_2 in $CHCl_3$). [c]A 200 W tungsten lamp (white light) at a distance of 20 cm (20000−20500 lx). [d]The time required for completion (with no detectable **1** by NMR) and the time for 50% conversion from **1** to **2** ($t_{1/2}$). N.D.: not determined. [e]Obtained from the integration of ^{1}H NMR spectra of the reaction mixture. N.R.: no reaction with starting material recovery. [f]Without light and under a thermal condition (40 °C). [g]C_{60}-mono-Bingel derivative (structure is provided in Figure S14, SI).

1 (runs 1−4), and these studies revealed that $CHCl_3$ was the most efficient solvent. This solvent effect may be partially related to the lifetime of the $^1O_2$ in each solvent (250 ± 10, 91 ± 10, 30 ± 10, and 54 μs for $CHCl_3$, CH_2Cl_2, THF, and CH_3CN, respectively[39,40]). The very slow reaction in CH_3CN (run 4) was presumably due to the low solubility of C_{60} in this polar solvent. A similar situation was observed in the reaction of the more soluble C_{60}−Bingel adduct (SI, Figure S14), in which a slightly faster reaction rate was shown compared to the less soluble pristine C_{60} (runs 5, 11). None or only trace product generation was observed in the absence of C_{60} or light (runs 8, 10). The saturated oxygen concentration was advantageous than the ambient condition with open flask (run 9).

Importantly, the oxidation of **1** with C_{60} proceeded in a clean manner to show a single product **2** in the crude extract (Figure 1) after a simple workup of precipitation of C_{60} fraction by MeOH and subsequent Celite filtration. However, the reaction efficiency was not sufficient when compared with TPP, a commonly used photosensitizer (runs 5, 12).As an alternative, we used C_{70} (99.5%, MTR Ltd.) as a catalyst, which has stronger absorbance of visible light (Figure S25) and a longer triplet state ($^3C_{70}$*) lifetime than C_{60} or TPP. As expected, the reaction with C_{70} was

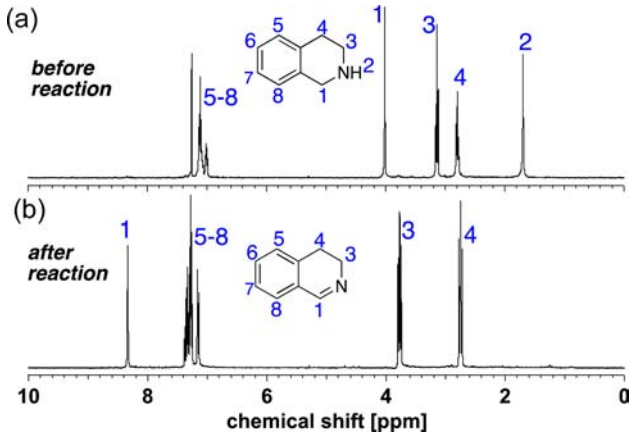


Figure 1. ^{1}H NMR spectra of the starting material **1** (a) and the crude extract of the reaction mixture (b) after white light irradiation with 0.1 mol % of C_{60} for 21 h in $CHCl_3$ at room temperature.

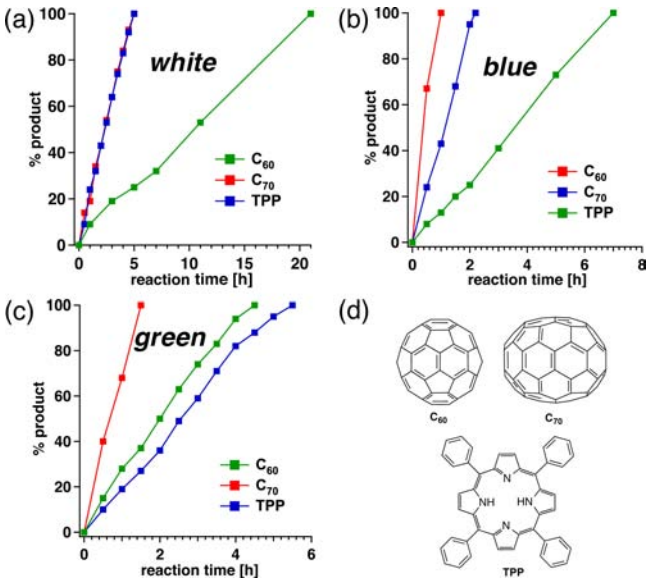


Figure 2. Reaction process of oxidation under (a) white tungsten lamp (200 W, 20000−20500 lx), (b) blue diode (emission maximum: 470 nm, 14000−14500 lx), (c) green diode (emission maximum: 520 nm, 73000−74000 lx). (d) Structures of the photosensitizers. The reactions were carried out using 0.1 mol % of photosensitizer and 50 mg (0.38 mmol) of amine **1** in $CHCl_3$. The value of % product was estimated by ^{1}H NMR spectra integration.

much faster than the one with C_{60} and almost the same as the one with TPP (runs 5, 12, 13 and Figure 2a). Importantly, we could lower the catalyst loading of C_{70} to 0.01 mol % and still complete the oxidation in a practical reaction time (28 h, run 15).

Based on the promising results of using C_{70} under white light above, along with the fact that C_{70} has absorbance in longer wavelength region, which has less risk of decomposition of the compounds involved in the reaction, we used commercially available, inexpensive diode lamps for irradiation. We compared the reaction rates in the presence of C_{60}, C_{70}, and TPP. As a result, under both blue (max: 470 nm, Figure 2b) and green (max: 520 nm, Figure 2c) LED lights, the reaction with C_{70} proceeded faster than those with either TPP or C_{60}, indicating the advantage in the use of C_{70} as a photocatalyst. In addition, under green light, the reaction of C_{60} was faster than that of TPP, despite the fact that the absorbance of TPP at around 520 nm is

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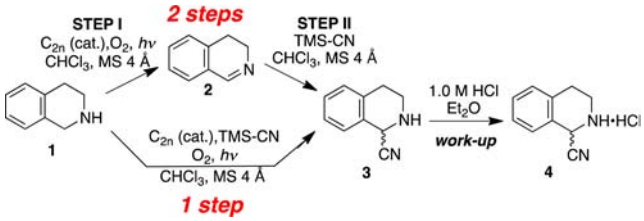
much higher than the one of C_{60} (Figure S25). This is presumably because the quantum yields in $^1O_2$ generation from photoexcited fullerenes are quite high (0.96 ± 0.04 for C_{60}[1] and 0.81 ± 0.15 for C_{70}[2] in benzene at 532 nm) compared to the one from TPP (0.62 ± 0.20 in benzene at 532 nm).[41]

Based on the above results for the efficient oxidation with C_{70}, we simultaneously carried out amine oxidation and nucleophilic addition (Table 2). An initial attempt of this one-step protocol

Table 2. Combination of Amine Oxidation and Nucleophilic Addition[a]



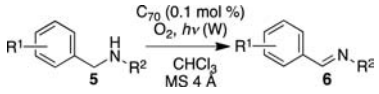
	two-step conditions						
	step I (light)			step II (dark)			
run	S (mol %)	hν	time [h]	TMS-CN [equiv]	time [h]	NMR yield of 3[b] [%]	yield of 4[c] [%]
1	C_{60} (1.0)	W	15	2.0	1.5	73	65
2	C_{70} (0.1)	W	7	1.5	4	>99	71
3	C_{70} (0.1)	B	2	1.5	4	>99	75
	one-step conditions (light)						
run	S (mol %)	hν		TMS-CN [equiv]	time [h]	NMR yield of 3[b] [%]	yield of 4[c] [%]
4	C_{60} (0.1)	W		1.5	45	<5	N.D.[d]
5	C_{70} (0.1)	W		1.5	10	>99	74
6	C_{70} (0.1)	B		1.5	3	>99	76

[a]Reactions were carried out using amine **1** (133 mg, 1.0 mmol). [b]The NMR yield was obtained by NMR integration. [c]Obtained yields of **4** by one-time precipitation in HCl/Et_2O. [d]Imine **2** was observed after slight generation of **3** in the reaction process by NMR (Figure S27).

using 0.1 mol % of C_{60} and white light resulted only in the generation of imine **2**, presumably due to the decomposition of **3** by white light irradiation (run 4). This was overcome by a one-pot/two-step protocol (run 1) involving an initial step of photooxidation with 1 mol % of C_{60} under white light and the subsequent second step of nucleophile addition in dark to provide **4** in 65% yield. By switching the photocatalyst to C_{70}, the yield by a one-pot/two-step protocol was improved to 71% (white light, run 2) and 75% (blue light, run 3) with shorter reaction times and lower catalyst loading. Furthermore, using C_{70} (0.1 mol %), the one-pot/one-step protocol was successfully achieved to provide **4** in good yield with shorter reaction intervals, especially under blue light irradiation (runs 5, 6).

The C_{70}-catalyzed photooxidation was applied to various benzylamines **5a**–**i** with substituents on the aromatic ring in the presence of C_{70} (0.1 mol %) under white light. As a result, all reactions provided the corresponding imines in good yields (>90%) within 20 h. There was no significant effect of substituents with electron-donating groups (Me and OMe, Table 3, runs 2, 3) or electron-withdrawing groups (F, Cl, and CF_3, runs 4, 5, and 8) in the *para*-position on the reaction rate. The *ortho*- and *meta*-substitution had a slight effect to diminish the reaction rate (runs 6, 7, 9), presumably due to steric hindrance. These results are very similar to recent reports by Seeberger and co-workers,[38] where TPP is used as a photo-

Table 3. Photoinduced Oxidation of Benzylamine Derivatives Catalyzed by C_{70}



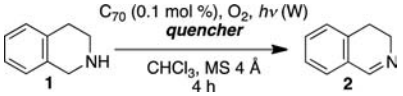
	substrate **5**				
run		R^1	R^2	reaction time [h]	yield[a] [%]
1	**5a**	H	Bn	7	97
2	**5b**	*p*-Me	*p*-MeBn	9	95
3	**5c**	*p*-OMe	*p*-OMeBn	6.5	92
4	**5d**	*p*-F	*p*-FBn	8	93
5	**5e**	*p*-Cl	*p*-ClBn	6	97
6	**5f**	*o*-Cl	*o*-ClBn	15	90
7	**5g**	*m*-Cl	*m*-ClBn	8	95
8	**5h**	*p*-CF_3	*p*-CF_3Bn	10	95
9	**5i**	*m*-CF_3	*m*-CF_3Bn	20	91

[a]Isolated yields.

catalyst, and indicate (1) that C_{70} itself does not have any influence in the selectivity of amine oxidation and (2) that oxidation is suitable for various kinds of benzylamine derivatives. In addition, when an aliphatic amine (e.g., piperidine) was used as a substrate, no imine formation was observed as a limitation of this amine oxidation reaction. Benzylamine oxidation works better presumably due to the stable benzylic radical formation as an important intermediate to provide imine.

In order to elucidate aspects of the reaction mechanism, the photooxidations were carried out in the presence of ROS quenchers. In a detailed examination previously reported by the groups of Seeberger[38] and Baciocchi,[42] two possible mechanisms were proposed for the $^1O_2$-mediated oxidation of amines. Both start from initial coordination of $^1O_2$ to amine nitrogen to cause an exciplex formation followed by the generation of benzylic radical through either (1) single-electron transfer to provide amine radical cation and $O_2^{\bullet-}$ and subsequent deprotonation at the benzyl position or (2) direct hydrogen abstraction. Since we used a photosensitizer with a higher oxidation potential as compared to TPP, it was important to clarify what kind of ROS is involved as reactive species in the current oxidation reaction. We used DABCO and benzoquinone as quenchers of $^1O_2$ and $O_2^{\bullet-}$, respectively. In addition, anthracene was added as a competitive substrate for oxidation by $^1O_2$ (cycloaddition). As shown in Table 4, significant suppression of the oxidation reaction was observed in the presence of DABCO (run 1) with a linear correlation in Stern–Volmer plotting (Figure S96), which

Table 4. Effects of ROS Quenchers on Oxidation[a]



run	quencher (equiv to amine)	solvent	reaction time [h]	NMR yield[b] [%]
1	DABCO (1.0)	$CHCl_3$	4	7
2	anthracene (1.0)	$CHCl_3$	4	85
3	benzoquinone (0.1)[c]	$CHCl_3$	4	25
4		$CHCl_3$	4	>99

[a]All reactions were carried out with amine **1** (15 mg, 0.11 mmol). [b]Observed by ^1H NMR of crude mixture. [c]Reaction was carried out in the presence of smaller amounts of quencher to avoid complex side reactions observed in the presence of larger amounts of benzoquinone.

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indicates that $^1O_2$ is an important reactive species involved in the oxidation. In addition, a moderate decrease of yield was observed in the presence of anthracene (run 2). On the other hand, a slower reaction was also observed in the presence of benzoquinone (run 3) indicating the involvement of $O_2^{\bullet-}$, which is probably generated by the electron transfer from an amine to $^1O_2$. The detailed investigation of the mechanism is still in progress.

Finally, the reaction was carried out on a larger scale to test the recovery of catalyst C_{70}. As described above, separation of C_{70} from reaction mixture is easily done by precipitation from MeOH. In a reaction of **1** (2.0 g) using 12.6 mg (0.1 mol %) of C_{70} (9 h under blue light), 10.1 mg of the C_{70} fraction was recovered, which was subjected to a recycled reaction with **1** (2.0 g) to provide 97% yield in 10 h reaction time under blue light. The recovered C_{70} fraction contained substantial amounts of C_{70} mono- and diepoxides as detected by HPLC and MALDI-TOF-MS (Figures S101, S102).[43] By thermal treatment (reflux in *o*-dichlorobenzene for 17 h), most of the C_{70} epoxides were easily converted back to underivatized C_{70} as indicated by both HPLC and MALDI-TOF-MS (Figures S103, S104).

In conclusion, we successfully developed a clean and efficient oxidation of benzylamines with a simple workup process. Due to the efficiency of C_{70} as a photosensitizer, we achieved lower catalyst loading and provided a high yield of the products. This photoexcited C_{70}-mediated oxidation reaction is also applicable to many benzylamine derivatives and is suitable for simultaneous nucleophilic additions. Easy recovery of C_{70} fraction, which can be converted by simple thermal treatment to C_{70}, enabled the recycling of the C_{70} catalyst.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03194.

Syntheses of amines; detail of photoinduced oxidation reaction; oxidation−nucleophile addition with full spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Arbogast, J. W.; Darmanyan, A. P.; Foote, C. S.; Rubin, Y.; Diederich, F. N.; Alvarez, M. M.; Anz, S. J.; Whetten, R. L. *J. Phys. Chem.* **1991**, *95*, 11.
(2) Arbogast, J. W.; Foote, C. S. *J. Am. Chem. Soc.* **1991**, *113*, 8886.
(3) Yamakoshi, Y.; Umezawa, N.; Ryu, A.; Arakane, K.; Miyata, N.; Goda, Y.; Masumizu, T.; Nagano, T. *J. Am. Chem. Soc.* **2003**, *125*, 12803.
(4) Nagano, T.; Arakane, K.; Ryu, A.; Masunaga, T.; Shinmoto, K.; Mashiko, S.; Hirobe, M. *Chem. Pharm. Bull.* **1994**, *42*, 2291.
(5) Tokuyama, H.; Yamago, S.; Nakamura, E.; Shiraki, T.; Sugiura, Y. *J. Am. Chem. Soc.* **1993**, *115*, 7918.
(6) Nakamura, E.; Isobe, H. *Acc. Chem. Res.* **2003**, *36*, 807.
(7) Tokuyama, H.; Nakamura, E. *J. Org. Chem.* **1994**, *59*, 1135.
(8) Jensen, A. W.; Daniels, C. *J. Org. Chem.* **2003**, *68*, 207.
(9) Latassa, D.; Enger, O.; Thilgen, C.; Habicher, T.; Offermanns, H.; Diederich, F. *J. Mater. Chem.* **2002**, *12*, 1993.
(10) Murahashi, S. I. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2443.
(11) Adams, J. P.; Robertson, G. *Contemp. Org. Synth.* **1997**, *4*, 183.
(12) Martin, S. F. *Pure Appl. Chem.* **2009**, *81*, 195.
(13) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626.
(14) Mukaiyama, T.; Kawana, A.; Fukuda, Y.; Matsuo, J. *Chem. Lett.* **2001**, 390.
(15) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 4077.
(16) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5192.
(17) Largeron, M. *Eur. J. Org. Chem.* **2013**, *2013*, 5225.
(18) Zhang, E.; Tian, H.; Xu, S.; Yu, X.; Xu, Q. *Org. Lett.* **2013**, *15*, 2704.
(19) Chu, G. B.; Li, C. B. *Org. Biomol. Chem.* **2010**, *8*, 4716.
(20) Hu, Z.; Kerton, F. M. *Org. Biomol. Chem.* **2012**, *10*, 1618.
(21) Sonobe, T.; Oisaki, K.; Kanai, M. *Chem. Sci.* **2012**, *3*, 3249.
(22) Choi, H.; Doyle, M. P. *Chem. Commun.* **2007**, 745.
(23) Ell, A. H.; Samec, J. S.; Brasse, C.; Backvall, J. E. *Chem. Commun.* **2002**, 1144.
(24) Lang, X. J.; Ma, W. H.; Chen, C. C.; Ji, H. W.; Zhao, J. C. *Acc. Chem. Res.* **2014**, *47*, 355.
(25) Patil, R. D.; Adimurthy, S. *Adv. Synth. Catal.* **2011**, *353*, 1695.
(26) Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 1480.
(27) Wendlandt, A. E.; Stahl, S. S. *J. Am. Chem. Soc.* **2014**, *136*, 506.
(28) Yuan, H.; Yoo, W. J.; Miyamura, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2012**, *134*, 13970.
(29) Wendlandt, A. E.; Stahl, S. S. *Org. Lett.* **2012**, *14*, 2850.
(30) Girard, S. A.; Knauber, T.; Li, C. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74.
(31) Nicewicz, D. A.; Nguyen, T. M. *ACS Catal.* **2014**, *4*, 355.
(32) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322.
(33) Yoon, T. P.; Ischay, M. A.; Du, J. *Nat. Chem.* **2010**, *2*, 527.
(34) Jiang, G.; Chen, J.; Huang, J. S.; Che, C. M. *Org. Lett.* **2009**, *11*, 4568.
(35) Berlicka, A.; König, B. *Photochem. Photobiol. Sci.* **2010**, *9*, 1359.
(36) Ushakov, D. B.; Gilmore, K.; Kopetzki, D.; McQuade, D. T.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2014**, *53*, 557.
(37) To, W. P.; Tong, G. S.; Lu, W.; Ma, C.; Liu, J.; Chow, A. L.; Che, C. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 2654.
(38) Ushakov, D. B.; Plutschack, M. B.; Gilmore, K.; Seeberger, P. H. *Chem. - Eur. J.* **2015**, *21*, 6528.
(39) Ogilby, P. R.; Foote, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 3423.
(40) Salokhiddinov, K. I.; Gurinovich, G. P.; Byteva, I. M. *J. Appl. Spectrosc.* **1981**, *34*, 561.
(41) Schmidt, R.; Afshari, E. *J. Phys. Chem.* **1990**, *94*, 4377.
(42) Baciocchi, E.; Del Giacco, T.; Lanzalunga, O.; Lapi, A. *J. Org. Chem.* **2007**, *72*, 9582.
(43) A trace amount of an amine adduct of C_{70} produced by nucleophilic addition was observed in the reaction mixture, but it was minor compared to the C_{70} epoxides.

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Organic LETTERS

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Electrostatically Enhanced Thioureas

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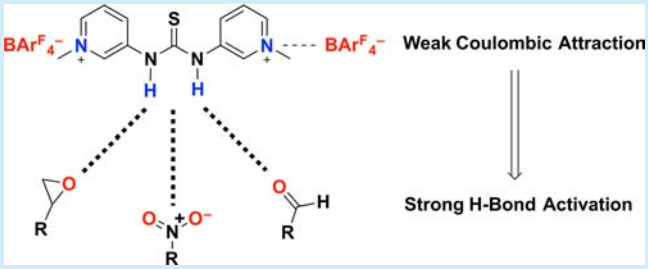
Supporting Information

ABSTRACT: A new class of readily prepared thiourea catalysts with one or more positively charged centers and no new hydrogen-bonding sites are exploited in several bond-forming reactions and are orders of magnitude more reactive than Schreiner's thiourea. These findings provide the basis for a new strategy for activating hydrogen-bond catalysts.



Small molecule metal-free hydrogen-bond catalysis has become an active and vibrant research area over the past two decades.[1] Numerous classes of compounds have been explored including binols,[2] silane diols,[3] squaramides,[1e,4] and α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs)[5] among others, but no species have received more attention than thioureas.[6] Of these, *N*,*N*′-bis(3,5-bis(trifluoromethyl)-phenyl)thiourea [(3,5-$(CF_3)_2C_6H_3NH)_2CS$], also known as Schreiner's thiourea,[7] occupies a privileged position because it is an especially effective catalyst leading to relatively rapid transformations. This has been attributed to its enhanced acidity due to the four electron-withdrawing trifluoromethyl groups[8] and weak C−H···S hydrogen bonds that are thought to play a factor in stabilizing the reactive *Z*,*Z*-conformer.[7b,c]

Cationic hydrogen bond donors such as amidinium,[9] ammonium,[10] guanidinium,[11] pyridinium,[12] and quinolinium[13] ions also have been extensively explored.[14] These species correspond to protonated neutral bases and consequently are more acidic than their corresponding conjugate bases. This may account for their enhanced reactivities, but conformational rigidity, changes in the binding site, and the potential use of an additional hydrogen bond are also important contributing effects. A different strategy for increasing the reactivity of neutral hydrogen bond catalysts, especially in nonpolar solvents where organic transformations of this sort are typically carried out, is to incorporate a charged center without introducing a new hydrogen bond site. A recent report by Berkessel et al. exploiting this novel approach to develop Coulombic anion-binding catalysts[15] and our observation that the catalytic ability of a phenol can be enhanced by orders of magnitude by the presence of a charged site[16] suggests that electrostatic enhancement of hydrogen-bond catalysts is a new general design strategy.[17]

To explore this hypothesis, thioureas with one and two *N*-methylpyridinium ion centers were prepared, and their reactivities in several different types of transformations were examined. These new catalysts were compared to *N*,*N*′-diphenylthiourea (**1**) and Schreiner's thiourea (**2**) (Figure 1) and are found to be orders of magnitude more reactive in nonpolar solvents.[18]

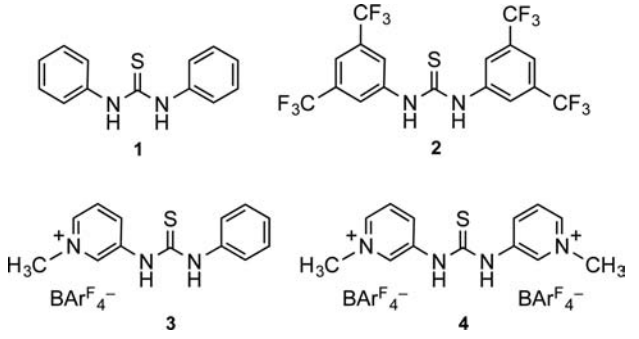


Figure 1. Thiourea catalysts employed in this work.

Mono- and di-*N*-methylpyridinium ions **3** and **4** were readily synthesized starting with commercially available 3-amino-pyridine (**5**) as illustrated in Figure 2. Thiophosgene was used to convert this amine into its isothiocyanate,[19] and this product was subsequently alkylated with methyl iodide to afford the corresponding pyridinium ion **7**. This key intermediate was reacted with aniline to afford the iodide salt of **3** (**3I**).

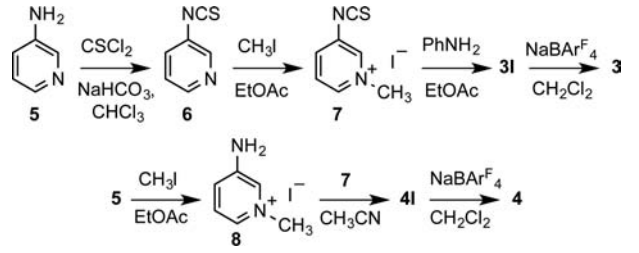


Figure 2. Synthetic routes for thioureas **3** and **4**.

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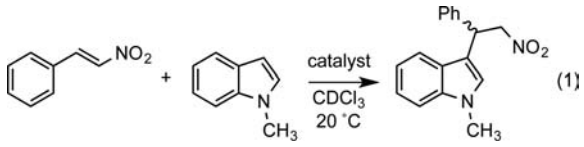
Alternatively, methylation of 3-aminopyridine occurs at the more nucleophilic ring nitrogen atom,[20] and the resulting pyridinium iodide **8** was reacted with **7** to yield the doubly charged thiourea derivative of **4** (**4I**). Both iodide salts have limited solubilities in weakly polar solvents and presumably form deactivating NH···I^- hydrogen bonds so they were converted to their tetrakis(3,5-bis(trifluoromethyl)phenyl)-borate (BAr^F_4) salts **3** and **4**. These metathesis reactions were readily accomplished by stirring **3I** or **4I** with $NaBAr^F_4$ in CH_2Cl_2.

To evaluate the catalytic activity of electrostatically enhanced thioureas **3** and **4**, the Friedel–Crafts alkylation of *trans*-*β*-nitrostyrene with *N*-methylindole was examined in $CDCl_3$ at room temperature (eq 1). This transformation was chosen



(1)

because the reaction rate has been observed to correlate with the acidity of hydrogen bond catalysts, whereas acetic acid does not promote this process.[21,22] Second-order rate constants were determined by monitoring the reaction via ^{1}H NMR spectroscopy, and the data are summarized in Table 1. Diphenylthiourea **1** is a poor catalyst in that it only speeds up the uncatalyzed process by a factor of 1.4, and more than a month is needed for half of the starting material to be converted to product. Schreiner's thiourea is 28 times more effective than **1**, but this transformation is still slow and has a half-life of 29 h. *N*-Methylpyridinium ion containing thioureas **3** and **4** are much more active than **2** and have half-lives of 5 h and 4 min, respectively. An acidic impurity in **3** or **4** acting as the active catalyst was discounted since 1 mol % of *p*-toluenesulfonic acid (*p*-TsOH) did not afford any observable product by ^{1}H NMR over 20 h. These results indicate that the one charged center in **3** is more effective than the four CF_3 groups in **2** by a factor of 7, and that the presence of two cationic sites affords an even more active catalyst that is 400 times more reactive.

Table 1. Kinetic Data for the Room-Temperature Friedel–Crafts Reaction of *trans*-*β*-Nitrostyrene with *N*-Methylindole

entry	cat.	mol %	solvent	k (M^{-1} h^{-1})	$t_{1/2}$ (h)	k_{rel}
1			$CDCl_3$	2.8×10^{-3}	1100	
2	**1**	10	$CDCl_3$	3.9×10^{-3}	820	0.035
3	**2**	10	$CDCl_3$	1.1×10^{-1}	29	1.0
4	**3**	10	$CDCl_3$	7.1×10^{-1}	4.5	6.5
5	**4**	10	$CDCl_3$	45	0.071 (4.3 m)	410
6	**4**	5	$CDCl_3$	11	0.29 (17 m)	
7	**4**	2.5	$CDCl_3$	9.1×10^{-1}	3.5	
8	**4**	1	$CDCl_3$	1.6×10^{-2}	200	
9	**4**	5	$C_6D_5CD_3$	14	0.23 (14 m)	
10	**4**	5	CD_2Cl_2	55	0.058 (3.5 m)	

Catalyst loading was explored for **4** (Table 1, entries 5–8), and as expected the Friedel–Crafts reaction rate increases with the amount of added catalyst. A linear dependence was not observed, but a straight line was obtained from a plot of the second-order rate constants versus the square of the catalyst concentrations (Figure 3). This suggests that the dimer of **4** is the active catalyst in this transformation, which is consistent with a previous report on thiourea catalysts.[23]

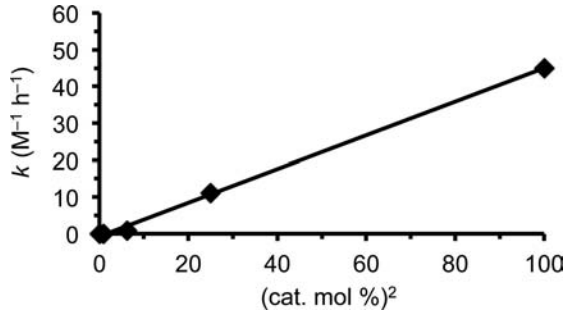
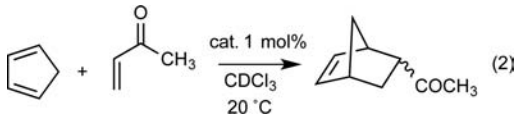


Figure 3. Linear least-squares fit of the second-order Friedel–Crafts rate constants vs (cat. %)^2; $k = 0.46(\text{cat. \%})^2 - 0.70$, $r^2 = 0.999$; Table 1, entries 5–8.

Carrying out the Friedel–Crafts alkylation in a few different solvents was also examined. Little impact was noted by switching from $CDCl_3$ to toluene-d_8, but a 5-fold increase was observed when the reaction was carried out in CD_2Cl_2. All three of these solvents have dielectric constants of less than 10, but the most polar one of these leads to the fastest transformation. This may be a reflection of the aggregation state of **4** in these solvents. In any case, the doubly charged thiourea salt is soluble in nonpolar media and displays excellent performance characteristics.

We next turned our attention to the Diels–Alder reaction between cyclopentadiene and methyl vinyl ketone (eq 2), in



(2)

part because Schreiner's thiourea previously has been reported to catalyze this transformation.[7b] At room temperature in $CDCl_3$ with 1 mol % of the catalyst, **2** accelerates this cycloaddition by less than a factor of 1.5 relative to the uncatalyzed process (Table 2). In contrast, the charge

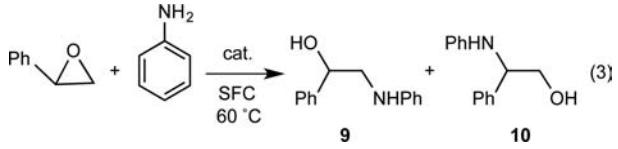
Table 2. Diels–Alder Kinetic Data

entry	cat.	k (M^{-1} h^{-1})	$t_{1/2}$	k_{rel}[a]	*endo*/*exo*
1		0.72	2.2 h		71:29
2	**2**	1.0	1.6 h	1.0	81:19
3	**3**	7.3	13 m	24	88:12
4	**4**	28	3.5 m	97	88:12

[a]Corrected for the rate of the uncatalyzed reaction.

containing thioureas **3** and **4** enhance the background-corrected rates by one and 2 orders of magnitude, respectively. The half-life for the latter transformation is also under 4 min. As for the selectivity, the major product is the *endo* isomer in each instance as expected. Its relative contribution, however, increases from 71% for the uncatalyzed process to 81% with Schreiner's thiourea and 88% when either **3** or **4** is used.

Lastly, the ring-opening aminolysis of styrene oxide with aniline was explored under solvent free conditions (SFC, eq 3).



(3)

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Product formation was monitored for each transformation and zero and first-order processes were found to fit the data depending upon which catalyst, if any, was used. Consequently, qualitative results are reported (Table 3), but it is apparent that

Table 3. Catalytic Results for the Solvent Free Aminolysis of Styrene Oxide with Aniline

entry	cat.	mol %	t (h)	% conv	9/10
1			2.33	5.8	38:62
2	**2**	1	2.33	39	35:65
3	3	1	2.33	55	13:87
4	**4**	1	0.5	93	10:90
5	**4**	0.1	0.5	53	10:90

3 and **4** are much more effective catalysts than **2**. That is, significantly higher selectivities and greater conversions are observed (e.g., **4** gives a 93% conversion in 0.5 h whereas only 39% of the starting material has reacted in 2.33 h with **2**). The dicharged thiourea was also found to outperform **2** even when 10 times less was used (i.e., 0.1 mol % of **4** led to a 53% conversion in 0.5 h whereas 39% of the reactant went on to product in 2.33 h with 1 mol % of **2**).[24]

Charged substituents are not especially effective in enhancing acidities and lowering pK_a values in polar solvents.[16,25] Based upon the 2.4 and 1.3 pK_a unit acidifying effect of a *m*-CF_3 group on phenol and *N*,*N*′-diphenylthiourea,[8,26] respectively, and the recently measured 5.5 pK_a difference between phenol and 3-hydroxy-*N*-octylpyrinium ion[16] all in dimethyl sulfoxide (DMSO), one can estimate that pK_a(**3**) = 10.4.[27] This value is essentially the same as incorporating two meta trifluoromethyl groups into **1** and consequently **3** is ∼2 pK_a units less acidic than Schreiner's thiourea.[8] In nonpolar solvents, a reversal in their relative acidities undoubtedly takes place. As a result, incorporation of a single positively charged center into a thiourea without adding a new hydrogen bond site was found to be catalytically more effective than the four electron-withdrawing trifluoromethyl groups in Schreiner's thiourea.[28] Addition of a second ionic center presumably enhances the DMSO acidity of **4** so that it is similar to **2** but leads to rate accelerations of $\sim 10^2$–10^3. These results represent a new strategy for activating hydrogen bond catalysts, and a potential means for improving stereoselectivities since lower temperatures typically can be employed when transformations occur more rapidly at room temperature.[29]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03213.

Experimental procedures, NMR spectra, and reaction data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (b) Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Noto, R. *Chem. Soc. Rev.* **2012**, *41*, 2406. (c) Wende, R. C.; Schreiner, P. R. *Green Chem.* **2012**, *14*, 1821. (d) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nat. Chem.* **2012**, *4*, 603. (e) Auvil, T. J.; Schafer, A. G.; Mattson, A. E. *Eur. J. Org. Chem.* **2014**, *2014*, 2633.

(2) (a) Yu, S.; Pu, L. *Tetrahedron* **2015**, *71*, 745. (b) Li, G.; Liu, F.; Wu, M. *ARKIVOC* **2015**, *6*, 140.

(3) (a) Tran, N. T.; Wilson, S. O.; Franz, A. K. *Org. Lett.* **2012**, *14*, 186. (b) Schafer, A. G.; Wieting, J. M.; Fisher, T. J.; Mattson, A. E. *Angew. Chem., Int. Ed.* **2013**, *52*, 11321. (c) Wieting, J. M.; Fisher, T. J.; Schafer, A. G.; Visco, M. D.; Gallucci, J. C.; Mattson, A. E. *Eur. J. Org. Chem.* **2015**, *2015*, 525.

(4) (a) Wurm, F. R.; Klok, H.-A. *Chem. Soc. Rev.* **2013**, *42*, 8220. (b) Tsakos, M.; Kokotos, C. G. *Tetrahedron* **2013**, *69*, 10199. (c) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal.* **2015**, *357*, 253.

(5) (a) Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92. (b) Pellissier, H. *Tetrahedron* **2008**, *64*, 10279. (c) Gratzer, K.; Gururaja, G. N.; Waser, M. *Eur. J. Org. Chem.* **2013**, *2013*, 4471.

(6) (a) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187. (b) Kotke, M.; Schreiner, P. R. In *Hydrogen Bonding in Organic Synthesis*; Pihko, P. M., Ed.; Wiley; New York, 2009; p 141. (c) Hof, K.; Lippert, M.; Schreiner, P. R. In *Asymmetric Organocatalysis, Science of Synthesis*; Maruoka, K., Ed.; Thieme: Stuttgart, Germany, 2012; Vol. 2, p 297. (d) Takemoto, Y.; Inokuma, T. In *Asymmetric Synthesis II*; Christmann, M., Bräse, S., Eds.; Wiley: New York, 2012; p 233. (e) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2013**, *11*, 7051. (f) Jakab, G.; Schreiner, P. R. In *Comprehensive Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley; New York, 2013; Vol. 2, p 315. (g) Jiang, J.; Gong, L.-Z. In *Catalytic Cascade Reactions*; Xu, P.-F., Wang, W., Eds.; Wiley; New York, 2014; p 53. (h) Fang, X.; Wang, C.-J. *Chem. Commun.* **2015**, *51*, 1185.

(7) (a) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217. (b) Wittkopp, A.; Schreiner, P. R. *Chem. - Eur. J.* **2003**, *9*, 407. (c) Lippert, K. M.; Hof, K.; Gerbig, D.; Ley, D.; Hausmann, H.; Guenther, S.; Schreiner, P. R. *Eur. J. Org. Chem.* **2012**, *2012*, 5919.

(8) Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. *Org. Lett.* **2012**, *14*, 1724.

(9) (a) Schuster, T.; Kurz, M.; Göbel, M. W. *J. Org. Chem.* **2000**, *65*, 1697. (b) Akalay, D.; Dürner, G.; Bats, J. W.; Bolte, M.; Göbel, M. W. *J. Org. Chem.* **2007**, *72*, 5618.

(10) Huang, J.; Corey, E. J. *Org. Lett.* **2004**, *6*, 5027.

(11) (a) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157. (b) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454. (c) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044. (d) Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 9228. (e) Leow, D.; Tan, C.-H. *Synlett* **2010**, 1589. (f) Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 5062. (g) Selig, P. *Synthesis* **2013**, *45*, 703.

(12) (a) Takenaka, N.; Sarangthem, R. S.; Seerla, S. K. *Org. Lett.* **2007**, *9*, 2819. (b) Takenaka, N.; Chen, J.; Captain, B.; Sarangthem, R. S.; Chandrakumar, A. *J. Am. Chem. Soc.* **2010**, *132*, 4536.

(13) (a) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418–3419. (b) Singh, A.; Yoder, R. A.; Shen, B.; Johnston, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 3466. (c) Singh, A.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 5866. (d) Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 16464.

(14) Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1758.

(15) Berkessel, A.; Das, S.; Pekel, D.; Neudörfl, J.-M. *Angew. Chem., Int. Ed.* **2014**, *53*, 11660.

DOI: 10.1021/acs.orglett.5b03213
Org. Lett. 2016, 18, 188–191

(16) Samet, M.; Buhle, J.; Zhou, Y.; Kass, S. R. *J. Am. Chem. Soc.* **2015**, *137*, 4678.
(17) For a related organometallic example, see: (a) Scherer, A.; Mukherjee, T.; Hampel, F.; Gladysz, J. A. *Organometallics* **2014**, *33*, 6709. (b) Mukherjee, T.; Ganzmann, C.; Bhuvanesh, N.; Gladysz, J. A. *Organometallics* **2014**, *33*, 6723.
(18) Fan, Y.; Samet, M.; Kass, S. R. U.S. provisional patent serial no. 62/169,371, filed Jun 15, 2015.
(19) Luo, R.; Laitinen, T.; Teng, L.; Nevalainen, T.; Lahtela-Kakkonen, M.; Zheng, B.; Wang, H.; Poso, A.; Zhang, X. *Lett. Drug Des. Discovery* **2013**, *10*, 640.
(20) Huang, S.; Wong, J. C. S.; Leung, A. K. C.; Chan, Y. M.; Wong, L.; Fernendez, M. R.; Miller, A. K.; Wu, W. *Tetrahedron Lett.* **2009**, *50*, 5018.
(21) Shokri, A.; Wang, X.-B.; Kass, S. R. *J. Am. Chem. Soc.* **2013**, *135*, 9525.
(22) Samet, M.; Kass, S. R. *J. Org. Chem.* **2015**, *80*, 7727.
(23) Rho, H. S.; Oh, S. H.; Lee, J. W.; Lee, J. Y.; Chin, J.; Song, C. E. *Chem. Commun.* **2008**, 1208.
(24) (Piperidinomethyl)polystyrene deprotonates **4** in $CDCl_3$, but the presence of an acid impurity being the active catalyst was addressed. Control experiments with acetic acid (ref 21) and *p*-TsOH reveal that these Brønsted acids are not as active as **4**. In the latter case, 0.1 mol % leads to a 34% conversion in 0.5 h.
(25) Bordwell, F. G. et al. Bordwell pK_a Table. University of Wisconsin—Madison, http://www.chem.wisc.edu/areas/reich/pkatable.
(26) Bordwell, F. G.; Cheng, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 1736.
(27) This value was obtained by solving the following equation: $1.3/2.4 = x/5.5$ and subtracting the result from the acidity of **2** (i.e., 13.4 as given in ref 8).
(28) Given the differences in activity between **3** and **4**, it seems unlikely that their methyl groups are serving as activating hydrogen bond donors in the reactions that were examined. Carbon−hydrogen bond donors acting as catalysts, however, recently were reported in a noteworthy contribution. See: Shirakawa, S.; Liu, S.; Kaneko, S.; Kumatabara, Y.; Fukuda, A.; Omagari, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 15767.
(29) Enhanced selectivities also often correlate with reactivity. For example, see: (a) Jensen, K. H.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 4748. (b) Jensen, K. H.; Sigman, M. S. *J. Org. Chem.* **2010**, *75*, 7194. (c) Li, X.; Deng, H.; Zhang, B.; Li, J.; Zhang, L.; Luo, S.; Cheng, J.-P. *Chem. - Eur. J.* **2010**, *16*, 450.

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Organic LETTERS

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Rh(III)-Catalyzed [4 + 2] Annulation of Indoles with Diazo Compounds: Access to Pyrimido[1,6-*a*]indole-1(2*H*)-ones

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Supporting Information

ABSTRACT: The Rh(III)-catalyzed regioselective C2−H bond carbenoid insertion/cyclization of *N*-amidoindoles with *α*-acyl diazo compounds has been developed. This method provides a novel approach to 2*H*-pyrimido[1,6-*a*]indol-1-ones with a broad range of functional group tolerance. The synthetic utilities of the approach are demonstrated by versatile chemical transformations.

Chelation-assisted C−H bond functionalizations represent an innovative strategy for the atom-economic construction of C−C and C−heteroatom bonds.[1] Among the various methodologies, rhodium-catalyzed cross-coupling of C−H bonds with carbenoids has attracted growing concerns because rhodium salts belong to particularly promising catalysts for this transformation.[2] Over the past decades, much progress has been achieved for carbenoid insertion into Csp^3-H bond,[3] and intramolecular aryl C−H bond coupling has also been well-established,[4] but highly regioselective cross-coupling of aryl C−H bonds with carbenoids has rarely been reported.[5] To date, the pioneering report by Yu in 2012 first described that an oxime group could induce an *ortho* C_{phenyl}−H bond cross-coupling reaction with diazomalonates in the presence of Rh(III) catalyst.[6] Since then, Rovis, Li, Glorius, and Chang further took advantage of the directing character of *O*-pivaloyl hydroxamic acid,[7] ammonium salts,[8] *N*-oxides,[9] and others[10] to enable the Rh-catalyzed *ortho* C_{phenyl}−H bond functionalization with diazo compounds for assembling nitrogen-containing heterocycles. However, despite significant progress in this field, existing reactions are generally limited to the phenyl C−H bond carbenoid functionalization. Therefore, developing transition metal-catalyzed site-selective heteroaryl C−H bond cross-coupling with carbenoids still remains challenging and important for exploring the potential synthetic access to more complex molecules.

However, the indole framework, especially for the 2*H*-pyrimido[1,6-*a*]indol-1-one (HPIO) is a privileged core structure in many bioactive molecules, natural products, and material chemistry (Figure 1),[11] and these important organics are most likely derived from the indole C2−H alkenylation/cyclization cascade. However, in comparison with the C2 position of indole, the C3 position is an inherently nucleophilic reactive site, and the cross-coupling of indoles with carbenoids could easily occur at the C3 position.[12] Nevertheless, heteroatom-directed cyclometalation strategy provides concise access to regioselective indole C2−H bond functionalization. In this regard, Schipper, Yoshikai, Kanai, and our group successively reported that N-substituted *N*,*N*-dimethylaminocarbonyl,[13]

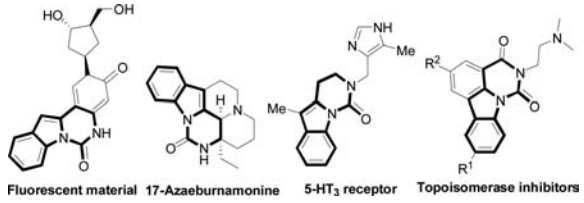
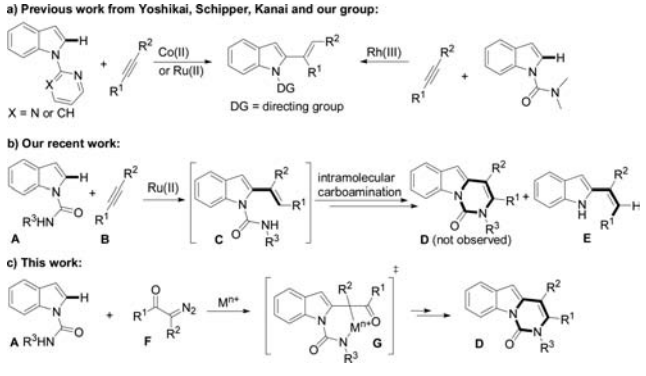


Figure 1. Selected examples of functional and bioactive HPIOs.

pyridyl,[14] or pyrimidyl group[15] from indoles could efficiently enhance intermolecular C2-alkenylation with alkynes in the presence of Rh(III), Co(II), and Ru(II) catalysts, respectively (Scheme 1a). In view of the importance of 2*H*-pyrimido[1,6-*a*]indol-1-ones in bioorganic and medicinal chemistry, we recently attempted to employ *N*-alkylaminocarbonyl as a directing group to produce C2-alkenylated indole intermediates **C** through the reductive cross-coupling with alkynes **B**, and followed by intramolecular carboamination and oxidation to construct HPIOs (**D**), but we ultimately obtained only the

Scheme 1. Transition Metal-Catalyzed Indole C2−H Alkenylation Strategies



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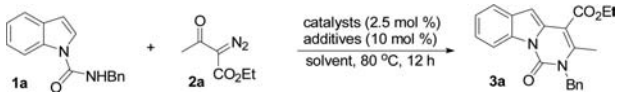
unexpected (*Z*)-alkenylated indole **E**, in which *N*-alkylaminocarbonyl group was removed via a one-pot process, and no cyclization product **D** was observed (Scheme 1b).[16] In this letter, we tried to switch the alkyne coupling partner (**B**) to the α-acyl diazo compound (**F**) and envisioned that a carboamido group could assist the formation of metallocyclic intermediate **G** through a transition metal-catalyzed C−H activation, intermolecular carbenoid insertion into indole C2−H bond and metal carbene migratory insertion process, then underwent an intramolecular cyclization reaction to furnish 2*H*-pyrimido[1,6-*a*]indol-1-ones (**D**) (Scheme 1c).

Initially, we performed the indole C2−H bond carbenoid insertion/cyclization cascade with α-acyldiazoacetate (**2a**) to screen various metal catalysts such as Ir(III), Co(III), Ru(II) salts, etc., in the presence of $AgClO_4$ (10 mol %) in 1,2-dichloroethane (DCE) at 80 °C under an Ar atmosphere for 12 h (Table 1, entries 1−7). To our delight, we soon found that dimer

Table 1. Optimization of the Reaction Parameters[a]



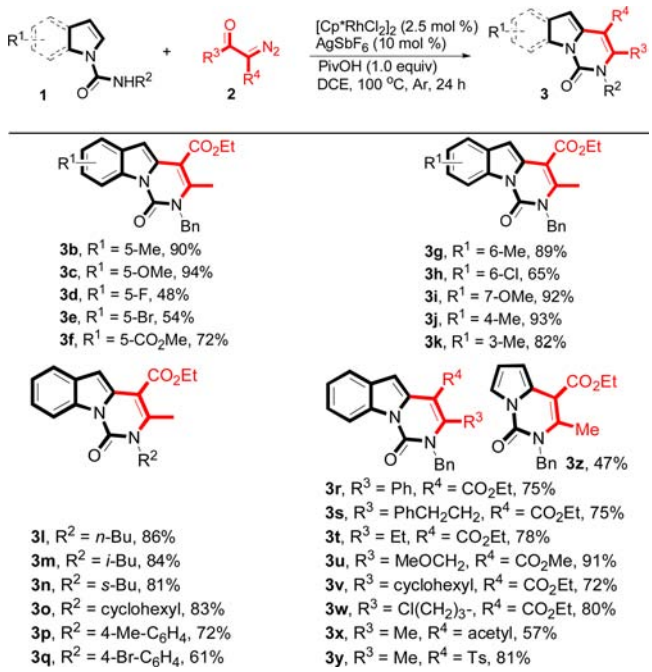
entry	catalysts	additives	solvent	yield (%)[b]
1	$[Cp^*IrCl_2]_2$	$AgClO_4$	DCE	17
2	$CoCp^*(CO)I_2$	$AgClO_4$	DCE	0
3	$[Ru(p\text{-cymene})Cl_2]$	$AgClO_4$	DCE	0
4	$Pd(OAc)_2$	$AgClO_4$	DCE	0
5	$RhCl_3$	$AgClO_4$	DCE	0
6	$Rh_2(C_8H_{16})_2Cl_2$	$AgClO_4$	DCE	0
7	$[Cp^*RhCl_2]_2$	$AgClO_4$	DCE	52
8	$[Cp^*RhCl_2]_2$	$AgBF_4$	DCE	55
9	$[Cp^*RhCl_2]_2$	$AgNTf_2$	DCE	62
10	$[Cp^*RhCl_2]_2$	AgOAc	DCE	58
11	$[Cp^*RhCl_2]_2$	$AgSbF_6$	DCE	64
12	$[Cp^*RhCl_2]_2$	$AgSbF_6$	CH_3CN	17
13	$[Cp^*RhCl_2]_2$	$AgSbF_6$	toluene	trace
14	$[Cp^*RhCl_2]_2$	$AgSbF_6$	DMSO	22
15	$[Cp^*RhCl_2]_2$	$AgSbF_6$	DCE	66[c]
16	$[Cp^*RhCl_2]_2$	$AgSbF_6$	DCE	72[c,d]
17	$[Cp^*RhCl_2]_2$	$AgSbF_6$	DCE	67[c,d,e]
18	$[Cp^*RhCl_2]_2$	$AgSbF_6$	DCE	92[c,d,f]
19	$[Cp^*RhCl_2]_2$	$AgSbF_6$	DCE	83[c,d,f,g]

[a]Unless otherwise noted, all the reactions were carried out using indole (**1a**) (0.10 mmol) and diazo compound (**2a**) (0.20 mmol) with catalysts (2.5 mol %) in the presence of silver salts additives (10 mol %) in solvent (2.0 mL) at 80 °C for 12 h under Ar in a sealed reaction tube. Followed by flash chromatography on SiO_2. [b]Isolated yield. [c]The reaction time is 24 h. [d]The reaction temperature is 100 °C. [e]1.0 equiv of AcOH was added. [f]1.0 equiv of PivOH was added. [g]0.5 mmol of **1a** and 1.0 mmol of **2a** was used.

catalyst $[Cp^*IrCl_2]_2$ and $[Cp^*RhCl_2]_2$ could give us the desired HPIO (**3a**) in 17% and 52% yields, respectively (entries 1 and 7). Subsequently, we continued to evaluate various additives and solvents for further improving the cross-coupling conversion using $[Cp^*RhCl_2]_2$ as catalyst. Among them, employing $AgSbF_6$ as additive could moderately increase yield of **3a** from 52% to 64% (compare entries 7−10 with 11), and DCE proved to be the optimal solvent for this transformation (compare entries 12−14 with 11). Moreover, a slight improvement of the reaction (72% yield of **3a**) was also achieved by extending the reaction time to 24 h and increasing the reaction temperature to 100 °C (entries 11 and 15 vs 16). Finally, considering that a proper proton source, which probably plays a role of Bronsted acid to activate the carbonyl group from α-acyldiazoacetate, several proton-donor additives including pivalic acid (PivOH), acetic acid, isopropyl alcohol, and water were investigated in the Rh(III)/$AgSbF_6$ system, and we pleasingly found PivOH could afford the best yield of **3a** (92% yield, entries 17 vs 18). By the way, when large-scale reaction was performed, we could still obtain 83% yield of **3a** (entry 19).

With an optimized catalytic system in hand, we then turned our attention to explore the generality of the current procedure by testing various *N*-benzylaminocarbonyl indoles (**1**) with 2-diazo-3-oxo-butyric acid ethyl ester (**2a**). As shown in Scheme 2,

Scheme 2. Substrate Scope[a,b]



[a]All the reactions were carried out using indole (**1**) (0.10 mmol) and diazo compound (**2**) (0.20 mmol) with $[Cp^*RhCl_2]_2$ (2.5 mol %) in the presence of $AgSbF_6$ (10 mol %) and PivOH (1.0 equiv) in DCE (2.0 mL) at 100 °C for 24 h under Ar in a sealed reaction tube. Followed by flash chromatography on SiO_2. [b]Isolated yield.

the reactivity of substituted indoles (**2**) was obviously dependent on the electronic properties of substitutents. 5-Substitution on the indole ring with electron-donating group (Me, MeO) afforded excellent yields of **3b** (90% yield) and **3c** (94% yield). In contrast, electron-withdrawing halogen substituents and ethoxylcarbonyl group significantly decreased the reaction conversion and produced moderate to good yield of **3d**−**3f** (48−72% yields). Notably, this reaction protocol could also smoothly convert 3-, 4-, 6-, or 7-substituted indoles to the desired HPIOs with excellent yields (65−93%), regardless of whether electron-deficient or electron-rich substituents were introduced into the indole rings (**3g**−**3k**). Moreover, *N*-alkylaminocarbonyl indoles (**3l**−**3o**) and *N*-phenylaminocarbonyl indoles (**3p** and **3q**) could also exhibit good reactivity with 61−86% yields, in which no significant effect of steric hindrance from *N*-substituted moiety was observed in this transformation.

Subsequently, we further investigated the scope of indole C2−H carbenoid insertion/cyclization cascade by employing differ-

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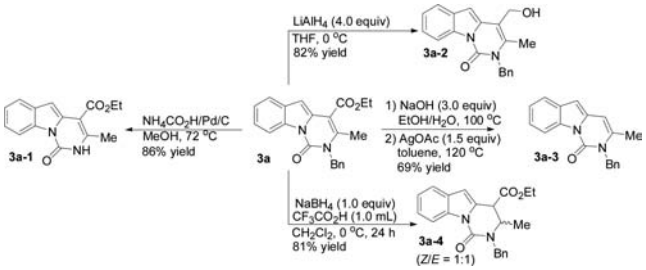
ent α-acyldiazo compounds. It was found that this protocol tolerated a wide range of diazo compounds. Among them, α-alkylacyl, α-arylacyl, and α-methyloxymethylacyl substituted diazoacetetes could easily enable assembly of the corresponding HPIOs with good to excellent yields (**3r**−**3w**). Moreover, when α-acyl diazoketone was employed as the substrate in this reaction system, the desired 4-acetyl-2-benzyl-3-methyl HPIO (**3x**) could be obtained with 57% yield. More importantly, α-acyl diazosulfone could also be rapidly converted to 4-sulfonyl-containing HPIO (**3y**) in 81% yield. Finally, we also found when *N*-benzylaminocarbonyl pyrrole was applied to the carbenoid insertion with diazo compound **1a**, the reaction still worked and produced the corresponding 2*H*-pyrrolo[1,2-*c*]pyrimidin-1-one (**3z**) in 47% yield. By the way, the structure of **3f** was already unambiguously assigned by its single crystal X-ray analysis (see SI for more details).

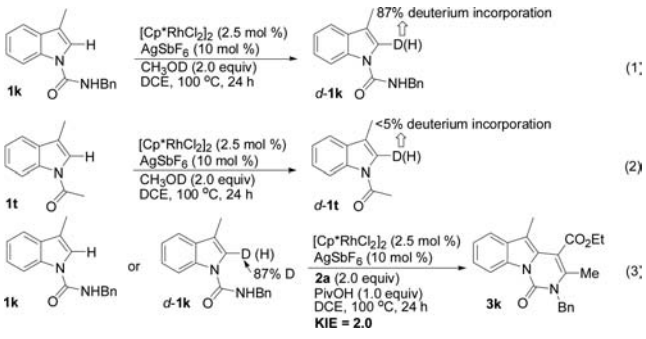
Finally, we converted **3a** to the corresponding free N−H **3a-1** (86% yield), alcohol **3a-2** (82% yield), and the decarbonylated HPIO **3a-3** (69% overall yield) through reduction, hydrolysis, and a decarbonylation process, respectively. Meanwhile, the carbon−carbon double bond in the pyrimidone ring could also be selectively reduced to produce 3,4-dihydro-2*H*-pyrimido[1,6-*a*]indol-1-one **3a-4** in 81% yield (Scheme 3). These HPIO derivatives could be further used for constructing more complex organic molecules.

Scheme 3. Synthetic Application for This Transformation



To investigate the possible mechanism of this transformation, the H/D exchane of *N*-benzylaminocarbonyl indole **1a** was conducted in Rh(III)/CH_3OD system for 24 h in the absence of diazo compounds, and 87% deuterium incorporation at the indole C2-position was observed (eq 1 in Scheme 4). On the contrary, no H/D exchange of *N*-propionyl indole **1t** was observed under the same conditions (eq 2 in Scheme 4). This result implied that amido moiety played a key role of chelation in promoting the indole C2−H bond cleavage. Subsequently, the intermolecular isotope effect (K_H/K_D = 2.0) further indicated

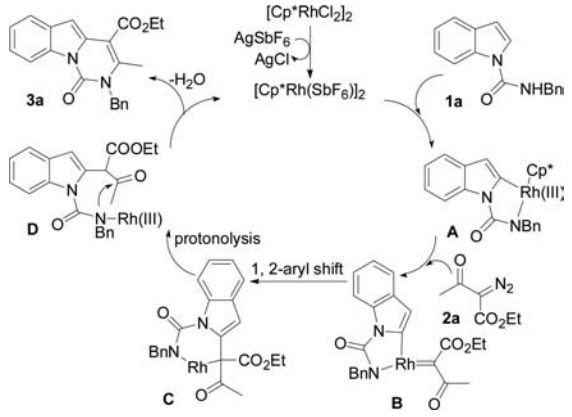
Scheme 4. Preliminary Mechanistic Studies



that C2−H bond-breaking was possibly involved in the rate-limiting step of this transformation (eq 3 in Scheme 4) (see SI for more details).

On the basis of the above-mentioned results, a plausible mechanism is proposed in Scheme 5. The initial *N*-coordination

Scheme 5. Proposed Mechanism



of substrate **1a** to Rh(III) catalyst followed by C2−H bond activation afforded rhodacycle intermediate **A** via a concerted metalation/deprotonation (CMD) process.[17] Subsequently, the coordination of diazo compound **2a** to Rh(III) species **A** was followed by the denitrogenation to generate Rh-carbene species **B**, which would undergo 1,1-aryl migratory insertion to form rhodacycle intermediate **C**.[18] Finally, the protonlysis/intramolecular cyclization of **C** furnished **3a** with regeneration of Rh(III) catalyst.[19]

In conclusion, we have developed a novel Rh(III)-catalyzed regioselective indole C2−H bond carbenoid insertion/cyclization with α-acyl diazocompounds for rapid assembly of 2*H*-pyrimido[1,6-*a*]indol-1-ones. This method tolerates a wide range of readily available indoles and diazo compounds. Further synthetic applications to bioactive molecules are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03231.

Detailed experimental procedures, characterization data, copies of ^{1}H NMR and ^{13}C NMR spectra for all isolated compounds (PDF)

Crystallographic data for **3f** (CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For selected reviews, see: (a) Ackermann, C. *Acc. Chem. Res.* **2014**, *47*, 281. (b) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (c) Huang, Z.; Lim, H. N.; Mo, F.; Young, M. C.; Dong, G. *Chem. Soc. Rev.* **2015**, *44*, 7764. (d) Shen, C.; Zhang, P.; Sun, Q.; Bai, S.; Hor, T. S. A.; Liu, X. *Chem. Soc. Rev.* **2015**, *44*, 291. (e) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107. (f) Schranck, J.; Tlili, A.; Beller, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 9426. (g) Zhang, F.; Spring, D. R. *Chem. Soc. Rev.* **2014**, *43*, 6906. (h) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369.

(2) For selected reviews, see: (a) Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236. (b) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814. (c) Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011**, *40*, 1857. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (e) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704.

(3) For selected reviews, see: (a) Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011**, *40*, 1857. (b) Davies, H. M. L.; Lian, Y. *Acc. Chem. Res.* **2012**, *45*, 923. For selected examples, see: (c) Thu, H. Y.; Tong, G. S. M.; Huang, J. S.; Chan, S. L. F.; Deng, Q. H.; Che, C. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 9747. (d) Qin, C.; Davies, H. M. L. *J. Am. Chem. Soc.* **2014**, *136*, 9792. (e) Guptill, D. M.; Davies, H. M. L. *J. Am. Chem. Soc.* **2014**, *136*, 17718.

(4) For selected examples, see: (a) Ma, B.; Chen, F. L.; Xu, X. Y.; Zhang, Y. N.; Hu, L. H. *Adv. Synth. Catal.* **2014**, *356*, 416. (b) Wang, H. L.; Wang, G. W.; Yang, S. D. *Chem. Commun.* **2011**, *47*, 11336. (c) Hashimoto, T.; Yamamoto, K.; Maruoka, K. *Chem. Commun.* **2014**, *50*, 3220. (d) Park, C. P.; Nagle, A.; Yoon, C. H.; Chen, C.; Jung, K. W. *J. Org. Chem.* **2009**, *74*, 6231.

(5) (a) Zhao, X.; Wu, G.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 3296. (b) Yu, Z.; Ma, B.; Chen, M.; Wu, H. H.; Liu, L.; Zhang, J. *J. Am. Chem. Soc.* **2014**, *136*, 6904.

(6) Chan, W. W.; Lo, S. F.; Zhou, Z.; Yu, W. Y. *J. Am. Chem. Soc.* **2012**, *134*, 13565.

(7) (a) Hyster, T. K.; Ruhl, K. E.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 5364. (b) Ye, B.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 7896.

(8) Yu, S.; Liu, S.; Lan, Y.; Wan, B.; Li, X. *J. Am. Chem. Soc.* **2015**, *137*, 1623.

(9) Jeong, J.; Patel, P.; Hwang, H.; Chang, S. *Org. Lett.* **2014**, *16*, 4598.

(10) For selected examples, see: (a) Yu, X.; Yu, S.; Xiao, J.; Wan, B.; Li, X. *J. Org. Chem.* **2013**, *78*, 5444. (b) Xia, Y.; Liu, Z.; Feng, S.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2015**, *80*, 223. (c) Li, X. G.; Sun, M.; Liu, K.; Jin, Q.; Liu, P. N. *Chem. Commun.* **2015**, *51*, 2380. (d) Hu, F.; Xia, Y.; Ye, F.; Liu, Z.; Ma, C.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 1364. (e) Zhao, D.; Kim, J. H.; Stegemann, L.; Strassert, C. A.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 4508. (f) Kim, J. H.; Gensch, T.; Zhao, D.; Stegemann, L.; Strassert, C. A.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 10975.

(11) (a) Mizuta, M.; Seio, K.; Miyata, K.; Sekine, M. *J. Org. Chem.* **2007**, *72*, 5046. (b) Kamata, J.; Okada, T.; Kotake, Y.; Niijima, J.; Nakamura, K.; Uenaka, T.; Yamaguchi, A.; Tsukahara, K.; Nagasu, T.; Koyanagi, N.; Kitoh, K.; Yoshimatsu, K.; Yoshino, H.; Sugumi, H. *Chem. Pharm. Bull.* **2004**, *52*, 1071. (c) Bandurco, V. T.; Wong, E. M.; Levine, S. D.; Zoltan, G.; Hajos, Z. G. *J. Med. Chem.* **1981**, *24*, 1455. (d) Wright, W. B., Jr.; Brabander, H. J. *J. Med. Chem.* **1968**, *11*, 1164. (e) Hammer, H.; Winterfeldt, E. *Tetrahedron* **1981**, *37*, 3609.

(12) For selected examples, see: (a) Muthusamy, S.; Gunanathan, C.; Babu, S. R.; Suresh, E.; Dastidar, P. *Chem. Commun.* **2002**, 824. (b) Qiu, H.; Li, M.; Jiang, L. Q.; Lv, F. P.; Zan, L.; Zhai, C. W.; Doyle, M. P.; Hu, W. H. *Nat. Chem.* **2012**, *4*, 733. (c) Chen, D. F.; Zhao, F.; Hu, Y.; Gong, L. Z. *Angew. Chem., Int. Ed.* **2014**, *53*, 10763. (d) Xing, D.; Jing, C.; Li, X.; Qiu, H.; Hu, W. *Org. Lett.* **2013**, *15*, 3578. (e) Du, Z.; Xing, Y.; Lu, P.; Wang, Y. *Org. Lett.* **2015**, *17*, 1192.

(13) (a) Schipper, D. J.; Hutchinson, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6910. (b) Ikemoto, H.; Yoshino, T.; Sakata, K.; Matsunaga, S.; Kanai, M. *J. Am. Chem. Soc.* **2014**, *136*, 5424.

(14) Liang, L.; Fu, S.; Lin, D.; Zhang, X. Q.; Deng, Y.; Jiang, H.; Zeng, W. *J. Org. Chem.* **2014**, *79*, 9472.

(15) Ding, Z.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2012**, *57*, 4698.

(16) Zhang, W.; Wei, J.; Fu, S.; Lin, D.; Jiang, H.; Zeng, W. *Org. Lett.* **2015**, *17*, 1349.

(17) (a) Davies, D. L.; Donald, S. M. A.; Al-Duaij, O.; Macgregor, S. A.; Pölleth, M. *J. Am. Chem. Soc.* **2006**, *128*, 4210. (b) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118.

(18) (a) Chen, X.; Xie, Y.; Xiao, X.; Li, G.; Deng, Y.; Jiang, H.; Zeng, W. *Chem. Commun.* **2015**, *51*, 15328. (b) Cheng, Y.; Bolm, C. *Angew. Chem., Int. Ed.* **2015**, *54*, 12349. (c) Zhou, B.; Chen, Z.; Yang, Y.; Ai, W.; Tang, H.; Wu, Y.; Zhu, W.; Li, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 12121. (d) Zhang, S.; Jiang, C.; Wu, J.; Liu, X.; Li, Q.; Huang, Z.; Li, D.; Wang, H. *Chem. Commun.* **2015**, *51*, 10240. (e) Shi, J.; Yan, Y.; Li, Q.; Xu, H. E.; Yi, W. *Chem. Commun.* **2014**, *50*, 6483.

(19) For selected examples, see: (a) Shi, Z.; Koester, D. C.; Boultadakis-Arapinis, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 12204. (b) Shi, L.; Yu, K.; Wang, B. *Chem. Commun.* **2015**, *51*, 17277. (c) Cheng, Y.; Bolm, C. *Angew. Chem., Int. Ed.* **2015**, *54*, 12349.

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Organic LETTERS

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Multicomponent Coupling Cyclization Access to Cinnolines via in Situ Generated Diazene with Arynes, and α-Bromo Ketones

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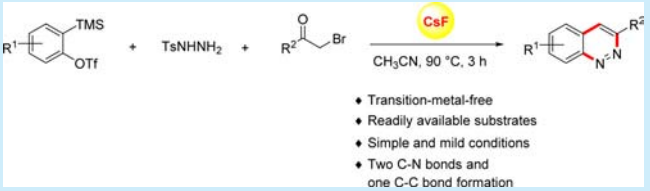
Supporting Information

ABSTRACT: A transition-metal-free multicomponent coupling cyclization reaction was explored involving arynes, tosylhydrazine, and α-bromo ketones. The reaction proceeds via a formal [2 + 2 + 2] cycloaddition, giving access to cinnoline derivatives in moderate yields under mild conditions. Three chemical bonds were formed—two C−N bonds and one C−C bond—in a single step.



In the past decades, arynes have emerged as powerful synthons widely used in the synthesis of heterocycles and complex natural products.[1] This is mainly because of the introduction of 2-(trimethylsilyl)aryl triflates as aryne precursors, which allow arynes to be generated under mild and easily controlled conditions, such as treatment with fluoride.[2] Arynes can also proceed to various chemical reactions, including nucleophilic addition,[3] cycloaddition,[4] annulation,[5] coupling,[6] insertion,[7] and others.[8] When transition metals, such as palladium and nickel, were introduced into benzyne chemistry, many unprecedented transformations (such as [2 + 2 + 2] cycloaddition) were quickly developed.[9]

Cinnoline is an important nitrogen-containing heterocyclic compound, and its derivatives exhibit widespread potent biological and pharmaceutical activities, such as inhibitory activity toward CSF-1R, inhibited ulceration, anti-inflammatory, antitumor, and anticancer activity (Figure 1).[10]

As cinnoline analogues exhibit superior properties, there are various approaches for the synthesis of cinnolines.[11] In recent years, Ge and co-workers reported distinguished work for the synthesis of cinnolines by copper-catalyzed aerobic dehydrogenative cyclization (Scheme 1a).[12] In addition, the You group developed a general route to cinnolines through the rhodium-catalyzed oxidative C−H activation/cyclization reaction (Scheme 1b).[13] Furthermore, Willis and co-workers exploited a copper-catalyzed tandem C−N bond formation reaction for the efficient synthesis of functionalized cinnolines (Scheme 1c).[14] More recently, Reddy and co-workers developed a directed C−H activation strategy for the synthesis of benzo[c]cinnolines through a sequential C−C and C−N bond formation.[15] Herein, a transition-metal-free multicomponent coupling cyclization reaction was developed for direct access to cinnolines (Scheme

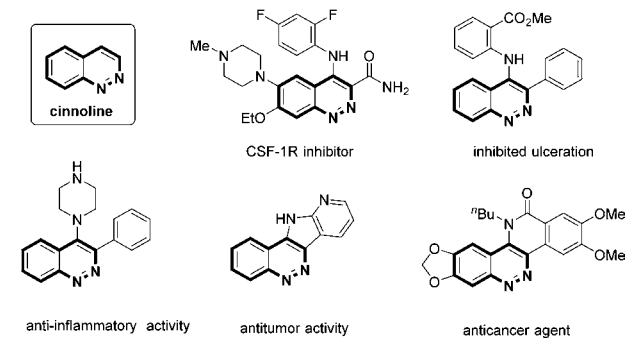
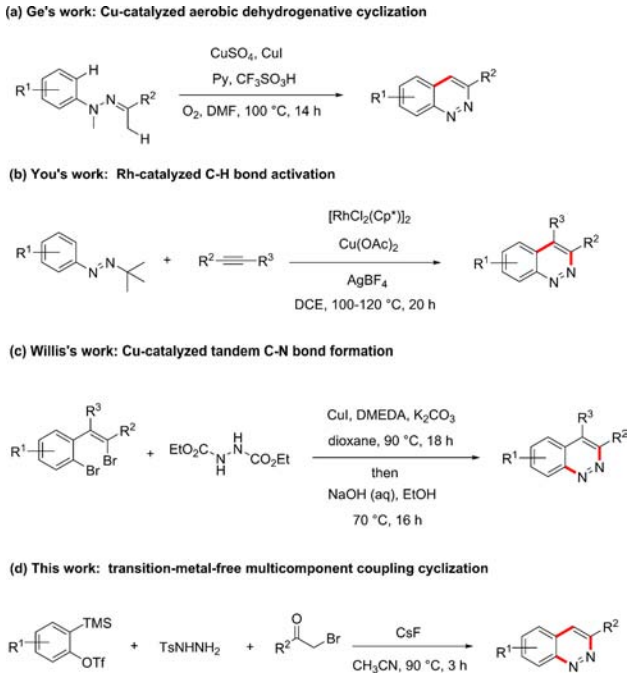


Figure 1. Selected biologically active cinnoline derivatives.

Scheme 1. Strategic Access to Cinnolines



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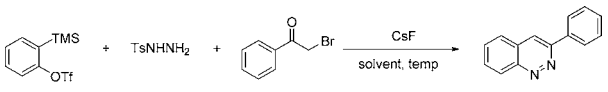
1d). Advantages of this method include the use of commercially available starting materials, mild reaction conditions, and the formation of three chemical bonds in a single step.

Our initial investigations of this new route to cinnolines focused on the three-component reaction of 2-(trimethylsilyl)-phenyl triflate (**1a**) and tosylhydrazine (**2**) with α-bromoacetophenone (**3a**). The desired product, 3-phenylcinnoline (**4aa**), was furnished with 34% yield when the reaction proceeded in the presence of 3.0 equiv of CsF at 80 °C for 3 h in CH_3CN (entry 1). Encouraged by the aforementioned result, other reaction conditions were investigated, and the results are summarized in Table 1. First, the amount of CsF was examined (entries 1−4).

Table 1. Optimization of the Reaction Conditions[a]



1a **2** **3a** **4aa**

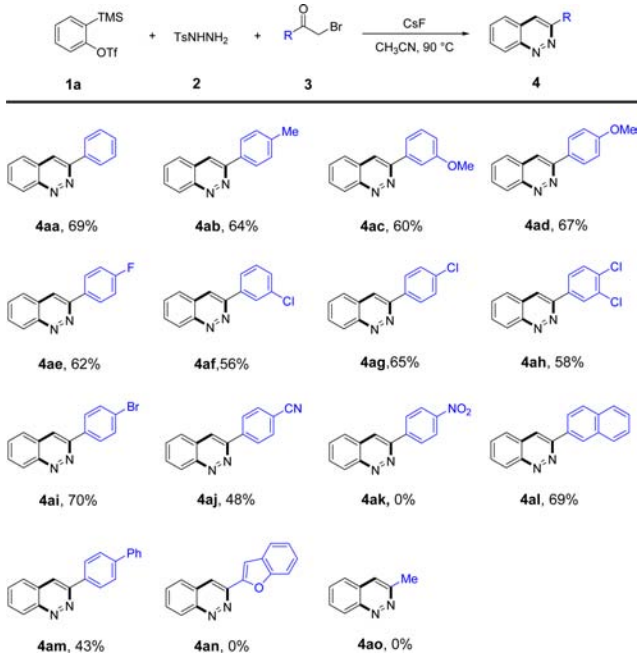
entry	solvent	CsF (equiv)	temp (°C)	yield (%)[b]
1	CH_3CN	3	80	34
2	CH_3CN	5	80	46
3	CH_3CN	6	80	57
4	CH_3CN	8	80	63
5	CH_3CN	8	rt	24
6	CH_3CN	8	40	46
7	CH_3CN	8	60	51
8	CH_3CN	8	70	60
9	**CH_3CN**	**8**	**90**	**69**
10	dioxane	8	80	trace
11	THF	8	70	27
12	DCE	8	80	trace
13	toluene	8	80	35
14	EtOAc	8	80	14

[a]Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2** (0.15 mmol, 1.5 equiv), **3a** (0.1 mmol, 1.0 equiv), CsF (0.8 mmol, 8.0 equiv), and solvent (2 mL) for 3 h in a sealed tube. [b]Isolated yields.

The desired product **4aa** was satisfactorily afforded in 63% yield when 8.0 equiv of CsF were used in CH_3CN at 80 °C (entry 4). Additionally, lowering the reaction temperature did not increase the yields of **4aa** (entries 5−8). However, increasing the temperature to 90 °C resulted in the best yield (entry 9). Subsequently, various solvents were screened, revealing that CH_3CN was the best choice for the reaction. A satisfactory yield of the desired product **4aa** was not obtained in other solvents (dioxane, THF, DCE, toluene, and EtOAc) (entries 10−14).

After optimizing the reaction conditions, we explored the substrate scope of α-bromo ketones (**3**), as shown in Scheme 2. It is noteworthy that the electronic properties of the substituents on the aromatic ring system were shown to have a significant influence on the efficiency of this transformation. The α-bromo ketones bearing electron-neutral (H), electron-donating (4-Me, 3-OMe, 4-OMe), and halo-substituted (4-F, 3-Cl, 4-Cl, 3,4-2Cl, 4-Br) groups attached to the benzene ring transformed smoothly into corresponding products in moderate to good yields (56%−70%; **4aa**−**4ai**). Much to our satisfaction, β-naphthyl and biphenyl group substrates were also compatible, giving the expected products **4al** and **4am** in 69% and 43% yield, respectively. However, the electron-withdrawing groups (4-CN, 4-NO_2) have a negative effect on this reaction, and the desired product **4aj** had a low yield (48%), and **4ak** was not

Scheme 2. Scope of α-Bromo Ketones[a]

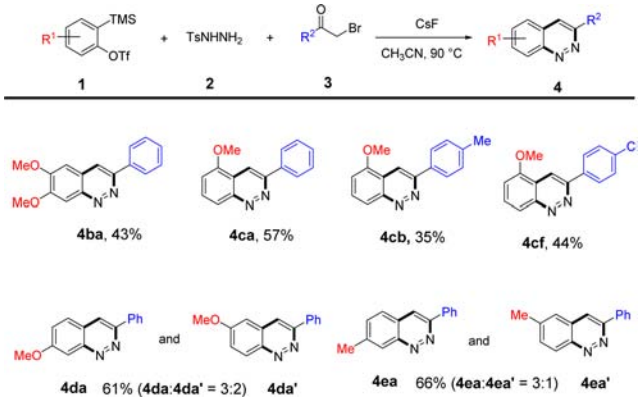


[a]Reactions were carried out with **1a** (0.5 mmol, 1.0 equiv), **2** (0.75 mmol, 1.5 equiv), **3** (0.5 mmol, 1.0 equiv), and CsF (8.0 equiv) in the CH_3CN (4 mL) at 90 °C for 3 h in a sealed tube. Isolated products.

detected. In addition, when the substituents were heterocyclic (2-benzofuryl) and alkyl (methyl) groups, the desired products **4an** and **4ao** were not afforded. The structure of **4aa** was identified by single-crystal X-ray diffraction (see Supporting Information (SI)).

Encouraged by the results described above, the scope of 2-(trimethylsilyl)aryl triflates (**1**) was subsequently examined (Scheme 3). First, symmetrically substituted aryne precursor

Scheme 3. Scope of 2-(Trimethylsilyl)aryl Triflates[a]



[a]Isolated products.

1b was explored, and the corresponding product **4ba** was obtained in moderate yield (43%). Moreover, when nonsymmetrical arynes derived from precursors **1d** and **1e** were used in the annulation, the products **4da**/**4da**′ and **4ea**/**4ea**′ were afforded as a mixture of two isomers in good yields (61% and 66%, respectively). However, the reaction of the 3-methoxy substituted aryne precursor **1c** gained the sole regioisomers, and

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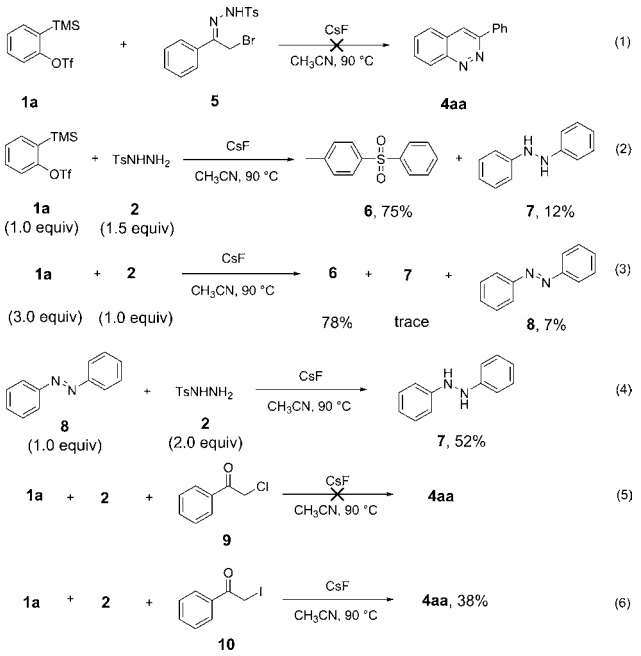
the corresponding products **4ca**–**4cf** were obtained in 35%–57% yields.

To gain insight into the reaction process, control experiments were performed (Scheme 4). The reaction of benzyne precursor

Scheme 4. Control Experiments[a]

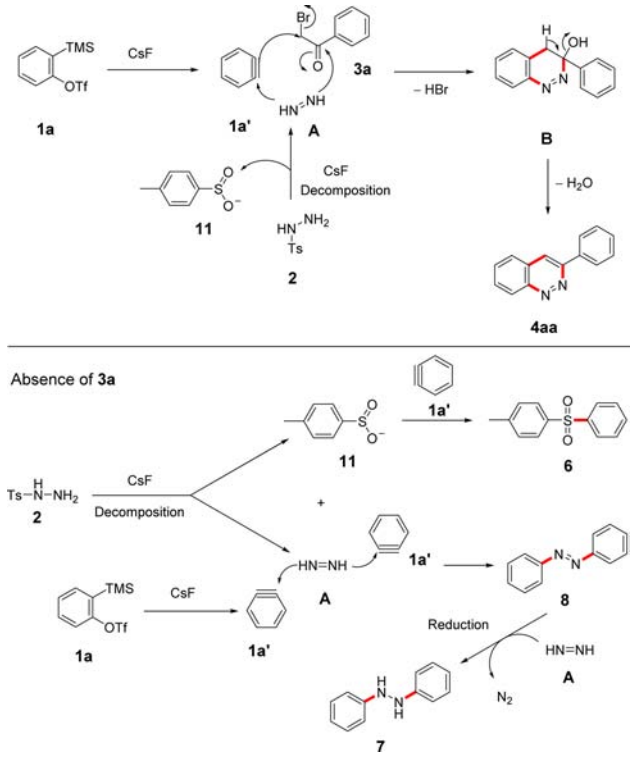


[a]Isolated products.

1a with tosylhydrazone **5**[16,17] did not afford the target product **4aa** under standard conditions. This result identified that compound **5** may not be the intermediate for this reaction (eq 1). Furthermore, the reaction between **1a** and **2** proceeded smoothly to give 1-methyl-4-(phenylsulfonyl)benzene **6** in 75% yield together with small amounts of diphenylhydrazine **7** (12%) (eq 2). When 3.0 equiv of **1a** and 1.0 equiv of **2** participated in this reaction, the main product was also compound **6** with a trace of **7** and a small quantity of (*E*)-1,2-diphenyldiazene **8** (7%) (eq 3). Moreover, the compound **8** could be reduced to **7** in 52% yield in the presence of tosylhydrazine **2** (eq 4). It was proven that diazene could be *in situ* generated in this reaction. In addition, other α-halo ketones have also been checked under standard conditions. The desired product **4aa** was not afforded when using α-chloroacetophenone **9** as a substrate (eq 5). However, the product **4aa** was obtained in 38% yield in the presence of α-iodoacetophenone **10** (eq 6).

On the basis of the above-mentioned experimental results, a possible reaction mechanism for this reaction is proposed as shown in Scheme 5 (using **4aa** as an example). Initially, 2-(trimethylsilyl)phenyl triflate **1a** furnishes the benzyne **1a**′ in the presence of CsF. Meanwhile, tosylhydrazine **2** decomposes into the 4-methylbenzenesulfinate anion **11** and intermediate diazene **A** in the presence of CsF.[18] Subsequently, the diazene **A** reacts with benzyne **1a**′ and α-bromoacetophenone **3a** through a coupling annulation reaction to afford intermediate **B**.[19] Finally, intermediate **B** is converted to the desired product **4aa** through an aromatization reaction with elimination of H_2O. On the other hand, in the absence of **3a**, the decomposed 4-methylbenzenesulfinate anion **11** and diazene **A** could capture benzyne **1a**′ to give 1-methyl-4-(phenylsulfonyl)benzene **6**, and (*E*)-1,2-diphenyldiazene **8**, respectively.[20] The (*E*)-1,2-diphenyldiazene

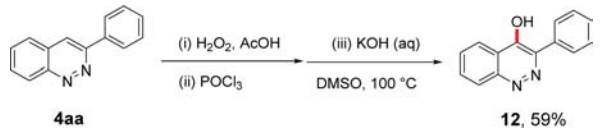
Scheme 5. A Possible Mechanism



8 could be reduced by diazene **A**, transforming into diphenylhydrazine **7**.[18,21]

We further explored the application of cinnolines in organic synthesis as shown in Scheme 6 (**4aa** as an example). 3-

Scheme 6. Synthetic Application (4aa as an Example)[a]



[a]Isolated products.

Phenylcinnoline **4aa** transformed into 3-phenylcinnolin-4-ol **12** in moderate yield (59%) through three-step reactions.[10a] Certain literature[10a,d] indicates that the cinnolin-4-ols are also very useful building blocks for the construction of pharmacologically active cinnoline derivatives.

In summary, we have developed a novel transition-metal-free multicomponent coupling cyclization reaction for the efficient and convenient synthesis of cinnoline derivatives by simple treatment with CsF in the absence of catalyst. This method allows the formation of new C–C and C–N bonds in a single step. Further studies on this method for the synthesis of other bioactive compounds and applications are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, product characterizations, crystallographic data, and copies of the ^{1}H and ^{13}C NMR spectra (PDF)
X-ray data for **4aa** (CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502−528. (b) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550−3577. (c) Rossini, A. F. C.; Muraca, A. C. A.; Casagrande, G. A.; Raminelli, C. *J. Org. Chem.* **2015**, *80*, 10033−10040. (d) Moschitto, M. J.; Anthony, D. R.; Lewis, C. A. *J. Org. Chem.* **2015**, *80*, 3339−3342.

(2) Wu, C.; Shi, F. *Asian J. Org. Chem.* **2013**, *2*, 116−125.

(3) (a) Zeng, Y.; Zhang, L.; Zhao, Y.; Ni, C.; Zhao, J.; Hu, J. *J. Am. Chem. Soc.* **2013**, *135*, 2955−2958. (b) Rao, B.; Zeng, X. *Org. Lett.* **2014**, *16*, 314−317. (c) Li, R.; Tang, H.; Fu, H.; Ren, H.; Wang, X.; Wu, C.; Wu, C.; Shi, F. *J. Org. Chem.* **2014**, *79*, 1344−1355. (d) Chen, Q.; Zhang, C.; Chen, L.; Wen, C.; Du, Z.; Chen, H.; Zhang, K. *Tetrahedron Lett.* **2015**, *56*, 2094−2097.

(4) (a) Li, J.; Wang, N.; Li, C.; Jia, X. *Org. Lett.* **2012**, *14*, 4994−4997. (b) Thangaraj, M.; Bhojgude, S. S.; Bisht, R. H.; Gonnade, R. G.; Biju, A. T. *J. Org. Chem.* **2014**, *79*, 4757−4762. (c) Tao, Y.; Zhang, F.; Tang, C.-Y.; Wu, X.-Y.; Sha, F. *Asian J. Org. Chem.* **2014**, *3*, 1292−1301. (d) Bhojgude, S. S.; Thangaraj, M.; Suresh, E.; Biju, A. T. *Org. Lett.* **2014**, *16*, 3576−3579. (e) Zhong, X.; Lv, J.; Luo, S. *Org. Lett.* **2015**, *17*, 1561−1564. (f) Sha, F.; Tao, Y.; Tang, C.-Y.; Zhang, F.; Wu, X.-Y. *J. Org. Chem.* **2015**, *80*, 8122−8123. (g) Chen, Y.; Willis, M. C. *Org. Lett.* **2015**, *17*, 4786−4789.

(5) (a) Zhao, M.-N.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Chem. Commun.* **2012**, *48*, 8105−8107. (b) Bunescu, A.; Piemontesi, C.; Wang, Q.; Zhu, J. *Chem. Commun.* **2013**, *49*, 10284−10286. (c) Pimparkar, S.; Jeganmohan, M. *Chem. Commun.* **2014**, *50*, 12116−12119. (d) Peng, X.; Wang, W.; Jiang, C.; Sun, D.; Xu, Z.; Tung, C.-H. *Org. Lett.* **2014**, *16*, 5354−5357. (e) Kaicharla, T.; Thangaraj, M.; Biju, A. T. *Org. Lett.* **2014**, *16*, 1728−1731. (f) Bunescu, A.; Wang, Q.; Zhu, J. *Org. Lett.* **2014**, *16*, 1756−1759. (g) Bhunia, A.; Roy, T.; Gonnade, R. G.; Biju, A. T. *Org. Lett.* **2014**, *16*, 5132−5135. (h) Wang, W.; Peng, X.; Qin, X.; Zhao, X.; Ma, C.; Tung, C.-H.; Xu, Z. *J. Org. Chem.* **2015**, *80*, 2835−2841.

(6) (a) Yoshioka, E.; Kohtani, S.; Miyabe, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 6638−6642. (b) Bhunia, A.; Roy, T.; Pachfule, P.; Rajamohanan, P. R.; Biju, A. T. *Angew. Chem., Int. Ed.* **2013**, *52*, 10040−10043. (c) Bhunia, A.; Porwal, D.; Gonnade, R. G.; Biju, A. T. *Org. Lett.* **2013**, *15*, 4620−4623. (d) Yoshioka, E.; Nishimura, M.; Nakazawa, T.; Kohtani, S.; Miyabe, H. *J. Org. Chem.* **2015**, *80*, 8464−8469.

(7) (a) Liu, F.-L.; Chen, J.-R.; Zou, Y.-Q.; Wei, Q.; Xiao, W.-J. *Org. Lett.* **2014**, *16*, 3768−3771. (b) Wallbaum, J.; Jones, P. G.; Werz, D. B. *J. Org. Chem.* **2015**, *80*, 3730−3734. (c) Pawliczek, M.; Garve, L. K. B.; Werz, D. B. *Org. Lett.* **2015**, *17*, 1716−1719. (d) Li, H.-Y.; Xing, L.-J.; Lou, M.-M.; Wang, H.; Liu, R.-H.; Wang, B. *Org. Lett.* **2015**, *17*, 1098−1101.

(8) (a) Yoshida, H.; Morishita, T.; Nakata, H.; Ohshita, J. *Org. Lett.* **2009**, *11*, 373−376. (b) Morishita, T.; Yoshida, H.; Ohshita, J. *Chem. Commun.* **2010**, *46*, 640−642. (c) Zeng, Y.; Li, G.; Hu, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 10773−10777.

(9) (a) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *J. Am. Chem. Soc.* **1999**, *121*, 5827−5828. (b) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *J. Org. Chem.* **2000**, *65*, 6944−6950. (c) Yoshikawa, E.; Radhakrishnan, K. V.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7280−7286. (d) Qiu, Z.; Xie, Z. *Angew. Chem., Int. Ed.* **2009**, *48*, 5729−5732. (e) Dong, Y.; Liu, B.; Chen, P.; Liu, Q.; Wang, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 3442−3446. (f) Feng, M.; Tang, B.; Wang, N.; Xu, H.-X.; Jiang, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 14960−14964.

(10) (a) Lowrie, H. S. *J. Med. Chem.* **1966**, *9*, 670−675. (b) Ruchelman, A. L.; Singh, S. K.; Wu, X.; Ray, A.; Yang, J.-M.; Li, T.-K.; Liu, A.; Liu, L. F.; LaVoie, E. J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3333−3336. (c) Ruchelman, A. L.; Singh, S. K.; Ray, A.; Wu, X. H.; Yang, J.-M.; Li, T.-K.; Liu, A.; Liu, L. F.; LaVoie, E. J. *Bioorg. Med. Chem.* **2003**, *11*, 2061−2073. (d) Lewgowd, W.; Stanczak, A. *Arch. Pharm.* **2007**, *340*, 65−80. (e) Scott, D. A.; Dakin, L. A.; Del Valle, D. J.; Bruce Diebold, R.; Drew, L.; Gero, T. W.; Ogoe, C. A.; Omer, C. A.; Repik, G.; Thakur, K.; Ye, Q.; Zheng, X. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1382−1384. (f) Parrino, B.; Carbone, A.; Muscarella, M.; Spanò, V.; Montalbano, A.; Barraja, P.; Salvador, A.; Vedaldi, D.; Cirrincione, G.; Diana, P. *J. Med. Chem.* **2014**, *57*, 9495−9511.

(11) (a) Baumgarten, H. E.; Anderson, C. H. *J. Am. Chem. Soc.* **1958**, *80*, 1981−1984. (b) Kimball, D. B.; Hayes, A. G.; Haley, M. M. *Org. Lett.* **2000**, *2*, 3825−3827. (c) Gomaa, M. A.-M. *Tetrahedron Lett.* **2003**, *44*, 3493−3496.

(12) Zhang, G.; Miao, J.; Zhao, Y.; Ge, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 8318−8321.

(13) Zhao, D.; Wu, Q.; Huang, X.; Song, F.; Lv, T.; You, J. *Chem. - Eur. J.* **2013**, *19*, 6239−6244.

(14) Ball, C. J.; Gilmore, J.; Willis, M. C. *Angew. Chem., Int. Ed.* **2012**, *51*, 5718−5722.

(15) Reddy, B. V. S.; Reddy, C. R.; Reddy, M. R.; Yarlagadda, S.; Sridhar, B. *Org. Lett.* **2015**, *17*, 3730−3733.

(16) Kylmälä, T.; Hämäläinen, A.; Kuuloja, N.; Tois, J.; Franzén, R. *Tetrahedron* **2010**, *66*, 8854−8861.

(17) (a) Bryant, M.; Smith, R.; Wong, L. *Aust. J. Chem.* **1982**, *35*, 2529−2540. (b) Salaheddine, H.; Titouani, S. L.; Soufiaoui, M.; Tahdi, A. *Tetrahedron Lett.* **2002**, *43*, 4351−4353.

(18) Cusack, N. J.; Reese, C. B.; Risius, A. C.; Roozepeikar, B. *Tetrahedron* **1976**, *32*, 2157−2162.

(19) Aithagani, S. K.; Dara, S.; Munagala, G.; Aruri, H.; Yadav, M.; Sharma, S.; Vishwakarma, R. A.; Singh, P. P. *Org. Lett.* **2015**, *17*, 5547−5549.

(20) Pandya, V. G.; Mhaske, S. B. *Org. Lett.* **2014**, *16*, 3836−3839.

(21) (a) Feth, M. P.; Rossen, K.; Burgard, A. *Org. Process Res. Dev.* **2013**, *17*, 282−293. (b) Castro, B.; Chaudret, R.; Ricci, G.; Kurz, M.; Ochsenbein, P.; Kretzschmar, G.; Kraft, V.; Rossen, K.; Eisenstein, O. *J. Org. Chem.* **2014**, *79*, 5939−5947. (c) Pieber, B.; Glasnov, T.; Kappe, C. O. *Chem. - Eur. J.* **2015**, *21*, 4368−4376.

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Organic LETTERS

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Unsymmetrically Extended Polyfused Aromatics Embedding Coronene and Perylene Frameworks: Syntheses and Properties

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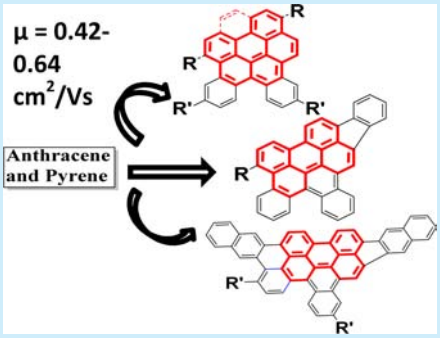
Supporting Information

ABSTRACT: A series of polyfused aromatics containing coronene and perylene in their frameworks was successfully constructed by a modified Ramirez–Corey–Fuchs reaction as the key reaction. Typical six-membered annulation and atypical five-membered annulation through controlled reaction conditions led to a range of extensively conjugate aromatics as possible candidates for organic semiconductors. A significant p-type field-effect mobility of 0.42–0.64 $cm^2/V{\cdot}s$ was obtained from one of the derivatives, dibenzo[*a*,*d*]coronene.

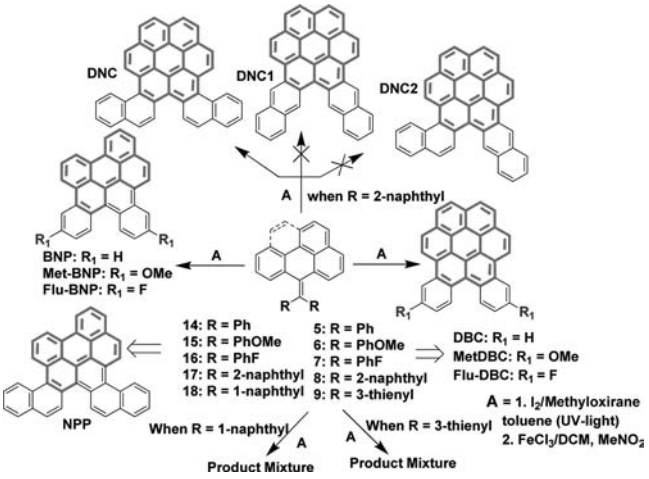


The organic skeletons with multiple benzene rings fused together in linear or nonlinear ways have always been a subject of intensive investigations due to their rich electronic properties and potential in diverse applications like nonlinear optics, light-emitting diodes, field-effect transistors, and solar cells.[1] The efficiency of charge conduction, photoluminescence, and related material features count on the size, shape, and functional groups decorated around the aromatic core, among others. The packing of these polyaromatics, as determined by the electrostatic, steric, and $\pi-\pi$ interactions between neighboring molecules, greatly influence those bulk properties to be used in the organic electronics.[2] Thus, the ability to design and synthesize new frameworks of polyfused aromatics is essential to fully explore the potential of these systems.

A plethora of synthetic approaches have been developed for highly symmetric polyfused aromatics like linear acenes, perylenes and coronene and their derivatives by Scholl, Clar, Müllen, and others.[3] The discovery of a parent coronene framework by Scholl and Meyer in 1932 created a new class of semiconductor materials with the extension of conjugation from the central coronene core.[4] For example, the symmetrically extended tetrabenzocoronene, hexa-*cata*-benzocoronene, hexa-*peri*-benzocoronene, and/or their ring-substituted derivatives have been reported to give decent field-effect mobility in thin film or single crystal state.[5] Extended polyaromatics with perylene as the central core have also been explored in various applications.[6] The unsymmetrically extended derivatives remain less explored,[7] presumably due to a lack of generalized synthetic strategies toward these compounds. In this work, we report the synthesis and spectroscopic characterization of a number of extended polyaromatics embedding perylene and coronene frameworks using common and uncommon pathways of Scholl reactions on the arylated olefinic derivatives. Field-effect transistor devices were also fabricated for selected samples to demonstrate their potential as charge conducting materials.

The major synthetic approaches are displayed in Schemes 1 and 3. In both schemes, similar central key starting polyaryl olefin derivatives are used (Scheme 2). These olefinic derivatives have been the primary building block in the structural design of many polyaromatic hydrocarbons and also an ideal candidate to study the Scholl reactions due to good solubility and low oxidation potential.[8] Many research plans

Scheme 1. Synthesis of Coronene- and Perylene-Embedded Derivatives



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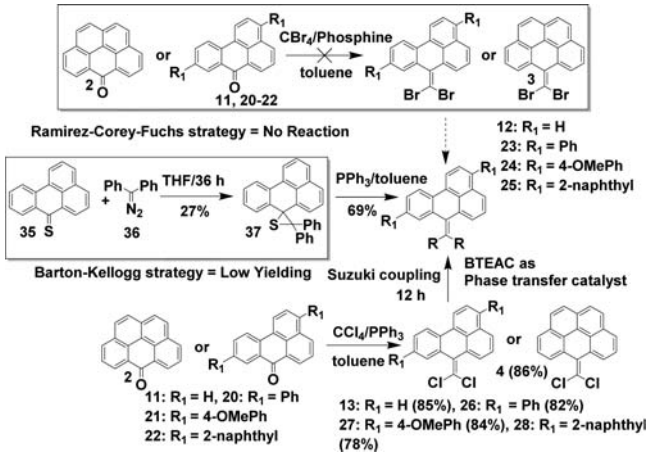
have been used to prepare these derivatives, featuring their applicability in the oxidative coupling and related reactions. Two powerful tools for the construction of these derivatives are Ramirez–Corey–Fuchs[9] and Suzuki coupling or the Barton–Kellogg reaction[10]–reaction between azomethine and thioketone, followed by dethionation reaction.

However, these were either low or even nonyielding for the ketones desired in our design (Scheme 2). For example, when

Scheme 2. Synthesis of Polyaryl Olefins

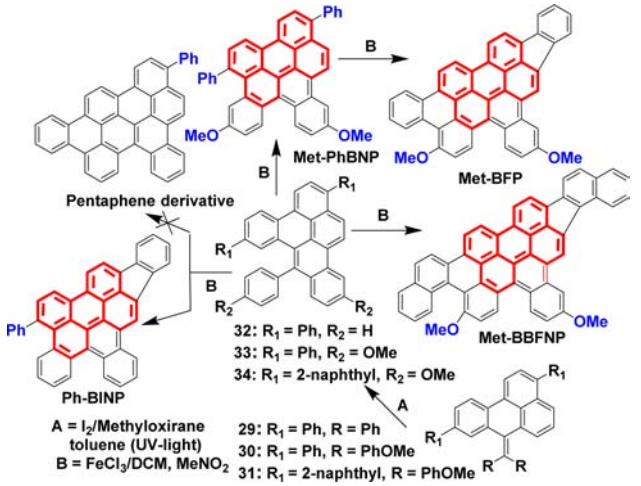


thioketone **35** reacted with azomethine **36**, the yield of thioepoxide **37** was rather low, at 27%. Additionally, the general Corey–Fuchs reaction on the ketones **2**, **11**, and **20**–**22** did not yield the desired dibromo olefin derivatives **3**, **12**, and **23**–**25** by employing triphenylphosphine or the more reactive trialkoxyphosphines.

Thus, a synthetic protocol for dibenzocorones and benzonapthoperylenes similar to that for tetrabenzocoronene and hexabenzocoronene cannot be used. Instead, a modified process with carbon tetrachloride and triphenylphosphine as the reagent (1/3/6, mole ratio with respect to the ketone reactant) was found to give the desired dichloro olefin derivatives. In addition, the scope of the reaction was expanded by enforcing a similar strategy on five ketones (**2**, **11**, and **20**–**22**) to obtain the dichloro olefin derivatives (**4**, **13**, and **26**–**28**) in excellent yields of 78–85% (Scheme 2). The reason for discriminative reactivity of aromatic ketones toward the reagents like carbon tetrabromide and carbon tetrachloride was considered on the basis of low flexibility of the aromatic core in the chosen ketones in accommodating the two bromo atoms on the other side of the double bond. The smaller chlorine atom allows the reaction to proceed smoothly. To prepare the polyarylolefins (**5**–**9**, **14**–**18**, and **29**–**31**), the dichloromethylene derivatives were treated with aryl boronic acid employing the palladium-catalyzed Suzuki coupling in the presence of phase-transfer catalyst. The use of phase-transfer catalyst not only reduced the reaction time but also led to purer products.

To obtain completely fused derivatives, derivatives **5**–**9**, **14**–**18**, and **29**–**31** were subjected to a two-step oxidative coupling strategy using iodine and iron chloride as the catalyst. A variety of reagents is available to carry out oxidative coupling (or cyclodehydrogenation) on these derivatives, like DDQ, iron chloride, or iodine (UV-mediated coupling). The rate of oxidative coupling depends on the oxidation potential of polyaryl olefins, functional groups, and the strength of the oxidizing reagents.[11] Due to failure of the first two reagents in our case, the derivatives **5**–**9**, **14**–**18**, and **29**–**31** were subjected to iodine-mediated oxidative coupling under UV irradiation. This nevertheless could not result in complete fusion, even in the presence of higher equivalency of iodine (2.5–5.0). In the case of **5**–**9** and **14**–**18**, the mixtures could not be purified, while the partially fused derivatives **32** and **33** were isolated in a pure state (Scheme 3).

Scheme 3. Synthesis of Perylene-Embedded Derivatives



Complete fusion of aryl groups to the desired aromatic nucleus was achieved using iron chloride in nitromethane. Although the coupling reaction carried out by use of Lewis acids are not free from side products from chlorination, polymerization, aryl transfer, or even rearrangement of the desired products,[12] higher yields of fully fused products in 71–85% can be achieved by controlling the reaction time and mole ratio of iron chloride used. The product skeletons were unraveled on the basis of NMR, MALDI-TOF mass, and also crystal XRD analyses for selected ones (Figure S87, SI). The product structures were constructed predominantly through six-membered ring oxidative coupling modes, although as will be elaborated later, abnormal five-membered ring coupling was also observed. The rate of coupling reaction for the polyaryl olefin derivatives was affected by their functional groups, which modulate the oxidation potential. Electron-donating substituents such as methoxy groups on the phenyl rings not only lowered the reaction time but also increased the yields of reactions (Table 1, entries 2, 7, 12, 13), whereas fluoro groups on the phenyls slightly deactivated the aromatic skeleton for the desired coupling reactions. For 3-thienylated derivative **9**, an inseparable mixture of annulated and polymerized products was obtained. Additionally, the derivative **18** substituted with a 1-naphthyl moiety gave a mixture of annulated products that could not be isolated in pure state. (Table 1, entry 10). The Scholl reaction of derivatives **8** and **17** led to the formation of the DNC and NPP by a regiospecific cyclodehydrogenation reaction. The possible formation of the other analogous hydrocarbons such as DNC1 or DNC2 was ruled out on the basis of the NMR and single-crystal XRD data.

When the Scholl reaction was applied on tetraphenyl-olefin **32**, a rare cyclodehydrogenation reaction with five-membered ring coupling gave indenoperylene derivative Ph-BINP in an excellent yield of 80%. One phenyl group remained unfused in

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Table 1. Conversion of Aryl Olefins to Fused Derivatives through Oxidative Coupling Reactions

entry	reactant	product	yield[c] (%)	time[d] (h)
1	**5**	DBC	76	24
2	**6**	Met-DBC	81	6
3	**7**	Flu-DBC	65	20
4	**8**	DNC	77	12
5	**9**	mixture[a]		12
6	**14**	BNP	70	24
7	**15**	Met-BNP	85	6
8	**16**	Flu-BNP	69	24
9	**17**	NPP	71	12
10	**18**	mixture[b]		24
11	**32**	Ph-BINP	80	36
12	**33**	Met-PhBNP	81	4
13	**33**	Met-BFP	82	12
14	**34**	Met-BBFNP		24

[a]Compound DTC could not be isolated pure. [b]In this case, mixtures of derivatives were obtained. [c,d]Yields and time are given for iron chloride-mediated oxidative coupling reactions.

this derivative even with excessive iron chloride, which also led to polymerization. Indeed, very few reports on this unexpected five-membered oxidative coupling are known. One precedent was described by Müllen et al. in their synthesis of benzoindenoperylene from structurally common naphthalene derivatives using Lewis acids like $FeCl_3$ and $AlCl_3$ at room and elevated temperatures, respectively.[13] The derivative **33** carrying methoxy groups produced fluorenthrenoperylene derivative Met-BFP via successive six-, five-, and six-membered cyclodehydrogenation reactions (Table 1, entry 12). Additionally, we were able to isolate pure Met-PhBNP with only 1-fold oxidative coupling reaction on **33** with a shorter reaction time of 4 h.

In order to rationalize the formation of Ph-BINP and DNC, two plausible mechanisms are suggested (Schemes S4 and S5, SI). The loss of one electron from the partially fused derivative **29** can result in a cation radical that allows the six- or five-membered ring fusion reactions. The existence of cation−radical intermediates in the oxidative coupling reactions is already well-acknowledged.[14] In the 3,9-substituted polyaryl olefins **31**−**33**, the five-membered ring closure occurred possibly due to difference in electron-richness[7,12b] on the benzoanthracene unit. The formation of the DNC was attributed to the higher reactivity of 1-position as compared to the 3-position of naphthyl unit, resulting from the resonance stabilization of cation-radicals.

The chemical transformation of polyaryl olefins into their ring-fused analogous was confirmed for DNC and PhBINP derivatives based on their single-crystal XRD analyses (Figure S88, SI). Indenoperylene derivative PhBINP was found to be slightly twisted due to steric hindrance at the bridging positions. An efficient $\pi-\pi$ overlap (overlap distance, 3.378 Å) was observed among polyaromatic segments in the crystal packing. Similarly, the X-ray crystal structure of DNC showed that the molecule was twisted at the naphthyl bridge, while there was efficient cofacial packing among the coronene units, with an interplanar distance of 3.3 Å.

Owing to their planar aromatic skeletons and polar functional groups, some perylenes[15] and other polyaromatic derivatives exhibit aggregation behavior in their solution states. Different stacking patterns such as J- and H-aggregates form depend on the concentration and the nature of the solvent.[16] This phenomenon was also observed for perylene derivative Met-BFP, when concentration-dependent NMR spectra were taken in solvents like DMSO-d_6 (Figure S89a, SI). Significant shifting and merging of NMR signals were observed upon increasing the derivative concentration in solution. The aggregation in this derivative can be explained based on the increased dipole moment and planarization of the molecule after fusion from the precursors A and B (Figure S89b, SI).

The DBC and BNP derivatives displayed light-yellow to yellow color, while indeno- and fluorenthrenoperylene derivatives gave orange color in their solid states. Absorption spectra of the derivatives as recorded in dilute dichloromethane solutions are illustrated in Figure 1a and S90−91, while related

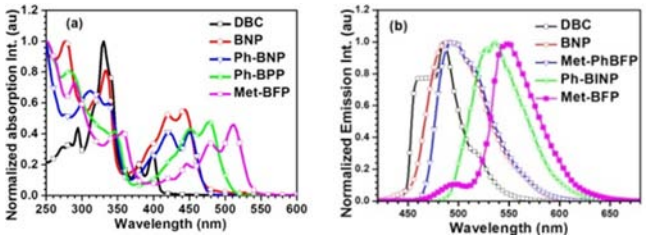

Figure 1. (a, b) Normalized absorption and emission spectra as recorded in dichloromethane.

data is summarized in Table S1 (SI). Coronene hydrocarbon exhibits four absorption bands in the region of ∼250−350 nm, with the maximum absorption observed at ∼300 nm. The absorption featured were assigned to be attributed due to the $\pi-\pi^*$ electronic transitions of coronene core.[17] The dibenzocoronene DBC displayed a bathochromic shift in absorption profile, with the structurally analogous absorption pattern centered at 293, 330, 379, and 399 nm. Thus, absorption features of both coronene and DBC are best described by similar electronic states with different energies. Perylene hydrocarbon shows absorption in the range of ∼250−435 nm,[18] whereas benzonaphthoperylene, indenoperylene, and fluorenthrenoperylene derivatives afford structurally similar but shifted absorption maxima toward higher wavelength region presumably due to extension of conjugation. In perylene derivatives, the HOMO is primarily localized in the perylene unit, indicating the electronic transitions could best be attributed by this core (Figure S95, SI). The DBC and BNP derivatives displayed blue to blue-green, Ph-BINP yellow, while Met-BFP orange emissions in their dilute solutions Figure 1b and S92−93, SI). In the derivatives BNP to Met-BFP, the emission color shifts from blue to orange presumably due to increased conjugation. To demonstrate the potential of these polyfused aromatics, single-crystal field-effect transistors (SCFETs) were fabricated with one of the derivatives. Thus, rod-shaped single crystals of the derivative DBC were obtained by the physical vapor transport method at 360 °C using helium as the carrier gas.

A top-contact, top-gate SCFET was fabricated by laminating the crystal on a glass substrate with painted colloidal graphite as the source and drain, perylene as the dielectric, and colloidal graphite on its top as the gate electrode. The channel length, width, and perylene thickness were 1.0−0.5 mm, 0.25−0.20 mm, and 1.8−2.5 μm, respectively. An average mobility of 0.42 $cm^2/V{\cdot}s$ and maximum mobility of 0.64 $cm^2/V{\cdot}s$ were obtained for DBC (Figures S96−98 and Table S2, SI).

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In conclusion, we have successfully synthesized new series of polyfused aromatics containing perylene and coronene frameworks through a multistep synthetic approach involving new ways of utilizing Scholl reactions. Newly constructed derivatives are well characterized by spectroscopic techniques such as NMR and MALDI−mass techniques. The chemical structures of DBC, Flu-DBC, DNC, and Ph-BINP were confirmed by single-crystal XRD analysis and were found to have face-to-face packing arrangements. One of the derivatives DBC (dibenzocorone) gave an average p-type field-effect mobility of 0.42 $cm^2/V·s$.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03291.

Detailed experimental procedures and complete spectroscopic analysis (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Bonaccorso, F.; Sun, Z.; Hasan, T.; Ferrari, A. C. *Nat. Photonics* **2010**, *4*, 611−622. (b) Omer, K. M.; Ku, S.-Y.; Cheng, J.-Z.; Chou, S.-H.; Wong, K.-T.; Bard, A. J. *J. Am. Chem. Soc.* **2011**, *133*, 5492−5499. (c) Duong, H. M.; Bendikov, M.; Steiger, D.; Zhang, Q.; Sonmez, G.; Yamada, J.; Wudl, F. *Org. Lett.* **2003**, *5*, 4433−4436. (d) Wong, W. W. H.; Ma, C.-Q.; Pisula, W.; Yan, C.; Feng, X.; Jones, D. J.; Müllen, K.; Janssen, R. A. J.; Bäuerle, P.; Holmes, A. B. *Chem. Mater.* **2010**, *22*, 457−466.

(2) (a) Xiao, K.; Liu, Y.; Qi, T.; Zhang, W.; Wang, F.; Gao, J.; Qiu, W.; Ma, Y.; Cui, G.; Chen, S.; Zhan, X.; Yu, G.; Qin, J.; Hu, W.; Zhu, D. *J. Am. Chem. Soc.* **2005**, *127*, 13281−13286. (b) Clarke, T. M.; Gordon, K. C.; Wagner, P.; Officer, D. L. *J. Phys. Chem. A* **2007**, *111*, 2385−2397.

(3) (a) Scholl, R.; Seer, C.; Weitzenböck, R. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 2202−2209. (b) Clar, E.; Schmidt, W. *Tetrahedron* **1977**, *33*, 2093−2097. (c) Henson, Z. B.; Müllen, K.; Bazan, G. C. *Nat. Chem.* **2012**, *4*, 699−704. (d) Scott, L. T.; Boorum, M. M.; McMahon, B. J.; Hagen, S.; Mack, J.; Blank, J.; Wegner, H.; de Meijere, A. *Science* **2002**, *295*, 1500−1503.

(4) Scholl, R.; Meyer, K. *Ber. Dtsch. Chem. Ges. B* **1932**, *65*, 902−907.

(5) (a) Pola, S.; Kuo, C.-H.; Peng, W.-T.; Islam, M. M.; Chao, I.; Tao, Y.-T. *Chem. Mater.* **2012**, *24*, 2566−2571. (b) Xiao, S.; Myers, M.; Miao, Q.; Sanaur, S.; Pang, K.; Steigerwald, M. L.; Nuckolls, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 7390−7394. (c) Hill, J. P.; Jin, W.; Kosaka, A.; Fukushima, T.; Ichihara, H.; Shimomura, T.; Ito, K.; Hashizume, T.; Ishii, N.; Aida, T. *Science* **2004**, *304*, 1481−1483.

(6) (a) Hansen, M. R.; Graf, R.; Sekharan, S.; Sebastiani, D. *J. Am. Chem. Soc.* **2009**, *131*, 5251−5256. (b) Tasios, N.; Grigoriadis, C.; Hansen, M. R.; Wonneberger, H.; Li, C.; Spiess, H. W.; Müllen, K.; Floudas, G. *J. Am. Chem. Soc.* **2010**, *132*, 7478−7487.

(7) Kelber, J.; Achard, M.-F.; Durola, F.; Bock, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 5200−5203.

(8) (a) Wu, Y.-T.; Kuo, M.-Y.; Chang, Y.-T.; Shin, C.-C.; Wu, T.-C.; Tai, C.-C.; Cheng, T.-H.; Liu, W.-S. *Angew. Chem., Int. Ed.* **2008**, *47*, 9891−9894. (b) Kumar, S.; Tao, Y.-T. *J. Org. Chem.* **2015**, *80*, 5066−5076.

(9) (a) Desai, N. B.; McKelvie, N.; Ramirez, F. *J. Am. Chem. Soc.* **1962**, *84*, 1745−1747. (b) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769−3772.

(10) (a) Plunkett, K. N.; Godula, K.; Nuckolls, C.; Tremblay, N.; Whalley, A. C.; Xiao, S. *Org. Lett.* **2009**, *11*, 2225−2228.

(11) (a) Grzybowski, M.; Skonieczny, K.; Butenschön, H.; Gryko, D. T. *Angew. Chem., Int. Ed.* **2013**, *52*, 9900−9930. (b) Zhang, X.; Jiang, X.; Zhang, K.; Mao, L.; Luo, J.; Chi, C.; Chan, H. S. O.; Wu, J. *J. Org. Chem.* **2010**, *75*, 8069−8077.

(12) Sarhan, A. A. O.; Bolm, C. *Chem. Soc. Rev.* **2009**, *38*, 2730−2744. (b) Rempala, P.; Kroulík, J.; King, B. T. *J. Am. Chem. Soc.* **2004**, *126*, 15002−15003. (c) Pradhan, A.; Dechambenoit, P.; Bock, H.; Durola, F. *J. Org. Chem.* **2013**, *78*, 2266−2274.

(13) Avlasevich, Y.; Kohl, C.; Müllen, K. *J. Mater. Chem.* **2006**, *16*, 1053−1057.

(14) (a) Rempala, P.; Kroulík, J.; King, B. T. *J. Org. Chem.* **2006**, *71*, 5067−5081. (b) Clowes, G. A. *J. Chem. Soc. C* **1968**, 2519−2526. (c) Zhai, L.; Shukla, R.; Wadumethrige, S.; Rathore, R. *J. Org. Chem.* **2010**, *75*, 4748−4760.

(15) (a) Sugiyasu, K.; Fujita, N.; Shinkai, S. *Angew. Chem.* **2004**, *116*, 1249−1249. (b) Shin, W. S.; Jeong, H.-H.; Kim, M.-K.; Jin, S. H.; Kim, M.-R.; Lee, J.-K.; Lee, J. W.; Gal, Y.-S. *J. Mater. Chem.* **2006**, *16*, 384−390.

(16) (a) Hong, Y.; Lam, J. W. Y.; Tang, B. Z. *Chem. Soc. Rev.* **2011**, *40*, 5361−5388.

(17) Hirayama, S.; Sakai, H.; Araki, Y.; Tanaka, M.; Imakawa, M.; Wada, T.; Takenobu, T.; Hasobe, T. *Chem. - Eur. J.* **2014**, *20*, 9081−9093.

(18) McCusker, C. E.; Castellano, F. N. *Chem. Commun.* **2013**, *49*, 3537−3539.

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Organic LETTERS

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Total Synthesis of Cyclomarin A, a Marine Cycloheptapeptide with Anti-Tuberculosis and Anti-Malaria Activity

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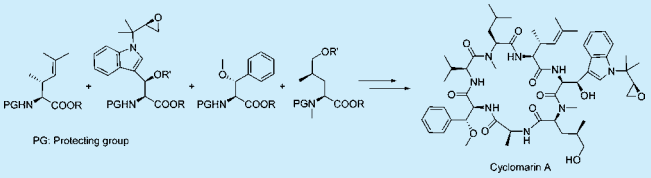
Supporting Information

ABSTRACT: An efficient synthetic protocol for the stereoselective synthesis of cyclomarin A is reported. Key steps in the syntheses of the building blocks are an asymmetric chelate–enolate Claisen rearrangement, an asymmetric hydrogenation, and highly diastereoselective additions of organozinc and -titanium reagents.



Most people in industrial nations believe that tuberculosis (TB) has been wiped out, but statistically almost every third human is infected by *Mycobacterium tuberculosis* (MTB).[1] Behind HIV/AIDS, TB stands at position two in the list of lethal infections.[2] Several multidrug resistant bacteria are resistant not only toward first-line medication but also toward second-line medicine.[3] Therefore, the development of new drugs, with a new mode of action, is highly desired.

In 1999, Clardy et al. described the isolation and structure elucidation of the cyclomarins from the marine streptomycete CNB-982 (Figure 1).[4] The crude extract showed a moderate

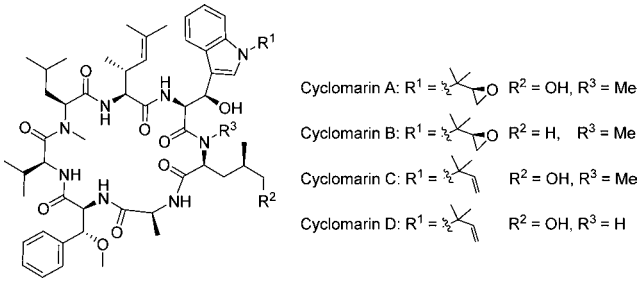


Figure 1. Natural occurring cyclomarins.

cytotoxicity, with an IC_{50} of ~2.5 μM of the major metabolite cyclomarin A (Cyc A) toward several cancer cell lines. The minor metabolites cyclomarin B and C (Cyc B and C) are only found in trace amounts (2–3%). Later, a further derivate cyclomarin D (Cyc D), missing an *N*-methyl group, was isolated from *Salinispora arenicola* CNS-205.[5] Besides the moderate cytotoxicity, the cyclomarins show some antiviral[6] and antibiotic activity, especially against MTB, while the exact mode of action was not clear until recently.[7] Detailed studies at Novartis identified ClpC1, a subunit of the caseinolytic protease, as the target protein. Very recently, the same researchers also reported significant antimalaria activity. Cyclomarin A selectively inhibits the $PfAp_3Ase$ of *Plasmodium falciparum* in a nanomolar range, but not the human homologue in FHIT.[8] To the best of our knowledge, a natural product with two different targets in two highly important human pathogens is unprecedented. To date, all studies have been carried out with cyclomarin A (and derivatives thereof) from fermentation, since no total synthesis has been reported. Only one synthesis of the minor metabolite cyclomarin C, lacking the epoxide functionality on the hydroxytryptophan, has been described by Yao et al.[9] Herein, we report the first total synthesis of cyclomarin A, which should open the way to synthetic derivatives for SAR studies to develop efficient drugs to fight both diseases.

Some of the unusual amino acids found in cyclomarins, e.g., 5-hydroxyleucine and the β-methoxyphenylalanine, are also present in other natural products.[10] Others, such as the *tert*-prenylated β-hydroxytryptophan and the adjacent 2-amino-3,5-dimethyl-4-hexenoic acid, are unique to cyclomarins. Although the synthesis of cyclomarin A has not been reported, several syntheses of building blocks have been described during the last several years.[11−14]

We developed our own synthetic protocols toward the required building blocks based on our long-term experience in amino acid synthesis.[15] When chelated amino acid ester enolates are used, β-hydroxy amino acids become easily available via an aldol reaction,[16] and γ,δ-unsaturated amino acids can be obtained either by transition-metal-catalyzed allylic alkylation[17] or chelate enolate Claisen rearrangement.[18] While allylic alkylation provides *anti*-configured products, the *syn* isomers can be obtained via Claisen rearrangement. Therefore, this approach was used here to generate the desired *N*-protected amino acid (2*S*,3*R*)-**4** (Scheme 1).

The chelate Claisen rearrangement of chiral ester (*S*)-**1** gave rise to the desired amino acid with perfect chirality transfer and diastereoselectivity.[18] After methylation, the double bond was cleaved via ozonolysis. Unfortunately, attempts to introduce the required terminal methyl group via Wittig reaction[9] failed. Even with a 5-fold excess of the Wittig reagent only 21% of the desired product **3** could be obtained, while the large excess of basic Wittig reagent caused complete epimerization of the β-methyl

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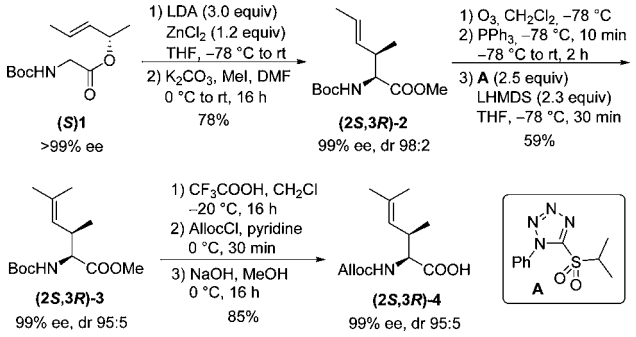
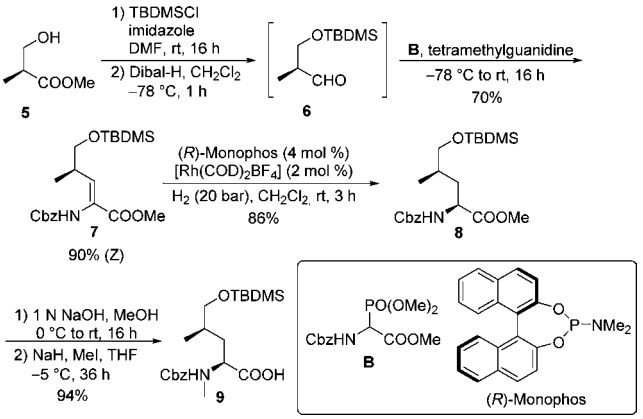
Scheme 1. Synthesis of (2*S*,3*R*)-4



group. Better results could be obtained using a modified Julia–Kocienski reaction,[19] normally used for (*E*)-selective olefinations. Sulfone **A** was deprotonated with LHMDS, and the solution was added to a fresh prepared aldehyde (without purification). Under these conditions, the protected amino acid **3** could be obtained without significant epimerization. During the synthesis, we recognized that the *N*-Boc-protecting group could not be removed in the peptide without several side reactions. Therefore, we replaced the Boc-protecting group by an Alloc group. Subsequent saponification gave rise to building block **4**.

The synthesis of protected 5-hydroxyleucine **9** (Scheme 2) started with the commercially available Roche ester **5**, which was

Scheme 2. Synthesis of (2*S*,4*R*)-9

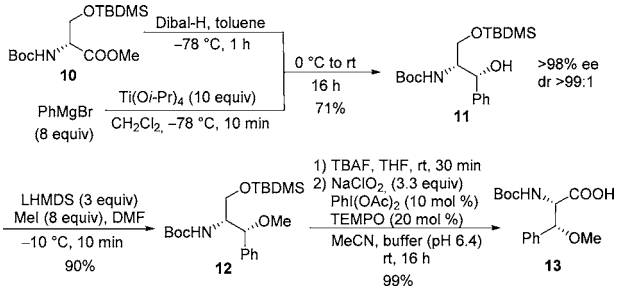


protected, reduced to the aldehyde **6**, and directly used in an olefination using Schmidt's phosphonoglycinate **B**.[20] The α,β-unsaturated amino acid derivative **7** obtained was subjected to a stereoselective hydrogenation[21] using (*R*)-monophos as a ligand.[22] Subsequent *N*-methylation and saponification provided amino acid **9** in high yield and selectivity.

The third unusual building block, β-methoxyphenylalanine **13**, should be accessible via chelate-controlled arylmetal addition toward a protected (*R*)-serinal, obtained from ester **10** (Scheme 3).[23] Our first attempts using phenylmagnesium bromide (3 equiv) gave the addition product in acceptable yield (60%) but only moderate diastereoselectivity (ratio 7:3). Much better results could be obtained with the corresponding titanium reagents,[24] providing **11** as a single diastereomer. *O*-Methylation, cleavage of the silyl ether, and subsequent oxidation gave rise to the desired acid **13** in excellent yield.

By far, most of our encounteded difficulties caused the synthesis of the *tert*-prenylated epoxidized β-hydroxytryptophan, mainly because of the lability of the β-OH group and the terminal

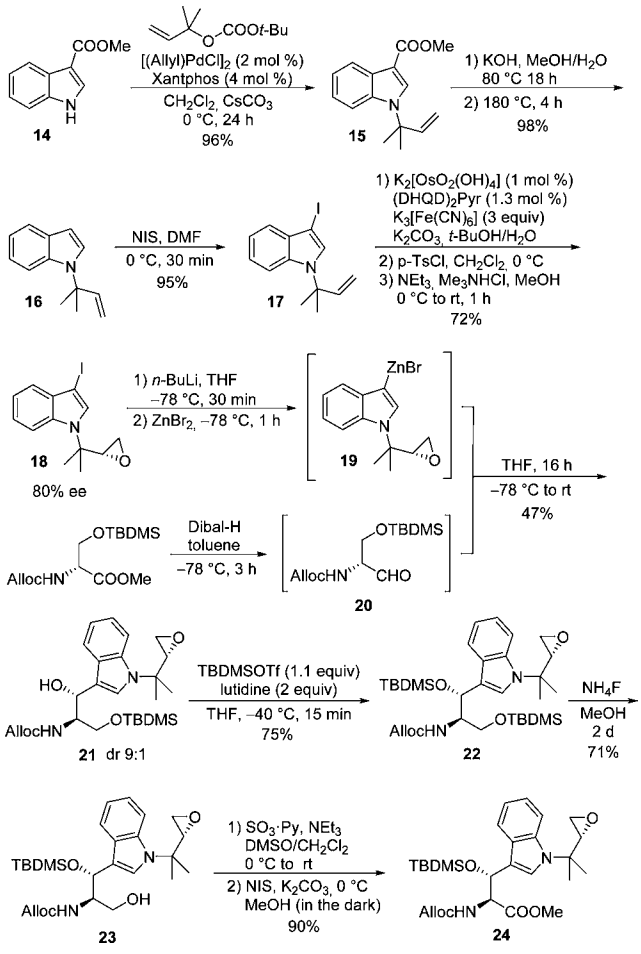
Scheme 3. Synthesis of (2*S*,3*R*)-13



double bond of the prenyl group. Recently, we reported the synthesis of an *N*-Boc-protected *tert*-prenylated β-hydroxytryptophan derivative,[25] which unfortunately could not be applied here, since the Boc-protecting group could not be removed without decomposition. Therefore, we had to develop a new protocol, introducing the epoxy group relatively early in the synthesis.

Recently, a new method was reported for the regioselective *tert*-prenylation of electron-demanding indoles.[26] We applied this Pd-catalyzed protocol to 3-indolecarboxylate **14**, giving rise to indole **15** in almost quantitative yield (Scheme 4). The reaction temperature was kept at 0 °C to suppress the competing *n*-prenylation. After saponification of the ester, the free acid was subjected to a thermal decarboxylation.[27] Heating the neat acid to 180 °C resulted in a clean decarboxylation in perfect yield. The

Scheme 4. Synthesis of (2*S*,3*R*)-25



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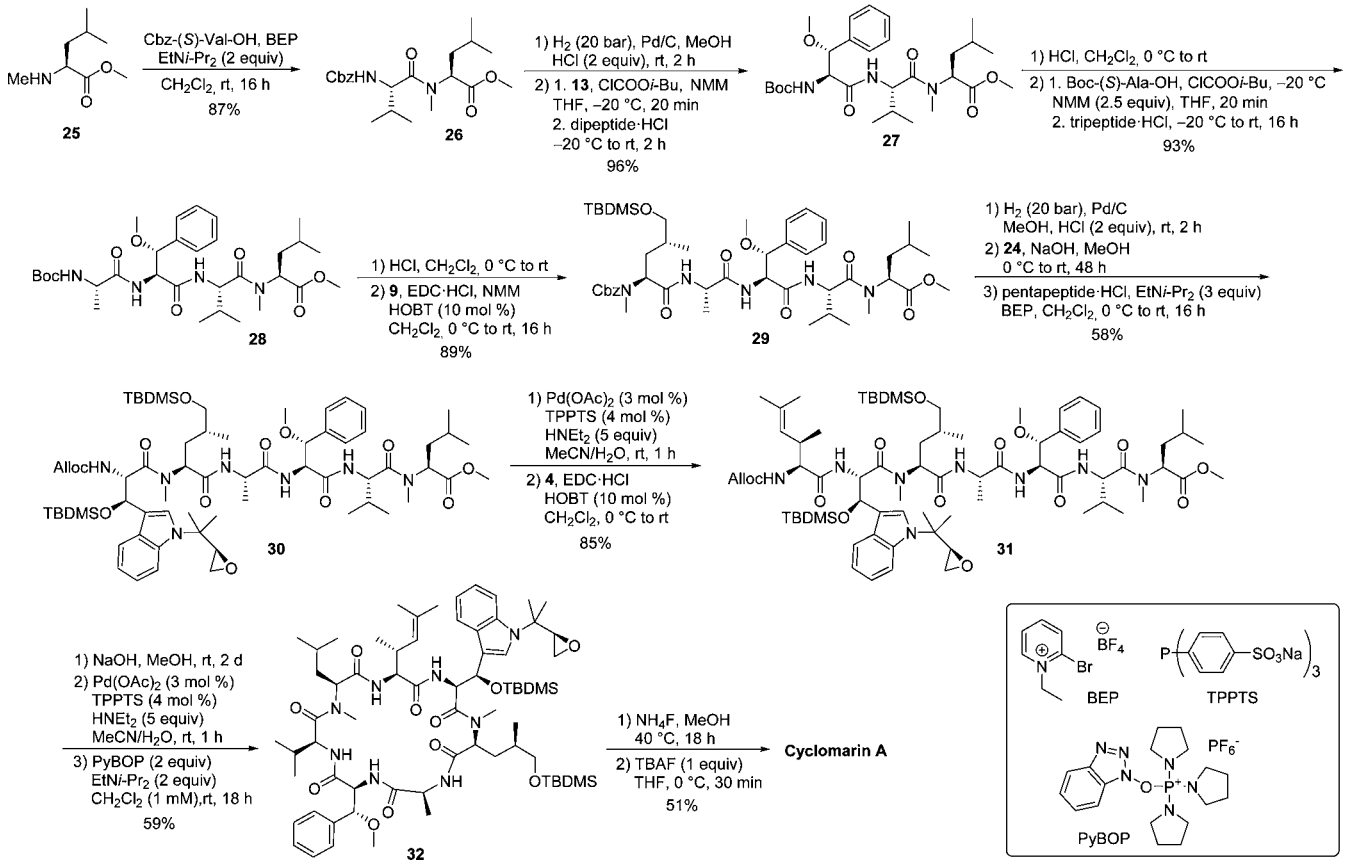
Scheme 5. Synthesis of Cyclomarin A



prenylated indole **16** was converted into the corresponding 3-iodo derivative **17**, and the terminal double bond was transformed into epoxide **18**[14b] using a Sharpless dihydroxylation as a stereodetermining step. Compound **18** was lithiated at −78 °C using BuLi and was subsequently transmetalated to the corresponding organozinc reagent **19**,[28] which was added to the solution of fresh prepared aldehyde **20**. The desired product **21** was formed in acceptable yield as a 9:1 diastereomeric mixture. Out of four possible stereoisomers, only two isomers were obtained and the isomeric mixture was the result of the moderate selectivity of the Sharpless dihydroxylation (80% ee). Therefore, the carbonyl addition toward chiral aldehyde **20** proceeded with excellent diastereoselectivity. The secondary OH functionality was subjected to silyl protection. While most silylation reactions caused complete decomposition of the molecule, only the combination of TBMDSOTf and lutidine gave acceptable results. At −40 °C the side reactions could be suppressed almost completely, and after only 15 min, the desired silyl ether **22** was obtained in good yield. The primary silyl group could selectively be removed in the presence of the secondary one using NH_4F in methanol.[29] This reagent is less reactive than the commonly used Bu_4NF, but it is therefore more selective. Interestingly, no complete conversion was observed, while the primary alcohol **23** was obtained diastereomerically pure. Obviously the silyl ether of the "wrong epoxide" does not undergo cleavage under these reaction conditions. Alcohol **23** was oxidized to the corresponding aldehyde,[30] a rather unstable compound. Workup had to be done at 0 °C and the crude aldehyde was directly converted into methyl ester **24** using *N*-iodosuccinimide (NIS) in MeOH.[31] This ester was saponified directly before the peptide coupling to avoid decomposition of the labile acid.

With these building blocks in hand, we started the synthesis of the linear heptapeptide. Ring closure was planned between the aminohexenoic acid and the *N*-methylated leucine. Therefore, the synthesis started with this amino acid. BEP (2-bromo-1-ethylpyridinium tetrafluoroborate)[32] was used for the coupling with protected valine. Surprisingly, the cleavage of the Cbz-protecting group required a pressure of 20 atm of H_2. HCl (2 equiv) was added to suppress the formation of diketopiperazine. The dipeptide salt was subjected in the next peptide coupling step with activated **13**. Since an excellent yield was obtained, the same protocol was also used in the next coupling step with comparable success. HOBT was used to activate the *N*-methyl-4-hydroxyleucine **9** to avoid epimerization during the coupling step. By this sequence, pentapeptide **29** could be obtained enantiomerically pure in gram scale. For the coupling of the highly sensitive hydroxytryptophan, methyl ester **24** was saponified and the crude product (without purification) was directly coupled using the BEP protocol to give **30** in acceptable yield. The alloc protecting group was removed under Pd catalysis, and the final amino acid **4** was connected. After removing the protecting groups, the deprotected heptapeptide was slowly added to a diluted solution of PyBOP (2 equiv) and base in CH_2Cl_2 (final concentration: 1 mM). Under these conditions, *O*-silylated cyclomarin A (**32**) could be obtained in good yield (Scheme 5). The removal of the two silyl protecting groups was more challenging than expected, since they could not be removed in one step without decomposition. Therefore, we decided to use a two-step protocol where the primary OH group was deprotected first using the NH_4F method. The secondary

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one was removed afterward using exactly 1 equiv of TBAF at 0 °C.

In conclusion, we can show that the unusual amino acids of the cyclomarins can be synthesized in enantiomerically pure form in high yields. With these building blocks in hand, cyclomarin A, the most complex representative of this family of cyclopeptides, could be obtained. Syntheses of the other family members and derivatives thereof for SAR studies are under investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03292.

Detailed experimental procedures and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) WHO. *Fact Sheet Tuberkulose*, http://www.who.int/mediacentre/factsheets/fs104/en/ (accessed Nov 30, 2015).

(2) WHO. *Global Tuberculosis Report 2014*, http://www.who.int/tb/publications/global_report/en/ (accessed Nov 30, 2015).

(3) (a) McClure, W. R.; Cech, C. L. *J. Biol. Chem.* **1978**, *253*, 8949−8956. (b) Rawat, R.; Whitty, A.; Tonge, P. J. *Proc. Natl. Acad. Sci. U. S. A.* **2003**, *100*, 13881−13886. (c) Zhang, Y. *Annu. Rev. Pharmacol. Toxicol.* **2005**, *45*, 529−64.

(4) Renner, M. K.; Shen, Y. C.; Cheng, X. C.; Jensen, P. R.; Frankmoelle, W.; Kauffman, C. A.; Fenical, W.; Lobkovsky, E.; Clardy, J. *J. Am. Chem. Soc.* **1999**, *121*, 11273−11276.

(5) Gontang, E. A.; Fenical, W.; Jensen, P. R. *Appl. Environ. Microbiol.* **2007**, *73*, 3272−3282.

(6) Pazoles, C. J.; Siegel, S. A. US Patent US5759995 A, 1998.

(7) (a) Schmitt, E. K.; Riwanto, N.; Sambandamurthy, V.; Roggo, S.; Miault, C.; Zwingelstein, C.; Krastel, P.; Noble, C.; Beer, D.; Rao, S. P. S.; Au, M.; Niyomrattanakit, P.; Lim, V.; Zheng, J.; Jeffery, D.; Pethe, K.; Camacho, L. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 5889−5891. (b) Vasudevan, D.; Rao, S. P. S.; Noble, C. G. *J. Biol. Chem.* **2013**, *288*, 30883−30891.

(8) (a) Schmitt, E. K.; Hoepfner, D.; Krastel, P. *J. Ind. Microbiol. Biotechnol.* **2015**, DOI: 10.1007/s10295-015-1691-9. (b) Buerstner, N.; Roggo, S.; Ostermann, N.; Blank, J.; Delmas, C.; Freuler, F.; Gerhartz, B.; Hinninger, A.; Hoepfner, D.; Liechty, B.; Mihalic, M.; Murphy, J.; Pistorius, D.; Rottmann, M.; Thomas, R. T.; Schirle, M.; Schmitt, E. K. *ChemBioChem* **2015**, *16*, 2433−2436.

(9) (a) Wen, S.-J.; Yao, Z.-J. *Org. Lett.* **2004**, *6*, 2721−2724. (b) Wen, S.-J.; Hu, T.-J.; Yao, Z.-J. *Tetrahedron* **2005**, *61*, 4931−4938.

(10) (a) Isogai, A.; Nakayama, J.; Takayama, S.; Kusai, A.; Suzuki, A. *Biosci., Biotechnol., Biochem.* **1992**, *56*, 1079−1085. (b) Ueda, K.; Xiao, J. Z.; Doke, N.; Nakatsuka, S. *Tetrahedron Lett.* **1992**, *33*, 5377−5380. (c) Tada, H.; Tozyo, T.; Terui, Y.; Hayashi, F. *Chem. Lett.* **1992**, *21*, 431−434.

(11) (2*S*,3*R*)-3-Methoxyphenylalanin: (a) Sugiyama, H.; Shiori, T.; Yokokawa, F. *Tetrahedron Lett.* **2002**, *43*, 3489−3492. (b) Hajra, S.; Karmakar, A. *Tetrahedron Lett.* **2004**, *45*, 3185−3188. (c) Hansen, D. B.; Joullié, M. M. *Tetrahedron: Asymmetry* **2005**, *16*, 3963−3969. (d) Hajra, S.; Karmakar, A.; Bhowmick, M. *Tetrahedron: Asymmetry* **2006**, *17*, 210−222.

(12) (2*S*,4*R*)-5-Hydroxyleucin: (a) Reference 14a. (b) Tarver, J. E., Jr.; Terranova, K. M.; Joullié, M. M. *Tetrahedron* **2004**, *60*, 10277−10284. (c) Sathish, K.; Reddy, G. P. K.; Mainkar, P. S.; Chandrasekhar, S. *Tetrahedron: Asymmetry* **2011**, *22*, 1568−1573.

(13) (2*S*,3*R*)-2-Amino-3,5-dimethyl-4-hexenoic acid: (a) Tarver, J. E., Jr.; Joullié, M. M. *J. Org. Chem.* **2004**, *69*, 815−820. (b) Reference 15a. (c) Nian, Y.; Wang, J.; Zhou, S.; Wang, S.; Moriwaki, H.; Kawashima, A.; Soloshonok, V. A.; Liu, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 12918−12922.

(14) (2*S*,3*R*)-3-Hydroxytryptophane: (a) Sugiyama, H.; Yokokawa, F.; Aoyama, T.; Shiori, T. *Tetrahedron Lett.* **2001**, *42*, 7277−7208. (b) Della Sala, G.; Izzo, I.; Spinella, A. *Synlett* **2006**, 1319−1322. (c) Hansen, D. B.; Lewis, A. S.; Gavalas, S. J.; Joullié, M. M. *Tetrahedron: Asymmetry* **2006**, *17*, 15−21.

(15) (a) Kazmaier, U.; Schauß, D.; Pohlman, M.; Raddatz, S. *Synthesis* **2000**, *2000*, 914−916. (b) Pohlman, M.; Kazmaier, U. *Org. Lett.* **2003**, *5*, 2631−2633. (c) Kazmaier, U.; Deska, J. *Curr. Org. Chem.* **2008**, *12*, 355−385.

(16) (a) Grandel, R.; Kazmaier, U. *Tetrahedron Lett.* **1997**, *38*, 8009−8012. (b) Kazmaier, U.; Grandel, R. *Eur. J. Org. Chem.* **1998**, *1998*, 1833−1840. (c) Grandel, R.; Kazmaier, U.; Rominger, F. *J. Org. Chem.* **1998**, *63*, 4524−4528.

(17) (a) Krebs, A.; Kazmaier, U. *Tetrahedron Lett.* **1996**, *37*, 7945−7946. (b) Kazmaier, U.; Schneider, C. *Synlett* **1996**, *1996*, 975−977. (c) Kazmaier, U.; Schneider, C. *Tetrahedron Lett.* **1998**, *39*, 817−818. (d) Kazmaier, U.; Schneider, C. *Synthesis* **1998**, *1998*, 1321−1326.

(18) (a) Kazmaier, U.; Deska, J.; Watzke, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4855−4858. (b) Deska, J.; Kazmaier, U. *Angew. Chem., Int. Ed.* **2007**, *46*, 4570−4573. (c) Deska, J.; Kazmaier, U. *Chem. - Eur. J.* **2007**, *13*, 6204−6211. (d) Kazmaier, U.; Stolz, D.; Krämer, K.; Zumpe, F. *Chem. - Eur. J.* **2008**, *14*, 1322−1329.

(19) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, *1998*, 26−28.

(20) Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, *1992*, 487−490.

(21) Schmidt, U.; Lieberknecht, A.; Kazmaier, U.; Griesser, H.; Jung, G.; Metzger, J. *Synthesis* **1991**, *1991*, 49−55.

(22) (a) Van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; Van Esch, J.; De Vries, A. H. M.; De Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539−11540. (b) Panella, L.; Aleixandre, A. M.; Kruidhof, J.; Robertus, G. J.; Feringa, B. L.; de Vries, J. D.; Minnaard, A. J. *J. Org. Chem.* **2006**, *71*, 2026−2036.

(23) Deska, J.; Hähn, S.; Kazmaier, U. *Org. Lett.* **2011**, *13*, 3210−3213.

(24) (a) Takahashi, H.; Tanahashi, K.; Higashiyama, K.; Onishi, H. *Chem. Pharm. Bull.* **1986**, *34*, 479−485. (b) Muramatsu, Y.; Harada, T. *Chem. - Eur. J.* **2008**, *14*, 10560−10563.

(25) Barbie, P.; Kazmaier, U. *Org. Biomol. Chem.* **2015**, *13*, 9267−9275.

(26) Johnson, K. F.; Van Zeeland, R.; Stanley, L. M. *Org. Lett.* **2013**, *15*, 2798−2801.

(27) (a) Piers, E.; Brown, R. K. *Can. J. Chem.* **1962**, *40*, 559−561. (b) Powers, J. C. *Tetrahedron Lett.* **1965**, *6*, 655−658. (c) Hendrickson, J. B.; Wang, J. *Org. Lett.* **2004**, *6*, 3−5.

(28) (a) Miller, F. P.; Metzger, A.; Schade, M. A.; Haag, B. A.; Gavrushin, A.; Knochel, P. *Chem. - Eur. J.* **2009**, *15*, 7192−7202. (b) Metzger, A.; Berhardt, S.; Manolikates, G.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 4665−4668.

(29) Kawai, A.; Hara, O.; Hamada, Y.; Shiori, T. *Tetrahedron Lett.* **1988**, *29*, 6331−6334.

(30) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

(31) McDonald, C.; Holcomb, H.; Kennedy, K.; Kirkpatrick, E.; Leathers, T.; Vanemon, P. *J. Org. Chem.* **1989**, *54*, 1213−1215.

(32) Li, P.; Xu, J. C. *J. Org. Chem.* **2000**, *65*, 2951−2958.

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3-Imidoallenylphosphonates: *In Situ* Formation and β-Alkoxylation

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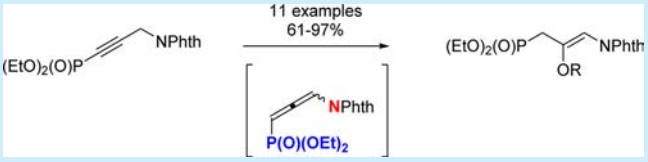
Supporting Information

ABSTRACT: 3-Imidoallenylphosphonates, allenes bearing both an electron-withdrawing and -donating group, were isolated for the first time. An alkoxy substituent was introduced into these unprecedented intermediates in a one-pot approach, yielding β-functionalized aminophosphonates in excellent yields and short reaction times. The mechanistic insights gained are important additions to the domain of allene chemistry. Addition of biologically important molecules, including monoglycerides, amino acids, and nucleosides, proves the general applicability of the developed method.

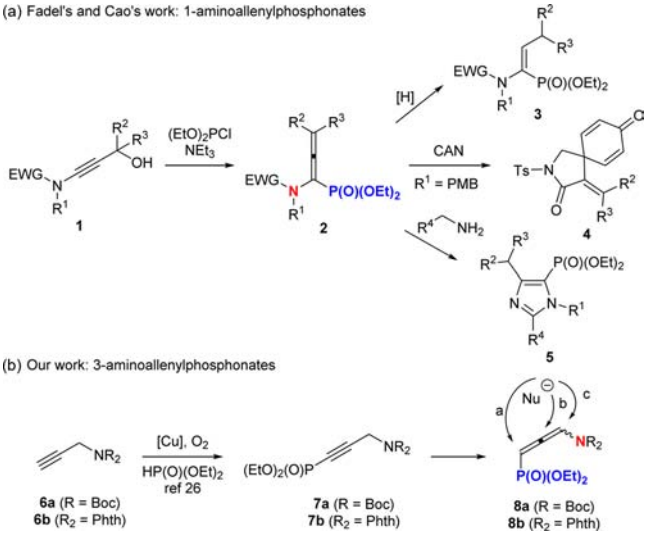


Allenes are highly interesting building blocks, displaying a broad range of reactivities owing to their unique molecular structure of cumulated double bonds.[1,2] Like alkynes,[3,4] they are excellent substrates for transition-metal-catalyzed cycloisomerizations and readily participate in cycloadditions.[5] They are, however, often underused because of their supposedly low stability. Amino-substituted allenes react with alcohols, thiols, and secondary amines to give 1,2-adducts[6] and react in [2 + 2] or [2 + 4] cycloadditions.[7] These electron-rich allenamines, however, are difficult to handle. They tend to polymerize even at low temperatures and are sensitive to moisture.[8] Amidoallenes, being less electron-rich, are more stable and display enamide reactivity. For instance, they are hydroaminated through Lewis acid activation of the proximal double bond[9] or undergo alkoxylation at the α- or γ-position, but usually not at the β-position.[10] On the other hand, nucleophilic addition to acceptor substituted allenes usually takes place at the β-position yielding either the nonconjugated (kinetic control) or the conjugated (thermodynamic control) product. In this work we explored the unique reactivity pattern of allenylphosphonates bearing an imide *N*-substituent. As part of our continuing interest in phosphonylated *N*-containing compounds,[11−15] we investigated the one-pot synthesis and conversion of these previously unreported 3-imidoallenylphosphonates **8** (Scheme 1b). The first synthesis of allenylphosphonates was reported simultaneously by Mark and Boisselle, employing a [2,3]-sigmatropic rearrangement of phosphonylated propargyl alcohols.[16,17] These allenylphosphonates were readily activated by electrophiles to produce oxaphospholenes through intramolecular cyclization.[18] Recently, the Fadel group reported the same sigmatropic rearrangement for ynamido-alcohols, yielding the corresponding 1-sulfonamidoallenylphosphonates **2**.[19] They could be selectively reduced to α-vinylaminophosphonates **3**, but also reacted in a 5-*endo*-*dig* cyclization upon deprotection of the PMB-group with CAN (Scheme 1a).[20] Reaction with primary amines produced phosphonylated imidazoles **5**.[21]

Phosphite addition to propyn iminium salts failed to produce 3-aminoallenylphosphonates, and to the best of our knowledge, there is no further information on the synthesis or reactivity of 3-aminoallenylphosphonates **8**.[22,23] Aside from the mechanistic interest, they are also precursors to γ-aminophosphonates. Aminophosphonates are bioisosteres of amino acids and can act as peptidomimetics in known antibacterial, antifungal, and herbicidal agents.[24] Allenes themselves can also play an important role in the metabolic stability of pharmaceuticals. Enprostil is a marketed prostaglandin analogue that is over 600 times more potent than PGE_2 in inhibiting gastric acid secretion.[25]

Our investigation started from phosphonylated propargylamines **7a−b**, which were easily prepared using an improved literature procedure. Gao reported an elegant phosphonylation

Scheme 1. Approaches for the Synthesis of Aminoallenylphosphonates



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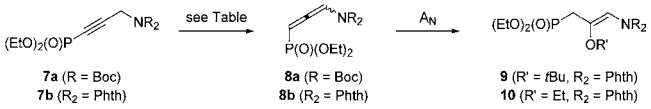
of alkynes under a dry air atmosphere, but only on a 0.5 mmol scale and requiring 16 h.[26] When scaling up the reaction we found that also Glaser coupling occurred, which could be suppressed by bubbling oxygen through the reaction mixture. The phosphonylated alkynes **7a**–**b** were obtained in high yields on a 10 mmol scale in drastically shortened reaction times (see Supporting Information). In preliminary experiments, phosphonylated *N*,*N*-di-Boc-propargylamine **7a** was used as starting material. At first, stoichiometric isomerization was evaluated with organolithium bases (BuLi, LDA) in aprotic media.[27,28] However, the isomeric allenic products could not be detected (Table 1, entries 1–2).[29]

Table 1. Optimization of Isomerization and Nucleophilic Addition Conditions



7a (R = Boc)
7b (R_2 = Phth)
8a (R = Boc)
8b (R_2 = Phth)
9 (R' = *t*Bu, R_2 = Phth)
10 (R' = Et, R_2 = Phth)

entry	equiv base	base	solvent	time (min)	*t* (°C)	**8** (%)[c]	**9**/**10** (%)[c]
1	1	BuLi	dry Et_2O	60	−78	0	0
2	1	LDA	dry Et_2O	180	0	0	0
3	1	NaH	dry THF	60	rt	32	0
4	0.2	NaH	dry THF	30	Δ	24	0
5	0.2	KO*t*Bu	DMSO	5	rt	0	7
6	1	KO*t*Bu	dry THF	1	rt	19	4
7[a]	0.2	KO*t*Bu	dry THF	2	0	47	0
8	1	KO*t*Bu	*t*-BuOH	5	40	34	25
9	2	KO*t*Bu	*t*-BuOH	1	40	0	100
10[b]	1	K_2CO_3	THF	8 days	rt	0	100
11[b]	1	Cs_2CO_3	THF	40	rt	0	100

[a]1 equiv of *t*-BuOH added. [b]1 equiv of EtOH added. [c]^{31}P NMR conversion.

Accordingly, phthalimidoyl protected alkyne **7b** was then used exclusively, as the Boc-groups of alkyne **7a** were not stable under the previously applied conditions. Next, the isomerization using a milder NaH or KO*t*Bu aprotic system was investigated. Using a stoichiometric amount of NaH, 32% of the starting material was converted into the allene within 1 h,[30] after which degradation quickly occurred (entry 3). Using a catalytic amount of NaH led to a lower conversion, while secondary reactions still occurred (entry 4). When performing the reaction in DMSO with KO*t*Bu as the base,[31] 7% conversion to an addition product **9** was observed (entry 5). Although allene **8b** was not detected, this addition product caught our interest given the position of the double bond.[32] Switching the solvent to THF and employing a stoichiometric amount of base[33] gave the allene intermediate **8b** and the addition product **9** together for the first time (entry 6). Providing a proton source by adding 1 equiv of *t*-BuOH markedly increased the conversion of the starting material, giving ∼50% of the allene in only 2 min at 0 °C (entry 7). Longer reaction times gave complex mixtures. Screening of different solvents in the KO*t*Bu/*t*-BuOH system revealed that conversion to allene **8b** was rapid but a conversion higher than 50% could not be achieved (SI, Table 1), as alkyne **7b** and allene **8b** were most likely in equilibrium. We then decided to scavenge the intermediate allene **8b** to obtain full conversion to the addition product.

Performing the addition in *t*-BuOH instead of adding just 1 equiv of *t*-BuOH as a proton source[34] clearly drives addition of the nucleophile to the allene intermediate (entry 8). Increasing the amount of KO*t*Bu to 2 equiv gave complete reaction in no more than 60 s (entry 9). We next investigated whether other—and eventually nonvolatile—nucleophiles could be added. To that end, a non-nucleophilic base, an aprotic solvent, and the use of a stoichiometric amount of the nucleophile were required (conditions A). Hence, K_2CO_3 and THF were selected, using 1 equiv of EtOH as the nucleophile. The addition product **10** was obtained as the single product, but full conversion required 8 days (entry 10). We reasoned that the limited solubility of the base hampered reaction progress. Thus, replacing K_2CO_3 with Cs_2CO_3 gave a completed reaction in only 40 min (entry 11).[35] NMR disclosed a *Z*-configuration of the olefin based on a 2.5% NOE-enhancement of the vinylic proton when irradiating CH_2P. No NOE-effects were observed between OCH_2 and the vinylic proton.

Next, we prepared a small library of derivatives. The addition of primary, secondary, and tertiary alcohols was first evaluated (Scheme 2, compounds **9**–**11**). As steric hindrance of the introduced nucleophile increased, the transformation proceeded more slowly, and in the case of *t*-BuOH, a complex mixture was obtained. With *i*-PrOH, the addition product was still the major product, along with some remaining alkyne and allene starting material and a multitude of minor impurities. For volatile nucleophiles, the nucleophile could be applied as the solvent (conditions B). With EtOH, addition was rapid (60 s), and the addition product **10** was isolated in 97% yield. The *i*-PrOH derivative **11** could similarly be obtained in 94% yield. Upon conducting the reaction in *t*-BuOH as a solvent, 82% conversion to **9** was achieved after 3 h at 40 °C. Longer reaction times gave secondary reactions that prevented isolation of **9**. Other primary alcohols such as *n*-BuOH and BnOH smoothly gave the desired compounds **12** and **14** in yields around 90% (conditions A), again without the need for purification. Phenol reacted rapidly to give a mixture of two addition products **13a** and **13b** in a 6:1 ratio and 90% yield. With the sterically demanding (−)-borneol as a nucleophile, the intermediacy of the allene was illustrated once again, but a conversion higher than 20% to the addition product **15** could not be achieved, nor could **15** be isolated. The presence of an electrophilic group in the substrate, such as the aldehyde in 5-HMF (5-hydroxymethylfurfural), did not complicate matters giving full conversion to **16** in 90% crude yield in 1 h. When preparing an analytical sample, the removal of some minor impurities required reversed phase flash chromatography causing partial degradation, which has been previously observed in the isolation of related HMF derivatives.[36] The coupling of two allene moieties with ethylene glycol also proved to be easily achievable as all of the starting material was converted into an easily separable 91/9 mixture of bis-adduct **17a** and monoadduct **17b**. When water was evaluated as a nucleophile, the formation of the corresponding ketone was expected, but we instead observed formation of a complex reaction mixture, probably due to aldol-type reactions.

Finally, the addition of more complex and biologically relevant molecules was investigated. Addition of DL-α-palmitin gave rise to phospholipid-type product **18**. Full conversion was obtained in 30 min, resulting in four addition products (ratio 9:34:50:7 in 96% crude yield), which could not be separately isolated (see SI). Addition of protected amino acids resulted in phosphonopeptides **19** and **20**. Phosphonopeptides often display important biological activities. Bialaphos for instance is an antibacterial metabolite, which also possesses strong herbicidal properties.[24] Adduct **19** was isolated in 63% yield as a 9/1 *Z*/*E* mixture. Partial

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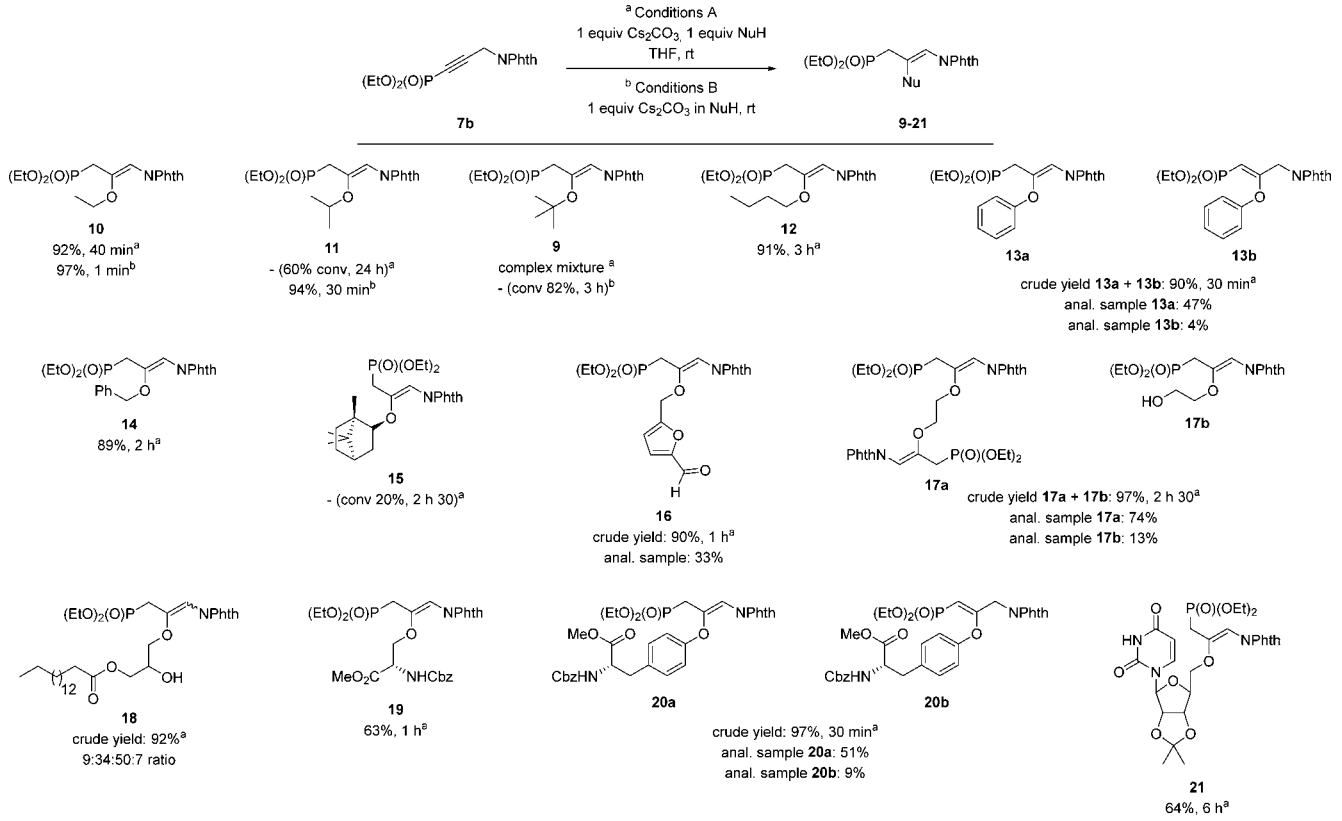
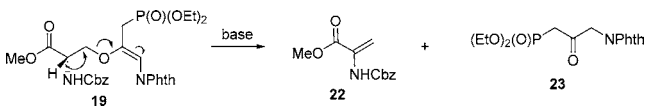
Scheme 2. Substrate Scope of Formation of β-Functionalized Aminophosphonates[a]



[a]Isolated yield and reaction time are indicated.

elimination of the addition product **19**, giving **22** and **23**, was unavoidable, even when running the reaction at 0 °C, and accounts for the slightly lowered yield in comparison to less complex nucleophiles (Scheme 3).

Scheme 3. Elimination of the *N*-*Z*-L-Serine Methyl Ester Addition Product

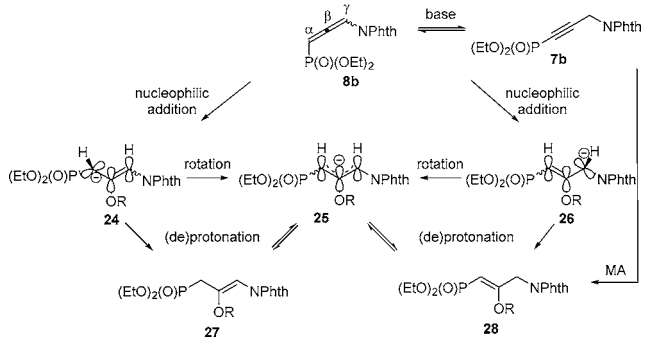


Addition of *N*-*Z*-L-tyrosine methyl ester did not suffer from this elimination reaction, as no acidic proton is present in the tyrosine methyl ester. As was the case with the addition of phenol, allylphosphonate **20a** and vinylphosphonate **20b** were swiftly formed in a 6:1 ratio in 97% crude yield, after which the regioisomers were separated from each other. The conformation of **20b** was confirmed to be *Z*, as a 2% NOE-effect was found on the vinylic proton when irradiating NCH_2. Ultimately, the addition of protected uridine was evaluated, as phosphonucleosides such as tenofovir and adefovir are used in the treatment of HIV. We were pleased to find that the uridine addition product **21** could be isolated in 64% yield. For all of the synthesized derivatives, addition selectively occurs at the central C-atom. This illustrates that 3-imidoallenylphosphonates behave as acceptor substituted allenes.

Finally, we investigated the mechanism of this alkoxylation reaction. Michael addition to alkyne **7b**[37] would initially produce vinylphosphonate **28** which can isomerize to yield the allylphosphonate **27**. Although vinylphosphonate **28** was never detected in NMR experiments, only alkoxylation of isolated allene **8b** can unambiguously rule out Michael addition. To this end, alkyne **7b** was isomerized (Cs_2CO_3/THF; see SI) to the allene **8b** resulting in the first ever isolation of the 3-imidoallenylphosphonate **8b** in 16% yield. First, it was found to be stable for several days, thus countering arguments that these allenes display low stability. Second, allene **8b** was indeed in equilibrium with alkyne **7b**, as 16% isomerization to **7b** was found under the same conditions.

Most importantly, full conversion of allene **8b** to allylphosphonate **27** in the presence of Cs_2CO_3 and EtOH is compelling evidence for the allene being the key intermediate in this one-pot, two-step reaction. However, it is clear that product **28** can also be produced from the addition to allene **8b** (Scheme 4). Regardless of the nucleophile adding across the $C_\alpha-C_\beta$ or the $C_\beta-C_\gamma$ double bond, the formation of a nonconjugated allyl anion, **24** or **26**,

Scheme 4. Proposed Mechanism



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results, owing to the unique orbital structure of allenes. These nonconjugated anions either can be immediately protonated to give **27** or **28** respectively or can rotate around their single bond, forming the conjugated allyl anion **25**. After protonation this can lead again to the formation of either the allylphosphonate **27** or the vinylphosphonate **28**.

During our syntheses we exclusively observed the formation of allylphosphonates **27**, except for phenolic nucleophiles. In the case of phenol addition at rt, a 6:1 **27**/**28** ratio was found. When this addition was repeated at 0 °C we found a 12:1 **27**/**28** ratio. This indicates either that the addition reaction is under kinetic control or that Michael addition to alkyne **7b** occurs (**7b** to **28**) and is suppressed at this lower temperature. Whatever the case, it was shown that the pathway does not primarily pass over **28**. Under the applied conditions (rt, Cs_2CO_3) **28** did not isomerize to **27**. Furthermore, **27** was shown to be the thermodynamically more stable product, as **28** was entirely converted to **27** upon 18 h of reflux. Thus, the formation of **28** is not a part of the major reaction pathway.[38] This is in accordance with literature data, as addition of NaN_3 to 3-phenylpropa-1,2-dienylphosphonate also gives the allylphosphonate, preserving the double bond conjugated to the aromatic group.[39]

In conclusion, the first synthesis of 3-imidoallenylphosphonates was demonstrated. This transformation proceeds via a prototropic rearrangement under very mild conditions, and the imidoallenylphosphonate was isolated and characterized. Moreover, it can be alkoxylated in a one-pot procedure in very short reaction times in excellent chemical yields. The method is applicable to an array of highly functionalized biologically relevant nucleophiles, furnishing these adducts in moderate to good yields. Purification on column was needed only in the case of the more complex nucleophiles (**15**−**21**).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03314.

Experimental details, product characterizations, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004.
(2) Fourgeaud, P.; Daydé, B.; Volle, J.; Vors, J.; Van der Lee, A.; Pirat, J.; Virieux, D. *Org. Lett.* **2011**, *13*, 5076.
(3) Debrouwer, W.; Seigneur, R. A. J.; Heugebaert, T. S. A.; Stevens, C. V. *Chem. Commun.* **2015**, *51*, 729.
(4) Debrouwer, W.; Heugebaert, T. S. A.; Roman, B. I.; Stevens, C. V. *Adv. Synth. Catal.* **2015**, *357*, 2975.
(5) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994.
(6) Klop, W.; Klusener, P. A. A.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 27.
(7) Klop, W.; Klusener, P. A. A.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 85.
(8) Lu, T.; Lu, Z.; Ma, Z. X.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2013**, *113*, 4862.
(9) Hill, A. W.; Elsegood, M. R.; Kimber, M. C. *J. Org. Chem.* **2010**, *75*, 5406.
(10) Horino, Y.; Takata, Y.; Hashimoto, K.; Kuroda, S.; Kimura, M.; Tamaru, Y. *Org. Biomol. Chem.* **2008**, *6*, 4105.
(11) Debrouwer, W.; Heugebaert, T. S.; Stevens, C. V. *J. Org. Chem.* **2014**, *79*, 4322.
(12) Debrouwer, W.; Heugebaert, T. S.; Van Hecke, K.; Stevens, C. V. *J. Org. Chem.* **2013**, *78*, 8232.
(13) Van Waes, F. E. A.; Debrouwer, W.; Heugebaert, T. S. A.; Stevens, C. V. *ARKIVOC* **2014**, 386.
(14) Dieltiens, N.; Moonen, K.; Stevens, C. V. *Chem. - Eur. J.* **2007**, *13*, 203.
(15) Moonen, K.; Van Meenen, E.; Verwee, A.; Stevens, C. V. *Angew. Chem., Int. Ed.* **2005**, *44*, 7407.
(16) Mark, V. *Tetrahedron Lett.* **1962**, *3*, 281.
(17) Boisselle, A. P.; Meinhardt, N. A. *J. Org. Chem.* **1962**, *27*, 1828.
(18) Macomber, R. S. *J. Am. Chem. Soc.* **1977**, *99*, 3072.
(19) Gomes, F.; Fadel, A.; Rabasso, N. *J. Org. Chem.* **2012**, *77*, 5439.
(20) Adler, P.; Gomes, F.; Fadel, A.; Rabasso, N. *Eur. J. Org. Chem.* **2013**, *2013*, 7546.
(21) Yu, L.; Deng, Y.; Cao, J. *J. Org. Chem.* **2015**, *80*, 4729.
(22) Reisser, M.; Maier, A.; Maas, G. *Eur. J. Org. Chem.* **2003**, *2003*, 2071.
(23) Reisser, M.; Maas, G. *J. Org. Chem.* **2004**, *69*, 4913.
(24) *Aminophosphonic and aminophosphinic acids: Chemistry and Biological Activity*; Kukhar, V. P., Hudson, H. R., Eds.; Wiley: Hoboken, NJ, 2000.
(25) Carpio, H.; Cooper, G. F.; Edwards, J. A.; Fried, J. H.; Garay, G. L.; Guzman, A.; Mendez, J. A.; Muchowski, J. M.; Roszkowski, A. P.; Van Horn, A. R. *Prostaglandins* **1987**, *33*, 169.
(26) Gao, Y.; Wang, G.; Chen, L.; Xu, P.; Zhao, Y.; Zhou, Y.; Han, L. *J. Am. Chem. Soc.* **2009**, *131*, 7956.
(27) Steinmetz, M. G.; Mayes, R. T. *J. Am. Chem. Soc.* **1985**, *107*, 2111.
(28) Doye, S.; Hotopp, T.; Wartchow, R.; Winterfeldt, E. *Chem. - Eur. J.* **1998**, *4*, 1480.
(29) With BuLi the alkyne was dephosphonylated, while LDA attacked the *t*Bu-group producing the carbamic acid which cyclized to produce the oxazolidinone.
(30) Sturtz, G.; Paugam, J. P.; Corbel, B. *Synthesis* **1974**, *1974*, 730.
(31) Selling, H. A.; Rompes, J. A.; Montijn, P. P.; Hoff, S.; van Boom, J. H.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 119.
(32) A $^2J_{HP}$ coupling constant of about 20 Hz is typical for a PC_{sp^3} fragment, indicating protonation of the carbon in α-position to the phosphonate had occurred.
(33) Lehrich, F.; Hopf, H. *Tetrahedron Lett.* **1987**, *28*, 2697.
(34) Deutsch, E. A.; Snider, B. B. *Tetrahedron Lett.* **1983**, *24*, 3701.
(35) It was noted that when a catalytic amount of Cs_2CO_3 was used, full conversion could not be obtained.
(36) Heugebaert, T. S. A.; Stevens, C. V.; Kappe, C. O. *ChemSusChem* **2015**, *8*, 1648.
(37) Panarina, A. E.; Dogadina, A. V.; Ionin, B. I. *Russ. J. Gen. Chem.* **2003**, *73*, 1729.
(38) Moreover, it was shown that the addition was irreversible under the applied conditions. No exchange of the alkoxy moiety was observed upon reacting **10** with BnOH and Cs_2CO_3.
(39) Abramovitch, R. A.; Konieczny, M.; Pennington, W.; Kanamathareddy, S.; Vedachalam, M. *J. Chem. Soc., Chem. Commun.* **1990**, 269.

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Organic LETTERS

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Ruthenium-Catalyzed Urea Synthesis Using Methanol as the C1 Source

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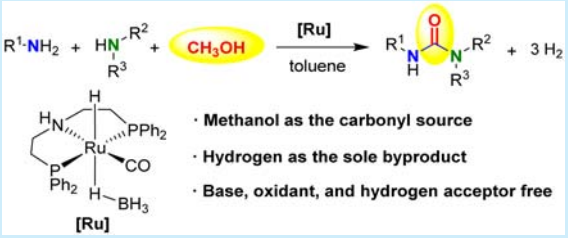
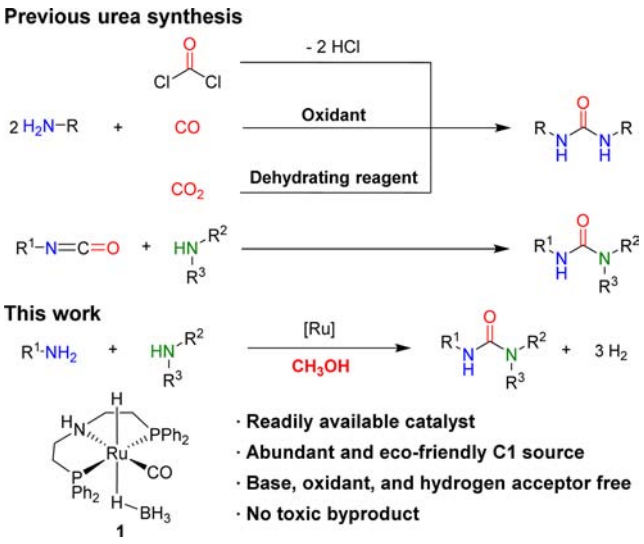
Supporting Information

ABSTRACT: An unprecedented protocol for urea synthesis directly from methanol and amine was accomplished. The reaction is highly atom-economical, producing hydrogen as the sole byproduct. Commercially available ruthenium pincer complexes were used as catalysts. In addition, no additive, such as a base, oxidant, or hydrogen acceptor, was required. Furthermore, unsymmetrical urea derivatives were successfully obtained via a one-pot, two-step reaction.



Urea derivatives are commonly found in widespread applications, such as biologically active compounds, pharmaceuticals, agricultural pesticides, dyes for cellulose fibers, and antioxidants in gasoline.[1] Many classical protocols and catalytic transformations have been developed for urea synthesis. Traditional syntheses of urea derivatives use phosgene and isocyanates, which cause tremendous toxicological and environmental problems (Scheme 1).[2] Alternative routes using carbon monoxide (CO) as the source of the carbonyl moiety have been developed;[3] these carbonylation reactions are generally carried out at high temperatures under high CO pressure with oxidants. In recent years, the utilization of CO_2 has attracted significant attention because it is a renewable carbon resource.[4] However, the required stoichiometric use of expensive and waste-producing dehydrating reagents, such as di-*tert*-butyl azodicarboxylate (DBAD), to generate the isocyanate intermediates still limits the utility of the reaction.[4] Therefore, versatile urea synthesis under mild conditions that avoids environmentally harmful reagents remains a major challenge.

Scheme 1. Synthesis of Urea Derivatives



Recently, environmentally benign and atom-economical C−N and C−C bond formation reactions utilizing alcohols, generating water[5] or hydrogen[6,7] as the byproduct, have attracted much attention. By applying the concept of acceptorless dehydrogenative activation of alcohols,[7] and based on the thermodynamic feasibility for the formation of 1,3-dimethyl urea from methylamine and methanol (ΔH°_{298} = −66.2 kJ/mol, ΔG°_{298} = −268.8 kJ/mol),[8] we envisioned an unprecedented strategy to synthesize urea derivatives directly from amines utilizing methanol as the C1 source.

Utilization of methanol as the C1 feedstock could be an ideal solution to reduce the predominant dependence on conventional toxic C1 sources, such as phosgene and isocyanates, for urea synthesis.[9] For intermolecular coupling of alcohols and amines, three pathways, i.e., imination,[10] alkylation,[7e] and amidation,[11] have been well reported. Recently, formylation of amines using methanol as the C1 source has been developed.[12] Inspired by previous works, we devised a possible strategy to synthesize urea utilizing methanol as follows: (1) Generation of formamide in situ and (2) coupling of the formamide with amine using an active catalyst that can mediate activation of formamide followed by dehydrogenation of the resultant hemiaminal intermediate.

To identify an active catalyst for the proposed urea synthesis, we investigated complex **4**, which was recently used for the

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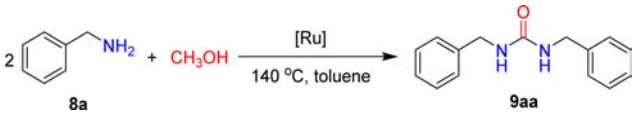
formylation of amine and nitrile with excess methanol.[12a] The reaction of benzylamine (**8a**) and methanol under modified conditions with less methanol (1.0 equiv vs amine) generated a trace amount of 1,3-dibenzyl urea (**9aa**, 5%) (Table 1, entry 5).

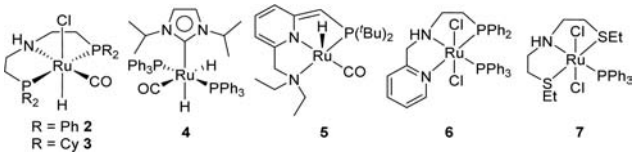
Table 1. Urea Synthesis from Methanol and Benzylamine Using Various Catalysts[a]



8a **9aa**

entry	Ru complex (0.5 mol %)	solvent	yield (%)
1	**1**	toluene	97
2[b]	**2**	toluene	93
3[b]	**3**	toluene	88
4[c]	[Ru(cod)(2-methylallyl)$_2$]	toluene	0
5	**4**	toluene	5
6	**5**	toluene	0
7[b]	**6**	toluene	0
8[b]	**7**	toluene	0
9	**1**	hexane	81
10	**1**	THF	80
11	**1**	dioxane	60
12	**1**	*p*-xylene	87

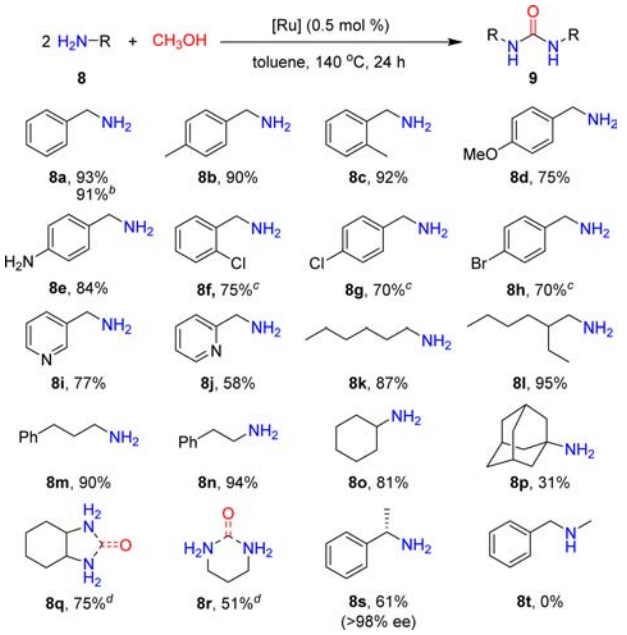
[a]Reaction conditions: benzylamine (2 mmol, 1.0 equiv), [Ru] (0.5 mol %), methanol (2 mmol), toluene (1.5 mL), 140 °C, 24 h in a closed vessel; NMR yield; *p*-xylene was used as a standard. [b]K_2CO_3 (0.5 mol %). [c][Ru(cod)(2-methylallyl)$_2$] (0.5 mol %), KO*t*Bu (1.5 mol %), and dicyclohexylimidazolium chloride (ICy-HCl, 1 mol %).



Inspired by this result, other Ru-based complexes that had been reported to catalyze acceptorless dehydrogenative coupling reactions were screened to improve the reaction efficiency. The N-formylation catalytic system developed by the Glorius group was not active for urea synthesis (entry 4).[12b] Milstein's catalyst (**5**)[11d] also did not produce any urea under the reaction conditions (entry 6). Complexes **6** and **7**, which showed excellent performance for hydrogenation of esters,[13] were not active for this reaction (entries 7 and 8). To our delight, Ru complex **2**, which is known as the Ru-MACHO catalyst,[6b,14] afforded desired product **9aa** in an excellent yield (93%) in the presence of a catalytic amount of K_2CO_3 (entry 2). Analogous complex **3** containing cyclohexyl groups on the phosphine moiety gave a slightly lower yield (88%, entry 3). Finally, when complex **1** (Ru-MACHO-BH) was used as a precatalyst, a quantitative amount of **9aa** was obtained under base-free conditions (entry 1). The reaction was optimized in a closed reaction vessel due to the low boiling point of methanol. Toluene was the best solvent among those tested (entries 9–12). Notably, the developed reaction is highly atom-economical, produces hydrogen gas as the sole byproduct, and is catalyzed by a low loading of the Ru catalyst (0.1 mol %, TONs ≈ 295, Table S2) without any additive such as a base, oxidant, or hydrogen acceptor.

Using the optimized conditions, the scope of the reaction was examined (Scheme 2). Various amines smoothly provided the corresponding symmetrical urea products in good to

Scheme 2. Symmetrical Urea Synthesis from Methanol and Amine[a]



[a]Reaction conditions: amine (2 mmol, 1.0 equiv), **1** (0.5 mol %), methanol (2 mmol), toluene (1.5 mL), 140 °C, 24 h in a closed vessel; isolated yield. [b]Amine (10 mmol, 1.0 equiv), **1** (0.5 mol %), [c]**1** (2 mol %), methanol (4 mmol), KOH (15 mol %). [d]Amine (1 mmol, 1.0 equiv), **1** (1 mol %), methanol (2 mmol).

excellent yields. Electron-rich benzylamines (**8a–e**) produced the corresponding ureas smoothly. The reaction worked efficiently even in a gram-scale reaction (1.07 g of **8a**, 91%). The use of chloride- and bromide-substituted benzylamines (**8f–8h**) required a higher catalyst loading (**1**, 2 mol %) and a base additive (KOH, 15 mol %) to obtain the products in good yields. Pyridine functional groups (**8i** and **8j**) were tolerated under the reaction conditions. Various kinds of aliphatic amines afforded the desired urea products in very good to excellent yields (**8k–8o**). In the case of 2-adamantyl amine (**8p**), a poor yield of **9pp** (31%) was observed and most of the **8p** remained; this was presumably due to high steric hindrance. Furthermore, the use of diamines **8q** and **8r** in the reaction resulted in the production of cyclic ureas. The yield of the product was relatively decreased probably due to the coordination effect of diamine. To our delight, subjection of chiral amine **8s** to the reaction generated urea product **9ss** with no epimerization. However, secondary amines, such as **8t**, and electron-deficient aryl amines, such as aniline, were not applicable under the developed reaction conditions. In the case of **8t**, the corresponding formamide was formed as the major product, which implies that the second nucleophilic addition of the secondary amine to formamide could be the limiting step for the urea synthesis. Aniline did not react at all under the reaction conditions. Therefore, in the case of 4-aminobenzyl amine (**8e**), selective urea formation on the aliphatic amine group was achieved in an 84% yield.

Next, we turned our attention to the synthesis of unsymmetrical urea derivatives. Traditionally, unsymmetrical ureas are synthesized via nucleophilic attack of amines on isocyanates. Recently, Buchwald and co-workers reported an unsymmetrical urea synthesis using an arylisocyanate intermediate synthesized by Pd-catalyzed cross-coupling of aryl

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chlorides and triflates with sodium cyanate.[15] Other efforts have been devoted to achieve in situ generation of isocyanates from different precursors, such as carboxylic acids, carbamic acids,[4c] carbamates,[16] acyl azides,[17] hydroxamic acids,[18] or acetoacetanilide.[19] They have also been prepared by functionalization of mother ureas via N-alkylation[20] or N-arylation.[21] Despite the significant advances in this field, many procedures still suffer from a limited availability of starting materials and a restricted substrate scope.

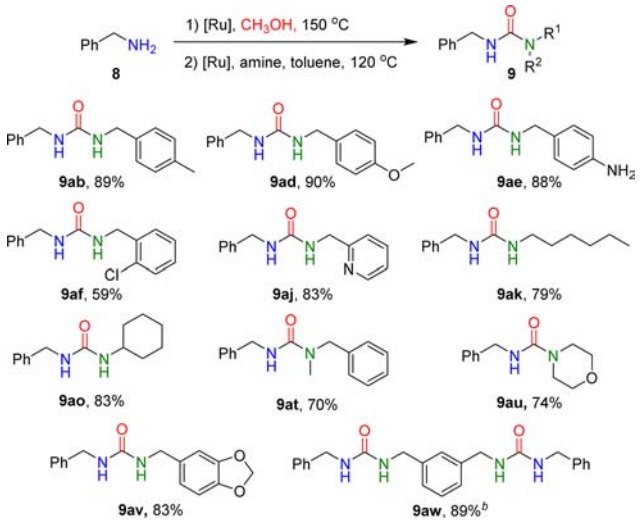
To elucidate the viability of the optimized reaction conditions for the synthesis of unsymmetrical urea, two different aliphatic amines, i.e., **8a** and **8k**, were reacted in a reaction vessel (Scheme S1). This reaction produced three of the corresponding urea derivatives with a statistical distribution: Symmetrical **9aa** (21%) and **9kk** (25%), and unsymmetrical **9ak** (48%). The reaction of 4-aminobenzyl amine (**8e**) with benzylamine resulted in a similar distribution of products. To improve the selectivity toward the unsymmetrical ureas, we devised a strategy comprising a sequential two-step reaction in one pot by first generating formamide from an amine and methanol, and then reacting the formamide with the second amine. This reaction strategy was proven to be viable by the reaction of **10** and **8k** to produce **9ak** in an excellent yield (94%) under the catalytic conditions of **1**. Recently, Reddy and co-workers reported Cu-catalyzed unsymmetrical urea synthesis from formamide and amines using *tert*-butylhydroperoxide (TBHP) as a stoichiometric oxidant at a relatively low efficiency (mostly <50% yields).[22] Here, an unsymmetrical urea synthesis from formamide and amine was achieved under oxidant-free conditions with high efficiency.

Combining the current strategy and the previous report of formamide synthesis using methanol,[12] we attempted selective unsymmetrical urea synthesis in one pot. After first generating benzyl formamide from **8** using methanol as the solvent, the methanol was removed in vacuum. Then, *n*-hexyl amine and toluene were added to the reaction tube with an additional loading of Ru complex **1** under inert conditions. After further reaction for 16 h at 120 °C, desired 1-benzyl-3-hexyl urea **9ak** was obtained in a good yield (79%).

The scope of the reaction was expanded to include a variety of coupling partners, and various unsymmetrical ureas were synthesized in good to excellent yields (Scheme 3). Reactions with amines containing heterocycles provided the corresponding ureas, i.e., **9aj** and **9av**, in very good yields. Notably, using secondary amines as the second cross partners was successful (**9at** and **9au**) although symmetrical urea synthesis of secondary amines was not possible; this implies that tertiary formamides are not reactive for further urea functionalization because of steric congestion. Unfortunately, the use of aniline in the reaction did not generate a urea derivative, as in the case of symmetrical urea synthesis. It is worthwhile to note that a diamine reacted with in situ generated formamide to afford a diurea compound (**9aw**).

An independent reaction with paraformaldehyde and benzylamine under our reaction conditions gave 1,3-dibenzylurea (Scheme S3a). To investigate the possibility of an isocyanate mediated mechanism, *N*-benzyl formamide was treated with aniline utilizing complex **1**, but no reaction occurred (Scheme S3b). Since benzyl isocyanate is easily reacted with aniline to form the corresponding urea,[23] the isocyanate mediated urea formation pathway was ruled out. In addition, isocyanate was not observed from *N*-benzyl formamide under our reaction conditions (Scheme S3b). Involvement of amidine was also

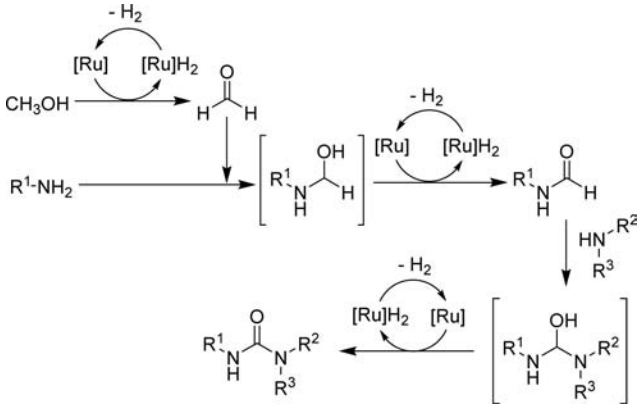
Scheme 3. Unsymmetrical Urea Synthesis from Methanol and Amine[a]



[a]Reaction conditions: (1) amine (0.5 mmol, 1.2 equiv), **1** (2 mol %), methanol (2 mL), 150 °C, 12 h in a closed vessel; (2) amine (0.42 mmol, 1 equiv), toluene (1.5 mL), **1** (4 mol %), 120 °C, 16 h in a closed vessel; isolated yield. [b]*m*-Xylylenediamine (0.21 mmol) in the second step.

excluded, as we could not observe the formation of amidine under our reaction conditions even in the presence of molecular sieves to remove water. Based on the results, the formation of urea is proposed to follow the pathway shown in Scheme 4. The primary amine is oxidatively coupled with

Scheme 4. Proposed Mechanism



formaldehyde, which is formed from dehydrogenation of methanol, to generate the formamide. Subsequent nucleophilic attack of an amine on the formamide generates the hemiaminal analogue, which is further dehydrogenated to the urea.

In conclusion, we reported a novel urea synthetic method directly from methanol and amines catalyzed by a readily available ruthenium PNP catalyst with hydrogen as the sole byproduct. No additive, such as a base, oxidant, or hydrogen acceptor, was required. Symmetrical and unsymmetrical urea derivatives were successfully obtained using methanol as the C1 feedstock by applying a dehydrogenative condensation strategy.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03328.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Gallou, I. *Org. Prep. Proced. Int.* **2007**, *39*, 355. (b) Bankston, D.; Dumas, J.; Natero, R.; Riedl, B.; Monahan, M.-K.; Sibley, R. *Org. Process Res. Dev.* **2002**, *6*, 777. (c) Matsuda, K. *Med. Res. Rev.* **1994**, *14*, 271.

(2) (a) Bigi, F.; Maggi, R.; Sartori, G. *Green Chem.* **2000**, *2*, 140. (b) Babad, H.; Zeiler, A. G. *Chem. Rev.* **1973**, *73*, 75.

(3) (a) Guan, Z.-H.; Lei, H.; Chen, M.; Ren, Z.-H.; Bai, Y.; Wang, Y.-Y. *Adv. Synth. Catal.* **2012**, *354*, 489. (b) Park, J. H.; Yoon, J. C.; Chung, Y. K. *Adv. Synth. Catal.* **2009**, *351*, 1233. (c) Orito, K.; Miyazawa, M.; Nakamura, T.; Horibata, A.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Yamazaki, T.; Tokuda, M. *J. Org. Chem.* **2006**, *71*, 5951. (d) Gabriele, B.; Salerno, G.; Mancuso, R.; Costa, M. *J. Org. Chem.* **2004**, *69*, 4741. (e) McCusker, J. E.; Main, A. D.; Johnson, K. S.; Grasso, C. A.; McElwee-White, L. *J. Org. Chem.* **2000**, *65*, 5216.

(4) (a) Honda, M.; Sonehara, S.; Yasuda, H.; Nakagawa, Y.; Tomishige, K. *Green Chem.* **2011**, *13*, 3406. (b) Kong, D.-L.; He, L.-N.; Wang, J.-Q. *Synlett* **2010**, *2010*, 1276. (c) Peterson, S. L.; Stucka, S. M.; Dinsmore, C. J. *Org. Lett.* **2010**, *12*, 1340. (d) Wu, C.; Cheng, H.; Liu, R.; Wang, Q.; Hao, Y.; Yu, Y.; Zhao, F. *Green Chem.* **2010**, *12*, 1811. (e) Jiang, T.; Ma, X.; Zhou, Y.; Liang, S.; Zhang, J.; Han, B. *Green Chem.* **2008**, *10*, 465. (f) Ion, A.; Parvulescu, V.; Jacobs, P.; Vos, D. D. *Green Chem.* **2007**, *9*, 158.

(5) (a) Kalutharage, N.; Yi, C. S. *Org. Lett.* **2015**, *17*, 1778. (b) Lee, D.-H.; Kwon, K.-H.; Yi, C. S. *J. Am. Chem. Soc.* **2012**, *134*, 7325. (c) Lee, D. H.; Kwon, K. H.; Yi, C. S. *Science* **2011**, *333*, 1613.

(6) (a) Fujita, K.-i.; Kawahara, R.; Aikawa, T.; Yamaguchi, R. *Angew. Chem., Int. Ed.* **2015**, *54*, 9057. (b) Nielsen, M.; Alberico, E.; Baumann, W.; Drexler, H. J.; Junge, H.; Gladiali, S.; Beller, M. *Nature* **2013**, *495*, 85. (c) Kawahara, R.; Fujita, K.-i.; Yamaguchi, R. *J. Am. Chem. Soc.* **2012**, *134*, 3643. (d) Kawahara, R.; Fujita, K.-i.; Yamaguchi, R. *Angew. Chem., Int. Ed.* **2012**, *51*, 12790. (e) Fujita, K.-i.; Yoshida, T.; Imori, Y.; Yamaguchi, R. *Org. Lett.* **2011**, *13*, 2278.

(7) (a) Gunanathan, C.; Milstein, D. *Chem. Rev.* **2014**, *114*, 12024. (b) Gunanathan, C.; Milstein, D. *Science* **2013**, *341*, 1229712. (c) Chen, C.; Hong, S. H. *Org. Biomol. Chem.* **2011**, *9*, 20. (d) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681. (e) Guillena, G.; Ramón, D. J.; Yus, M. *Chem. Rev.* **2010**, *110*, 1611.

(8) (a) Kabo, G. J.; Kozyro, A. A.; Diky, V. V.; Simirsky, V. V. *J. Chem. Eng. Data* **1995**, *40*, 371. (b) Davies, R. H.; Finch, A.; Hill, J. O. *Thermochim. Acta* **1991**, *184*, 243.

(9) (a) Chan, L. K. M.; Poole, D. L.; Shen, D.; Healy, M. P.; Donohoe, T. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 761. (b) Ogawa, S.; Obora, Y. *Chem. Commun.* **2014**, *50*, 2491. (c) Sun, C.; Zou, X.; Li, F. *Chem. - Eur. J.* **2013**, *19*, 14030. (d) Li, F.; Xie, J.; Shan, H.; Sun, C.; Chen, L. *RSC Adv.* **2012**, *2*, 8645. (e) Moran, J.; Preetz, A.; Mesch, R. A.; Krische, M. J. *Nat. Chem.* **2011**, *3*, 287.

(10) (a) Oldenhuis, N. J.; Dong, V. M.; Guan, Z. *Tetrahedron* **2014**, *70*, 4213. (b) Zhang, G.; Hanson, S. K. *Org. Lett.* **2013**, *15*, 650. (c) Gnanaprakasam, B.; Zhang, J.; Milstein, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 1468.

(11) (a) Chen, C.; Zhang, Y.; Hong, S. H. *J. Org. Chem.* **2011**, *76*, 10005. (b) Ghosh, S. C.; Muthaiah, S.; Zhang, Y.; Xu, X.; Hong, S. H. *Adv. Synth. Catal.* **2009**, *351*, 2643. (c) Nordstrøm, L. U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 17672. (d) Gunanathan, C.; Ben-David, Y.; Milstein, D. *Science* **2007**, *317*, 790.

(12) (a) Kang, B.; Hong, S. H. *Adv. Synth. Catal.* **2015**, *357*, 834. (b) Ortega, N.; Richter, C.; Glorius, F. *Org. Lett.* **2013**, *15*, 1776.

(13) (a) Cabrero-Antonino, J. R.; Alberico, E.; Drexler, H.-J.; Baumann, W.; Junge, K.; Junge, H.; Beller, M. *ACS Catal.* **2016**, *6*, 47. (b) Spasyuk, D.; Smith, S.; Gusev, D. G. *Angew. Chem., Int. Ed.* **2013**, *52*, 2538. (c) Spasyuk, D.; Smith, S.; Gusev, D. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 2772.

(14) (a) Zhang, L.; Han, Z.; Zhao, X.; Wang, Z.; Ding, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 6186. (b) Kim, S. H.; Hong, S. H. *ACS Catal.* **2014**, *4*, 3630. (c) Han, Z. B.; Rong, L. C.; Wu, J.; Zhang, L.; Wang, Z.; Ding, K. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 13041. (d) Kuriyama, W.; Matsumoto, T.; Ogata, O.; Ino, Y.; Aoki, K.; Tanaka, S.; Ishida, K.; Kobayashi, T.; Sayo, N.; Saito, T. *Org. Process Res. Dev.* **2012**, *16*, 166.

(15) Vinogradova, E. V.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 11132.

(16) Gallou, I.; Eriksson, M.; Zeng, X.; Senanayake, C.; Farina, V. *J. Org. Chem.* **2005**, *70*, 6960.

(17) (a) Donovan, A. C.; Valliant, J. F. *J. Org. Chem.* **2009**, *74*, 8133. (b) Lebel, H.; Leogane, O. *Org. Lett.* **2006**, *8*, 5717.

(18) Dubé, P.; Nathel, N. F. F.; Vetelino, M.; Couturier, M.; Aboussafy, C. L.; Pichette, S.; Jorgensen, M. L.; Hardink, M. *Org. Lett.* **2009**, *11*, 5622.

(19) Wei, Y.; Liu, J.; Lin, S.; Ding, H.; Liang, F.; Zhao, B. *Org. Lett.* **2010**, *12*, 4220.

(20) Li, F.; Sun, C.; Shan, H.; Zou, X.; Xie, J. *ChemCatChem* **2013**, *5*, 1543.

(21) Breitler, S.; Oldenhuis, N. J.; Fors, B. P.; Buchwald, S. L. *Org. Lett.* **2011**, *13*, 3262.

(22) Kumar, G. S.; Kumar, R. A.; Kumar, P. S.; Reddy, N. V.; Kumar, K. V.; Kantam, M. L.; Prabhakar, S.; Reddy, K. R. *Chem. Commun.* **2013**, *49*, 6686.

(23) Lengyel, I.; Patel, H. J.; Stephani, R. A. *Heterocycles* **2007**, *73*, 349.

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Silver-Catalyzed Oxidative Cyclization of Propargylamide-Substituted Indoles: Synthesis of Phosphorated Indoloazepinones Derivatives

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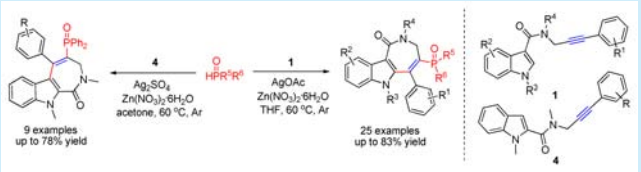
Supporting Information

ABSTRACT: A silver-catalyzed oxidative cyclization of 2- or 3-propargylamide-substituted indoles to synthesize phosphorated indoloazepinone derivatives is described. This reaction displays a difunctionalizalion of alkynes with diphenylphosphine oxides to construct a seven-membered ring through a radical cyclization process. The indoloazepinones derivatives are common structural motifs found in many natural products and pharmaceuticals.



Pyrroloazepinones are considered important structural motifs, which are present in various natural and pharmaceutical products, such as Hymenialdisine,[1] Paullones,[2] and Lantonduine A (Figure 1).[3] Moreover, pyrroloazepinone

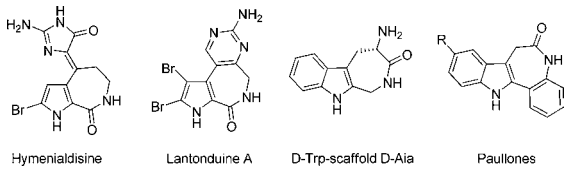


Figure 1. Pyrrolo- and indolo-azepinone derivatives.

derivatives have been identified to inhibit different protein kinases for the treatment of a variety of diseases.[4] Owing to their biological properties, a series of powerful strategies for the synthesis of pyrrolo- and indolo-azepinones have been developed.[5] In general, the construction of the bicyclic ring system is the key step to synthesizing pyrrolo- and indolo-azepinones derivatives.[6−8] For example, in 2009, the Beller group reported the intramolecular cyclization of pyrrolos with alkynes to synthesize pyrroloazepinones in the presence of gold or platinum salts.[7] Rominger and co-workers disclosed a gold-catalyzed alkynyl-substituted indole-3-carboxaminde to construct azepino[3,4-*b*]indol-1-ones.[8] However, these methods have some significant drawbacks, as they require a metal catalyst, high temperature, and long reaction time. Consequently, developing a new and effective method to solve these limitations is highly desired.

Phosphorus-containing heterocycles have broad applications in the field of material science,[9] medicinal chemistry,[10] organic synthesis,[11] and ligand chemistry.[12] In the past decades, in light of their importance, the construction of C−P bonds has attracted great attention, and enormous efforts have been expended. The traditional strategies for C−P bond formation include transition-metal-catalyzed cross-coupling reactions[13] and electrophilic phosphorus reagents with a carbon nucleophile.[14] With the development of radical chemistry, the active P-radicals [R_1R_2P-(O)·] tandem procedures and alternative methods to construct the C−P bond have been explored.[15,16] Specifically, the phosphorus radical exhibits high reactivity with alkynes and inactivated alkynes (Scheme 1).[16] In 2013, Ag-catalyzed oxidative C−H/P−H functionalization of diphenylphosphine oxide with internal alkynes was established by Miura[16a] and Duan,[16b] independently. Recently, Zhang[16d] and Wu[16e] developed the difunctionalization phosphonation of alkynes to synthesize coumarin derivatives. Not long ago, our group[16c,f] also described two silver-mediated C−P bond formation reactions of alkynes via a P-radical tandem cyclization process. However, these reports all described the formation of five- or six-membered rings, difunctionalizalion of alkynes with a phosphorus radical to synthesize the products containing a seven-membered ring have been rarely reported. Herein, we described an example of phosphorus radicals participating in the oxidative cyclization reaction of 2- or 3-propargylamide-substituted indole to synthesize indoloazepinones derivatives.

Our investigation beagn with 3-propargylamide-substituted indole **1a** and diphenylphosphine oxide in the presence of $AgNO_3$ (10 mol %) and $Zn(NO_3)_2·6H_2O$ (2.0 equiv) in MeCN under argon, and the desired product was obtained in 42% yield (Table 1, entry 1). The structure of **3a** was determined by X-ray crystal structure analysis (see the Supporting Information).[17] Motivated by this result, a series of representational silver salts and solvents were tested, the result indicated that AgOAc (10 mol %) and THF could remarkably enhance the yield up to 73%

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Scheme 1. P-Radicals Participating in Oxidative Cyclization Reaction with Alkynes

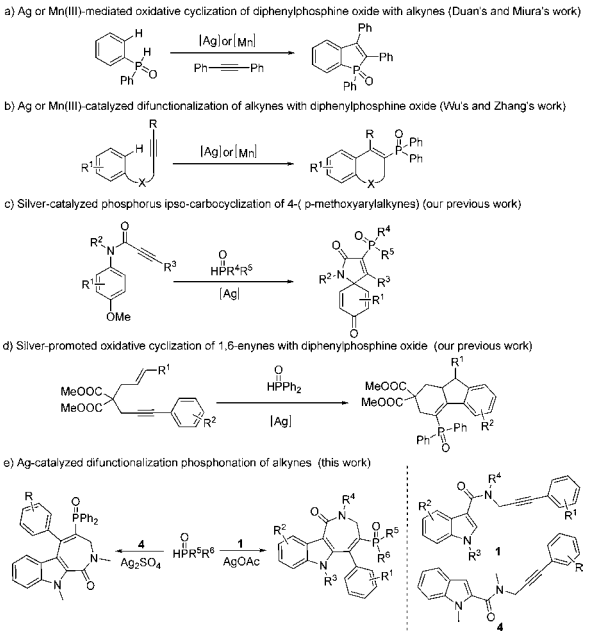
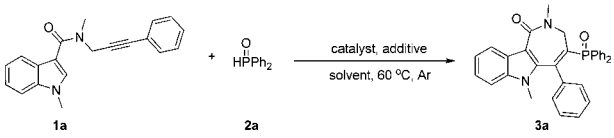


Table 1. Optimization of the Reaction Conditions[a]



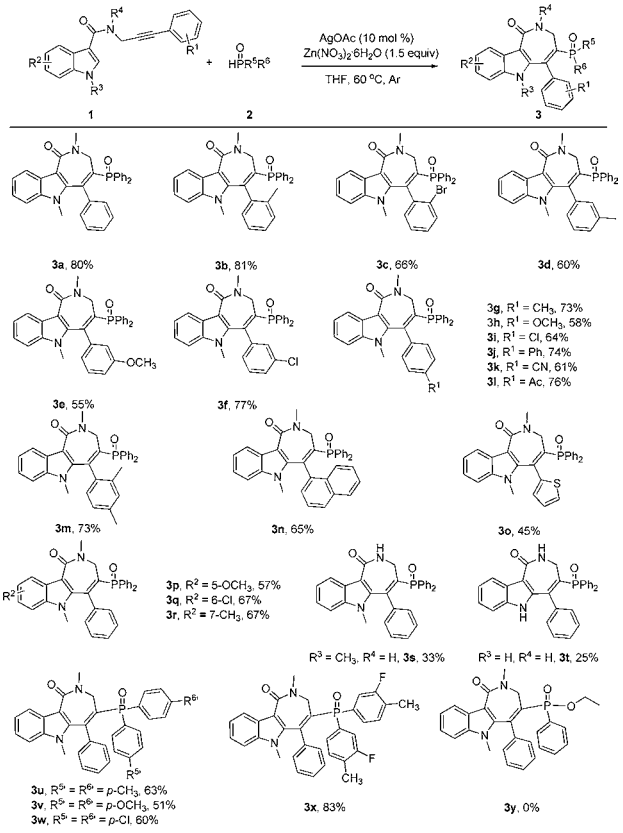
entry	cat. (mol %)	additive (equiv)	solvent	yield[b] (%)
1	$AgNO_3$ (10)	$Zn(NO_3)_2{\cdot}6H_2O$ (2.0)	MeCN	42
2	AgOAc (10)	$Zn(NO_3)_2{\cdot}6H_2O$ (2.0)	MeCN	60
3	AgOTf (10)	$Zn(NO_3)_2{\cdot}6H_2O$ (2.0)	MeCN	53
4	Ag_2O (10)	$Zn(NO_3)_2{\cdot}6H_2O$ (2.0)	MeCN	51
5	Ag_2CO_3 (10)	$Zn(NO_3)_2{\cdot}6H_2O$ (2.0)	MeCN	50
6	$AgBF_4$ (10)	$Zn(NO_3)_2{\cdot}6H_2O$ (2.0)	MeCN	45
7	AgOAc (10)	$Zn(NO_3)_2{\cdot}6H_2O$ (2.0)	DCE	64
8	AgOAc (10)	$Zn(NO_3)_2{\cdot}6H_2O$ (2.0)	THF	73
9	AgOAc (10)	$Zn(NO_3)_2{\cdot}6H_2O$ (2.0)	acetone	54
10	AgOAc (10)	$Zn(NO_3)_2{\cdot}6H_2O$ (2.0)	toluene	27
11	AgOAc (10)	$Zn(NO_3)_2{\cdot}6H_2O$ (2.0)	DMF	trace
12	AgOAc (10)	$Mg(NO_3)_2{\cdot}6H_2O$ (2.0)	THF	57
13	AgOAc (10)	$Cu(NO_3)_2{\cdot}3H_2O$ (2.0)	THF	trace
14	AgOAc (10)	$Ce(NO_3)_2{\cdot}6H_2O$ (2.0)	THF	trace
15	AgOAc (10)	$Zn(NO_3)_2{\cdot}6H_2O$ (1.0)	THF	70
16	**AgOAc (10)**	**$Zn(NO_3)_2{\cdot}6H_2O$ (1.5)**	**THF**	**80**
17	AgOAc (20)	$Zn(NO_3)_2{\cdot}6H_2O$ (1.5)	THF	67
18	AgOAc (5)	$Zn(NO_3)_2{\cdot}6H_2O$ (1.5)	THF	71
19	–	$Zn(NO_3)_2{\cdot}6H_2O$ (1.5)	THF	0
20	AgOAc (10)	–	THF	0
21	AgOAc (100)	–	THF	0

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst, and additive in anhydrous solvents (2 mL) with stirring at 60 °C under argon for 10 h. [b]Isolated yield.

(Table 1, entries 2−11). Other nitrate additives such as $Mg(NO_3)_2{\cdot}6H_2O$, $Cu(NO_3)_2{\cdot}3H_2O$, and $Ce(NO_3)_2{\cdot}6H_2O$ were also examined in this reaction, but no better yields were obtained (Table 1, entries 12−14). A yield of 80% was isolated after decreasing the amount of $Zn(NO_3)_2{\cdot}6H_2O$ to 1.5 equiv (Table 1, entries 15−16). In addition, increasing or decreasing AgOAc loadings led to lower yields (Table 1, entries 17−18). Control experiments indicated that no reaction took place in the absence of the catalyst or additives (Table 1, entries 19−21).

With optimized conditions in hand, we next explored the scope of the substrates and the results are summarized in Scheme 2. First, the effect of substituents on the aryl groups attached to the alkynes was examined. The substrates bearing electron-donating (Me, OMe) and electron-withdrawing (Br, Cl) groups on the *ortho*- or *meta*-position reacted successfully and gave the desired products in moderate to good yields (**3a**−**3f**). Substituent groups on the *para*-position of the substrates had no obvious electronic effect in this reaction, providing the corresponding compounds in good yields (**3g**−**3l**). With two substituents on the phenyl ring, the substrate was tolerated well to give the desired product **3m** in 73% yield. Gratifyingly, substrates with naphthalene **1n** and thiophene **1o** attached to the triple bond could also proceed smoothly, affording the desired products **3n** and **3o** in 65% and 45% yields, respectively. When the substituent group R^2 (such as OMe, Cl, Me) was situated at the 5-, 6-, 7-position of the *N*-methylindole, the substrates converted into the corresponding products in moderate yields (**3q**−**3r**). In addition, the substrate with one or two N−H groups only gave a trace amount of the desired products (**3s, 3t**). We considered the lower yields might be due to the fact that the N−H group affects the eletrophilicity of the 2-position of the *N*-methylindole. The scope of phosphorylations was also explored.

Scheme 2. Scope of Phosphonation of 3-Propargylamide-Substituted Indoles[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), AgOAc (0.02 mmol), and $Zn(NO_3)_2{\cdot}6H_2O$ (0.3 mmol) in anhydrous THF (2 mL) at 60 °C under argon for 10 h. [b]Isolated yields.

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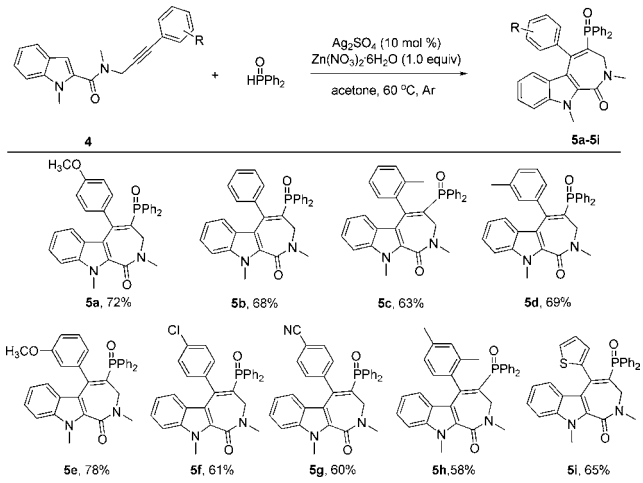
For *para*-substituted diphenylphosphine oxides, both electron-donating (Me, OMe) and electron-withdrawing (Cl) groups obtained the desired products in moderate yields (**3u**−**3w**); even a substrate with disubstituent groups gave **3x** in 83% yield. Unfortunately, ethyl phenylphosphinate was not compatible with the reaction conditions due to the decreased nucleophilicity of the phosphorus radical (**3y**).

Encouraged by the above results, we intended to broaden the reaction scope with 2-propargylamide-substituted indoles and diphenylphosphine oxide. As shown in Scheme 3, in the presence

Scheme 3. . Scope of Phosphonation of 2-Propargylamide-Substituted Indoles[a,b]



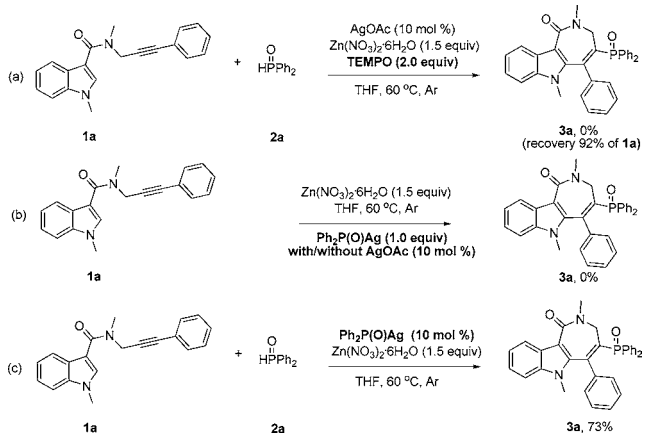
[a]Reaction conditions: **4** (0.2 mmol), **2a** (0.4 mmol), Ag_2SO_4 (0.02 mmol), and $Zn(NO_3)_2{\cdot}6H_2O$ (0.2 mmol) in anhydrous acetone (2 mL) at 60 °C under argon for 15 h. [b]Isolated yields.

of Ag_2SO_4 (10 mol %) and $Zn(NO_3)_2{\cdot}6H_2O$ (1.0 equiv), the reaction of **4a** with diphenylphosphine oxide was conducted in acetone giving the desired product **5a** in 72% yield.[18] It was noted that the substrates bearing electron-donating groups were more favorable than electron-withdrawing groups (**5a**−**5h**). Furthermore, substrates with thiophene **4i** attached to the triple bond could also proceed successfully, affording the desired product **5i** in 65% yields. Thus, both 2- or 3-propargylamide-substituted indoles could be compatible with the reaction conditions to give corresponding compounds.

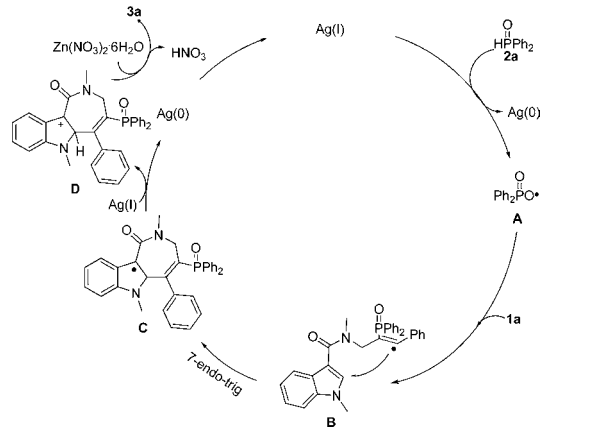
In order to investigate the mechanism more clearly, control experiments were conducted (Scheme 4). The phosphorylation reaction of **1a** was strongly inhibited to produce the desired product in the presence of TEMPO, and 92% of **1a** was recovered, which suppressed the transformation toward a radical process (Scheme 4a). When the [$Ph_2P(O)Ag$] complex was used in a stoichiometric fashion, in the presence or absence of AgOAc, the expected product **3a** was not detected (Scheme 4b). However, [$Ph_2(O)PAg$] (10 mol %) could catalyze the phosphorylation reaction of **1a** to give **3a** in 73% yield. Hence, we considered that the P-radical is generated from $Ph_2P(O)H$ in the presence of silver salt; however, in contrast to previous reports,[15c] the [$Ph_2P(O)Ag$] complex was not an active intermediate in our reaction.

On the basis of the above experiments and previous reports on the phosphorus radical, a plausible mechanism was proposed (Scheme 5). First, the P-radical **A** is generated from diphenylphosphine oxide by a Ag(I) salt under the standard conditions. Subsequently, the selective addition of the P-radical **A** to the

Scheme 4. Control Experiments



Scheme 5. Plausible Mechanism



carbon−carbon triple bond of **1a** generates vinyl radical intermediate **B**, which undergoes a 7-endo-trig process to form intermediate **C**. The intermediate **C** goes through a single-electron transfer process, giving intermediate **D**. Finally, intermediate **D** undergoes deprotonation to give the targeted product **3a**.

In summary, we have reported a silver-catalyzed oxidative cyclization of propargylamide-substituted indoles. The reaction provided a novel method to synthesize various phosphorated indoloazepinone derivatives with moderate to good yields in a simple, cheap, and efficient protocol. The indoloazepinone derivatives are common structural motifs in many natural products and pharmaceuticals. In addition, we have presented an interesting example of the difunctionalizalion of alkynes with diphenylphosphine oxide to synthesize the compounds containing a seven-membered ring through a radical cyclization process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03329.

Detailed experimental procedures, spectral data for all new compounds, and crystallographic data (PDF)

CIF information for **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Wan, Y.; Hur, W.; Cho, C. Y.; Liu, Y.; Adrian, F. J.; Lozach, O.; Bach, S.; Meijer, L.; Gray, N. S. *Chem. Biol.* **2004**, *11*, 247. (b) He, Q.; Chen, W.; Qin, Y. *Tetrahedron Lett.* **2007**, *48*, 1899.

(2) Schultz, C.; Link, A.; Leost, M.; Zaharevitz, D. W.; Gussio, R.; Sausville, A. A.; Meijer, L.; Kunick, C. J. *J. Med. Chem.* **1999**, *42*, 2909.

(3) Linington, R. G.; Williams, D. E.; Tahir, A.; van Soest, R.; Andersen, R. J. *Org. Lett.* **2003**, *5*, 2735.

(4) (a) Martinez, R.; Avila, J. G.; Ramirez, M. T.; Pérez, A.; Martinez, A. *Bioorg. Med. Chem.* **2006**, *14*, 4007. (b) Dessalew, N.; Bharatam, P. V. *Biophys. Chem.* **2007**, *128*, 165.

(5) For selected examples, see: (a) Ferrer, C.; Escribano-Cuesta, A.; Echavarren, A. M. *Tetrahedron* **2009**, *65*, 9015. (b) Hirano, K.; Inaba, Y.; Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Adv. Synth. Catal.* **2010**, *352*, 368. (c) Li, G.; Liu, Y. *J. Org. Chem.* **2010**, *75*, 3526. (d) Stewart, S. G.; Ghisalberti, E. L.; Skelton, B. W.; Heath, C. H. *Org. Biomol. Chem.* **2010**, *8*, 3563.

(6) For selected examples, see: (a) He, Q.; Chen, W.; Qin, Y. *Tetrahedron Lett.* **2007**, *48*, 1899. (b) Piras, L.; Genesio, E.; Ghiron, C.; Taddei, M. *Eur. J. Org. Chem.* **2008**, *2008*, 2789. (c) Cincinelli, R.; Dallavalle, S.; Merlini, L.; Nannei, R.; Scaglioni, L. *Tetrahedron* **2009**, *65*, 3465.

(7) (a) Gruit, M.; Michalik, D.; Tillack, A.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7212. (b) Gruit, M.; Michalik, D.; Krüger, K.; Spannenberg, A.; Tillack, A.; Pews-Davtyan, A.; Beller, M. *Tetrahedron* **2010**, *66*, 3341. (c) Gruit, M.; Pews-Davtyan, A.; Beller, M. *Org. Biomol. Chem.* **2011**, *9*, 1148.

(8) Hashmi, A. S. K.; Yang, W.; Rominger, F. *Adv. Synth. Catal.* **2012**, *354*, 1273.

(9) For selected recent examples see: (a) Cho, Y. J.; Lee, J. Y. *Chem. - Eur. J.* **2011**, *17*, 11415. (b) Jeon, S. O.; Lee, J. Y. *J. Mater. Chem.* **2012**, *22*, 7239. (c) Benin, V.; Durganala, S.; Morgan, A. B. *J. Mater. Chem.* **2012**, *22*, 1180.

(10) (a) Sivendran, S.; Jones, V.; Sun, D.; Wang, Y.; Grzegorzewicz, A. E.; Scherman, M. S.; Napper, A. D.; Mc Cammon, J. A.; Lee, R. E.; Diamond, S. L.; Mc Neil, M. *Bioorg. Med. Chem.* **2010**, *18*, 896.

(11) (a) Baumgartner, T.; Reau, R. *Chem. Rev.* **2006**, *106*, 4681. (b) Choudhury, A. R.; Mukherjee, S. *Adv. Synth. Catal.* **2013**, *355*, 1989.

(12) (a) Birkholz (née Gensow), M. N.; Freixa, Z.; van Leeuwen, P. W. N. M. *Chem. Soc. Rev.* **2009**, *38*, 1099. (b) Fernández-Pérez, H.; Etayo, P.; Panossian, A.; Vidal-Ferran, A. *Chem. Rev.* **2011**, *111*, 2119.

(13) For selected recent publications, see: (a) Liu, L.; Wang, Y.; Zeng, Z.; Xu, P.; Gao, Y.; Yin, Y.; Zhao, Y. *Adv. Synth. Catal.* **2013**, *355*, 659. (b) Berger, O.; Petit, C.; Deal, E. L.; Montchamp, J.-L. *Adv. Synth. Catal.* **2013**, *355*, 1361. (c) Gatignol, J.; Alayrac, C.; Lohier, J.-F.; Ballester, J.; Taillefer, M.; Gaumont, A.-C. *Adv. Synth. Catal.* **2013**, *355*, 2822. (d) Xu, K.; Yang, F.; Zhang, G.; Wu, Y. *Green Chem.* **2013**, *15*, 1055. (e) Feng, C.-G.; Ye, M.; Xiao, K.-J.; Li, S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 9322. (f) Xu, J.; Zhang, P.; Gao, Y.; Chen, Y.; Tang, G.; Zhao, Y. *J. Org. Chem.* **2013**, *78*, 8176. (g) Xue, Q.-C.; Xie, J.; Jin, H.-M.; Cheng, Y.-X.; Zhu, C.-J. *Org. Biomol. Chem.* **2013**, *11*, 1606. (h) Yang, B.; Yang, T.-T.; Li, X.-A.; Wang, J.-J.; Yang, S.-D. *Org. Lett.* **2013**, *15*, 5024. (i) Wang, T.; Sang, S.; Liu, L.; Qiao, H.; Gao, Y.; Zhao, Y. *J. Org. Chem.* **2014**, *79*, 608. (j) Wu, Y.; Liu, L.; Yan, K.; Xu, P.; Gao, Y.; Zhao, Y. *J. Org. Chem.* **2014**, *79*, 8118. (k) Li, X.; Yang, F.; Wu, Y.; Wu, Y. *Org. Lett.* **2014**, *16*, 992. (l) Hu, G.; Gao, Y.; Zhao, Y. *Org. Lett.* **2014**, *16*, 4464. (m) Wang, T.; Chen, S.; Shao, A.; Gao, M.; Huang, Y.; Lei, A. *Org. Lett.* **2015**, *17*, 118. (n) Gao, Y.; Deng, H.; Zhang, S.; Xue, W.; Wu, Y.; Qiao, H.; Xu, P.; Zhao, Y. *J. Org. Chem.* **2015**, *80*, 1192.

(14) For selected examples, see: (a) Brands, K. M. J.; Jobson, R. B.; Conrad, K. M.; Williams, J. M.; Pipik, B.; Cameron, M.; Davies, A. J.; Houghton, P. G.; Ashwood, M. S.; Cottrell, F.; Reamer, R. A.; Kennedy, D. J.; Dolling, U.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 4771. (b) Slowinski, F.; Aubert, C.; Malacria, M. *J. Org. Chem.* **2003**, *68*, 378. (c) Wu, H.-C.; Yu, J.-Q.; Spencer, J. B. *Org. Lett.* **2004**, *6*, 4675. (d) Xiang, D.; Huang, P.; Wang, K.; Zhou, G.; Liang, Y.; Dong, D. *Chem. Commun.* **2008**, *44*, 6236. (e) Xu, Q.; Zhao, C.-Q.; Han, L.-B. *J. Am. Chem. Soc.* **2008**, *130*, 12648. (f) Pu, X.; Qi, X.; Ready, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 10364. (g) Amareshwar, V.; Mishra, N. C.; Ila, H. *Org. Biomol. Chem.* **2011**, *9*, 5793. (h) Zhou, X.-A.; Mao, L.-L.; Wang, G.-W.; Yang, S.-D. *Chem. Commun.* **2014**, *50*, 8529. (i) Wang, H.; Cui, X.; Pei, Y.; Zhang, Q.; Bai, J.; Wei, D.; Wu, Y. *Chem. Commun.* **2014**, *50*, 14409.

(15) (a) Pan, X.-Q.; Zou, J.-P.; Zhang, G.-L.; Zhang, W. *Chem. Commun.* **2010**, *46*, 1721. (b) Pan, X.-Q.; Wang, L.; Zou, J.-P.; Zhang, W. *Chem. Commun.* **2011**, *47*, 7875. (c) Li, Y.-M.; Sun, M.; Wang, H.-L.; Tian, Q.-P.; Yang, S.-D. *Angew. Chem., Int. Ed.* **2013**, *52*, 3972. (d) Zhang, C.; Li, Z.; Zhu, L.; Yu, L.; Wang, Z.; Li, C. *J. Am. Chem. Soc.* **2013**, *135*, 14082. (e) Chu, X.-Q.; Zi, Y.; Meng, H.; Xu, X.-P.; Ji, S.-J. *Chem. Commun.* **2014**, *50*, 7642. (f) Chen, X.-L.; Li, X.; Qu, L.-B.; Tang, Y.-C.; Mai, W.-P.; Wei, D.-H.; Bi, W.-Z.; Duan, L.-K.; Sun, K.; Chen, J.-Y.; Ke, D.-D.; Zhao, Y.-F. *J. Org. Chem.* **2014**, *79*, 8407. (g) Mi, X.; Wang, C.; Huang, M.; Wu, Y.; Wu, Y. *Org. Biomol. Chem.* **2014**, *12*, 8394. (h) Zhang, B.; Daniliuc, C. G.; Studer, A. *Org. Lett.* **2014**, *16*, 250. (i) Zhou, S. F.; Li, D. P.; Liu, K.; Zou, J. P.; Asekun, O. T. *J. Org. Chem.* **2015**, *80*, 1214. (j) Yi, N.; Wang, R.; Zou, H.; He, W.; Fu, W.; He, W. *J. Org. Chem.* **2015**, *80*, 5023. (k) Zhou, M.; Chen, M.; Zhou, Y.; Yang, K.; Su, J.; Du, J.; Song, Q. *Org. Lett.* **2015**, *17*, 1786.

(16) (a) Unoh, Y.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 12975. (b) Chen, Y.-R.; Duan, W.-L. *J. Am. Chem. Soc.* **2013**, *135*, 16754. (c) Wang, L.-J.; Wang, A.-Q.; Xia, Y.; Wu, X.-X.; Liu, X.-Y.; Liang, Y.-M. *Chem. Commun.* **2014**, *50*, 13998. (d) Li, D.-P.; Pan, X.-Q.; An, L.-T.; Zou, J.-P.; Zhang, W. *J. Org. Chem.* **2014**, *79*, 1850. (e) Mi, X.; Wang, C.; Huang, M.; Zhang, J.; Wu, Y.; Wu, Y. *Org. Lett.* **2014**, *16*, 3356. (f) Zhou, Z.-Z.; Jin, D.-P.; Li, L.-H.; He, Y.-T.; Zhou, P.-X.; Yan, X.-B.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2014**, *16*, 5616.

(17) CCDC 1430218 (**3a**) contains the supplementary crystallographic data for this paper. See the Supporting Information for details.

(18) See the Supporting Information for detailed data.

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A Unified Strategy to *Plakortin* Pentalenes: Total Syntheses of (±)-Gracilioethers E and F

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Supporting Information

ABSTRACT: A unified route to oxygenated *Plakortin* pentalenes is described. Along with the previously disclosed total synthesis of hippolachnin A, the potential of this scheme is demonstrated by the first total synthesis of gracilioether E, as well as the total synthesis of gracilioether F. Key features of the unified synthetic strategy include the concise construction of common key intermediate **1** and a topological-strategy guided functionalization of a highly substituted cyclobutene providing efficient access to the core skeletons.

The *Plakortin* polyketides are a large family of marine natural products characterized by rich chemical diversity and promising biological activities (Figure 1). The family owes its name to plakortin, the initial secondary metabolite that was isolated by Faulkner in 1978 from sponges of the genus *Plakortis*.[1a] Ever since, new members of the *Plakortin* family have been continuously reported (in particular by Faulkner[1]), and to date, an impressive number of these marine, sponge-derived natural products are known.[2] In recent years, the groups of Nakao, Zampella, and Han have described the most complex members of the *Plakortins*, namely the gracilioethers A (**2**) and E–K (**3**–**6**), and hippolachnin A (**7**) (Figure 1A).[3] A number of these compounds demonstrate significant antimalarial and antifungal properties, as well as pregnane-X-receptor (PXR) agonistic efficacies. With the exception of gracilioether J, the *Plakortin* pentalenes share a densely functionalized tricyclic core that varies in its degree and pattern of oxidation. In light of their unique molecular frameworks and their promising biological profiles, any member of the tricyclic oxygenated *Plakortin* pentalenes poses an attractive synthetic challenge.

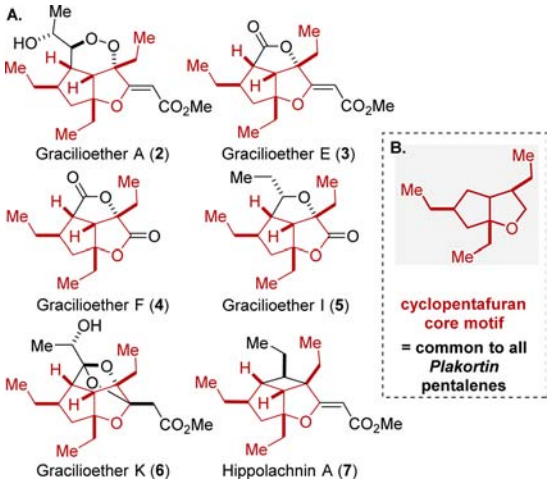

Figure 1. (A) Selected members of the *Plakortin* pentalenes. (B) Structural motif common to this class of natural products.

Cognizant of the structural similarities between the *Plakortin* pentalenes, which is reflected by the common cyclopentafuran core motif (Figure 1B), we sought to develop a unified synthetic approach that would enable the synthesis of several distinct gracilioethers and hippolachnin A (**7**).[4] We envisioned that alcohol **1** and in particular ethylidenecyclobutane **8** (**8a**: R = CH_2CO_2Me, **8b**: R = H, Figure 2) could serve as a flexible handle, enabling the total synthesis of several members of this intriguing class of marine natural products. Herein, we report the realization of such an endeavor culminating in the total syntheses of (±)-gracilioether E (**3**) and (±)-gracilioether F (**4**) (Figure 2).[5,6]

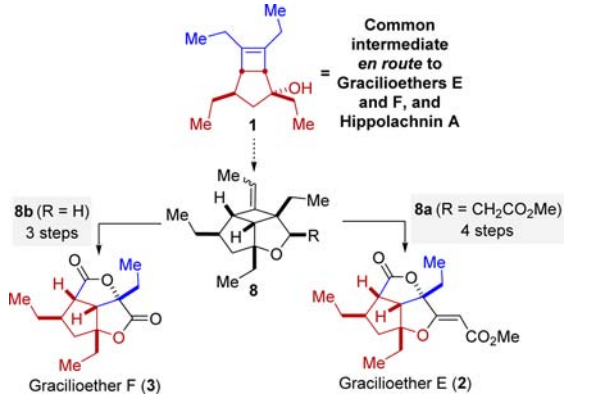

Figure 2. Synthesis of gracilioethers F (**4**) and E (**3**) from a common intermediate from the hippolachnin A (**7**) synthesis.

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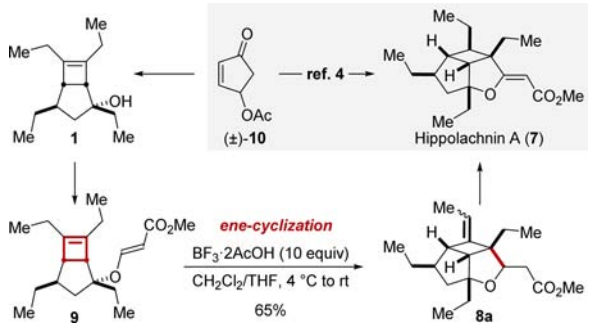
We recently reported the first total synthesis of hippolachnin A (7).[4] Key to our synthesis was the topological strategy-guided functionalization of a highly substituted cyclobutene (Scheme 1). In this context, BF_3·2AcOH mediated ene-type function-

Scheme 1. Total Synthesis of Hippolachnin A (7) Enabled through Ene-Type Functionalization of Cyclobutene 9



alization of α,β-unsaturated ester **9**, accessible in five steps from (±)-4-acetoxy-cyclopentenone (**10**), provided rapid access to pivotal cyclopentafurane **8a**. Stereoselective hydrogenation of the concomitantly generated ethylidenecyclobutane moiety, and oxidation of the pendant side chain then completed the total synthesis of hippolachnin A (7).

We were intrigued by the possibility of advancing cyclopentafurane **8a** into gracilioether E (**3**) through the implementation of merely two synthetic transformations; namely: (1) oxidative fragmentation/rearrangement of the ethylidenecyclobutane and (2) formation of the vinylogous carbonate (Figure 3A). In addition to relying on a traditional

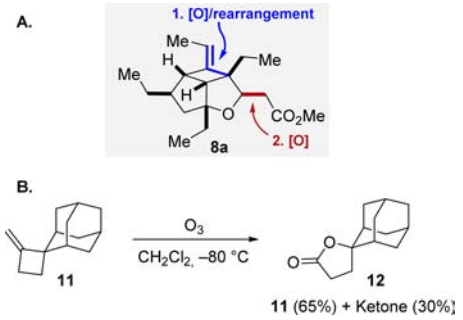
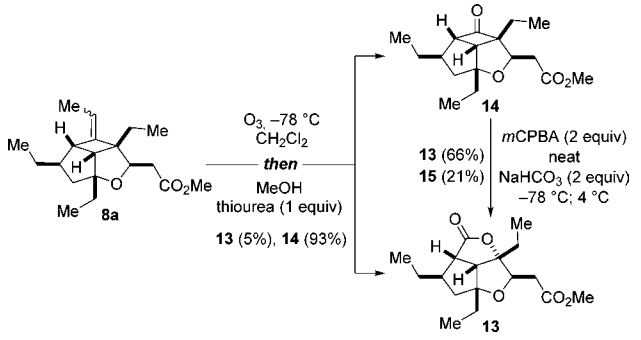


Figure 3. (A) Envisioned formal synthetic steps necessary toward completing the total synthesis of gracilioether E (**3**). (B) de Boer's seminal report on one-step methylenecyclobutane-to-γ-lactone transformations.

sequence involving cleavage of the methylenecyclobutene to the corresponding ketone and subsequent Baeyer–Villiger oxidation, we became interested in exploring the implementation of de Boer's direct one-step lactone formation from strained olefins. In this respect, α-substituted methylenecyclobutanes have been observed to undergo ozonolysis cleavage, as shown for the conversion of 2-adamantyl methylenecyclobutane **11** into γ-lactone **12**.[7]

Following de Boer's procedure, ozonolysis of alkene **8a** indeed afforded γ-lactone **13**, albeit in small amounts (5% yield) (Scheme 2). The major product corresponded to the ozonolysis product, cyclobutane **14** (93% yield). Since changes to the reaction temperature, reaction time, or the workup conditions failed to improve the yield of γ-lactone **13**, we

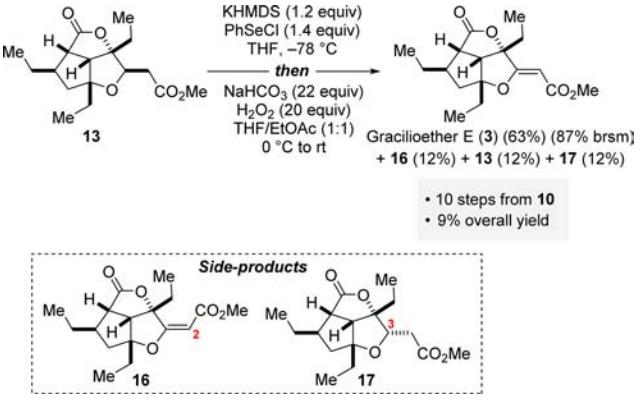
Scheme 2. Construction of the Key γ-Lactone Motif en Route to Gracilioether E (3)



started evaluating the Baeyer–Villiger oxidation of ketone **14**. The transformation **14** → **13**, however, turned out to be more challenging than initially anticipated. Attempts involving *m*CPBA, as well as combinations of *m*CPBA and Lewis acids such as BF_3·OEt_2, $Sc(OTf)_3$, and $In(OTf)_3$ that are known to enhance Baeyer–Villiger oxidations,[8] proved unsuccessful, and ketone **14** was recovered unchanged. Upon turning to more demanding conditions the low reactivity of ketone **14** could, however, be successfully overcome. Thus, employing Uenishi's solvent-free Baeyer–Villiger oxidation conditions (*m*CPBA + solid $NaHCO_3$)[9] ensured clean conversion of cyclobutanone **14** yielding γ-lactone **13** along with its regioisomer **15** (*not shown*)[10] as a separable mixture in a combined yield of 87% and an isomeric ratio of 2.8:1. Notably, the low reaction temperature initially employed (−78 °C, then 4 °C) proved to be beneficial toward the observed regioselectivity.[11]

With γ-lactone **13** in hand, we set out to test conditions for the installation of the vinylogous carbonate (Scheme 3).

Scheme 3. Completion of the Total Synthesis of Gracilioether E (3)



Application of previously successful oxidation conditions (NaHMDS, PhSeCl; then H_2O_2)[4] afforded exclusively (*E*)-olefin **16**.[10] The use of LDA hampered the enolate reactivity toward electrophilic reagents such as (but not limited to) TMSCl and PhSeCl only leading to C(3)-epimerization (→ **17**).[10] Anticipating that a larger counterion might be beneficial toward reactivity and selectivity, we investigated the efficacy of KHMDS. Submission of ester **13** to a two-step selenoxide elimination protocol utilizing KHMDS as base indeed afforded gracilioether E (**3**) in 63% yield, thus completing its first total synthesis in 10 steps and an overall yield of 9% starting from (±)-4-acetoxy-2-cyclopentenone (**10**). The spectroscopic data

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of the synthetic material were in full accordance with those reported for natural gracilioether E (**3**).[3b]

Having developed synthetic routes to gracilioether E (**3**) and hippolachnin A (**7**), both of which feature a common vinylogous carbonate functionality, we next focused on the synthesis of a cyclopentafuranone containing gracilioether, such as gracilioether F (**4**). In light of the successful ene-type cyclization of α,β-unsaturated ester **9**, we wondered whether alcohol **1** (the direct precursor to **9**) could be utilized with equal efficiency for analogous cationic cyclizations. Along these lines, we decided to probe the possibility of engaging alcohol **1** in a Prins cyclization with either paraformaldehyde or its masked equivalent dimethoxymethane (Figure 4A). If successful, the obtained ethylidenecyclobutane **8b** would set the stage for the synthesis of cyclopentafuranone **4** (Figure 4B).

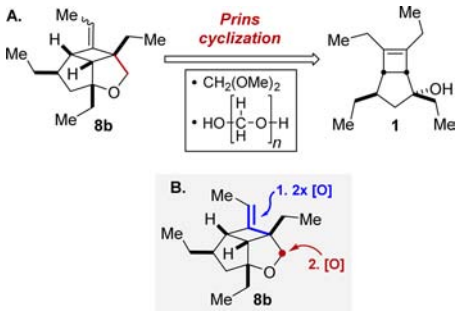
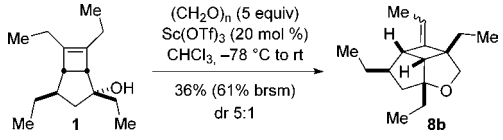


Figure 4. (A) Topological strategy-guided Prins cyclization of cyclobutene **1**. (B) Envisioned synthetic strategy toward gracilioether F (**4**) from putative Prins cyclization product **8b**.

In accordance with our earlier observations,[4] the anticipated participation of the sterically hindered tertiary alcohol in a Prins cyclization turned out to be quite challenging. After several setbacks involving the labile character of alcohol **1** toward (Lewis) acidic media, we were pleased to note that the desired transformation could be triggered in the presence of $Sc(OTf)_3$ and paraformaldehyde.[12] Following extensive experimentation, we found that the reaction was best conducted in $CHCl_3$ at low temperature using catalytic amounts of $Sc(OTf)_3$. In the experiment, when a 0.35 M solution of alcohol **1** in $CHCl_3$ at −78 °C was treated with 5 equiv of paraformaldehyde and 20 mol % $Sc(OTf)_3$, annulated cyclization product **8b** was obtained in 36% yield as an inseparable 5:1 mixture of olefin diastereomers, as judged by ^{1}H NMR spectroscopy of the unpurified reaction mixture (Scheme 4). However, considerable

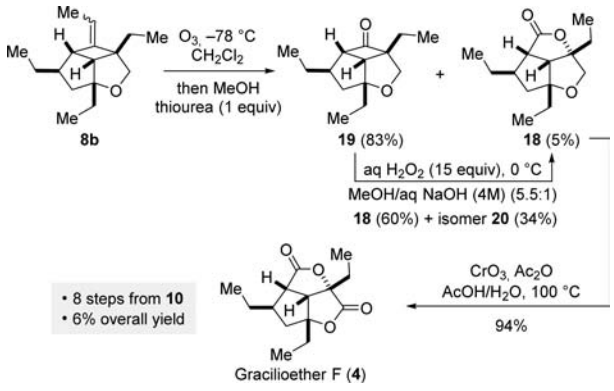
Scheme 4. Topological Strategy-Guided Prins Cyclization of Cyclobutene 1



amounts of unreacted alcohol **1** were recovered (41%), rendering the overall process in 61% yield, based on recovered starting material. Efforts to increase the efficiency of this transformation using dimethoxymethane instead of paraformaldehyde remained fruitless.[12]

Having secured access to ethylidenecyclobutane **8b**, we sought to explore its use in the synthesis of gracilioether F (**4**). To our delight, γ-lactone **18** could be obtained smoothly from alkene **8b** employing a two-step sequence (Scheme 5).

Scheme 5. Completion of the Total Synthesis of Gracilioether F (4)



Ozonolysis of ethylidenecyclobutane **8b** at −78 °C delivered ketone **19** in 83% yield, and in turn small amounts of γ-lactone **18** (5% yield). Notably, short reaction times were found to be necessary to ensure cyclobutanone **19** was obtained in high yields, as otherwise significant overoxidation takes place. Treatment of ketone **19** with aqueous H_2O_2 produced a separable mixture of both Baeyer−Villiger oxidation products, lactones **18** and **20** (*not shown*) in 94% combined yield, and an isomeric ratio of 1.8:1, as determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. With γ-lactone **18** in hand, we started evaluating conditions for the ether oxidation. While the use of *in situ* generated RuO_4 ($RuCl_3{\cdot}6H_2O/NaIO_4$)[13] or PCC[14] failed to effect the C−H oxidation, we were pleased to find that excess CrO_3 in a hot aqueous mixture of Ac_2O and AcOH afforded gracilioether F (**4**) in 94% isolated yield.[15] The spectroscopic data, including MS, IR, and NMR, were in full agreement with those of the natural product reported by Zampella[3b] and of the material reported by Brown.[5]

In conclusion, we have described a unified route to oxygenated *Plakortin* pentalenes. Central to our unified strategy is the use of common key intermediate **1** and the topological strategy-guided functionalization of a highly substituted cyclobutene. In this context, rapid access to the mutual cyclopentafuran core was secured by strategic applications of a cationic cyclization on alcohol **1** (Prins) or its ester derivative **9** (ene-type). The thus obtained ethylidenecyclobutanes served as flexible intermediates for further elaboration into gracilioethers E and F and, as previously shown, into hippolachnin A. Notably, with completion of the herein described total syntheses, we have successfully employed our unified strategy toward members of each of the three structural subclasses comprising the tricyclic oxygenated *Plakortin* pentalenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03356.

Experimental procedures and full spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Higgs, M. D.; Faulkner, D. J. *J. Org. Chem.* **1978**, *43*, 3454. (b) Ravi, B. N.; Armstrong, R. W.; Faulkner, D. J. *J. Org. Chem.* **1979**, *44*, 3109. (c) Stierle, D. B.; Faulkner, D. J. *J. Org. Chem.* **1979**, *44*, 964. (d) Stierle, D. B.; Faulkner, D. J. *J. Org. Chem.* **1980**, *45*, 3396. (e) Ravi, B. N.; Faulkner, D. J. *Tetrahedron Lett.* **1980**, *21*, 23. (f) Kushlan, D. M.; Faulkner, D. J. *J. Nat. Prod.* **1991**, *54*, 1451. (g) Schmidt, E. W.; Faulkner, D. J. *Tetrahedron Lett.* **1996**, *37*, 6681. (h) Qureshi, A.; Salvá, J.; Harper, M. K.; Faulkner, D. J. *J. Nat. Prod.* **1998**, *61*, 1539. (i) Compagnone, R. S.; Piña, I. C.; Rangel, H. R.; Dagger, F.; Suárez, A. I.; Venkata, M.; Reddy, R.; Faulkner, D. J. *Tetrahedron* **1998**, *54*, 3057. (j) Sandler, J. S.; Colin, P. L.; Hooper, J. N. A.; Faulkner, D. J. *J. Nat. Prod.* **2002**, *65*, 1258.

(2) For a review on isolated metabolites from sponges of the genus *Plakortis*, see: Rahm, F.; Hayes, P. Y.; Kitching, W. *Heterocycles* **2004**, *64*, 523.

(3) (a) Ueoka, R.; Fusetani, N.; Kawatsu, S.; Yaegashi, J.; Matsumoto, Y.; Matsunaga, S.; Furihata, K.; van Soest, R. W. M.; Fusetani, N. *J. Org. Chem.* **2009**, *74*, 4203. (b) Festa, C.; De Marino, S.; D'Auria, M. V.; Deharo, E.; Gonzalez, G.; Deyssard, C.; Petek, S.; Bifulco, G.; Zampella, A. *Tetrahedron* **2012**, *68*, 10157. (c) Festa, C.; D'Amore, C.; Renga, B.; Lauro, G.; De Marino, S.; D'Auria, M. V.; Bifulco, G.; Zampella, A.; Fiorucci, S. *Mar. Drugs* **2013**, *11*, 2314. (d) Piao, S.-J.; Song, Y.-L.; Jiao, W.-H.; Yang, F.; Liu, X.-F.; Chen, W.-S.; Han, B.-N.; Lin, H.-W. *Org. Lett.* **2013**, *15*, 3526.

(4) (a) Ruider, S. A.; Sandmeier, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 2378. This is part of a program focused on the synthesis of caged natural products, see: (b) Schindler, C. S.; Stephenson, C. R. J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 8852. (c) Schindler, C. S.; Bertschi, L.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9229. (d) Weiss, M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11501. (e) Jeker, O. F.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3474. (f) Huwyler, N.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 13066. (g) Diethelm, S.; Carreira, E. M. *J. Am. Chem. Soc.* **2013**, *135*, 8500. (h) Breitler, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 11168. (i) Diethelm, S.; Carreira, E. M. *J. Am. Chem. Soc.* **2015**, *137*, 6084. (j) Ebner, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 11227.

(5) For the first total synthesis of (±)-gracilioether F, see: Rasik, C. M.; Brown, M. K. *Angew. Chem., Int. Ed.* **2014**, *53*, 14522.

(6) For the total syntheses of the proposed biosynthetic immediate precursors of the polycyclic gracilioethers and hippolachnin A, see: (a) Norris, M. D.; Perkins, M. V.; Sorensen, E. J. *Org. Lett.* **2015**, *17*, 668. (b) Akiyama, M.; Isoda, Y.; Nishimoto, M.; Kobayashi, A.; Togawa, D.; Hirao, N.; Kuboki, A.; Ohira, S. *Tetrahedron Lett.* **2005**, *46*, 7483.

(7) (a) van Velzen, J. C.; van Tunen, W. C. J.; de Boer, T. J. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 225. (b) Rømming, C.; Skattebøl, L.; Stenstrøm, Y. *Acta Chem. Scand.* **1986**, *40*, 434. (c) Bailey, P. S. *Ozonation in Organic Chemistry*; Academic Press: New York, 1976.

(8) For examples, see: (a) McClure, J. D.; Williams, P. H. *J. Org. Chem.* **1962**, *27*, 24. (b) Kotsuki, H.; Arimura, K.; Araki, T.; Shinohara, T. *Synlett* **1999**, *1999*, 462. (c) Zhou, L.; Liu, X.; Ji, J.; Zhang, Y.; Hu, X.; Lin, L.; Feng, X. *J. Am. Chem. Soc.* **2012**, *134*, 17023.

(9) Yakura, T.; Kitano, T.; Ikeda, M.; Uenishi, J. *Tetrahedron Lett.* **2002**, *43*, 6925.

(10) See the Supporting Information for experimental details.

(11) Higher reaction temperatures are detrimental to the isomeric ratio **13**:**15**. If the reaction is carried out at ambient temperature or at 4 °C the isomeric ratio decreases from 1.5 to 1 and 2.0 to 1, respectively.

(12) See the Supporting Information for selected screening results.

(13) (a) Ashby, E. C.; Goel, A. B. *J. Org. Chem.* **1981**, *46*, 3934. (b) Ghosh, S.; Raychaudhuri, S. R.; Salomon, R. G. *J. Org. Chem.* **1987**, *52*, 83. (c) Shah, U.; Chackalamannil, S.; Ganguly, A. K.; Chelliah, M.; Kolotuchin, S.; Buevich, A.; McPhail, A. *J. Am. Chem. Soc.* **2006**, *128*, 12654.

(14) Salim, H.; Piva, O. *J. Org. Chem.* **2009**, *74*, 2257.

(15) (a) Gibson, T. W.; Erman, W. F. *J. Am. Chem. Soc.* **1969**, *91*, 4771. (b) Cainelli, G.; Kamber, B.; Keller, J.; Mihailović, M.; Lj; Arigoni, D.; Jeger, O. *Helv. Chim. Acta* **1961**, *44*, 518.

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Organic LETTERS

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Tricyclohexylphosphine-Catalyzed Cycloaddition of Enynoates with [60]Fullerene and the Application of Cyclopentenofullerenes as n-Type Materials in Organic Photovoltaics

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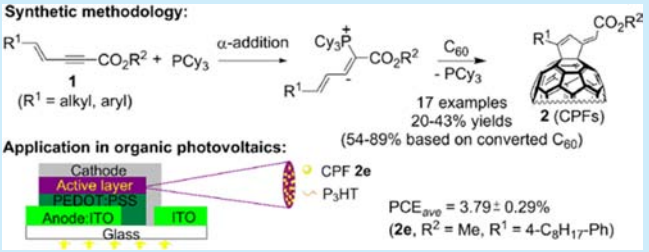
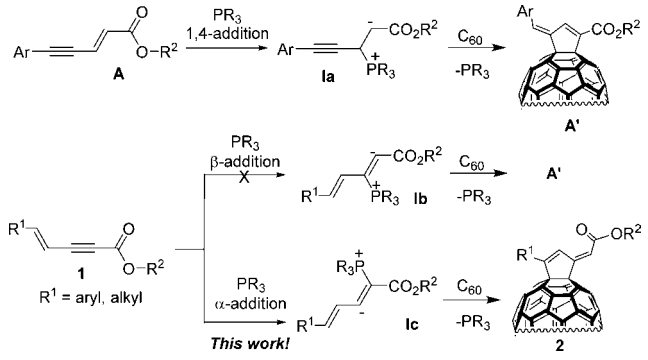
Supporting Information

ABSTRACT: The tricyclohexylphosphine-catalyzed [3 + 2] cycloaddition of (*E*)-alkyl 5-substituted phenylpent-4-en-2-ynoates with [60]fullerene was studied. This reaction undergoes an initial 1,3-addition of phosphines toward the α-carbons of enynoates. Subsequent cycloaddition of the generated 1,3-dipoles with [60]fullerene and elimination of tricyclohexylphosphines resulted in cyclopentenofullerenes in 20−43% yields. The isolated cyclopentenofullerenes were observed to serve as n-type materials in organic photovoltaics, providing a maximum average power conversion efficiency of 3.79 ± 0.29% upon embedding with P3HT in the active layer.



Conjugate addition is an important methodology in the field of applied synthetic chemistry.[1] Organophosphines behave as nucleophiles to initiate chemical reactions via addition reactions to electron-deficient alkenoates, allenoates, and alkynoates, thereby generating reactive 1,3-dipolar species in situ for further reactions with electrophiles.[2] In this context, conjugate 1,*n*-addition (*n* = even number), such as 1,2-,[3] 1,4- or (β),[4] and 1,6-addition[5] patterns, have been observed because of resonance stabilization. The evolution of new addition patterns governing conjugated systems toward phosphines inspired us to explore this topic. One unusual three-component reaction was demonstrated to undergo addition of phosphines at the $\alpha(\delta')$-carbon of enyndioates followed by addition to aldehydes and cyclization to generate lactones.[6] Furthermore, the addition pattern was shown to be substrate-dependent because swapping the functionality on the conjugated π-systems resulted in different addition patterns. For instance, ynenoates **A** proceeded through 1,4-addition reactions, evidenced by formation of cyclopentenofullerenes **A′** through cycloaddition of the generated dipoles **Ia** with C_{60} (Scheme 1).[7] Recently, we demonstrated a unique conjugate 1,3-addition reaction for oligoynoates toward phosphines.[8] Our continuing interest in finding new conjugated π-systems susceptible to α-addition led us to evaluate the regioselectivity of enynoates **1** with phosphines. Two possible addition pathways, 1,4- or 1,3- (α) addition, toward phosphines were envisioned via dipolar species **Ib** or **Ic**. These two 1,3-dipoles can undergo addition to C_{60} followed by cyclization and elimination of phosphines, thereby generating isomeric cyclopentenofullerenes **A′** and **2**, respectively. Unequivocally distinguishing between these two addition patterns is not possible without solid evidence for the structures of the isolated products. Furthermore, to our knowledge, the 1,3-addition (α) pattern is less common compared to other existing 1,*n*-addition (*n* = even number) patterns.[4] In a report, Nagao et al. demonstrated that PBu_3 catalyzed the *anti*-carboboration of an enynoate with organoboranes via 1,4-addition of phosphine.[9]

Scheme 1. Reactivity of Ynenoates A and Enynoates 1 toward the Conjugate Addition of Phosphines



In the context of using fullerenes in organic photovoltaics, light harvesting with greener and renewable approaches is essential in materials science research for the development of solar technology. Thin-film organic photovoltaics (OPVs) with a conducting polymer, poly(3-hexylthiophene) (P3HT), and a fullerene derivative, [6,6]-phenyl-C_{61} butyric acid methyl ester ($PC_{61}BM$),[10] as the active layer have been demonstrated to efficiently generate power under illumination.[11] Several other representative functionalized fullerene derivatives have been utilized for OPV applications.[12] However, the disclosed

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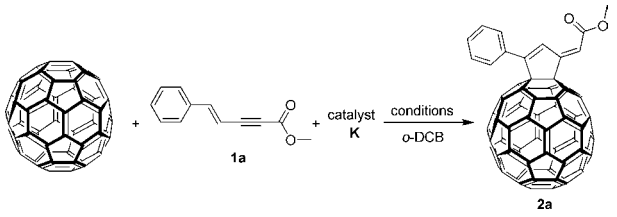
fullerene materials for OPVs with higher power conversion efficiencies (PCEs) exceeding that of P3HT/$PC_{61}BM$ have been constructed using bisadducts of fullerenes[13] because of the demand for n-type materials with higher LUMO energy levels.[14] By combining synthetic methodologies and applications, we here report the formal catalytic 1,3-addition of phosphines to enynoates through reaction scope analyses and solid evidence of product crystal structures. Furthermore, the isolated cyclopentenofullerenes (CPFs) are demonstrated to be a new class of efficient n-type fullerene materials upon being embedded with P3HT as the active layer for organic photovoltaics, providing PCEs comparable to those of P3HT/$PC_{61}BM$.

To commence this study, we first investigated the reaction conditions with enynoate **1a** and C_{60} catalyzed by PCy_3 using variable reactant molar ratios (Table 1). Preliminary screening

Table 1. Optimization of the Reaction Conditions[a]



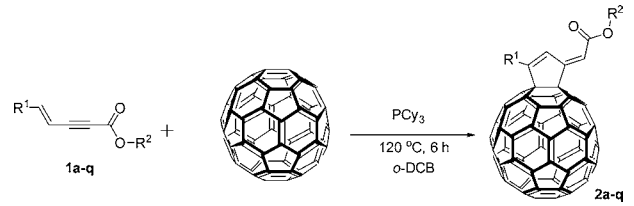
entry	C_{60}:**1a**:**K** (equiv)	catalyst (**K**)	temp (°C)	time (h)	yield[b] (%)
1	1:1:0.1	PCy_3	120	6	16(77)
2	1:1:0.2	PCy_3	120	6	22(81)
3	1:1:0.3	PCy_3	120	6	30(73)
4	1:1:0.4	PCy_3	120	6	34(80)
5	1:1:1	PCy_3	120	6	33(79)
6	1:1.2:0.4	PCy_3	120	6	38(89)
7	1:1.8:0.4	PCy_3	120	6	19(60)
8	1:2.4:0.4	PCy_3	120	6	16(28)
9	1:1.2:0.4	PCy_3	130	6	19(80)
10	1:1.2:0.4	PCy_3	110	6	36(79)
11	1:1.2:0.4	PCy_3	100	6	17(93)
12	1:1.2:0.4	PCy_3	rt	6	trace
13	1:1.2:0.4	PCy_3	rt	24	trace
14	1:1.2:0.4	PCy_3[c]	120	6	11(31)
15	1:1.2:0.4	PMe_3	rt	24	trace
16	1:1.2:0.4	PBu_3	rt	24	trace
17	1:1.2:0.4	PBu_3	120	6	9(32)
18	1:1.2:0.4	DBU	120	6	0
19	1:1.2:0.4	DMAP	120	6	0

[a]Reaction conditions: C_{60} (72 mg, 0.10 mmol) in 10 mL of anhydrous 1,2-dichlorobenzene (*o*-DCB). [b]Isolated yields after column chromatography; values in parentheses were based on conversion of C_{60}. [c]PCy_3 was generated from $HPCy_3^+BF_4^-$/NaH.

(entries 1−5) showed that a reaction with 40 mol % of PCy_3 at 120 °C for 6 h (entry 4) provided one of the best yields (34%). Slightly increasing the molar amount of enynoate **1a** to 1.2 equiv increased the yield (38%; 89% based on consumed C_{60}, entry 6); however, those with 1.5 and 2 equiv of **1a** gave lower yields of monoadducts because of the increased formation of bisadducts (entries 7−8). Furthermore, the reaction performed poorly when carried out at a higher temperature (130 °C), likely because of the competing reaction of **1a** with 1,3-dipoles, as evidenced by dark-colored baseline materials (entry 9). Reactions conducted at a lower temperature (110 °C) also resulted in a comparable yield (entry 10); reactions run at 100 °C provided approximately half the yield obtained using the best reaction conditions. The formation of 1,3-dipoles became notably sluggish at room temperature, leading to a nearly full recovery of the starting material **1a** (entries 12−13). We also observed that the reaction was less efficient when the source of the catalyst was switched to tricyclohexylphosphonium tetrafluoroborate and sodium hydride ($HPCy_3^+BF_4^-$/NaH, entry 14). Our attempts to use other organophosphine catalysts such as PBu_3 or PMe_3 yielded trace amounts of the desired products at room temperature (entries 15−16); however, PBu_3 produced a substantial amount of **2a** under standard conditions (9%, entry 17). Finally, reactions with amino catalysts did not yield the desired products (entries 18−19), but instead gave polymeric baseline materials, with a C_{60} recovery greater than 80%.

With the optimal reaction conditions in hand, we next examined the scope of PCy_3-catalyzed cycloaddition reactions of [60]fullerene with various enynoates **1a−l** (Table 2).

Table 2. Study of the Reaction Scope[a]



entry	**1**	R^1	R^2	**2**	yield [%][b]
1	**1a**	Ph	Me	**2a**	38(89)
2	**1b**	4-Me-Ph	Me	**2b**	27(73)
3	**1c**	4-C_4H_9-Ph	Me	**2c**	33(74)
4	**1d**	4-C_6H_{13}-Ph	Me	**2d**	35(75)
5	**1e**	4-C_8H_{17}-Ph	Me	**2e**	42(83)
6	**1f**	4-$C_{10}H_{21}$-Ph	Me	**2f**	33(73)
7	**1g**	4-$C_{12}H_{25}$-Ph	Me	**2g**	33(61)
8	**1h**	4-*tert*-butyl-Ph	Me	**2h**	35(71)
9	**1i**	4-OMe-Ph	Me	**2i**	43(81)
10	**1j**	3-OMe-Ph	Me	**2j**	36(73)
11	**1k**	4-F-Ph	Me	**2k**	27(73)
12	**1l**	C_6H_{13}	Me	**2l**	20(54)
13	**1m**	Ph	Et	**2m**	31(59)
14	**1n**	Ph	*n*-Bu	**2n**	27(57)
15	**1o**	Ph	iso-Bu	**2o**	29(59)
16	**1p**	Ph	*n*-hexyl	**2p**	30(69)
17	**1q**	Ph	*n*-octyl	**2q**	26(66)

[a]Reaction conditions: C_{60} (72 mg, 0.10 mmol), enynoates **1** (0.12 mmol), PCy_3 (0.04 mmol) in 10 mL of anhydrous *o*-DCB. [b]Isolated yields (%) after column chromatography; values in parentheses were based on conversion of C_{60}.

Enynoates bearing different substituted phenyl or alkyl groups (R^1) all underwent PCy_3-catalyzed cycloaddition with C_{60} to afford cyclopenteno[60]fullerenes (**2a−l**) in 20−43% isolated yields (54−89% based on recovered C_{60}, entries 1−12). The relatively poor yields resulted from the substrates **1** with an R^1 group consisting of a 4-fluorophenyl group (entry 11) or alkyl functionality (*n*-hexyl, entry 12). The less-reactive substrate **1k** may have been incurred through resonance of the fluoro-substituent on the phenyl moiety toward the alkynyl α-carbon. Because of electronic effects, the alkynyl α-carbon of **1l** became less positively charged and was thus less electrophilic toward phosphines. Furthermore, variations of the R^2 alkyl function-

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alities of the alkyl ester also resulted in the formation of **2m−q** in 26−31% yield (57−69% based on recovered C_{60}, entries 13−17). Among the prepared fullerene derivatives, compounds **2c−g** and **2n−q** were much more soluble in chloroform or dichloromethane, rendering them good candidate materials for solution-processed bulk heterojunction organic photovoltaic (OPVs) applications. The cyclopentenofullerenes (**2**) were characterized by MS, ^{1}H, and ^{13}C NMR and infrared spectroscopy. Cyclopentenofullerene **2i** (Figure 1) was

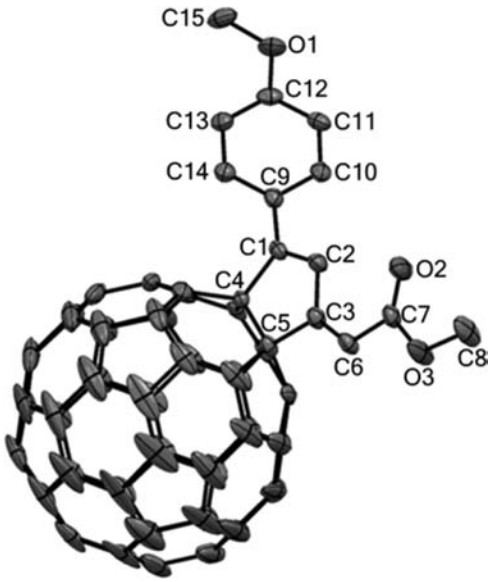
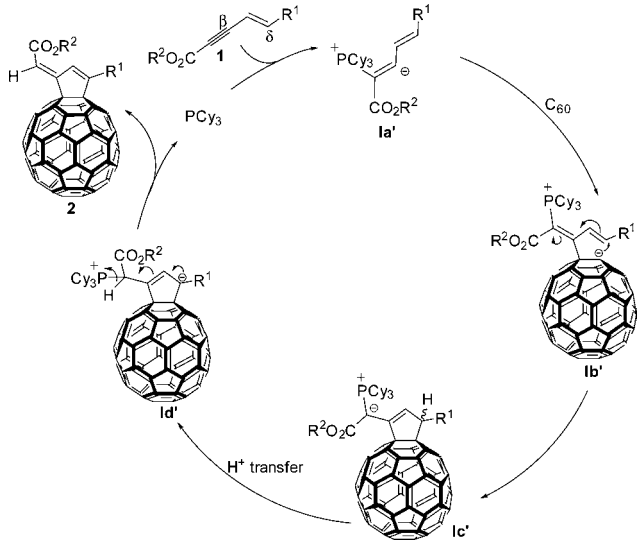


Figure 1. Solid-state structure of compound **2i**.

successfully crystallized from a CS_2/toluene solution through slow evaporation of CS_2,[15] affirming that the product structure was formed through a [3 + 2] cycloaddition reaction. Additionally, X-ray single-crystal diffraction analysis confirmed that the new covalent bond with C_{60} was formed through the β- and δ-carbons of enynoates **1**.

A plausible catalytic cycle is presented in Scheme 2. Because of the new covalent bonds of β- and δ-carbons of enynoates **1** with C_{60}, the reaction pathway via an initial nucleophilic attack

Scheme 2. Proposed Catalytic Cycle



of a phosphine to the β-carbon of enynoates **1** was excluded. Thus, an initial α-addition (1,3-addition) of PCy_3 to enynoates **1** was proposed to generate the 1,3-dipolar species **Ia′**. Addition of **Ia′** to C_{60} and subsequent *5-endo-trig* cyclization provided intermediates **Ic′**. After proton transfer and elimination of PCy_3 from **Id′**, products **2** were formed. We attempted to isolate unstable intermediate **Ic′** from the reaction in entry 9 (Table 2) and observed that it produced the product in ca. 4% yield. The retrieved flash mass data with m/z = 1217.4 (M^++1) by atmospheric pressure chemical ionization APCI, as well as ^{1}H and ^{31}P NMR data (Figures S92−S93), supported the possible existence of proposed intermediate **Ic′** during the course of the reaction.

Cyclic voltammetry (CV) studies revealed that the first half-wave reduction potentials ($^1E_{1/2}$) of **2** were similar in value; these reduction potentials ranged from −1.16 to −1.20 V (Table S2). Among the various cyclopentenofullerenes, compound **2h**, which was substituted with a 4-*tert*-butylphenyl group, exhibited the lowest $^1E_{1/2}$ value of −1.20 V and thus exhibited the highest LUMO energy level. We fabricated photovoltaic cells with layer configurations of glass/ITO/PEDOT:PSS/P3HT:CPFs/Ca/Al in a preliminary application study; these cells were prepared by spin-coating the blends of P3HT and CPFs in an *o*-DCB solution as the active layer (P3HT:CPFs, 15 mg mL^{-1}). Table S3 lists the summary of the device performance parameter data for each CPF in the active layer with an active layer composition ratio for P3HT:CPFs of 1:0.9 (w/w) for **2b−g** and 1:1 (w/w) for **2o−q**. In our experience, the devices incorporating CPFs **2d** and **2e** with 4-*n*-hexyl- and 4-*n*-octylphenyl solubilizing moieties exhibited relatively higher PCEs of the studied CPFs (entries 3 and 4), with average PCEs of 3.71 ± 0.37% and 3.79 ± 0.29%, respectively. In particular, the devices with **2d** and **2e** in the active layer reached PCEs of up to 4.1%. However, devices with CPFs with much shorter or longer solubilizing groups (R^1 = 4-methyl- and 4-*n*-butylphenyl, entries 1−2; R^1 = 4-*n*-decylphenyl and 4-*n*-dodecylphenyl, entries 5−6) did not exhibit better PCEs. Furthermore, substituting the alkyl functionalities on the alkyl esters with longer alkyl chains resulted in PCEs > 3.0% (entries 7−9). Among the devices fabricated with **2o−q**, superior performance was displayed by the device with **2p**, which exhibited a PCE_{ave} of 3.57 ± 0.10%. These OPV results indicate that these compounds compose another new class of fullerene derivatives to be utilized as efficient n-type materials in thin-film bulk heterojunction organic photovoltaic studies. The preparation of CPFs required four synthetic steps from corresponding aryl halide precursors (see Supporting Information).

In summary, we demonstrated the tricyclohexylphosphine-catalyzed [3 + 2] cycloaddition of (*E*)-alkyl 5-substituted phenylpent-4-en-2-ynoates with [60]fullerene. This reaction proceeded through an initial nucleophilic 1,3-addition of phosphines toward the α-carbon of enynoates to generate reactive 1,3-dipole species. The structures of these fullerene derivatives were supported by single-crystal X-ray diffraction analyses. Furthermore, the isolated cyclopentenofullerene derivatives acted as efficient n-type materials in organic photovoltaics, providing power conversion efficiencies comparable to that of P3HT/PC_{61}BM when embedded with P3HT in the active layer.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03293.

Procedures and spectroscopic data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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■ REFERENCES

(1) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992.

(2) (a) Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140. (b) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035. (c) Lu, X.; Du, Y.; Lu, C. *Pure Appl. Chem.* **2005**, *77*, 1985. (d) Fan, Y. C.; Kwon, O. *Chem. Commun.* **2013**, *49*, 11588. (e) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535.

(3) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639.

(4) (a) Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 3470. (b) Wang, L.-C.; Luis, A. L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402. (c) Ma, J.; Xie, P.; Hu, C.; Huang, Y.; Chen, R. *Chem. - Eur. J.* **2011**, *17*, 7418. (d) Kalek, M.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 9438. (e) Wang, D.; Wang, G.-P.; Sun, Y.-L.; Zhu, S.-F.; Wei, Y.; Zhou, Q.-L.; Shi, M. *Chem. Sci.* **2015**, *6*, 7319.

(5) Lin, Y.-W.; Deng, J.-C.; Hsieh, Y.-Z.; Chuang, S.-C. *Org. Biomol. Chem.* **2014**, *12*, 162.

(6) (a) Deng, J.-C.; Chuang, S.-C. *Org. Lett.* **2011**, *13*, 2248. (b) Chuang, S.-C.; Deng, J.-C.; Chan, F.-W.; Chen, S.-Y.; Huang, W.-J.; Lai, L.-H.; Rajeshkumar, V. *Eur. J. Org. Chem.* **2012**, *2012*, 2606.

(7) Tseng, B.-Y.; Chuang, S.-C. *Adv. Synth. Catal.* **2013**, *355*, 2165.

(8) Deng, J.-C.; Kuo, C.-W.; Chuang, S.-C. *Chem. Commun.* **2014**, *50*, 10580.

(9) Nagao, K.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2014**, *136*, 10605.

(10) Hummelen, J. C.; Knight, B. W.; LePeq, F.; Wudl, F. *J. Org. Chem.* **1995**, *60*, 532.

(11) For selected references, see: (a) Yu, G.; Gao, J.; Hummelen, J. C.; Wudl, F.; Heeger, A. J. *Science* **1995**, *270*, 1789. (b) Liu, X.; Chen, H.; Tan, S. *Renewable Sustainable Energy Rev.* **2015**, *52*, 1527. (c) Wang, F.; Tan, Z.; Li, Y. *Energy Environ. Sci.* **2015**, *8*, 1059. (d) Zhou, H.; Zhang, Y.; Mai, C.-K.; Collins, S. D.; Bazan, G. C.; Nguyen, T.-Q.; Heeger, A. J. *Adv. Mater.* **2015**, *27*, 1767. (e) Chen, H.-Y.; Hou, J.; Zhang, S.; Liang, Y.; Yang, G.; Yang, Y.; Yu, L.; Wu, Y.; Li, G. *Nat. Photonics* **2009**, *3*, 649. (f) Molina-Ontoria, A.; Gallego, M.; Echegoyen, L.; Perez, E. M.; Martin, N. *RSC Adv.* **2015**, *5*, 31541.

(12) (a) Li, C. Z.; Chien, S. C.; Yip, H. L.; Chueh, C. C.; Chen, F. C.; Matsuo, Y.; Nakamura, E.; Jen, A. K. Y. *Chem. Commun.* **2011**, *47*, 10082. (b) Huang, S.; Zhang, G.; Knutson, N. S.; Fontana, M. T.; Huber, R. C.; Ferreira, A. S.; Tolbert, S. H.; Schwartz, B. J.; Rubin, Y. *J. Mater. Chem. A* **2016**, *4*, 416. (c) Chen, C.-P.; Lin, Y.-W.; Horng, J.-C.; Chuang, S.-C. *Adv. Energy Mater.* **2011**, *1*, 776.

(13) (a) He, Y.; Chen, H.-Y.; Hou, J.; Li, Y. *J. Am. Chem. Soc.* **2010**, *132*, 1377. (b) Lenes, M.; Wetzelaer, G.-J. A. H.; Kooistra, F. B.; Veenstra, S. C.; Hummelen, J. C.; Blom, P. W. M. *Adv. Mater.* **2008**, *20*, 2116. (c) Miller, N. C.; Sweetnam, S.; Hoke, E. T.; Gysel, R.; Miller, C. E.; Bartelt, J. A.; Xie, X.; Toney, M. F.; McGehee, M. D. *Nano Lett.* **2012**, *12*, 1566. (d) Wong, W. W. H.; Subbiah, J.; White, J. M.; Seyler, H.; Zhang, B.; Jones, D. J.; Holmes, A. B. *Chem. Mater.* **2014**, *26*, 1686. (e) Backer, S. A.; Sivula, K.; Kavulak, D. F.; Fréchet, J. M. J. *Chem. Mater.* **2007**, *19*, 2927.

(14) Baran, D.; Erten-Ela, S.; Kratzer, A.; Ameri, T.; Brabec, C. J.; Hirsch, A. *RSC Adv.* **2015**, *5*, 64724.

(15) X-ray crystallographic data for compound **2i**: black bricks; crystal size: 0.30 × 0.30 × 0.06 mm^3; formula: $C_{73}H_{12}O_3$; crystal system: monoclinic; space group: *P*21/*c*; *d* = 1.529 mg m^{-3}, *V* = 5071 (2) $Å^3$; *a* = 12.4010(4) Å; *b* = 19.0870(5) Å; *c* = 17.2580(5) Å; α = 90°; β = 94.747(6)°; γ = 90°; R_1 = 0.0885; R_w = 0.2317. CCDC 1432221 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Transition-Metal-Free Deacylative Cleavage of Unstrained C(sp^3)–C(sp^2) Bonds: Cyanide-Free Access to Aryl and Aliphatic Nitriles from Ketones and Aldehydes

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Supporting Information

ABSTRACT: A transition-metal-free deacylative C(sp^3)–C(sp^2) bond cleavage for the synthetically practical oxidative amination of ketones and aldehydes to nitriles is first described, using cheap and commercially abundant $NaNO_2$ as the oxidant and the nitrogen source. Various nitriles bearing aryl, heteroaryl, alkyl, and alkenyl groups could be smoothly obtained from ketones and aldehydes in high yields, avoiding highly toxic cyanides or transition metals.

The selective cleavage of unstrained C–C bonds has been progressing in recent years.[1−4] The cleavage of unstrained C–C single bonds[2] has always been a critical issue due to its uncontrollable selectivity and inertness compared to the strained C–C bonds such as cyclopropanes with strained small rings or tertiary alcohols with high steric repulsion.[3,4] Transition-metal-catalyzed C–C bond activation has been frequently reported using palladium and copper as catalysts. For example, Murakami and co-workers developed palladium-catalyzed C–C bond cleavage of three to five membered rings.[3] Jiao and co-workers reported copper-catalyzed deacylative C–C bond cleavage under oxidative conditions, patterned in a Bayer–Villager type of oxidative C–C bond cleavage.[2] To date, the deacylative C–C bond cleavaging oxidative amination reaction toward nitriles under transition-metal-free conditions has not yet reported. Nitriles are ubiquitous building blocks in organic synthesis, pharmaceutics (Figure 1), and chemical engineering, as they can be easily transformed into aldehydes, amines, amides, thioamides, acids, esters, heterocyclic compounds, etc.[5,6] Conventional methods to access nitriles, such as the Sandmeyer and Rosenmund von Braun reactions, were widely employed in the early years.[7] Recently, metal cyanides, metalloid cyanides [MCN (M = Na, K, Zn, Cu), TMSCN, ^{n}Bu$_3$SnCN, $K_3Fe(CN)_6$],[8] and organonitriles[9,10] as direct CN sources have also been established. Other methods have also been reported.[11,12] Nevertheless, to the best of our knowledge, no example has been reported to date in which nitriles were directly prepared through C–C bond cleavage from carbonyl compounds under transition-metal-free conditions. Herein, we report a practical $AlCl_3$-promoted oxidative amination of ketones and aldehydes using $NaNO_2$ via unstrained C(sp^3)–C(sp^2) bond cleavage.

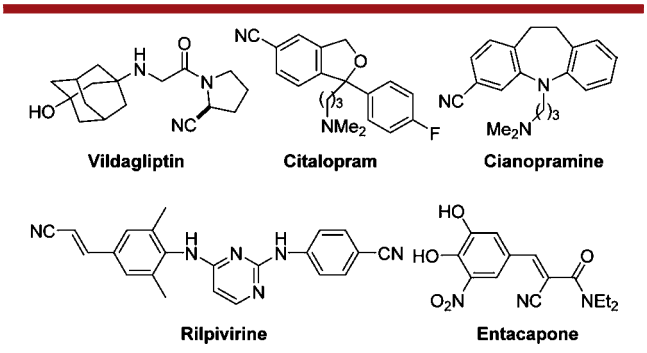

Figure 1. Nitrile-containing pharmaceuticals.

Initially, using the oxidative amination of 1-phenyl-2-actone (**1a**) as a model reaction, different nitrogen sources were selected to optimize conversions (Table 1). Using anhydrous aluminum chloride as the Lewis acid and $NaNO_2$ as the oxidant as well as nitrogen source, **1a** was obtained in 90% conversion (entry 1). It was found out that both $AlCl_3$ and $NaNO_2$ were necessary for the oxidative amination of **1a** to **2a** (entries 2 and 3). One advantage for this approach was that the reaction was not air or moisture sensitive and could be run under open air. The reaction under argon atmosphere afforded the same conversion as that under open air (entries 5 and 1), indicating that air was not the oxygen source. Other nitrogen sources such as $NaNO_3$ and *t*-BuONO gave much lower conversions (entries 6 and 7). Using ammonium hydroxide as the nitrogen source was not successful (entry 8). The radical trapping agent TEMPO could partially inhibit the reaction (entry 9). Brønsted acids such as acetic acid

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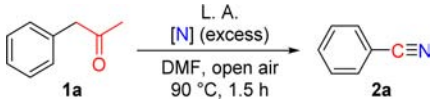
Table 1. Reaction Conditions[a]



entry	Lewis acid (equiv)	[N]	atmosphere	conv[b] (%)
1	$AlCl_3$ (2)	$NaNO_2$	open air	90
2		$NaNO_2$	open air	0
3	$AlCl_3$ (2)		open air	0
4	$AlCl_3$ (1)	$NaNO_2$	argon	53
5	$AlCl_3$ (2)	$NaNO_2$	argon	90
6	$AlCl_3$ (2)	$NaNO_3$	open air	53
7	$AlCl_3$ (2)	*t*BuONO	open air	39
8	$AlCl_3$ (2)	$NH_3{\cdot}H_2O$	open air	0
9[c]	$AlCl_3$ (2)	$NaNO_2$	open air	16
10	AcO_2H (1)	$NaNO_2$	open air	1
11	TfOH (1)	$NaNO_2$	open air	11
12	$BF_3{\cdot}OEt_2$ (1.0)	$NaNO_2$	open air	16

[a]Reaction conditions: **1a** (0.5 mmol), $AlCl_3$ (2 equiv), [N] (10 equiv), DMF (0.5 M), 90 °C, open air, 1.5 h. [b]Determined by GC using dioxane as the internal standard. [c]With 1.6 equiv TEMPO to $NaNO_2$. See the Supporting Information for details.

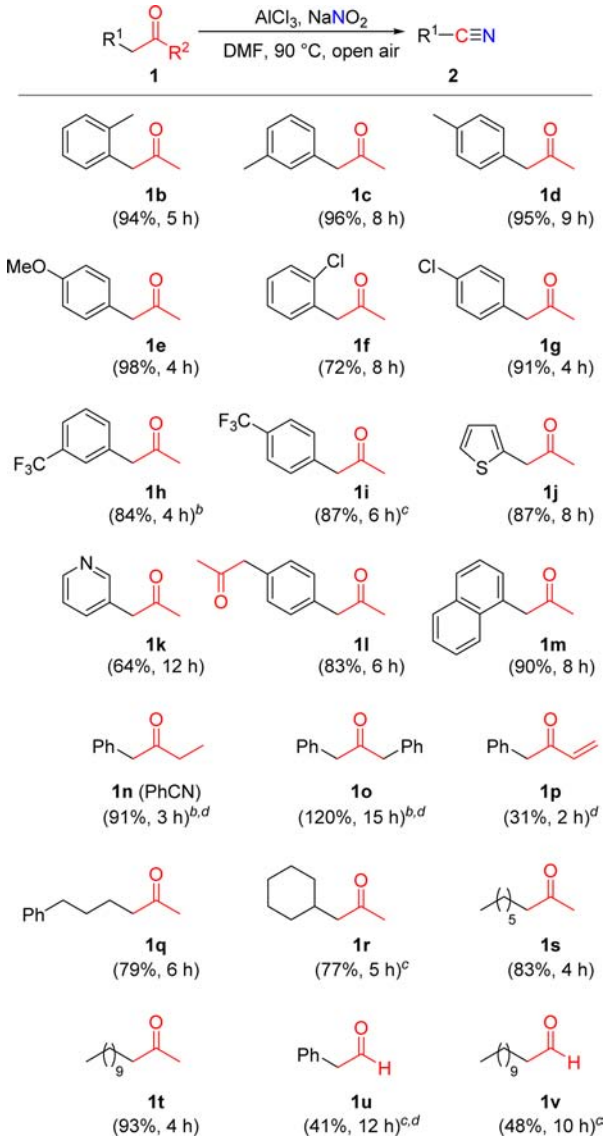
and TfOH and $BF_3{\cdot}OET_2$ fail to promote this reaction (entries 10−12). The conditions described in entry 1 were chosen as the standard conditions for further study.

The scope of this deacylative C−C bond cleavage oxidative amination of ketones and aldehydes to nitriles was then investigated. Aryl and alkyl ketones and aldehydes could be smoothly converted to the desired nitriles (Scheme 1). For example, various aryl and heteroaryl nitriles were obtained in high isolated yields (**1b−m**). The substrates bearing other carbonyl groups instead of an acetyl group could also give the desired nitriles in high yields (Scheme 1, **1n** and **1o**). Similar to the reaction of **1o**, both PhCN and MeCN have been detected by GC. Actually, under open air, most MeCN was evaporated. However, acetic acid was also afforded. After workup, only PhCN was isolated in 91% yield. The unstable enone substrate **1p** could give the corresponding product in acceptable yield. Besides (hetero)aryl ketones, this method is also suitable for conversion of aliphatic ketones to the corresponding nitriles in high yields (Scheme 1, **1q−t**). What should be noted is that aldehydes **1u** and **1v** were also successfully converted to nitriles.

The kinetic isotope effect (KIE) for **1a** is described in Scheme 2. A second-order KIE with a value of 0.7 was found for **1a-D** (Scheme 2, top). For the compound **1a′-D**, a k_H/k_D of 1 was observed. No KIE of **1a-D** or **1a′-D** indicates the rate-determining step is a C−H cleavage step. Compound **3** was initially hypothesized as a possible intermediate for the conversion to nitrile **2a**, and a first-order KIE was observed (Scheme 2, bottom). Another possible intermediate **4a** was observed by GC−MS. Compound **4a** could not be directly detected by ^1H NMR, whereas 1,2-dione **5a** was observed by ^1H NMR. Oxime **4a** could be converted to nitrile **2a** in 78% yield under standard reaction conditions, but the substrate **1a′** bearing an *α*-methyl group is difficult to convert to **2a** (Scheme 3). Therefore, **4a** could be the intermediate in this reaction.

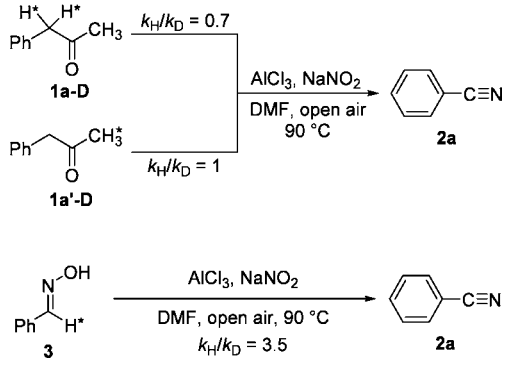
A possible reaction mechanism is proposed in Scheme 4. First, **1a** reacts with $NaNO_2$ and $AlCl_3$ probably via nitric oxide radical to form intermediate **A**,[4a] which quickly tautomerized to **B**. The existence of **B** is supported by observation of **4a** by GC−MS

Scheme 1. Reaction Scope[a]



[a]Reaction conditions: **1** (2 mmol), $NaNO_2$ (10 equiv), $AlCl_3$ (2.0 equiv), DMF (0.5 M), 90 °C, monitored by TLC; isolated yields. [b]120 °C. [c]100 °C. [d]Determined by GC using dioxane as an internal standard. See the Supporting Information for details.

Scheme 2. Kinetic Isotope Effects



experiments (Scheme 3). Intermediate **B** transforms to final target nitrile **2a** via Beckmann fragmentation.

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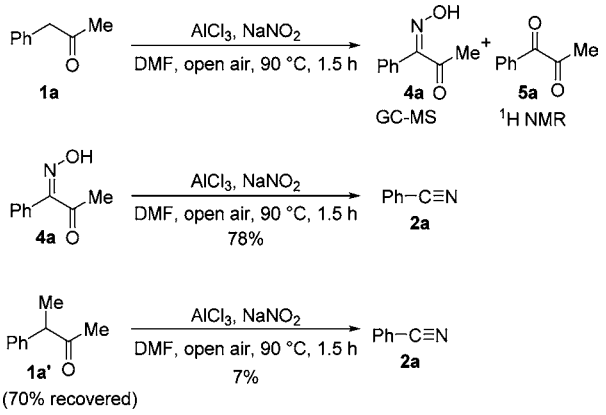
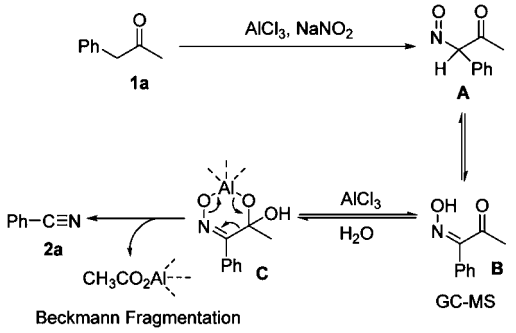
Scheme 3. Control Experiments



Scheme 4. Proposed Mechanism



In conclusion, we have developed a new approach to selective unstrained C−C bond cleavage which provides highly efficient and synthetically practical cyanide-free access to oxidative amination of ketones and aldehydes to nitriles in high yields and wide scope. The use of cheap and commercially abundant $AlCl_3$ as Lewis acid and $NaNO_2$ as the oxidant as well as the nitrogen source avoids highly toxic cyanides and expensive transition metals. The mechanistic studies illustrated a possible radical pathway, providing new access to unstrained C−C bond cleavage. Studies on a new type of C−C bond cleavage using this approach are underway in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03367.

Experimental details and spectroscopic data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews, see: (a) Murakami, M.; Matsuda, T. *Chem. Commun.* **2011**, *47*, 1100. (b) Ruhland, K. *Eur. J. Org. Chem.* **2012**, *2012*, 2683. (c) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610. (d) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870.

(2) Recent references on unstrained C−C bonds cleavage: (a) Lei, Z.-Q.; Pan, F.; Li, H.; Li, Y.; Zhang, X.-S.; Chen, K.; Wang, X.; Li, Y.-X.; Sun, J.; Shi, Z.-J. *J. Am. Chem. Soc.* **2015**, *137*, 5012. (b) Huang, X.; Li, X.; Zou, M.; Song, S.; Tang, C.; Yuan, Y.; Jiao, N. *J. Am. Chem. Soc.* **2014**, *136*, 14858. (c) Tang, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 6528. (d) Zhang, C.; Feng, P.; Jiao, N. *J. Am. Chem. Soc.* **2013**, *135*, 15257.

(3) Representative references on strained C−C bond cleavage: (a) Ishida, N.; Ikemoto, W.; Murakami, M. *J. Am. Chem. Soc.* **2014**, *136*, 5912. (b) Souillart, L.; Parker, E.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 3001. (c) Masarwa, A.; Didier, D.; Zabrodski, T.; Schinkel, M.; Ackermann, L.; Marek, I. *Nature* **2013**, *505*, 199. (d) Ishida, N.; Shimamoto, Y.; Yano, T.; Murakami, M. *J. Am. Chem. Soc.* **2013**, *135*, 19103. (e) Bowring, M. A.; Bergman, R. G.; Tilley, T. D. *J. Am. Chem. Soc.* **2013**, *135*, 13121. (f) Masuda, Y.; Hasegawa, M.; Yamashita, M.; Nozaki, K.; Ishida, N.; Murakami, M. *J. Am. Chem. Soc.* **2013**, *135*, 7142. (g) Mukai, C.; Ohta, Y.; Oura, Y.; Kawaguchi, Y.; Inagaki, F. *J. Am. Chem. Soc.* **2012**, *134*, 19580. (h) Seiser, T.; Cramer, N. *J. Am. Chem. Soc.* **2010**, *132*, 5340. (i) Ohmura, T.; Taniguchi, H.; Kondo, Y.; Suginome, M. *J. Am. Chem. Soc.* **2007**, *129*, 3518. (j) Murakami, M.; Itahashi, T.; Ito, Y. *J. Am. Chem. Soc.* **2002**, *124*, 13976. (k) Murakami, M.; Amii, H.; Shigeto, K.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 8285. (l) Murakami, M.; Amii, H.; Ito, Y. *Nature* **1994**, *370*, 540.

(4) Representative references on C−C bond cleavage via *β*-carbon elimination (with highly steric repulsion): (a) Baidya, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2011**, *133*, 13880. (b) Li, H.; Li, Y.; Zhang, X.-S.; Chen, K.; Wang, X.; Shi, Z.-J. *J. Am. Chem. Soc.* **2011**, *133*, 15244. (c) Sai, M.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 3294. (d) Niwa, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 2643. (e) Wakui, H.; Kawasaki, S.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2004**, *126*, 8658.

(5) (a) Rappoport, Z. *The Chemistry of the Cyano Group*; Interscience Publishers: New York, 1970. (b) Fatiadi, A. C. In *Preparation and Synthetic Applications of Cyano Compounds*; Patai, S., Rappaport, Z., Eds; Wiley: New York, 1983; Chapter 26. (c) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989.

(6) Review on nitrile-containing pharmaceuticals and natural products: (a) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. *J. Med. Chem.* **2010**, *53*, 7902. (b) Fleming, F. F. *Nat. Prod. Rep.* **1999**, *16*, 597.

(7) (a) Sandmeyer, T. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1633. (b) Hodgson, H. H. *Chem. Rev.* **1947**, *40*, 251. (c) Galli, C. *Chem. Rev.* **1988**, *88*, 765. (d) Rosenmund, K. W.; Struck, E. *Ber. Dtsch. Chem. Ges. B* **1919**, *52*, 1749. (e) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

(8) For reviews, see: (a) Anbarasan, P.; Schareina, T.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 5049. (b) Ellis, G. P.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779. For recent progress, see: (c) Cohen, D. T.; Buchwald, S. L. *Org. Lett.* **2015**, *17*, 202. (d) Yan, G.; Kuang, C.; Zhang, Y.; Wang, J. *Org. Lett.* **2010**, *12*, 1052. (e) Yeung, P. Y.; So, C. M.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 8918. (f) Jia, X.; Yang, D.; Zhang, S.; Cheng, J. *Org. Lett.* **2009**, *11*, 4716. (g) Buono, F. G.; Chidambaram, R.; Mueller, R. H.; Waltermire, R. E. *Org. Lett.* **2008**, *10*, 5325. (h) Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, 1388. (i) Yang, C.; Williams, J. M. *Org. Lett.* **2004**, *6*, 2837. (j) Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 2890. (k) Okano, T.; Iwahara, M.; Kiji, J. *Synlett* **1998**, *1998*, 243. (l) Tschaen, D. M.; Desmond, R.; King, A. O.; Fortin, M. C.; Pipik, B.; King, S.; Verhoeven, T. R. *Synth. Commun.* **1994**, *24*, 887. (m) Sakakibara, Y.; Okuda, F.; Shimobayashi, A.; Kirino, K.; Sakai, M.; Uchino, N.; Takagi, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1985. (n) Chatani, N.; Hanafusa, T. *J. Org. Chem.* **1986**, *51*, 4714.

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Org. Lett. 2016, 18, 228−231

(9) For a review, see: Kim, J.; Kim, H. J.; Chang, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 11948.
(10) (a) Yang, Y.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2014**, *53*, 8677. (b) Gong, T.; Xiao, B.; Cheng, W.; Su, W.; Xu, J.; Liu, Z.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 10630. (c) Zheng, S.; Yu, C.; Shen, Z. *Org. Lett.* **2012**, *14*, 3644. (d) Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 519. (e) Kamijo, S.; Hoshikawa, T.; Inoue, M. *Org. Lett.* **2011**, *13*, 5928. (f) Park, E. J.; Lee, S.; Chang, S. *J. Org. Chem.* **2010**, *75*, 2760. (g) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661. (h) Suzuki, H.; Kobayashi, T.; Osuka, A. *Chem. Lett.* **1983**, 589.
(11) (a) Ding, S.; Jiao, N. *J. Am. Chem. Soc.* **2011**, *133*, 12374. (b) Ren, X.; Chen, J.; Chen, F.; Cheng, J. *Chem. Commun.* **2011**, *47*, 6725. (c) Kim, J.; Chang, S. *J. Am. Chem. Soc.* **2010**, *132*, 10272.
(12) (a) Shen, T.; Wang, T.; Qin, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 6677. (b) Okamoto, N.; Ishikura, M.; Yanada, R. *Org. Lett.* **2013**, *15*, 2571. (c) Wang, T.; Jiao, N. *J. Am. Chem. Soc.* **2013**, *135*, 11692. (d) Lamani, M.; Prabhu, K. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 6622. (e) Yamaguchi, K.; Fujiwara, H.; Ogasawara, Y.; Kotani, M.; Mizuno, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 3922. (f) Iida, S.; Togo, H. *Tetrahedron* **2007**, *63*, 8274. (g) Choi, E.; Lee, C.; Na, Y.; Chang, S. *Org. Lett.* **2002**, *4*, 2369. (h) Ishihara, K.; Furuya, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 2983.

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Organic LETTERS

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Access to 3-Acyl-(2*H*)-indazoles via Rh(III)-Catalyzed C−H Addition and Cyclization of Azobenzenes with α-Keto Aldehydes

Taejoo Jeong,[†,§] Sang Hoon Han,[†,§] Sangil Han,[†] Satyasheel Sharma,[†] Jihye Park,[†] Jong Suk Lee,[‡] Jong Hwan Kwak,[†] Young Hoon Jung,[†] and In Su Kim*[,†]

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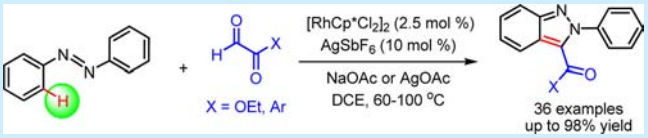
Supporting Information

ABSTRACT: The rhodium(III)-catalyzed direct C−H functionalization of azobenzenes with ethyl glyoxalate and aryl glyoxals is described. This protocol provides the facile and efficient formation of various C3-acylated-(2*H*)-indazoles in moderate to high yields.



The indazole heterocycle has been recognized as a crucial structural core found in natural products and pharmaceuticals with a broad spectrum of medicinal applications.[1] In particular, the 3-acyl indazole motif is present in molecules that possess anticancer, antiemetic, viral polymerase inhibition, and anti-inflammatory activities (Figure 1).[2] The classical routes to 3-acyl indazoles involve (1) *N*-nitrosation of acetanilides followed by intramolecular cyclization onto the *ortho*-methylene group, (2) multistep synthesis from isatins via hydrolysis of the amide unit, diazotization and reduction, and (3) direct lithiation at the C3-position followed by the addition of electrophiles.[3] Surprisingly, however, the catalytic preparation of 3-acyl indazole scaffolds remains virtually unexplored.

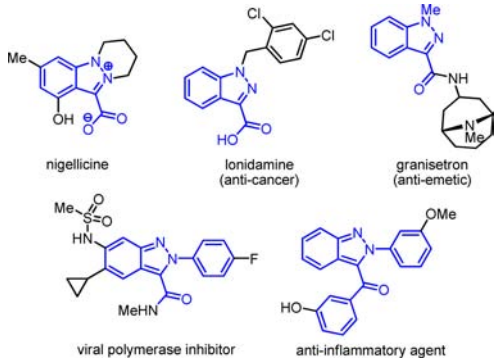
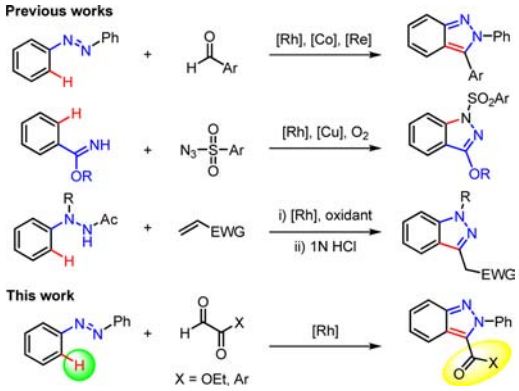


Figure 1. Bioactive 3-acyl indazole compounds.

With advances in transition-metal-catalyzed C−H bond functionalization, great effort has been devoted to the formation of various heterocycles.[4] In this area, recent progress has been focused on the preparation of indazoles via the oxidative annulation process of hydrazones under palladium, copper, and iron catalysis.[5] Lavis and Ellman disclosed beautiful works on the synthesis of 2,3-diaryl-2*H*-indazoles via the Rh(III)- or Co(III)-catalyzed redox-neutral coupling of azobenzenes with aryl aldehydes (Scheme 1).[6]

Scheme 1. Indazole Synthesis via C−H Functionalization



In addition, Glorius demonstrated the Rh- and Cu-catalyzed tandem C−N and N−N bond formations between arylimidates and sulfonyl azides providing 3-oxo-(1*H*)-indazoles.[7] Recently, our group reported a new strategy for the construction of 2,3-dihydro-(1*H*)-indazoles from arylhydrazines with various olefins under Rh(III) catalysis.[8] Moreover, Wang reported the recatalyzed annulation of azobenzenes and aldehydes affording 2,3-diaryl-(2*H*)-indazoles.[9] In continuation of our recent studies on the rhodium-catalyzed C−H functionalization and heterocycle synthesis,[10] we herein present the Rh(III)-catalyzed direct C−H addition followed by intramolecular cyclization of azobenzenes with α-keto aldehydes, such as ethyl glyoxalate and aryl glyoxals, affording 3-acyl-(2*H*)-indazoles.

The optimization of reaction conditions was initiated by examining the coupling of azobenzene (**1a**) and ethyl glyoxalate (**2a**) under rhodium catalysis (Table 1). To our delight, the cationic rhodium complex, derived from $[Cp^*RhCl_2]_2$ and $AgSbF_6$, was found to promote the coupling of **1a** and **2a** in DCE at 60 °C to provide the monoalkylated compound **3aa** in

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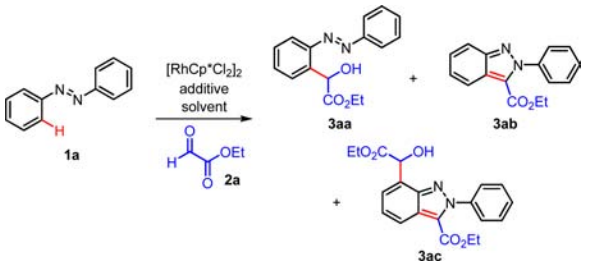
Table 1. Selected Optimization for Reaction Conditions[a]



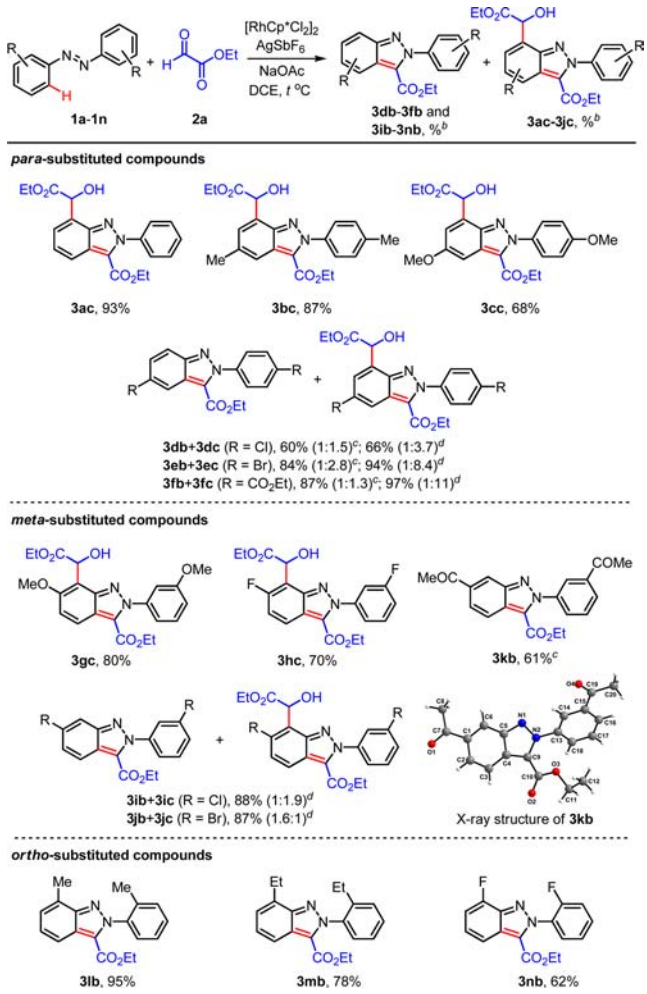
entry	additive (mol %)	solvent	yield (%),[b] ratio[c]
1	$AgSbF_6$ (10)	DCE	30 (8:1:1)
2	$AgSbF_6$ (10)	MeOH	N.R.
3	$AgSbF_6$ (10)	*t*-AmOH	trace
4	$AgSbF_6$ (10)	toluene	trace
5	$AgSbF_6$ (10)	dioxane	12 (1:0:1)
6	$AgSbF_6$ (10), NaOAc (30)	DCE	60 (5:1:4)
7	$AgSbF_6$ (10), KOAc (30)	DCE	55 (6:1:3)
8	$AgSbF_6$ (10), AgOAc (30)	DCE	56 (5:1:4)
9	$AgSbF_6$ (10), $Cu(OAc)_2$ (30)	DCE	20 (1:2:1)
10[d]	$AgSbF_6$ (10), NaOAc (30)	DCE	95 (0:1:48)

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), additive (quantity noted), solvent (1 mL) at 60 °C for 20 h under air in reaction tubes. [b]Isolated yield by column chromatography. [c]Parentheses shows ratio of **3aa**/**3ab**/**3ac**. [d]Compound **2a** (0.6 mmol) was used.

concomitant with indazole compounds **3ab** and **3ac** (Table 1, entry 1). Screening of solvents such as MeOH, *t*-AmOH, toluene, and 1,4-dioxane did not provide the coupling products in a satisfactory yield (Table 1, entries 2−5). However, the addition of NaOAc as an additive showed an increment of the formation of coupling products in 60% combined yield (Table 1, entry 6). This reaction was found to be comparable with KOAc and AgOAc additives, but $Cu(OAc)_2$ was less effective in this coupling reaction (Table 1, entries 7−9). In all cases, we could not control the formation of alkylated azobenzene **3aa** and indazoles **3ab** and **3ac**. However, increasing the amount of ethyl glyoxalate (**2a**) to 3 equiv, indazole **3ac** was exclusively formed in high yield (Table 1, entry 10).

To evaluate the scope of this process, the optimal reaction conditions were subjected to a range of azobenzenes **1a**−**1n** (Scheme 2). In case of *para*-substituted azobenzenes **1b** and **1c** with electron-rich groups, high yields of C7-alkylated indazole compounds **3bc** and **3cc** were obtained. However, electron-deficient azobenzenes **1d**−**1f** underwent the formation of indazole products **3db**−**3fb** and **3dc**−**3fc** at elevated temperature (100 °C) in good to high yields, but lower ratio between indazoles **3db**−**3fb** and C7-alkylated indazoles **3dc**−**3fc** was detected. Thus, with the increased loading of **2a** (5 equiv), a good level of ratio and improved yields of indazole products were obtained. Interestingly, *meta*-substituted azobenzenes **1g** and **1h** with OMe and F groups, respectively, provided good to high yields of C7-alkylated indazoles **3gc** and **3hc**. In contrast, azobenzenes **1i** and **1j** containing halogen groups (Cl and Br) at the *meta*-position, provided indazoles **3ib** and **3jb** along with C7-alkylated indazoles **3ic** and **3jc** in high yields. However, sterically congested *meta*-acetyl azobenzene **1k** provided only C3-acylated indazole **3kb**. Additionally, *ortho*-substituted azobenzenes **1l**−**1n** proved to be good substrates for the formation of indazoles **3lb**−**3nb**.

Scheme 2. Scope of Azobenzenes[a]



[a]Reaction conditions: **1a**−**1n** (0.2 mmol), **2a** (0.6 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), NaOAc (30 mol %), DCE (1 mL) at 60 °C for 20 h under air in reaction tubes. [b]Isolated yield by flash column chromatography. [c]Reactions were performed at 100 °C for 20 h. [d]Reactions were performed with **2a** (1.0 mmol) at 100 °C for 20 h.

To further explore the scope and limitation of this transformation, various glyoxals **2b**−**2k** were screened, as shown in Scheme 3. Initially, *ortho*-substituted azobenzene **1m** was coupled with phenyl glyoxal (**2b**) under the optimized reaction conditions to afford the desired indazole **4b** in 46% yield. However, the addition of AgOAc instead of NaOAc provided an improved yield (56%) of **4b**. Other reaction conditions were found to be inferior for the coupling of **1m** and **2b**. The modified conditions were applied to various aryl glyoxals **2c**−**2i** to give the corresponding products **4c**−**4i** in moderate yields. To our delight, heteroaryl glyoxal **2j** and alkyl glyoxal **2k** also participated in the coupling reaction to furnish indazoles **4j** and **4k**, respectively. In addition, in the case of *para*- and *meta*-substituted azobenzenes **1b** and **1j**, C3-acylated indazoles **4l** and **4m** were exclusively formed, and C7-alkylated indazoles were not observed presumably due to fast intramolecular cyclization of monoalkylated intermediates.

Further investigation of unsymmetrical azobenzenes **1o** and **1p** with **2a** revealed that this transformation can predominantly occur at the *ortho*-C−H bonds on the electron-rich aromatic ring to provide the corresponding indazoles (**5a** and **6a′**) as major

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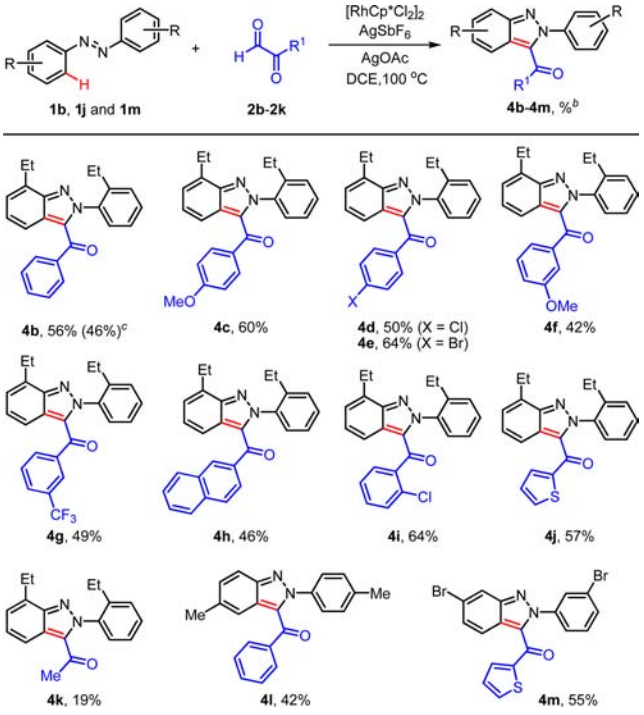
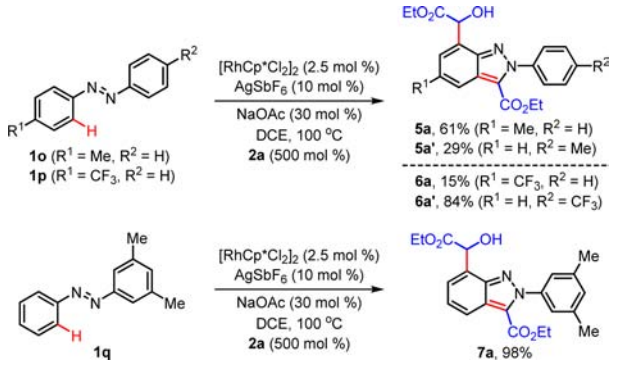
Scheme 3. Scope of Glyoxals[a]



[a]Reaction conditions: **1b**, **1j**, and **1m** (0.2 mmol), **2b**−**2k** (0.6 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), AgOAc (30 mol %), DCE (1 mL) at 100 °C for 20 h under air in reaction tubes. [b]Isolated yield by flash column chromatography. [c]NaOAc (30 mol %) was used.

products (Scheme 4). In addition, when we performed the reaction of azobenzene **1q** containing sterically different

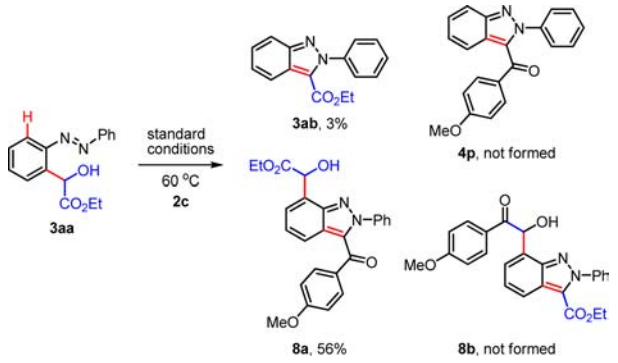
Scheme 4. Reactions of Unsymmetrical Azobenzenes



aromatic rings, a single product **7a** was obtained in 98% yield. This result indicates that the steric environment of azobenzene is also crucial to tune the site-selectivity of this transformation.

To gain mechanistic insight, we carried out an experiment of **3aa** with aryl glyoxal **2c** under the standard reaction conditions (Scheme 5). A trace amount of **3ab** and no crossover product **4p** was observed. This result indicates irreversible addition of α-keto aldehydes to the rhodacycle intermediate, which is in contrast to those of the Rh(III)- and Co(III)-catalyzed reversible insertion of aldehydes, imines, and isocyanates.[11] For an example on irreversible insertion of aldehydes, Li demonstrated the Rh(III)-catalyzed C−H addition of phenylpyridines to ethyl glyoxalate,[12] which is thermodynamically favorable due to aldehyde destabilization as opposed to additions to standard aldehydes.

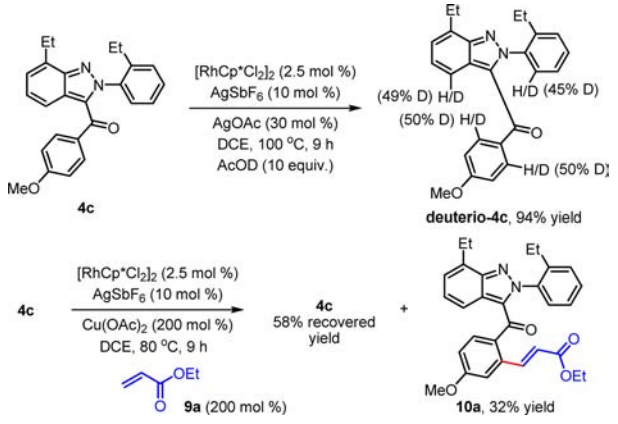
Scheme 5. Reversibility and Competition Experiment



Thus, our reaction afforded C7-alkylated indazole **8a** as a major product in 56% yield, and no formation of **8b** was detected, which shows that intramolecular cyclization of α-hydroxy ketones generated from aryl glyoxals is faster than α-hydroxy esters generated from ethyl glyoxalate. The above results also support the formation of indazoles **4l** and **4m** through monoalkylation followed by fast intramolecular cyclization. In sharp contrast, in the case of ethyl glyoxalate, the formation of bis-alkylation took place faster than intramolecular cyclization to give C7-alkylated indazole products.

Next, we envisioned the sequential C−H activation of our products by assisting indazole and carbonyl directing groups. Thus, the deuterium-labeling experiment of **4c** was performed, which resulted in H/D exchanges at all C−H bonds in the proximity of indazole and carbonyl directing groups (Scheme 6). However, the sequential C−H functionalization of **4c** with acrylate **9a** took place preferentially on the 4-methoxyphenyl ring to furnish mono-olefination product **10a** in 32% yield.

Scheme 6. Deuterium-Labelling Experiment and Sequential C−H Functionalization of Indazole Product



Based on the precedent literatures on the C−H functionalization of azobenzenes with carbonyl compounds,[6,9,10b,d] a plausible mechanistic pathway for the formation of *ortho*-alkylated azobenzenes and indazoles is depicted in Scheme 7. First, coordination of an azo group in azobenzene **1a** to a cationic Rh(III) catalyst and subsequent C−H cleavage generates a five-membered rhodacycle species **I**.[13] Then coordination of ethyl glyoxalate **2a** to **I** affords an intermediate **II**. An irreversible insertion of α-keto aldehydes to a Rh−carbonyl bond of intermediate **II** forms the seven-membered rhodacycle **III**,[12] which undergoes protonation to give the alkylated product **3aa**

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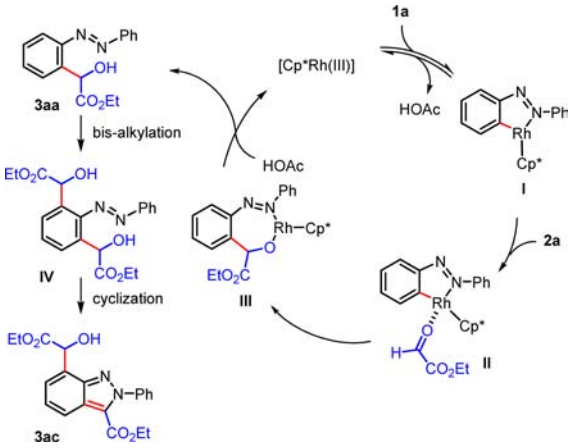
Scheme 7. Plausible Reaction Pathway



and an active Rh(III) catalyst. Further alkylation of **3aa** affords bis-alkylated intermediate **IV**, which on cyclization and subsequent aromatization delivers indazole **3ac**.

In conclusion, we disclosed the rhodium(III)-catalyzed direct insertion of ethyl glyoxalate and aryl glyoxals to azobenzenes C−H bonds followed by intramolecular cyclization affording highly substituted indazoles. This approach allows the generation of an array of C3-carbonylated indazoles, which are known to be crucial scaffolds of biologically active compounds. Further mechanistic investigations revealed that the insertion step of α-keto aldehydes to rhodacycle intermediate is irreversible, which is in sharp contrast to those of other π-unsaturates under Rh- and Co-catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03368.

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all compounds (PDF)
X-ray crystallographic data (CIF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Elguero, J. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Eds.; Pergamon: New York, 1984; Vol. 5, pp 167−303. (b) Cerecetto, H.; Gerpe, A.; González, M.; Arán, V. J.; de Ocáriz, C. O. *Mini-Rev. Med. Chem.* **2005**, *5*, 869. (c) Magano, J.; Waldo, M.; Greene, D.; Nord, E. *Org. Process Res. Dev.* **2008**, *12*, 877. (d) Haddadin, M. J.; Conrad, W. E.; Kurth, M. J. *Mini-Rev. Med. Chem.* **2012**, *12*, 1293.

(2) (a) Atta-ur-Rahman; Malik, S.; Cun-heng, H.; Clardy, J. *Tetrahedron Lett.* **1985**, *26*, 2759. (b) De Lena, M.; Lorusso, V.; Latorre, A.; Fanizza, G.; Gargano, G.; Caporusso, L.; Guida, M.; Catino, A.; Crucitta, E.; Sambiasi, D.; Mazzei, A. *Eur. J. Cancer* **2001**, *37*, 364. (c) Cupissol, D. R.; Serrou, B.; Cabel, M. *J. Cancer Clin. Oncol.* **1990**, *26*, S23. (d) Halim, R.; Harding, M.; Hufton, R.; Morton, C. J.; Jahangiri, S.; Pool, B. R.; Jeynes, T. P.; Draffan, A. G.; Lilly, M. J.; Frey, B. WO 2012051659 A1, 2011. (e) Steffan, R. J.; Matelan, E. M. WO 2006050006 A2, 2006.

(3) (a) Yoshida, T.; Matsuura, N.; Yamamoto, K.; Doi, M.; Shimada, K.; Morie, T.; Kato, S. *Heterocycles* **1996**, *43*, 2701. (b) Snyder, H. R.; Thompson, C. B.; Hinman, R. L. *J. Am. Chem. Soc.* **1952**, *74*, 2009. (c) Welch, W. M.; Hanau, C. E.; Whalen, W. M. *Synthesis* **1992**, *1992*, 937. (d) Bunnell, A.; O'Yang, C.; Petrica, A.; Soth, M. J. *Synth. Commun.* **2006**, *36*, 285. (e) Luo, G.; Chen, L.; Dubowchik, G. *J. Org. Chem.* **2006**, *71*, 5392. (f) Unsinn, A.; Knochel, P. *Chem. Commun.* **2012**, *48*, 2680.

(4) For recent selected reviews on the synthesis of heterocycles via C−H bond functionalization, see: (a) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107. (b) Kuhl, N.; Schröder, N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443. (c) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651.

(5) (a) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007**, *9*, 2931. (b) Zhang, T.; Bao, W. *J. Org. Chem.* **2013**, *78*, 1317. (c) Li, X.; He, L.; Chen, H.; Wu, W.; Jiang, H. *J. Org. Chem.* **2013**, *78*, 3636.

(6) (a) Lian, Y.; Bergman, R. G.; Lavis, L. D.; Ellman, J. A. *J. Am. Chem. Soc.* **2013**, *135*, 7122. (b) Hummel, J. R.; Ellman, J. A. *J. Am. Chem. Soc.* **2015**, *137*, 490.

(7) Yu, D.-G.; Suri, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 8802.

(8) Han, S.; Shin, Y.; Sharma, S.; Mishra, N. K.; Park, J.; Kim, M.; Kim, M.; Jang, J.; Kim, I. S. *Org. Lett.* **2014**, *16*, 2494.

(9) Geng, X.; Wang, C. *Org. Lett.* **2015**, *17*, 2434.

(10) (a) Mishra, N. K.; Park, J.; Sharma, S.; Han, S.; Kim, M.; Shin, Y.; Jang, J.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Chem. Commun.* **2014**, *50*, 2350. (b) Sharma, S.; Han, S. H.; Han, S.; Ji, W.; Oh, J.; Lee, S.-Y.; Oh, J. S.; Jung, Y. H.; Kim, I. S. *Org. Lett.* **2015**, *17*, 2852. (c) Park, J.; Mishra, N. K.; Sharma, S.; Han, S.; Shin, Y.; Jeong, T.; Oh, J. S.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *J. Org. Chem.* **2015**, *80*, 1818. (d) Han, S.; Mishra, N. K.; Sharma, S.; Park, J.; Choi, M.; Lee, S.-Y.; Oh, J. S.; Jung, Y. H.; Kim, I. S. *J. Org. Chem.* **2015**, *80*, 8026.

(11) For selected examples on the Rh-catalyzed reversible insertion of π-unsaturates to C−H bonds, see: (a) Zhang, X.-S.; Chen, K.; Shi, Z.-J. *Chem. Sci.* **2014**, *5*, 2146. (b) Li, Y.; Li, B.-J.; Wang, W.-H.; Huang, W.-P.; Zhang, X.-S.; Chen, K.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 2115. (c) Tsai, A. S.; Tauchert, M. E.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 1248. (d) Li, H.; Li, Y.; Zhang, X.-S.; Chen, K.; Wang, X.; Shi, Z.-J. *J. Am. Chem. Soc.* **2011**, *133*, 15244. (e) Li, H.; Li, Y.; Zhang, X.-S.; Chen, K.; Wang, X.; Shi, Z.-J. *J. Am. Chem. Soc.* **2011**, *133*, 15244. (f) Chen, K.; Li, H.; Lei, Z.-Q.; Li, Y.; Ye, W.-H.; Zhang, L.-S.; Sun, J.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 9851. (g) Li, Y.; Zhang, X.-S.; Li, H.; Wang, W.-H.; Chen, K.; Li, B.-J.; Shi, Z.-J. *Chem. Sci.* **2012**, *3*, 1634. (h) Zhang, X.-S.; Li, Y.; Li, H.; Chen, K.; Lei, Z.-Q.; Shi, Z.-J. *Chem. - Eur. J.* **2012**, *50*, 16214. (i) Li, Y.; Zhang, X.-S.; Zhu, Q.-L.; Shi, Z.-J. *Org. Lett.* **2012**, *14*, 4498. (j) Li, Y.; Zhang, X.-S.; Chen, K.; He, K.-H.; Pan, F.; Li, B.-J.; Shi, Z.-J. *Org. Lett.* **2012**, *14*, 636. (k) Zhang, X.-S.; Zhu, Q.-L.; Luo, F.-X.; Chen, G.; Wang, X.; Shi, Z.-J. *Eur. J. Org. Chem.* **2013**, *2013*, 6530. (l) Jeong, T.; Han, S.; Mishra, N. K.; Sharma, S.; Lee, S.-Y.; Oh, J. S.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *J. Org. Chem.* **2015**, *80*, 7243 For Co-catalyzed reversible insertion of aldehydes to C−H bonds, see ref 6b.

(12) Yang, L.; Correia, C. A.; Li, C.-J. *Adv. Synth. Catal.* **2011**, *353*, 1269.

(13) For a selected review for the heteroatom-directed rhodacycle intermediates, see: Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624.

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Organic LETTERS

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Asymmetric Direct 1,2-Addition of Aryl Grignard Reagents to Aryl Alkyl Ketones

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Supporting Information

ABSTRACT: The enantioselective addition of Grignard reagents to ketones was promoted by a BINOL derivative bearing alkyl chains at the 3,3′-positions. This is the first asymmetric direct aryl Grignard addition to ketones reported to date. A variety of tertiary diaryl alcohols could be obtained in high yields and enantioselectivities without using any other metal source.

Enantiopure tertiary alcohols are important structural motifs in organic chemistry and are ubiquitous in natural products and pharmaceutical compounds.[1] The simplest approach to constructing these structures involves the enantioselective 1,2-addition of organometallics to ketones.[2,3] The addition of alkyl groups to ketones has been achieved by developing catalysts using organozinc,[4] titanium,[4] and aluminum.[5] By contrast, the enantioselective addition of readily available Grignard reagents has proven to be more difficult.[6] Recently, copper-catalyzed asymmetric additions of alkyl Grignard reagents were reported.[7] Only a few Grignard reagent additions have been achieved without the use of additional metals, and these reactions have required more than stoichiometric amounts of a chiral ligand to achieve a high enantioselectivity.[8,9]

The addition of aryl groups to ketones was first achieved using an asymmetric reaction of $ZnPh_2$, as reported by Fu et al. in 1998.[10] Over the two subsequent decades, several approaches to obtaining chiral tertiary alcohols have been explored using arylzinc,[11] -titanium,[12] -boron compounds,[13] and -aluminum.[14] These reports showed excellent results; however, they are disadvantaged in their requirement for nucleophile preparation. For example, the preparation of arylzinc reagents from excess $ZnEt_2$ and arylboron compounds required elevated temperatures and long reaction times. Triarylaluminum compounds were prepared from $AlCl_3$ and 3 equiv of aryl Grignard reagents in THF over 12 h. In comparison with these preparations, asymmetric direct aryl Grignard additions to ketones are very simple procedures and efficient methods for reduction of other metal wastes. Although enantioselective catalytic additions of aryl Grignard reagents with excess amounts of $Ti(O^iPr)_4$ were reported recently,[15] to the best of our knowledge, no examples of enantioselective aryl Grignard addition to simple ketones without the use of other metals have yet been described.[16]

We previously reported the enantioselective alkynylation of lithium acetylide to ketones using lithium binaphtholate as a catalyst.[17] Here, we report the first direct asymmetric addition of aryl Grignard reagents to simple ketones using magnesium binaphtholate as a chiral ligand, providing tertiary diaryl alcohols in high yields and enantioselectivities.

Initially, we attempted the addition of a THF solution of 2′-acetonaphthone (**1a**) to phenylmagnesium bromide (**2a**) (3.5 equiv) and (*R*)-BINOL (**3a**) (100 mol %) as a chiral ligand in THF at −45 °C (Table 1, entry 1). In our research, 2 equiv of the Grignard reagent was consumed during deprotonation of the chiral ligand, and more than 1 equiv of the reagent was essential for the reaction with a ketone; therefore, we first used 3.5 equiv of **2a**. The reaction proceeded smoothly to give the tertiary alcohol **4a** in good yield and low ee. The stereoselectivity was improved by investigating other BINOL derivatives. The desired product was obtained in moderate enantioselectivity in the presence of (*R*)-3,3′-diphenyl-1,1′-binaphthol **3b**, which was the best catalyst identified in our previous alkynylation reactions (entry 2). This result suggested that the high stereoinduction of tertiary alcohols was essential for obtaining steric effects at the 3,3′-positions of the BINOL skeleton. We next tested the 2,6-dimethylphenyl-substituted BINOL derivative **3c**, but no enantioselectivity was achieved (entry 3).

BINOLs with substituents at the 3,3′-positions are versatile C_2-symmetric chiral ligands; however, few examples have described the use of compounds bearing alkyl groups in these positions as asymmetric ligands.[18] Therefore, we accepted the challenge associated with synthesizing these new types of BINOL ligands. The BINOL derivatives **3d** and **3e**, bearing benzyl and 1-methoxy-1-methylethyl groups, provided a poor yield and poor enantioselectivity (entries 4 and 5); however, the ligand **3f**, which included 2-methoxy-2-methylpropyl groups, yielded an improved enantioselectivity (entry 6). The ligand **3g** gave almost the same result (entry 7). We next introduced bulky aliphatic chains at the 3,3′-positions of BINOL (entries 8 and 9).

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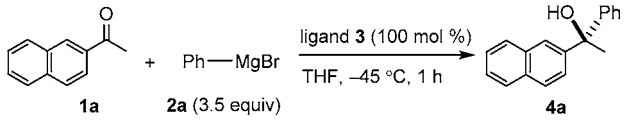
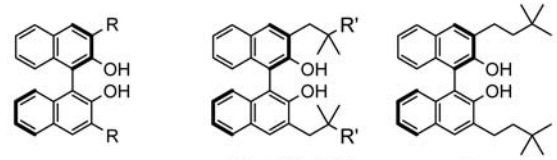
Table 1. Optimization of the Chiral Ligands[a]



1a 2a (3.5 equiv) 4a

entry	3	yield (%)	ee (%)
1	**3a**	87	18
2	**3b**	92	50
3	**3c**	80	2
4	**3d**	81	3
5	**3e**	24	−25
6	**3f**	96	72
7	**3g**	89	72
8	**3h**	95	78
9	**3i**	92	90
10[b]	**3i**	**94**	**93**



R = H (**3a**)
R = Ph (**3b**)
R = 2,6-$Me_2C_6H_3$ (**3c**)
R = Benzyl (**3d**)
R = $C(CH_3)_2OMe$ (**3e**)

R' = OMe (**3f**)
R' = OEt (**3g**)
R' = Me (**3h**)

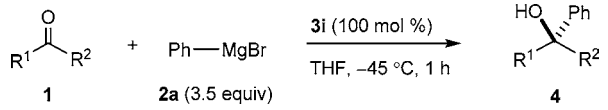
3i

[a]Unless otherwise noted, the reactions were conducted using the following procedure: A THF solution of 2′-acetonaphthone (**1a**) (0.5 mmol) was added to a solution of phenylmagnesium bromide (**2a**) (1.75 mmol) and ligand **3** (0.5 mmol) in THF (1.0 mL) at −45 °C. [b]Phenylmagnesium bromide (**2a**) (1.75 mmol) was added to the solution of 2′-acetonaphthone (**1a**) (0.5 mmol) and ligand **3** (0.5 mmol) in THF (1.0 mL) at −45 °C.

Gratifyingly, we succeeded in improving the enantioselectivity. The tertiary alcohol was obtained in a 92% yield and 90% ee using ligand **3i** with 3,3-dimethylbutyl groups. Furthermore, reactions unrelated to the ligand were partially suppressed by addition of phenylmagnesium bromide (**2a**) to the mixture of 2′-acetonaphthone (**1a**) and the ligand **3i** in THF, yielding the corresponding product in 94% yield and 93% ee (entry 10).[19] In our procedure, the reaction reached completion within 1 h. The reaction time was shorter than the time required for the corresponding aryl organometallics, which generally required over 12 h. Although we used stoichiometric amounts of the chiral ligand **3i**, this ligand was easily recovered and reused.[20]

The conditions optimized for ketone **1a** were applied to the reactions of other simple ketones **1b**–**g** (Table 2). 1′-Acetonaphthone (**1b**) showed a lower chemical yield than **1a**, although the obtained product **4b** displayed an excellent enantioselectivity (entry 2). Although the product **4e** displayed a slightly lower enantioselectivity, the aromatic ketones **1c**–**e** bearing electron-donating and -withdrawing groups smoothly reacted to give the tertiary alcohols **4c**–**e** in very high yields and enantioselectivities (entries 3–5). 2-Naphthyl ethyl ketone (**1f**), which included bulkier R^2 groups than **1a**, reacted with an acceptable enantioselectivity (entry 6). Cyclohexyl methyl ketone (**1g**) gave a high yield with a low ee (entry 7). Therefore, intermolecular interactions such as $\pi-\pi$ stacking between the aromatic ketone and the Grignard reagent appeared to play a key role in the transition state of the 1,2-addition.

Table 2. Various Simple Ketones Were Tested for the Preparation of the Tertiary Alcohols[a]



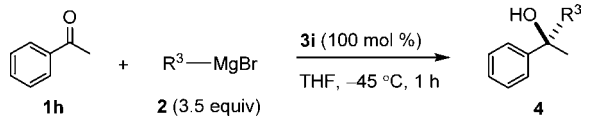
1 2a (3.5 equiv) 4

entry	1	R^1	R^2	4	yield (%)	ee (%)
1	**1a**	2-naphthyl	Me	**4a**	94	93
2	**1b**	1-naphthyl	Me	**4b**	70	96
3	**1c**	4-$MeOC_6H_4$	Me	**4c**	95	91
4	**1d**	4-BrC_6H_4	Me	**4d**	92	91
5	**1e**	4-ClC_6H_4	Me	**4e**	98	86
6	**1f**	2-naphthyl	Et	**4f**	97	86
7	**1g**	^{c}Hex	Me	**4g**	92	30

[a]All reactions were conducted using ketone **1** (0.5 mmol), phenylmagnesium bromide (**2a**) (1.75 mmol), and ligand **3i** (0.5 mmol) in THF (1.0 mL) at −45 °C.

We next investigated the reactions of various Grignard reagents with acetophenone (**1h**) (Table 3). 2-Naphthylmagnesium bromide (**2b**) afforded the product *ent*-**4a** in good yield with a high enantioselectivity (entry 1) with an absolute configuration opposite that of the product **4a** derived from the phenyl addition to 2′-acetonaphthone. The use of **2c** and **2d**, which bore electron-donating groups at the 4′-, and 3′-positions of the aromatic group, slightly decreased the enantioselectivities of the tertiary alcohols *ent*-**4c** and **4h** (entries 2 and 3). A methoxy group at the 2′-position dramatically decreased the ee (entry 4). This effect was attributed to chelation at the metal center. The methyl-substituted Grignard reagents **2f** and **2g** generated the product in a high yield and acceptable ee (entries 5 and 6). Compounds **2h** and **2i**, which bore electron-withdrawing groups, provided a slightly lower chemical yield, but the ee values of the tertiary alcohols **4l** and *ent*-**4e** were excellent (entries 7 and 8). A reaction of cyclohexylmagnesium bromide (**2j**) dramatically decreased the yield of the product, accompanied by a moderate ee (entry 9). The basicity of the aliphatic Grignard reagent was stronger than that of the aromatic reagent; therefore, enolization of the ketone occurred as the main side reaction.

Table 3. Various Grignard Reagents Were Tested for the Preparation of the Tertiary Alcohols[a]



1h 2 (3.5 equiv) 4

entry	2	R3	4	yield (%)	ee (%)
1	**2b**	2-naphthyl	*ent*-**4a**	80	94
2	**2c**	4-$MeOC_6H_4$	*ent*-**4c**	94	84
3	**2d**	3-$MeOC_6H_4$	**4h**	90	87
4	**2e**	2-$MeOC_6H_4$	**4i**	97	6
5	**2f**	4-MeC_6H_4	**4j**	96	88
6	**2g**	2-MeC_6H_4	**4k**	98	90
7	**2h**	4-FC_6H_4	**4l**	83	94
8	**2i**	4-ClC_6H_4	*ent*-**4e**	70	97
9	**2j**	^{c}Hex	*ent*-**4g**	10	59

[a]All reactions were conducted using acetophenone (**1h**) (0.5 mmol), Grignard reagent **2** (1.75 mmol), and ligand **3i** (0.5 mmol) in THF (1.0 mL) at −45 °C.

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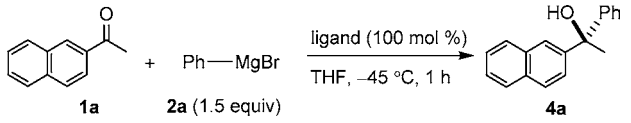
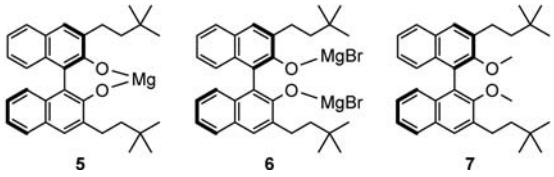
The mechanism underlying the stereoinduction was investigated by examining the structure of the Mg salt of the ligand (Table 4). BINOL derivatives have two oxygen atoms; therefore,

Table 4. Investigation of the Structure of the Mg Salt[a]



1a 2a (1.5 equiv) 4a

entry	ligand	yield (%)	ee (%)
1	**5**	66	26
2	-	77	-
3	**7**	82	0



5 6 7

[a]Ligand **5** was prepared in situ by stirring a 1:1 ratio of **3i** and $^{n}Bu_2Mg$.

two compounds, the monomagnesium salt **5** and the dimagnesium salt **6**, were presumed to be present. Monomagnesium binaphtholate was used as a good asymmetric catalyst and could be readily prepared from BINOL and $^{n}Bu_2Mg$.[21] We tried to use this species in our Grignard addition; however, the product was obtained in a moderate yield and a low ee (entry 1). We attempted a reaction of **1a** and 1.5 equiv of **2a** in the absence of ligand **3i**, and the tertiary alcohol was obtained in 77% yield (entry 2). This chemical yield was lower than that obtained in the presence of the ligand. No enantioselectivity was achieved from the *O*-methylated BINOL derivative **7** (entry 3).

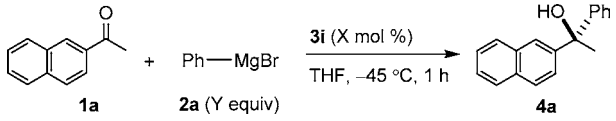
We next examined the relationship between the ee values of the ligand **3i** and those of the product **4a**. No clear nonlinear effects were observed in the 1,2-addition between **1a** and **2a**.[22] Aggregation has been reported in magnesium binaphtholate;[21a,e] however, we assumed that the monomeric species acted as an asymmetric auxiliary in the transition state.

These results suggested that the dimagnesium salt **6** was generated in the reaction and coordinated to the Grignard reagent as a Lewis base to enhance the nucleophilicity. Furthermore, the magnesium atom of **6** was effective in activating the ketone, and substituents at the 3,3′-positions of BINOLs controlled the direction of nucleophilic attack on the prochiral carbon atom. Although further investigations of the mechanism are required to fully understand this method, the transition state appeared to be a monomeric dimagnesium salt **6**.

Finally, we examined the effects of the ratio between the chiral ligand **3i** and the Grignard reagent (Table 5). Interestingly, even 50 mol % of **3i** gave the product in a good yield and an ee of 90% (entry 3); however, reducing the amounts of the chiral ligand tended to reduce the yield and ee (entries 4 and 5). These results suggested that the complex between the Grignard reagent and **3i** was more reactive than the Grignard reagent alone. Therefore, a well-designed BINOL may provide a high ee in a catalytic version of this asymmetric Grignard addition. We are currently investigating the synthesis of more effective BINOL derivative.

In conclusion, we have demonstrated the first example of enantioselective direct aryl Grignard additions to aryl alkyl ketones to afford the tertiary diaryl alcohols. Our protocol is very simple and does not require other metals or long reaction times.

Table 5. Reduction of the Amounts of Chiral Ligand 3i and Phenylmagnesium Bromide (2a)[a]



1a 2a (Y equiv) 4a

entry	*X*	*Y*	yield (%)	ee (%)
1	100	3.5	94	93
2	100	3.0	90	92
3	50	2.0	81	90
4	30	1.6	70	64
5	20	1.4	68	47

[a]Each reaction was conducted using 2′-acetonaphthone (**1a**) (0.5 mmol), phenylmagnesium bromide (**2a**) (*Y* equiv), and ligand **3i** (*X* mol %) in THF (1.0 mL) at −45 °C.

Our new BINOL derivative **3i** is easily recyclable and may potentially afford catalytic activity. Further investigations toward achieving BINOL-catalyzed direct Grignard additions are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03379.

Experimental procedures and spectral data for all new products (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Lebel, H.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 9624−9625. (b) Lu, G.; Li, X.; Jia, X.; Chan, W. L.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5057−5058. (c) Madduri, A. V.; Harutyunyan, S. R.; Minnaard, A. J. *Drug Discovery Today: Technol.* **2013**, *10*, e21−e27. (d) Ameen, D.; Snape, T. J. *MedChemComm* **2013**, *4*, 893−907.

(2) For reviews for synthesis of tertiary alcohols, see: (a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757−824. (b) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, *2007*, 5969−5994. (c) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873−888. (d) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853−2873. (e) Hatano, M.; Ishihara, K. *Synthesis* **2008**, *2008*, 1647−1675.

(3) For alternative methods for the synthesis of chiral tertiary alcohols, see: (a) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature* **2008**, *456*, 778−782. (b) Bagutski, V.; French, R. M.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5142−5145.

(4) (a) Funabashi, K.; Jachmann, M.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5489−5492. (b) Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 1239−1242. (c) García, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970−10971. (d) DiMauro, E. F.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2002**, *124*, 12668−12669. (e) Jeon, S.-J.; Li, H.; García, C.; LaRochelle, L. K.; Walsh, P. J. *J. Org. Chem.* **2005**, *70*, 448−455. (f) Hussain, M. M.; Walsh, P. J. *Acc. Chem.*

DOI: 10.1021/acs.orglett.5b03379
Org. Lett. 2016, 18, 236−239

Res. **2008**, *41*, 883−893. (g) Huelgas, G.; LaRochelle, L. K.; Rivas, L.; Luchinina, Y.; Toscano, R. A.; Carroll, P. J.; Walsh, P. J.; Anaya de Parrodi, C. *Tetrahedron* **2011**, *67*, 4467−4474.

(5) (a) Siewert, J.; Sandmann, R.; von Zezschwitz, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7122−7124. (b) Biradar, D. B.; Gau, H.-M. *Org. Lett.* **2009**, *11*, 499−502.

(6) For examples of the catalytic nonasymmetric addition of Grignard reagents to ketones, see: (a) Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc.* **2006**, *128*, 9998−9999. (b) Hatano, M.; Ito, O.; Suzuki, S.; Ishihara, K. *J. Org. Chem.* **2010**, *75*, 5008−5016. (c) Hatano, M.; Ito, O.; Suzuki, S.; Ishihara, K. *Chem. Commun.* **2010**, *46*, 2674−2676.

(7) (a) Madduri, A. V. R.; Minnaard, A. J.; Harutyunyan, S. R. *Chem. Commun.* **2012**, *48*, 1478−1480. (b) Madduri, A. V. R.; Minnaard, A. J.; Harutyunyan, S. R. *Org. Biomol. Chem.* **2012**, *10*, 2878−2884. (c) Madduri, A. V. R.; Harutyunyan, S. R.; Minnaard, A. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 3164−3167. (d) Caprioli, F.; Lutz, M.; Meetsma, A.; Minnaard, A. J.; Harutyunyan, S. R. *Synlett* **2013**, *24*, 2419−2422. (e) Caprioli, F.; Madduri, A. V. R.; Minnaard, A. J.; Harutyunyan, S. R. *Chem. Commun.* **2013**, *49*, 5450−5452. (f) Ortiz, P.; Del Hoyo, A. M.; Harutyunyan, S. R. *Eur. J. Org. Chem.* **2015**, *2015*, 72−76. (g) Rong, J.; Oost, R.; Desmarchelier, A.; Minnaard, A. J.; Harutyunyan, S. R. *Angew. Chem., Int. Ed.* **2015**, *54*, 3038−3042.

(8) (a) Inch, T. D.; Lewis, G. J.; Sainsbury, G. L.; Sellers, D. J. *Tetrahedron Lett.* **1969**, *10*, 3657−3660. (b) Tomioka, K.; Nakajima, M.; Koga, K. *Chem. Lett.* **1987**, 65−68. (c) Weber, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 84−86. (d) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 6117−6128.

(9) For examples of diastereoselective alkyl Grignard addition to ketones bearing intramolecular chiral auxiliary, see: (a) Eliel, E. L.; Koskimies, J. K.; Lohri, B. *J. Am. Chem. Soc.* **1978**, *100*, 1614−1616. (b) Mukaiyama, T.; Sakito, Y.; Asami, M. *Chem. Lett.* **1978**, 1253−1256.

(10) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445−446.

(11) (a) Hatano, M.; Miyamoto, T.; Ishihara, K. *Org. Lett.* **2007**, *9*, 4535−4538. For reaction of Ti with arylzinc, see: (b) Prieto, O.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1955−1957. (c) García, C.; Walsh, P. J. *Org. Lett.* **2003**, *5*, 3641−3644. (d) Forrat, V. J.; Prieto, O.; Ramón, D. J.; Yus, M. *Chem. - Eur. J.* **2006**, *12*, 4431−4445. (e) Forrat, V. J.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2009**, *20*, 65−67.

(12) (a) Zhou, S.-L.; Chen, C.-R.; Gau, H.-M. *Org. Lett.* **2010**, *12*, 48−51. (b) Wu, K.-H.; Kuo, Y.-Y.; Chen, C.-A.; Huang, Y.-L.; Gau, H.-M. *Adv. Synth. Catal.* **2013**, *355*, 1001−1008.

(13) (a) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3353−3356. (b) Martina, S. L. X.; Jagt, R. B. C.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Chem. Commun.* **2006**, 4093−4095. (c) Lai, H.; Huang, Z.; Wu, Q.; Qin, Y. *J. Org. Chem.* **2009**, *74*, 283−288.

(14) (a) Chen, C.-A.; Wu, K.-H.; Gau, H.-M. *Angew. Chem., Int. Ed.* **2007**, *46*, 5373−5376. (b) Wu, K.-H.; Chuang, D.-W.; Chen, C.-A.; Gau, H.-M. *Chem. Commun.* **2008**, 2343−2345. (c) Chen, C.-A.; Wu, K.-H.; Gau, H.-M. *Adv. Synth. Catal.* **2008**, *350*, 1626−1634. (d) Zhou, S.-L.; Wu, K.-H.; Chen, C.-A.; Gau, H.-M. *J. Org. Chem.* **2009**, *74*, 3500−3505. (e) Biradar, D. B.; Zhou, S.-L.; Gau, H.-M. *Org. Lett.* **2009**, *11*, 3386−3389.

(15) Fernández-Mateos, E.; Maciá, B.; Yus, M. *Eur. J. Org. Chem.* **2014**, *2014*, 6519−6526.

(16) For examples of diastereoselective aryl Grignard addition to ketones bearing an intramolecular chiral auxiliary, see: (a) Akhoon, K. M.; Myles, D. C. *J. Org. Chem.* **1997**, *62*, 6041−6045. (b) Antczak, M. I.; Cai, F.; Ready, J. M. *Org. Lett.* **2011**, *13*, 184−187. (c) Nakakita, T.; Miura, M.; Toriyama, M.; Motohashi, S.; Barybin, M. V. *Tetrahedron Lett.* **2014**, *55*, 1090−1092.

(17) (a) Tanaka, K.; Kukita, K.; Ichibakase, T.; Kotani, S.; Nakajima, M. *Chem. Commun.* **2011**, *47*, 5614−5616. (b) Kotani, S.; Kukita, K.; Tanaka, K.; Ichibakase, T.; Nakajima, M. *J. Org. Chem.* **2014**, *79*, 4817−4825.

(18) (a) Qian, C.; Huang, T.; Zhu, C.; Sun, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2097−2104. (b) Qian, C.; Zhu, C.; Huang, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2131−2132. (c) Graves, C. R.; Zhou, H.; Stern, C. L.; Nguyen, S. T. *J. Org. Chem.* **2007**, *72*, 9121−9233. (d) Zou, X.; Zhang, S.; Cheng, Y.; Liu, Y.; Huang, H.; Wang, C. *J. Appl. Polym. Sci.* **2007**, *106*, 821−827.

(19) Although we screened other solvents, temperatures, and halogen atoms in the Grignard reagent, these results could not be improved. We tested 3.0 equiv of **2a**, and the tertiary alcohol **4a** was obtained in a 90% yield and 92% ee (Table 5, entry 2). Hence, the procedure using entry 10 was deemed to be the best.

(20) The quantitative amounts of all ligand **3** were recovered after asymmetric 1,2-addition. The R_f values of ligand **3i** and product **4a** were 0.74 and 0.15 (hexane/CH_2Cl_2 = 1/1), and the R_f values of all other products **4** were similar to those of **4a**.

(21) (a) Du, H.; Zhang, X.; Wang, Z.; Bao, H.; You, T.; Ding, K. *Eur. J. Org. Chem.* **2008**, *2008*, 2248−2254. (b) Bao, H.; Wu, J.; Li, H.; Wang, Z.; You, T.; Ding, K. *Eur. J. Org. Chem.* **2010**, *2010*, 6722−6726. (c) Hatano, M.; Horibe, T.; Ishihara, K. *Org. Lett.* **2010**, *12*, 3502−3505. (d) Lin, L.; Zhang, J.; Ma, X.; Fu, X.; Wang, R. *Org. Lett.* **2011**, *13*, 6410−6413. (e) Hatano, M.; Horibe, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 4549−4553. (f) Zhang, J.; Liu, X.; Wang, R. *Chem. - Eur. J.* **2014**, *20*, 4911−4915. (g) Wang, L.; Yang, D.; Li, D.; Wang, R. *Org. Lett.* **2015**, *17*, 3004−3007.

(22) The ee values of the obtained tertiary alcohol **4a** were 55%, 41%, and 19% using ligand **3i** with ee values of 66%, 44%, and 20%, respectively. See the Supporting Information for details.

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Organic LETTERS

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Synthesis of Spiro Ketals, Orthoesters, and Orthocarbonates by CpRu-Catalyzed Decomposition of α-Diazo-β-ketoesters

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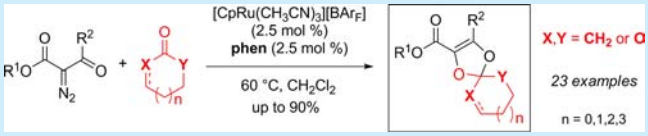
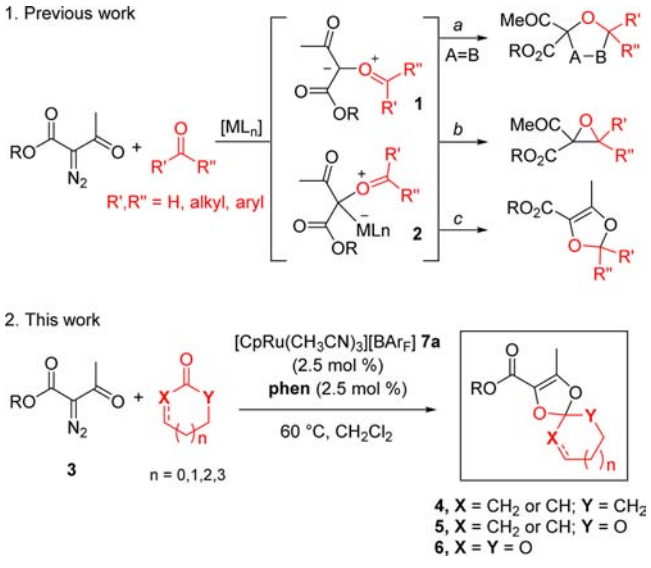
Supporting Information

ABSTRACT: Reactions of α-diazo-β-ketoesters with cyclic ketones, lactones, and carbonates are reported. Thanks to the combined use of salt $[CpRu(CH_3CN)_3][BAr_F]$ and 1,10-phenanthroline as catalyst for the diazo decomposition, effective and practical syntheses of spiro bicyclic ketals, orthoesters, and orthocarbonates are afforded.



Electrophilic metal carbenes are known to react with nucleophilic carbonyl groups and form carbonyl ylides.[1] These reactive intermediates, metal-free **1** or metal-bound **2** (Scheme 1), behave as 1,3-dipoles and are known to react in [3 + 2]-dipolar cycloadditions to yield oxygenated 5-membered heterocycles (Scheme 1, route *a*).[2] Alternatively, carbonyl ylides **1** or **2** may condense to form epoxides and dioxolenes (routes *b* and *c*). While these intramolecular reactions occur with carbonyl ylides derived from aldehydes and ketones,[2b,c,3] they are unknown with ylides made by additions of esters and carbonates.[1a,4,5] Herein, in a general development, reactions of α-diazo-β-ketoesters **3** with cyclic ketones are reported but also with lactones and cyclic carbonates. Effective and reliable syntheses of spiro ketals **4**, orthoesters **5**, and orthocarbonates **6** are afforded thanks to the combined use of $[CpRu(CH_3CN)_3][BAr_F]$ **7a** (Cp = C_5H_5, BAr_F = tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate)[6] and 1,10-phenanthroline (**phen**)[7] as diazo decomposition catalyst.[8] A mild counterion effect[9] is also reported as **7a** is shown to be more reactive than classical $[CpRu(CH_3CN)_3][PF_6]$ **7b**;[10] the increased reactivity of **7a** allowing in general a use of a 1:1 stoichiometry between diazo reagents and reactive carbonyl groups in these intermolecular condensations.

Scheme 1. Selective Formation of Spiro Ketals, Orthoesters, and Orthocarbonates



Recently, in the context of *syn*-stereoselective epoxide openings, it was shown that $[CpRu(CH_3CN)_3][BAr_F]$ **7a** efficiently catalyzes the decomposition of α-diazo-β-ketoesters and promotes condensation reactions of the generated carbenes with oxirane substrates.[6,11] This salt leads to higher substrate conversion, reaction selectivity, and catalyst turnovers than **7b**.[12] It was then logical to test the combination of **7a** and **phen** in other condensation reactions, and that of reactive carbonyl groups in particular.

First, the catalytic combination of **7a** and **phen** was tested with cyclohexanone **8a**. α-Diazo-β-ketoesters **3a** to **3f** were used as substrates in a 1:1 stoichiometry, and positive results were obtained in these initial experiments (Scheme 2). In practice, diazo **3a** to **3f** (1 equiv) were added to solutions of **8a** (1 equiv) in CH_2Cl_2 together with $[CpRu(CH_3CN)_3][BAr_F]$ **7a** and **phen** (2.5 mol % each). After 3 h at 60 °C, full conversions were usually achieved; the conversions being determined by ^1H NMR spectroscopy (400 MHz, crude mixtures).[13] With bulkier ^{t}Bu ester **3d**, a prolonged reaction time of 4.5 h was necessary to afford full decomposition of the diazo reagent. Spiroketal adducts **4a** to **4d** were isolated in moderate to good yields (55−79%, Scheme 2). For the formation of **4a**, it was shown that the reaction is easily scaled up to a 1 g scale (see Supporting Information). With a linear propyl chain α to the carbonyl group (**3e**), similar reactivity and yields were obtained (**4e**, 85%), while, with a phenyl substituent, the reaction was slower and a lower yield of ketal was achieved (**4f**, 15%).[14] With these reactions and

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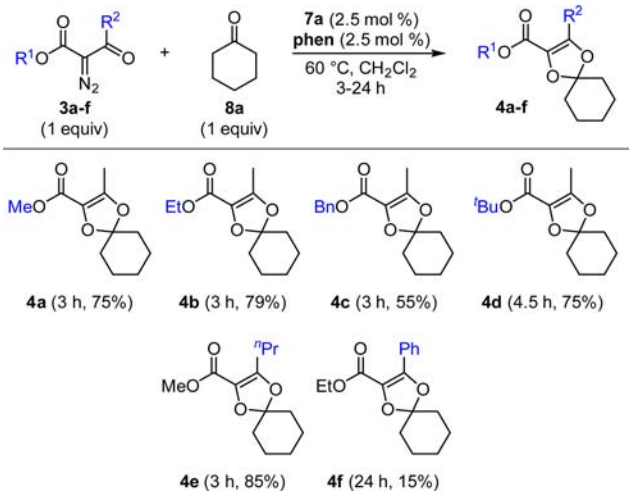
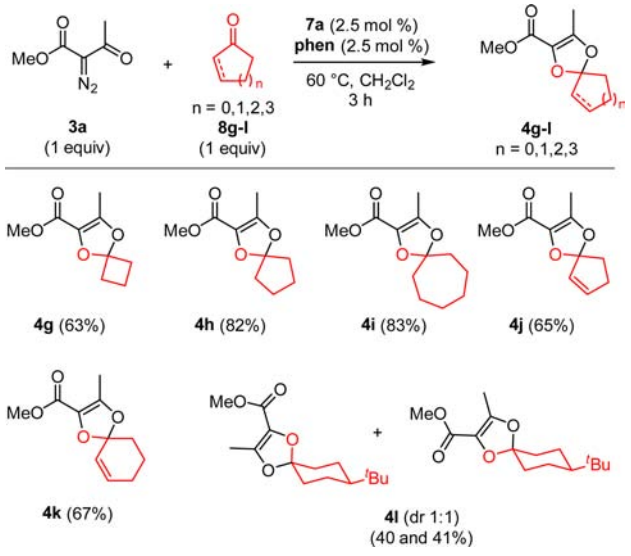
Scheme 2. Spiro Ketal Synthesis: Initial Experiments



conditions in hand, a comparison of the reactivity of BAr_F **7a** and PF_6 **7b** complexes was performed. The results are reported in Table S1 (Supporting Information). The difference is moderate for most substrates but strong in case of a steric hindrance, i.e., for **4d**. As a rule, an increased reactivity is observed for the BAr_F complex **7a**, which was kept for further experiments.

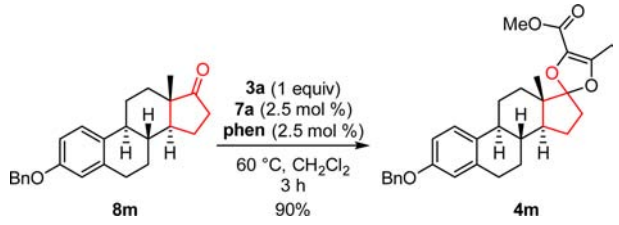
Cyclic saturated and unsaturated ketones **8g** to **8l** were then used to afford spiro dioxolenes **4g** to **4l** as only products in yields up to 83% (Scheme 3). Epoxides were never observed in the

Scheme 3. Spiro Ketal Synthesis: Extension



crude reaction mixtures nor cyclopropanes in the reactions of unsaturated substrates **8j** and **8k**.[15] Increasing the ring size, from four to seven, improved the stability of the corresponding ketals. In fact, products **4** are quite sensitive to acidic conditions decomposing upon standing over silica gel and after a few hours in $CDCl_3$. Although unlikely, the possibility to perform this reaction stereoselectively was examined with 4-^{t}Bu-cyclohexanone **8l** (Scheme 3). As expected, a 1:1 mixture of diastereomers was afforded.[16] The isomers of **4l** displayed a rather large difference in retardation factors (0.57 and 0.43, TLC silica gel, pentane/ether 9:1) and could be separated on column chromatography (40 and 41%, respectively). This lack of selectivity was confirmed with estrone **8m** (Scheme 4) for which an excellent yield of product **4m** was obtained (90%) albeit

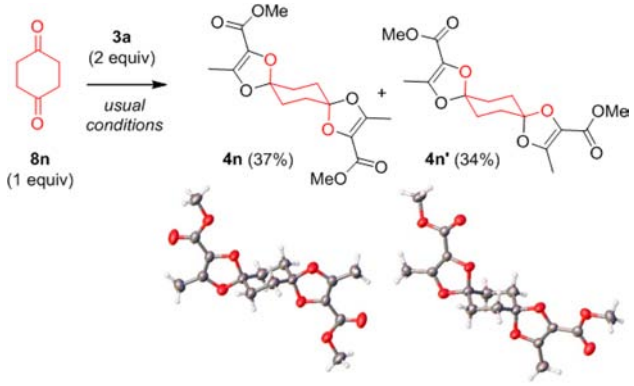
Scheme 4. Reactivity with Estrone



as a 1:1 mixture of diastereoisomers.[15] This result shows that the dioxolene reactivity is general, even in the case of rigid sterically encumbered substrates.

Treating cyclohexane-1,4-dione **8n** with two equivalents of **3a** afforded products of double cycloadditions and a 1:1 mixture of *trans*-**4n** and *cis*-**4n′** was also obtained (Scheme 5). It was again

Scheme 5. Bis Spiro Ketal Synthesis[a]



[a]Reaction conditions: **3a** (2.0 equiv), **7a** and **phen** (2.5 mol % each), 60 °C, CH_2Cl_2, 3 h, c = 0.5 M. OLEX views of the crystal structure of **4n** and **4n′**. Thermal ellipsoids are drawn at 50% probability.

possible to separate the adducts by chromatography (37 and 34% yield, respectively). The *trans* and *cis* configurations and the solid-state conformations were established by X-ray diffraction analyses.[17]

A mechanistic rationale, consistent with the experimental results, is proposed in Scheme 6. Complex **7a** reacts with **phen** to generate $[CpRu(\mathbf{phen})(CH_3CN)][BAr_F]$, which, upon dissociation of acetonitrile, forms the 16-electron catalytically active species **A**. The diazo moiety reacts with **A** to afford metal carbene intermediate **B** by nitrogen extrusion. At this stage, a nucleophilic attack of the cyclic ketone occurs to form the carbonyl ylide intermediate **C**. Subsequent ring closure affords the desired products of condensation (**C** → **D**). The spiro products are then released and the catalytic cycle continues.

Based on this proposal, the reactivity of lactones and cyclic carbonates with carbene intermediates of type **B** was envisaged. Saturated and unsaturated lactones **9a** to **9f** (Scheme 7) were first tested under previously developed conditions (3 h reaction time, 1 equiv of **3a**). A lower reactivity was immediately noticed as conversions of only 60% were observed. To obtain the corresponding orthoesters **5a** to **5f** in moderate to good yields (57−82%), it was necessary to increase both reaction time (up to 24 h) and stoichiometry (**3a**, 3 equiv). As before, with unsaturated lactones **9d** and **9e**, evidence of competing

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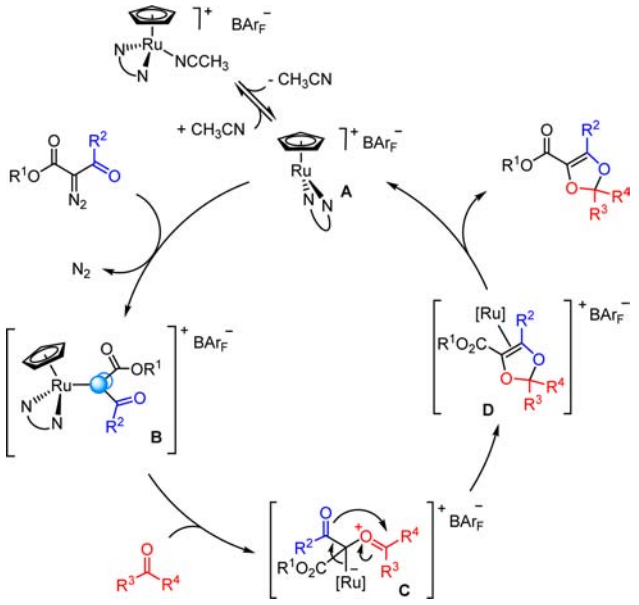
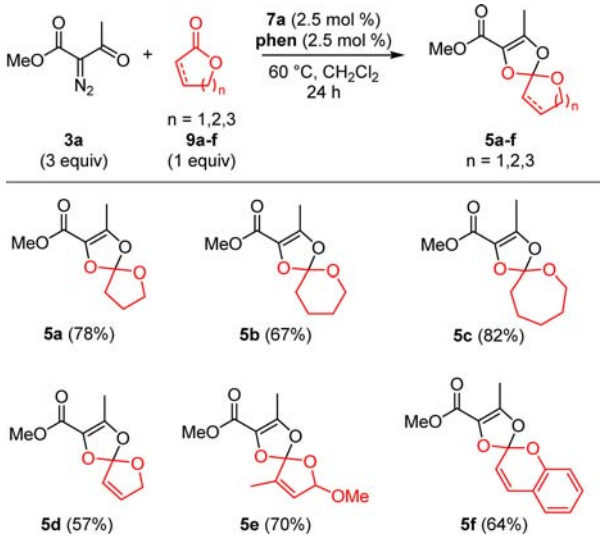
Scheme 6. Mechanistic Rational



Scheme 7. Orthoester Synthesis

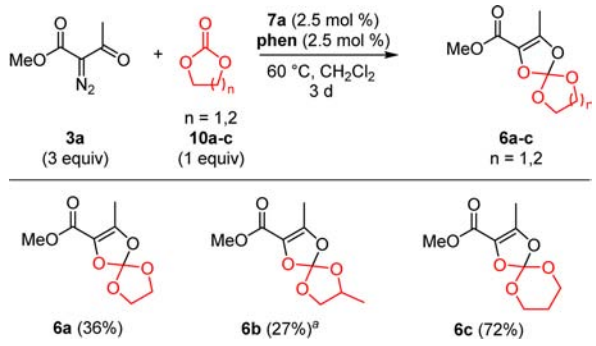


cyclopropanation or epoxide formations could not be found. Also, using coumarin **9f**, a complete formation of desired product was monitored but trioxospiro **5f** decomposed partially during the chromatography (SiO_2 or Al_2O_3) to be afforded in only 64% yield.[18]

Reactions with cyclic carbonates **10a** to **10c** to form corresponding adducts **6a** to **6c** were even slower (Scheme 8). Three days were necessary to ensure complete conversion. In the case of orthocarbonates **6a** and **6b**, the isolation was complicated by their sensitivity (yields up to 36% only). In the case of **6b**, a 1:1 mixture of diastereoisomer was observed by ^1H NMR analysis, and only one diastereoisomer could be isolated (27%). Using 6-membered ring **10c**, product **6c** was however obtained in good yield (72%).

This lower reactivity of lactones **9** and cyclic carbonates **10** is not trivially explained. One rationalization could have been a stronger complexation of catalyst [CpRu(**phen**)][BAr_F] **A** with compounds **9** or **10**, which would have slowed the release of **A** and hence the catalytic cycle. However, a comparative analysis of

Scheme 8. Orthocarbonate Synthesis[a]



[a]Only one diastereoisomer isolated.

Gutmann's scale of solvent Lewis basicity indicates that ketones, esters, and (to a lesser degree) carbonates present similar Donor Numbers (15−18 kcal·mol^{-1}).[19] It is therefore more likely that lactones and cyclic carbonates are less nucleophilic than ketones for the trapping of the electrophilic carbene (step **B** → **C**, Scheme 6).

In conclusion, using a combination of [$CpRu(CH_3CN)_3$]-[BAr_F] **7a** and 1,10-phenanthroline, it was found that α-diazo-β-ketoesters **3** react with a large range of cyclic carbonyl moieties. The reaction conditions are mild and spiro ketals, orthoesters, and orthocarbonates are generated selectively. Due to a general acid sensitivity of the products, care must be taken during their purification, and moderate to good yields are obtained (up to 90%). Interestingly, these reactions seem to be the first examples of intermolecular condensations of metal carbenes with esters and carbonates leading afterward to an intramolecular ring closure. In terms of potential application, a use of compounds **4**, **5**, and **6** can be furthermore foreseen in protecting group strategies as masked forms of cyclic ketones, esters, and carbonates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03380.

Experimental procedures and full spectroscopic data (PDF)

Crystallographic information (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern catalytic methods for organic synthesis with diazo compounds: from cyclopropanes to ylides*; Wiley: New York, 1998; p xvii. (b) Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50−61.

DOI: 10.1021/acs.orglett.5b03380
Org. Lett. 2016, 18, 240−243

(2) (a) Russell, A. E.; Brekan, J.; Gronenberg, L.; Doyle, M. P. *J. Org. Chem.* **2004**, *69*, 5269−5274. (b) Padwa, A. *J. Organomet. Chem.* **2005**, *690*, 5533−5540. (c) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263−309. (d) Padwa, A. *Chem. Soc. Rev.* **2009**, *38*, 3072−3081.
(3) (a) Padwa, A. *Helv. Chim. Acta* **2005**, *88*, 1357−1374. (b) Muthusamy, S.; Krishnamurthi, J.; Babu, S. A.; Suresh, E. *J. Org. Chem.* **2007**, *72*, 1252−1262. (c) Zhang, Z. H.; Wang, J. B. *Tetrahedron* **2008**, *64*, 6577−6605. (d) Austeri, M.; Rix, D.; Zeghida, W.; Lacour, J. *Org. Lett.* **2011**, *13*, 1394−1397.
(4) Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem.* **1989**, *54*, 817−824.
(5) (a) Ueda, K.; Takebaya, M.; Ibata, T. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2779−2782. (b) Ibata, T.; Toyoda, J. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2489−2493. (c) Ibata, T.; Toyoda, J.; Sawada, M.; Tanaka, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1266−1267. (d) Padwa, A.; Stull, P. D. *Tetrahedron Lett.* **1987**, *28*, 5407−5410. (e) Padwa, A.; Carter, S. P.; Nimmesgern, H.; Stull, P. D. *J. Am. Chem. Soc.* **1988**, *110*, 2894−2900. (f) Hildebrandt, K.; Debaerdemaeker, T.; Friedrichsen, W. *Tetrahedron Lett.* **1988**, *29*, 2045−2046. (g) Plug, C.; Friedrichsen, W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1035−1040. (h) Kitagaki, S.; Yasugahira, M.; Anada, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron Lett.* **2000**, *41*, 5931−5935. (i) Nakhla, M. C.; Lee, C.-W.; Wood, J. L. *Org. Lett.* **2015**, *17*, 5760−5763.
(6) Tortoreto, C.; Achard, T.; Austeri, M.; Zeghida, W.; Lacour, J. *Chimia* **2014**, *68*, 243−247.
(7) (a) Renaud, J. L.; Bruneau, C.; Demerseman, B. *Synlett* **2003**, 408−410. (b) Mbaye, M. D.; Demerseman, B.; Renaud, J. L.; Toupet, L.; Bruneau, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5066−5068. (c) Mbaye, M. D.; Demerseman, B.; Renaud, J. L.; Bruneau, C. *J. Organomet. Chem.* **2005**, *690*, 2149−2158.
(8) Globally, cyclopentadienyl ruthenium(II) complexes are effective catalysts for the decomposition of diazo reagents: (a) Maas, G.; Werle, T.; Alt, M.; Mayer, D. *Tetrahedron* **1993**, *49*, 881−888. (b) Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S.-B.; Itoh, K. *J. Am. Chem. Soc.* **1994**, *116*, 2223−2224. (c) Nishiyama, H.; Itoh, Y.; Sugawara, Y.; Matsumoto, H.; Aoki, K.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1247−1262. (d) Baratta, W.; DelZotto, A.; Rigo, P. *Chem. Commun.* **1997**, 2163−2164. (e) Del Zotto, A.; Baratta, W.; Rigo, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3079−3081. (f) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067−2096. (g) Zhou, C.-Y.; Yu, W.-Y.; Che, C.-M. *Org. Lett.* **2002**, *4*, 3235−3238. (h) Che, C.-M.; Huang, J.-S. *Coord. Chem. Rev.* **2002**, *231*, 151−164. (i) Zhou, C.-Y.; Yu, W.-Y.; Chan, P. W. H.; Che, C.-M. *J. Org. Chem.* **2004**, *69*, 7072−7082. (j) Maas, G. *Chem. Soc. Rev.* **2004**, *33*, 183−190. (k) Le Maux, P.; Roisnel, T.; Nicolas, I. N.; Simonneaux, G. R. *Organometallics* **2008**, *27*, 3037−3042. (l) Chan, W.-W.; Yeung, S.-H.; Zhou, Z.; Chan, A. S. C.; Yu, W.-Y. *Org. Lett.* **2009**, *12*, 604−607. (m) Basato, M.; Tubaro, C.; Biffis, A.; Bonato, M.; Buscemi, G.; Lighezzolo, V.; Lunardi, P.; Vianini, C.; Benetollo, F.; Del Zotto, A. *Chem. - Eur. J.* **2009**, *15*, 1516−1526. (n) Xia, L.; Lee, Y. R. *Adv. Synth. Catal.* **2013**, *355*, 2361−2374. (o) Tortoreto, C.; Achard, T.; Zeghida, W.; Austeri, M.; Guenee, L.; Lacour, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 5847−5851. (p) Moulin, S.; Zhang, H. Y.; Raju, S.; Bruneau, C.; Derien, S. *Chem. - Eur. J.* **2013**, *19*, 3292−3296.
(9) (a) Kündig, E. P.; Saudan, C. M.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1219−1223. (b) Krossing, I.; Raabe, I. *Angew. Chem., Int. Ed.* **2004**, *43*, 2066−2090.
(10) (a) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067−2096. (b) Kündig, E. P.; Monnier, F. R. *Adv. Synth. Catal.* **2004**, *346*, 901−904. (c) Mercier, A.; Yeo, W. C.; Chou, J. Y.; Chaudhuri, P. D.; Bernardinelli, G.; Kundig, E. P. *Chem. Commun.* **2009**, 5227−5229.
(11) Achard, T.; Tortoreto, C.; Poblador-Bahamonde, A. I.; Guenee, L.; Burgi, T.; Lacour, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 6140−6144.
(12) In the cyclopentadienyl series, the BAr_F counterion activates the reactivity of metal complexes (see ref 9a), while, with *p*-cymene complexes, the enhanced stability seems to be detrimental as shown by Castarlenas, R.; Eckert, M.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 2576−2579.
(13) Crude mixtures in these reactions contain only starting materials and products **4**, **5**, or **6** providing trivial NMR spectra with well-distinguished signals and excellent baselines.
(14) The lower reactivity of diazo benzoylacetonates is common in this type of reactions. See refs 8o and 11.
(15) Wang, H. B.; Guptill, D. M.; Varela-Alvarez, A.; Musaev, D. G.; Davies, H. M. L. *Chem. Sci.* **2013**, *4*, 2844−2850.
(16) The diastereomeric ratio was determined by ^{1}H NMR spectroscopy (400 MHz).
(17) CCDC 1438101−1438102 contain the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(18) Using 5-bromofuran-2(5*H*)-one and 3,4-dibromofuran-2(5*H*)-one, no reactivity was detected.
(19) The analysis is reported in the supporting information and the values are based on Cataldo, F. *Eur. Chem. Bull.* **2015**, *4*, 92−97 and references therein.

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Organic LETTERS

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Neosartoryadins A and B, Fumiquinazoline Alkaloids from a Mangrove-Derived Fungus *Neosartorya udagawae* HDN13-313

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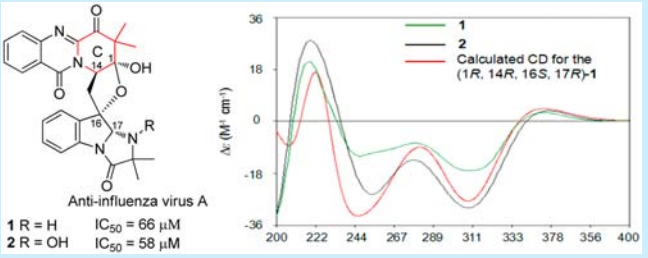
Supporting Information

ABSTRACT: Neosartoryadins A (**1**) and B (**2**), both with a unique 6/6/6/5 quinazoline ring system connected directly to a 6/5/5 imidazoindolone ring, together with three biogenetically related compounds **3**−**5**, were isolated from the endophytic fungus *Neosartorya udagawae* HDN13-313. The absolute configurations of new compounds **1**−**4** were established. Compounds **1** and **2** displayed anti-influenza virus A (H1N1) activities with IC_{50} values of 66 and 58 μM, respectively (ribavirin as positive control, IC_{50} = 94 μM).



The quinazoline-containing indole alkaloids, which possess pyrimido[2,1-*b*]quinazoline and imidazo[1,2-*a*]indole moieties linked by a methylene (and in some cases further linked via additional spiro-bridges), were first isolated from *Aspergillus fumigates* in 1992 and named fumiquinazolines A−C.[1] In the following decades, about 40 fumiquinazoline analogues with these structural characteristics were reported from various fungal genera, including *Aspergillus* sp.,[1] *Acremonium* sp.,[2] and *Neosartorya* sp.,[3] and named fiscalins,[3] aniquinazolines,[4] quinadolines,[5] etc. (Figure S1, Supporting Information, SI). Biogenetically, they are all derived from anthranilic acid (ATA) and tryptophan, together with two other amino acids, including alanine, valine, glycine, leucine, 2-aminoisobutyric acid (Aib), etc.[6] As an important class of tremorgenic mycotoxins, they show potent biological properties such as antifungal,[2] cytotoxic,[7] antifeedant,[8] and antiviral[9] activities. Because of their structural novelty and attractive bioactivities, these compounds have attracted broad interest from chemical and biosynthetic scientists.

During our search for novel bioactive secondary metabolites from microorganisms derived from diverse ecological environments,[10−12] an endophytic fungus *Neosartorya udagawae* HDN13-313, isolated from the root of the mangrove plant *Aricennia marina*, was selected for investigation due to its extract's interesting HPLC−UV profile and weak cytotoxicity (41% inhibition of P388 cells at 100 μg/mL). Further examination of a bulk culture led to the discovery of four new quinazoline-containing indole alkaloids, named neosartoryadins A and B (**1** and **2**) and fiscalins E and F (**3** and **4**), along with a known biogenetic related compound fiscalin C (**5**)[3] (Figure 1). The absolute configurations of new compounds **1**−**4** were established on the basis of NOESY spectra, electronic circular dichroism (ECD), or single-crystal X-ray diffraction analysis (for compound **3**). Distinguishing **1** and **2** from classic fumiquinazoline alkaloids such as compounds **3**−**5** is the unprecedented pyrido[2,1-*b*]-

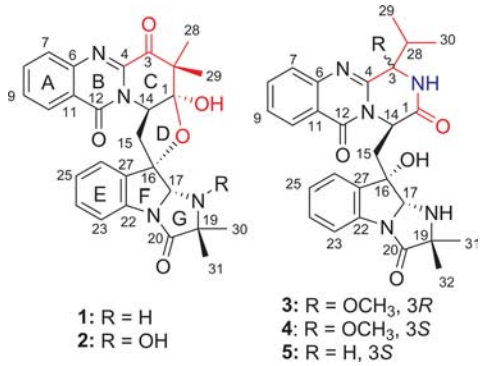


Figure 1. Structures of compounds **1**−**5**.

quinazoline moiety with the quinazoline conjugated to a pyridine (C ring) rather than to a pyrimidine ring and the existence of a unique tetrahydrofuran ring (D ring). Compounds **1** and **2** showed potential antiviral activity against influenza virus A (H1N1). Herein, we report the details for the isolation, structure elucidation, bioactivity, and a plausible biogenetic pathway to **1** and **2**.

Compounds **1** and **2** were obtained as white amorphous powders. Their molecular formulas were established as $C_{27}H_{26}N_4O_5$ and $C_{27}H_{26}N_4O_6$ according to the HRESIMS-protonated molecular ions detected at *m*/*z* 487.1966 and 503.1924, respectively. The 1D NMR data of **1** and **2** included four methyls, one methylene, 10 methines (including eight aromatic methines), and 12 nonprotonated carbons (including three carbonyls) (Table 1). Analysis of the 1D and 2D NMR data of **1** and **2** revealed two sets of four contiguous sp^2

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Table 1. ^{1}H (500 MHz), ^{13}C (125 MHz) and ^{15}N (50 MHz) NMR Data of Compounds 1 and 2 in DMSO-d_6 (δ ppm)

	1		2	
no.	$\delta_{C/N}$	δ_H (J, Hz)	δ_C	δ_H (J, Hz)
1	106.2		106.2	
2	50.5		50.6	
3	192.8		193.0	
4	144.2		144.6	
5	281.7[b]			
6	146.8		146.7	
7	129.3	7.90−7.93[a]	129.4	7.85−7.91[a]
8	135.2	7.90−7.93[a]	135.1	7.85−7.91[a]
9	129.0	7.66, m	128.9	7.65, t (7.6)
10	126.7	8.23, d (7.9)	126.6	8.22, d (8.0)
11	122.8		122.6	
12	161.1		161.1	
13	264.0[b]			
14	61.7	4.93, d (6.6)	61.9	4.98, d (6.8)
15	40.1	3.52, dd (15.3, 6.8)	42.5	3.48, dd (15.3, 6.9)
		2.63, d (15.3)		2.76, d (15.5)
16	85.6		85.3	
17	82.4	4.98, d (9.8)	87.0	4.74, s
18	277.9[b]	2.36, d (9.8)		
19	65.3		71.2	
20	176.0		171.8	
21	289.2[b]			
22	138.8		137.8	
23	115.3	7.29, d (7.6)	114.8	7.31−7.37[a]
24	130.4	7.37, t (7.6)	130.3	7.31−7.37[a]
25	125.5	7.24, t (7.6)	125.4	7.23, t (7.9)
26	126.9	7.63, d (7.6)	127.3	7.71, d (7.6)
27	137.0		137.3	
28	16.4	1.18, s	16.4	1.20, s
29	21.0	1.11, s	20.9	1.14, s
30	25.6	1.06, s	17.3	1.01, s
31	26.3	1.03, s	23.4	1.09, s
1-OH		6.92, s		6.90, s
18-OH				5.94, s

[a]Signals were overlapped. [b]Obtained from $^{1}H-^{15}N$ HMBC spectrum.

aromatic proton signals (δ_H 8.24−7.22), indicating the presence of two *ortho*-disubstituted aromatic rings.

Similar to the fumiquinazolines, the presence of a quinazoline ring system (A and B rings) in **1** was deduced from characteristic ^{13}C NMR resonances (Table 1; C-4 to C-12),[1] along with the HMBC correlations from H-10 (δ_H 8.23) to C-6 (δ_C 146.8)/C-12 (δ_C 161.1), from H-9 (δ_H 7.66) to C-11 (δ_C 122.8) and the $^{1}H-^{15}N$ HMBC correlation from H-7 to N-5 (δ_N 281.7). The quinazoline ring was further fused with a pyridine (C ring) to form a pyrido[2,1-*b*]quinazoline moiety which was established from HMBC correlations between H-14 (δ_H 4.93) to C-1 (δ_C 106.2)/C-4 (δ_C 144.2), H_3-28 (δ_H 1.18)/H_3-29 (δ_H 1.11) to C-1/C-2 (δ_C 50.5)/C-3 (δ_C 192.8), and from 1-OH (δ_H 6.92) to C-1/C-2/C-14 (δ_C 61.7).

The HMBC correlations from H-26 (δ_H 7.63) to C-16 (δ_C 85.6) and C-22 (δ_C 138.8), from H-23 (δ_H 7.29) to C-27 (δ_C 137.0), from H-17 (δ_H 4.98) to C-16, and the $^{1}H-^{15}N$ HMBC correlation from H-17 to N-21 (δ_N 289.2) suggested the presence of a substituted indole moiety. The imidazo[1,2-*a*]indole moiety (E, F, and G rings) was further constructed on the basis of the HMBC correlations from H_3-30 (δ_H 1.06)/H_3-31 (δ_H 1.03) to C-19 (δ_C 65.3)/C-20 (δ_C 176.0), from 18-NH (δ_H 2.36) to C-16/C-17/C-30 (δ_C 25.6)/C-31 (δ_C 26.3), and the $^{1}H-^{15}N$ HMBC correlations from H-17 to N-18 (δ_N 277.9), and from H_3-30/H_3-31 to N-18. The chemical shifts of the 6/5/5 imidazo[1,2-*a*]indole moiety also agree with those reported for the fumiquinazolines.[1]

The imidazo[1,2-*a*]indole and the pyrido[2,1-*b*]quinazoline moieties were linked by C-15 (δ_C 40.1) based on HMBC correlations from H_2-15 (δ_H 3.52, 2.63) to C-1 and C-14 in ring C and C-16, C-17 and C-27 in F and from H-14 to C-16 and the $^{1}H-^{15}N$ HMBC correlation from H_2-15 to N-13 (δ_N 264.0). Finally, the planar structure of **1** was completed by a furan ring (D ring) evidenced by the chemical shifts of C-16 (δ_C 85.6) and the distinctive hemiketal carbon (δ_C 106.2, C-1), as well as the required degrees of unsaturation.

The NMR data of **2** were very similar to those of **1**. The major differences between them included the multiplicity of H-17, which was changed from a doublet in **1** to a singlet in **2**, and the replacement of nitrogen-linked H-18 (δ_H 2.36) in **1** by a hydroxyl group (δ_H 5.94, 18-OH), which was further supported by the HMBC correlation from 18-OH to C-17 (Figure S2, SI), and the chemical shifts of C-17 and C-19 similar to those in the reported tryptoquivaline L.[13]

The relative configurations of **1** and **2** were established on the basis of NOESY and NOE spectral data (Figure 2 and

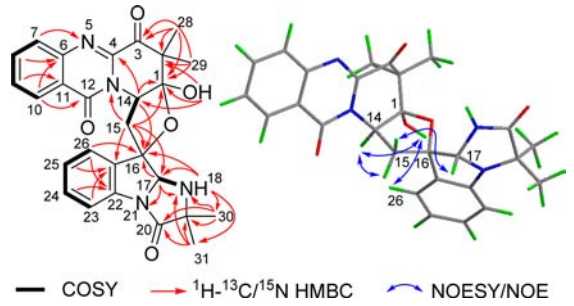

Figure 2. Key COSY, HMBC, NOESY, and NOE correlations of **1**.

Figure S3, SI). The NOESY and NOE spectra displayed correlations from 1-OH to H-14 and H-26 and between H-15a (δ_H 3.52 in **1** and δ_H 3.48 in **2**) and H-14, indicating that 1-OH, H-14, H-15a, and H-26 were on the same side of the furan ring. The correlations between H-15b (δ_H 2.63 in **1** and δ_H 2.76 in **2**) and H-17 suggested that H-17 was on the other side.

The absolute configuration of **1** was determined by comparing experimental and calculated ECD spectra using time-dependent density-functional theory (TDDFT). The DFT reoptimization of the initial MMFF minima of the arbitrarily selected (1*R*,14*R*,16*S*,17*R*)-**1**, which was performed at the B3LYP/TZVP level with a PCM solvent model for MeOH, resulted in only one optimized conformer (Figure S4, SI). Subsequently, the absolute configuration of compound **1** was established from close agreement of the TDDFT-calculated ECD spectrum of (1*R*,14*R*,16*S*,17*R*)-**1** with that determined experimentally (Figure 3). Since compounds **1** and **2** exhibited almost identical ECD spectra, the absolute configuration of **2** was also established as 1*R*,14*R*,16*S*,17*S* (Figure 3).

Compounds **3** and **4** had the same molecular formula of $C_{28}H_{31}N_5O_5$ based on the HRESIMS ions detected at *m*/*z* 518.2393 $[M + H]^+$ and 518.2398 $[M + H]^+$, respectively. Their 1D NMR data (Table S2, SI) indicated the presence of five methyls (including a methoxy), one methylene, 11 methines (including eight aromatic methines), and 11 non-

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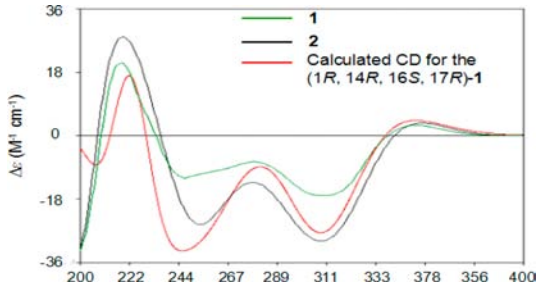


Figure 3. Experimental ECD spectra of compounds **1** and **2** and the calculated spectrum for (1*R*,14*R*,16*S*,17*R*)-**1**.

protonated carbons (including three carbonyls) and suggested that they possessed quinazoline-containing indole alkaloid skeleton, similar to *epi*-fiscalin C and fiscalin C (**5**).[3,13] Further analysis of the 2D NMR data revealed that compounds **3** and **4** had the same planar structure and the main differences to **5** were the replacement of H-3 in **5** by methoxy group in **3** and **4** (Figure S2, SI).

The absolute configuration of **3** was determined unambiguously by the X-ray diffraction (CCDC 1413444) as 3*R*,14*R*,16*S*,17*R* (Figure 4), with Flack parameter −0.05 (17).

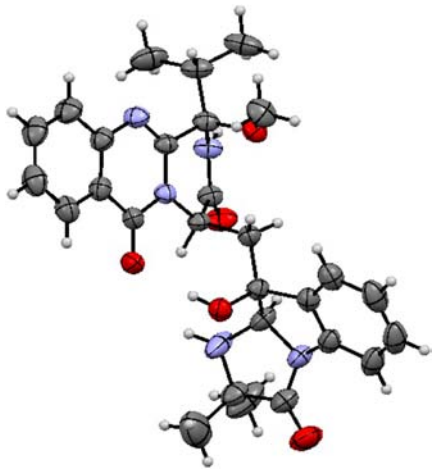


Figure 4. X-ray ORTEP diagram of compound **3**.

The ^{1}H and ^{13}C NMR spectra of **3** and **4** were very similar but not identical. The most significant difference between them in the ^{13}C NMR spectra (Table S2, SI) was the signals of C-28 (δ_C 30.5 in **3** and δ_C 37.6 in **4**), which indicated that they are epimers with different absolute configuration at C-3.[7,9,13] The relative configuration of **4** was further deduced as 3*S**,14*R**,16*S**,17*R** according to the NOESY correlation between H_3-29 (δ_H 0.91) and H-15b (δ_H 2.57), H-17 (δ_H 5.19) and H-15b, and H-14 (δ_H 5.33) and OH-16 (δ_H 5.80) (Figure S3, SI). The absolute configuration of compound **4** was finally determined as 3*S*,14*R*,16*S*,17*R* based on the similar ECD curve between **3** and **4** (Figure 5).[7,9] In addition, the similar ECD curves of compounds **3** and **4** to fiscalin C suggested that they shared the same absolute configuration at C-14, C-16, and C-17, which indicated that the configuration of C-3 has almost no effect on the ECD spectra of them.[3,7,9,13]

Compounds **1** and **2** represent a new class of quinazoline-containing indole alkaloids with a unique 6/6/6/5 quinazoline ring system connected directly to a 6/5/5 imidazoindolone ring system, requiring a different process from the classic ones to

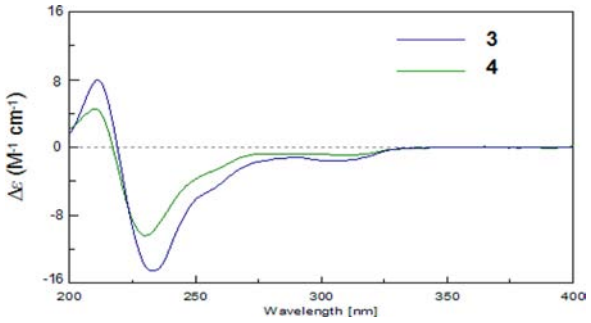
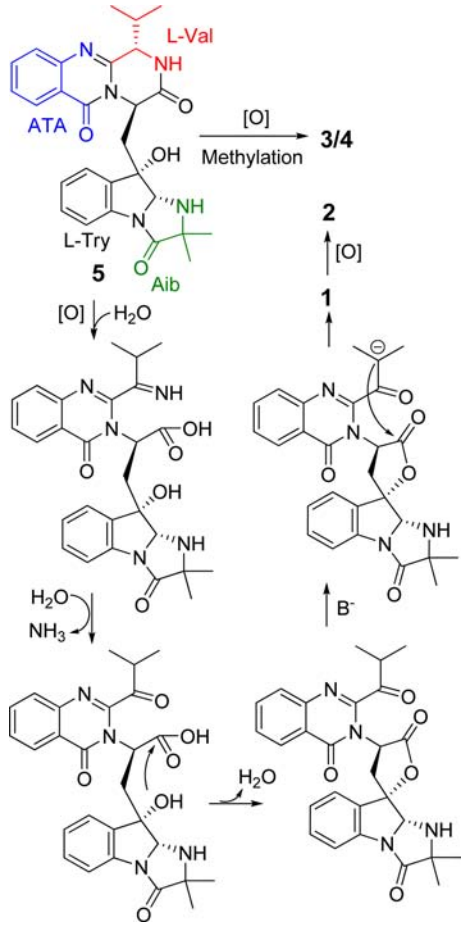


Figure 5. Experimental ECD spectra of compounds **3** and **4**.

form the pyrido[2,1-*b*]quinazoline unit. Similar to the reported biogenetic pathway for fumiquinazoline A,[1,14] compounds **1** and **2** are also speculated to be biosynthesized from L-tryptophan, ATA, L-valine, and 2-aminoisobutyric acid (Aib) (Scheme 1). Different from the formation of **3** and **4**,[15]

Scheme 1. Hypothetical Biogenetic Pathway of Compounds 1−4



compounds **1** and **2** are generated by further modification of the key intermediate **5** including oxidation, hydrolysis, nucleophilic attack by water, dehydration, deprotonation, and subsequently aldol reaction to form the unprecedented C ring.[6]

The cytotoxicity of **1**−**5** was tested using the methylthiazolotrazolium (MTT) method against the HL-60 cancer cell line,[16] but no activity was detected (IC_{50} > 50 μM). The antiviral activity of them was also evaluated against influenza A virus

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(H1N1) using the cytopathic effect (CPE) inhibition assay.[17] Compounds **1** and **2** exhibited inhibitory effects with IC_{50} values of 66 μM and 58 μM, respectively (ribavirin as positive control, IC_{50} = 94 μM).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02964.

Experimental details, 1D and 2D NMR spectra of **1**−**4**, structures of fumiquinazoline analogues, and computational calculation details (PDF)

X-ray data for compound **3** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Numata, A.; Takahashi, C.; Matsushita, T.; Miyamoto, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Inoue, M.; Ohishi, H.; Shingu, T. *Tetrahedron Lett.* **1992**, *33*, 1621−1624.

(2) Belofsky, G. N.; Anguera, M.; Jensen, P. R.; Fenical, W.; Köck, M. *Chem. - Eur. J.* **2000**, *6*, 1355−1360.

(3) Wong, S. M.; Musza, L. L.; Kydd, G. C.; Kullnig, R.; Gillum, A. M.; Cooper, R. *J. Antibiot.* **1993**, *46*, 545−553.

(4) An, C. Y.; Li, X. M.; Li, C. S.; Wang, M. H.; Xu, G. M.; Wang, B. G. *Mar. Drugs* **2013**, *11*, 2682−2694.

(5) Koyama, N.; Inoue, Y.; Sekine, M.; Hayakawa, Y.; Homma, H.; Ōmura, S.; Tomoda, H. *Org. Lett.* **2008**, *10*, 5273−5276.

(6) Gao, X.; Chooi, Y. H.; Ames, B. D.; Wang, P.; Walsh, C. T.; Tang, Y. *J. Am. Chem. Soc.* **2011**, *133*, 2729−2741.

(7) Takahashi, C.; Matsushita, T.; Doi, M.; Minoura, K.; Shingu, T.; Kumeda, Y.; Numata, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, *18*, 2345−2353.

(8) Li, X. J.; Zhang, Q.; Zhang, A. L.; Gao, J. M. *J. Agric. Food Chem.* **2012**, *60*, 3424−3431.

(9) Peng, J. X.; Lin, T.; Wang, W.; Gu, Q. Q.; Zhu, T. J.; Li, D. H. *J. Nat. Prod.* **2013**, *76*, 1133−1140.

(10) Wu, G. W.; Sun, X. H.; Yu, G. H.; Wang, W.; Zhu, T. J.; Gu, Q. Q.; Li, D. H. *J. Nat. Prod.* **2014**, *77*, 270−275.

(11) Yu, G. H.; Wu, G. W.; Wang, W.; Zhu, T. J.; Gu, Q. Q.; Li, D. H. *J. Asian Nat. Prod. Res.* **2015**, *17*, 120−124.

(12) Li, L. Y.; Li, D. H.; Luan, Y. P.; Gu, Q. Q.; Zhu, T. J. *J. Nat. Prod.* **2012**, *75*, 920−927.

(13) Buttachon, S.; Chandrapatya, A.; Manoch, L.; Silva, A.; Gales, L.; Bruyère, C.; Kiss, R.; Kijjoa, A. *Tetrahedron* **2012**, *68*, 3253−3262.

(14) Ames, B. D.; Haynes, S. W.; Gao, X.; Evans, B. S.; Kelleher, N. L.; Tang, Y.; Walsh, C. T. *Biochemistry* **2011**, *50*, 8756−8769.

(15) Snider, B. B.; Zeng, H. B. *J. Org. Chem.* **2003**, *68*, 545−563.

(16) Du, L.; Zhu, T. J.; Liu, H. B.; Fang, Y. C.; Zhu, W. M.; Gu, Q. Q. *J. Nat. Prod.* **2008**, *71*, 1837−1842.

(17) Peng, J. X.; Jiao, J. Y.; Li, J.; Wang, W.; Gu, Q. Q.; Zhu, T. J.; Li, D. H. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3188−3190.

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Organic LETTERS

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Platform for Ring-Fluorinated Benzoheterole Derivatives: Palladium-Catalyzed Regioselective 1,1-Difluoroallylation and Heck Cyclization

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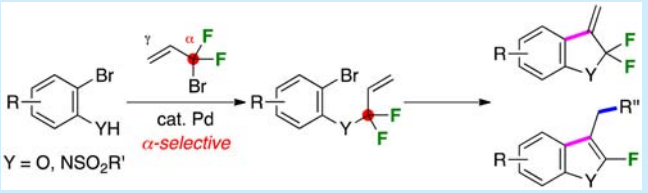
Supporting Information

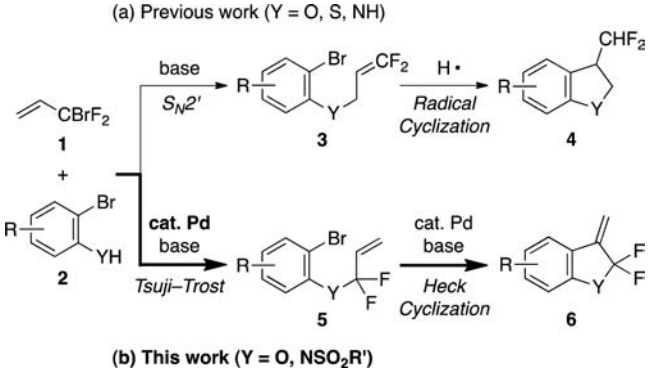
ABSTRACT: The synthesis of difluoromethylene-containing heterocycles was achieved via the palladium-catalyzed 1,1-difluoroallylation of heteronucleophiles followed by intramolecular Heck reaction. The allylic substitution of 3-bromo-3,3-difluoropropene was regioselectively accomplished by heteronucleophiles without rearrangement to give the corresponding 1,1-difluoroallylated compounds whose Heck cyclization proceeded in a 5-*exo* manner to afford ring-difluorinated indolines and dihydrobenzofurans. Their defluorinative allylic substitution further provided 2-fluoroindoles and 2-fluorobenzofurans.



Allylic substitutions including nucleophilic reactions (S_N2' and S_N2 reaction) and palladium-catalyzed reactions (the Tsuji–Trost reaction) have been applied in various synthetic processes as one of the most important organic reactions.[1] Despite the versatility of allylic substitution, it is often difficult to control the regioselectivity of unsymmetrically substituted allylic substrates. For example, *gem*-difluoroallylic electrophiles have served as two-fluorine-containing three-carbon building blocks; substitution on their carbon atoms α or γ to the fluorine substituents affords 1,1- or 3,3-difluoroallylic compounds, respectively.[2−4] The regioselectivity in such reactions has not been well controlled; however, it has been typically determined by the choice of substrate. Even worse for product selectivity, both of the difluoroallylated products are susceptible to further C−F substitution by nucleophiles.

In recent times, we developed a base-mediated selective S_N2' reaction of 3-bromo-3,3-difluoropropene (**1**) with brominated heteronucleophiles **2** (Scheme 1a).[5] In this previous report, the subsequent 5-*exo* radical cyclization of the obtained 3,3-difluoroallyl compounds **3** afforded 3-difluoromethylated 2,3-dihydrobenzoheteroles. In contrast, we herein disclose the complete switching of the regioselectivity in the reactions of **1** with heteronucleophiles **2** using a palladium catalyst (Scheme 1b). The α-selective substitution of **1** with 2-bromophenols **2a** and 2-bromoanilines **2b** selectively proceeded via the Tsuji–Trost reaction to afford *O*- and *N*-(1,1-difluoroallyl) compounds **5**.[6] Furthermore, their subsequent 5-*exo* Heck reaction[7] provided ring-difluorinated benzoheterole derivatives **6**.[8]

Scheme 1. Regioswitchable Allylic Substitution of 3-Bromo-3,3-difluoropropene (1)



First, we sought a suitable base for the α-selective Tsuji–Trost reaction using 2-bromophenol (**2aa**) in the presence of 4 mol % of $Pd(OAc)_2$ and 16 mol % of PPh_3 (Table 1). Weak bases ($NaHCO_3$ and $KHCO_3$) were found to be ineffective in this reaction (entries 2 and 3). The use of NaOMe promoted the selective formation of the α-substitution product **5aa**, albeit in low yield (entry 4). Both the yield of **5aa** and the **5aa**/**3aa** ratio were drastically improved by the use of *t*-BuOK or NaH without the loss of the C−Br bond of **2aa** (entries 5 and 6). When the amount of $Pd(OAc)_2$ was reduced to 1 mol % (entry 7), **5aa** was obtained in 97% isolated yield. Notably, the Pd catalysts switched the regioselectivity in the allylic substitution of **1** with **2aa** since γ-selective substitution proceeded with Cs_2CO_3 in the absence of Pd catalysts, as we have reported previously (entry 1).[5]

The α-selective Tsuji–Trost reaction of 2-bromophenols **2a** was then investigated with the optimal conditions obtained above (Table 2). Phenols **2ab** and **2ac** with electron-donating methyl and methoxy groups along with phenol **2ad** with an electron-withdrawing cyano group successfully underwent regioselective allylation with **1** in the presence of the Pd

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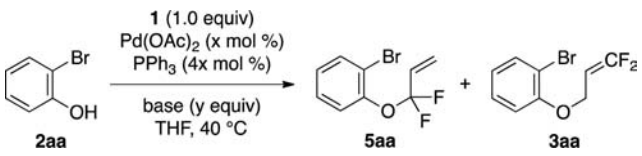
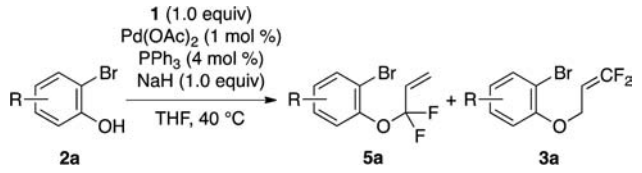
Table 1. Screening of Bases for the α-Selective Tsuji–Trost Reaction with Phenol 2aa



entry	x	base (y equiv)	time (min)	5aa[a] (%)	3aa[a] (%)
1[b]		Cs_2CO_3 (1.0)	30	16[c]	79[c]
2	4	$NaHCO_3$ (1.0)	60	2	2
3	4	$KHCO_3$ (1.0)	60	2	2
4	4	NaOMe (1.1)	30	27	2
5	4	*t*-BuOK (1.0)	30	92	3
6	4	NaH (1.0)	15	96	4
7	**1**	**NaH (1.0)**	**30**	**97**[c]	**3**

[a]Yield was determined by ^{19}F NMR measurements using $PhCF_3$ as an internal standard. [b]**1** (2.0 equiv), *N*-methyl-2-pyrrolidone (NMP), 90 °C. See ref 5. [c]Isolated yield.

Table 2. 1,1-Difluoroallylation of Phenols 2a



entry	2a	time (min)	5a (%)[a]	3a (%)[b]
1	**2aa** (R = H)	30	**5aa** 97	**3aa** 3
2	**2ab** (R = Me)	20	**5ab** 94	**3ab** 3
3	**2ac** (R = OMe)	20	**5ac** 93	**3ac** 4
4	**2ad** (R = CN)	30	**5ad** 95	**3ad** 1
5	**2ae** (R = Cl)	60	**5ae** 96	**3ae** 3
6	**2af**	10	**5af** 94	**3af** 1

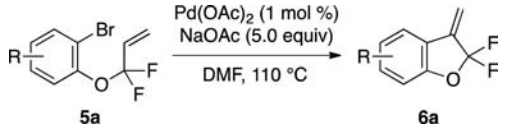
[a]Isolated yield. [b]Yield was determined by ^{19}F NMR measurement using $PhCF_3$ as an internal standard.

catalyst. The corresponding 1,1-difluoroallylated compounds **5ab–ad** were obtained in 94, 93, and 95% yields, respectively (entries 2–4). The 1,1-difluoroallylation of chlorine-substituted bromophenol **2ae** proceeded without the loss of its C–Cl and C–Br bonds, leading to the formation of **5ae** in 96% yield (entry 5). 1-Bromo-2-naphthol (**2af**) also participated in the reaction to give **5af** in 94% yield (entry 6).[9]

The obtained 1,1-difluoroallylated compounds **5a** underwent an intramolecular Heck reaction in a 5-*exo* manner to afford 2,2-difluorinated 3-methylene-2,3-dihydrobenzofuran **6a** (Table 3). Upon treatment of **5aa** with 1 mol % of $Pd(OAc)_2$ and 5.0 equiv of NaOAc, dihydrobenzofuran **6aa** was synthesized in 94% yield. Irrespective of the substituents on the aromatic rings, the 5-*exo* Heck reactions of **5ab–af** successfully proceeded to afford the corresponding difluorinated dihydrobenzofuran **6ab–af** in high to excellent yields (entries 2–6).

Next, we sought suitable conditions for the 1,1-difluoroallylation of sulfonamides with 3-bromo-3,3-difluoropropene (**1**) using *N*-(2-bromophenyl)-4-methylbenzenesulfonamide (**2ba**) as a model substrate (Table 4). Although the

Table 3. Synthesis of Dihydrobenzofurans 6a



entry	5a	time (min)	6a (%)[a]
1	**5aa** (R = H)	30	**6aa** 94
2	**5ab** (R = Me)	20	**6ab** 85
3	**5ac** (R = OMe)	20	**6ac** 93
4[b]	**5ad** (R = CN)	20	**6ad** 96
5[b]	**5ae** (R = Cl)	30	**6ae** 88
6	**5af**	30	**6af** 96

[a]Isolated yield. [b]1,2,2,6,6-Pentamethylpiperidine was used instead of NaOAc.

reaction of **2ba** with **1** was conducted under the optimal conditions for phenols **2a**, both the 1,1-difluoroallylated compound **5ba** and 3,3-difluoroallylated compound **3ba** were obtained in an almost 1:1 ratio (entry 1). To improve the yield and the regioselectivity, several bidentate phosphine ligands were used with $Pd_2(dba)_3{\cdot}CHCl_3$ (entries 2–5). Among them, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), which was used with NaH, provided the highest total yield of **5ba** and **3ba** (entry 5), albeit with no selectivity. Other bases used with Xantphos were thus examined for α-selective substitution (entries 6–9). Although *t*-BuOK was comparable to NaH (entry 6), lithium bases (LiH, LDA, and LHMDS) improved the **5ba**/**3ba** ratios, providing excellent total yields of **5ba** and **3ba** (entries 7–9). Further screening of solvents and temperatures (entries 10–15) revealed that LHMDS exhibited the best efficiency in ether at 0 °C (entry 15).

Since the isolation of **5b** from **3b** proved troublesome, we attempted the direct synthesis of *N*-sulfonyl-2,2-difluoro-3-methyleneindolines **6b** via the 1,1-difluoroallylation of *N*-sulfonylanilines **2b** followed by Heck cyclization using the mixtures of **5b** and **3b** obtained immediately after aqueous workup (Table 5). When a crude mixture of **5ba** and **3ba** prepared with 1.1 equiv of **1** under the optimal conditions above was treated with 1 mol % of $Pd(OAc)_2$, 10 mol % of NEt_3, and 1.2 equiv of sodium benzoate, *N*-tosyl-2,2-difluoro-3-methyleneindoline (**6ba**) was obtained in 84% isolated yield from **2ba** (entry 1). Similarly, *N*-tosylanilines **2bb** and **2bc** bearing electron-donating groups (Me and OMe) and **2bd–bf** bearing halogen substituents (F, Cl, and Br) successfully underwent the sequence of 1,1-difluoroallylation and Heck cyclization to afford the corresponding indolines **6bb–bf** in high yields (entries 2–6). Notably, in each case, the selective and almost quantitative formation of **5b** in the 1,1-difluoroallylation step was confirmed by ^{19}F NMR measurement. 1,1-Difluoroallylation of *N*-mesylanilines **2bg** and **2bh** also proceeded at room temperature, leading to selective formation of **5bg** and **5bh**, whose Heck cyclization gave *N*-mesylindolines **6bg** and **6bh** in good yields (entries 7 and 8).

In addition, the 2,2-difluorinated 3-methylene-2,3-dihydrobenzoheteroles obtained via the aforementioned sequence were further transformed into 2-fluorobenzoheteroles (eqs 1–3).[8a,10] 2,2-Difluorinated dihydronaphthofuran **6af** under-

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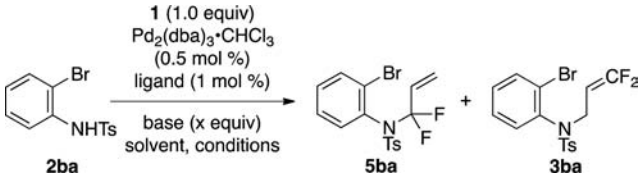
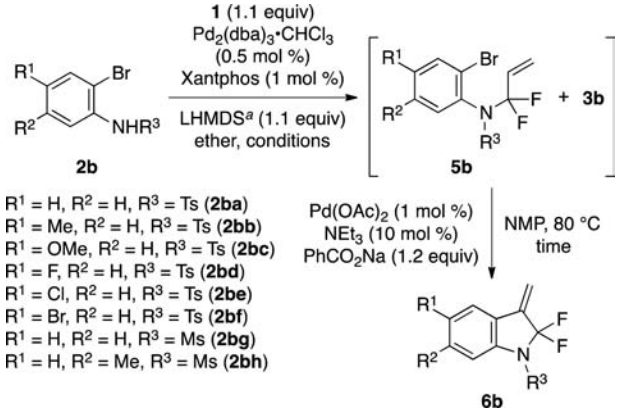
Table 4. Screening of Conditions for the α-Selective Tsuji–Trost Reaction with Aniline 2ba



entry	ligand	base (x equiv)	solvent	conditions	**5ba**[a] (%)	**3ba**[a] (%)
1[b]	PPh_3	NaH (1.0)	THF	40 °C, 4 h	36	39
2	dppe	NaH (1.0)	THF	40 °C, 2 h	ND[c]	3
3	dppb	NaH (1.0)	THF	40 °C, 2 h	ND[c]	3
4	dppf	NaH (1.0)	THF	40 °C, 2 h	25	28
5	Xantphos	NaH (1.0)	THF	40 °C, 2 h	49	48
6	Xantphos	*t*-BuOK (1.0)	THF	40 °C, 1 h	47	49
7	Xantphos	LiH (1.0)	THF	40 °C, 3 h	62	36
8	Xantphos	LDA (1.2)	THF	40 °C, 0.5 h	55	31
9	Xantphos	LHMDS (1.2)[d]	THF	40 °C, 0.5 h	63	37
10	Xantphos	LHMDS (1.2)[d]	DMF	40 °C, 1 h	54	46
11	Xantphos	LHMDS (1.2)[d]	hexane	40 °C, 4 h	13	5
12	Xantphos	LHMDS (1.2)[d]	ether	40 °C, 4 h	50	10
13	Xantphos	LHMDS (1.2)[d]	ether	rt, 0.5 h	86	14
14	Xantphos	LHMDS (1.2)[e]	ether	rt, 0.5 h	91	9
15	**Xantphos**	**LHMDS (1.2)[e]**	**ether**	**0 °C, 1 h**	**92**	**8**

[a]Yield was determined by ^{19}F NMR measurement using $PhCF_3$ as an internal standard. [b]$Pd(OAc)_2$ (1 mol %), PPh_3 (4 mol %). [c]ND = not detected. [d]THF solution. [e]Ether solution.

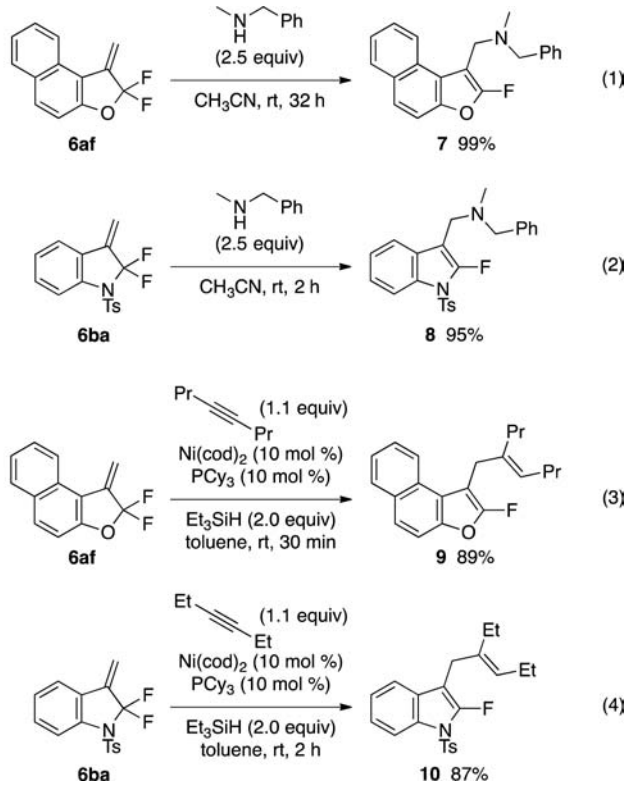
Table 5. Synthesis of Indolines 6b from Anilines 2b



entry	**2b**	conditions	**5b** + **3b**[b] (%)	**5b**:**3b**[c]	time (h)	**6b**[d] (%)
1	**2ba**	0 °C, 1 h	99	93:7	1	**6ba**, 84
2	**2bb**	0 °C, 2 h	quant	92:8	2	**6bb**, 82
3	**2bc**	0 °C, 2 h	quant	92:8	2	**6bc**, 88
4[e]	**2bd**	0 °C, 2 h	quant	93:7	0.5	**6bd**, 78
5	**2be**	0 °C, 0.5 h	98	94:6	0.5	**6be**, 78
6	**2bf**	0 °C, 0.5 h	quant	95:5	0.5	**6bf**, 82
7	**2bg**	rt, 0.5 h	94	91:9	1	**6bg**, 60
8	**2bh**	rt, 0.5 h	97	93:7	1	**6bh**, 60

[a]Ether solution. [b]Yield was determined by ^{19}F NMR measurement using $PhCF_3$ as an internal standard. [c]Ratio was determined by ^{19}F NMR measurement. [d]Isolated yield. [e]NEt_3 (4 mol %).

went S_N2' substitution with benzylmethylamine to afford 3-(aminomethyl)-2-fluoronaphthofuran **7** in 99% yield, requiring neither catalysts nor additives (eq 1).[3] In the case of indoline derivative **6ba**, the S_N2' reaction was completed more quickly to give the corresponding *N*-tosylated 2-fluoroindole **8** in 95% yield (eq 2). The nickel-catalyzed defluorinative coupling of



6af with 4-octyne via β-fluorine elimination also proceeded in the presence of Et_3SiH to afford the 3-allylated 2-fluoronaphthofuran **9** in 89% yield (eq 3).[11] Similarly, indoline **6ba** underwent nickel-catalyzed coupling with 3-hexyne to give the corresponding 2-fluoroindole **10** in 87% yield (eq 4).

In summary, we have disclosed that (i) 1,1-difluoroallylation of phenols and *N*-sulfonylanilines with 3-bromo-3,3-difluor-

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opropene (**1**) was accomplished by a palladium catalyst and (ii) its practical use provided a facile synthetic platform for ring-fluorinated benzoheterole derivatives. In light of our previously reported synthesis of difluoromethylated dihydrobenzoheteroles via the base-mediated 3,3-difluoroallylation with **1**,[5] the current method serves as a complementary approach to fluorine-containing benzoheterole derivatives, which are promising for pharmaceutical and agrochemical uses.[12]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03390.

Experimental details, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected recent reviews on allylic substitution, see: (a) Diéguez, M.; Pàmies, O. *Acc. Chem. Res.* **2010**, *43*, 312−322. (b) Hartwig, J. F.; Stanley, L. M. *Acc. Chem. Res.* **2010**, *43*, 1461−1475. (c) Bandini, M.; Cera, G.; Chiarucci, M. *Synthesis* **2012**, *2012*, 504−512. (d) Sundararaju, B.; Achard, M.; Bruneau, C. *Chem. Soc. Rev.* **2012**, *41*, 4467−4483. (e) Yoshikai, N.; Nakamura, E. *Chem. Rev.* **2012**, *112*, 2339−2372. (f) Liu, W.; Zhao, X. *Synthesis* **2013**, *45*, 2051−2069. (g) Oliver, S.; Evans, P. A. *Synthesis* **2013**, *45*, 3179−3198. (h) Baeza, A.; Nájera, C. *Synthesis* **2013**, *46*, 25−34. (i) Arnold, J. S.; Zhang, Q.; Nguyen, H. M. *Eur. J. Org. Chem.* **2014**, *2014*, 4925−4948.

(2) For S_N2' and S_N2 reactions of difluoroallylic electrophiles, see: (a) Capuzzi, L.; Bettarini, F.; Meazza, G.; Massardo, P. *Gazz. Chim. Ital.* **1991**, *121*, 53−54. (b) Shi, G.-q.; Cai, W.-l. *Synlett* **1996**, *1996*, 371−372. (c) Tellier, F.; Baudry, M.; Sauvêtre, R. *Tetrahedron Lett.* **1997**, *38*, 5989−5992.

(3) Defluorinative allylic substitutions via nucleophilic reactions proceed in an S_N2' manner. See: (a) Ichikawa, J. *Chim. Oggi* **2007**, *25* (4), 54−57 and references cited therein. (b) Ichikawa, J. *J. Synth. Org. Chem., Jpn.* **2010**, *68*, 1175−1184 and references cited therein. (c) Yanai, H.; Okada, H.; Sato, A.; Okada, M.; Taguchi, T. *Tetrahedron Lett.* **2011**, *52*, 2997−3000. (d) Bergeron, M.; Johnson, T.; Paquin, J.-F. *Angew. Chem., Int. Ed.* **2011**, *50*, 11112−11116. (e) Bergeron, M.; Guyader, D.; Paquin, J.-F. *Org. Lett.* **2012**, *14*, 5888−5891.

(4) For the Tsuji−Trost reactions of fluoroallylic electrophiles, see: (a) Shi, G.-q.; Huang, X.-h.; Zhang, F.-J. *Tetrahedron Lett.* **1995**, *36*, 6305−6308. (b) Kirihara, M.; Takuwa, T.; Okumura, M.; Wakikawa, T.; Takahata, H.; Momose, T.; Takeuchi, Y.; Nemoto, H. *Chem. Pharm. Bull.* **2000**, *48*, 885−888. (c) Kawatsura, M.; Wada, S.; Hayase, S.; Itoh, T. *Synlett* **2006**, *2006*, 2483−2485. (d) Narumi, T.; Tomita, K.; Inokuchi, E.; Kobayashi, K.; Oishi, S.; Ohno, H.; Fujii, N. *Org. Lett.* **2007**, *9*, 3465−3468. (e) Pigeon, X.; Bergeron, M.; Barabé, F.; Dubé, P.; Frost, H. N.; Paquin, J.-F. *Angew. Chem., Int. Ed.* **2010**, *49*, 1123−1127. (f) Ref 2b.

(5) Fujita, T.; Sanada, S.; Chiba, Y.; Sugiyama, K.; Ichikawa, J. *Org. Lett.* **2014**, *16*, 1398−1401.

(6) Most recently, Zhang et al. reported the palladium-catalyzed regioselective 1,1-difluoroallylation of aromatic carbons by using arylboronic acids. See: (a) Min, Q.-Q.; Yin, Z.; Feng, Z.; Guo, W.-H.; Zhang, X. *J. Am. Chem. Soc.* **2014**, *136*, 1230−1233. (b) Zhang, B.; Zhang, X. *Chem. Commun.* **2016**, DOI: 10.1039/C5CC08394J.

(7) For recent reports on heterocycle construction via the 5-*exo* Heck cyclization, see: (a) Lubkoll, J.; Millemaggi, A.; Perry, A.; Taylor, R. J. K. *Tetrahedron* **2010**, *66*, 6606−6612. (b) Newman, S. G.; Lautens, M. *J. Am. Chem. Soc.* **2010**, *132*, 11416−11417. (c) Zhong, Y.; Wang, L.; Ding, M.-W. *Tetrahedron* **2011**, *67*, 3714−3723. (d) Lei, M.; Tian, W.; Li, W.; Lu, P.; Wang, Y. *Tetrahedron* **2014**, *70*, 3665−3674. (e) Kröger, D.; Schlüter, T.; Fischer, M.; Geibel, I.; Martens, J. *ACS Comb. Sci.* **2015**, *17*, 202−207.

(8) For synthesis of 2,2-difluorinated dihydrobenzoheteroles, see: (a) Bailey, J.; Plevey, R. G.; Tatlow, J. C. *Tetrahedron Lett.* **1975**, *16*, 869−870. (b) Maksimov, A. M.; Platonov, V. E. *Heteroat. Chem.* **1992**, *3*, 373−384.

(9) Use of 2-bromobenzenethiol instead of 2-bromophenols afforded the corresponding *S*-3,3-difluoroallylated product exclusively, even in the presence of the Pd catalyst.

(10) For synthesis of 2-fluorobenzofurans and 2-fluoroindoles, see: (a) Nash, S. A.; Gammill, R. B. *Tetrahedron Lett.* **1987**, *28*, 4003−4006. (b) Hodson, H. F.; Madge, D. J.; Widdowson, D. A. *Synlett* **1992**, *1992*, 831−832. (c) Hodson, H. F.; Madge, D. J.; Slawin, A. N. Z.; Widdowson, D. A.; Williams, D. J. *Tetrahedron* **1994**, *50*, 1899−1906. (d) Ichikawa, J.; Wada, Y.; Okauchi, T.; Minami, T. *Chem. Commun.* **1997**, 1537−1538. (e) Martín-Santamaría, S.; Carroll, M. A.; Carroll, C. M.; Carter, C. D.; Pike, V. W.; Rzepa, H. S.; Widdowson, D. A. *Chem. Commun.* **2000**, 649−650. (f) Ichikawa, J.; Wada, Y.; Fujiwara, M.; Sakoda, K. *Synthesis* **2002**, *2002*, 1917−1936. (g) Ichikawa, J.; Nadano, R.; Mori, T.; Wada, Y. *Org. Synth.* **2011**, *83*, 111−120. (h) Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc.* **2013**, *135*, 9342−9345. (i) Shao, Q.; Huang, Y. *Chem. Commun.* **2015**, *51*, 6584−6586.

(11) Ichitsuka, T.; Fujita, T.; Ichikawa, J. *ACS Catal.* **2015**, *5*, 5947−5950.

(12) For the bioactivity of ring-(di)fluorinated heterocyclic compounds, see: Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529−2591 and references cited therein.

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Chiral Diarylmethanes via Copper-Catalyzed Asymmetric Allylic Arylation with Organolithium Compounds

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Supporting Information

ABSTRACT: A highly enantioselective copper/*N*-heterocyclic carbene catalyzed allylic arylation with organolithium compounds is presented. The use of commercial or readily prepared aryllithium reagents in the reaction with allyl bromides affords a variety of chiral diarylvinylmethanes, comprising a privileged structural motif in pharmaceuticals, in high yields with good to excellent regio- and enantioselectivities. The versatility of this new transformation is illustrated in the formal synthesis of the marketed drug tolterodine (Detrol).

The enantioselective synthesis of diarylmethane tertiary stereogenic centers, a structural motif that is present in many natural products and pharmaceuticals, has attracted considerable attention in recent years.[1] Examples of compounds bearing this subunit include podofilox (Condylox),[1b] nomifensine, CDP-840,[1c] (+)-sertraline (Zoloft),[1d] and (*R*)-tolterodine,[1e] the latter being a drug with blockbuster status. Catalytic asymmetric synthesis methods to access these compounds comprise both stereospecific and enantioselective transformations.[2−7,10] The first approaches, based on chiral starting materials, include a nickel-catalyzed cross-coupling of 1,1-diaryl ethers described by the group of Jarvo[3a] and a stereoretentive rhodium-catalyzed decarbonylation of enantioenriched *β*,*β*-diarylpropionaldehydes reported by the group of Carreira.[3b] Catalytic enantioselective strategies include Friedel−Crafts reactions,[4a] iridium-catalyzed asymmetric hydrogenation of 1,1-diarylalkenes,[4b,c] a cooperative rhodium/phosphoric acid-catalyzed asymmetric arylation of *α*-aryl-*α*-diazo compounds with aniline derivates,[4d] and a copper-catalyzed enantioselective electrophilic arylation of allylic amides with diaryliodonium salts.[4e] Another attractive approach has been reported by Fu and co-workers, where racemic benzylic alcohols were converted into 1,1-diarylalkanes using an enantioselective nickel-catalyzed cross-coupling protocol.[4f]

Transition-metal-catalyzed 1,4-addition of organoboron compounds to substituted electron-deficient styrenes has also been shown to be effective in accessing this structural motif, in particular using a rhodium-based catalyst.[5] Additionally, the catalytic enantiotopic group selective cross-coupling of achiral geminal bis(pinacolboronates)[6] and the recently developed additions of malonates[7a] or boron reagents[7b,c] to quinone methides provide useful chiral *gem*-diarylmethines and boronic esters derivates.

Diarylmethane stereogenic centers can also be accessed via metal-catalyzed arylation of aryl-substituted allyl electrophiles using organometallic reagents.[2a,8d−g] We envisioned that an asymmetric allylic arylation (AAAr) with highly reactive aryllithium reagents, as presented here, would provide a viable and attractive alternative to access these chiral structures. In the case of copper, the use of the corresponding alkyl nucleophiles has been well established, and AAA reactions of a wide range of alkyl metal reagents and allylic systems have been reported.[8a−e,9] In contrast, the introduction of less reactive aryl groups continues to provide major challenges, and several groups embarked on the development of a general and efficient catalytic system for the formation of chiral diarylmethanes based on this transformation.[10] High regio- and enantioselectivity was demonstrated by Hoveyda and co-workers using chiral bidentate *N*-heterocyclic carbenes (NHC) for the AAAr with aryldialkylaluminum reagents,[10a] derived from the corresponding organolithium compounds. Bidentate NHC have also been employed by the group of Hayashi in the allylic substitution with less reactive arylboronates and allyl phosphates.[10b,c] Additionally, aryl Grignard reagents have been employed by Tomioka and co-workers using chiral monodentate *N*-heterocyclic carbenes.[10d,e]

Recently, we reported that organolithium compounds, among the most widely used reagents in organic synthesis, can be directly used as nucleophiles in copper-catalyzed AAA with a variety of allyl systems.[11] The use of Taniaphos or monodentate phosphoramidites as chiral ligands in dichloromethane and *n*-hexane as solvent and cosolvent, allowed us to control the high reactivity of these compounds and obtain excellent regio- and enantioselectivities in AAA reactions. Disappointingly, the reaction with PhLi under these conditions consistently led to poor regioselectivities.[11a] As aryllithium compounds are commercially available or readily accessible by lithium−halogen exchange[12] and, moreover, they are often employed as precursors

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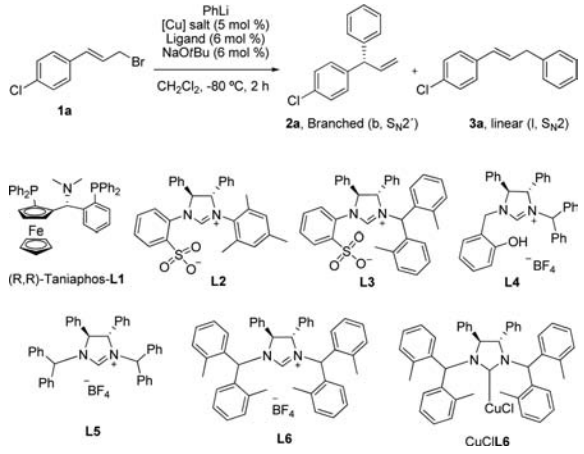
for other organometallic compounds (Al, B, Zn), the development of a general AAAr method using these reagents is highly desirable.

Herein, we report the first regio- and enantioselective method for the copper-catalyzed AAAr with aryllithium compounds to afford optically active diarylvinylmethanes with excellent regio- and enantioselectivities ($S_N2':S_N2$ up to 98:2, er up to 97:3).

The reaction between allyl bromide **1a** and commercially available PhLi, in the presence of catalytic amounts of CuBr·SMe_2 and chiral ligands, was used for the initial optimization (Table 1).[11a] PhLi was diluted with hexane and added over 2 h to a solution of allyl bromide in CH_2Cl_2 at −80 °C. As the use of chiral phosphorus ligands, which provided high selectivity for alkyllithium reagents,[11] did not lead to satisfactory results (entry 1, Table 1 and results not shown), we decided to evaluate a series of strong σ-donating NHCs. The use of chiral bidentate NHC−Cu catalysts, in situ prepared by deprotonating imidazolinium salt **L2**[10a] and structurally related imidazolinium salts **L3** and **L4**, led to low or moderate regioselectivities (entries 2−4, Table 1).[13] We then examined sterically demanding chiral monodentate NHC ligands, and an improved regio- and good enantioselectivity were observed when the catalyst derived from imidazolinium salt **L5**[10d] was used (entry 5, Table 1). To our delight, the catalyst derived from **L6**, having *o*-tolyl moieties, led to a major increase in regioselectivity toward the branched product **2a** (b,l = 97:3) with excellent enantioselectivity (97:3 er, entry 6). A possible rationale is that the use of bulkier aryl substituents on the N atoms enhances the reductive elimination step favoring the S_N2' product.[14] Importantly, the isolated air-stable CuCl−NHC complex derived from **L6** gave the same result, avoiding the use of NaO*t*Bu and simplifying the procedure (entry 7).

Table 1. Screening of Different Ligands[a]

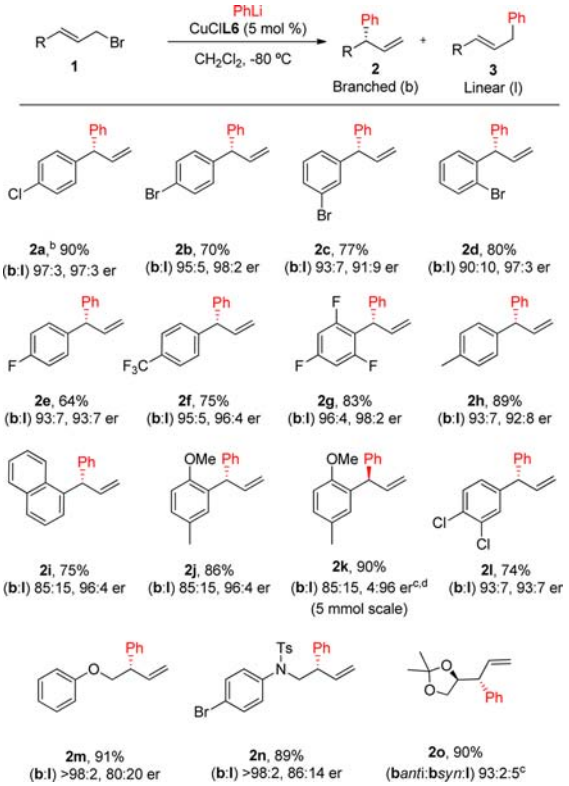


entry	L	[Cu]	2a:3a[b]	2a, er[c]
1	**L1**	CuBr·SMe_2	10:90	n.d.
2	**L2**	CuBr·SMe_2	70:30	n.d.
3	**L3**	CuBr·SMe_2	47:53	n.d.
4	**L4**	CuBr·SMe_2	37:63	n.d.
5	**L5**	CuBr·SMe_2	63:37	94:6
6	**L6**	CuBr·SMe_2	97:3	97:3
7	CuCl**L6**		97:3	97:3

[a]Conditions: allyl bromide (0.2 mmol) in CH_2Cl_2 (2 mL). PhLi (0.3 mmol, 1.8 M solution in dibutyl ether diluted with hexane to a final concentration of 0.4 M) added over 2 h. All reactions gave full conversion. [b]**2a**/**3a** ratios and conversions determined by GC−MS and ^{1}H NMR spectroscopy. [c]Determined by chiral HPLC after conversion to the corresponding primary alcohol using a hydroboration−oxidation procedure (see the SI).

Having established optimal conditions, we next investigated the substrate scope and generality of this arylation reaction by using PhLi; the results are summarized in Scheme 1.

Scheme 1. Substrate Scope for the Cu-Catalyzed Enantioselective Allylic Arylation[a]



[a]Conditions: allyl bromide **1** (0.2 mmol) in CH_2Cl_2 (2 mL). PhLi (0.3 mmol, 1.8 M solution in dibutyl ether diluted with hexane to a final concentration of 0.4 M) added over 2 h. All reactions gave full conversion. **2**/**3** ratios and conversions determined by GC−MS and ^{1}H NMR spectroscopy. Er determined by chiral HPLC after conversion to the corresponding primary alcohol using a hydroboration−oxidation procedure (see the SI). [b]The absolute configuration of **2a** was assigned by comparing the sign of the optical rotation with the literature value (ref 10d). [c](4*R*,5*R*)-**L6** was used instead. [d]5 mmol (1.2 g) scale reaction using 3 mol % of catalyst.

The presence of chloro or bromo substituents at the aromatic ring of the substrate were well tolerated, affording the corresponding diarylvinylmethanes in high yields and selectivities and providing synthetically useful functionalities for further transformations (**2a**−**d**). Importantly, no evidence of lithium−halogen exchange was observed, highlighting the high chemoselectivity of the reaction. Trifluoromethylated and fluorinated compounds, which are very important in the agrochemical and pharmaceutical industries,[15] were also suitable substrates furnishing the corresponding *gem*-biaryl products with excellent selectivities (**2e**−**g**). High selectivities were also obtained when electron-donating substituents (**1h**, **1j**, and **1k**) or sterically demanding substrates such as 1-naphthyl-substituted allyl bromide (**1i**) or compounds **1j** and **1k** were used with this Cu−NHC-based catalyst system. Arylation of compound **1l** was accomplished with good regio- and enantioselectivity, providing **2l**, which is an advanced intermediate in the synthesis of

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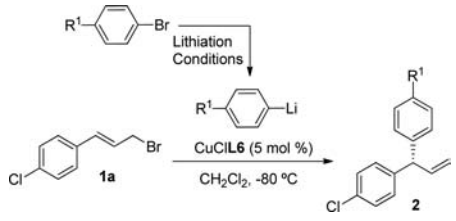
sertraline,[10d] a major pharmaceutical for the treatment of depression. Compound **2k** bearing *m*-methyl and *o*-methoxy substituents at the aryl ring was also prepared with excellent regio- (97:3) and enantioselectivity (96:4) serving as precursor for the synthesis of (*R*)-tolterodine (see below). Importantly, when this reaction was performed on a larger scale (5 mmol, 1.2 g), using a lower catalyst loading (3 mol %), product **2k** was still obtained with the same selectivities without erosion of yield. Allylic bromides bearing a phenol ether or protected amine provided highly functionalized chiral building blocks **2m** and **2n**, with excellent yields and regioselectivity although the enantioselectivity decreased slightly. The use of a dioxolane-containing allylic bromide **1o** led to the diastereoselective formation of valuable 1,2-hydroxyallyl moiety **2o** with excellent stereocontrol for the *anti*-isomer.[16]

We next explored the scope of the reaction with respect to the aryllithium component using **1a** as the electrophilic counterpart. However, to our surprise, no conversion was observed when *p*-tolyllithium or (*p*-methoxyphenyl)lithium solutions, prepared in THF via bromide−lithium exchange using *t*-BuLi, were employed in the reaction under previously optimized conditions (entries 1 and 2, Table 2).

Table 2. Screening of Different Conditions for the Preparation of Reactive Homemade Aryllithium Compounds[a]

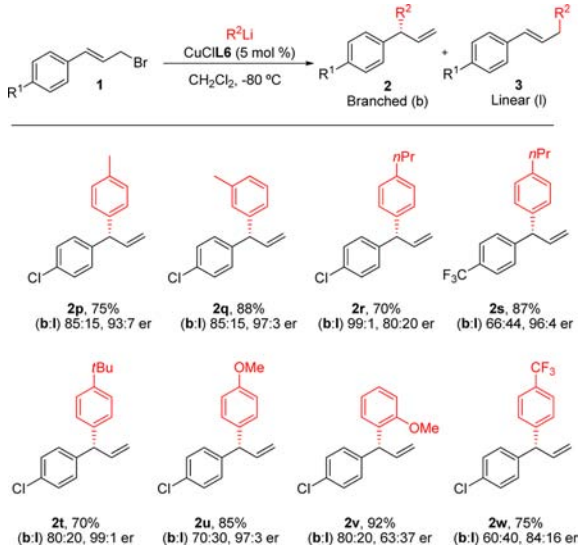


entry	R^1	lithiation cond (final conc, M)	conv (%)/**2**:**3**, **2a** er
1	OMe	*t*-BuLi, −30 °C to rt, 1 h 1:2 THF/pentane (0.57)	0
2	Me	*t*-BuLi, −30 °C to rt, 1 h 1:2 THF/pentane (0.57)	0
3	Me	*t*-BuLi, −30 °C to rt, 1 h 1:2 Et_2O/pentane (0.57)	0
4	Me	Li, Et_2O, rt, 2 h (1.5)	0
5[b]	Me	Li, Et_2O, rt, 2 h (1.5)	47/95:5
6	Me	*n*-BuLi, −30 °C to rt, 1 h 4:3 Et_2O/hexane (0.69)	>99/85:15, **2a** 97:3

[a]Conditions: allyl bromide (0.2 mmol) in CH_2Cl_2 (2 mL). RLi (0.4 mmol) was diluted with hexane to a final concentration of 0.4 M and was added over 2 h. **2a**/**3a** ratios and conversions determined by GC−MS and ^{1}H NMR spectroscopy. Er determined by chiral HPLC after conversion to the corresponding primary alcohol using a hydroboration−oxidation procedure (see the SI). [b]1-Chloro-4-methylbenzene was used instead.

Changing THF to less coordinating Et_2O as solvent led to the same result (entry 3, Table 2). As the use of *t*-BuLi to effect lithium−halogen exchange generates 1 equiv of 2-methylpropene, which may coordinatively interfere with the Cu catalyst, we decided to use a different method for the lithiation. Lithium metal[17] in combination with *p*-bromotoluene was still unsatisfactory, although the use of *p*-chlorotoluene allowed us to reach 47% conversion in the corresponding AAAr reaction (entry 5). Finally, we found that the use of *n*-BuLi and Et_2O as solvent, which avoids S_N2 reaction[18] of the resulting ArLi and *n*-BuBr, allowed us to obtain the desired product with full conversion and high regio- and enantioselectivity (entry 6, Table 2, and **2p**, Scheme 2). Under these conditions, aryllithiums bearing

Scheme 2. Scope of Aryllithium Compounds[a]

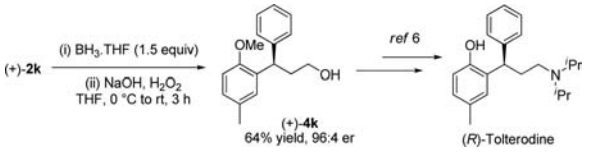


[a]Conditions: allyl bromide (0.2 mmol) in CH_2Cl_2 (2 mL). R^2Li (0.4 mmol) was diluted with hexane to a final concentration of 0.4 M and added over 2 h. All reactions gave full conversion. **2**/**3** ratios and conversions determined by GC−MS and ^{1}H NMR spectroscopy. Er determined by chiral HPLC after conversion to the corresponding primary alcohol using a hydroboration−oxidation procedure (see the SI).

electron-donating methoxy- and alkyl groups as well as electron-withdrawing $-CF_3$ substituents participate in the reactions with allyl bromides **1a**,**f** in good to excellent yields and regio- and enantioselectivities (Scheme 2). A limitation found for this Cu−NHC-based catalytic system is that the use of *o*-methoxy-substituted phenyllithium suffered from diminished enantioselectivity as seen for compound **2v**.

To finally demonstrate the efficiency and applicability of the present methodology, we performed the synthesis of chiral alcohol **4k**,[6] a precursor of (*R*)-tolterodine (Detrol). Here, the catalytic allylic arylation of **2k** with phenyllithium is followed by a one-pot hydroboration−oxidation to afford advanced intermediate **4k** in 64% yield (96:4 er) (Scheme 3). (*R*)-Tolterodine is a potent competitive muscarine receptor antagonist for the treatment of urinary incontinence and cystitis.[1e]

Scheme 3. Conversion of (*R*)-2k into (*R*)-4k, a Synthetic Intermediate of Tolterodine



In summary, the highly enantioselective Cu-catalyzed direct allylic arylation using organolithium compounds has been described. The use of readily available aryllithium reagents in combination with allyl bromides and use of a copper−NHC catalyst are key factors for the success of this reaction. The only stoichiometric waste produced in this novel transformation is LiBr. The use of *n*-BuLi was found to be essential for the

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preparation of aryllithium compounds. The broad substrate and reagent scope and the application of the new method in the formal catalytic enantioselective synthesis of (*R*)-tolterodine illustrates the potential of this allylic arylation for the synthesis of important chiral diarylmethane structures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03396.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Recent reviews: (a) Ameen, D.; Snape, T. J. *MedChemComm* **2013**, *4*, 893. For selected examples, see: (b) Xu, H.; Lv, M.; Tian, X. *Curr. Med. Chem.* **2009**, *16*, 327. (c) Hughes, B.; Howat, D.; Lisle, H.; Holbrook, M.; James, T.; Gozzard, N.; Blease, K.; Hughes, P.; Kingaby, R.; Warrellow, G.; Alexander, R.; Head, J.; Boyd, E.; Eaton, M.; Perry, M.; Wales, M.; Smith, B.; Owens, R.; Catterall, C.; Lumb, S.; Russell, A.; Allen, R.; Merriman, M.; Bloxham, D.; Higgs, G. Br. *J.Pharmacol.* **1996**, *118*, 1183. (d) McRae, A. L.; Brady, K. T. *Expert Opin. Pharmacother.* **2001**, *2*, 883. (e) Rovner, E. S.; Wein, A. J. *Eur. Urol.* **2002**, *41*, 6.

(2) (a) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, *115*, 9587. (b) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, *35*, 454. (c) *Comprehensive Asymmetric Catalysis: Supplement 2*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag, 2004.

(3) (a) Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389. (b) Fessard, T. C.; Andrews, S. P.; Motoyoshi, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 9331.

(4) (a) See: Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 6488. (b) Tolstoy, P.; Engman, M.; Paptchikhine, A.; Bergquist, J.; Church, T. L.; Leung, A. W.-M.; Andersson, P. G. *J. Am. Chem. Soc.* **2009**, *131*, 8855. (c) Bess, E. N.; Sigman, M. S. *Org. Lett.* **2013**, *15*, 646 and references cited therein. (d) Xu, B.; Li, M.-L.; Zuo, X.-D.; Zhu, S.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2015**, *137*, 8700. (e) Cahard, E.; Male, H. P. J.; Tissot, M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 7986. (f) Do, H.-Q.; Chandrashekar, E. R. R.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 16288.

(5) Reviews: (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (b) Tian, P.; Dong, H.-Q.; Lin, G.-Q. *ACS Catal.* **2012**, *2*, 95. Recent example: Lim, K. M.-H.; Hayashi, T. *J. Am. Chem. Soc.* **2015**, *137*, 3201.

(6) Sun, C.; Potter, B.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 6534.

(7) (a) Chu, W.-D.; Zhang, L.-F.; Bao, X.; Zhao, X.-H.; Zeng, C.; Du, J.-Y.; Zhang, G.-B.; Wang, F.-X.; Ma, X.-Y.; Fan, C.-A. *Angew. Chem., Int. Ed.* **2013**, *52*, 9229. (b) Lou, Y.; Cao, P.; Jia, T.; Zhang, Y.; Wang, M.; Liao, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 12134. (c) Luan, Y.; Schaus, S. E. *J. Am. Chem. Soc.* **2012**, *134*, 19965.

(8) General reviews: (a) Geurts, K.; Fletcher, S. P.; van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. *Pure Appl. Chem.* **2008**, *80*, 1025. (b) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824. (c) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pámies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796. (d) Langlois, J.-B.; Alexakis, A. In *Transition Metal Catalyzed Allylic Substitution in Organic Synthesis*; Kazmaier, U., Ed.; Springer-Verlag: Berlin, 2012; pp 235−268. (e) Baslé, O.; Denicourt-Nowicki, A.; Crévisy, C.; Mauduit,M. In *Copper-Catalyzed Asymmetric Synthesis*; Alexakis, A., Krause, N., Woodward, S., Eds.; Wiley-VCH: Weinheim, 2014; Chapter 4. Ir-catayzed AAAr reactions: (f) Alexakis, A.; Hajjaji, S. E.; Polet, D.; Rathgeb, X. *Org. Lett.* **2007**, *9*, 3393. (g) Polet, D.; Rathgeb, X.; Falciola, C. A.; Langlois, J. B.; El Hajjaji, S.; Alexakis, A. *Chem. - Eur. J.* **2009**, *15*, 1205 and references cited therein.

(9) Selected examples: (a) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2426. (b) López, F.; van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2006**, 409. (c) Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4554. (d) Langlois, J.-B.; Alexakis, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 1877. (e) Shido, Y.; Yoshida, M.; Tanabe, M.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2012**, *134*, 18573. (f) You, H.; Rideau, E.; Sidera, M.; Fletcher, S. P. *Nature* **2015**, *517*, 351.

(10) (a) Gao, F.; Lee, Y.; Mandai, K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 8370. (b) Shintani, R.; Takatsu, K.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 8656. (c) Takeda, M.; Takatsu, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2014**, *79*, 2354. (d) Selim, K. B.; Matsumoto, Y.; Yamada, K.; Tomioka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 8733. (e) Selim, K. B.; Nakanishi, H.; Matsumoto, Y.; Yamamoto, Y.; Yamada, K.; Tomioka, K. *J. Org. Chem.* **2011**, *76*, 1398.

(11) (a) Pérez, M.; Fañanás-Mastral, M.; Bos, P. H.; Rudolph, A.; Harutyunyan, S. R.; Feringa, B. L. *Nat. Chem.* **2011**, *3*, 377. (b) Fañanás-Mastral, M.; Pérez, M.; Bos, P. H.; Rudolph, A.; Harutyunyan, S. R.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 1922. (c) Bos, P. H.; Rudolph, A.; Pérez, M.; Fañanás-Mastral, M.; Harutyunyan, S. R.; Feringa, B. L. *Chem. Commun.* **2012**, *48*, 1748. (d) Pérez, M.; Fañanás-Mastral, M.; Hornillos, V.; Rudolph, A.; Bos, P. H.; Harutyunyan, S. R.; Feringa, B. L. *Chem. - Eur. J.* **2012**, *18*, 11880. (e) Guduguntla, S.; Fañanás-Mastral, M.; Feringa, B. L. *J. Org. Chem.* **2013**, *78*, 8274.

(12) (a) *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley−VCH: Weinheim, 2004. (b) *Lithium Compounds in Organic Synthesis*; Luisi, R., Capriati, V., Eds.; Wiley-VCH: Weinheim, 2014.

(13) Nucleophilic addition of PhLi to the sulfonate group in chiral NHC-Cu complexes, obtained from bidentate **L2** or **L3** may occur to some extent, changing the original nature of these ligands.

(14) (a) Yoshikai, N.; Nakamura, E. *Chem. Rev.* **2012**, *112*, 2339. (b) Tseng, C. C.; Paisley, S. D.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2884.

(15) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432.

(16) Fañanás-Mastral, M.; ter Horst, B.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2011**, *47*, 5843.

(17) Screttas, C. G.; Steele, B. R.; Micha-Screttas, M.; Heropoulos, G. A. *Org. Lett.* **2012**, *14*, 5680.

(18) (a) Merrill, R. E.; Negishi, E. *J. Org. Chem.* **1974**, *39*, 3452. (b) Schneider, Y.; Prévost, J.; Gobin, M.; Legault, C. Y. *Org. Lett.* **2014**, *16*, 596.

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Organic LETTERS

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Amine−Amine Electronic Coupling through a Dibenzo[*a*,*e*]pentalene Bridge

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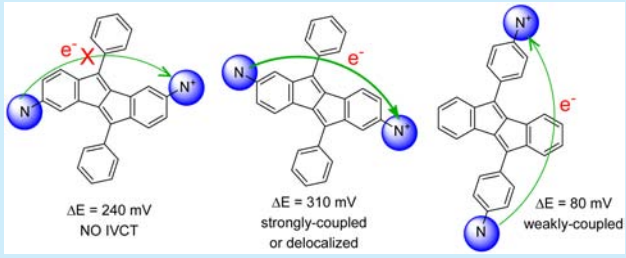
Supporting Information

ABSTRACT: Three dibenzo[*a*,*e*]pentalene derivatives containing two redox-active amine substituents have been prepared. The degree of amine−amine electronic coupling through the dibenzo[*a*,*e*]pentalene bridge greatly depends on the substitution positions. Three monoamine compounds have been prepared for comparison studies. The experimental data and analysis were corroborated by time-dependent density functional theory results of mixed-valent compounds.



Dibenzo[*a*,*e*]pentalene (DBP) is a ladder-type ring-fused hydrocarbon with unique electronic and antiaromatic properties.[1] Thanks to recent successes in the development of synthetic methodology,[2] DBP derivatives have now become readily available from ordinary starting materials. This has greatly stimulated the studies of DBP derivatives in various fields of organic electronics and optoelectronics, including organic field-effect transistors,[3] organic photovoltaics,[4] and photoluminescence.[5] We report herein the use of DBP as a conjugated bridge to mediate the electronic coupling between two mixed-valent redox sites. Interestingly, the placement of redox sites on different positions of the DBP core gives rise to significantly different degrees of coupling.

Electronic communications between mixed-valent redox-active components have received continuous attention since the pioneering work of Creutz and Taube.[6] Apart from inorganic or organometallic complexes,[7] purely organic redox-active components have been used as redox termini in mixed-valent compounds.[8,9] Three C_2-symmetric compounds with two amine substituents on the 2,7- (**1**), 3,8- (**2**), and 5,10- (**3**) positions of the DBP core have been prepared for the purpose of electronic coupling studies (Figure 1). In addition, three DBP derivatives **4**−**6** with one amine substituent have been prepared for comparison. Triarylamines are useful redox sites for constructing organic mixed-valent systems due to the well-defined $N^{\bullet+/0}$ process in a relatively low potential region and a high extinction coefficient of intervalence charge-transfer (IVCT) transitions.[9] The attachment of long alkyl chains (C_8H_{17}) is beneficial for improving the solubility of these compounds. These compounds were prepared via a $Pd(dba)_2$-catalyzed (dba = dibenzylideneacetone) C−N coupling of di(*p*-octylphenyl)amine with 2,7-dichloro-5,10-diphenylDBP, 3,8-dichloro-5,10-diphenylDBP, or 5,10-di(*p*-chlorophenyl)DBP, which were in turn synthesized via a $Pd(OAc)_2$/*n*-Bu_4NOAc-catalyzed homoannulation[10] of a chloro-substituted *o*-alkynylaryl iodide substrate. The details of synthesis and characterization are provided in the Supporting Information (SI).

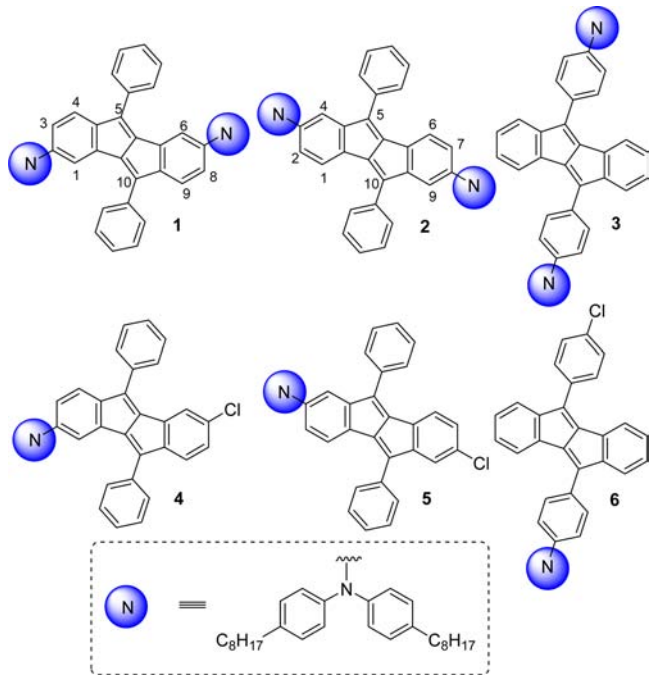


Figure 1. Diamine compounds **1**−**3** with a dibenzo[*a*,*e*]pentalene bridge and monoamine model compounds **4**−**6**.

Compounds **1** and **2** show two well-defined $N^{\bullet+/0}$ redox couples in the potential window between +0.4 and +1.2 V vs Ag/AgCl, as displayed by the cyclic voltammograms (CVs) in Figure 2a. The potential splitting (ΔE) between two waves is

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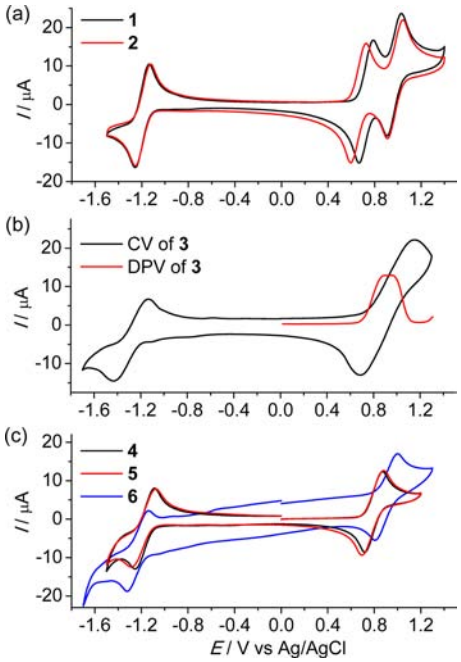

Figure 2. (a) CVs of **1** and **2**. (b) CV and DPV of **3**. (c) CVs of **4**–**6**. Measurement conditions: glassy carbon working electrode; Pt wire counter electrode; Ag/AgCl in aq NaCl as reference electrode; 0.1 M Bu_4NClO_4/CH_2Cl_2. Potentials are summarized in Table 1.

240 and 310 mV for **1** and **2**, respectively. Both compounds have a large comproportionation constant K_c for the equilibrium $[N^0–N^0] + [N^{\bullet+}–N^{\bullet+}] \rightarrow 2[N^0–N^{\bullet+}]$ (Table 1),

Table 1. Electrochemical Data[a]

compd	E_1 (V)	E_2 (V)	E_{cath}[b] (V)	ΔE[c] (mV)	K_c[d]
1	+0.72	+0.96	−1.19	240	1.2×10^4
2	+0.66	+0.97	−1.19	310	1.8×10^5
3	+0.88	+0.96	−1.28	80	23
4	+0.80		−1.17		
5	+0.79		−1.18		
6	+0.90		−1.23		

[a]Potentials are reported vs Ag/AgCl. Potentials vs ferrocene$^{0/+}$ can be estimated by subtracting 0.45 V. [b]Potentials of the cathodic scan. [c]$\Delta E = E_2 - E_1$. [d]$K_c = 10^{(\Delta E/59)}$.

indicating that the one-electron-oxidized state has good thermodynamic stability. In comparison, the potential splitting between two $N^{\bullet+/0}$ processes of **3** is much smaller (around 80 mV, Figure 2b), and the splitting is more discernible from the differential pulse voltammogram (DPV). The monoamine compounds **4**–**6** show one $N^{\bullet+/0}$ redox wave at similar potential region (Figure 2c). In addition, one cathodic redox wave around −1.2 V attributed to the reduction of the DBP core[3] is observed for all of the six compounds prepared.

In order to examine the electronic coupling of the above compounds, they are subjected to oxidative electrolysis at a transparent indium–tin oxide (ITO) glass electrode. Figure 3 shows the absorption spectral changes of three diamine compounds recorded during the oxidative spectroelectrochemical measurements. In the first one-electron oxidation step of **1** (single oxidation; potential was gradually increased from +0.70 to +0.90 V vs Ag/AgCl), some new absorption bands between 700 and 1200 nm appeared. In the second one-electron

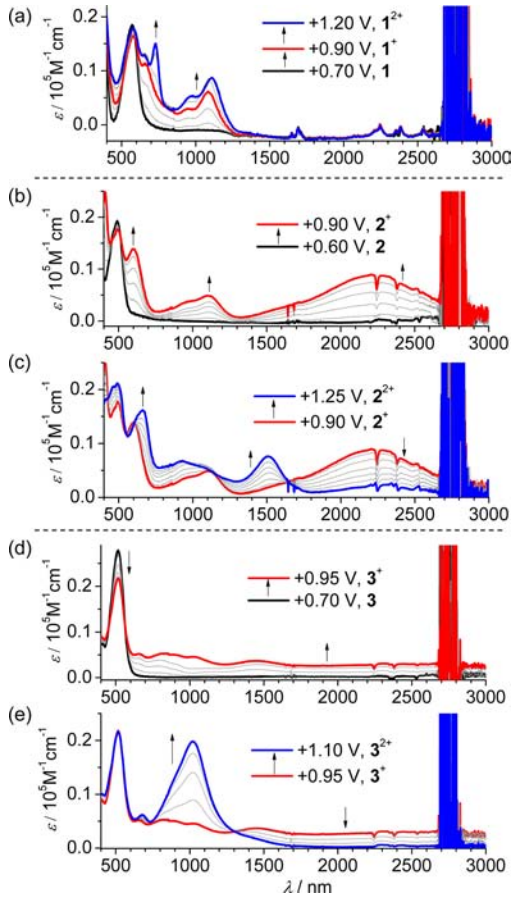

Figure 3. Absorption spectral changes of **1** (a), **2** (b, c), and **3** (d, e) in 0.1 M Bu_4NClO_4/CH_2Cl_2 by stepwise electrolysis at an ITO glass electrode. The applied potentials shown in the insets are referenced vs Ag/AgCl.

oxidation step (double oxidation; potential was further increased to +1.20 V), these new bands continued to increase. The sharp absorption band around at 750 nm of $\mathbf{1}^{2+}$ is characteristic of the $N^{\bullet+}$-localized transition.[9,11] The main absorption bands at 1100 nm of $\mathbf{1}^{\bullet+}$ and $\mathbf{1}^{2+}$ are attributable to the bridge to $N^{\bullet+}$ charge-transfer (BNCT) transitions, as supported by the time-dependent density functional theory (TDDFT) results below. It is surprising that no lower energy absorptions that could be assigned to potential IVCT transitions were observed for $\mathbf{1}^{\bullet+}$.

In stark contrast, an intense and broad absorption band at 2200 nm (ε_{max} = 8900 M^{-1} cm^{-1}) appeared in the single oxidation of **2**, which decreased in the double-oxidation step (Figure 3b,c). This band is attributed to the IVCT transitions of $\mathbf{2}^{\bullet+}$, and this assignment is further supported by the TDDFT results discussed below. For compound **3** with a smaller potential splitting, shallow and broad IVCT absorptions were observed in the single oxidation step (Figure 3d, ε_{max} < 3000 M^{-1} cm^{-1}).

When the three monoamine compounds **4**–**6** were subjected to similar oxidative electrolysis, only the appearance of the BNCT transitions (between 800 and 1500 nm) and the $N^{\bullet+}$-localized transition (around 700 nm) were observed (Figure S1, SI). No other lower energy absorptions appeared. This is in agreement with the assignment of the near-infrared absorptions of $\mathbf{1}^{\bullet+}$–$\mathbf{3}^{\bullet+}$; namely, IVCT transitions are only observed for $\mathbf{2}^{\bullet+}$ and $\mathbf{3}^{\bullet+}$.

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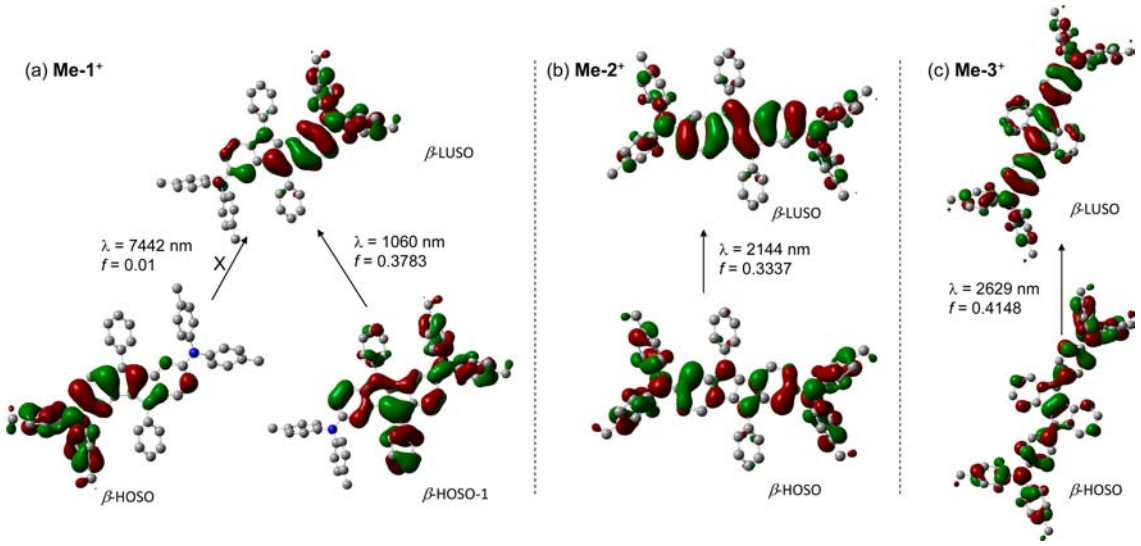

Figure 4. TDDFT results **Me-1**$^+$ (a), **Me-2**$^+$ (b), and **Me-3**$^+$ (c).

The IVCT band of $\mathbf{2}^{\bullet+}$ is well separated from the higher energy absorptions (Figure S2). The full bandwidth at half-height ($\Delta\tilde{\nu}_{1/2}$, 1700 cm^{-1}) is much narrower with respect to the theoretical value for a class II system, as determined by $\Delta\tilde{\nu}_{1/2,\mathrm{theo}} = (2310E_{\mathrm{op}})^{1/2} = 3200$ cm^{-1},[12] where E_{op} is the energy of the IVCT band (4500 cm^{-1}). In addition, the IVCT band of $\mathbf{2}^{\bullet+}$ is distinctly asymmetric with some shallow shoulder bands on the high energy side (probably from vibronic structures). This indicates that $\mathbf{2}^{\bullet+}$ is a strongly coupled system and likely belongs to a delocalized class III system. The electronic coupling V_{ab} can either be estimated by $2V_{\mathrm{ab}} = E_{\mathrm{op}}$ (for a class III system, $V_{\mathrm{ab,III}} = 2250$ cm^{-1}) or $V_{\mathrm{ab}} = (\mu_{\mathrm{ge}}E_{\mathrm{op}})/eR_{\mathrm{ab}}$ (see details in the SI for a strongly coupled class II system, $V_{\mathrm{ab,II}} = 480$ cm^{-1}), where μ_{ge} is the transition dipole moment (6.0 D), e is the elementary charge, and R_{ab} is the diabatic electron transfer (ET) distance and taken to be the geometrical N−N distance (11.6 Å). The large deviation between the $V_{\mathrm{ab,III}}$ and $V_{\mathrm{ab,II}}$ values suggests a large error in estimating the ET distance.[13]

The IVCT band of $\mathbf{3}^{\bullet+}$ is very broad, and the center of the band is located around 2700−2800 nm, where big noises from the solvent are present. It is difficult to distinguish the whole shape of the IVCT band. The near-infrared absorptions of $\mathbf{3}^{\bullet+}$ were thus fitted to multiple symmetric curves using Gaussian functions (Figure S3). The deconvoluted IVCT band has a reasonable $\Delta\tilde{\nu}_{1/2}$ value of 3200 cm^{-1} (see details in the SI). The V_{ab} value is estimated to be 250 cm^{-1} by analyzing the higher energy side of the deconvoluted IVCT band using $V_{\mathrm{ab}} = 0.0206(\varepsilon_{\mathrm{max}}E_{\mathrm{op}}\Delta\tilde{\nu}_{1/2})^{1/2}/(R_{\mathrm{ab}})$,[12] where R_{ab} is again taken to be geometrical N−N distance (14.6 Å). Note that for a symmetric IVCT band, this equation gives exactly the same value as $V_{\mathrm{ab}} = (\mu_{\mathrm{ge}}E_{\mathrm{op}})/eR_{\mathrm{ab}}$. Due to the error in deconvoluting the IVCT band and estimating the ET distance, the calculated V_{ab} value should be taken with care.

The V_{ab} values of $\mathbf{1}^{\bullet+}$ ($V_{\mathrm{ab,II}}$) and $\mathbf{3}^{\bullet+}$ are smaller than that of 4,4′-bis(*N*,*N*-di-*p*-anisylamino)tolane with a conjugated bridge but comparable N−N distance ($R_{\mathrm{ab}} = 12.48$ Å; $V_{\mathrm{ab}} = 3.1$ kcal/mol =1080 cm^{-1}).[14] However, this comparison should be taken with great care because the estimated V_{ab} values are greatly dependent on the measurement conditions and calculation methods.

TDDFT calculations have been performed on the DFT-optimized structures of the open-shell compounds **Me-1**$^+$, **Me-2**$^+$, and **Me-3**$^+$ by replacing the octyl chains of $\mathbf{1}^+$−$\mathbf{3}^+$ with methyl groups (see details in Table S1, Figure 4, and Figures S4−S6). The predicted D_1 excitation of **Me-1**$^+$ have potential IVCT character, which is dominated by the spin transition from the β-highest occupied spin orbital (HOSO) to the β-lowest unoccupied spin orbital (LUSO). However, this excitation has very weak oscillator strength ($f = 0.01$) and very low energy ($\lambda = 7442$ nm), which means that the IVCT transition of this compound is essentially forbidden. The predicted D_3 excitation of **Me-1**$^+$ ($f = 0.3783$, $\lambda = 1060$ nm) is responsible for the observed absorptions at 1100 nm of $\mathbf{1}^+$. This excitation has the dominant spin transition from β-HOSO-1 to β-LUSO, attributable to the BNCT transitions. In comparison, IVCT transitions with large oscillator strengths have been reproduced for **Me-2**$^+$ and **Me-3**$^+$ at 2144 and 2629 nm, respectively. Both transitions are dominated by the β-HOSO → β-LUSO excitations, where the p orbitals of the amine atom are in out-of-phase and in-phase combination, respectively, and both orbitals have large contributions from the bridge segment. This kind of excitations and orbital compositions are observed in most TDDFT results of mixed-valent bistriarylamines.[9d,h,15] In the higher energy region, BNCT, amine-to-bridge charge transfer, and bridge-localized transitions are predicted (Table S1). It should be kept in mind that DFT calculations often tend to overestimate delocalization and give symmetrical delocalized structures. The TDDFT results based on these structures should be taken with care since $\mathbf{3}^{\bullet+}$ is clearly a class II compound from the experimental side.

It is strange that the no IVCT band has been observed and predicted for $\mathbf{1}^{\bullet+}$ or **Me-1**$^+$. The β-HOSO and β-LUSO orbitals of **Me-1**$^+$ are localized on the triarylamine segment; however, those of **Me-2**$^+$ and **Me-3**$^+$ are delocalized. A similar situation is present for the spin density distribution (Figure S7, again keeping in mind the apparent delocalization of DFT calculations). The DFT-calculated energy splitting between the highest occupied molecular orbital (HOMO) and HOMO−1 of neutral **Me-1**, **Me-2**, and **Me-3** is 0.022, 0.31, and 0.22 eV, respectively (Figure S8). This trend does reproduce that of the experimentally determined degree of electronic coupling of $\mathbf{1}^{\bullet+}$−$\mathbf{3}^{\bullet+}$. The attachment of two amine

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substituents on the 2,7-positions of the DBP core results in near-degenerate HOMO and HOMO−1 orbitals, which is in agreement with the absence of efficient amine−amine coupling in $\mathbf{1}^{\bullet+}$.

In summary, the degree of amine−amine electronic coupling through the DBP bridge was found to be greatly dependent on the substitution pattern of the redox sites. Efficient coupling is present between two amine substituents on the 3,8- and 5,10-positions of DBP. However, little coupling is present between the two distal amine sites through the 2,7-positions of the bridge. The latter system is dominated by the bridge to aminium charge transfer in the one-electron oxidized state. This information is of great significance for the design of new mixed-valent systems and DBP derivatives for optoelectronic applications. In addition, the amine-substituted DBP derivatives possess appealing electrochemical properties and rich electronic absorptions at different redox states, which may make them useful in near-infrared electrochromism and redox-driven molecular switches.[16]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03408.

Complete synthesis and experimental details, TDDFT results, and NMR and mass spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Saito, M. *Symmetry* **2010**, *2*, 950. (b) Hopf, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 12224. (c) Kawase, T.; Nishida, J.-i. *Chem. Rec.* **2015**, *15*, 1045.

(2) (a) Zhang, H.; Karasawa, T.; Yamada, H.; Wakamiya, A.; Yamaguchi, S. *Org. Lett.* **2009**, *11*, 3076. (b) Kawase, T.; Konishi, A.; Hiro, Y.; Matsumoto, K.; Kurata, H.; Kubo, T. *Chem. - Eur. J.* **2009**, *15*, 2653. (c) Levi, Z. U.; Tilley, T. D. *J. Am. Chem. Soc.* **2009**, *131*, 2796. (d) Xu, F.; Peng, L.; Orita, A.; Otera, J. *Org. Lett.* **2012**, *14*, 3970. (e) Maekawa, T.; Segawa, Y.; Itami, K. *Chem. Sci.* **2013**, *4*, 2369. (f) Zhao, J.; Oniwa, K.; Asao, N.; Yamamoto, Y.; Jin, T. *J. Am. Chem. Soc.* **2013**, *135*, 10222. (g) Chen, C.; Harhausen, M.; Liedtke, R.; Bussmann, K.; Fukazawa, A.; Yamaguchi, S.; Petersen, J. L.; Daniliuc, C. G.; Fröhlich, R.; Kehr, G.; Erker, G. *Angew. Chem., Int. Ed.* **2013**, *52*, 5992. (h) London, G.; von Wantoch Rekowski, M.; Dumele, O.; Schweizer, W. B.; Gisselbrecht, J.-P.; Boudon, C.; Diederich, F. *Chem. Sci.* **2014**, *5*, 965. (i) Li, H.; Wang, X.-Y.; Wei, B.; Xu, L.; Zhang, W.-X.; Pei, J.; Xi, Z. *Nat. Commun.* **2014**, *5*, 4508.

(3) (a) Nakano, M.; Osaka, I.; Takimiya, K.; Koganezawa, T. *J. Mater. Chem. C* **2014**, *2*, 64. (b) Li, C.; Liu, C.; Li, Y.; Zhu, X.; Wang, Z. *Chem. Commun.* **2015**, *51*, 693. (c) Dai, G.; Chang, J.; Zhang, W.; Bai, S.; Huang, K.-W.; Xu, J.; Chi, C. *Chem. Commun.* **2015**, *51*, 503. (d) Liu, C.; Xu, S.; Zhu, W.; Zhu, X.; Hu, W.; Li, Z.; Wang, Z. *Chem. - Eur. J.* **2015**, *21*, 17016.

(4) Kawase, T.; Fujiwara, T.; Kitamura, C.; Konishi, A.; Hirao, Y.; Matsumoto, K.; Hurata, H.; Kubo, T.; Shinamura, S.; Mori, H.; Miyazaki, E.; Takimiya, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 7728.

(5) Xu, F.; Peng, L.; Shinohara, K.; Nishida, T.; Wakamatsu, K.; Uejima, M.; Sato, T.; Tanaka, K.; Machida, N.; Akashi, H.; Orita, A.; Otera, J. *Org. Lett.* **2015**, *17*, 3014.

(6) Creutz, C.; Taube, H. *J. Am. Chem. Soc.* **1969**, *91*, 3988.

(7) (a) Aguirre-Etcheverry, P.; O'Hare, D. *Chem. Rev.* **2010**, *110*, 4839. (b) Chisholm, M. H.; Lear, B. J. *Chem. Soc. Rev.* **2011**, *40*, 5254. (c) Hildebrandt, A.; Lang, H. *Organometallics* **2013**, *32*, 5640. (d) Kubiak, C. P. *Inorg. Chem.* **2013**, *52*, 5663. (e) Mandal, A.; Agarwala, H.; Ray, R.; Plebst, S.; Mobin, S. M.; Priego, J. L.; Jimenez-Aparicio, R.; Kaim, W.; Lahiri, G. K. *Inorg. Chem.* **2014**, *53*, 6082. (f) Pieslinger, G. E.; Albores, P.; Slep, L. D.; Baraldo, L. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 1293. (g) Canzi, G.; Goeltz, J. C.; Henderson, J. S.; Park, R. E.; Maruggi, C.; Kubiak, C. P. *J. Am. Chem. Soc.* **2014**, *136*, 1710. (h) Cao, Z.; Xi, B.; Jodoin, D. S.; Zhang, L.; Cummings, S. P.; Gao, Y.; Tyler, S. F.; Fanwick, P. E.; Crutchley, R. J.; Ren, T. *J. Am. Chem. Soc.* **2014**, *136*, 12174. (i) Shao, J.-Y.; Zhong, Y.-W. *Chem. - Eur. J.* **2014**, *20*, 8702.

(8) (a) Nelsen, S. F. *Chem. - Eur. J.* **2000**, *6*, 581. (b) Hankache, J.; Wenger, O. S. *Chem. Rev.* **2011**, *111*, 5138. (c) Heckmann, S.; Lambert, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 326.

(9) (a) Lambert, C.; Nöll, G. *J. Am. Chem. Soc.* **1999**, *121*, 8434. (b) Lambert, C.; Nöll, G.; Schelter, J. *Nat. Mater.* **2002**, *1*, 69. (c) Jones, S. C.; Coropceanu, V.; Barlow, S.; Kinnibrugh, T.; Timofeeva, T.; Brédas, J.-L.; Marder, S. R. *J. Am. Chem. Soc.* **2004**, *126*, 11782. (d) Barlow, S.; Risko, C.; Chung, S.-J.; Tucker, N. M.; Coropceanu, V.; Jones, S. C.; Levi, Z.; Brédas, J.-L.; Marder, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 16900. (e) Lacroix, J. C.; Chane-Ching, K. I.; Maquere, F.; Maurel, F. *J. Am. Chem. Soc.* **2006**, *128*, 7264. (f) Sakamoto, R.; Sasaki, T.; Honda, N.; Yamamura, T. *Chem. Commun.* **2009**, 5156. (g) Völker, S. F.; Renz, M.; Kaupp, M.; Lambert, C. *Chem. - Eur. J.* **2011**, *17*, 14147. (h) Barlow, S.; Risko, C.; Odom, S. A.; Zheng, S.; Coropceanu, V.; Beverina, L.; Bredas, J.-L.; Marder, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 10146. (i) Nie, H.-J.; Chen, X.; Yao, C.-J.; Zhong, Y.-W.; Hutchison, G. R.; Yao, J. *Chem. - Eur. J.* **2012**, *18*, 14497. (j) Parthey, M.; Vincent, K. B.; Renz, M.; Schauer, P. A.; Yuft, D. S.; Howard, J. A. K.; Kaupp, M.; Low, P. J. *Inorg. Chem.* **2014**, *53*, 1544.

(10) Shen, J.; Yuan, D.; Qiao, Y.; Shen, X.; Zhang, Z.; Zhong, Y.; Yi, Y.; Zhu, X. *Org. Lett.* **2014**, *16*, 4924.

(11) Sreenath, K.; Thomas, T. G.; Gopidas, K. R. *Org. Lett.* **2011**, *13*, 1134.

(12) Hush, N. S. *Coord. Chem. Rev.* **1985**, *64*, 135.

(13) (a) Oh, D. H.; Boxer, S. G. *J. Am. Chem. Soc.* **1990**, *112*, 8161. (b) Nelsen, S. F.; Konradsson, A. E.; Weaver, M. N.; Telo, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 12493. (c) Heckmann, A.; Lambert, C.; Goebel, M.; Wortmann, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 5851.

(14) Lambert, C.; Noll, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 2107.

(15) (a) Renz, M.; Theilacker, K.; Lambert, C.; Kaupp, M. *J. Am. Chem. Soc.* **2009**, *131*, 16292. (b) Sutton, C.; Korzdorfer, T.; Coropceanu, V.; Bredas, J.-L. *J. Phys. Chem. C* **2014**, *118*, 3925.

(16) (a) Bill, N. L.; Lim, J. M.; Davis, C. M.; Bahring, S.; Jeppesen, J. O.; Kim, D.; Sessler, J. L. *Chem. Commun.* **2014**, *50*, 6758. (b) Chang, C.-C.; Yueh, H.; Chen, C.-T. *Org. Lett.* **2011**, *13*, 2702. (c) Yao, B.; Ye, X.; Zhang, J.; Wan, X. *Org. Lett.* **2014**, *16*, 5378.

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Organic LETTERS

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Organocatalytic Enantioselective Vinylogous Aldol Reaction of Allyl Aryl Ketones to Activated Acyclic Ketones

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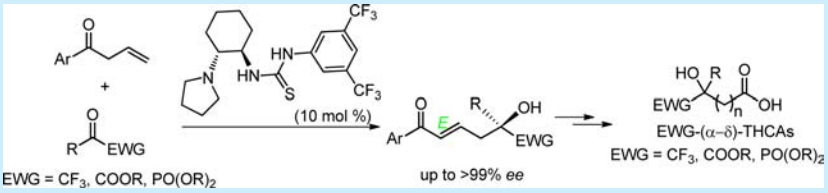
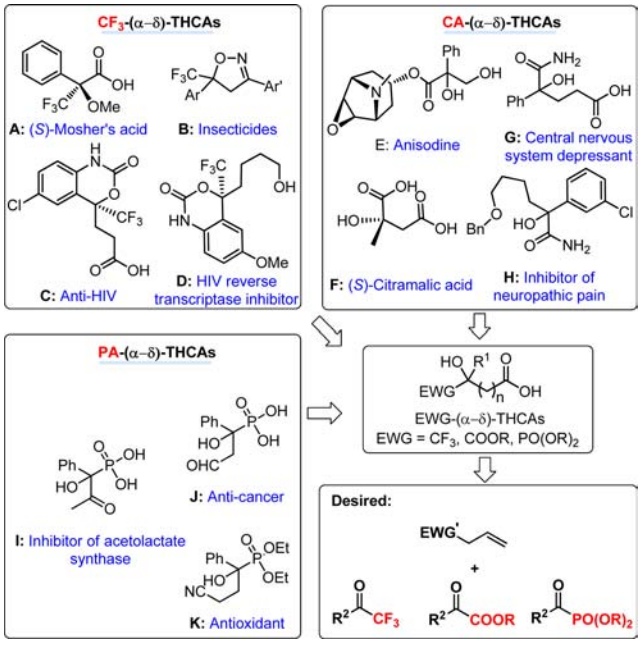
Supporting Information



ABSTRACT: The first catalytic asymmetric vinylogous aldol reaction of activated allyls to activated acyclic ketones is disclosed. A variety of activated acyclic ketones, such as trifluoromethyl ketones, α-ketoesters, and α-keto phosphonates, were found to be involved forming diverse γ-selective aldol adducts with high enantioselectivities (up to >99% ee). The method provides an effective, general strategy to access valuable chiral electron-withdrawing group-substituted tertiary hydroxyl-based carboxylic acids.

Chiral electron-withdrawing-group-functionalized tertiary hydroxy-based carboxylic acids (EWG-THCAs) constitute a wide range of key structural motifs in molecules with important biological activities (Scheme 1). Over 2800 compounds with potential bioactivities feature CF_3-α-THCA as the structural unit,[1,2] especially Mosher's acid[1a,2] **A**, which is widely used in asymmetric synthesis. The trifluoromethyl-substituted 2-isoxazolines (**B**) as CF_3-β-THCAs[3] found in almost 27000 molecules have synthetic applications in veterinary medicine and agrochemicals. Notably, CF_3-γ-THCAs (e.g., molecule **C**) and CF_3-δ-THCAs (e.g., molecule **D**) often exhibit anti-HIV activities.[4] THCAs featuring other electron-withdrawing groups, such as carboxylic acid derivatives (CA-THCAs, e.g., molecules **E**–**H**) and phosphonates (PA-THCAs, e.g., molecules **I**–**K**), on the α–δ positions of carboxylic acids are also important frameworks of many bioactive compounds.[5] Despite the existence of key catalytic asymmetric strategies to diverse enantiomerically enriched EWG-THCAs,[6−8] a divergent strategy to simultaneously furnish chiral CF_3-(α–δ)-THCAs, CA-(α–δ)-THCAs, and PA-(α–δ)-THCAs is lacking. It is thus highly desirable to devise a practical and efficient method to realize this important task.

Scheme 1. Representative Bioactive Compounds



In recent years, asymmetric vinylogous aldol (AVA) reaction has been demonstrated to be expedient in generating multifunctional chiral alcohols with an easily modified unsaturated long carbon skeleton, thereby allowing structurally complex chiral molecules with divergent synthetic targets.[9] Retrosynthetic analyses (Scheme 1) of a general AVA reaction of activated allyls to activated acyclic ketones, including trifluoromethyl ketones, γ-ketoesters, and α-keto phosphonates, reveal the possibility of achieving the divergent synthesis of these desired chiral EWG-(α–δ)-THCAs.

In 2009, Shibasaki and co-workers described a highly enantio- and γ-selective aldol reaction of allyl cyanide to simple acyclic ketones, to pioneer the work of activated allyls in the

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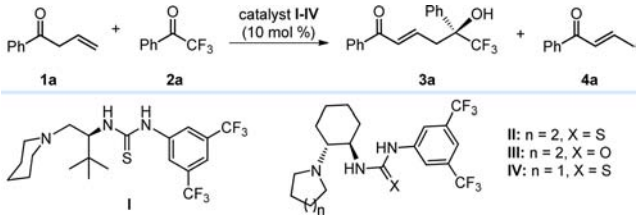
asymmetric vinylogous reaction.[10] Reports of vinylogous reactions involving activated allyls as nucleophiles have been described since then.[11] Nonetheless, the AVA reaction of activated allyls to activated acyclic ketones is still unmet, and two formidable challenges remain. The first is γ-selectivity. Lower electron density on the γ position of activated allyl-generating dienolates than the α position often leads to the poor γ-selectivity.[12] For example, asymmetric allylic alkylation of Morita–Baylis–Hillman carbonates with allyl ketones is highly α-selective.[12c] For more sterically hindered cyclic ketimines, good α-selectivity is found in the asymmetric Mannich reaction of allyl ketones.[12d] To discriminate the reactive enolate site, shielding the α position by introducing a bulky modifier at the α-position[13] or using an additional catalyst[14c] is necessary.

Another issue is enantioselectivity and universality. No example to date has been reported of an asymmetric vinylogous reaction of activated allyls to trifluoromethyl ketones and α-keto phosphonates, and only modest enantioselectivity was obtained for the asymmetric reaction of allyl cyanide with α-ketoesters.[10] Universality-wise, no asymmetric protocol has been able to be effectively performed on trifluoromethyl ketones, α-ketoesters, and α-keto phosphonates electrophiles. Herein, we report the first catalytic asymmetric VA reaction of activated allyls to activated acyclic ketones. The strategy is general in that it is applicable to diverse activated acyclic ketones, including trifluoromethyl ketones, α-ketoesters, and α-keto phosphonates, thus furnishing the desired divergent synthesis of chiral EWG-(α–δ)-THCAs.

Allyl ketones[11b,12c,d,14] are easily prepared and most commonly used as activated allyls for asymmetric direct vinylogous reactions.[14] To probe the feasibility of the desired reaction on its reactivity, regioselectivity, and stereoselectivity, our study was thus initiated with the model reaction between allyl phenyl ketone **1a** and trifluoromethyl acetophenone **2a**. The reaction was first performed in toluene at 25 °C, using 10 mol % of L-leucine-derived tertiary amine–thiourea **I** as the catalyst[15] (Table 1, entry 1). It was observed that most of **1a** was transformed to the α,β-alkene **4a** via proton transfer, and the desired AVA adduct **3a** was obtained in only 12% yield. Although the reactivity was poor, moderate enantioselectivity and excellent *E*-selectivity were observed, indicating the effectiveness of the bifunctional catalyst. Takemoto's chiral 1,2-cyclohexanediamine-based tertiary amine–thiourea **II**[16] was then examined, providing **3a** in 17% yield with 91% ee and modest *E*-selectivity (entry 2). We replaced the thiourea of **II** by the urea, but the corresponding catalyst **III** promoted **1a** to completely generate **4a** (entry 3). Next, the reaction was performed in different solvents using 10 mol % of **II** as the catalyst (entries 4–7). The results revealed that *tert*-butylbenzene was the most suitable solvent, affording **3a** in 28% yield with 92% ee and an 8:1 *E*/*Z* ratio (entry 7). A variation of the reaction temperature showed that the *E*/*Z* ratio of **3a** could be raised to >20:1 at a lower temperature (entries 8–10) and −10 °C was optimal (entry 9). When the amount of **1a** was increased to 3.0 equiv, 65% yield of **3a** was achieved (entry 11). The adduct **3a** could be obtained in 87% yield and 94% ee by utilizing catalyst **IV**,[16c] an analogue of catalyst **II** with a pyrrolidine as the tertiary amine moiety (entry 12). The basic Na_3PO_4 additive was found to further positively influence both yield and enantioselectivity (entry 13).

With the optimal reaction conditions in hand, we investigated direct AVA reaction of distinct allyl aryl ketones **1** to various trifluoromethyl ketones **2** (Scheme 2). The reactions were often complete within 24–72 h, providing adducts **3a–y** with yields of 60–98%, enantioselectivites of 70–99% ee, and *E*/*Z* ratios of more than 20:1. It should be noted that allyl ketones **1** with the ortho-substituents on phenyl rings (**3r** and **3w**) gave depressed enantiomeric excesses, whereas allyl 2-thienyl ketone gave **3y** with excellent enantioselectivity.

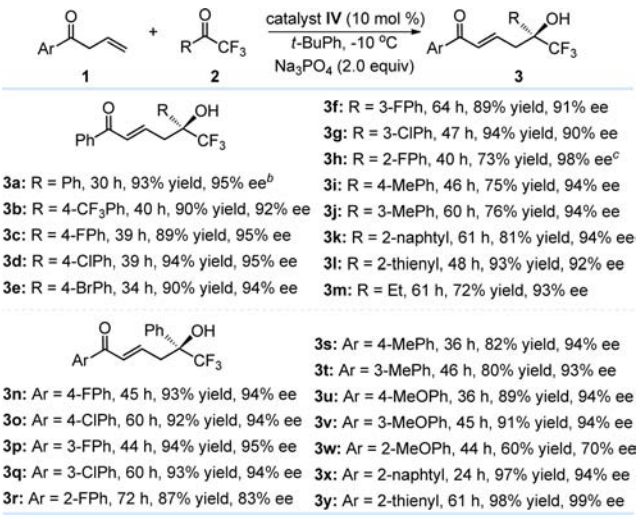
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	temp (°C)	*t* (h)	yield (%)[b]	ee (%)[c]	*E*/*Z*[d]
1	**I**	toluene	25	45	12	77	>20:1
2	**II**	toluene	25	45	17	91	4:1
3	**III**	toluene	25	45	trace	N.A.	N.A.
4	**II**	THF	25	45	N.R.	N.A.	N.A.
5	**II**	DCM	25	45	10	80	3:1
6	**II**	Et_2O	25	45	14	88	>20:1
7	**II**	*t*-BuPh	25	45	28	92	8:1
8	**II**	*t*-BuPh	0	45	43	95	>20:1
9	**II**	*t*-BuPh	−10	45	42	96	>20:1
10	**II**	*t*-BuPh	−20	45	44	96	>20:1
11[e]	**II**	*t*-BuPh	−10	62	65	96	>20:1
12[e]	**IV**	*t*-BuPh	−10	38	87	94	>20:1
13[e,f]	**IV**	*t*-BuPh	−10	38	91	95	>20:1

[a]Reaction conditions: **1a** (0.075 mmol), **2a** (0.05 mmol), catalyst (0.005 mmol), 0.5 mL of solvent. [b]Yield of isolated product. [c]Determined by HPLC analysis on a chiral stationary phase. [d]Determined by crude ^1H NMR spectra. [e]**1a**:**2a** = 3:1. [f]2.0 equiv of Na_3PO_4 were used as an additive.

Scheme 2. Direct AVA Reaction between 1 and 2[a]



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.1 mmol), catalyst (0.01 mmol), Na_3PO_4 (0.2 mmol), 1.0 mL of *t*BuPh. [b]After a single recrystallization, ee > 99%. [c]The ee value and yield were obtained after a single recrystallization. Initial data: 80% yield, 85% ee.

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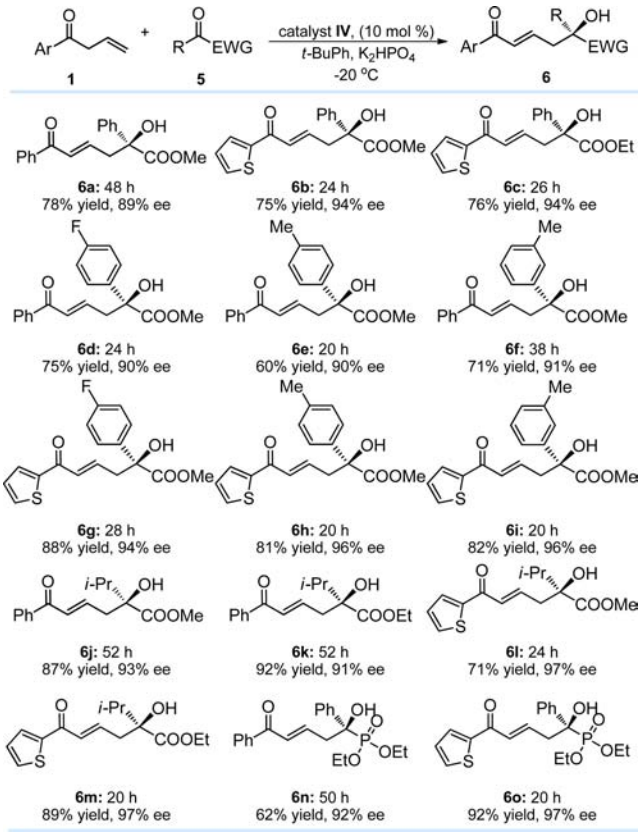
We then selected two classes of acylic activated ketones **5**, i.e. α-ketoesters and α-ketophosphonates for further examination (Scheme 3). Under slightly modified reaction conditions (10 mol % of catalyst **IV**, 2.0 equiv of K_2HPO_4, −20 °C), a range of α-ketoesters were first explored, including aromatic substrates with diverse substitution patterns and methyl/ethyl α-ketoisovalerate as the representative of aliphatic substrates. The corresponding AVA adducts (**6a**−**m**) were obtained in 60−92% yields with 89−97% ee and >20:1 *E*-selectivity within 20−52 h. The different ester groups of α-ketoesters resulted in similar reactivity and enantioselectivity. α-Ketophosphonate also proved to be a viable substrate, giving α-hydroxyphosphonates **6n**−**o** in excellent enantioselectivity.

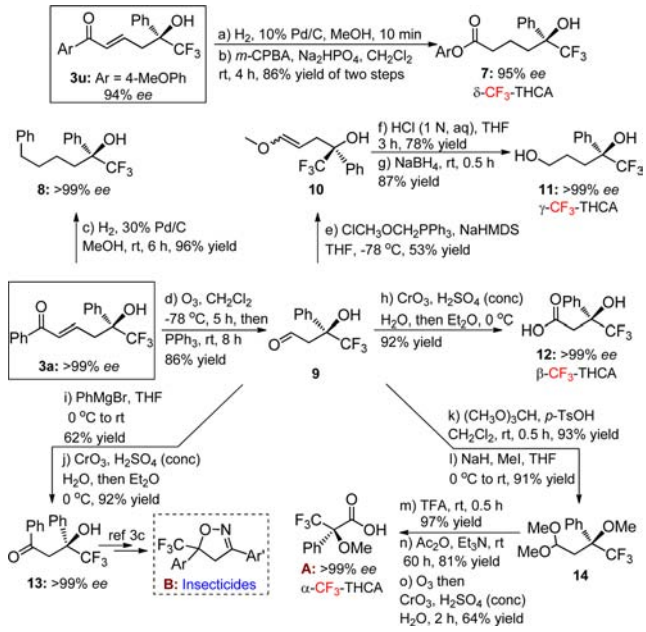
Scheme 3. Direct AVA Reaction of 1 to 5[a]



[a]Reaction conditions: **1** (0.3 mmol), **5** (0.1 mmol), catalyst **IV** (0.01 mmol), K_2HPO_4 (0.2 mmol), 0.8 mL *t*-BuPh, −20 °C.

To demonstrate the synthetic value of this work, a series of transformations from vinylogous aldol adducts were then performed (Scheme 4). The δ-CF_3-THCA derivative **7** was obtained in 86% yield with 95% ee from the reduction of **3u** with H_2 on Pd/C, followed by a Baeyer−Villiger rearrangement (BVR) with *m*-CPBA. Reduction of adduct **3a** with H_2 on Pd/C for 6 h afforded CF_3-based tertiary alcohol **8** featuring a long carbon chain and without compromising the ee value. After ozonolysis, **3a** could be conveniently converted to aldehyde **9**, which herein is demonstrated as a common intermediate to access (α−γ)-CF_3-THCAs (Scheme 1). First, through a sequence of Wittig reaction, hydrolysis, and reduction, alcohol **11** as the γ-CF_3-THCA derivative was attainable with >99% ee. Jones oxidation of **9** presented β-CF_3-THCA **12** in 92% yield. By treatment of PhMgBr and then Jones reagents (CrO_3, H_2SO_4, and H_2O), ketone **13** as the precursor of insecticides **B**[3c] was obtained with >99% ee. Since the aldehyde group of **9** inhibited the methylation of the tertiary alcohol, an acetal protecting method by using trimethyl orthoformate was attempted. Unsurprisingly, yields of both protection and the corresponding deprotection by TFA were excellent. Following an efficient acetylation of aldehyde and ozonization, (*R*)-Mosher's acid **A** was obtained with >99% ee. Clearly, these strategies could be readily employed to address the divergent synthesis of chiral CA-(α−δ)-THCAs and PA-(α−δ)-THCAs.

Scheme 4. Synthesis of (α−δ)-CF_3-THCAs



In summary, we have developed the first catalytic asymmetric AVA reaction of activated allyls to activated acyclic ketones. A series of activated acyclic ketones, such as trifluoromethyl ketones, γ-ketoesters, and α-keto phosphonates, were suitable in the established strategy, thus generating diverse γ-selective aldol adducts with high enantioselectivities (up to >99% ee). The reported synthetic method provides an expedient approach to various biologically important chiral EWG-substituted tertiary hydroxy-based α-, β-, γ-, and δ-carboxylic acids through divergent synthesis with excellent results. Further investigations into the employment of activated allyls in unprecedented AVA reactions, and the resulting divergent synthesis of significant bioactive molecules, are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03412.

General information, general experimental procedures, procedures of divergent synthesis of THCAs, characterization of adducts including HPLC and NMR spectra of the compounds (PDF)

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Author Contributions

†Z.J. and X.B. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Rew, Y.; DeGraffenreid, M.; He, X.; Jaen, J. C.; McMinn, D. L.; Sun, D.; Tu, H.; Ursu, S.; Powers, J. P. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3786. (b) Wang, P.; Feng, L.-W.; Wang, L.; Li, J.-F.; Liao, S.; Tang, Y. *J. Am. Chem. Soc.* **2015**, *137*, 4626.

(2) (a) Dull, D. L.; Mosher, H. S. *J. Am. Chem. Soc.* **1967**, *89*, 4230. (b) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (c) Hub, L.; Mosher, H. S. *J. Org. Chem.* **1970**, *35*, 3691. (d) Pareja, C.; Martín-Zamora, E.; Fernández, R.; Lassaletta, J. M. *J. Org. Chem.* **1999**, *64*, 8846. (e) Brown, M. L.; Eidam, H. A.; Paige, M.; Jones, P. J.; Patel, M. K. *Bioorg. Med. Chem.* **2009**, *17*, 7056.

(3) (a) Carceller, E.; Merlos, M.; Giral, M.; Almansa, C.; Bartrolí, J.; García-Rafanell, J.; Forn, J. *J. Med. Chem.* **1993**, *36*, 2984. (b) Matoba, K.; Kawai, H.; Furukawa, T.; Kusuda, A.; Tokunaga, E.; Nakamura, S.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 5762 and references therein. (c) Kawai, H.; Okusu, S.; Tokunaga, E.; Shibata, N. *Eur. J. Org. Chem.* **2013**, *2013*, 6506.

(4) (a) Valdez, J. *PCT Appl.* 2005, WO 2005062979 A2 20050714. (b) Fujieda, H.; Otsu, H.; Yasufuku, S.; Shirai, M. *PCT Int. Appl.* 2007, WO 2007142158 A1 20071213.

(5) For chiral CA-α-THCAs, see: (a) Whitman, C. P.; Craig, J. C.; Kenyon, G. L. *Tetrahedron* **1985**, *41*, 1183. (b) Chen, H.; Chen, Y.; Du, P.; Han, F. *J. Pharm. Biomed. Anal.* **2007**, *44*, 773. For chiral PA-α-THCAs, see: (c) Abell, L. M.; Hanna, W. S.; Kunitsky, K. J.; Kerschen, J. A. *Pestic. Sci.* **1995**, *44*, 89. (d) Habel, L. W.; Meier, C. *Nucleosides Nucleotides* **1997**, *16*, 1311. For chiral CA-β-THCAs, see: (e) Quan, M. L.; Ellis, C. D.; Liauw, A. Y.; Alexander, R. S.; Knabb, R. M.; Lam, G.; Wright, M. R.; Wong, P. C.; Wexler, R. R. *J. Med. Chem.* **1999**, *42*, 2760. For chiral PA-β-THCAs, see: (f) Perera, S.; Naganaboina, V. K.; Wang, L.; Zhang, B.; Guo, Q.; Rout, L.; Zhao, C.-G. *Adv. Synth. Catal.* **2011**, *353*, 1729. For chiral CA-γ-THCAs, see: (g) Fleuren, H. L. J.; Verwey-van Wissen, C. P. W.; van Rossum, J. M. *Eur. J. Clin. Pharmacol.* **1980**, *17*, 59. For chiral PA-γ-THCAs, see: (h) Aouani, I.; Lahbib, K.; Touil, S. *Med. Chem.* **2015**, *11*, 206. For chiral CA-δ-THCAs, see: (i) Nishimura, Y.; Mori, K. *Eur. J. Org. Chem.* **1998**, *1998*, 233. (j) Walls, T. H.; Grindrod, S. C.; Beraud, D.; Zhang, L.; Baheti, A. R.; Dakshanamurthy, S.; Patel, M. K.; Brown, M. L.; MacArthur, L. H. *Bioorg. Med. Chem.* **2012**, *20*, 5269.

(6) (a) Gathergood, N.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 12517. (b) Zhuang, W.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2001**, *66*, 1009. (c) Török, B.; Abid, M.; London, G.; Esquibel, J.; Török, M.; Mhadgut, S. C.; Yan, P.; Prakash; Surya, G. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3086. (d) Zhao, J.-L.; Liu, L.; Sui, Y.; Liu, Y.-L.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2006**, *8*, 6127. (e) Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Lett.* **2007**, *36*, 666. (f) Shen, L.-T.; Shao, P.-L.; Ye, S. *Adv. Synth. Catal.* **2011**, *353*, 1943. (g) Mo, J.; Chen, X.; Chi, Y. R. *J. Am. Chem. Soc.* **2012**, *134*, 8810. (h) Duangdee, N.; Harnying, W.; Rulli, G.; Neudörfl, J.-M.; Gröger, H.; Berkessel, A. *J. Am. Chem. Soc.* **2012**, *134*, 11196. (i) Zheng, Y.; Xiong, H.-Y.; Nie, J.; Hua, M.-Q.; Ma, J.-A. *Chem. Commun.* **2012**, *48*, 4308. (j) Wu, S.; Pan, D.; Cao, C.; Wang, Q.; Chen, F.-X. *Adv. Synth. Catal.* **2013**, *355*, 1917. (k) Zong, H.; Huang, H.; Bian, G.; Song, L. *J. Org. Chem.* **2014**, *79*, 11768 and refs 1b and 3b.

(7) (a) Tomita, D.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4138. (b) Wang, F.; Xiong, Y.; Liu, X.; Feng, X. *Adv. Synth. Catal.* **2007**, *349*, 2665. (c) Zheng, K.; Qin, B.; Liu, X.; Feng, X. *J. Org. Chem.* **2007**, *72*, 8478. (d) Xu, X.-Y.; Tang, Z.; Wang, Y.-Z.; Luo, S.-W.; Cun, L.-F.; Gong, L.-Z. *J. Org. Chem.* **2007**, *72*, 9905. (e) Mikami, K.; Kawakami, Y.; Akiyama, K.; Aikawa, K. *J. Am. Chem. Soc.* **2007**, *129*, 12950. (f) Liu, J.; Yang, Z.; Wang, Z.; Wang, F.; Chen, X.; Liu, X.; Feng, X.; Su, Z.; Hu, C. *J. Am. Chem. Soc.* **2008**, *130*, 5654. (g) Raj, M.; Parashari, G. S.; Singh, V. K. *Adv. Synth. Catal.* **2009**, *351*, 1284. (h) Zhu, X.; Lin, A.; Fang, L.; Li, W.; Zhu, C.; Cheng, Y. *Chem. - Eur. J.* **2011**, *17*, 8281. (i) Barnett, D. S.; Schaus, S. E. *Org. Lett.* **2011**, *13*, 4020. (j) Crespo-Peña, A.; Monge, D.; Martín-Zamora, E.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 12912. (k) Rose, C. A.; Gundala, S.; Fagan, C.-L.; Franz, J. F.; Connon, S. J.; Zeitler, K. *Chem. Sci.* **2012**, *3*, 735. (l) Kohn, B. L.; Ichiishi, N.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2013**, *52*, 4414. (m) Cui, Y.; Li, W.; Sato, T.; Yamashita, Y.; Kobayashi, S. *Adv. Synth. Catal.* **2013**, *355*, 1193.

(8) (a) Samanta, S.; Zhao, C.-G. *J. Am. Chem. Soc.* **2006**, *128*, 7442. (b) Huang, J.; Wang, J.; Chen, X.; Wen, Y.; Liu, X.; Feng, X. *Adv. Synth. Catal.* **2008**, *350*, 287. (c) Kong, S.; Fan, W.; Wu, G.; Miao, Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 8864. (d) Serrano, I.; Monge, D.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *Chem. Commun.* **2015**, *51*, 4077 and refs 5f and 7f.

(9) For selected reviews, see: (a) Casiraghi, G.; Zanardi, F. *Chem. Rev.* **2000**, *100*, 1929. (b) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2000**, *100*, 1891. (c) Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682. (d) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076. (e) Pansare, S. V.; Paul, E. K. *Chem. - Eur. J.* **2011**, *17*, 8770. (f) Bisai, V. *Synthesis* **2012**, *44*, 1453. (g) Yan, L.; Wu, X.; Liu, H.; Xie, L.; Jiang, Z. *Mini-Rev. Med. Chem.* **2013**, *13*, 845. (h) Zhang, Q.; Liu, X.; Feng, X. *Curr. Org. Synth.* **2013**, *10*, 764.

(10) Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 3195.

(11) (a) Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 5522. (b) Zhu, B.; Zhang, W.; Lee, R.; Han, Z.; Yang, W.; Tan, D.; Huang, K.-W.; Jiang, Z. *Angew. Chem., Int. Ed.* **2013**, *52*, 6666. (c) Li, T.-Z.; Jiang, Y.; Guan, Y.-Q.; Sha, F.; Wu, X.-Y. *Chem. Commun.* **2014**, *50*, 10790.

(12) (a) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley-Interscience: New York, 1996; p 45. (b) Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, *14*, 2433. (c) Tong, G.; Zhu, B.; Lee, R.; Yang, W.; Tan, D.; Yang, C.; Han, Z.; Yan, L.; Huang, K.-W.; Jiang, Z. *J. Org. Chem.* **2013**, *78*, 5067. (d) Qiao, B.; Huang, Y.-J.; Nie, J.; Ma, J.-A. *Org. Lett.* **2015**, *17*, 4608.

(13) Cassani, C.; Melchiorre, P. *Org. Lett.* **2012**, *14*, 5590.

(14) (a) Jiang, L.; Lei, Q.; Huang, X.; Cui, H.-L.; Zhou, X.; Chen, Y.-C. *Chem. - Eur. J.* **2011**, *17*, 9489. (b) Zhan, G.; He, Q.; Yuan, X.; Chen, Y.-C. *Org. Lett.* **2014**, *16*, 6000. (c) Gu, Y.; Wang, Y.; Yu, T.-Y.; Liang, Y.-M.; Xu, P.-F. *Angew. Chem., Int. Ed.* **2014**, *53*, 14128.

(15) Zhao, X.; Zhu, B.; Jiang, Z. *Synlett* **2015**, *26*, 2216.

(16) (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (b) *Asymmetric Organocatalysis*; List, B., Vol. Ed.; Topics in Current Chemistry 291; Springer-Verlag: Berlin, Heidelberg, 2010. (c) Tripathi, C. B.; Mukherjee, S. *Org. Lett.* **2014**, *16*, 3368.

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Organic LETTERS

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Quantitative Scale for the Trifluoromethylthio Cation-Donating Ability of Electrophilic Trifluoromethylthiolating Reagents

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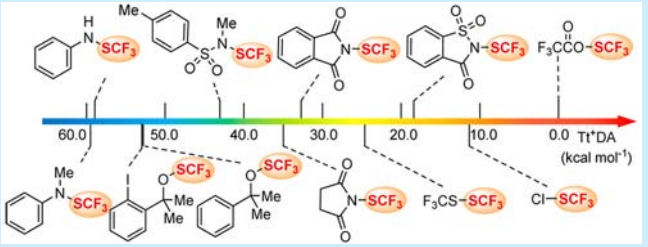
Supporting Information

ABSTRACT: A new parameter, trifluoromethylthio cation-donating ability (Tt^+DA), is introduced as a quantitative descriptor for the propensity of electrophilic trifluoromethylthiolating reagents to transfer a CF_3S moiety in organic synthesis. The first Tt^+DA scale of popular reagents has been established through DFT calculations. Excellent correlation has been identified between the Tt^+DAs of *N*-SCF_3-type reagents and the pK_a of the corresponding acids, offering a powerful avenue for the rational design of novel reagents.



The trifluoromethylthio moiety (CF_3S) is one of the most lipophilic substituents.[1] Introduction of a CF_3S group into drug candidates could significantly enhance their cell membrane permeabilities.[2] The high electronegativity of the CF_3S group could substantially improve the metabolic stability of drug candidates.[3] Hence, this unique group has attracted substantial interest from pharmaceutical and agrochemical industries as well as the academic community for its use in isostere-based drug design.[2,4]

In response to a growing demand for CF_3S-containing compounds in medicinal chemistry, chemists are continuously seeking efficient and practical strategies for selective installation of the CF_3S group onto the desired scaffold.[2,4,5] Among the powerful methods developed,[2,4,5] electrophilic trifluoromethylthiolation has attracted considerable interest in recent years.[4e,i] The rapid progress of this direction is due to the invention of a series of power-variable electrophilic CF_3S transfer reagents[6−15] (Figure 1) by several groups, such as Munavalli,[8a] Billard and Langlois,[9a,10a] Lu and Shen,[11a,13a,14] and Shibata.[15] The availability of these reagents has greatly accelerated the discovery of new trifluoromethylthiolation reactions[16] and thus contributed significantly to an efficient synthesis of compounds possessing fabulous biological properties. Surprisingly, despite significant achievements in developing various reagents and great synthetic utility, scant attention has been devoted to detailed structure−reactivity relationship studies. Consequently, the rational design of novel reagents has been seriously hampered. Very recently, Shen and Lu presented an excellent structure−reactivity study on their trifluoromethanesulfenate reagent (Figure 1, Lu and Shen 2013). On this basis, they were able to find simple and cheaper second-generation reagents (Figure 1, Lu and Shen 2015).[14] Additionally, since the available reagents showed very rich and diverse reactivity,[4e,i] this field would be well served by a scale to quantitatively rank the trifluoromethylthiolating abilities of various reagents. However, such a scale was not available. As a sequence, the current development of new reactions and optimization of reagents still rely largely on the traditional trial-and-error approach. Therefore, establishment of such a scale is urgently needed.

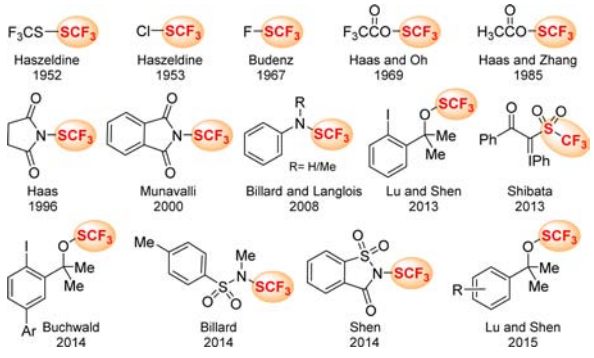


Figure 1. Typical electrophilic CF_3S transfer reagents.

Herein, we introduce a previously unexplored parameter, the trifluoromethylthio cation-donating ability (Tt^+DA), as a quantitative descriptor of the tendency of a given reagent to release the trifluoromethylthio cation. The Tt^+DA parameter of a reagent is defined as the Gibbs free energy change of the reaction (ΔG_{rxn}) at 298.15 K in eq 1, which was obtained by DFT calculations. On the basis of DFT calculations, the first Tt^+DA scale of popular reagents is established, and a good correspondence has been found between the computed Tt^+DA

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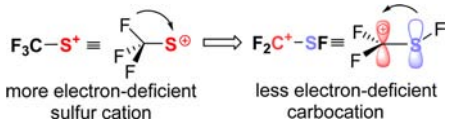
(1)

values of the reagents and the experimentally observed relative trifluoromethylthiolating capabilities. Furthermore, the effect of structure variations on the trifluoromethylthio cation-donating abilities is disclosed.

Truhlar et al.'s M06-2X hybrid functional has been shown to provide accurate predictions for main group thermochemistry.[17] Accordingly, the M06-2X functional was employed for calculating the Tt$^+$DA values. Geometry optimizations and frequency computations were performed using Gaussian 09[18] at the M06-2X/[6-31+G(d)+LANL2DZ(I)] level of theory,[17] in conjunction with the SMD model[19] to account for the solvation effects of dichloromethane (DCM), a commonly used solvent in electrophilic trifluoromethylthiolations. To obtain more accurate electronic energies, single-point energy calculations were performed at the SMD-M06-2X/[6-311++G(2df, 2p)+Def2-QZVPPD(I)] level with the SMD-M06-2X/[6-31+G-(d)+LANL2DZ(I)] structures. Notably, this level of theory provides reliable predictions of the known experimental C/N/O−S bond dissociation enthalpies with a mean unsigned error of 1.1 kcal mol^{-1} (for details, see Table S1).

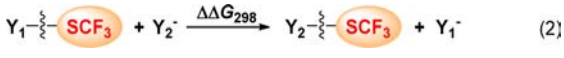
The free "CF_3S^+" intermediate has been proposed to be involved in trifluoromethylthiolations.[20] However, it is found in this calculation that the geometry optimization of the CF_3S^+ species always led to a $^+CF_2SF$ species (Scheme 1), suggesting

Scheme 1. Sulfur Cation versus Carbocation



that the putative CF_3S^+ intermediate should not be an energy minimum on the potential energy surface and, hence, should not be recommended for trifluoromethylthiolation as a valid intermediate. Though at first glance, this may not be so conceivable, by closer inspection, one could find that this is indeed reasonable. As a result of the relatively high electronegativity of the sulfur atom compared to carbon, the electron-deficient sulfur cation (if generated) should be significantly less stable than the carbocation, thus resulting in its rapid isomerization to the $^+CF_2SF$ species. It is worth emphasizing that this has an important implication for the mechanism of electrophilic trifluoromethylthiolations. That is, electrophilic transfer of a CF_3S group from reagent to substrate should not proceed via an S_N1-type of process involving a free CF_3S^+ intermediate but rather via an S_N2-type mechanism.

The unexpected finding mentioned above led us to evaluate the Tt$^+$DA value of a given reagent in a relative manner by using the CF_3S exchange reaction in eq 2. One merit that eq 2 can offer



(2)

is the cancellation of potential error. In this study, the relative Tt$^+$DA values anchored to the $CF_3CO_2SCF_3$ with an arbitrarily assigned value of 0.0 kcal mol^{-1}. The calculated relative Tt$^+$DA values for 46 electrophilic CF_3S transfer reagents in DCM are presented in Table 1. To elucidate the effects of structural variations on their Tt$^+$DAs, these reagents are grouped into three categories according to the heteroatom to which SCF_3 is

Table 1. Calculated Relative Tt$^+$DA Values of Electrophilic CF_3S Transfer Reagents in DCM

CF_3S^+ source		Tt$^+$DA in DCM (kcal mol^{-1})	CF_3S^+ source		Tt$^+$DA in DCM (kcal mol^{-1})
1.	R = H	**1A$_1$** 17.9		R = H	**1B$_1$** 33.0
	OMe	**1A$_2$** 19.3		OMe	**1B$_2$** 34.1
	Me	**1A$_3$** 19.1		Me	**1B$_3$** 33.4
	F	**1A$_4$** 16.2		F	**1B$_4$** 31.3
	Cl	**1A$_5$** 15.6		Cl	**1B$_5$** 30.5
	Br	**1A$_6$** 15.0		Br	**1B$_6$** 30.4
	CF_3	**1A$_7$** 14.0		CF_3	**1B$_7$** 29.4
	CN	**1A$_8$** 13.2		CN	**1B$_8$** 28.0
	NO_2	**1A$_9$** 13.0		NO_2	**1B$_9$** 27.8
		1C 34.9			**1E** 81.4
	R = H	**1D$_1$** 59.7			**1F** 47.1
	OMe	**1D$_2$** 63.1			**1G** 59.1
	Me	**1D$_3$** 61.4			
	F	**1D$_4$** 59.9			**1H** 43.0
	Cl	**1D$_5$** 57.0			
	Br	**1D$_6$** 57.1			
	CF_3	**1D$_7$** 52.8			
	CN	**1D$_8$** 48.7			
	NO_2	**1D$_9$** 44.4			
2.		**2A** 53.7			**2B** 52.0
		2C 53.6			**2D** 56.1
		2E 56.4			**2F** 57.0
		2G 52.5			**2H** 50.5
		2I 57.4		F_3CCO_2–SCF_3	**2J** 0.0
				H_3CCO_2–SCF_3	**2K** 22.0
3.	Cl–SCF_3	**3A** 11.1		F–SCF_3	**3B** 18.3
	F_3CS–SCF_3	**3C** 25.1			

attached: (1) *N*-SCF_3 reagents (**1A**−**1H**); (2) *O*-SCF_3 reagents (**2A**−**2K**); and (3) F-SCF_3, Cl-SCF_3, and CF_3S-SCF_3 reagents (**3A**−**3C**). Among these reagents, the *N*-SCF_3 family is arguably the most popular CF_3S^+ source and has been utilized in trifluoromethylthiolation of a wide range of nucleophiles. The calculation predicted that Shen's *N*-trifluoromethylthiosaccharin **1A$_1$**[13a] has the lowest Tt$^+$DA value of 17.9 kcal mol^{-1} among these reported *N*-SCF_3 reagents, meaning that it should be the most powerful *N*-SCF_3 reagent reported so far. Replacing the sulfonyl unit of Shen's reagent **1A$_1$** with a carbonyl group leads to a significant decrease in the ability to transfer a trifluoromethylthio cation, as seen for Munavalli's reagent **1B$_1$**[8a] (33.0 kcal mol^{-1}). The decreased ability to release a trifluoromethylthio cation from Munavalli's reagent **1B$_1$** than from Shen's reagent **1A$_1$** could be because the resulting nitrogen anion stabilized by the carbonyl group is not as effective as by the sulfonyl group.[1b] Removing the π-system of Munavalli's reagent **1B$_1$** yields Haas's reagent **1C**,[7a] which is 1.9 kcal mol^{-1} less favorable to transfer a trifluoromethylthio cation compared to reagent **1B$_1$**. Replacement of two carbonyl groups of Haas's reagent **1C** with a phenyl group and a hydrogen leads to a dramatic increase in the Tt$^+$DA value, as seen for Billard and Langlois's reagent **1D$_1$**[9a] (59.7 kcal mol^{-1}). Substitution of the phenyl of reagent **1D$_1$** with a benzyl further increases the Tt$^+$DA value by ca. 22 kcal mol^{-1} (**1D$_1$** 59.7 vs **1E**[9a] 81.4 kcal mol^{-1}), while an electron-withdrawing carbobenzyloxy substitution (**1F**[9a]) decreases the Tt$^+$DA value by ca. 12 kcal mol^{-1}. The Tt$^+$DA values of Billard and Langlois's reagents **1D$_1$** and **1G** are very close to each other (**1D$_1$** 59.7 vs **1G** 59.1 kcal mol^{-1}). Replacing the phenyl group with an electron-withdrawing *p*-toluenesulfonyl group yields Billard's second-generation reagent **1H**,[9a] which is ca. 16 kcal mol^{-1} more favorable to transfer a trifluoromethylthio cation than reagent

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1G. Finally, examination of a remote substituent effect on the Tt$^+$DAs of the three most popular *N*-SCF$_3$ reagents **1A$_1$**, **1B$_1$**, and **1D$_1$** obtained a good linear correlation between the Tt$^+$DA values and the Hammett σ_p constants (see Figure S1), allowing their trifluoromethylthio cation-donating abilities to be fine-tuned by substituents.

For the *O*-SCF$_3$ reagents, the Tt$^+$DA values of Lu and Shen's first- (**2A**) and second- (**2C-2I**) generation reagents[11a,14] display a narrow distribution around 50.5−57.4 kcal mol^{-1}, indicating that the change of structures does not affect their trifluoromethylthio cation transfer abilities much. This is mainly because the substituents are located far apart from the reaction center. In contrast, direct substitution at the reaction center with the electron-withdrawing acetyl and trifluoroacetyl groups can enhance the ability to transfer a trifluoromethylthio cation by around 32 and 54 kcal mol^{-1} for Haas's reagents **2J**[21] and **2K**,[21b] respectively. Finally, calculation predicted that the Tt$^+$DA values of reagents Cl-SCF$_3$ (**3A**),[22] F-SCF$_3$ (**3B**),[23] and CF$_3$S-SCF$_3$ (**3C**)[6] are 11.1, 18.3, and 25.1 kcal mol^{-1}, respectively, suggesting that their electrophilic trifluoromethylthiolating capability should be stronger than that of Munavalli's reagent.

Interestingly, plotting the Tt$^+$DAs of *N*-SCF$_3$ reagents against the pK_a values[24] of the corresponding acids yields an excellent linear relationship with a regression coefficient of 0.998 (Figure 2), indicating that the linear free energy relationship holds in

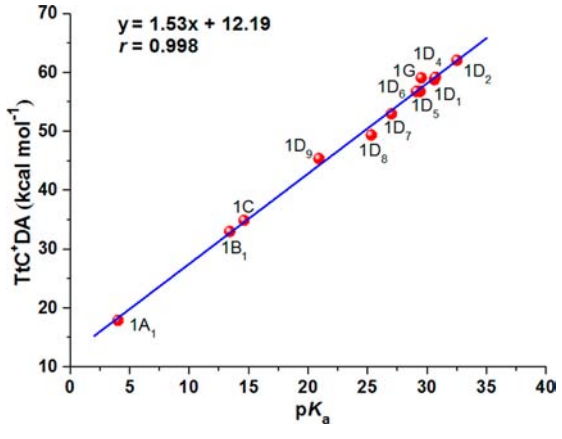

Figure 2. Plot of calculated Tt$^+$DAs of CF$_3$S transfer reagents against experimental pK_a values (DMSO) of the corresponding acids.

these two systems.[26] This offers a good opportunity for future design of new reagents, considering that substantial pK_a data have already been accumulated in the past.[24,25]

Finally, for easy comparison, we compiled a Tt$^+$DA scale for representative electrophilic trifluoromethylating reagents (Figure 3). With the Tt$^+$DA scale in hand, we naturally wanted to know how well these theoretically obtained results can explain experiments. Indeed, the practical value of the Tt$^+$DA scale has

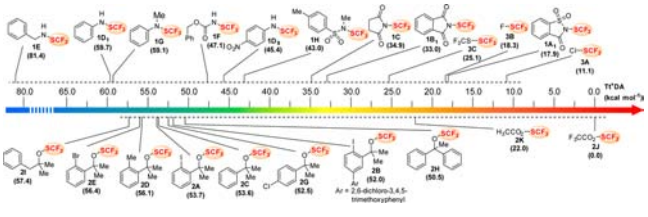

Figure 3. Relative trifluoromethylthio cation-donating ability scale of representative reagents in dichloromethane.

been verified. For instance, Lu and Shen found that the reagents in Figure 4 exhibited dramatically different reactivity in the

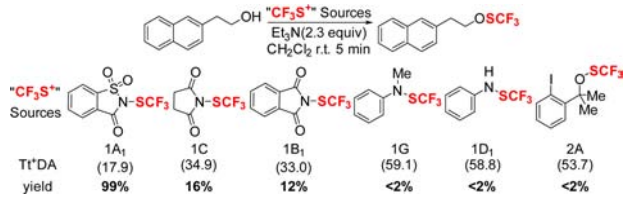

Figure 4. Electrophilic trifluoromethylthiolation of 2-(naphthalen-2-yl)ethanol.

trifluoromethylthiolation of 2-(naphthalen-2-yl)ethanol.[4i,13a] Clearly, one can see that there is good correspondence between the computed Tt$^+$DAs and the experimentally observed reactivities of these reagents. Moreover, Lu and Shen's first- (**2A**) and second- (**2C-2I**) generation reagents showed very similar efficiency in the trifluoromethylthiolation of β-ketoester,[12,14] which, again, can be explained by a similarity of their Tt$^+$DA values. Furthermore, this calculation predicted that Billard's trifluoromethanesulfanylamides[9a] (**1D$_1$** and **1G**) should have a relatively weak electrophilic trifluoromethylthiolating ability. This corresponds well with the experimental observations that a strong Lewis/Brønsted acid was required as an activator in the related transformations.[4e,j] Note that the Tt$^+$DA scale, like other thermodynamic measures, such as the recently developed methyl cation affinity scale[27] and halenium affinity (HalA) scale,[28] may be applied under thermodynamically controlled conditions. For cases where kinetic factors play a role, energetic analyses of transition states and reaction paths would have to be considered.

In summary, we have developed a quantitative scale for the trifluoromethylthio cation-donating ability of electrophilic CF$_3$S transfer reagents. Excellent linear correlation has been found between the Tt$^+$DAs of *N*-SCF$_3$-type electrophilic trifluoromethylthiolating reagents and the pK_a values of the corresponding acids, which would offer a desired quantitative guide for future rational design of novel reagents and reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03433.

Table S1, Figure S1, complete ref 18, and optimized geometries of all computed species (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Leo, A.; Hansch, C.; Elkins, D. *Chem. Rev.* **1971**, *71*, 525. (b) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

(2) (a) Leroux, F.; Jeschke, P.; Schlosser, M. *Chem. Rev.* **2005**, *105*, 827. (b) Boiko, V. N. *Beilstein J. Org. Chem.* **2010**, *6*, 880.

(3) Yagupol'skii, L. M.; Il'chenko, A. Y.; Kondratenko, N. V. *Russ. Chem. Rev.* **1974**, *43*, 32.

(4) (a) Manteau, B.; Pazenok, S.; Vors, J.-P.; Leroux, F. R. *J. Fluorine Chem.* **2010**, *131*, 140. (b) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214. (c) Tlili, A.; Billard, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 6818. (d) Besset, T.; Poisson, T.; Pannecoucke, X. *Chem. - Eur. J.* **2014**, *20*, 16830. (e) Toulgoat, F.; Alazet, S.; Billard, T. *Eur. J. Org. Chem.* **2014**, *2014*, 2415. (f) Chu, L.; Qing, F.-L. *Acc. Chem. Res.* **2014**, *47*, 1513. (g) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826. (h) Xu, X.-H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731. (i) Shao, X.; Xu, C.; Lu, L.; Shen, Q. *Acc. Chem. Res.* **2015**, *48*, 1227. (j) Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015**, *115*, 765. (k) Zhang, K.; Xu, X. H.; Qing, F.-L. *Youji Huaxue* **2015**, *35*, 556.

(5) For examples of direct trifluoromethylthiolations, see: (a) Teverovskiy, G.; Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 7312. (b) Chen, C.; Xie, Y.; Chu, L.; Wang, R.-W.; Zhang, X.; Qing, F.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 2492. (c) Zhang, C.-P.; Vicic, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 183. (d) Chen, C.; Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2012**, *134*, 12454. (e) Weng, Z.; He, W.; Chen, C.; Lee, R.; Tan, D.; Lai, Z.; Kong, D.; Yuan, Y.; Huang, K.-W. *Angew. Chem., Int. Ed.* **2013**, *52*, 1548. (f) Lefebvre, Q.; Fava, E.; Nikolaienko, P.; Rueping, M. *Chem. Commun.* **2014**, *50*, 6617. (g) Nikolaienko, P.; Pluta, R.; Rueping, M. *Chem. - Eur. J.* **2014**, *20*, 9867. (h) Zhang, K.; Liu, J. B.; Qing, F.-L. *Chem. Commun.* **2014**, *50*, 14157. (i) Chen, C.; Xu, X.-H.; Yang, B.; Qing, F.-L. *Org. Lett.* **2014**, *16*, 3372. (j) Xiang, H.; Yang, C. *Org. Lett.* **2014**, *16*, 5686. (k) Zhu, X. L.; Xu, J. H.; Cheng, D. J.; Zhao, L. J.; Liu, X. Y.; Tan, B. *Org. Lett.* **2014**, *16*, 2192. (l) Wu, H.; Xiao, Z.; Wu, J.; Guo, Y.; Xiao, J.-C.; Liu, C.; Chen, Q.-Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 4070. (m) Liu, J.-B.; Xu, X.-H.; Chen, Z.-H.; Qing, F.-L. *Angew. Chem., Int. Ed.* **2015**, *54*, 897. (n) Yin, G.; Kalvet, I.; Englert, U.; Schoenebeck, F. *J. Am. Chem. Soc.* **2015**, *137*, 4164. (o) Guo, S.; Zhang, X.; Tang, P. *Angew. Chem., Int. Ed.* **2015**, *54*, 4065. (p) Li, C.; Zhang, K.; Xu, X.-H.; Qing, F.-L. *Tetrahedron Lett.* **2015**, *56*, 6273.

(6) Brandt, G. A. R.; Emeleus, H. J.; Haszeldine, R. N. *J. Chem. Soc.* **1952**, 2198.

(7) (a) Haas, A.; Möller, G. *Chem. Ber.* **1996**, *129*, 1383. (b) Liao, K.; Zhou, F.; Yu, J. S.; Gao, W. M.; Zhou, J. *Chem. Commun.* **2015**, *51*, 16255.

(8) For the report of Munavalli's reagent, see: (a) Munavalli, S.; Rohrbaugh, D. K.; Rossman, D. I.; Berg, F. J.; Wagner, G. W.; Durst, H. D. *Synth. Commun.* **2000**, *30*, 2847. For its applications, see: (b) Bootwicha, T.; Liu, X.; Pluta, R.; Atodiresei, I.; Rueping, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 12856. (c) Pluta, R.; Rueping, M. *Chem. - Eur. J.* **2014**, *20*, 17315. (d) Rueping, M.; Liu, X.; Bootwicha, T.; Pluta, R.; Merkens, C. *Chem. Commun.* **2014**, *50*, 2508. (e) Xiao, Q.; He, Q.; Li, J.; Wang, J. *Org. Lett.* **2015**, *17*, 6090.

(9) For seminal report of trifluoromethanesulfanylamides, see: (a) Ferry, A.; Billard, T.; Langlois, B. R.; Bacqué, E. *J. Org. Chem.* **2008**, *73*, 9362. For their applications, see: (b) Ferry, A.; Billard, T.; Langlois, B. R.; Bacqué, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 8551. (c) Baert, F.; Colomb, J.; Billard, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10382. (d) Ferry, A.; Billard, T.; Bacqué, E.; Langlois, B. R. *J. Fluorine Chem.* **2012**, *134*, 160. (e) Yang, Y.; Jiang, X.; Qing, F.-L. *J. Org. Chem.* **2012**, *77*, 7538. (f) Alazet, S.; Ollivier, K.; Billard, T. *Beilstein J. Org. Chem.* **2013**, *9*, 2354. (g) Alazet, S.; Zimmer, L.; Billard, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 10814. (h) Liu, J. B.; Chu, L. L.; Qing, F.-L. *Org. Lett.* **2013**, *15*, 894. (i) Xiao, Q.; Sheng, J.; Chen, Z.; Wu, J. *Chem. Commun.* **2013**, *49*, 8647. (j) Sheng, J.; Fan, C.; Wu, J. *Chem. Commun.* **2014**, *50*, 5494. (k) Sheng, J.; Wu, J. *Org. Biomol. Chem.* **2014**, *12*, 7629. (l) Xiao, Q.; Zhu, H.; Li, G.; Chen, Z. *Adv. Synth. Catal.* **2014**, *356*, 3809. (m) Chen, D. Q.; Gao, P.; Zhou, P. X.; Song, X. R.; Qiu, Y. F.; Liu, X. Y.; Liang, Y. M. *Chem. Commun.* **2015**, *51*, 6637. (n) Jereb, M.; Gosak, K. *Org. Biomol. Chem.* **2015**, *13*, 3103.

(10) For the report of second-generation trifluoromethanesulfenamide, see: (a) Alazet, S.; Zimmer, L.; Billard, T. *Chem. - Eur. J.* **2014**, *20*, 8589. For its applications, see: (b) Alazet, S.; Billard, T. *Synlett* **2014**, *26*, 76. (c) Alazet, S.; Ismalaj, E.; Glenadel, Q.; Le Bars, D.; Billard, T. *Eur. J. Org. Chem.* **2015**, *2015*, 4607. (d) Alazet, S.; Zimmer, L.; Billard, T. *J. Fluorine Chem.* **2015**, *171*, 78. (e) Glenadel, Q.; Alazet, S.; Billard, T. *J. Fluorine Chem.* **2015**, *179*, 89.

(11) For the seminal report of trifluoromethanesulfenate reagent, see: (a) Shao, X. X.; Wang, X. Q.; Yang, T.; Lu, L.; Shen, Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 3457. For its applications, see: (b) Wang, X. Q.; Yang, T.; Cheng, X. L.; Shen, Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 12860. (c) Yang, T.; Shen, Q.; Lu, L. *Chin. J. Chem.* **2014**, *32*, 678. (d) Ma, B.; Shao, X.; Shen, Q. *J. Fluorine Chem.* **2015**, *171*, 73.

(12) Vinogradova, E. V.; Muller, P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2014**, *53*, 3125.

(13) For the report of *N*-trifluoromethylthiosaccharin reagent, see: (a) Xu, C. F.; Ma, B. Q.; Shen, Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 9316. For its applications, see: (b) Wang, Q.; Qi, Z.; Xie, F.; Li, X. *Adv. Synth. Catal.* **2015**, *357*, 355. (c) Maeno, M.; Shibata, N.; Cahard, D. *Org. Lett.* **2015**, *17*, 1990. (d) Xu, C.; Shen, Q. *Org. Lett.* **2015**, *17*, 4561.

(14) Shao, X.; Xu, C.; Lu, L.; Shen, Q. *J. Org. Chem.* **2015**, *80*, 3012.

(15) Yang, Y. D.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N. *J. Am. Chem. Soc.* **2013**, *135*, 8782.

(16) For examples of trifluoromethylthiolations using electrophilic CF_3S transfer reagents, see: (a) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 18237. (b) Zhu, S.-Q.; Xu, X.-H.; Qing, F.-L. *Eur. J. Org. Chem.* **2014**, *2014*, 4453. (c) Hu, F.; Shao, X. X.; Zhu, D. H.; Lu, L.; Shen, Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 6105. (d) Kang, K.; Xu, C.; Shen, Q. *Org. Chem. Front.* **2014**, *1*, 294. (e) Shao, X.; Liu, T.; Lu, L.; Shen, Q. *Org. Lett.* **2014**, *16*, 4738. (f) Xu, C.; Shen, Q. *Org. Lett.* **2014**, *16*, 2046. (g) Pluta, R.; Nikolaienko, P.; Rueping, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 1650. (h) Deng, Q.-H.; Rettenmeier, C.; Wadepohl, H.; Gade, L. H. *Chem. - Eur. J.* **2014**, *20*, 93. (i) Wang, Q.; Xie, F.; Li, X. *J. Org. Chem.* **2015**, *80*, 8361. (j) Yang, T.; Lu, L.; Shen, Q. *Chem. Commun.* **2015**, *51*, 5479. (k) Huang, Z.; Yang, Y.-D.; Tokunaga, E.; Shibata, N. *Asian J. Org. Chem.* **2015**, *4*, 525. (l) Arimori, S.; Takada, M.; Shibata, N. *Org. Lett.* **2015**, *17*, 1063. (m) Huang, Z.; Yang, Y. D.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2015**, *17*, 1094. (n) Glenadel, Q.; Alazet, S.; Tlili, A.; Billard, T. *Chem. - Eur. J.* **2015**, *21*, 1. (o) Xiong, H. Y.; Besset, T.; Cahard, D.; Pannecoucke, X. *J. Org. Chem.* **2015**, *80*, 4204. (p) Arimori, S.; Takada, M.; Shibata, N. *Dalton Trans.* **2015**, *44*, 19456.

(17) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157.

(18) Frisch, M. J.; et al. *Gaussian 09*, revision B.01; Gaussian, Inc.: Wallingford, CT, 2009.

(19) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378.

(20) (a) Li, Y.; Li, G.; Ding, Q. *Eur. J. Org. Chem.* **2014**, *2014*, 5017. (b) Sheng, J.; Li, S.; Wu, J. *Chem. Commun.* **2014**, *50*, 578. (c) Wu, W.; Zhang, X.; Liang, F.; Cao, S. *Org. Biomol. Chem.* **2015**, *13*, 6992. (d) Jiang, L.; Qian, J.; Yi, W.; Lu, G.; Cai, C.; Zhang, W. *Angew. Chem., Int. Ed.* **2015**, *54*, 14965.

(21) (a) Haas, A.; Oh, D. Y. *Chem. Ber.* **1969**, *102*, 77. (b) Haas, A.; Lieb, M.; Zhang, Y. *J. Fluorine Chem.* **1985**, *29*, 297.

(22) Haszeldine, R. N.; Kidu, J. M. *J. Chem. Soc.* **1953**, 3219.

(23) Seel, F.; Gombler, W.; Budenz, R. *Angew. Chem.* **1967**, *79*, 686.

(24) Internet Bond-Energy Databank Home Page. http://ibond.nankai.edu.cn (accessed Nov 14, 2015).

(25) For computational pK_a values, see: (a) Fu, Y.; Liu, L.; Li, R.-Q.; Liu, R.; Guo, Q.-X. *J. Am. Chem. Soc.* **2004**, *126*, 814. (b) Shields, G. C.; Seybold, P. G. *Computational Approaches for the Prediction of pK_a Values*; CRC Press: Boca Raton, FL, 2014.

(26) (a) Xian, M.; Zhu, X.-Q.; Lu, J.; Wen, Z.; Cheng, J.-P. *Org. Lett.* **2000**, *2*, 265. (b) Cheng, J.-P.; Xian, M.; Wang, K.; Zhu, X.; Yin, Z.; Wang, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 10266.

(27) Wei, Y.; Sastry, G. N.; Zipse, H. *J. Am. Chem. Soc.* **2008**, *130*, 3473.

(28) Ashtekar, K. D.; Marzijarani, N. S.; Jaganathan, A.; Holmes, D.; Jackson, J. E.; Borhan, B. *J. Am. Chem. Soc.* **2014**, *136*, 13355.

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Organic LETTERS

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Tetraphenylphosphonium Tetrafluoroborate/1,1,1,3,3,3-Hexafluoroisopropanol (Ph_4PBF_4/HFIP) Effecting Epoxide-Initiated Cation−Olefin Polycyclizations

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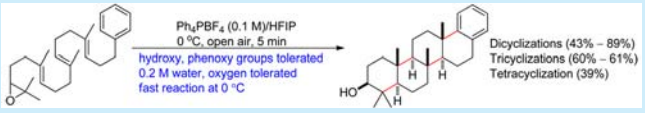
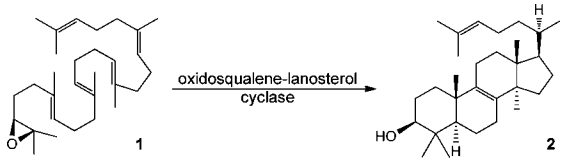
Supporting Information

ABSTRACT: The use of an excess amount of tetraphenylphosphonium tetrafluoroborate in 1,1,1,3,3,3-hexafluoroisopropanol, which can stabilize the intermediate cation in the reaction, efficiently promoted epoxide-initiated cation−olefin polycyclization reactions with broad functional group tolerance and water and oxygen tolerance.



The one-step epoxide-initiated cation−olefin polycyclization of (3*S*)-2,3-oxidosqualene (**1**), a linear epoxy polyene, to form the polycyclic steroid lanosterol (**2**) is efficiently catalyzed by enzymes in living systems (Scheme 1).[1]

Scheme 1. Biosynthesis of Lanosterol



Mimicking this process has long interested synthetic organic chemists.[2] Pioneering work by Goldsmith and van Tamelen revealed that $BF_3{\cdot}Et_2O$ catalyzes epoxide-initiated cation−olefin polycyclizations.[3] Corey established that $MeAlCl_2$ and analogous compounds are efficient catalysts, and they have been used to construct many natural polycyclic terpenoids.[4] Other Lewis acids (e.g., $InBr_3$,[5a] $Sc(OTf)_3$,[5b] $SnCl_4$,[2c,5c] $FeCl_3$,[5d,e] $TiCl_4$[5f]), zeolites,[1c,6] and radical catalysts (Ti^{3+})[7] also catalyze cascade cyclizations. Although enzymatic cation−olefin polycyclization initiates through protonation of the epoxide by an aspartic acid residue,[1] Brønsted acid-catalyzed polycyclizations give mostly monocyclized products because of the premature termination of the cation intermediates.[4m,8]

1,1,1,3,3,3-Hexafluoroisopropanol (HFIP) has high polarity, high ionizing power, and weak nucleophilicity.[9] These properties make it a good solvent for the stabilization of cations and radicals.[10] HFIP acts as a Brønsted acid (pK_a = 9.3) catalyst of reactions normally catalyzed by Lewis acids.[11] Bégué et al. reported that HFIP promotes epoxide ring opening by aromatic amines.[11h] Mayr et al. and our group found that trifluoroethanol (TFE) and HFIP promote inter- and intramolecular Friedel−Crafts alkylation reactions between electron-rich arenes and epoxides.[11i,j] Herein, we report that the use of an excess amount of Ph_4PBF_4 in HFIP efficiently promotes epoxide-initiated cation−olefin polycyclizations with very high chemical yields and broad functional group tolerance.

Our aim was to find a practical method to construct polycyclic frameworks by cationic polycyclizations,[11k] and we chose the challenging tricyclization of epoxy olefin **3** as a model reaction (Table 1). Stirring a 0.01 M solution of **3** in HFIP at 0 °C for 24 h gave the desired tricyclized product **4** (40%), oxygen-bridged monocyclized product **5** (27%), and a mixture of incompletely cyclized products **6** (32%; inseparable by column chromatography, Table 1, entry 1). The yield of **4** decreased when the reaction was carried out at room temperature or at a higher concentration (entries 2 and 3). Replacing HFIP with TFE (pK_a = 12.4) or perfluoro-*tert*-butanol (PFTB, p*K*a = 5.4) resulted in no reaction after 24 h (entries 4 and 5). Epoxy olefin **3** was rapidly consumed when treated with *p*-toluenesulfonic acid in CH_2Cl_2, but the yield of **4** was only 23% (entry 6); the major byproducts were **5** (19%) and incompletely cyclized products (56%). Salts were added to increase the polarity of the reaction medium. Metal salts were insoluble in HFIP, and the reaction rate and yield did not change when Bu_4NBr or Bu_4NClO_4 was added (entries 7 and 8). Surprisingly, Bu_4NBF_4 markedly accelerated the reaction (which was complete after slow addition of the substrate to the salt-containing HFIP solution at 0 °C, t = 5 min), and the yield of **4** increased to 51% (entry 9). The commonly used ionic liquid $BMIMBF_4$ had similar effects (entry 10). The yield of **4** was highest when 0.1 M Ph_4PBF_4 was used (60%, entry 11). Decreasing the Ph_4PBF_4 concentration decreased the yield (entry 12), but the reaction was still fast. HFIP freezes at −4 °C, but the reaction temperature could be lowered by dissolving more salts in the HFIP. Reaction at −45 °C in a mixture of 20 mmol of Bu_4NBF_4 in 10 mL of HFIP ([Bu_4NBF_4] = 2 M), which was a gluey liquid even at this temperature, gave **4** in 57% yield (entry 13), which is

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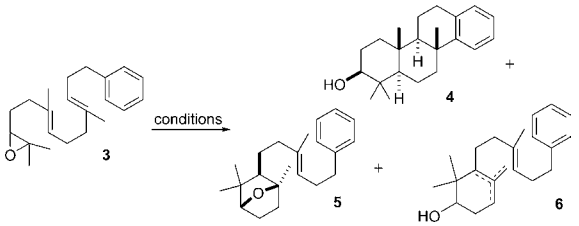
Table 1. Solvent and Salt Effects on Tricyclization[a]



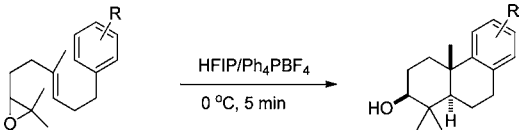
entry	solvent + additive	time	temp (°C)	yield of 4[b] (%)
1	HFIP	24 h	0	40
2	HFIP	12 h	rt	30
3[c]	HFIP	7 h	0	35
4	TFE	24 h	0	NR
5	PFTB	24 h	0	NR
6	CH_2Cl_2 + *p*-TSA (0.1 equiv)	15 min	0	23
7	HFIP + Bu_4NBr (0.1 M)	6 h	0	35
8	HFIP + Bu_4NClO_4 (0.1 M)	24 h	0	43
9	HFIP + Bu_4NBF_4 (0.1 M)	5 min	0	51
10	HFIP + $BMIMBF_4$ (0.1 M)	5 min	0	52
11	HFIP + Ph_4PBF_4 (0.1 M)	5 min	0	60
12	HFIP + Ph_4PBF_4 (0.04 M)	5 min	0	42
13	HFIP + Bu_4NBF_4 (2 M)	5 min	−45	57
14	HFIP + Bu_4NPF_6 (0.1 M)	5 min	0	51
15	HFIP + Bu_4NSbF_6 (0.1 M)	6 h	0	54
16	HFIP + Bu_4NBARF (0.02 M)	48 h	0	48
17	HFIP + Bu_4NBARF (0.02 M) + HF (0.001 M)	5 min	0	51
18	HFIP + HF (0.001 M)	5 min	0	37
19	DCM + Ph_4PBF_4 (0.1 M) + HF (0.001 M)	24 h	0	NR
20[d]	HFIP + Ph_4PBF_4 (0.1 M) + H_2O (0.2 M)	5 min	0	56

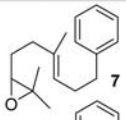
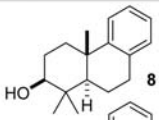
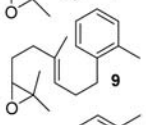
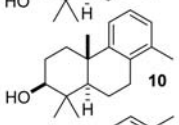
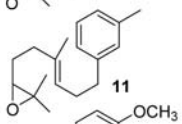
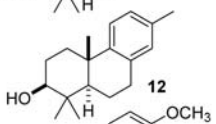
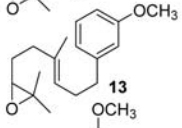
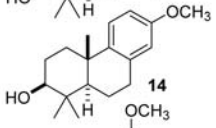
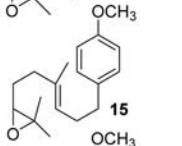
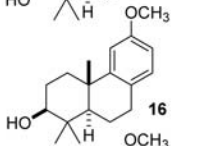
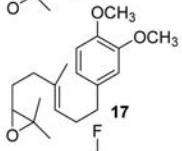
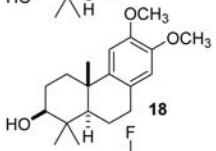
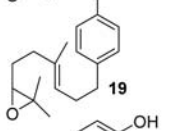
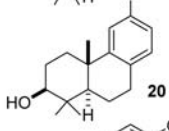
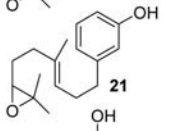
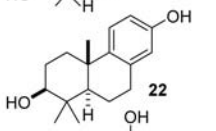
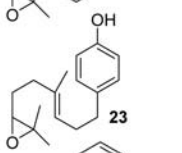
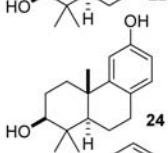
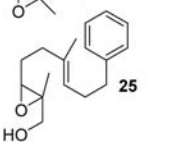
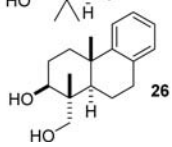
[a]Reaction conditions: **3** (0.1 mmol) was gradually added to the solution (10 mL). [b]Isolated yield. [c]HFIP (1 mL) was used. [d]H_2O (2 mmol) was added.

comparable to the yield at 0 °C (entry 11). We also tested other F-containing noncoordinating salts (entries 14−16). The yields of these reactions were higher than with HFIP alone and were similar to the yield for Bu_4NBF_4/HFIP. Compared to BF_4 salts, Bu_4NSbF_6 and Bu_4NBARF gave similar yields, but the reactions were much slower, whereas the reaction with the PF_6 salt was as fast as that with BF_4 salts. Both PF_6 and BF_4 salts can hydrolyze in aqueous solution to form HF (pK_a = 3.17),[12] which explains why the reactions with these salts were fast. Adding 0.1 equiv of HF to the Bu_4NBARF/HFIP system resulted in instantaneous reaction, but the yield was the same (entry 17). Adding 0.1 equiv of HF to HFIP alone also greatly accelerated the reaction but had no effect on the yield (compare entries 1 and 18). This indicated that traces of HF from the decomposition of PF_6 or BF_4 salts accelerated the reaction and that the noncoordinating F anions increased the yield. A control reaction in dichloromethane with HF and Ph_4PBF_4 did not proceed even after 24 h, indicating the essential role of HFIP (entry 19). Among these reaction media, Ph_4PBF_4/HFIP gave the highest yield and a high reaction rate (entry 11).[13] A reaction carried out under strictly anhydrous conditions gave a similar yield as a reaction in air. In fact, when we added 20 equiv of water to the reaction medium, **4** was obtained in similar yield (entry 20).[14] Excess water resulted in diol formation via epoxy olefin hydrolysis.

The Ph_4PBF_4/HFIP system was then tested in the dicyclization of phenyl substrate **7**. The reaction was complete in 5 min and afforded **8** in 88% yield (Table 2, entry 1), with

Table 2. Dicyclizations of Epoxy Olefins[a]



entry	epoxy olefin	product	isolated yield (%)
1			88
2			89
3			83
4			87 *para-lortho-* = 1.6:1
5			85
6			85
7			43
8			88 *para-lortho-* = 2.5:1
9			85
10			62

[a]Reaction conditions: epoxy olefin (0.1 mmol) was gradually added to HFIP (10 mL) containing Ph_4PBF_4 (1 mmol) at 0 °C.

the oxygen-bridged product as the only byproduct. In pure HFIP, the same substrate also provided **8** (86%), but the reaction time was 1 h. The substrate scope was studied by varying the substituents on the phenyl ring (entries 2−9). Unlike the method using Lewis acid catalysts, this method does not require protection of substrates with a phenoxy group (entries 8 and 9). Hydroxy-substituted substrate **25** reacted directly, but the yield was only 62% (entry 10), probably

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because the hydroxy group destabilized the partial positive charge that developed during heterolytic cleavage of the nearby oxirane ring.[2c]

Tricyclization of 1 mmol of **3** in Ph_4PBF_4/HFIP (50 mL) at 0 °C was complete in 5 min (42%), (Table 3, entry 1), and

Table 3. Tri- and Tetracyclizations of Epoxy Olefins[a]

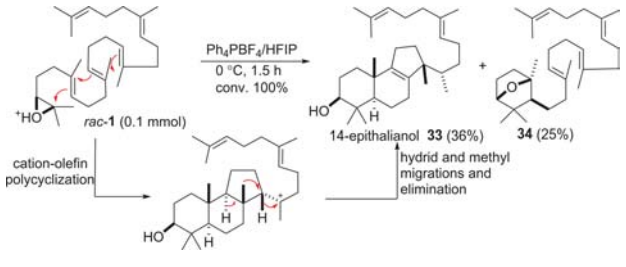
entry	epoxy olefin	product	isolated yield (%)
1[b]	**3** (1 mmol)	**4**	42
2	**27**	**28**	61
3	**29**	**30**	60
4	**31**	**32**	39

[a]Reaction conditions: epoxy olefin (0.1 mmol) was added to HFIP (10 mL) containing Ph_4PBF_4 (1 mmol) at 0 °C for 5 min. [b]HFIP (50 mL) containing Ph_4PBF_4 (5 mmol).

after the HFIP was distilled off, Ph_4PBF_4 was precipitated by addition of excess EtOAc to the residue. Thus, both HFIP and Ph_4PBF_4 could be recycled. We evaluated the efficiency of reactions in this new medium by preparing other tri- and tetracyclic products. Substrates **27** and **29**, which bear a methoxy or phenolic hydroxy substituent, gave tricyclization products (61% and 60%, entries 2 and 3), and epoxide **31** gave a tetracyclization product (39% yield, ~79% per ring formed, entry 4).

We wondered whether the method could be used to cyclize 2,3-oxidosqualene, in which the terminating group is an olefin. After reaction for 1.5 h at 0 °C, 2,3-oxidosqualene (*rac*-**1**, 0.1 mmol) gave 14-epithalianol (**33**, 36% yield) via cation–olefin tricyclization, a hydride and methyl 1,2-shift, and proton elimination, with oxygen-bridged product **34** as the byproduct (25%, Scheme 2).

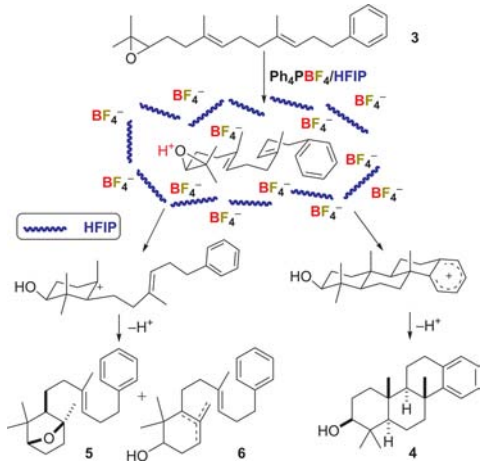
Scheme 2. Tricyclization of 2,3-Oxidosqualene



Prearrangement of the polyene into the proper conformation is believed to be crucial for polycyclization.[5a,15] HFIP forms helical hydrogen-bonding networks in the solid and liquid states.[16] Thus, we suspected that in HFIP the linear polyene adopt a more compacted conformation due to the hydrophobic interactions between HFIP hydrogen-bonding clusters and hydrocarbon substrate[17,18] (note that trifluoroethanol and perfluoro-*tert*-butanol did not promote the polycyclization reaction, and the fluorocarbon–hydrocarbon interactions[19] may not be the driving force for folding of the substrates).

We propose that in HFIP, the epoxide substrate in a more organized chair–chair–chair conformation was activated by traces of HF generated by BF_4 solvolysis in HFIP, initiating complete cyclization to give **4** (Scheme 3).[20] The intermediate

Scheme 3. Proposed Reaction Pathways of 3 in Ph_4PBF_4/HFIP



cation was stabilized by HFIP[10] or by BF_4 anions,[10g,21] which offered more protection to the intermediate cation from the nucleophilic attack or elimination by a intermolecular nucleophile.[22] The intermediate cation either was trapped by oxygen to give the oxygen-bridged product or underwent a side reaction to give products of incomplete cyclization.[3c] The inability of traces of water to quench the reaction may have been due to the fact that the excess HFIP diminished the nucleophilicity of water via the formation of strong hydrogen bonds.[23]

In conclusion, a new reaction medium (Ph_4PBF_4/HFIP), acting as both Brønsted acid catalyst and solvent, efficiently promoted epoxide-initiated polycyclizations in the absence of a metal catalyst. High yields, broad functional-group tolerance, water and oxygen tolerance, and a short reaction time make this an attractive method for preparing polycyclic terpenoids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03438.

Experimental details, NMR spectra, HRMS, and X-ray crystal data of **18** and **30** (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2812−2833. (b) Wendt, K. U. *Angew. Chem., Int. Ed.* **2005**, *44*, 3966−3971. (c) Lodeiro, S.; Xiong, Q.-B.; Wilson, W. K.; Kolesnikova, M. D.; Onak, C. S.; Matsuda, S. P. T. *J. Am. Chem. Soc.* **2007**, *129*, 11213−11222.

(2) (a) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730−4756. (b) Kürti, L.; Chein, R.-J.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 9031−9036. (c) Rajendar, G.; Corey, E. J. *J. Am. Chem. Soc.* **2015**, *137*, 5837−5844.

(3) (a) Goldsmith, D. J. *J. Am. Chem. Soc.* **1962**, *84*, 3913−3918. (b) van Tamelen, E. E.; Storni, A.; Hessler, E. J.; Schwartz, M. *J. Am. Chem. Soc.* **1963**, *85*, 3295−3296. (c) Goldsmith, D. J.; Phillips, C. F. *J. Am. Chem. Soc.* **1969**, *91*, 5862−5870. (d) van Tamelen, E. E.; McCormick, J. P. *J. Am. Chem. Soc.* **1969**, *91*, 1847−1848. (e) van Tamelen, E. E.; Carlson, J. G.; Russell, R. K.; Zawacky, S. R. *J. Am. Chem. Soc.* **1981**, *103*, 4615−4616. (f) van Tamelen, E. E.; Leiden, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 2061−2062. (g) Tanis, S. P. *J. Org. Chem.* **1988**, *53*, 4929−4938.

(4) (a) Corey, E. J.; Sodeoka, M. *Tetrahedron Lett.* **1991**, *32*, 7005−7008. (b) Corey, E. J.; Lee, J. *J. Am. Chem. Soc.* **1993**, *115*, 8873−8874. (c) Corey, E. J.; Lin, S. *J. Am. Chem. Soc.* **1996**, *118*, 8765−8766. (d) Corey, E. J.; Luo, G.; Lin, S. *J. Am. Chem. Soc.* **1997**, *119*, 9927−9928. (e) Huang, A. X.; Xiong, Z.-M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999−10000. (f) Zhang, J.-H.; Corey, E. J. *Org. Lett.* **2001**, *3*, 3215−3216. (g) Mi, Y.; Schreiber, J. V.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 11290−11291. (h) Behenna, D. C.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 6720−6721. (i) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 8865−8869. (j) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2009**, *131*, 13928−13929. (k) Shenvi, R. A.; Corey, E. J. *Org. Lett.* **2010**, *12*, 3548−3551. (l) Xu, S.-Y.; Gu, J.-X.; Li, H.-L.; Ma, D.-H.; Xie, X.-G.; She, X.-G. *Org. Lett.* **2014**, *16*, 1996−1999. (m) Suzuki, K.; Yamakoshi, H.; Nakamura, S. *Chem. - Eur. J.* **2015**, *21*, 17605−17609.

(5) For other Lewis acids, see: (a) Zhao, J.-F.; Zhao, Y.-J.; Loh, T.-P. *Chem. Commun.* **2008**, 1353−1355. (b) Bogenstätter, M.; Limberg, A.; Overman, L. E.; Tomasi, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 12206−12207. (c) van Tamelen, E. E.; Willet, J.; Schwartz, M.; Nadeau, R. *J. Am. Chem. Soc.* **1966**, *88*, 5937−5938. (d) Sen, S. E.; Roach, S. L.; Smith, S. M.; Zhang, Y.-Z. *Tetrahedron Lett.* **1998**, *39*, 3969−3972. (e) Cherney, E. C.; Green, J. C.; Baran, P. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 9019−9022. (f) Corey, E. J.; Liu, K. *J. Am. Chem. Soc.* **1997**, *119*, 9929−9930.

(6) (a) Sen, S. E.; Zhang, Y.-Z.; Roach, S. L. *J. Org. Chem.* **1996**, *61*, 9534−9537. (b) Sen, S. E.; Zhang, Y.-Z.; Smith, S. M. *J. Org. Chem.* **1998**, *63*, 4459−4465.

(7) (a) Justicia, J.; Rosales, A.; Buñuel, E.; Oller-López, J. L.; Valdivia, M.; Haïdour, A.; Oltra, J. E.; Barrero, A. F.; Cárdenas, D. J.; Cuerva, J. M. *Chem. - Eur. J.* **2004**, *10*, 1778−1788. (b) Domingo, V.; Arteaga, J. F.; Pérez, J. L. L.; Peláez, R.; Quílez del Moral, J. F.; Barrero, A. F. *J. Org. Chem.* **2012**, *77*, 341−350.

(8) van Tamelen, E. E.; Hwu, J. R. *J. Am. Chem. Soc.* **1983**, *105*, 2490−2491.

(9) (a) Bégué, J.-P.; Bonnet-Delpon, D.; Crousse, B. *Synlett* **2004**, 18−29. (b) Shuklov, I. A.; Dubrovina, N. V.; Börner, A. *Synthesis* **2007**, *2007*, 2925−2943.

(10) (a) McClelland, R. A.; Mathivanan, N.; Steenken, S. *J. Am. Chem. Soc.* **1990**, *112*, 4857−4861. (b) Steenken, S.; McClelland, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 9648−9649. (c) McClelland, R. A.; Chan, C.; Cozens, F.; Modro, A.; Steenken, S. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1337−1339. (d) Burdisso, M.; Gandolfi, R.; Toma, L.; Oberti, R. *Tetrahedron* **1991**, *47*, 6725−6736. (e) Cozens, F. L.; McClelland, R. A.; Steenken, S. *J. Am. Chem. Soc.* **1993**, *115*, 5050−5055. (f) Leonard, N. J.; Neelima. *Tetrahedron Lett.* **1995**, *36*, 7833−7836. (g) Mo, X.; Yakiwchuk, J.; Dansereau, J.; McCubbin, J. A.; Hall, D. G. *J. Am. Chem. Soc.* **2015**, *137*, 9694−9703. (h) Ricardo, C. L.; Mo, X.; McCubbin, J. A.; Hall, D. G. *Chem. - Eur. J.* **2015**, *21*, 4218−4223.

(11) (a) De, K.; Legros, J.; Crousse, B.; Bonnet-Delpon, D. *J. Org. Chem.* **2009**, *74*, 6260−6265. (b) Dumitrescu, L.; Azzouzi-Zriba, K.; Bonnet-Delpon, D.; Crousse, B. *Org. Lett.* **2011**, *13*, 692−695. (c) Saito, A.; Kasai, J.; Konishi, T.; Hanzawa, Y. *J. Org. Chem.* **2010**, *75*, 6980−6982. (d) Trillo, P.; Baeza, A.; Nájera, C. *J. Org. Chem.* **2012**, *77*, 7344−7354. (e) Ratnikov, M. O.; Tumanov, V. V.; Smit, W. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9739−9742. (f) Kesavan, V.; Bonnet-Delpon, D.; Bégué, J.-P. *Tetrahedron Lett.* **2000**, *41*, 2895−2898. (g) Legros, J.; Crousse, B.; Bonnet-Delpon, D.; Bégué, J.-P. *Eur. J. Org. Chem.* **2002**, *2002*, 3290−3293. (h) Das, U.; Crousse, B.; Kesavan, V.; Bonnet-Delpon, D.; Bégué, J.-P. *J. Org. Chem.* **2000**, *65*, 6749−6751. (i) Westermaier, M.; Mayr, H. *Chem. - Eur. J.* **2008**, *14*, 1638−1647. (j) Li, G.-X.; Qu, J. *Chem. Commun.* **2010**, *46*, 2653−2655. (k) Zhang, F.-Z.; Tian, Y.; Li, G.-X.; Qu, J. *J. Org. Chem.* **2015**, *80*, 1107−1115.

(12) (a) Swatloski, R. P.; Holbrey, J. D.; Rogers, R. D. *Green Chem.* **2003**, *5*, 361−363. (b) Freire, M. G.; Neves, C. M. S. S.; Marrucho, I. M.; Coutinho, J. A. P.; Fernandes, A. M. *J. Phys. Chem. A* **2010**, *114*, 3744−3749.

(13) See the Supporting Information for the combined use of other Brønsted acids and HFIP. Combined use of Lewis acids and HFIP has been reported, but we found that adding catalytic amounts of Lewis acids (Ir or Fe salts) did not affect the yield of the reactions.

(14) Loh et al. found that traces of water are tolerated in $InBr_3$-catalyzed polycyclizations,[5a] but yields are relatively low.

(15) (a) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890−1904. (b) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068−5077. (c) Eschenmoser, A.; Arigoni, D. *Helv. Chim. Acta* **2005**, *88*, 3011−3050.

(16) (a) Berkessel, A.; Adrio, J. A.; Hüttenhain, D.; Neudörfl, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 8421−8426. (b) Czarnik-Matusewicz, B.; Pilorz, S.; Zhang, L.-P.; Wu, Y. *J. Mol. Struct.* **2008**, *883*−*884*, 195−202.

(17) van Tamelen, E. E. *Acc. Chem. Res.* **1968**, *1*, 111−120.

(18) The NOE difference spectra of 2,3-oxidosqualene in HFIP-d_2 and in $CDCl_3$ were studied; see the Supporting Information.

(19) (a) Scott, R. L. *J. Am. Chem. Soc.* **1948**, *70*, 4090−4093. (b) Hildebrand, J. H.; Cochran, D. R. F. *J. Am. Chem. Soc.* **1949**, *71*, 22−25. (c) Myers, K. E.; Kumar, K. *J. Am. Chem. Soc.* **2000**, *122*, 12025−12026.

(20) Corey, E. J.; Staas, D. D. *J. Am. Chem. Soc.* **1998**, *120*, 3526−3527.

(21) (a) Begouin, J.-M.; Niggemann, M. *Chem. - Eur. J.* **2013**, *19*, 8030−8041. (b) Feeney, K.; Berionni, G.; Mayr, H.; Aggarwal, V. K. *Org. Lett.* **2015**, *17*, 2614−2617.

(22) In the Friedel−Crafts reaction between anisole and styrene oxide in HFIP, addition of BF_4 salts could suppress epoxide ring-opening by HFIP; see the Supporting Information.

(23) Ammer, J.; Mayr, H. *J. Phys. Org. Chem.* **2013**, *26*, 59−63.

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Organic LETTERS

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Tunable and Diastereoselective Brønsted Acid Catalyzed Synthesis of β-Enaminones

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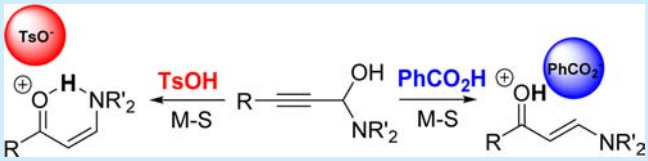
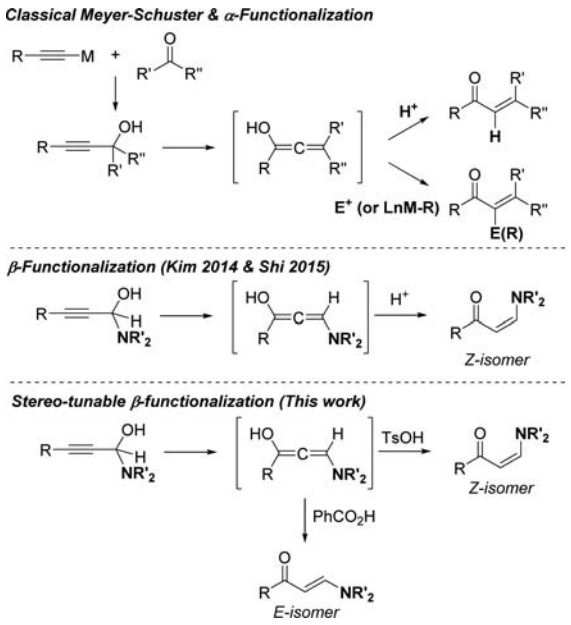
Supporting Information

ABSTRACT: The Brønsted acid catalyzed Meyer−Schuster reaction of hemiaminals was studied for the stereoselective synthesis of β-enaminones. Hemiaminals were formed from propargyl aldehydes (or the oxidation of propargyl alcohols) and amines in the presence of Brønsted acids. A critical step to control the stereochemistry of the products is the protonation of the corresponding allenol intermediate, which is dictated by the Brønsted acid used, the steric effect of the amine, and the electronic effect of the propargyl aldehyde.



The classical Meyer−Schuster rearrangement has previously been employed to convert propargyl alcohols to α,β-unsaturated carbonyl compounds under various metal-catalyzed and metal-free conditions.[1−4] Extensive studies on the mechanism and investigation into efficient catalytic systems have been conducted. In addition to this simple rearrangement of propargyl alcohols to α,β-unsaturated carbonyl compounds, tandem approaches have been demonstrated (Scheme 1) involving the in situ formation of propargyl alcohols, which is followed by Meyer−Schuster rearrangement; this avoids the need for a separate synthesis of propargyl alcohols. By adding external electrophiles or organometallic species to propargyl alcohols, α-functionalized unsaturated carbonyl compounds have been obtained via Meyer−Schuster reaction followed by α-addition.[5] β-Functionalized unsaturated carbonyl compounds are also synthesized by a tandem protocol involving nucleophilic addition to propargyl carbonyl compounds to form hemiaminal intermediates, which subsequently undergo Meyer−Schuster rearrangement. A gold-catalyzed reaction of propargyl aldehydes with primary amides and a metal-free reaction of propargyl aldehydes with amines were reported as recent examples of the synthesis of β-functionalized unsaturated carbonyl compounds.[2l,6]

Scheme 1. Meyer−Schuster Rearrangement



Although classical Meyer−Schuster reactions are known to occur in the presence of Brønsted acids such as sulfuric acid, acetic acid, and formic acid, the effect of these acids on the stereochemistry of the product has not been extensively studied. In the case of the Meyer−Schuster reactions of hemiaminals, *Z*-alkenes have previously been observed as major products (Scheme 1).[2l,6] In the gold-catalyzed rearrangement of hemiaminals, additional treatment of the reaction mixtures was required to alter the stereochemistry of the products.[2l] However, to the best of our knowledge, there is no catalytic reaction to direct the selective formation of *E* or *Z* isomers during the Meyer−Schuster rearrangement of hemiaminals. In this study, we present the stereocontrolled Brønsted acid-catalyzed rearrangement of hemiaminals to afford synthetically and biologically useful β-enaminones (Scheme 1).[7−10]

The reaction between phenylpropargyl aldehyde **1a** and morpholine **1b** was run in the presence of several Brønsted acid catalysts (0.25 equiv) at 80 °C in air (see Table 1). Optimization began with isopropyl alcohol (IPA) and hexafluoroisopropyl alcohol (HFIP) (entries 1 and 2, respectively). While sterically similar, the pK_a values of these two alcohols are very different. Upon addition of HFIP, the

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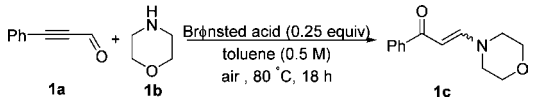
Table 1. Optimization of the Synthesis of 1c



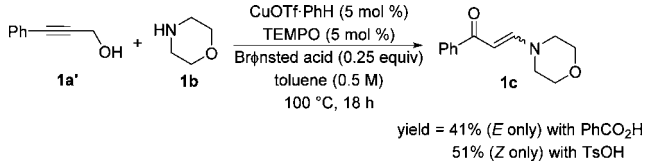
entry	acid catalysts	pK_a*	yield (%)	ratio (E/Z)
1	IPA	16.5	31	1:3.7
2	HFIP	9.3	55	2.6:1
3	4-OMePhOH	10.2	48	1:2.8
4	PhOH	9.95	56	1:2.7
5	4-NO_2PhOH	7.1	60	3.1:1
6	phenylacetic acid	4.76	79	*E* only
7	$PhCO_2H$	4.2	88	*E* only
8	2-NO_2PhCO_2H	2.2	82	*E* only
9	TFA	−0.25	47	1:3.2
10	TsOH	2.1	60	1:12.5
11	camphorsulfonic acid	1.5	74	1:6.3
12			23	1:2.7

*Evans' pK_a values in H_2O.

yield of **1c** was increased compared to that upon addition of IPA. Furthermore, while the IPA-catalyzed reaction was found to favor the *Z*-isomer, the HFIP-catalyzed reaction predominately formed the *E*-isomer. Phenol (PhOH), which has similar acidity to HFIP, catalyzed the reaction to afford **1c** in 56% yield, which is comparable to the HFIP-catalyzed reaction (55% yield); however, the *Z*-isomer was the major product (entries 2 and 4). Phenol derivatives possessing an electron-donating group (OMe) and an electron-withdrawing group (NO_2) produced **1c** in 48% (E/Z = 1:2.8) and 60% (E/Z = 3.1:1) yield, respectively (entries 3 and 5). Following the use of these alcohols as acid catalysts, several carboxylic acid derivatives were also tested; phenylacetic acid, benzoic acid, 2-nitrobenzoic acid, and trifluoroacetic acid (TFA) (entries 6−9). Except for TFA, these additives were found to improve the yield of **1c**, favoring complete *E*-stereoselectivity. In the case of sulfonic acids, *p*-toluenesulfonic acid (TsOH), and camphorsulfonic acid, *Z*-**1c** was isolated as the major product (entries 10 and 11). In the absence of an acid catalyst, the reaction still proceeded to afford **1c** in 23% yield with an E/Z ratio of 1:2.7 (entry 12). On the basis of the Brønsted acid screening, it is apparent that benzoic acid derivatives preferentially form *E*-**1c**, while sulfonic acids form *Z*-**1c** with synthetically useful selectivity.

In our previous reports on oxidative coupling reactions using propargyl alcohols, we demonstrated that the combination of copper salts and TEMPO induces the oxidation of propargyl alcohols, which leads to good yield in the subsequent Cu-catalyzed reaction.[11] Among copper−TEMPO-catalyzed oxidative reactions, the dealkynylation of propargyl alcohols occurs via hemiacetal intermediates, which are the common intermediates of the Meyer−Schuster rearrangement.[11b] Various copper salts were tested in order to suppress undesired dealkynylation and promote the desired Meyer−Schuster rearrangement of hemiaminals. The best yield of the desired product was achieved in the presence of CuOTf·benzene (see the Supporting Information). Phenylpropargyl alcohol **1a′** was subjected to a tandem reaction involving CuOTf·benzene-catalyzed oxidation followed by Brønsted acid catalyzed Meyer−Schuster reaction (Scheme 2). The reaction of **1a′** and **1b** in the presence of CuOTf·benzene and benzoic acid afforded exclusively *E*-**1c** in 41% yield. Conversely, when

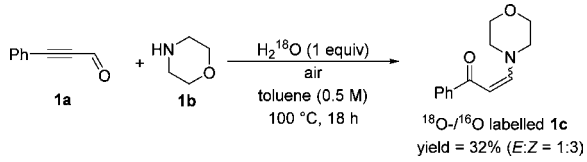
Scheme 2. Tandem Oxidation and Meyer−Schuster Rearrangement of 1a′



benzoic acid was replaced with TsOH, *Z*-**1c** was exclusively obtained in 51% yield. Compared to the reaction using aldehydes, this tandem approach using both copper and Brønsted acid catalysts still suffers from copper-catalyzed oxidation-dealkynylation alongside the desired copper-catalyzed oxidation−Meyer−Schuster rearrangement, resulting in decreased yields. Nevertheless, the stereoselectivity was controlled by Brønsted acids in a similar manner to the analogous reaction of aldehydes.

To probe the mechanism of the Brønsted acid catalyzed Meyer−Schuster reaction, an ^{18}O-labeling experiment was conducted using aldehyde **1a** (Scheme 3). The reaction of **1a**

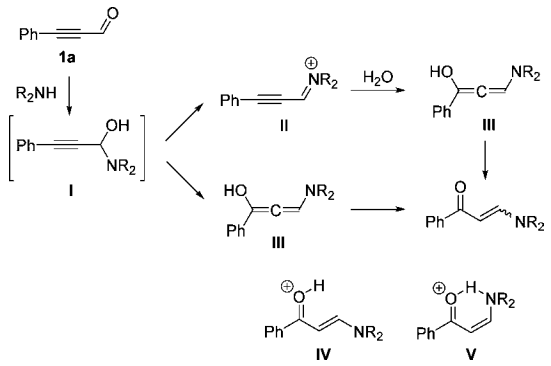
Scheme 3. ^{18}O-Labeling Experiment



and **1b** in the presence of $H_2{}^{18}O$ provided **1c** with the *Z*-isomer as the major product (E/Z = 1:3). In both *Z* and *E* isomers, more amounts of ^{16}O-labeled **1c** than ^{18}O-labeled **1c** were observed (see the Supporting Information).

In light of these ^{18}O-labeling experiments, the reaction mechanism is proposed in Scheme 4. Propargyl aldehyde **1a**

Scheme 4. Proposed Reaction Mechanism



undergoes an addition with an amine to afford hemiaminal **I**. This intermediate would be converted to allenol **III**, either through the complete dissociation of water or a 1,3-shift of the hydroxyl group across the triple bond. On the basis of ^{18}O-labeling experiments, while both routes occur, the 1,3-shift is slightly more favored. To elucidate E/Z isomer formation, independently synthesized *E* and *Z* isomers were re-exposed to Brønsted acidic conditions, as shown in Scheme 5. The ability of TsOH to promote the formation of *Z*-isomers was applied to the reaction of *E*-**1c**, resulting in no isomerization. The reaction of benzoic acid with *Z*-**1c** also showed no isomerization.

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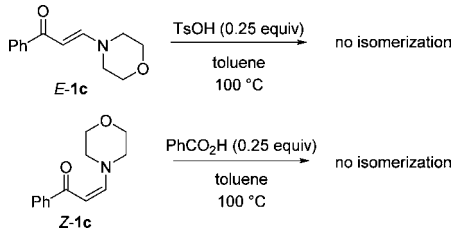
Scheme 5. Reactions of *E* and *Z* Isomers with Brønsted Acids



Accordingly, the stereochemistry of the β-enaminone products may be determined during the protonation of allenol **III**. The intramolecular hydrogen bonding of intermediate **V** results in *Z*-stereoselectivity, while *E*-isomers are formed via intermediate **IV**. The cationic intermediates **IV** and **V** are presumed to exist alongside a counteranion. Depending on the electrostatic interaction of the counter-anions with the corresponding cationic intermediates, the ratio between **IV** and **V** can be varied, resulting in a different ratio of *E*/*Z* products. Benzoates may bind tightly to the cation, which builds up the steric hindrance on the protonated carbonyl group to prevent intramolecular hydrogen bonding. Sulfonates may act as weakly bound anions to promote the intramolecular hydrogen bonding required for the formation of *Z*-products.[12] Because this reaction is conducted in a nonpolar solvent, toluene, electrostatic interactions play an important role in controlling the stereochemistry of the product.

Next, the scope of the reaction was examined (Figure 1). Substituted aromatic propargyl aldehydes were subjected to the

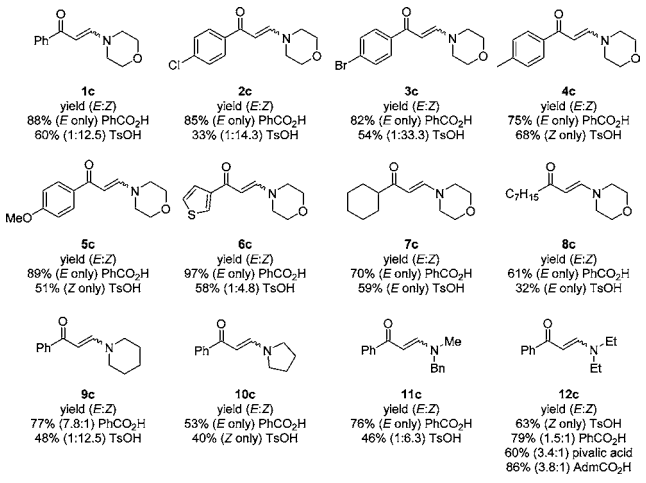


Figure 1. Substrate scope.

established Brønsted acid catalyzed Meyer−Schuster rearrangement conditions to afford β-enaminones **1c**−**6c** in good yields with high stereoselectivities. The benzoic acid catalyzed reaction favored the formation of *E* isomers in good yields, while the TsOH-catalyzed reaction provided the desired products in slightly lower yields with good *Z*-selectivity. In contrast, aliphatic propargyl aldehydes afforded **7c** and **8c** with *E*-selectivity, regardless of the Brønsted acid catalyst used. Following this, different amines were screened; piperidine, pyrrolidine, and *N*-benzylmethylamines showed a similar product distribution upon the addition of benzoic acid and TsOH (**9c**−**11c**). The reactions of diethylamine with propargyl aldehyde afforded *Z*-**12c** in the presence of TsOH and a mixture of *E* and *Z* isomers in the presence of benzoic acid (*E*:*Z* = 1.5:1). Applying bulky carboxylic acids, such as pivalic acid and adamantanecarboxylic acid ($AdmCO_2H$) increased the proprtion of *E*-**12c**. Presumably, the reaction of diethylamine favors the reaction via intermediate **V** to afford *Z*-**12c** (Scheme 4). However, the coordination of a bulky counteranion to the protonated carbonyl group switches the preferred stereochemistry to the *E*-isomer. According to these results for different substrates, the *E*/*Z* stereoselectivity of this reaction is mainly controlled by the Brønsted acids used, but the size of the amine and the electronic properties of the propargyl aldehyde also have an impact on electrostatic interaction and intramolecular hydrogen bonding.

In conclusion, we have presented the stereocontrolled Meyer−Schuster rearrangement of hemiaminals derived from propargyl aldehydes and amines, in which Brønsted acids increase the yield of the product and direct the stereochemistry of the resulting β-enaminones. A key factor controlling this stereochemistry is the intramolecular hydrogen bonding present in the protonated β-enaminone. Weak electrostatic interaction of the tosylate anion with the protonated β-enaminone promotes intramolecular hydrogen bonding to afford *Z*-isomers, while strong electrostatic interactions favors formation of the *E*-isomer. In addition to the effect caused by various Brønsted acids, the steric effect of the amine and the electronic properties of the propargyl aldehyde affected the intramolecular hydrogen bonding of the intermediates to produce a different distribution of *E*/*Z* products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03445.

Experimental procedures and spectra of **1c**−**12c**, copper salts screening results for Scheme 2, and the mass spectra of ^{18}O-/^{16}O-labeled **1c** (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected review articles on the Meyer−Schuster rearrangement, see: (a) Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429−438. (b) Engel, D. A.; Dudley, G. B. *Org. Biomol. Chem.* **2009**, *7*, 4149−4158. (c) Cadierno, V.; Crochet, P.; García-Garrido, S. E.;

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Org. Lett. 2016, 18, 272−275

Gimeno, J. *Dalton Trans.* **2010**, *39*, 4015−4031. (d) Zhu, Y.; Sun, L.; Lu, P.; Wang, Y. *ACS Catal.* **2014**, *4*, 1911−1925.

(2) For selected articles on the Au-catalyzed Meyer−Schuster rearrangement, see: (a) Engel, D. A.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 4027−4029. (b) Lee, S. I.; Baek, J. Y.; Sim, S. H.; Chung, Y. K. *Synthesis* **2007**, *2007*, 2107−2114. (c) Lopez, S. S.; Engel, D. A.; Dudley, G. B. *Synlett* **2007**, 949−953. (d) Marion, N.; Carlqvist, P.; Gealageas, R.; de Frémont, P.; Maseras, F.; Nolan, S. P. *Chem. - Eur. J.* **2007**, *13*, 6437−6451. (e) Egi, M.; Yamaguchi, Y.; Fujiwara, N.; Akai, S. *Org. Lett.* **2008**, *10*, 1867−1870. (f) Zhang, G.; Peng, Y.; Cui, L.; Zhang, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 3112−3115. (g) Ramón, R. S.; Marion, N.; Nolan, S. P. *Tetrahedron* **2009**, *65*, 1767−1773. (h) Ramón, R. S.; Gaillard, S.; Slawin, A. M. Z.; Porta, A.; D'Alfonso, A.; Zanoni, G.; Nolan, S. P. *Organometallics* **2010**, *29*, 3665−3668. (i) Pennell, M. N.; Unthank, M. G.; Turner, P.; Sheppard, T. D. *J. Org. Chem.* **2011**, *76*, 1479−1482. (j) Gómez-Suárez, A.; Oonishi, Y.; Meiries, S.; Nolan, S. P. *Organometallics* **2013**, *32*, 1106−1111. (k) Hansmann, M. M.; Hashmi, A. S. K.; Lautens, M. *Org. Lett.* **2013**, *15*, 3226−3229. (l) Kim, S. M.; Lee, D.; Hong, S. H. *Org. Lett.* **2014**, *16*, 6168−6171. (m) An, J.-H.; Yun, H.; Shin, S.; Shin, S. *Adv. Synth. Catal.* **2014**, *356*, 3749−3754. (n) Yu, Y.; Yang, W.; Pflästerer, D.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2014**, *53*, 1144−1147.

(3) For selected articles on Sc- and Bi-catalyzed Meyer_Schuster rearrangements, see: (a) Engel, D. A.; Lopez, S. S.; Dudley, G. B. *Tetrahedron* **2008**, *64*, 6988−6996. (b) Okamoto, N.; Sueda, T.; Yanada, R. *J. Org. Chem.* **2014**, *79*, 9854−9859.

(4) For the metal-free Meyer_Schuster rearrangement, see: Huang, X.; Jiao, N. *Org. Biomol. Chem.* **2014**, *12*, 4324−4328.

(5) (a) Collins, B. S. L.; Suero, M. G.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 5799−5802. (b) Xiong, Y.-P.; Wu, M.-Y.; Zhang, X.-Y.; Ma, C.-L.; Huang, L.; Zhao, L.-J.; Tan, B.; Liu, X.-Y. *Org. Lett.* **2014**, *16*, 1000−1003. (c) Chen, M.; Peng, J.; Mao, T.; Huang, J. *Org. Lett.* **2014**, *16*, 6286−6289.

(6) Shi, W.; Sun, S.; Wu, M.; Catano, B.; Li, W.; Wang, J.; Guo, H.; Xing, Y. *Tetrahedron Lett.* **2015**, *56*, 468−471.

(7) For review articles on enaminone synthesis, see: (a) Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277−294. (b) Elassar, A. A.; El-Khair, A. A. *Tetrahedron* **2003**, *59*, 8463−8480.

(8) For selected recent articles on enaminone synthesis, see: (a) Cacchi, S.; Fabrizi, G.; Filisti, E. *Org. Lett.* **2008**, *10*, 2629−2632. (b) Seki, H.; Georg, G. I. *J. Am. Chem. Soc.* **2010**, *132*, 15512−15513. (c) Koduri, N. D.; Scott, H.; Hileman, B.; Cox, J. D.; Coffin, M.; Glicksberg, L.; Hussaini, S. R. *Org. Lett.* **2012**, *14*, 440−443. (d) Xu, X.; Du, P.; Cheng, D.; Wang, H.; Li, X. *Chem. Commun.* **2012**, *48*, 1811−1813. (e) Yu, D.; Sum, Y. N.; Ean, A. C. C.; Chin, M. P.; Zhang, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 5125−5128.

(9) For selected recent articles on heterocyclic compound synthesis using enaminones, see: (a) Niphakis, M. J.; Turunen, B. J.; Georg, G. I. *J. Org. Chem.* **2010**, *75*, 6793−6805. (b) Lu, J.; Cai, X.; Hecht, S. M. *Org. Lett.* **2010**, *12*, 5189−5191. (c) Pettersson, B.; Hasimbegovic, V.; Bergman, J. *J. Org. Chem.* **2011**, *76*, 1554−1561. (d) Gayon, E.; Szymczyk, M.; Gérard, H.; Vrancken, E.; Campagne, J.-M. *J. Org. Chem.* **2012**, *77*, 9205−9220. (e) Xiang, D.; Xin, X.; Liu, X.; Zhang, R.; Yang, J.; Dong, D. *Org. Lett.* **2012**, *14*, 644−647. (f) Bezenšek, J.; Stare, K.; Svete, J.; Stanovnik, B. *Tetrahedron* **2012**, *68*, 516−522.

(10) For selected articles on the synthesis of natural products using enaminones, see: (a) Caplan, J. F.; Zheng, R.; Blanchard, J. S.; Vederas, J. C. *Org. Lett.* **2000**, *2*, 3857−3860. (b) Li, G.; Hsung, R. P.; Slafer, B. W.; Sagamanova, I. K. *Org. Lett.* **2008**, *10*, 4991. (c) Moreau, J.; Hubert, C.; Batany, J.; Toupet, L.; Roisnel, T.; Hurvois, J.-P.; Renaud, J.-L. *J. Org. Chem.* **2009**, *74*, 8963−8973. (d) Tsukanov, S. V.; Comins, D. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8626−8628. (e) Edwankar, R. V.; Edwankar, C. R.; Namjoshi, O. A.; Deschamps, J. R.; Cook, J. M. *J. Nat. Prod.* **2012**, *75*, 181−188.

(11) (a) Kang, Y.-W.; Choi, Y.-J.; Jang, H.-Y. *Org. Lett.* **2014**, *16*, 4842−4845. (b) Kang, Y.-W.; Cho, Y. J.; Ko, K.-Y.; Jang, H.-Y. *Catal. Sci. Technol.* **2015**, *5*, 3931−3934.

(12) (a) Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072−7080. (b) Kathmann, E. E.; White, L. A.; McCormick, C. L. *Macromolecules* **1996**, *29*, 5273−5278.

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Synthesis of *N*-Boc-Propargylic and Allylic Amines by Reaction of Organomagnesium Reagents with *N*-Boc-Aminals and Their Oxidation to *N*-Boc-Ketimines

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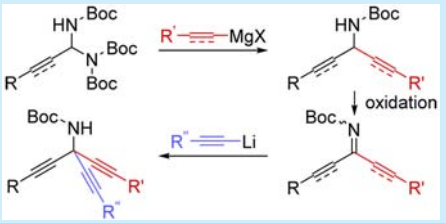
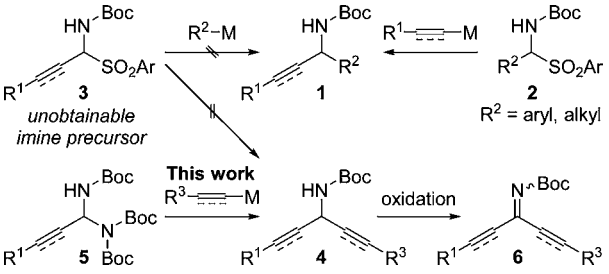
Supporting Information

ABSTRACT: Previously inaccessible *N*-Boc-protected propargylic and allylic amines were synthesized by the reaction between *N*-Boc-aminals and organomagnesium reagents through the in situ generated *N*-Boc-imine intermediates. The obtained *N*-Boc-propargylic amines could be readily converted into unprecedented *N*-Boc-ketimines by oxidation with manganese dioxide.



Propargylic and allylic amines represent an important class of versatile building blocks for the synthesis of nitrogen-containing organic compounds.[1] Among these, synthetically useful *N*-Boc-protected propargylic and allylic amines **1** are readily prepared from the nucleophilic addition of alkynyl and alkenyl metal reagents to *N*-Boc-imines, which can be generated from their precursors **2** upon treatment with bases including basic nucleophiles (Scheme 1).[2,3] However, this

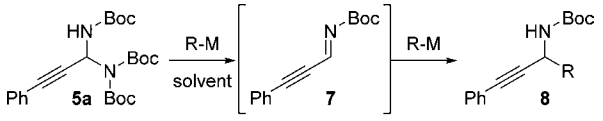
Scheme 1. Synthesis of *N*-Boc-Protected Propargylic and Allylic Amines



method is applicable to *N*-Boc-imines with *C*-aryl or *C*-alkyl groups, as most *N*-Boc-imine precursors **3** with a *C*-alkynyl or *C*-alkenyl group still remain unobtainable.[4] Accordingly, in the synthesis of *N*-Boc-protected propargylic and allylic amines **1**, alkynyl and alkenyl groups should be introduced as nucleophiles and not as part of electrophiles. Therefore, α-alkynyl and α-alkenyl-substituted *N*-Boc-propargylic and allylic amines **4** have not been synthesized to date.[5] Herein, we report the synthesis of previously inaccessible *N*-Boc-propargylic and allylic amines **4** via the reaction of *N*-Boc-aminals **5** with organomagnesium reagents and the subsequent oxidation to furnish unprecedented *N*-Boc-ketimines **6** that can be used for the generation of tetrasubstituted carbon centers.

We have previously reported that the treatment of *N*-Boc-protected aminals with an inorganic base can generate *N*-Boc-imines with various substituents on the imine carbon atom.[6] Based on these results, we initially examined the synthesis of *N*-Boc-propargylic amines via the in situ generated *N*-Boc-imine **7** from the reaction of *N*-Boc-aminal **5a** with organometallic bases and nucleophiles (Scheme 2). When butyllithium was

Scheme 2. Reactions of *N*-Boc-Aminal 5a with Organometallic Reagents



BuLi, THF-hexane, −78 °C, 15 min **8a** (R = Bu) 25%
MeMgBr, THF, −20 °C, 20 min **8b** (R = Me) 93%
Et_2Zn, CH_2Cl_2-hexane, 0 °C, 1 h **8c** (R = Et) 88%

employed at −78 °C, *N*-Boc-aminal **5a** was consumed immediately. However, the desired addition product **8a** (R = Bu) was obtained in low yield, probably due to the presence of multiple reaction sites in **5a** and **7**. Indeed, cleavage of the Boc group was observed for **5a**. Conversely, treatment of **5a** with methylmagnesium bromide at −20 °C afforded the desired adduct **8b** (R = Me) cleanly.[7] Furthermore, diethylzinc could also be used for the synthesis of propargylic amine **8c** (R = Et). Consequently, we chose the readily available organomagnesium reagents as nucleophiles for further investigations into the scope of this reaction.

Initially, *N*-Boc-aminals **5** with *C*-alkynyl and *C*-alkenyl groups were treated with alkynyl and alkenylmagnesium halides in THF at −20 °C (Table 1). The desired 1,2-addition to the resulting *N*-Boc-imines proceeded exclusively and furnished unprecedented *N*-Boc-propargylic and allylic amines **4** in good yields, while possible 1,4-adducts were not observed. The

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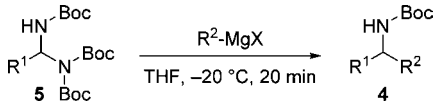
Table 1. Synthesis of α-Alkynyl and α-Alkenyl-Substituted *N*-Boc-Propargylic and Allylic Amines 4[a]



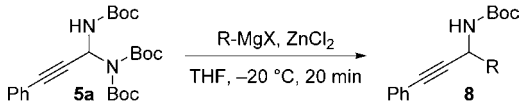
entry	R^1	R^2-MgX	(equiv)	yield (%)[b]	
1[c]	Ph—≡—ξ	Bu—≡—MgCl	3.3	**4a**	78
2		Cy—≡—MgCl	3.3	**4b**	64
3		Ph—≡—MgBr	4.4	**4c**	82
4		$(EtO)_2C$—≡—MgCl	3.3	**4d**	74
5		TMS—≡—MgCl	3.3	**4e**	81
6[d]		MgBr	2.2	**4f**	90
7		MgBr	2.2	**4g**	81
8	Pent—≡—ξ	TMS—≡—MgCl	4.4	**4h**	75
9		MgBr	2.2	**4i**	99
10[e]	Ph	Ph—≡—MgBr	6.6	**4j**	84
11[f]		TMS—≡—MgCl	6.6	**4k**	85
12[f]		MgBr	2.2	**4l**	82
13[g]	Ph	Ph—≡—MgBr	6.6	**4m**	84
14[g]		TMS—≡—MgCl	6.6	**4n**	71
15[g]		MgBr	2.2	**4o**	90

[a]The reaction between **5** (0.05 mmol) and the corresponding organomagnesium reagent (0.11−0.33 mmol) was carried out in THF (0.5 mL) at −20 °C. [b]Isolated yield. [c]Performed on a 2.2 mmol scale. [d]Performed on a 1.0 mmol scale. [e]*Cis*/*trans* = 15/1. [f]*Cis*/*trans* = >20/1. [g]*Cis*/*trans* = 1/>20.

reactions of *N*-Boc-imine intermediates containing a *C*-alkenyl group afforded the corresponding *cis*/*trans* isomerized product in only trace amounts (entries 10−15).

We then investigated the scope of this method by examining a variety of alkyl and arylmagnesium reagents (Table 2). While the reaction of **5a** with linear alkylmagnesium reagents afforded the desired adducts **8a** (R = Bu) and **8b** (R = Me) in good yields (entries 1 and 2), the use of isopropylmagnesium chloride resulted in the generation of **8d** (R = *i*-Pr) in low yield on account of the undesired reduction of the *N*-Boc-imine intermediate (entry 3). Interestingly, the addition of zinc chloride proved to be effective in suppressing this side reaction, leading to a significantly increased yield (entry 4).[8] Positive effects of zinc chloride were also observed in the reaction of allylmagnesium chloride (entry 6 vs 7). Aromatic and heteroaromatic magnesium reagents also furnished *N*-Boc-propargylic amines **8g** (R = Ph) and **8h** (R = 2-furyl) in good yields (entries 8 and 9).

Table 2. Synthesis of Various *N*-Boc-Propargylic Amines 8[a]

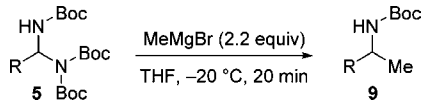


entry	R-MgX	(equiv)	$ZnCl_2$ (equiv)	yield (%)[b]	
1	Bu-MgCl	2.2	0	**8a**	70
2	Me-MgBr	2.2	0	**8b**	93
3	*i*-Pr-MgCl	3.3	0	**8d**	19
4	*i*-Pr-MgCl	3.3	1.1	**8d**	93
5	*t*-Bu-MgCl	4.4	1.5	**8e**	69
6	Allyl-MgCl	3.3	0	**8f**	19
7[c]	Allyl-MgCl	3.3	1.1	**8f**	78
8	Ph-MgBr	2.2	0	**8g**	93
9	2-Furyl-MgBr	3.3	0	**8h**	89

[a]The reaction between **5a** (0.05 mmol) and the corresponding organomagnesium reagent (0.11−0.22 mmol) was carried out in the presence of $ZnCl_2$ (0−0.08 mmol) in THF (0.5 mL) at −20 °C. [b]Isolated yield. [c]*t* = 40 min.

The present method was found to be applicable to a wide variety of *N*-Boc-aminals (Table 3). The in situ generated *N*-Boc-imine intermediate from an *N*-Boc-aminal with a 1-heptynyl group contains an acidic proton at the γ-position, and its deprotonation under basic conditions seems to be a possible side reaction. However, even with highly basic methylmagnesium bromide, the desired adduct **9a** (R = 1-heptynyl) was obtained in good yield (entry 1). The addition of methylmagnesium bromide to an *N*-Boc-aminal carrying a 2-phenylethyl group proceeded in preference to the deprotonation of the α-proton of the in situ generated *N*-Boc-imine intermediate (entry 4). The use of a phenyl-substituted *N*-Boc-aminal afforded adduct **9e** (R = Ph) in high yield (entry 5), and the reaction of Cbz-protected aminal **10** with methylmagnesium bromide furnished Cbz-protected propargylic amine **11** in good yield (Scheme 3).

Table 3. Synthesis of *N*-Boc-Amines 9 Having Various α-Substituents[a]



entry	R		yield (%)[b]	entry	R		yield (%)[b]
1	Pent—≡—ξ	**9a**	83	4	Ph—ξ	**9d**	94
2[c]	Ph	**9b**	92	5	Ph-ξ	**9e**	99
3[d]	Ph—ξ	**9c**	85				

[a]The reaction between **5** (0.05 mmol) and the corrsponding organomagnesium reagent (0.11 mmol) was carried out in THF (0.5 mL) at −20 °C. [b]Isolated yield. [c]*Cis*/*trans* = >20/1. [d]*Cis*/*trans* = 1/>20.

The obtained α-vinyl-substituted *N*-Boc-propargylic amine **4f** could be converted into *N*-Boc-protected 1,2-aminoalcohol **12** in good yield by an ozonolysis and a subsequent reduction with $NaBH_4$ (Scheme 4). In this transformation, the vinyl group reacted with ozone selectively, despite the presence of the phenylethynyl group.[9]

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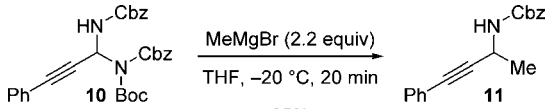
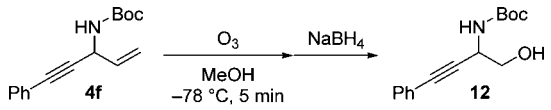
Scheme 3. Reaction of *N*-Cbz-Aminal 10 with Methylmagnesium Bromide

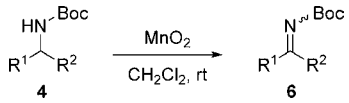


Scheme 4. Synthesis of *N*-Boc-1,2-Aminoalcohol 12



N-Boc-protected ketimines are valuable prochiral electrophiles to produce *N*-Boc-protected chiral α-tertiary amines.[10] To the best of our knowledge, however, available *N*-Boc-ketimines have been limited to those substituted with aryl or electron-withdrawing groups.[11] In the course of the present study on *N*-Boc-protected imines, we became interested in developing an efficient method for the synthesis of novel *N*-Boc-ketimines. We found that the oxidation of α-alkynyl and alkenyl-substituted *N*-Boc-propargylic amines **4** with manganese dioxide afforded unprecedented *N*-Boc-protected dialkynyl ketimines and alkenyl alkynyl ketimines **6** in good yields (Table 4).[12,13] While *N*-Boc-dialkynyl ketimines were obtained

Table 4. Oxidation of *N*-Boc-Propargylic Amines 4 To Furnish *N*-Boc-ketimines 6[a]



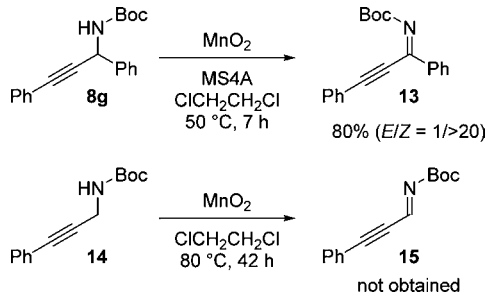
entry	R^1	R^2	time (h)		yield (%)[b]
1[c,d]	Ph—	Bu—	11	**6a**	93
2		Ph—	23	**6b**	99
3		TMS—	14	**6c**	75
4[e,d,f]		Ph	3	**6d**	81
5[g]	Pent—	TMS—	14	**6e**	85

[a]The reaction between **4** (0.05 mmol) and manganese dioxide (1.0 mmol) was carried out in dichloromethane (0.5 mL) at room temperature. [b]Isolated yield. [c]Performed in 1,2-dichloroethane at 50 °C. [d]Performed on a 1.0 mmol scale. [e]*E*/*Z* = 1/>20. [f]*Cis*/*trans* = 1/>20. [g]Performed in 1,2-dichloroethane at 80 °C.

as a 1:1 mixture of *E*- and *Z*-isomers (entries 1–3 and 5), *Z*-ketimine **6d** was formed exclusively in the case of an *N*-Boc-alkenyl alkynyl ketimine (entry 4), and a *cis*/*trans* isomerization of the styryl group was not observed (entry 4).[14]

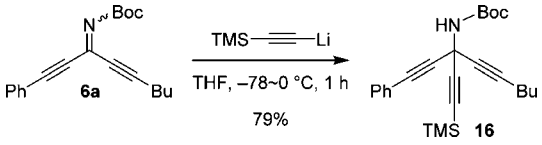
While oxidation of *N*-Boc-protected α-phenylpropargylic amine **8g** with manganese dioxide afforded the corresponding *N*-Boc-ketimine **13** exclusively as the *Z*-isomer in good yield,[11q] the reaction of the non-α-substituted *N*-Boc-propargylic amine **14** did not yield the desired *N*-Boc-aldimine **15**, even at higher temperature (Scheme 5). These results suggested that the presence of an alkynyl, alkenyl, or aryl substituent is necessary at the α-position for the oxidation to proceed.

Scheme 5. Effects of the α-Substituent in *N*-Boc-Propargylic Amines on the Oxidation To Give *N*-Boc-Imines



Treatment of the obtained dialkynyl imine **6a** with lithium trimethylsilylacetylide resulted in the formation of the *N*-Boc-protected tris(alkynyl)methylamine **16** with three different terminal substituents (Scheme 6).[15] The Boc group was cleanly deprotected by treatment with trimethylsilyl iodide in acetonitrile (see Supporting Information).

Scheme 6. Synthesis of *N*-Boc-Tris(alkynyl)methylamine 16



In summary, we have synthesized *N*-Boc-protected propargylic and allylic amines via the reaction between *N*-Boc-aminals and organomagnesium reagents, in which *N*-Boc-imines are generated as reactive intermediates under basic conditions and are subsequently subjected to an addition reaction. This process allows direct synthetic access to unprecedented α-alkynyl and α-alkenyl-substituted *N*-Boc-propargylic and allylic amines in an operationally simple process. The obtained *N*-Boc-propargylic and allylic amines are readily oxidized by manganese dioxide to afford previously unobtainable ketimines. Accordingly, this method represents a rare example for the oxidation of *N*-Boc-amines to *N*-Boc-ketimines. We are currently exploring applications of the newly obtained *N*-Boc-ketimines in other transformations including catalytic asymmetric reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03446.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For representative reviews on the synthesis of propargylic and allylic amines, see: (a) Zani, L.; Bolm, C. *Chem. Commun.* **2006**, 4263. (b) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963. (c) Tejedor, D.; López-Tosco, S.; Cruz-Acosta, F.; Méndez-Abt, G.; García-Tellado, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 2090. (d) Skucas, E.; Ngai, M.-Y.; Komanduri, V.; Krische, M. J. *Acc. Chem. Res.* **2007**, *40*, 1394. (e) Skoda, E. M.; Davis, G. C.; Wipf, P. *Org. Process Res. Dev.* **2012**, *16*, 26.

(2) Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970.

(3) (a) Zhang, J.; Wei, C.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 5731. (b) Lee, E.-S.; Yeom, H.-S.; Hwang, J.-H.; Shin, S. *Eur. J. Org. Chem.* **2007**, *2007*, 3503. (c) Blay, G.; Brines, A.; Monleón, A.; Pedro, J. R. *Chem. - Eur. J.* **2012**, *18*, 2440. (d) Trost, B. M.; Hung, C.-I; Koester, D. C.; Miller, Y. *Org. Lett.* **2015**, *17*, 3778.

(4) An *N*-Boc-imine with an *E*-styryl group has previously been reported: (a) Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4564. (b) Kano, T.; Sakamoto, R.; Akakura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2012**, *134*, 7516.

(5) For selected reviews on related syntheses of propargylic and allylic amines, see: (a) Gommermann, N.; Koradin, C.; Knochel, P. *Synthesis* **2002**, *2002*, 2143. (b) Korbad, B. L.; Lee, S.-H. *Eur. J. Org. Chem.* **2014**, *2014*, 5089.

(6) Kano, T.; Kobayashi, R.; Maruoka, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 8471.

(7) No reaction, even at room temperature, was observed when an *N*,*N*′-bis(Boc)-protected aminal was used instead of *N*,*N*,*N*′-tris(Boc)-protected aminal **5a**.

(8) (a) Hatano, M.; Yamashita, K.; Mizuno, M.; Ito, O.; Ishihara, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 2707. (b) Hatano, M.; Yamashita, K.; Ishihara, K. *Org. Lett.* **2015**, *17*, 2412.

(9) McCurry, P. M., Jr.; Abe, K. *Tetrahedron Lett.* **1974**, *15*, 1387.

(10) For recent reviews, see: (a) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873. (b) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, *2007*, 5969. (c) Connon, S. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1176. (d) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853. (e) Kumagai, N.; Shibasaki, M. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 503.

(11) (a) Boyer, J. H.; Fu, P. P. *J. Org. Chem.* **1972**, *37*, 3556. (b) Jung, M. E.; Shishido, K.; Light, L.; Davis, L. *Tetrahedron Lett.* **1981**, *22*, 4607. (c) Kupfer, R.; Meier, S.; Würthwein, E.-U. *Synthesis* **1984**, *1984*, 688. (d) Trione, C.; Toledo, L. M.; Kuduk, S. D.; Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1993**, *58*, 2075. (e) Dessipri, E.; Tirrell, D. A. *Macromolecules* **1994**, *27*, 5463. (f) Moldenhauer, J.-P.; Möller, M. H.; Rodewald, U.; Würthwein, E.-U. *Liebigs Ann.* **1995**, *1995*, 1015. (g) Osipov, N. S.; Golubev, A. S.; Sewald, N.; Michel, T.; Kolomiets, A. F.; Fokin, A. V.; Burger, K. *J. Org. Chem.* **1996**, *61*, 7521. (h) Calí, P.; Begtrup, M. *Synthesis* **2002**, *2002*, 63. (i) Armstrong, A.; Edmonds, I. D.; Swarbrick, M. E.; Treweeke, N. R. *Tetrahedron* **2005**, *61*, 8423. (j) Jorgensen, C. G.; Clausen, R. P.; Hansen, K. B.; Brauner-Osborne, H.; Nielsen, B.; Metzler, B. B.; Kehler, J.; Krogsgaard-Larsen, P.; Madsen, U. *Org. Biomol. Chem.* **2007**, *5*, 848. (k) Mikami, K.; Murase, T.; Zhai, L.; Kawauchi, S.; Itoh, Y.; Ito, S. *Tetrahedron Lett.* **2010**, *51*, 1371. (l) Hashimoto, T.; Yamamoto, K.; Maruoka, K. *Chem. Lett.* **2011**, *40*, 326. (m) Qian, Y.; Jing, C.; Zhai, C.; Hu, W.-h. *Adv. Synth. Catal.* **2012**, *354*, 301. (n) Yan, W. J.; Wang, D.; Feng, J. C.; Li, P.; Zhao, D. P.; Wang, R. *Org. Lett.* **2012**, *14*, 2512. (o) Sankar, M. G.; Garcia-Castro, M.; Wang, Y.; Kumar, K. *Asian J. Org. Chem.* **2013**, *2*, 646. (p) Han, J.; Jeon, M.; Pak, H. K.; Rhee, Y. H.; Park, J. *Adv. Synth. Catal.* **2014**, *356*, 2769. (q) Trost, B. M.; Biannic, B. *Org. Lett.* **2015**, *17*, 1433. (r) Wang, D.-L.; Liang, Z.-Q.; Chen, K.-Q.; Sun, D.-Q.; Ye, S. *J. Org. Chem.* **2015**, *80*, 5900.

(12) For reviews on the oxidation of *N*-carbamate-protected amines to ketimines, see: (a) Buchi, G.; Botkin, J. H.; Lee, G. C. M.; Yakushijin, K. *J. Am. Chem. Soc.* **1985**, *107*, 5555. (b) Matsuo, J.; Tanaki, Y.; Kido, A.; Ishibashi, H. *Chem. Commun.* **2006**, 2896 and references cited therein.10.1039/b605882e

(13) For reviews on the synthesis of dialkynyl ketimines, see: (a) Ito, Y.; Inouye, M.; Murakami, M. *Tetrahedron Lett.* **1988**, *29*, 5379. (b) Ito, Y.; Inouye, M.; Murakami, M. *Chem. Lett.* **1989**, 1261.

(14) The oxidation of *N*-Boc-propargylic amine **4j** with manganese dioxide afforded the *N*-Boc-protected phenylethynyl *cis*-styryl imine, which readily underwent *cis*/*trans* isomerization of the styryl group to give *trans*-isomer **6d** as a major stereoisomer at room temperature.

(15) Convertino, V.; Manini, P.; Schweizer, W. B.; Diederich, F. *Org. Biomol. Chem.* **2006**, *4*, 1206.

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Organic LETTERS

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Metal-Free Three-Component Domino Approach to Phosphonylated Triazolines and Triazoles

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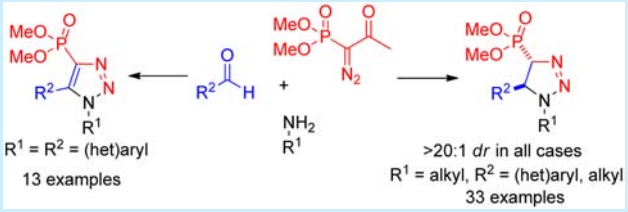
Supporting Information

ABSTRACT: An efficient, three-component domino reaction between aldehydes, amines, and the Bestmann−Ohira reagent is reported that enables a general, mild, and straightforward access to 1,4,5-trisubstituted 1,2,3-triazolines and triazoles. The reaction proceeds through a domino-condensation/1,3-dipolar cycloaddition sequence to afford the triazoline derivatives with excellent diastereoselectivity. Moreover, when both amine and aldehyde employed for this reaction are aromatic, a spontaneous oxidation afforded 1,4,5-trisubstituted triazoles in moderate yields.



1,4,5-Trisubstituted triazolines are an important class of heterocycle which in addition to their exceptional biological profiles[1] serve as versatile precursors to important compounds such as aziridines,[2] triazoles,[3] and β-amino alcohols (Figure 1).[4]

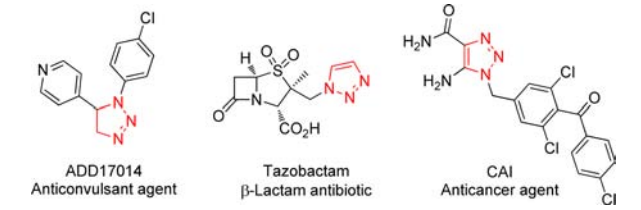


Figure 1. Selected examples for bioactive triazoline and triazole derivatives.

The most direct and common method for the synthesis of substituted triazolines is through the 1,3-dipolar cycloaddition reaction of azides with activated olefins (Figure 2, eq 1).[5]

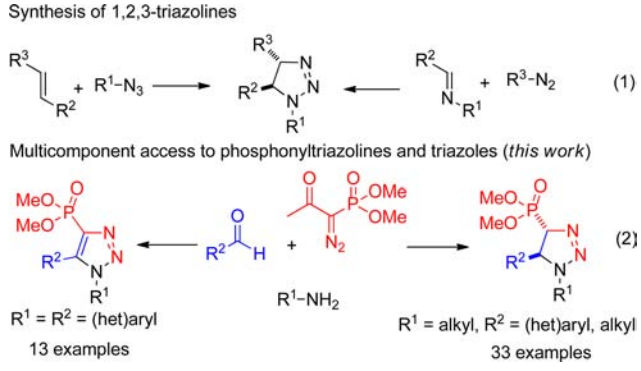


Figure 2. Synthesis of 1,4,5-trisubstituted triazolines.

However, this approach is effective only for the activated olefins, limiting the applications of this method to a few useful examples. An alternative process that relies on the cycloaddition reactions of various diazo compounds with preformed Schiff bases is also in use to achieve the synthesis of triazolines.[6] Despite the fact that these reactions are well-established, most such reactions exhibit a narrow substrate scope and require elevated temperature or catalysts, preventing the use of these methods in chemical biology. In this respect, novel protocols for the mild, efficient, cost-effective, and stereoselective synthesis of triazolines are highly desirable.

The ready availability, mild reaction conditions, and high functional group tolerance make dimethyl α-diazo-β-oxopropylphosphonate (Bestmann−Ohira reagent, BOR) a frequently used reagent for the synthesis of homologated alkynes from aldehydes bearing fragile functional groups.[7] Later, notable reports by Namboothiri and Smietana, as well as recent advances, have shown that the dimethyl (diazomethyl)phosphonate anion (DAMP) generated in situ from BOR could be employed as a versatile 1,3-dipole for the synthesis of phosphonylpyrazoles.[8−10] However, to the best of our knowledge, the application of BOR in the synthesis of heterocyclic compounds remains limited to the synthesis of phosphonylpyrazoles. The relevance of triazolines and triazoles as key structural constituents of numerous biologically active compounds inspired us to investigate further the utility of BOR in devising novel protocols for accessing this particular class of compound (Figure 1). We speculated that if an in situ generated Schiff base was treated with BOR, it would undergo a dipolar cycloaddition reaction to generate the triazoline molecule. For this strategy to be successful, Schiff base formation and the subsequent cyclization would have to be

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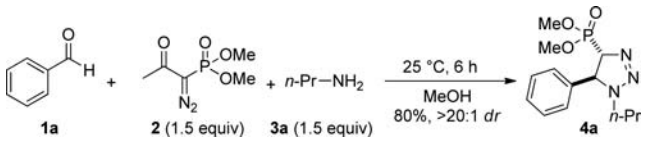
faster than the undesired aldehyde homologation by in situ generated DAMP anion from BOR. Our hypothesis was successfully realized herein, demonstrating for the first time that BOR can be employed in a domino multicomponent reaction involving aldehydes and amines for the diastereoselective synthesis of 1,4,5-trisubstituted 1,2,3-triazolines (Figure 2, eq 2). Of note, this reaction proceeds through *trans*-selective cyclization with respect to 5-aryl/alkyl substitution and phosphonate. Notably, the phosphonyltriazolines are stable and the conversion to aziridines through denitrogenation has not been observed under the present reaction conditions. Furthermore, an attempt to expand the scope of the reaction revealed that phosphonyltriazoles could be synthesized if arylamines are employed in the reaction instead of aliphatic ones.

Our hypothesis was initially tested by performing a reaction between benzaldehyde **1a**, *n*-propylamine **3a**, and BOR **2** in the presence of potassium carbonate in methanol, and pleasingly, the reaction afforded 4-phosphonyltriazoline **4a** in 80% yield with excellent diastereoselectivity. Upon further optimization of the reaction conditions, the diastereoselective formation of 1,2,3-triazolines was achieved without the aid of a base and desiccant with the same yield, and these optimized conditions were selected for further studies (Scheme 1).

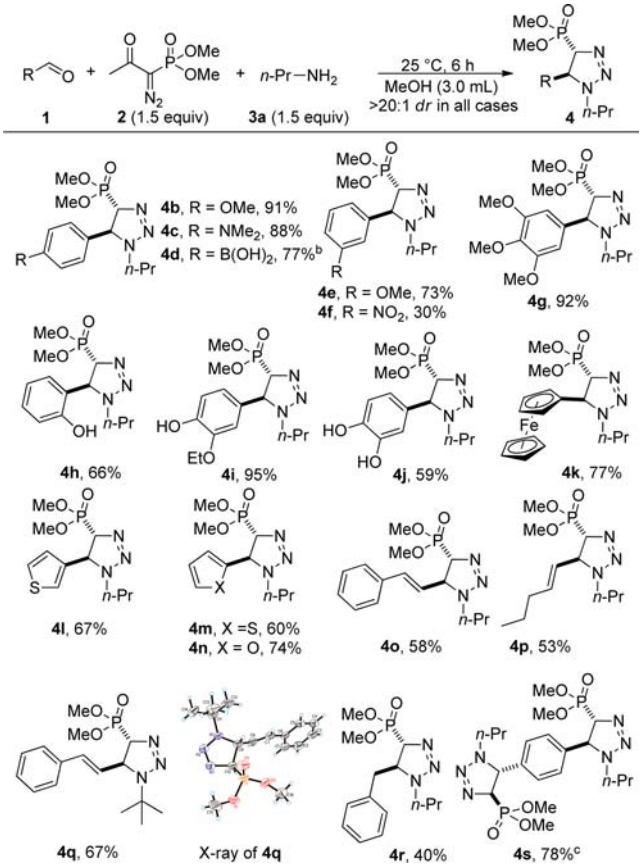
Scheme 1. Synthesis of 1,2,3-Triazolines



Having identified the conditions for the synthesis of triazolines, we next examined the scope of this facile three-component reaction. *n*-Propylamine **3a** was selected as the amine participant to validate the scope of the aldehyde moiety (Scheme 2). Interestingly, electron-neutral and electron-releasing substituents at the 4-position of the aromatic aldehyde were found to be equally efficient and did not influence the efficiency of the present domino reaction (**4b–d**), while electron-withdrawing substituents such as nitro- and trifluoromethyl groups failed to deliver the product. Importantly, a boronic acid moiety was demonstrated to be compatible with the reaction, and triazoline **4d** was obtained in 77% yield. Subsequently, various aldehydes having electronically different substituents at different positions were reacted with propylamine in the presence of BOR and proven to be effective (**4e–g**). A variety of hydroxyaryl aldehydes were tolerated and provided the triazolines in good yields (**4h–j**). The reaction attempted with ferrocenecarboxaldehyde also worked well (**4k**). When aryl aldehydes were replaced by heteroaryl and aliphatic aldehydes, the reaction proceeded smoothly leading to the formation of the corresponding triazolines, albeit in moderate yields (**4l–q**). For instance, cinnamaldehyde underwent facile reaction with *tert*-butylamine to afford the product **4q** in 67% yield, and the structure of **4q** was confirmed by X-ray diffraction analysis.[11] Notably, the reaction carried out using terephthalaldehyde afforded the anticipated bis-triazoline **4s** in 78% yield.

Scheme 3 illustrates the scope of the amine component in the reaction. The reaction was found to be high yielding in most cases where linear aliphatic amines were used (**4t–w**). Besides linear amines, *tert*-butyl- and allylamines afforded the triazoline derivatives in good yields (**4x,y**). The reaction proceeded well

Scheme 2. Substrate Scope for the Multicomponent Reaction: Variation of Aldehydes[a]



[a]Yields given are isolated after SiO_2 column chromatographic purification. [b]2.5 equiv of **3a** was used. [c]With 4.0 equiv of each **2** and **3a**.

with isopropyl and benzylamine yielding the triazoline derivatives in moderate yields (**4z,aa**). Phenethyl-, cyclohexyl-, and adamantylamines were also suitable partners for the reaction, affording the products in good yields (**4ab–ad**). Interestingly, the reaction was feasible with amines bearing additional functional groups, and the reaction was tolerant of functional groups such as hydroxyl and disubstituted amines. The reaction was also explored using various substituted aliphatic amines such as diethylaminoethylamine and morpholinopropylamine (**4af,ag**).

The broad substrate scope exhibited by the reaction prompted us to explore the possibility of using aromatic amines, and surprisingly, the reaction involving aniline, benzaldehyde, and BOR led to the formation of phosphonyltriazole (Figure 2, eq 2). Presumably, the initially formed triazoline derivative undergoes a spontaneous air oxidation to afford triazoles, constituting an efficient, single-step protocol for synthesizing densely functionalized triazoles from readily available starting materials. This multicomponent strategy provides an efficient alternative to the metal- and organocatalyzed cycloaddition reactions for the synthesis of substituted triazoles.[12,13] In view of the extensive applications of 1,4,5-trisubstituted 1,2,3-triazoles in the pharmaceutical industry as HIV protease inhibitors, anticancer drugs, antituberculosis drugs, antifungal agents, anticancer drugs, and antibacterial drugs, this metal-free synthesis of triazole was further investigated for better reaction conditions.[14] Further

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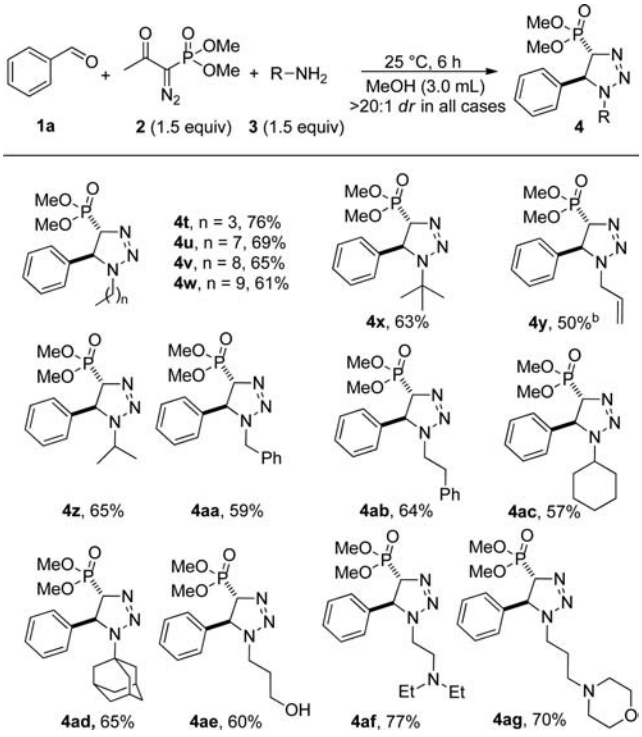
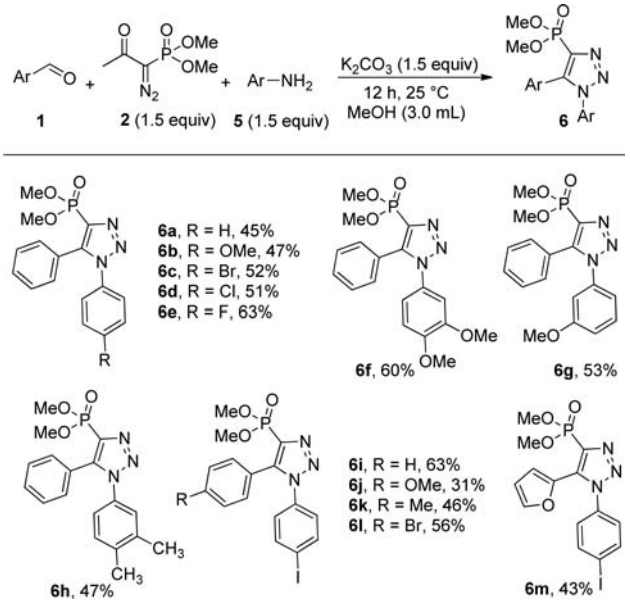
Scheme 3. Substrate Scope for the Multicomponent Reaction: Variation of Amines[a]



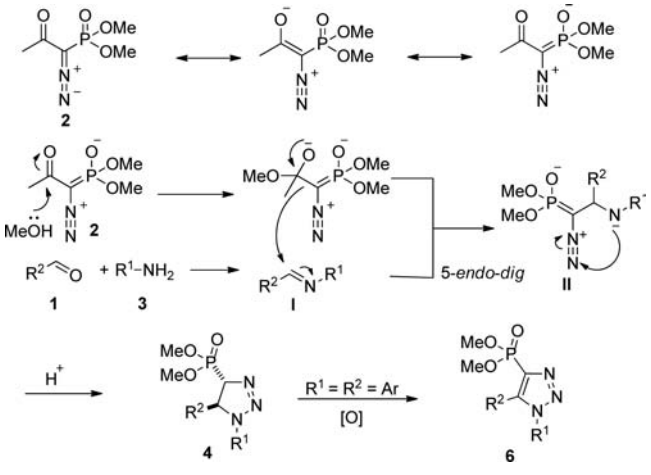
[a]Yields given are of isolated products after SiO_2 column chromatographic purification. [b]2.0 equiv of K_2CO_3 was used.

Scheme 4. Substrate Scope for the Multicomponent Reaction: Synthesis of Triazoles[a]



[a]Yields given are of isolated products after SiO_2 column chromatographic purification.

Scheme 5. Proposed Mechanistic Pathway



development of the reaction revealed the need for a mild organic/inorganic base in a stoichiometric amount to deliver the triazole derivative in a reasonable yield. This observation may be attributed to the lower basicity of aromatic amines in comparison to aliphatic amines, and a brief screening of various bases showed that K_2CO_3 provided the product **6a** in 45% yield.

Subsequent to the optimization of the reaction conditions, we next explored the generality of this unique strategy for triazole synthesis (Scheme 4). The reaction proceeded well with a series of anilines bearing diverse substitutions at the 4-position of the arene ring, and the corresponding triazole derivatives were isolated in modest yields (**6a−e**). Notably, the reaction worked well with 3- and 3,4-disubstituted anilines to generate the corresponding triazoles in good yields (**6f−h**). Next, aldehyde scope was examined for the reaction using 4-iodoaniline as the amine substrate, and electronically different substituents have barely shown any influence on the outcome of the reaction. For instance, substrates with electron-rich and electron-withdrawing substitutions at the 4-position of the aryl ring furnished the synthetically useful iodoaryltriazoles in reasonable yield (**6i−l**). Remarkably, the reaction attempted with furfural was effective, and the product was obtained in 43% yield (**6m**). The reactions attempted with aliphatic aldehydes were unsuccessful.

In accordance with the previous reports on the synthesis of phosphonylpyrazoles, a mechanistic rationale for this domino-multicomponent synthesis of triazolines and triazoles is proposed as shown in Scheme 5. The reaction is likely to be initiated by in situ generation of Schiff base **I**. Next, dimethyl diazomethylphosphonate (DAMP) anion generated in situ from BOR undergoes nucleophilic addition to the intermediate **I**. The resulting intermediate **II** would subsequently undergo a 5-*endo-dig* cyclization to afford the product **4**. When amine and aldehyde moieties are aromatic, product **4** further undergoes a spontaneous air-assisted oxidative aromatization to provide triazole derivatives **6**.

In summary, a metal-free, efficient, facile, and simple three-component synthesis of 1,4,5-trisubstituted triazolines and triazoles has been developed. The reaction proceeds under mild conditions (room temperature and no catalyst/base) and employs inexpensive and readily available aldehydes, amines, and BOR, making this strategy a versatile and unique method for accessing a novel class of phosphonylated triazolines and triazoles with consistently high efficiency in the former case. Given the relevance of these heterocyclic scaffolds in the agrochemical and pharmaceutical industries, we anticipate that this new method for the synthesis of phosphonyltriazoles will find potential applicability.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03437.

X-ray data for **4q** (CIF)

Detailed experimental procedures, complete characterization data, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated with best regards to Dr. Vijay Nair on the occasion of his 75th birthday.

■ REFERENCES

(1) (a) Dürüst, Y.; Karakus, H.; Kaiser, M.; Tasdemir, D. *Eur. J. Med. Chem.* **2012**, *48*, 296. (b) Kadaba, P. K.; Dixit, T. *Curr. Med. Chem.* **2003**, *10*, 2109. (c) Kadaba, P. K. *Biomed. Pharmacother.* **1996**, *50*, 163. (d) Kadaba, P. K. *Drugs Future* **1990**, *15*, 1013. (e) Kadaba, P. K. *J. Med. Chem.* **1988**, *31*, 196. (f) Kadaba, P. K.; Slevin, J. T. *Epilepsia* **1988**, *29*, 330.

(2) (a) Chung, T. S.; Lopez, S. A.; Houk, K. N.; Garcia-Garibay, M. A. *Org. Lett.* **2015**, *17*, 4568. (b) de Loera, D.; Stopin, A.; Garcia-Garibay, M. A. *J. Am. Chem. Soc.* **2013**, *135*, 6626. (c) de Loera, D.; Garcia-Garibay, M. A. *Org. Lett.* **2012**, *14*, 3874. (d) Troyer, T. L.; Muchalski, H.; Hong, K. B.; Johnston, J. N. *Org. Lett.* **2011**, *13*, 1790. (e) Hong, K. B.; Donahue, M. G.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 2323. (f) Röper, S.; Franz, M. H.; Wartchow, R.; Hoffmann, H. M. R. *Org. Lett.* **2003**, *5*, 2773. (g) Pocar, D.; Trimarco, P.; Bombieri, G. *J. Heterocycl. Chem.* **1998**, *35*, 687. (h) Hansen, P. E.; Undheim, K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 305. (i) Broeckx, W.; Overbergh, N.; Samyn, C.; Smets, G.; L'Abbe, G. *Tetrahedron* **1971**, *27*, 3527.

(3) (a) Baskar, B.; Wittstein, K.; Sankar, M. G.; Khedkar, V.; Schürmann, M.; Kumar, K. *Org. Lett.* **2012**, *14*, 5924. (b) Zeghada, S.; Bentabed-Ababsa, G.; Derdour, A.; Abdelmounim, S.; Domingo, L. R.; Sáez, J. A.; Roisnel, T.; Nassar, E.; Mongin, F. *Org. Biomol. Chem.* **2011**, *9*, 4295. (c) Kadaba, P. K.; Edelstein, S. B. *J. Org. Chem.* **1990**, *55*, 5891.

(4) Scheiner, P. In *Triazoline Decomposition In Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1970; Vol. *1*, p 327.

(5) (a) Hemming, K.; Chambers, C. S.; Jamshaid, F.; O'Gorman, P. A. *Molecules* **2014**, *19*, 16737. (b) Bodnar, B. S.; Miller, M. J. *J. Org. Chem.* **2007**, *72*, 3929. (c) Rejzek, M.; Stockman, R. A.; van Maarseveen, J. H.; Hughes, D. L. *Chem. Commun.* **2005**, 4661. (d) Mahoney, J. M.; Smith, C. R.; Johnston, J. N. *J. Am. Chem. Soc.* **2005**, *127*, 1354. (e) Munk, M. E.; Kim, Y. K. *J. Am. Chem. Soc.* **1964**, *86*, 2213. (f) Wolff, L. *Liebigs. Ann.* **1913**, *399*, 274. (g) Wolff, L. *Liebigs. Ann.* **1912**, *394*, 23.

(6) (a) Kuznetsov, A.; Gulevich, A. V.; Wink, D. J.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2014**, *53*, 9021. (b) Bartnik, R.; Leśniak, S.; Wasiak, P. *Tetrahedron Lett.* **2004**, *45*, 7301. (c) Kadaba, P. K.; Stevenson, P. J.; P-Nnane, I.; Damani, L. A. *Bioorg. Med. Chem.* **1996**, *4*, 165. (d) Kadaba, P. K.; Stanovnik, B.; Tiscler, M. *Adv. Heterocycl. Chem.* **1984**, *37*, 217. (e) Kadaba, P. K. *Tetrahedron* **1969**, *25*, 3053. (f) Kadaba, P. K. *Tetrahedron* **1966**, *22*, 2453.

(7) (a) Habrant, D.; Rauhala, V.; Koskinen, A. M. P. *Chem. Soc. Rev.* **2010**, *39*, 2007. (b) Quesada, E.; Raw, S. A.; Reid, M.; Roman, E.; Taylor, R. J. K. *Tetrahedron* **2006**, *62*, 6673. (c) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, *1996*, 521. (d) Ohira, S. *Synth. Commun.* **1989**, *19*, 561.

(8) (a) Shelke, A. M.; Suryavanshi, G. *Org. Biomol. Chem.* **2015**, *13*, 8669. (b) Pramanik, M. M. D.; Kant, R.; Rastogi, N. *Tetrahedron* **2014**, *70*, 5214. (c) Kumar, R.; Nair, D.; Namboothiri, I. N. N. *Tetrahedron* **2014**, *70*, 1794. (d) Kumar, R.; Verma, D.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Lett.* **2012**, *14*, 4070. (e) Martin, A. R.; Mohanan, K.; Toupet, L.; Vasseur, J.-J.; Smietana, M. *Eur. J. Org. Chem.* **2011**, *2011*, 3184. (f) Verma, D.; Mobin, S. M.; Namboothiri, I. N. N. *J. Org. Chem.* **2011**, *76*, 4764. (g) Muruganantham, R.; Namboothiri, I. N. N. *J. Org. Chem.* **2010**, *75*, 2197. (h) Mohanan, K.; Martin, A. R.; Toupet, L.; Smietana, M.; Vasseur, J.-J. *Angew. Chem., Int. Ed.* **2010**, *49*, 3196. (i) Muruganantham, R.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Lett.* **2007**, *9*, 1125.

(9) Review of the Bestmann−Ohira reagent: Mohapatra, S.; Bhanja, C.; Jena, S.; Chakroborty, S.; Nayak, S. *Synth. Commun.* **2013**, *43*, 1993.

(10) (a) Gupta, A. K.; Ahamad, S.; Gupta, E.; Kant, R.; Mohanan, K. *Org. Biomol. Chem.* **2015**, *13*, 9783. (b) Ahamad, S.; Gupta, A. K.; Kant, R.; Mohanan, K. *Org. Biomol. Chem.* **2015**, *13*, 1492.

(11) CCDC 1423046 (**4q**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(12) (a) Li, Y.-J.; Li, X.; Zhang, S.-X.; Zhao, Y.-L.; Liu, Q. *Chem. Commun.* **2015**, *51*, 11564. (b) Chen, Y.; Nie, G.; Zhang, Q.; Ma, S.; Li, H.; Hu, Q. *Org. Lett.* **2015**, *17*, 1118. (c) Smith, C. D.; Greaney, M. F. *Org. Lett.* **2013**, *15*, 4826. (d) Wang, Z.; Bi, X.; Liao, P.; Zhang, R.; Liang, Y.; Dong, D. *Chem. Commun.* **2012**, *48*, 7076. (e) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952. (f) Majireck, M. M.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 8680. (g) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998.

(13) (a) John, J.; Thomas, J.; Dehaen, W. *Chem. Commun.* **2015**, *51*, 10797. (b) Ramachary, D. B.; Shashank, A. B.; Karthik, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 10420. (c) Thomas, J.; John, J.; Parekh, N.; Dehaen, W. *Angew. Chem., Int. Ed.* **2014**, *53*, 10155. (d) Cheng, G.; Zeng, X.; Shen, J.; Wang, X.; Cui, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 13265. (e) Ramachary, D. B.; Shashank, A. B. *Chem. - Eur. J.* **2013**, *19*, 13175. (f) Belkheira, M.; El Abed, D.; Pons, J.-M.; Bressy, C. *Chem. - Eur. J.* **2011**, *17*, 12917. (g) Ramachary, D. B.; Ramakumar, K.; Narayana, V. V. *Chem. - Eur. J.* **2008**, *14*, 9143. (h) Tome, A. C. In *Science of Synthesis*; Storr, R. C., Gilchrist, T. L., Eds.; Thieme: New York, 2004; Vol. *13*, p 415.

(14) (a) Lauria, A.; Delisi, R.; Mingoia, F.; Terenzi, A.; Martorana, A.; Barone, G.; Almerico, A. M. *Eur. J. Org. Chem.* **2014**, *2014*, 3289. (b) Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev.* **2013**, *113*, 4905. (c) Hou, J.; Liu, X.; Shen, J.; Zhao, G.; Wang, P. G. *Expert Opin. Drug Discovery* **2012**, *7*, 489. (d) Lau, Y. H.; Rutledge, P. J.; Watkinson, M.; Todd, M. H. *Chem. Soc. Rev.* **2011**, *40*, 2848. (e) Sheng, C.; Zhang, W. *Curr. Med. Chem.* **2011**, *18*, 733. (f) Moorhouse, A. D.; Moses, J. E. *ChemMedChem* **2008**, *3*, 715. (g) Bohacek, R. S.; McMartin, C.; Guida, W. C. *Med. Res. Rev.* **1996**, *16*, 3.

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Diastereoselective Synthesis of the Aminocyclitol Core of Jogyamycin via an Allene Aziridination Strategy

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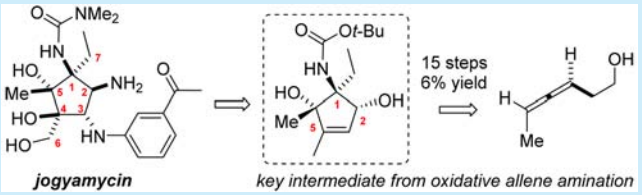
Supporting Information

ABSTRACT: Oxidative allene amination provides rapid access to densely functionalized amine-containing stereotriads through highly reactive bicyclic methyleneaziridine intermediates. This strategy has been demonstrated as a viable approach for the construction of the densely functionalized aminocyclitol core of jogyamycin, a natural product with potent antiprotozoal activity. Importantly, the flexibility of oxidative allene amination will enable the syntheses of modified aminocyclitol analogues of the jogyamycin core.



Jogyamycin (**1**) was first isolated in 2012 from a culture broth of *Streptomyces* sp. a-WM-JG-16.2, joining a family of aminocyclopentitols that include pactamycin (**2**), cranomycin (**3**), and TM-026 (**4**) (Figure 1).[1] Jogyamycin itself exhibits

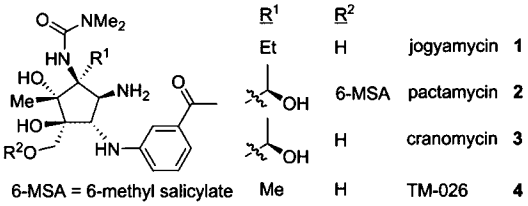
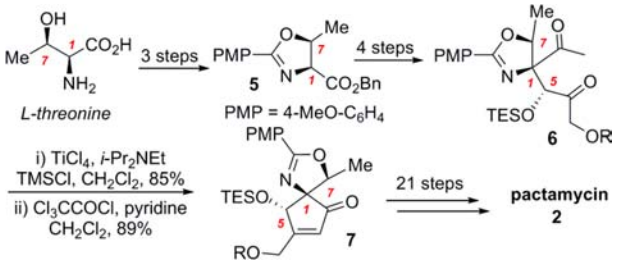


Figure 1. Biologically active aminocyclitol natural products.

potent antiprotozoal activity against important diseases including malaria and African sleeping sickness, while pactamycin and analogs have been shown to possess anticancer, antiviral, and antimicrobial activity in addition to antiprotozoal activity.[1,2] Crystal structures of pactamycin with the ribosomal 30S subunit indicate it acts as a universal inhibitor of translocation in a highly conserved region of the ribosome, explaining the wide range of biological activity exhibited by this family of molecules.[3] Subtle structural changes in the aminocyclitol motif have been shown to alter the activity of these natural products significantly.[2d−g] Further exploration of the structure−activity relationship of this family of molecules may help attenuate the cytotoxicity that these compounds possess.

In addition to their potent biological activity, jogyamycin and its analogs pose a significant synthetic challenge that has drawn the interest of a number of research groups.[4] All members of this class of compounds exhibit a fully substituted cyclopentane ring system with a heteroatom present on each carbon. Three contiguous quaternary carbons, as well as the dense functionalization around the ring that includes sensitive urea and aniline moieties, have inspired various strategies to achieve the syntheses of these challenging motifs.[4] Pactamycin was the first molecule in this family to yield to total synthesis, as reported by Hanessian and co-workers in 2011 (Scheme 1).[4a] This landmark synthesis

Scheme 1. Hanessian's Approach to Pactamycin



converted L-threonine into the oxazoline **5** to set the C-7 stereocenter. This stereochemical information was parlayed to the C-1 stereocenter through an aldol reaction, yielding **6** after a short sequence of steps. A series of functional group interconversions and a Ti-mediated aldol reaction/condensation led to the formation of **7**, which was eventually transformed to **2** in 21 subsequent steps.

The most recent synthesis of pactamycin was completed by the Johnson group in 2013 (Scheme 2).[4b] This fundamentally different strategy first sets the C-2 stereocenter via an asymmetric Mannich reaction between **8** and **9**, albeit with the incorrect configuration. Stereochemistry at the urea-bearing C-1, as well as at C-7, was set using a desymmetrizing β-diketone monoreduction to yield **10**. Intramolecular aldol condensation/selective epimerization of **11** delivered **12** with the correct C-2 stereochemistry, which was then carried on to **2** in 7 steps.

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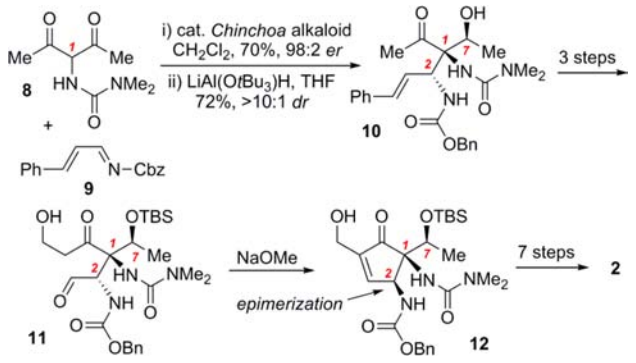
Scheme 2. Johnson's Approach to Pactamycin



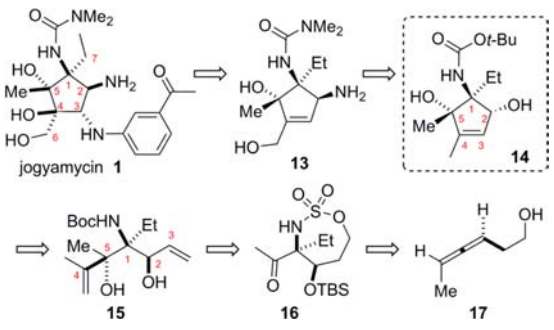
Two similarities between the Hanessian and Johnson syntheses are the intramolecular aldol condensations to close the cyclopentene rings and the use of the exocyclic C-7 stereocenter as the linchpin of the synthetic strategy. Hanessian used C-7 to set the important C-1 stereocenter that, in turn, was employed to set all subsequent stereocenters in the synthesis.

Johnson also engaged the C-7 stereocenter to set the correct stereochemistry at C-1 and used both C-1 and C-7 to "correct" the C-2 stereochemistry. This strategic use of the C-7 stereocenter proved vital to both Johnson and Hanessian's work.

In contrast to pactamycin, both jogyamycin **1** and **4** lack a C-7 stereocenter. It has been shown that the subtle changes of the C-1 side chain have a significant effect on the biological activity.[2c,g] Furthermore, attempts by Johnson and co-workers to cleave the alcohol at C-7 during studies directed toward analogue synthesis were unsuccessful.[2f] Therefore, we felt that it would be useful to develop a synthesis of **1** that could accommodate flexibility in the oxidation state at C-7. We also wanted to develop a strategy that would eventually be capable of delivering access to a broad range of jogyamycin analogues where the positioning, identity, and stereochemistry of heteroatoms in the cyclopentane core could be controlled at will. Finally, developing a potentially asymmetric synthesis of **1** would be an interesting challenge in the absence of the diastereocontrol provided by the handle at C-7.[4b]

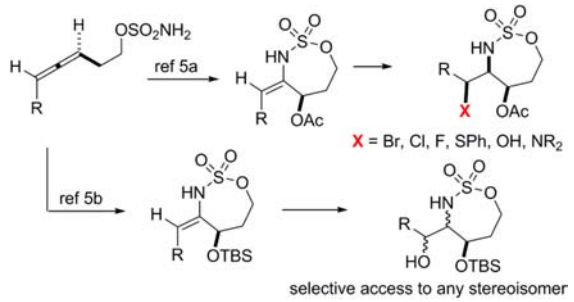
With these goals in mind, we proposed to apply our recently developed oxidative allene amination method to the construction of the cyclopentitol core of jogyamycin.[5] The retrosynthetic analysis is shown in Scheme 3. Moving from **1** to **13**, we envisaged that the alcohol at C-4 and the aniline at C-3 could arise through an epoxidation/epoxide opening sequence of **13**. The exocyclic alcohol could be installed via a selective allylic C–H oxidation and the amine at C-2 from a functional group interconversion of the 2° alcohol in the key target **14**. The

Scheme 3. Proposed Retrosynthetic Approach towards the Jogyamycin Core Using Oxidative Allene Amination



cyclopentene ring of **14** would arise from a ring-closing metathesis of the diene **15**. The relative stereochemistry at C-5 was predicted to be set through an addition of isopropenylmagnesium bromide to the carbonyl of **16** through chelation control. The olefin at C-3 of **15** could be formed through a sulfamate cleavage/elimination sequence of **16**. Amino ketone **16** would arise from the allene **17** through an enesulfamate intermediate, as described in more detail in Scheme 4.

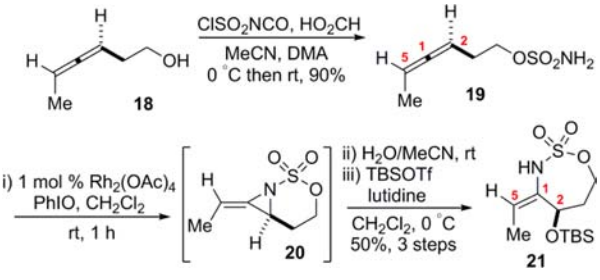
Scheme 4. Oxidative Allene Amination for the Synthesis of Densely Functionalized Amine Triads



Previous work in our group has shown that allene aziridination yields enesulfamate intermediates that serve as tunable and versatile scaffolds for further functionalization (Scheme 4).[5] By using different electrophiles, the installation of various heteroatoms at the three original allene carbons can be accomplished in a stereodefined manner in two steps. In addition to heteroatom diversity, our methods provide stereochemical diversity, as illustrated by work showing all four O/N/O triads are accessible from a single allene precursor.[5b] Effective transfer of the axial chirality of the allene to the triad enables the syntheses of enantiomerically enriched amine products. This flexibility indicated oxidative allene amination would be an ideal vehicle for not only the synthesis of **1**, but more importantly, functionally and stereochemically diverse analogues of **1** that could be employed for SAR studies of jogyamycin.

The substrate homoallenic sulfamate **19** was synthesized in one step from commercially available homoallenic alcohol **18** (Scheme 5).[6] Rh-catalyzed intramolecular aziridination of **19** is

Scheme 5. Synthesis of the Key Enesulfamate 21



observed exclusively at the proximal double bond of the allene in a > 20:1 *E*/*Z* ratio; no aziridination of the distal bond occurs. Due to its relative instability, **20** is not isolated but is subjected to ring opening with water following a quick solvent exchange. The crude alcohol is then protected with a TBS group prior to isolation to furnish the enesulfamate **21** in good yield over the three steps with just a single purification step. This reaction sequence has been performed several times on scales up to 8 g with consistent yields obtained.

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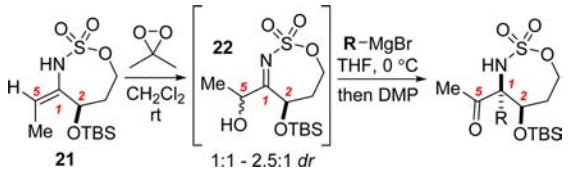
With significant quantities of **21** in hand, the next goal was to develop conditions for setting the important C-1 stereocenter. Epoxidation of **21**, followed by immediate rearrangement, yielded the imino alcohol **22** in near-quantitative yields but with low *dr* (Table 1). While the stereocenter at C-5 appeared to

Table 1. Setting the Relative Stereochemistries at C1 and C2



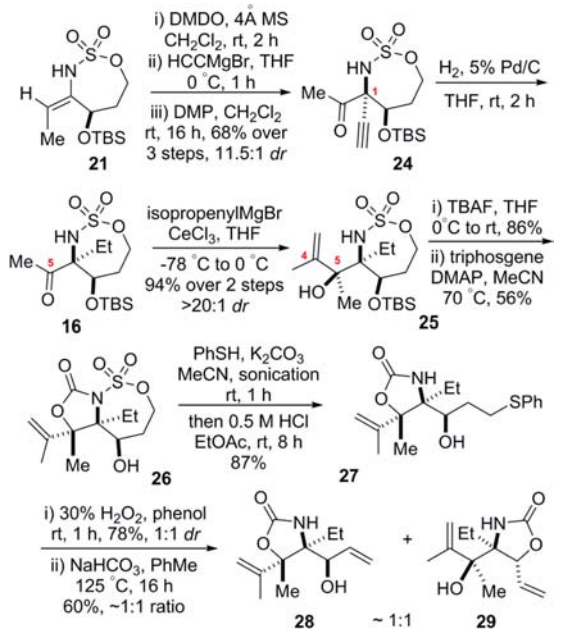
entry	R	product	yield	*dr*[a]
1[b]	Et	**16**	29%[c]	1.9:1
2	CH=CH$_2$	**23**	45%	2:1
3	C≡CH	**24**	48%	2.3:1
4[d]	C≡CH	**24**	68%	11.5:1

[a]Based on ^{1}H NMR analysis of crude product. [b]Reaction using CH_2Cl_2 as the solvent. [c]Isolated yield and *dr* are before DMP oxidation. Hydride reduction was a significant byproduct observed in 18% yield. [d]Grignard prestirred at 0 °C for 1 h prior to addition. Yield refers to isolated material.

be of little importance, as it is later destroyed via oxidation to a ketone, this low *dr* could be transferred to the C-1 stereocenter if chelation control operates in the addition of the organometallic reagent to the imine of **22**, which was observed in prior studies. Changing the temperature had little effect on the *dr* of **22**; the greatest effect on *dr* seemed to be the age of the DMDO solution, with older solutions giving decreased *dr*. To complicate the situation, low yields were generally observed when EtMgBr was used as the nucleophile for addition to **22**, as significant competing hydride reduction was observed (Table 1, entry 1). Addition of anhydrous $CeCl_3$ or $LaCl_3$−2LiCl to the EtMgBr did not yield any improvements.[7] Reaction of vinylmagnesium bromide or ethynylmagnesium bromide with **22** gave slightly better yields, but the selectivity of the organometallic addition still mirrored that of the DMDO oxidation (entries 2, 3). However, cooling the ethynylmagnesium bromide solution at 0 °C for approximately 30 to 60 min prior to addition of **22** resulted in both higher yields and significantly improved *dr* (entry 4). This cooling protocol resulted in the formation of considerable amounts of precipitate, leading to the hypothesis that perturbation of the Schlenk equilibrium yields formation of higher-order species that increase the propensity for attack opposite the bulky −OTBS group, irrespective of the C-5 stereocenter.[4c,5b,8] Addition of acetylides to similar imines has previously proven to be a viable strategy for introducing new functionality that can later be manipulated into the desired functional groups.[9] The stereochemical relationship between C-1 and C-2 of **24** was confirmed by X-ray crystallography (see the Supporting Information (SI) for further details).

Having set the C-1 stereocenter, the alkyne was reduced to form **16** (Scheme 6). Reaction of the carbonyl of **16** with isopropenyl MgBr in the presence of $CeCl_3$ occurred through chelation control to deliver **25** and set the C-5 stereocenter; isopropenyl MgBr alone gave only recovered starting material, likely due to enolization of the sterically encumbered ketone outcompeting the desired nucleophilic addition.[7a] The product **25** was isolated as a single diastereomer in high yield over the two steps. The relative stereochemical relationships between C1−

Scheme 6. First Attempted Route to the Key Core 14



C2−C5 in **25** were confirmed by X-ray crystallography (see the SI for further details).

Next, we set about activating the nitrogen of **25** by installing an electron-withdrawing group to render the sulfamate susceptible to nucleophilic ring opening. Unfortunately, the sulfamate nitrogen of **25** proved resistant to further functionalization using a variety of electrophiles, likely due to the large steric bulk around the nitrogen coupled with its weak nucleophilic character. As this strategy was unsuccessful, attempts to alleviate some of the steric bulk by removing the TBS group were carried out. Although subsequent reaction of the nitrogen still proved difficult, the oxazolidinone **26** could be formed using forcing conditions with triphosgene. With the nitrogen sufficiently activated, the sulfamate of **26** could be cleaved using thiophenol as a pro-nucleophile, followed by extended stirring with aqueous HCl to liberate SO_3 and yield **27**.[10] Selective oxidation to the sulfoxide, followed by thermolysis, yielded **28** and **29** as approximately a 1:1 mixture.[11] Unfortunately, all attempts to cleave the oxazolidinone were unsuccessful, as were attempts to carry out ring closing metathesis.

Due to the inability to cleave the oxazolidinone in **28** and **29**, we opted to avoid such intermediates by attempting to functionalize the less hindered nitrogen prior to addition of the isopropenyl group. The isopropenyl subunit could later be installed after cleavage of the sulfamate. Unfortunately, all attempts to functionalize the nitrogen of **16** led to recovered starting material. Attempts to install the urea directly on **24**, using dimethylcarbamoyl chloride or methyl isocyanate, led to either recovered starting material or complex mixtures of products. However, reaction of **24** with Boc_2O yielded **30** in high yield (Scheme 7). Attempts to hydrogenate **30** to the alkane yielded **16** (see Scheme 6), presumably due to the increased sterics posed by the ethyl group as compared to the alkyne. To circumvent this issue, **30** was reacted directly with thiophenol to yield **31** in near-quantitative yield. Oxidation to the sulfoxide permitted reduction of the alkyne under high pressures of H_2 which, after thermolysis, yielded **32** in good yield. Addition of the isopropenyl subunit to C-5 of **32** to deliver **33** initially proved more difficult than anticipated due to oxazolidinone formation

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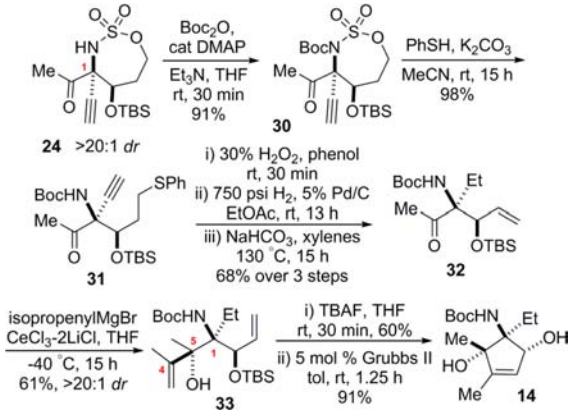
Scheme 7. Successful Route to the Key Core Structure 14



with the tertiary alkoxide resulting from nucleophilic addition to the ketone. Ultimately, we found that performing the addition in the presence of $CeCl_3$−2LiCl at −40 °C slowed down the attack of the resulting alkoxide on the Boc group such that diene **33** could be isolated as the major product in >20:1 *dr*.[7b] Desilylation of **33**, followed by ring closing metathesis using the Grubbs II catalyst, delivered **14** in excellent yield. The configuration of the C-5 stereocenter was confirmed by 1D nOesy analysis, indicating that the organometallic addition to **32** proceeds through chelation control, where the C-5 stereochemistry is dictated by the configuration at C-1.

In conclusion, we have established a reliable route to a densely functionalized cyclopentene motif **14** which maps onto the core of jogyamycin. The challenging C-5 and C-1 quaternary stereocenters are set at an early stage using oxidative allene aziridination as a key step. Employing this approach allows deoxygenation to be achieved at C-7 of jogyamycin, which has proven challenging using reported routes to pactamycin. Another nice feature of this strategy is our anticipated ability to utilize different allene substrates, easily install diverse nucleophiles at either the C1 or C-2 stereocenters, introduce different side chains at C5, and manipulate oxidation of the alkene of the cyclopentene core to enable the versatile syntheses of novel analogues. Work to complete the synthesis of jogyamycin is currently underway and is focused on amination at the C-2 position, oxidation of the C-6 position, and establishment of the C-3 and C-4 stereocenters. The beautiful work carried out in the total syntheses of pactamycin will aid us in this endeavor.[4a−c]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03453.

Experimental procedures and characterization for all new compounds (PDF)
NMR spectra (PDF)
Crystallographic data for **24** (CIF)
Crystallographic data for a derivative of **25** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Iwatsuki, M.; Nishihara-Tsukashima, A.; Ishiyama, A.; Namatame, M.; Watanabe, Y.; Handasah, S.; Pranamuda, H.; Marwoto, B.; Matsumoto, A.; Takahashi, Y.; Otoguro, K.; Ōmura, S. *J. Antibiot.* **2012**, *65*, 169.

(2) (a) White, F. R. *Cancer Chemotherapy Reports* **1962**, *24*, 75. (b) Ito, T.; Roongsawang, N.; Shirasaka, N.; Lu, W.; Flatt, P. M.; Kasanah, N.; Miranda, C.; Mahmud, T. *ChemBioChem* **2009**, *10*, 2253. (c) Lu, W.; Roongsawang, N.; Mahmud, T. *Chem. Biol.* **2011**, *18*, 425. (d) Otoguro, K.; Iwatsuki, M.; Ishiyama, A.; Namatame, M.; Nishihara-Tukashima, A.; Shibahara, S.; Kondo, S.; Yamada, H.; Ōmura, S. *J. Antibiot.* **2010**, *63*, 381. (e) Hanessian, S.; Vakiti, R. R.; Chattopadhyay, A. K.; Dorich, S.; Lavallée, C. *Bioorg. Med. Chem.* **2013**, *21*, 1775. (f) Sharpe, R. J.; Malinowski, J. T.; Sorana, F.; Luft, J. C.; Bowerman, C. J.; DeSimone, J. M.; Johnson, J. S. *Bioorg. Med. Chem.* **2015**, *23*, 1849. (g) Almabruk, K. H.; Lu, W.; Li, X.; Abugreen, M.; Kelly, J. X.; Mahmud, T. *Org. Lett.* **2013**, *15*, 1678.

(3) (a) Egebjerg, J.; Garrett, R. A. *Biochimie* **1991**, *73*, 1145. (b) Carter, A. P.; Clemons, W. M.; Brodersen, D. E.; Morgan-Warren, R. J.; Wimberly, B. T.; Ramakrishnan, V. *Nature* **2000**, *407*, 340. (c) Dinos, G.; Wilson, D. N.; Teraoka, Y.; Szaflarski, W.; Fucini, P.; Kalpaxis, D.; Nierhaus, K. H. *Mol. Cell* **2004**, *13*, 113. (d) Tourigny, D. S.; Fernández, I. S.; Kelley, A. C.; Vakiti, R. R.; Chattopadhyay, A. K.; Dorich, S.; Hanessian, S.; Ramakrishnan, V. *J. Mol. Biol.* **2013**, *425*, 3907.

(4) (a) Hanessian, S.; Vakiti, R. R.; Dorich, S.; Banerjee, S.; Lecomte, F.; DelValle, J. R.; Zhang, J.; Deschênes-Simard, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 3497. (b) Malinowski, J. T.; Sharpe, R. J.; Johnson, J. S. *Science* **2013**, *340*, 180. (c) Malinowski, J. T.; McCarver, S. J.; Johnson, J. S. *Org. Lett.* **2012**, *14*, 2878. (d) Loertscher, B. M.; Young, P. R.; Evans, P. R.; Castle, S. L. *Org. Lett.* **2013**, *15*, 1930. (e) Haussener, T. J.; Looper, R. E. *Org. Lett.* **2012**, *14*, 3632. (f) Knapp, S.; Yu, Y. *Org. Lett.* **2007**, *9*, 1359. (g) Tsujimoto, T.; Nishikawa, T.; Urabe, D.; Isobe, M. *Synlett* **2005**, 433. (h) Hanessian, S.; Vakiti, R. R.; Dorich, S.; Banerjee, S.; Deschênes-Simard, B. *J. Org. Chem.* **2012**, *77*, 9458.

(5) (a) Adams, C. S.; Boralsky, L. A.; Guzei, I. A.; Schomaker, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 10807. (b) Adams, C. S.; Grigg, R. D.; Schomaker, J. M. *Chem. Sci.* **2014**, *5*, 3046.

(6) Fiori, K. W.; Espino, C. G.; Brodsky, B. H.; Du Bois, J. *Tetrahedron* **2009**, *65*, 3042.

(7) (a) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233. (b) Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 497.

(8) Xia, A.; Heeg, M. J.; Winter, C. H. *Organometallics* **2003**, *22*, 1793.

(9) Fleming, J. J.; Du Bois, J. *J. Am. Chem. Soc.* **2006**, *128*, 3926.

(10) Kenworthy, M. N.; Taylor, R. J. *Org. Biomol. Chem.* **2005**, *3*, 603.

(11) Xu, W. L.; Li, Y. Z.; Zhang, Q. S.; Zhu, H. S. *Synthesis* **2004**, *2*, 227.

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Pd(II)-Catalyzed Asymmetric Addition of Arylboronic Acids to Isatin-Derived Ketimines

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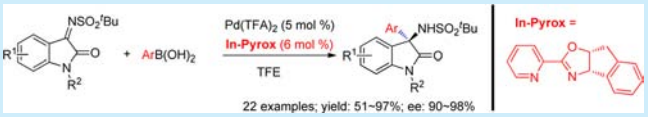
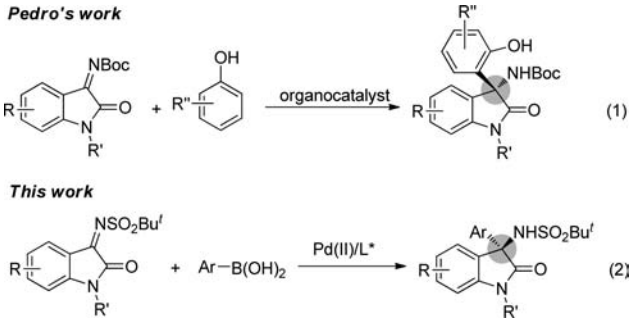
Supporting Information

ABSTRACT: A Pd(II)/Pyrox-catalyzed enantioselecitve addition of arylboronic acids to 3-ketimino oxindoles was developed, providing chiral 3-amino-2-oxindoles with a quaternary stereocenter in high yields and with good enantioselectivities. A variety of functionalized 3-ketimino oxindoles can be used, and the method tolerates some variation in arylboronic acid scope. This asymmetric arylation provides an alternative efficient catalytic method for the preparation of chiral 3-aryl-3-amino-2-oxindoles, which also represents the first example of a Pd(II)-catalyzed addition of arylborons to exocyclic ketimines.



Transition-metal-catalyzed asymmetric additions of organometallic reagents to imines represent useful strategies for the construction of chiral α-polysubstituted amines.[1] Initiated by the pioneering work of the Hayashi group, asymmetric additions of arylboron reagents to imines have become an important research topic.[2−6] In 2010, the Hayashi group reported the first example of a rhodium-catalyzed asymmetric addition of arylboron reagents to ketimines.[3] Furthermore, the groups of Lam,[4] Xu,[5] and Lin/Feng[6] have also reported the asymmetric addition of organoboron reagents to ketimines catalyzed by rhodium complexes. However, the asymmetric addition of arylboron reagents to different types of ketimines is comparatively rare. Methodology that utilizes chiral palladium complexes as catalysts in the same reaction is attractive because of the lower cost of palladium salts compared with rhodium.[7−9] Several groups have studied the addition of arylboron to imine using their own chiral palladium catalysts.[7c−j] Only recently, palladium catalytic systems were developed for the addition of arylboronic acids to ketimines.[8] However, only endocyclic ketimines have been used as substrates, possibly due to the strained configuration of these types of compounds and their stability to hydrolysis.

Recently, the catalytic asymmetric construction of chiral 3,3-disubstituted 2-oxindoles has attracted much attention due to their unique bioactivity.[10] Oxindole compounds bearing chiral α-tertiary amines at the C3 position have been reported to be biologically active against a variety of targets.[11] Several groups have developed different strategies to construct the core structural motif of these types of chiral compounds.[12−17] One procedure involves concurrent generation of the chiral tetrasubstituted carbon stereocenters and asymmetric intramolecular construction of the oxindole skeleton. An intramolecular α-arylation of α-amino amides and an intramolecular reductive addition of arylhalides to α-ketimino amides have been developed by the groups of Kündig and Ley, respectively.[13] A general strategy utilizes the asymmetric addition of 3-monosubstituted oxindoles to carbon or nitrogen electrophiles.[14,15] Another complementary strategy involves the addition of nucleophiles to 3-ketimino-2-oxindoles. Chiral organocatalysts and Lewis acid catalysts have been used to catalyze the addition of a number of nucleophiles, such as silyl ketene imines, pyrazolones, nitroalkanes, 1,3-dicarbonyl compounds, alcohols, peroxides, and thiols.[16] However, the enantioselective catalytic addition of aryl nucleophiles to 3-ketimino-2-oxindoles is still a challenge. Recently, Pedro and coworkers reported an interesting and efficient organocatalytic asymmetric addition of naphthols and electron-rich phenols to 3-ketimino-2-oxindoles (eq 1),[17] but this methodology is only



suitable for electron-rich ArOH as aryl nucleophiles. We propose that the transition-metal-catalyzed asymmetric addition of arylboron reagents will provide an alternative methodology for the arylation of 3-ketimino oxindoles.[18] Herein we report an asymmetric Pd(II)-catalyzed addition of arylboronic acids to 3-ketimino oxindoles (eq 2).

Initially, different ketimine nitrogen protecting groups (R^1) were investigated using phenylboronic acid as the boron reagent, employing $Pd(TFA)_2$ as the palladium source and *t*-Bu-Nicox as the chiral ligand (Table 1). The Boc-protected substrate, which has been widely used in other asymmetric catalytic additions of nucleophiles to 3-ketimino oxindoles, is not an active substrate

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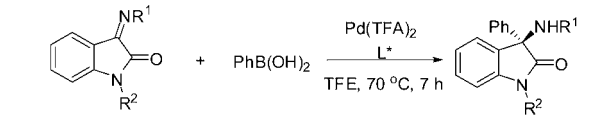
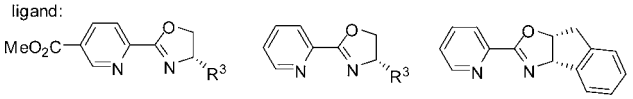
Table 1. Reaction Optimization[a]



substrate:

1: R^1 = Boc, R^2 = Bn
2: R^1 = Ts, R^2 = Bn
3: R^1 = $SO_2{}^tBu$, R^2 = Bn
4: R^1 = $SO_2{}^tBu$, R^2 = Me
5: R^1 = $SO_2{}^tBu$, R^2 = α-naphthalenemethyl
6: R^1 = $SO_2{}^tBu$, R^2 = 2-O_2N-benzyl
7: R^1 = $SO_2{}^tBu$, R^2 = 2,6-diCl-benzyl

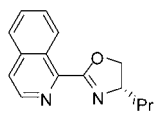
ligand:



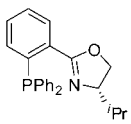
R^3 = ^{i}Pr: ***i*-Pr-Nicox**
R^3 = ^{t}Bu: ***t*-Bu-Nicox**
R^3 = Cy: **Cy-Nicox**
R^3 = Bn: **Bn-Nicox**

R^3 = ^{i}Pr: ***i*-Pr-Pyrox**
R^3 = ^{t}Bu: ***t*-Bu-Pyrox**

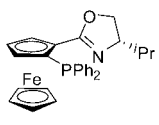
In-Pyrox



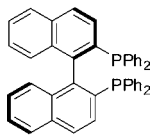
***i*-Pr-IsoQuinox**



***i*-Pr-Phox**



***i*-Pr-FcPhox**



Binap

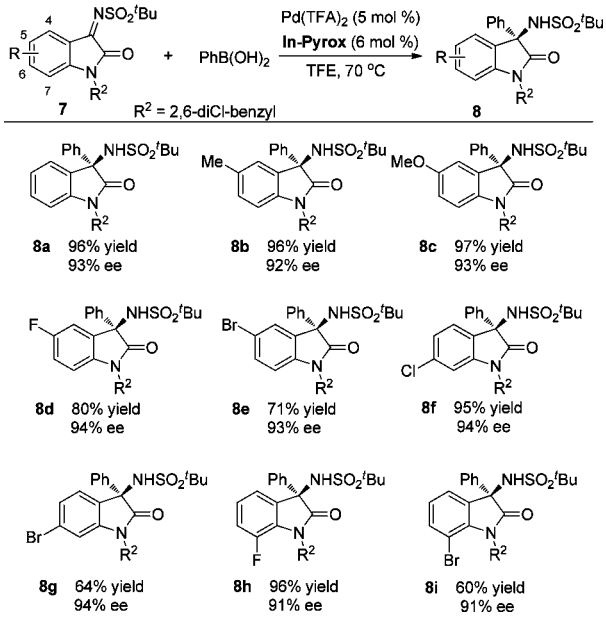
entry	substrate	ligand	yield[b] (%)	ee[c] (%)
1	**1**	*t*-Bu-Nicox	NR	
2	**2**	*t*-Bu-Nicox	64	30
3	**3**	*t*-Bu-Nicox	81	84
4	**4**	*t*-Bu-Nicox	69	30
5	**5**	*t*-Bu-Nicox	51	91
6[d]	**6**	*t*-Bu-Nicox		
7	**7**	*t*-Bu-Nicox	87	90
8	**7**	*i*-Pr-Nicox	81	84
9	**7**	Bn-Nicox	94	72
10	**7**	Cy-Nicox	93	87
11	**7**	*i*-Pr-Pyrox	91	85
12	**7**	*t*-Bu-Pyrox	88	90
13	**7**	In-Pyrox	96	93
14	**7**	*i*-Pr-IsoQuinox	96	85
15[e]	**7**	*i*-Pr-Phox	23	66
16[e]	**7**	*i*-Pr-FcPhox	37	96
17[e]	**7**	Binap	NR	

[a]Reaction conditions: 0.10 mmol of substrate, 5 mol % of $Pd(TFA)_2$, 6.0 mol % of ligand, and $PhB(OH)_2$ (0.20 mmol) in unpurified TFE (1.5 mL) at 70 °C for 7 h under an air atmosphere. TFA = trifluoroacetic acetate, TFE = trifluoroethanol. [b]Yield of isolated product. [c]Determined by HPLC using a chiral Daicel column. [d]Substrate or product decomposed. [e]24 h.

for this Pd(II)-catalyzed addition reaction (entry 1). We were pleased to discover that the addition proceeded smoothly with sulfonyl-protected ketimines (entry 2). Good enantioselectivity was observed with the sterically bulky protecting group, *tert*-butyl sufonyl (84% ee, entry 3). Different protecting groups (R^2) for the oxindole nitrogen were also screened. Poor results were obtained with methyl as the R^2 group (entry 4). Substrate **5** bearing an *α*-naphthalenemethyl protecting group showed better enantioselectivity but lower yield compared to substrate **3** (entry 5). We speculated that a bulky and electron-withdrawing R^2 group would improve the reactivity and enantioseletivity of the catalytic reaction. Therefore, substrates **6** and **7** were prepared, which bear 2-nitrobenzyl or 2,6-dicholobenzyl as protecting groups, respectively. The catalytic results showed that substrate **6** was not stable under the reaction conditions, and substrate **7** provided the best reults among all the prepared substrates (entries 6 and 7). Subsequently, ligand screening was conducted using **7** as the substrate (entries 7−17). A ligand bearing a chiral indane-fused oxazoline group at the pyridine showed the best chiral inducing ability (entries 13 vs 7−12,14). Nicox[19a] and IsoQuinox[19b] gave the desired product with similar results when the corresponding Pyrox[19c] ligands were used (entries 7−14). Due to the lower cost of starting material and easier preparation of Pyrox compared to the other two types of ligands, we chose it as the optimized ligand. Other types of ligands such as Phox,[19d−f] FcPhox,[19g,h] and Binap[19i] were also tested, all of which gave poor results (entries 15−17). Other conditions such as solvents and Pd source were also screened, but lower reactivity were observed.[8a] Thus, the optimized reaction conditions were found to be using In-Pyrox as the chiral ligand and $Pd(TFA)_2$ as palladium source in TFE solvent at 70 °C (entry 13).

With the optimized reaction conditions in hand, different 3-ketimino-2-oxindoles were tested. As shown in Scheme 1,

Scheme 1. Substrate Scope[a]



[a]Reactions conditions: 0.10 mmol of substrate, 5 mol % of $Pd(TFA)_2$, 6.0 mol % of ligand, and $PhB(OH)_2$ (0.20 mmol) in unpurified TFE (1.5 mL) at 70 °C for 7−36 h under an air atmosphere. [b]Yield of isolated product. [c]Determined by HPLC using a chiral column.

different substituents at different positions of the substrates all gave similar enantioselectivities (**8a−i**). Substituents at the 7-position decreased the enantioselectivity only slightly. The reaction proceeds smoothly with substrates bearing electron-rich substituents (**8b,c**) and halides, except bromide, maybe due to some side reactions caused by bromide (**8d−i**). Unfortunately, the reaction of 4-substituted 3-ketimino-2-oxindole failed to proceed, possibly due to steric hindrance.

The arylboronic acid scope was also investigated (Scheme 2). Various *para*-substituted arylboronic acids reacted with **7** to furnish 3-amino-2-oxindoles in excellent yields and with high enantioseletivities (**8j−p**). Arylboronic acids possessing *meta*-substituents also gave the addition products with good results (**8q−s**). Good yields and ee's were also obtained for disubstituted arylboronic acids (**8t,u**). The results showed that arylboronic acids bearing oxygen substituents at the *meta*

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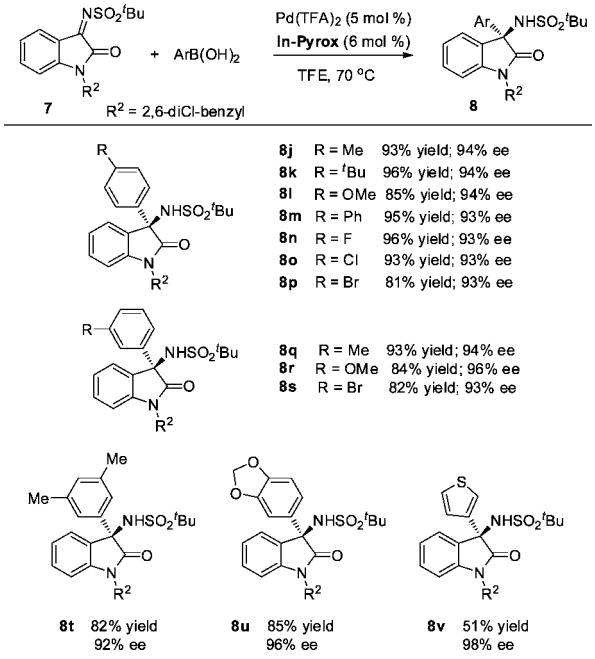
Scheme 2. Arylboronic Acid Scope[a]



[a]Reactions were carried out on a 0.10 mmol scale using 5 mol % of $Pd(TFA)_2$, 6.0 mol % of ligand, and arylboronic acid (0.20 mmol) in TFE (1.5 mL) at 70 °C for 4−48 h under air atmosphere. [b]Yield of isolated product. [c]Determined by HPLC using a chiral column.

position were able to marginally improve the ee (**8r**,**u**). However, no reaction occurred using *o*-tolylboronic acid as the nucleophile. A heteroaromatic boronic acid was also examined, and the desired product was obtained with excellent ee (98%) but only moderate yield (**8v**).

The absolute configuration of the product **8a** was determined to be *R* and the absolute configuration of the C═N bond of the substrate **7** was determined to be (*E*) by X-ray crystallographic analysis (Figure 1). This stereochemical outcome can be

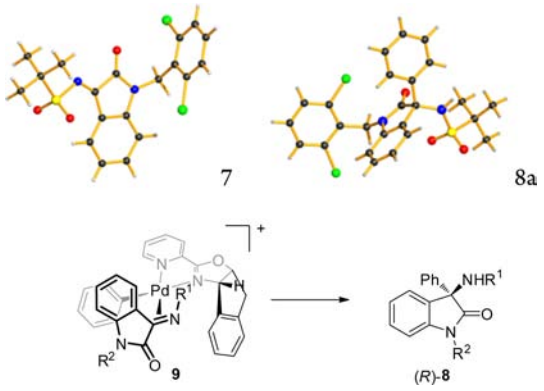
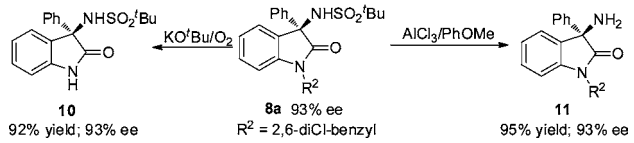


Figure 1. ORTEP representation of **8a** and **7** and model for explaining the origin of asymmetric induction.

explained using the model shown in Figure 1. The aryl group is bound to the Pd center and is *cis* to the pyridine group of the **Pyrox**; the ketimine is bound at the position that is *trans* to the pyridine moiety. When the imine group of the substrate has an (*E*) geometry, the R^1 group of the ketimine is oriented upward and thus positioned away from the chiral group of the oxazoline (**9**) in the favored transition state. This leads to (*R*)-**8** as the major product.

The R^2 group was deprotected using a simple ^{t}BuOK/O_2-deprotecting method, affording **10** in 92% yield without a reduction in ee value.[20a] The ^{t}BuSO$_2$ group can also be removed efficiently using an $AlCl_3$−PhOMe system (Scheme 3).[20b]

Scheme 3. Deprotections of Product 8a



In summary, we have developed a palladium-catalyzed asymmetric arylation of 3-ketimino oxindoles with arylboronic acids. The desired 2-oxindoles bearing chiral α-tertiary amines at the 3-position were prepared in good yields and with high enantioselectivities. A relatively wide substrate scope of oxindoles and arylboronic acids are compatible with the mild reaction conditions. This reaction is the first example of a Pd(II)-catalyzed addition of arylborons to exocyclic ketimines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03458.

General procedures, X-ray crystal structure data, and spectra of new products (PDF)
X-ray data for (*E*)-**7a** (CIF)
X-ray data for (*R*)-**8a** (CIF)

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Author Contributions

†Q.H. and L.W. contributed equally.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews on synthesis of chiral α-tertiary amines, see: (a) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (b) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873. (c) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, *2007*, 5969. (d) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853.

(2) (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (b) Yoshida, K.; Hayashi, T. In *Modern Rhodium-Catalyzed Organic*

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Org. Lett. 2016, 18, 288−291

Reactions; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; pp 55−77. (c) Miyaura, N. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535. (d) Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G. *Chem. Soc. Rev.* **2010**, *39*, 2093. (e) Feng, X.; Du, H. *Asian J. Org. Chem.* **2012**, *1*, 204. (f) Tian, P.; Dong, H.-Q.; Lin, G.-Q. *ACS Catal.* **2012**, *2*, 95. (g) Li, Y.; Xu, M.-H. *Chem. Commun.* **2014**, *50*, 3771. (h) Dong, H.-Q.; Xu, M.-H.; Feng, C.-G.; Sun, X.-W.; Lin, G.-Q. *Org. Chem. Front.* **2015**, *2*, 73.

(3) (a) Shintani, R.; Takeda, M.; Tsuji, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 13168. (b) Shintani, R.; Takeda, M.; Soh, Y.-T.; Ito, T.; Hayashi, T. *Org. Lett.* **2011**, *13*, 2977. (c) Nishimura, T.; Noishiki, A.; Tsui, G. C.; Hayashi, T. *J. Am. Chem. Soc.* **2012**, *134*, 5056. (d) Nishimura, T.; Ebe, Y.; Fujimoto, H.; Hayashi, T. *Chem. Commun.* **2013**, *49*, 5504.

(4) (a) Luo, Y.; Carnell, A. J.; Lam, H. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 6762. (b) Luo, Y.; Hepburn, H. B.; Chotsaeng, N.; Lam, H. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 8309.

(5) (a) Wang, H.; Jiang, T.; Xu, M.-H. *J. Am. Chem. Soc.* **2013**, *135*, 971. (b) Wang, H.; Xu, M.-H. *Synthesis* **2013**, *45*, 2125. (c) Wang, H.; Li, Y.; Xu, M.-H. *Org. Lett.* **2014**, *16*, 3962. (d) Jiang, T.; Wang, Z.; Xu, M.-H. *Org. Lett.* **2015**, *17*, 528.

(6) Chen, Y.-J.; Chen, Y.-H.; Feng, C.-G.; Lin, G.-Q. *Org. Lett.* **2014**, *16*, 3400.

(7) (a) Dai, H.; Lu, X. *Org. Lett.* **2007**, *9*, 3077. (b) He, P.; Lu, Y.; Hu, Q.-S. *Tetrahedron Lett.* **2007**, *48*, 5283. (c) Dai, H.; Yang, M.; Lu, X. *Adv. Synth. Catal.* **2008**, *350*, 249. (d) Zhang, Q.; Chen, J.; Liu, M.; Wu, H.; Cheng, J.; Qin, C.; Su, W.; Ding, J. *Synlett* **2008**, *2008*, 935. (e) Dai, H.; Lu, X. *Tetrahedron Lett.* **2009**, *50*, 3478. (f) Ma, G.-N.; Zhang, T.; Shi, M. *Org. Lett.* **2009**, *11*, 875. (g) Marques, C. S.; Burke, A. J. *Eur. J. Org. Chem.* **2010**, *2010*, 1639. (h) Liu, Z.; Shi, M. *Tetrahedron* **2010**, *66*, 2619. (i) Chen, J.; Lu, X.; Lou, W.; Ye, Y.; Jiang, H.; Zeng, W. *J. Org. Chem.* **2012**, *77*, 8541. (j) Beisel, T.; Manolikakes, G. *Org. Lett.* **2013**, *15*, 6046.

(8) (a) Yang, G.; Zhang, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 7540. (b) Jiang, C.; Lu, Y.; Hayashi, T. *Angew. Chem., Int. Ed.* **2014**, *53*, 9936. (c) Quan, M.; Yang, G.; Xie, F.; Gridnev, I. D.; Zhang, W. *Org. Chem. Front.* **2015**, *2*, 398. (d) Schrapel, C.; Peters, R. *Angew. Chem., Int. Ed.* **2015**, *54*, 10289. (e) Álvarez-Casao, Y.; Monge, D.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *Org. Lett.* **2015**, *17*, 5104.

(9) For selected reviews and papers on Pd(II)-catalyzed asymmetric addition of arylboron to C═C bonds, see: (a) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, *2007*, 1279. (b) Gutnov, A. *Eur. J. Org. Chem.* **2008**, *2008*, 4547. (c) Yamamoto, Y.; Nishikata, T.; Miyaura, N. *Pure Appl. Chem.* **2008**, *80*, 807. (d) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 2768. (e) Nishikata, T.; Yamamoto, Y.; Gridnev, I. D.; Miyaura, N. *Organometallics* **2005**, *24*, 5025. (f) Lu, X.; Lin, S. *J. Org. Chem.* **2005**, *70*, 9651. (g) Zhang, T.; Shi, M. *Chem. - Eur. J.* **2008**, *14*, 3759. (h) Lin, S.; Lu, X. *Org. Lett.* **2010**, *12*, 2536. (i) Kikushima, K.; Holder, J. C.; Gatti, M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2011**, *133*, 6902. (j) Gottumukkala, A. L.; Matcha, K.; Lutz, M.; de Vries, J. G.; Minnaard, A. J. *Chem. - Eur. J.* **2012**, *18*, 6907. (k) Ibrahem, I.; Ma, G.; Afewerki, S.; Córdova, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 878. (l) Mei, T.-S.; Patel, H. H.; Sigman, M. S. *Nature* **2014**, *508*, 340. (m) He, Q.; Xie, F.; Fu, G.; Quan, M.; Shen, C.; Yang, G.; Gridnev, I. D.; Zhang, W. *Org. Lett.* **2015**, *17*, 2250.

(10) (a) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (b) Zhou, F.; Liu, Y. L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381. (c) Shen, K.; Liu, X.; Lin, L.; Feng, X. *Chem. Sci.* **2012**, *3*, 327. (d) Klein, J. E. M. N.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2011**, *2011*, 6821.

(11) For selected examples, see: (a) Badillo, J. J.; Hanhan, N. V.; Franz, A. K. *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 758. (b) Bernard, K.; Bogliolo, S.; Ehrenfeld, J. *Br. J. Pharmacol.* **2005**, *144*, 1037. (c) Decaux, G.; Soupart, A.; Vassart, G. *Lancet* **2008**, *371*, 1624. (d) Shimazaki, T.; Iijima, M.; Chaki, S. *Eur. J. Pharmacol.* **2006**, *543*, 63. (e) Puleo, L.; Marini, P.; Avallone, R.; Zanchet, M.; Bandiera, S.; Baroni, M.; Croci, T. *Bioorg. Med. Chem.* **2012**, *20*, 5623.

(12) For selected examples employing chiral auxilaries, see: (a) Lesma, G.; Landoni, N.; Pilati, T.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2009**, *74*, 4537. (b) Jung, H. H.; Buesking, A. W.; Ellman, J. A. *Org. Lett.* **2011**, *13*, 3912. (c) Yan, W.; Wang, D.; Feng, J.; Li, P.; Wang, R. *J. Org. Chem.* **2012**, *77*, 3311. (d) Chen, D.; Xu, M.-H. *J. Org. Chem.* **2014**, *79*, 7746.

(13) (a) Jia, Y.-X.; Hillgren, J. M.; Watson, E. L.; Marsden, S. P.; Kündig, E. P. *Chem. Commun.* **2008**, 4040. (b) Tolstoy, P.; Lee, S. X. Y.; Sparr, C.; Ley, S. V. *Org. Lett.* **2012**, *14*, 4810.

(14) (a) Cheng, L.; Liu, L.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2009**, *11*, 3874. (b) Yang, Z.; Wang, Z.; Bai, S.; Shen, K.; Chen, D.; Liu, X.; Lin, L.; Feng, X. *Chem. - Eur. J.* **2010**, *16*, 6632. (c) Mouri, S.; Chen, Z.; Mitsunuma, H.; Furutachi, M.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 1255. (d) Zhou, F.; Ding, M.; Liu, Y.-L.; Wang, C.-H.; Ji, C.-B.; Zhang, Y.-Y.; Zhou, J. *Adv. Synth. Catal.* **2011**, *353*, 2945. (e) Zhong, F.; Dou, X.; Han, X.; Yao, W.; Zhu, Q.; Meng, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 943. (f) Deng, Q.-H.; Bleith, T.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2013**, *135*, 5356.

(15) (a) Chen, W.-B.; Wu, Z.-J.; Hu, J.; Cun, L.-F.; Zhang, X.-M.; Yuan, W. C. *Org. Lett.* **2011**, *13*, 2472. (b) Kato, S.; Yoshino, T.; Shibasaki, M.; Kanai, M.; Matsunaga, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 7007. (c) Du, D.; Jiang, Y.; Xu, Q.; Shi, M. *Adv. Synth. Catal.* **2013**, *355*, 2249. (d) Cao, Y.-M.; Shen, F.-F.; Zhang, F.-T.; Wang, R. *Chem. - Eur. J.* **2013**, *19*, 1184. (e) Fu, Z.-K.; Pan, J.-Y.; Xu, D.-C.; Xie, J.-W. *RSC Adv.* **2014**, *4*, 51548. (f) Cai, H.; Zhou, Y.; Zhang, D.; Xu, J.; Liu, H. *Chem. Commun.* **2014**, *50*, 14771. (g) Tan, F.; Lu, L.; Yang, Q.-Q.; Guo, W.; Bian, Q.; Chen, J.-R.; Xiao, W.-J. *Chem. - Eur. J.* **2014**, *20*, 3415. (h) Wang, L.; Yang, D.; Li, D.; Liu, X.; Zhao, Q.; Zhu, R.; Zhang, B.; Wang, R. *Org. Lett.* **2015**, *17*, 4260. (i) Kayal, S.; Mukherjee, S. *Org. Lett.* **2015**, *17*, 5508.

(16) (a) Yan, W.; Wang, D.; Feng, J.; Li, P.; Zhao, D.; Wang, R. *Org. Lett.* **2012**, *14*, 2512. (b) Arai, T.; Matsumura, E.; Masu, H. *Org. Lett.* **2014**, *16*, 2768. (c) Holmquist, M.; Blay, G.; Pedro, J. R. *Chem. Commun.* **2014**, *50*, 9309. (d) Yin, X.-P.; Zeng, X.-P.; Liu, Y.-L.; Liao, F.-M.; Yu, J.-S.; Zhou, F.; Zhou, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 13740. (e) Zhao, J.; Fang, B.; Luo, W.; Hao, X.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 241. (f) Engl, O. D.; Fritz, S. P.; Wennemers, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 8193. (g) Arai, T.; Tsuchiya, K.; Matsumura, E. *Org. Lett.* **2015**, *17*, 2416. (h) Nakamura, S.; Takahashi, S. *Org. Lett.* **2015**, *17*, 2590. (i) Bao, X.; Wang, B.; Cui, L.; Zhu, G.; He, Y.; Qu, J.; Song, Y. *Org. Lett.* **2015**, *17*, 5168.

(17) Montesinos-Magraner, M.; Vila, C.; Cantón, R.; Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R. *Angew. Chem., Int. Ed.* **2015**, *54*, 6320.

(18) (a) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3353. (b) Liu, Z.; Gu, P.; Shi, M.; McDowell, P.; Li, G. *Org. Lett.* **2011**, *13*, 2314.

(19) (a) Schiffner, J. A.; Machotta, A. B.; Oestreich, M. *Synlett* **2008**, *2008*, 2271. (b) He, W.; Yip, K.-T.; Zhu, N.-Y.; Yang, D. *Org. Lett.* **2009**, *11*, 5626. (c) Brunner, H.; Obermann, U.; Wimmer, P. *J. Organomet. Chem.* **1986**, *316*, C1. (d) VonMatt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566. (e) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769. (f) Dawson, G. L.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 3149. (g) Nishibayashi, Y.; Uemura, S. *Synlett* **1995**, *1995*, 79. (h) Richards, C. J.; Damalidis, T.; Hibbs, D. E.; Hursthouse, M. B. *Synlett* **1995**, *1995*, 74. (i) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932.

(20) (a) Arnott, G.; Brice, H.; Clayden, J.; Blaney, E. *Org. Lett.* **2008**, *10*, 3089. (b) Mita, T.; Sugawara, M.; Saito, K.; Sato, Y. *Org. Lett.* **2014**, *16*, 3028.

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Ir(III)-Catalyzed Synthesis of Isoquinoline *N*-Oxides from Aryloxime and α-Diazocarbonyl Compounds

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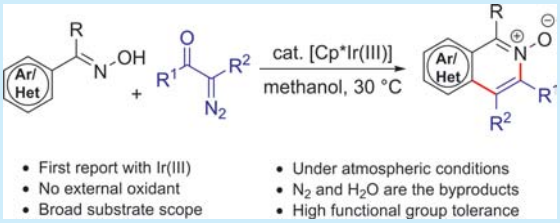
Supporting Information

ABSTRACT: An efficient Ir(III)-catalyzed C−H activation and annulations of aryloxime with α-diazocarbonyl compounds has been developed for the synthesis of substituted isoquinoline *N*-oxides. The reaction proceeds under mild atmospheric conditions, without any external oxidants and releases N_2 and H_2O as the byproducts. In addition, synthetic applications of the *N*-oxide products have been established by performing further functionalization. An interesting dimeric iridacyclic complex allied through a bis-silver carboxylate bridge has been isolated that efficiently catalyzed the reaction.



The *N*-oxide of isoquinoline and pyridine derivatives represents an important structural unit found in various natural products,[1] pharmaceutical agents,[2] and chiral ligands.[3] Besides this, *N*-oxides are isolable synthons with widespread utility in the functionalization of heterocycles and the synthesis of natural products.[4] Traditional synthesis of *N*-oxides involves the direct oxidation of parent heterocycles with a stoichiometric amount of peroxides or peracids.[5] The major limitations of these methods are the prerequisite of a completely fabricated heterocyclic unit and the compatibility of the sensitive functional group present on the substrate. The use of transition-metal-catalyzed transformations had, to some extent, addressed the oxidation under mild conditions.[6] Recently, C−H activation approaches have taken precedence over traditional methods, especially in the context of the synthesis of isoquinoline(oxide) derivatives by the annulation of simple imines/oximes with easily accessible alkenes/alkynes.[7] The inaugural entry in this regard was documented by Huang et al. and involves the Pd-catalyzed annulations of aryloximes and diary acetylenes via an C−H activation approach leading to isoquinoline *N*-oxides.[8] However, the requirement of high temperature and a stoichiometric amount of acids and alkyne scope are the major limitations of this approach. Recently, the Glorius group reported an elegant example of a Rh(III)-catalyzed intermolecular annulation reaction using vinyl or aryloximes and diazo compounds for the synthesis of pyridine and isoquinoline *N*-oxides.[9a]

Although substantial progress has been made in this type of C−H functionalization, the scope is mainly limited to Rh(III) catalytic systems.[9,10] Consequently, finding alternative catalytic systems for the synthesis of (hetero)aryl-fused pyridine *N*-oxides and their derivatives with a divergent product scope is of leading research interest. To explore a new catalyst with a versatile reaction scope, our attention has been focused on the Cp*Ir(III) catalyst system because of its excellent performance in C−H bond functionalization.[11−13] Inspired by these results, we envisioned the feasibility of directed C−H activation and annulation of aryloxime and α-diazocarbonyl compounds under iridium catalytic systems. Herein, we report the first Ir(III)-catalyzed intermolecular C−H functionalization and annulations of aromatic oxime with α-diazocarbonyl compounds affording diversely substituted isoquinoline *N*-oxides that allows a considerable expansion of C−H activation and annulations approaches (Scheme 1). Additionally, the present reaction

Scheme 1. Isoquinoline *N*-Oxide Synthesis

conditions provide a straightforward approach to the preparation of phosphorylated heterocycles, which have numerous applications in organic synthesis and material science.

To initiate the study, acetophenone oxime **1a** and Ohira-Bestman's diazophosphonate **2a** were selected as model substrates to screen the reaction parameters. After performing a few optimization experiments, we were pleased to find that the reaction proceeded very well to give **3a** in 95% yield, using 2.0 mol % of the $[IrCp^*Cl_2]_2$ and 8.0 mol % of $AgNTf_2$ in methanol at 30 °C (Scheme 1). The effect of solvent is found to be very crucial for the reaction, and methanol is found to be the best solvent (see the Supporting Information for a detailed optimization table). Interestingly, under similar conditions, a

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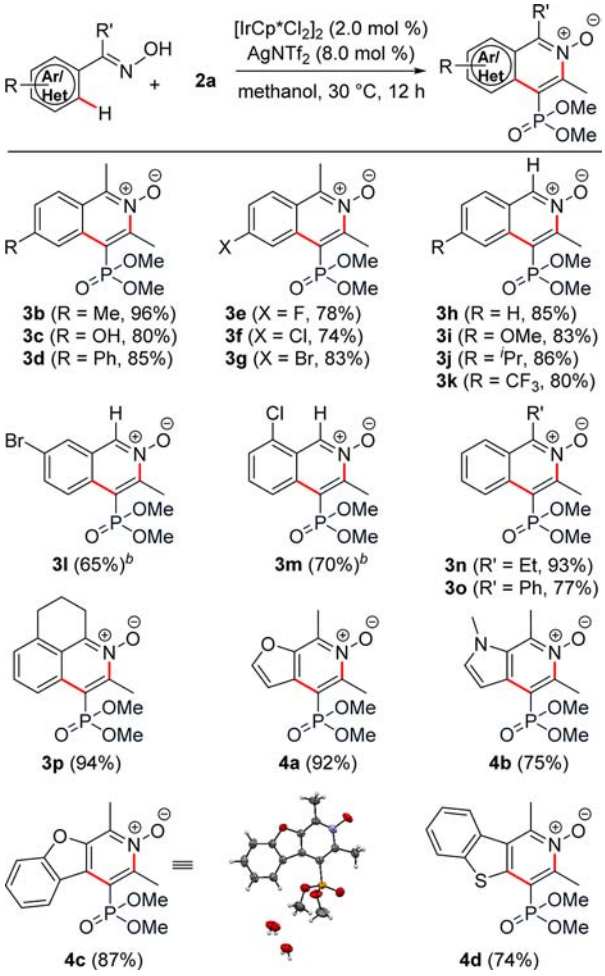
[Cp*Rh(III)] catalytic system was found to be less efficient (55% crude yield).

With the optimized reaction conditions in hand, we next examined the substrate scope of this transformation (Scheme 2).

Scheme 2. Substrate Scope of (Hetero)Aryl Oxime[a]



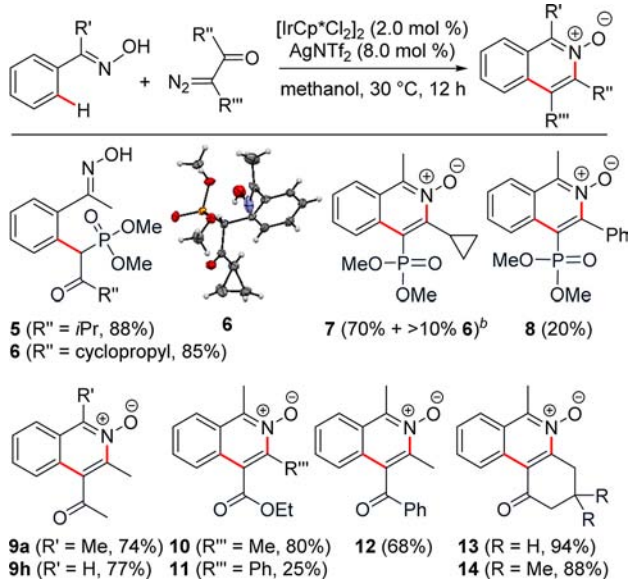
[a]Isolated yields are given. [b]Reaction carried out at 60 °C.

Substrates bearing both electron-donating groups (**3b**, **3c**) and electron-withdrawing groups (**3d**−**3g**) were compatible in this transformation and provided the corresponding *N*-oxide products in excellent yields. Next, the scope of the reaction was extended to benzaldehyde oxime derivatives. We were gratified to observe that not only benzaldehyde oxime **3h** but also substrates with electron-donating substituents **3i**−**3j** and electron-withdrawing substituents **3k**−**3m** were found to be compatible and provided the requisite *N*-oxide products in excellent yield. The reaction with substrates bearing substitution at *meta* (**3l**) and *ortho* (**3m**) positions were found to be sluggish under standard reaction conditions. However, the reaction yields could be increased to considerable amounts upon increasing the reaction temperature to 60 °C. Further, the effect of substitution on the methyl side of acetophenone oxime was studied. For instance, the reaction of oximes derived from acetophenone (**2n**), benzophenone (**2o**), and α-tetralone (**2p**) provided the cyclized products **3n**, **3o**, and **3p**, respectively, in excellent yields. However, reaction with vinyl and alkenyl oxime substrates was found to be very sluggish under the present conditions.

After successful conversion of aryloximes to isoquinoline *N*-oxide derivatives, we studied the feasibility of heteroaryloxime derivatives. We were pleased to see that the reaction of 1-(furan-2-yl)ethanone oxime with **2a** under standard reaction conditions gave the desired product **4a** in 92% yield (Scheme 2). Similarly, other heteroaromatic oximes derived from *N*-methylpyrrole (**4b**), benzofuran (**4c**), and benzothiophene (**4d**) were found to be compatible under these conditions. Additionally, the structure of **4c** was confirmed by X-ray crystallographic analysis.

With the established oxime scope in hand, we then explored the substituent effect on the diazo compound by changing the carbonyl substituent. Surprisingly, with treatment of dimethyl(1-diazo-3-methyl-2-oxobutyl)phosphonate, only the alkylated product **5** was observed in excellent yield, without further cyclization (Scheme 3). Likewise, the cyclopropyl-substituted

Scheme 3. Scope of α-Diazocarbonyl Compounds[a]



[a]Isolated yields are given. [b]Reaction carried out at 60 °C.

diazo compound gives exclusively the alkylated product **6** in high yield. The molecular structure of **6** was unambiguously established with the help of single-crystal X-ray structural analysis. At this stage, we hypothesized that maybe the higher energy barrier for the keto−enol isomerization is the reason for the isolation of the alkylated products and presumed that the increase in the reaction temperature is required to push the reaction to the final cyclized products. In fact, when the reaction was carried out at 60 °C, the cyclized *N*-oxide product **7** was obtained as the major product (70%) along with minor amount of alkylated products. This observation concludes that the overall reaction proceeds via alkylation followed by cyclization to give the isoquinoline *N*-oxide product. When phenyl-substituted diazo compound was used under standard conditions, only the cyclized product **8** was obtained in poor yield, maybe due to the steric bulkiness of the diazo compounds.

To further extend the generality of our reaction, the diazo compound without a phosphonate group was screened to afford various 4-substituted isoquinoline *N*-oxide (Scheme 3). The reaction of 3-diazopentane-2,4-dione occurred smoothly with both acetophenone oxime and benzaldehyde oxime to furnish desired *N*-oxide products **9a** and **9h**, respectively, in very good yield. Similarly, reaction of ethyl-2-diazo-3-oxobutanoate with **1a**

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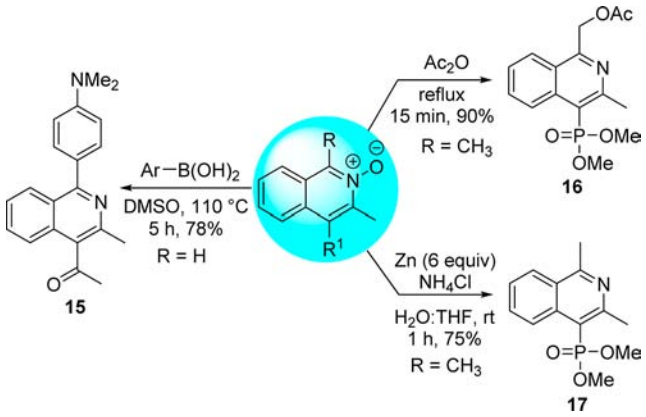
gave the desired product **10** in 80% yield. Sterically bulky ethyl-2-diazo-3-oxo-3-phenylpropanoate gave product **11** in poor yields. When the reaction was performed with sterically unsymmetrical 2-diazo-1-phenylbutane-1,3-dione, cyclization occurred exclusively with the less sterically hindered carbonyl group to give **12** in good yields. Similarly, cyclic diazocarbonyl compounds like 2-diazocyclohexane-1,3-dione and 2-diazo-5,5-dimethylcyclohexane-1,3-dione were found to be very efficient coupling partners to afford the corresponding tricyclic products **13** and **14** in excellent yield. However, 2-diazo-1-(piperidin-1-yl)butane-1,3-dione having an amide functionality was found to be an ineffective diazo source under the present conditions.

To shed light on the synthetic applicability of the *N*-oxide products, selected *N*-oxides were subjected to further functionalization (Scheme 4). For example, refluxing compound **9h** with

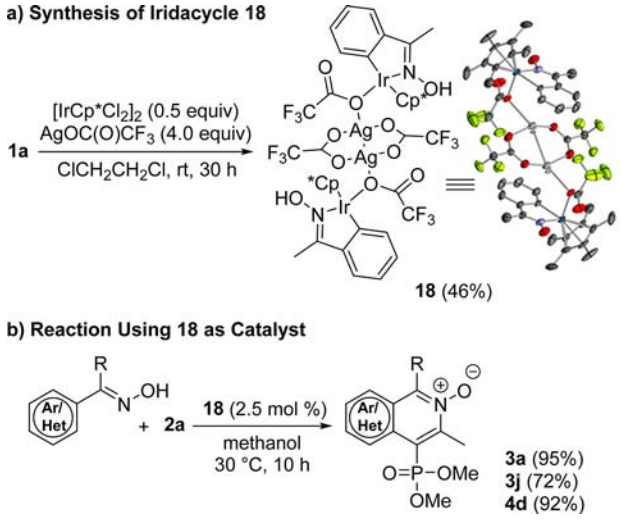
Scheme 4. Synthetic Application of *N*-Oxide Products



4-(dimethylamino)phenylboronic acid in DMSO gave the corresponding 1-arylated product **15** in good yield.[14] Selective acetoxylation of the C1-methyl of **3a** was achieved by refluxing with acetic anhydride to get product **16** in quantitative yield.[15] Further reduction of the N−O bond of **3a** using Zn and NH_4Cl gave the isoquinoline product **17** in good yields.[16]

To gain more mechanistic insight, we carried out several preliminary mechanistic experiments. A notable deuterium scrambling was observed when the reaction was performed in CD_3OD in the absence of diazo compound, indicating the reversibility of the C−H activation step. Performing the same reaction in the presence of **2a**, after 12 h of reaction, **3e** was isolated in 93%. Analysis of **3e** by ^1H NMR and ESI-MS showed no deuterium incorporation of the *ortho* proton (see the Supporting Information), suggesting the C−C bond formation to be significantly faster than the back reaction of the C−H activation step.[17] A relatively low value of primary kinetic isotope effects (KIE) was measured in parallel experiments (KIE = 1.43) and intramolecular competition reaction (KIE = 1.67). Although it is not convincing at the present stage, these KIE values indicate that the C−H bond cleavage may not be the rate-limiting stage.[12,18] After treatment of **2a** with $[IrCp^*Cl_2]_2$ and excess silver trifluoroacetate in 1,2-dichloroethane, a stable cyclometalated Ir(III) complex (**18**) was obtained, initially assumed to be monomeric Ir(III) complex.[19] The complex alone catalyzes the reaction without any Ag additives to give 95% of **3a**, which indicates the relevancy of C−H activation. X-ray crystallography analysis of the complex revealed that the complex contains two iridacycles connected through a dimeric silver bridge, as shown in Scheme 5a. To the best of our knowledge, this is the first isolation

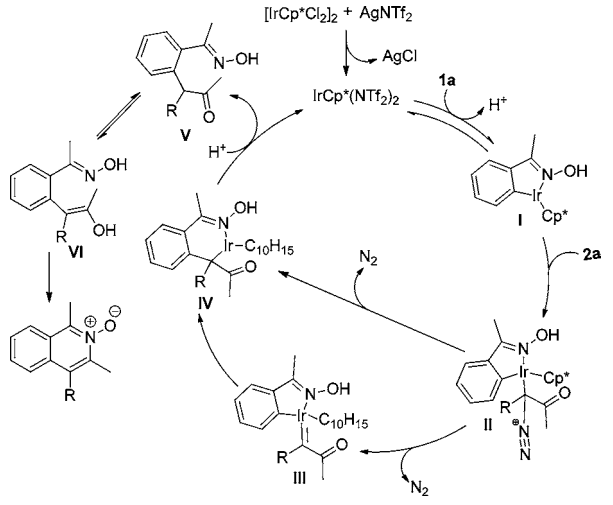
Scheme 5. Synthesis of Complex 18 and Its Catalytic Activity



of such types of bimetallic Ir complexes, which can catalyze the C−H activation very efficiently. Further, **18** was used as the catalyst for selected (hetero)aryloximes to furnish **3j** and **4d** in good to excellent yields (Scheme 5b).

Based on the above observed data and precedent literature reports,[9,13,20] a mechanistic pathway is proposed in Scheme 6.

Scheme 6. Proposed Catalytic Pathway



The first step is the generation of a cationic Ir(III) species from the $[IrCp^*Cl_2]_2$ with $AgNTf_2$ additive, which facilitates the key C−H bond activation to afford a five-membered iridacyclic intermediate **I**. The diazonium intermediate **II** may form by the coordination of the diazo compound with **I**. Generation of the carbene intermediate **III** is assumed to take place before the subsequent migratory insertion of carbene to the C−Ir bond, leading to **IV**.[20] Alternatively, intramolecular 1,2-migratory insertion of the aryl group would give **IV**.[13] Next, protonolysis of **IV** delivers the alkylated product **V**, which is supposed to be in equilibrium with the corresponding enol intermediate **VI**. Finally, intermediate **VI** undergoes dehydration either via 6π electrocyclization or nucleophilic cyclization to give the desired product.[9]

In summary, we have developed an Ir(III)-catalyzed mild and external oxidant-free approach for the synthesis of isoquinoline

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and heretoaromatic-fused pyridine *N*-oxide derivatives. In addition, the present protocol provides a straightforward approach for the synthesis of phosphorylated heterocycles, an important structural feature in organic synthesis and material chemistry. During the course of the mechanistic investigations, we isolated a rare dimer of bimetallic species containing two iridacyclic units, which catalyzes the reaction without any additives. Further studies on the dimeric Ir complex and studies to expand this methodology for the synthesis of pyridine *N*-oxide derivatives are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03462.

Experimental procedure,characterization of new compounds (^{1}H, ^{13}C NMR spectra) and X-ray crystallographic data (PDF)

X-ray data for **4c** (CIF)

X-ray data for **6** (CIF)

X-ray data for **18** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Nicholas, G. M.; Blunt, J. W.; Munro, M. H. G. *J. Nat. Prod.* **2001**, *64*, 341. (b) O'Donnell, G.; Poeschl, R.; Zimhony, O.; Gunaratnam, M.; Moreira, J. B. C.; Neidle, S.; Evangelopoulos, D.; Bhakta, S.; Malkinson, J. P.; Boshoff, H. I.; Lenaerts, A.; Gibbons, S. *J. Nat. Prod.* **2009**, *72*, 360.

(2) (a) Xia, B.; Ma, W.; Zheng, B.; Zhang, X.; Fan, B. *Eur. J. Med. Chem.* **2008**, *43*, 1489. (b) Reux, B.; Nevalainen, T.; Raitio, K. H.; Koskinen, A. M. P. *Bioorg. Med. Chem.* **2009**, *17*, 4441. (c) Rajanarendar, E.; Raju, S.; Reddy, M. N.; Krishna, S. R.; Kiran, L. H.; Reddy, A. R. N.; Reddy, Y. N. *Eur. J. Med. Chem.* **2012**, *50*, 274.

(3) For a review, see: (a) Derdau, V.; Laschat, S.; Hupe, E.; Konig, W. A.; Dix, I.; Jones, P. G. *Eur. J. Inorg. Chem.* **1999**, *1999*, 1001. (b) Malkov, A. V.; Kocovsky, P. *Eur. J. Org. Chem.* **2007**, *2007*, 29. For recent representative examples, see: (c) Takenaka, N.; Sarangthem, R. S.; Captain, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 9708. (d) Chen, J.; Takenaka, N. *Chem. - Eur. J.* **2009**, *15*, 7268.

(4) (a) Campeau, L. C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. (b) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291.

(5) (a) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642. (b) Albini, A.; Pietra, S. *Heterocyclic N-Oxides*; CRC Press: Boca Raton, FL, 1991. (c) Youssif, S. *ARKIVOC* **2005**, *2001*, 242.

(6) For selected examples, see: (a) Yeom, H.-S.; Kim, S.; Shin, S. *Synlett* **2008**, *2008*, 924. (b) Yeom, H.-S.; Lee, Y.; Lee, J.-E.; Shin, S. *Org. Biomol. Chem.* **2009**, *7*, 4744. (c) Ding, Q.; Wang, D.; Sang, X.; Lin, Y.; Peng, Y. *Tetrahedron* **2012**, *68*, 8869. (d) Wang, H.; Zhu, M.; Ye, S.; Wu, J. *RSC Adv.* **2013**, *3*, 13626.

(7) Selected recent reviews on C−H activation: (a) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (b) Hashiguchi, B. G.; Bischof, S. M.; Konnick, M. M.; Periana, R. A. *Acc. Chem. Res.* **2012**, *45*, 885. (c) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (d) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (e) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (f) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74. (g) Noisier, A. F. M.; Brimble, M. A. *Chem. Rev.* **2014**, *114*, 8775. (h) Yang, L.; Huang, H. *Chem. Rev.* **2015**, *115*, 3468. (i) Song, G.; Li, X. *Acc. Chem. Res.* **2015**, *48*, 1007. (j) Ye, B.; Cramer, N. *Acc. Chem. Res.* **2015**, *48*, 1308.

(8) Li, B.; Jiao, P.; Zhong, H.; Huang, J. *Synlett* **2013**, *24*, 2431.

(9) (a) Shi, Z.; Koester, D. C.; Boultadakis-Arapinis, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 12204. (b) Sun, P.; Wu, Y.; Yang, T.; Wu, X.; Xu, J.; Lin, A.; Yao, H. *Adv. Synth. Catal.* **2015**, *357*, 2469.

(10) (a) Hu, F.; Xia, Y.; Ma, C.; Zhang, Y.; Wang, J. *Chem. Commun.* **2015**, *51*, 7986. (b) Cheng, Y.; Bolm, C. *Angew. Chem., Int. Ed.* **2015**, *54*, 12349. (c) Shi, L.; Yu, K.; Wang, B. *Chem. Commun.* **2015**, *51*, 17277.

(11) For selected examples of $[Cp^*IrCl_2]_2$-catalyzed C−H activation, see: (a) Ryu, J.; Kwak, J.; Shin, K.; Lee, D.; Chang, S. *J. Am. Chem. Soc.* **2013**, *135*, 12861. (b) Itoh, M.; Hirano, K.; Satoh, T.; Shibata, Y.; Tanaka, K.; Miura, M. *J. Org. Chem.* **2013**, *78*, 1365. (c) Pan, S.; Wakaki, T.; Ryu, N.; Shibata, T. *Chem. - Asian J.* **2014**, *9*, 1257. (d) Ai, W.; Yang, X.; Wu, Y.; Wang, X.; Li, Y.; Yang, Y.; Zhou, B. *Chem. - Eur. J.* **2014**, *20*, 17653. (f) Kang, T.; Kim, Y.; Lee, D.; Wang, Z.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 4141. (g) Xie, F.; Qi, Z.; Yu, S.; Li, X. *J. Am. Chem. Soc.* **2014**, *136*, 4780. (h) Kim, H.; Shin, K.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 5904. (i) Pan, C.; Jin, N.; Zhang, H.; Han, J.; Zhu, C. *J. Org. Chem.* **2014**, *79*, 9427. (j) Shin, K.; Chang, S. *J. Org. Chem.* **2014**, *79*, 12197.

(12) Selected recent examples of $[Cp^*IrCl_2]_2$-catalyzed C−H activation: (a) Ai, W.; Wu, Y.; Tang, H.; Yang, X.; Yang, Y.; Li, Y.; Zhou, B. *Chem. Commun.* **2015**, *51*, 7871. (b) Chen, H.; Huestis, M. P. *ChemCatChem* **2015**, *7*, 743. (c) Lee, D.; Chang, S. *Chem. - Eur. J.* **2015**, *21*, 5364. (d) Hou, W.; Yang, Y.; Ai, W.; Wu, Y.; Wang, X.; Zhou, B.; Li, Y. *Eur. J. Org. Chem.* **2015**, *2015*, 395. (e) Wu, Y.; Yang, Y.; Zhou, B.; Li, Y. *J. Org. Chem.* **2015**, *80*, 1946. (f) Wang, H.; Xie, F.; Qi, Z.; Li, X. *Org. Lett.* **2015**, *17*, 920. (g) Suzuki, C.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2015**, *17*, 1597. (h) Zhou, T.; Li, L.; Li, B.; Song, H.; Wang, B. *Org. Lett.* **2015**, *17*, 4204.

(13) For Cp*Ir(III)-catalyzed metal carbene migratory insertion, see: (a) Zhang, S.-S.; Jiang, C.-Y.; Wu, J.-Q.; Liu, X.-G.; Li, Q.; Huang, Z.-S.; Li, D.; Wang, H. *Chem. Commun.* **2015**, *51*, 10240. (b) Xia, Y.; Liu, Z.; Feng, S.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2015**, *80*, 223.

(14) (a) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (b) Bering, L.; Antonchick, A. P. *Org. Lett.* **2015**, *17*, 3134.

(15) Boekelheide, V.; Linn, W. J. *J. Am. Chem. Soc.* **1954**, *76*, 1286.

(16) Aoyagi, Y.; Abe, T.; Ohta, A. *Synthesis* **1997**, *1997*, 891.

(17) (a) Li, L.; Brennessel, W. W.; Jones, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 12414. (b) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908.

(18) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066.

(19) (a) Boutadla, Y.; Davies, D. L.; Jones, R. C.; Singh, K. *Chem. - Eur. J.* **2011**, *17*, 3438. (b) Watanabe, M.; Kashiwame, Y.; Kuwata, S.; Ikariya, T. *Eur. J. Inorg. Chem.* **2012**, *2012*, 504. (c) Patel, P.; Chang, S. *Org. Lett.* **2014**, *16*, 3328.

(20) (a) Chan, W.-W.; Lo, S.-F.; Zhou, Z.; Yu, W.-Y. *J. Am. Chem. Soc.* **2012**, *134*, 13565. (b) Hyster, T. K.; Ruhl, K. E.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 5364. (c) Shin, K.; Park, S.-W.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 8584. (d) Dateer, R. B.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 4908.

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Organic LETTERS

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Cytochrome P450 for Citreohybridonol Synthesis: Oxidative Derivatization of the Andrastin Scaffold

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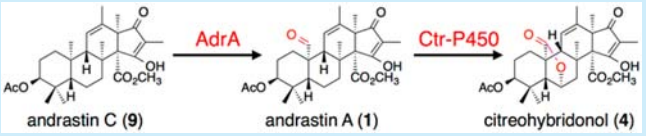
Supporting Information

ABSTRACT: A biosynthetic gene cluster similar to that for andrastin A (**1**) was discovered in *Emericella variecolor* NBRC 32302. Ctr-P450, a cytochrome P450 uniquely present in the cluster, was coexpressed with the andrastin A biosynthetic genes, leading to the production of the antifeedant agent citreohybridonol (**4**), along with four new andrastin derivatives. The results revealed the unusual multifunctionality of Ctr-P450 and indicated that this approach can be applied for further natural product diversification.



The most remarkable and important feature of natural products is their structural diversity, as this contributes to their wide range of biological properties. The fungal meroterpenoids are a representative class of natural products with diverse structures and bioactivities,[1,2] and especially, those synthesized via the aromatic polyketide, 3,5-dimethylorsellinic acid (DMOA), include numerous compounds, often with intriguing molecular architectures. The biosynthetic gene clusters and complete biosynthetic pathways of four DMOA-derived meroterpenoids, namely, terretonin, austinol, anditomin, and andrastin A, have been reported.[3−10] With the accumulation of genomic data of many fungal strains, gene clusters including a putative DMOA synthase can now be found in several publicly available genomes, suggesting that functional analyses and manipulations of these gene clusters will lead to the production of novel natural products.

Andrastin A (**1**), isolated as an inhibitor of the Ras farnesyltransferase,[11−13] is biosynthesized by nine dedicated enzymes encoded by the *adr* cluster in *Penicillium chrysogenum*.[10] In the biosynthetic process, the nonreducing polyketide synthase (NR-PKS) AdrD forms the aromatic compound DMOA. This is followed by the farnesylation, methyl esterification, epoxidation, and cyclization catalyzed by the prenyltransferase AdrG, the methyltransferase AdrK, the flavin-dependent mono-oxygenase AdrH, and the terpene cyclase AdrI, respectively. Subsequently, andrastin E (**2**), the tetracyclic intermediate generated thereby, undergoes tailoring reactions performed by four enzymes: **2** is converted into **1** by the short-chain dehydrogenase AdrF, the ketoreductase AdrE, the acetyltransferase AdrJ, and the cytochrome P450 mono-oxygenase AdrA (Figure 1A).

Interestingly, many meroterpenoids possessing the same scaffold as andrastins have been isolated but modified further or in a different manner. These molecules include citreohybridonol (**4**),[14] citreohybridones,[15−17] isocitreohybridones,[16−19] citreohybriddiones,[18,20] and atlantinones[21,22] (Figure 1B), and some of these compounds reportedly exhibit antifeedant and insecticidal activities. Considering their biological activities, biosynthetic analyses or engineering of natural products with the andrastin scaffold could facilitate the development of new pharmaceuticals or agrochemicals. In this study, we found a gene cluster that is similar to the *adr* cluster and demonstrated that a cytochrome P450 mono-oxygenase encoded by the cluster (Ctr-P450) is responsible for the transformation of **1** into **4**. Significantly, four new metabolites were also obtained by the introduction of this single P450 to the production system of **1**.

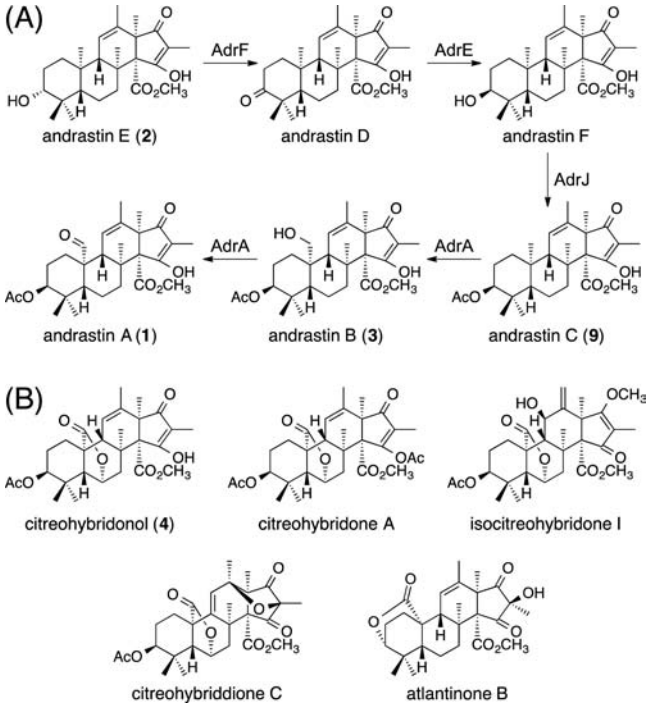


Figure 1. (A) Biosynthesis of andrastin A (**1**). (B) Structures of selected fungal meroterpenoids with the andrastin scaffold.

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In our previous study on the biosynthesis of anditomin, we performed the whole genome sequencing analysis of *Emericella variecolor* NBRC 32302.[9] Interestingly, we found that the fungus possesses another gene cluster that might be responsible for meroterpenoid biosynthesis, which consists of 11 ORFs (Figure 2 and Figure S1, DDBJ/EMBL/GenBank accession number

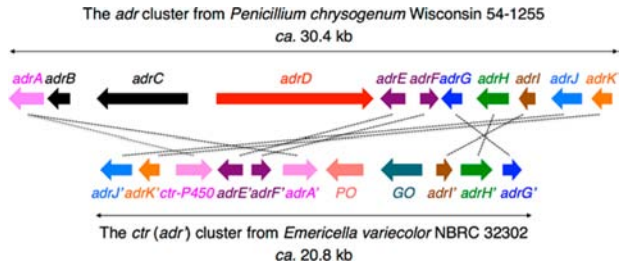

Figure 2. Schematic representation of the *ctr* (*adr'*) cluster and the *adr* cluster. Hashed lines indicate each corresponding gene in the other cluster.

LC102187). Although the cluster does not encode a PKS, which is typically found in biosynthetic gene clusters for polyketide-derived meroterpenoids, the products from 8 out of the 11 genes are highly similar to those encoded by the *adr* cluster[10] (43−69% identity with each corresponding enzyme). Intriguingly, two of the three additional enzymes are homologous to DyP-type peroxidase (PO) and galactose oxidase (GO), respectively, which have never been found in the previously characterized gene clusters for fungal meroterpenoids. The remaining protein is a putative cytochrome P450 mono-oxygenase, which is somewhat similar to AdrA and the other P450 encoded by the cluster (~45% identity). It should be noted that *P. chrysogenum* encodes a highly homologous protein with this putative P450 (Pc16g00090, 65% identity), but the gene is located outside the *adr* cluster, and its function has yet to be elucidated. Collectively, we reasoned that the cluster could synthesize an oxidized derivative of **1**.

To analyze the functions of the three proteins, their genes were introduced and heterologously expressed in the *Aspergillus oryzae* NSAR1[23] transformant harboring *adrF*, *E*, *J*, and *A*, which was constructed in our previous work.[10] The transformant was cultivated in the presence of **2**, and the metabolites were analyzed by HPLC. While the control strain without the additional genes produced **1** and **3**, the seven-gene expression system gave the major product **4**, which was not observed in the control transformant (Figure 3A, lanes i and ii). The molecular formula of **4** was deduced to be $C_{28}H_{36}O_8$, based on the HR-EI-MS analysis, and therefore, **4** is 14 Da larger than **1**, with the molecular formula $C_{28}H_{38}O_7$. After large-scale cultivation, **4** was purified, isolated, and then subjected to NMR analyses. The ^{1}H NMR spectrum of **4** was indeed similar to that of **1** but revealed the disappearance of the signal derived from the aldehyde proton and the presence of an oxymethine signal at 4.85 ppm. Further 2D NMR spectral analyses illuminated the lactone ring formation between the C-6 and C-23 positions and revealed the complete structure of **4**, which was found to be a known natural product, citreohybridonol[14] (Figure 3B, Table S3, and Figures S7−S12).

To clarify the contributions by the three proteins to the generation of **4**, six-gene expression systems lacking one of the three genes were constructed and incubated with **2**. As a result, **4** was obtained from the strains expressing the P450/PO or P450/GO, but **4** was not produced in the transformant with PO/GO,

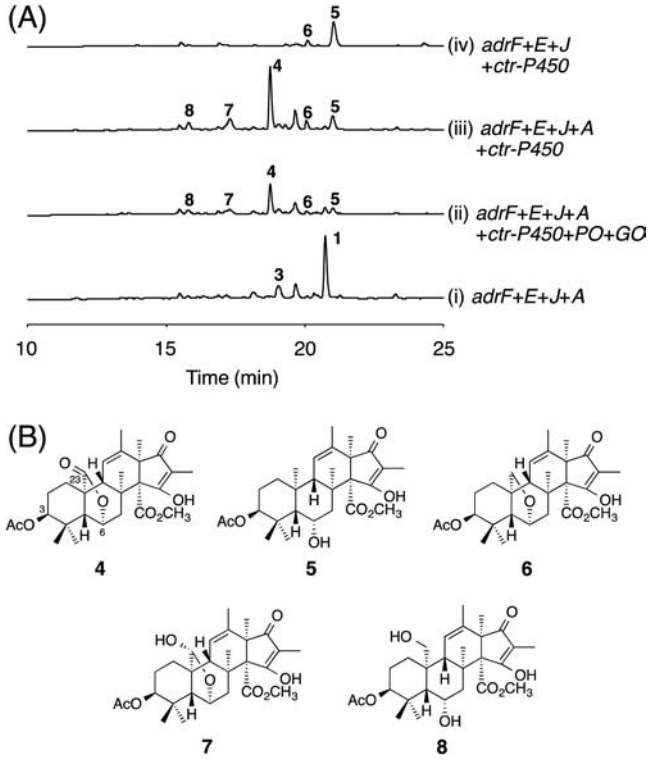

Figure 3. Biotransformation of andrastin E (**2**). (A) HPLC chromatograms of metabolites derived from *A. oryzae* transformant incubated with **2**: transformants harboring (i) *adrF* + *E* + *J* + *A*; (ii) *adrF* + *E* + *J* + *A* + *ctr-P450* + *PO* + *GO*; (iii) *adrF* + *E* + *J* + *A* + *ctr-P450*; (iv) *adrF* + *E* + *J* + *ctr-P450*. (B) Structures of compounds **4**−**8** isolated in this study. The chromatograms were monitored at 254 nm.

which lacked the P450 (Figure S3). These observations clearly indicated that the PO and GO are not involved in the formation of **4**, and that the addition of the P450 is sufficient for the synthesis of **4**. To further confirm this hypothesis, the five-gene expression system lacking both the PO and GO was constructed. As expected, the transformant successfully converted **2** into **4** (Figure 3A, lane iii), which ruled out the possibility that the PO or GO participates in the biosynthesis of **4**. The P450 was hereby named Ctr-P450.

In the course of analyzing the metabolites produced by both the seven and five-gene-expressing transformants, we realized that four other minor products (**5**−**8**) were also produced (Figure 3A, lanes ii and iii). All four compounds were isolated and characterized by MS and NMR analyses (Figure 3B, Tables S4−S7, and Figures S13−S36), and we found that none of them was previously described and they did not seem to be derived from **1**, suggesting that Ctr-P450 works before the reaction by the other P450 AdrA. Compound **5** is an oxidized form of andrastin C (**9**) with a 6α-hydroxyl functionality and thus was designated as 6α-hydroxyandrastin C. The structure of **6**, which was named 23-deoxocitreohybridonol, was somewhat surprising since it has an ether linkage between C-6 and C-23 and is apparently derived from the direct oxidation of **5**. Compound **7**, named dihydrocitreohybridonol, is the hydroxylated form of **6** containing a hemiacetal moiety, while **8** was found to be the 6α-hydroxyl derivative of andrastin B (**3**).

Since the isolation of the above-described molecules evoked the question of the intermediacy of these compounds in citreohybridonol biosynthesis, we then sought to elucidate the pathway leading to **4** and to obtain deeper insight into the Ctr-

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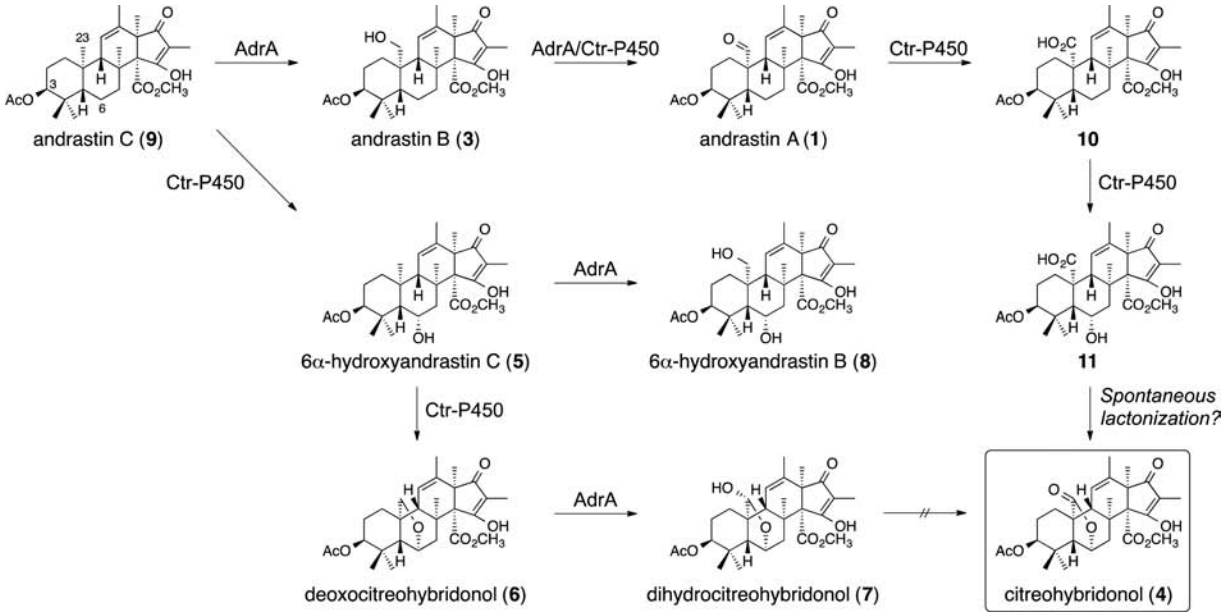
Scheme 1. Proposed Biosynthetic Mechanism of Citreohybridonol (4) and New Andrastin Analogues (5−8)



P450-catalyzed reactions. First, we constructed the transformant with four genes, *adrF*, *adrE*, *adrJ*, and *ctr-P450*, to investigate whether the P450 AdrA was essential. The four-gene expression system without *adrA* transformed **2** into 6α-hydroxyandrastin C (**5**) and 23-deoxocitreohybridonol (**6**), but the production of **4** was not observed in this strain (Figure 3A, lane iv). This confirmed that AdrA is indispensable for the citreohybridonol synthesis and indicated that Ctr-P450 accepts **9** as a substrate to perform C-6 α-hydroxylation and heterocyclization. Subsequently, bioconversion experiments using only Ctr-P450 or AdrA were performed to reveal the roles of each P450. Single-gene-expressing transformants harboring one of the two P450 genes were constructed and cultivated in the presence of one of the obtained compounds. In the experiments with Ctr-P450, **1** and **3** were efficiently converted into **4** (Figure S4). In contrast, **5** was only transformed to **6**, and dihydrocitreohybridonol (**7**) and 6α-hydroxyandrastin B (**8**) remained unconverted (Figure S4). The other P450, AdrA, transformed **5** and **6** into **8** and **7**, respectively (Figure S5), which were not accepted by Ctr-P450 as substrates, as mentioned above. Consistently, the bioconversion tests with **7** and **8** confirmed that these molecules are not further oxidized by AdrA (Figure S5). Taken together, only **1** and **3** can be incorporated into the biosynthetic line of **4**, and none of the four new compounds isolated in this study is a pathway intermediate for **4** (Scheme 1).

Although **1** was proved to be the precursor of **4**, some ambiguity still remained in the biosynthetic route between **1** and **4**, as we were not able to isolate any intermediate for this conversion. However, if Ctr-P450 hydroxylates the C-6 position of **1**, the resulting product would be converted to the hemiacetal **7** that cannot be further transformed into **4**, and therefore, the occurrence of the C-6 hydroxylation of **1** seems unlikely. Consistently, **7** was not detected in the bioconversion of **1** with Ctr-P450. Thus, one of the plausible explanations would be that Ctr-P450 initially oxidizes C-23 of **1** to yield the corresponding carboxylic acid **10** and then hydroxylates the C-6 position to give **11**, which could spontaneously undergo lactonization to provide **4**, as seen in gibberellin biogenesis[24] (Scheme 1).

It should be emphasized that the introduction of a cytochrome P450 to the already established system led to the generation of five additional metabolites, including four novel molecules. In terms of biosynthetic mechanisms, the multifunctionality of Ctr-P450 is noteworthy, and the ether bridge formation to yield **6** from **9** is especially interesting because this reaction represents a rare example in which a single P450 catalyzes both hydroxylation and heterocyclization. A similar reaction is catalyzed in aureothin biosynthesis, in which the P450 AurH initially hydroxylates the allylic methylene and then forms a THF moiety with the allylic methyl group,[25] and therefore, ether formation by Ctr-P450 should proceed in a manner resembling that proposed for AurH (Figure S6). The reaction by Ctr-P450, however, differs in that the enzyme oxidizes an aliphatic methylene/methyl to generate the THF ring. Additionally, although P450-catalyzed ether linkage formation is commonly seen in the biosynthesis of fungal meroterpenoids, such as indole diterpenoids,[26,27] Ctr-P450 seems to be the first example of the generation of the ether bridge by the utilization of a methyl group in the fungal natural product pathways.

Combinatorial biosynthesis approaches have been widely utilized to create natural product analogues and are considered to be a promising methodology to afford novel drug leads.[28] As demonstrated in this study, DMOA-derived meroterpenoids are a good starting point to perform combinatorial biosynthesis since several gene clusters for these compounds have been identified and many others will soon be available in this postgenomic era. Unfortunately, we could not detect the PO and GO activities encoded by the *ctr* cluster, but this could be attributed to the possibility that the cluster might be a dead or inactive cluster with many mutations. This hypothesis is supported by the fact that the cluster lacks a PKS gene and that no andrastin-like molecule has been isolated from *Aspergillus* (or *Emericella*) *variecolor*. Quite interestingly, gene clusters similar to the *adr* or *ctr* cluster, with putative PO and GO genes, are also present in several publicly available genomes, such as those of *P. expansum* ATCC 24692, *P. camemberti* FM 013, and *P. fellutanum* ATCC 48694 (Figure S2). The cluster from *P. expansum* is quite similar to the *adr* cluster, in terms of the gene organization, but contains additional PO and

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GO genes homologous to those found in the *ctr* cluster, as well as another PO gene that is less similar to that in the *ctr* cluster. Two PO and one GO gene sets are also present in the cluster from *P. camemberti*, but the cluster does not encode the homologous enzymes to AdrF, E, and J, which are responsible for the C-3 epimerization and acetylation. The absence of the genes for the C-3 modifications is similarly observed in the cluster from *P. fellutanum*, and the cluster possesses only one PO gene. Thus, the clusters from *P. camemberti* and *P. fellutanum* might produce andrastin-like molecules without C-3 epimerization, such as atlantinones.[21,22] Combinatorial biosynthesis with the aid of the gene products derived from the above-described clusters could provide new andrastin derivatives, perhaps with improved biological activities.

In conclusion, we have derivatized the andrastin scaffold into five compounds with Ctr-P450, using an *A. oryzae* heterologous expression system. We believe that this simple approach will be applicable not only to obtain further new andrastin analogues but also to derivatize different classes of fungal metabolites, which will definitely lead to the expanded diversity of natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03465.

Experimental details, supplementary figures, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Geris, R.; Simpson, T. J. *Nat. Prod. Rep.* **2009**, *26*, 1063−1094.
(2) Matsuda, Y.; Abe, I. *Nat. Prod. Rep.* **2016**, *33*, 26−53.
(3) Itoh, T.; Tokunaga, K.; Radhakrishnan, E. K.; Fujii, I.; Abe, I.; Ebizuka, Y.; Kushiro, T. *ChemBioChem* **2012**, *13*, 1132−1135.
(4) Matsuda, Y.; Awakawa, T.; Itoh, T.; Wakimoto, T.; Kushiro, T.; Fujii, I.; Ebizuka, Y.; Abe, I. *ChemBioChem* **2012**, *13*, 1738−1741.
(5) Guo, C.-J.; Knox, B. P.; Chiang, Y.-M.; Lo, H.-C.; Sanchez, J. F.; Lee, K.-H.; Oakley, B. R.; Bruno, K. S.; Wang, C. C. *Org. Lett.* **2012**, *14*, 5684−5687.
(6) Matsuda, Y.; Iwabuchi, T.; Wakimoto, T.; Awakawa, T.; Abe, I. *J. Am. Chem. Soc.* **2015**, *137*, 3393−3401.
(7) Lo, H.-C.; Entwistle, R.; Guo, C.-J.; Ahuja, M.; Szewczyk, E.; Hung, J.-H.; Chiang, Y.-M.; Oakley, B.; Wang, C. C. *J. Am. Chem. Soc.* **2012**, *134*, 4709−4720.
(8) Matsuda, Y.; Awakawa, T.; Wakimoto, T.; Abe, I. *J. Am. Chem. Soc.* **2013**, *135*, 10962−10965.
(9) Matsuda, Y.; Wakimoto, T.; Mori, T.; Awakawa, T.; Abe, I. *J. Am. Chem. Soc.* **2014**, *136*, 15326−15336.
(10) Matsuda, Y.; Awakawa, T.; Abe, I. *Tetrahedron* **2013**, *69*, 8199−8204.
(11) Shiomi, K.; Uchida, R.; Inokoshi, J.; Tanaka, H.; Iwai, Y.; Omura, S. *Tetrahedron Lett.* **1996**, *37*, 1265−1268.
(12) Omura, S.; Inokoshi, J.; Uchida, R.; Shiomi, K.; Masuma, R.; Kawakubo, T.; Tanaka, H.; Iwai, Y.; Kosemura, S.; Yamamura, S. *J. Antibiot.* **1996**, *49*, 414−417.
(13) Uchida, R.; Shiomi, K.; Inokoshi, J.; Sunazuka, T.; Tanaka, H.; Iwai, Y.; Takayanagi, H.; Omura, S. *J. Antibiot.* **1996**, *49*, 418−424.
(14) Kosemura, S.; Miyata, H.; Matsunaga, K.; Yamamura, S. *Tetrahedron Lett.* **1992**, *33*, 3883−3886.
(15) Kosemura, S.; Matsunaga, K.; Yamamura, S.; Kubota, M.; Ohba, S. *Tetrahedron Lett.* **1991**, *32*, 3543−3546.
(16) Kosemura, S.; Yamamura, S. *Tetrahedron Lett.* **1997**, *38*, 6221−6224.
(17) Kosemura, S. *Tetrahedron Lett.* **2002**, *43*, 1253−1256.
(18) Kosemura, S.; Matsunaga, K.; Yamamura, S. *Chem. Lett.* **1991**, *20*, 1811−1814.
(19) Kosemura, S. *Tetrahedron* **2003**, *59*, 5055−5072.
(20) Kosemura, S.; Matsuo, S.; Yamamura, S. *Phytochemistry* **1996**, *43*, 1231−1234.
(21) Wang, X.; Sena Filho, J. G.; Hoover, A. R.; King, J. B.; Ellis, T. K.; Powell, D. R.; Cichewicz, R. H. *J. Nat. Prod.* **2010**, *73*, 942−948.
(22) Dalsgaard, P. W.; Petersen, B. O.; Duus, J. Ø.; Zidorn, C.; Frisvad, J. C.; Christophersen, C.; Larsen, T. O. *Metabolites* **2012**, *2*, 214−220.
(23) Jin, F. J.; Maruyama, J.; Juvvadi, P. R.; Arioka, M.; Kitamoto, K. *FEMS Microbiol. Lett.* **2004**, *239*, 79−85.
(24) Bömke, C.; Rojas, M. C.; Gong, F.; Hedden, P.; Tudzynski, B. *Appl. Environ. Microbiol.* **2008**, *74*, 5325−5339.
(25) Richter, M. E.; Traitcheva, N.; Knüpfer, U.; Hertweck, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 8872−8875.
(26) Nicholson, M. J.; Koulman, A.; Monahan, B. J.; Pritchard, B. L.; Payne, G. A.; Scott, B. *Appl. Environ. Microbiol.* **2009**, *75*, 7469−7481.
(27) Liu, C.; Tagami, K.; Minami, A.; Matsumoto, T.; Frisvad, J. C.; Suzuki, H.; Ishikawa, J.; Gomi, K.; Oikawa, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 5748−5752.
(28) Kim, E.; Moore, B. S.; Yoon, Y. J. *Nat. Chem. Biol.* **2015**, *11*, 649−659.

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Cobalt-Catalyzed N-Alkylation of Amines with Alcohols

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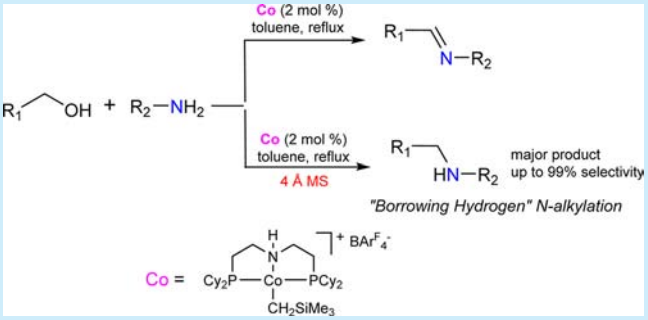
Supporting Information

ABSTRACT: A well-defined nonprecious metal cobalt(II) catalyst based on a pincer PNP ligand has been employed for the efficient N-alkylation of both aromatic and aliphatic amines with alcohols. A subtle change of reaction conditions (simply adding 4 Å molecular sieves) was observed to readily switch the resulting products (amines vs imines) with high chemoselectivity. A range of alcohols and amines including both aromatic and aliphatic substrates were efficiently converted to secondary amines in good-to-excellent yields when 2 mol % cobalt catalyst was used. Additional experiments indicate that a hydrogen-borrowing mechanism is responsible for the tandem acceptorless dehydrogenation/condensation/hydrogenation process.



Precious metal (Ru, Ir, Pd, etc.) catalysis has been involved in most crucial organic transformations to date, including some C−C and C−N bond-forming reactions.[1] High catalytic activity and turnover frequencies have been achieved by using such precious metal catalysts.[1] However, the scarcity, cost, and toxicity of precious metals can be problematic, making them less attractive for widespread and large-scale commercial applications in industry. In recent decades, the replacement of precious metal catalysts with earth-abundant element alternatives has become a focused research theme, in consideration of "greener" and more sustainable chemistry for the future.[2] Significant progress has been made in the development of homogeneous base metal (Fe, Co, Ni, etc.) catalysts,[3,4] although major challenges remain as the first-row transition metals tend to undergo one-electron changes in oxidation state and radical reactions, which has limited their applications as catalysts.

The catalytic N-alkylation of amines with alcohols provides a green and atom-economic pathway for the synthesis of substituted amines that have important synthetic applications in pharmaceutical chemistry.[5−7] Precious metal Ir- and Ru-catalyzed amine alkylation by alcohols has been previously reported by several groups.[8−10] In these examples, a "hydrogen-borrowing" mechanism has been proposed that involves three successive steps, i.e., acceptorless dehydrogenation of alcohols, imine formation, and the hydrogenation of imines using the hydrogen equivalents generated from the previous dehydrogenation step.[11] Despite such advances, well-defined molecular catalysts composed of earth-abundant metals for direct amine alkylation remain extremely scarce to date.[12−14] The only homogeneous catalyst system involving a Co^{II} complex that catalyzed N-alkylation of aromatic amines by alcohols was reported very recently but required the use of a strong base (potassium *tert*-butoxide).[14] Therefore, the discovery of new molecular catalysts based on nonprecious metals enabling this type of reaction is still highly desirable.

Recently, we have observed that an ionic cobalt(II) alkyl complex $[(PNHP^{Cy})Co(CH_2SiMe_3)][BAr^F_4]$ (**2**, Scheme 1) built on a pincer-type PNP ligand carries out hydrogenation reactions as a precatalyst under mild conditions and at low H_2 pressure (1−4 atm).[15−18] The catalyst was found to be versatile for the highly efficient reduction of a broad range of chemicals including alkenes, aldehydes, ketones, and imines[15,16] and the transfer hydrogenation of a variety of polar double bonds, indicating great potential of cobalt in replacing precious metal hydrogenation catalysts.[17] Furthermore, it was revealed that the same cobalt complex catalyzed the acceptorless dehydrogenation of alcohols as well as the formation of imines from alcohols and amines upon heating a toluene solution of both substrates in the presence of in situ formed catalyst **2** (Scheme 2).[18] The capability of cobalt **2** in catalyzing acceptorless dehydrogenation has been further established by the Jones group very recently.[19] During the course of cobalt-catalyzed imine formation from alcohols and amines, we noticed that in a few cases reduced imines (amines) were formed as byproducts in less than 10% yield. We envisaged that a hydrogenation process of imine in the same catalytic system should have occurred and that it might be possible to switch the major products from imines to amines by altering the reaction conditions. Indeed, after many attempts, we were pleased to find that by simply adding 4 Å molecular sieves (MS) to the same reaction system the selective formation of monoalkylated amines occurred in high yields (Scheme 2).

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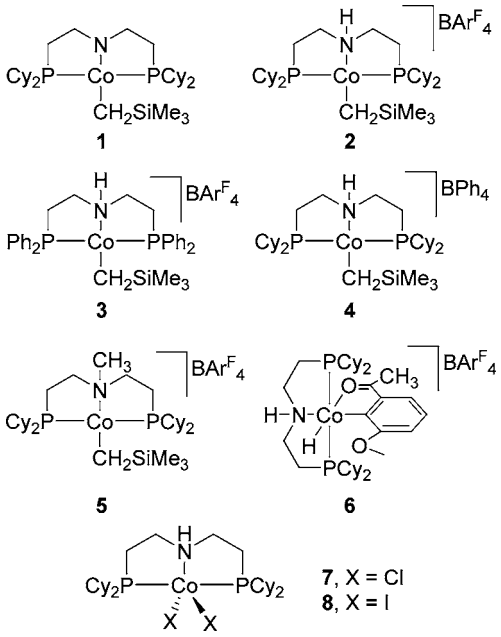
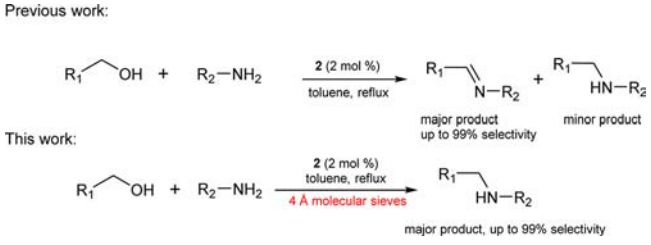
Scheme 1. Cobalt Complexes Studied for Catalytic N-Alkylation



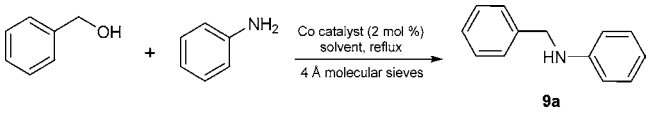
Scheme 2. Comparison of Distinct Product Selectivities in Cobalt-Catalyzed C−N Bond Formation



Therefore, we present herein the versatile cobalt complex catalyzed direct N-alkylation of various amines with alcohols, highlighting the importance of homogeneous earth abundant cobalt catalysts in C−N bond coupling reactions that involve a hydrogen-borrowing mechanism.

Several related cobalt complexes (**1**−**6**, Scheme 1) previously reported were first screened for the reaction between benzyl alcohol and aniline (1.2 equiv) in toluene at reflux in a 100 mL Schlenk tube with added 4 Å MS, and the results are summarized in Table 1. It was quite delightful to observe that when **2** (2 mol % based on alcohol, generated in situ by the reaction of **1** and $H[BAr^F_4]\cdot(Et_2O)_2$) was used as a catalyst, the desired *N*-alkylated amine **9a** was detected in 98% GC yield and the imine byproduct was largely suppressed to only a trace amount, while neutral complex **1** did not favor the formation of **9a** (entries 2 and 3, Table 1). However, in the latter case, the formation of an imine product in 12% yield was confirmed by GC analysis. In contrast, a control experiment in the presence of 4 Å MS, without the addition of a cobalt catalyst, gave no reaction at all (entry 1). In addition, changing the substituent (phenyl group vs cyclohexyl group) on the phosphorus atom of the PNP ligand (**3**) or the counteranion (**4**, BPh_4^- instead of $BAr^F_4{}^-$) resulted in lower yields of **9a** (entries 4 and 5), and adding a methyl group on the nitrogen atom of the ligand (**5**) also affected the reactivity (entry 6). Interestingly, the cobalt(III) complex **6**[16] was found to be an active catalyst as well, displaying comparable catalytic

Table 1. Screening of Reaction Conditions for the Selective N-Alkylation of Aniline by Benzyl Alcohol[a]



entry	catalyst	solvent	yield[b] (%)
1	no	toluene	0
2[c]	**1**	toluene	0
3	**2**	toluene	98
4	**3**	toluene	55
5	**4**	toluene	85
6	**5**	toluene	81
7	**6**	toluene	97
8	**7**	toluene	2
9	**8**	toluene	4
10	**2**	THF	45
11	**2**	1,4-dioxane	66
12	**2**	fluorobenzene	51
13[d]	**2**	toluene	49
14[e]	**2**	toluene	45
15[f]	**2**	toluene	78

[a]Conditions: benzyl alcohol (0.5 mmol), aniline (0.6 mmol), cobalt catalyst (2 mol %), 4 Å MS (0.5 g), and solvent (4 mL) refluxed in a 100 mL Schlenk tube, 48 h. [b]Determined by GC with hexamethylbenzene as internal standard. [c]12% imine was observed. [d]Reaction run at 80 °C. [e]Reaction run in a 50 mL Schlenk tube. [f]1 mol % of **2** was used.

efficacy to the cobalt(II) catalyst **2** (entry 7). Two new cobalt(II) dihalide complexes (**7** and **8**, see the SI) were also examined under the same conditions, yet no significant catalytic activity was detected (entries 8 and 9). Other solvents including THF, 1,4-dioxane, and fluorobenzene were tested using **2** (2 mol %) as a catalyst, but only inferior results were obtained (entries 10−12). Furthermore, lowering the reaction temperature drastically decreased the yield of **9a**, and reducing the volume of the reaction vial to 50 mL also suppressed the formation of the product (entries 13 and 14). Finally, it was found that the use of only 1 mol % of **2** also afforded the desired product in 78% GC yield (entry 15). Remarkably, no basic additives were required for the highly selective formation by using the active catalyst **2**, in sharp contrast to the previously reported $Co(PN_5P)$ precatalyst, where the presence of an excess amount of strong base, potassium *tert*-butoxide, was necessary for good catalytic performance.[14]

Having established the optimal catalytic conditions for the effective N-alkylation of aniline with benzyl alcohol, we sought to apply this methodology to other substrates, i.e., various alcohols and amines. First, we tested the reactions of benzyl alcohol with various aniline derivatives under standard reaction conditions (2 mol % of **2** and 4 Å MS in toluene at reflux), and the products were isolated by silica gel column chromatography after workup. The results are listed in Table 2. It was observed that electron-donating substituents such as isopropyl and methoxy groups in the *ortho*- or *para*-position of aniline favored the formation of *sec*-amine products, and **9b**−**d** were isolated in excellent yields (entries 2−4, Table 2). In contrast, *para*-substituents on aniline with electron-withdrawing groups led to slightly lower yields, and in the case of 4-fluoroaniline, 4% imine as a byproduct was observed on the basis of GC analysis (entry 5, Table 2). Next, we investigated the reactions of substituted benzylic alcohols with

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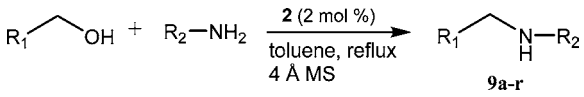
Table 2. Substrate Scope of the N-Alkylation Reactions of Different Amines by Alcohols[a]



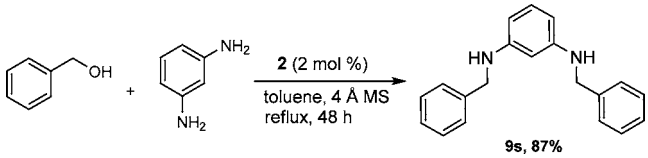
entry	alcohol (R_1 =)	amine (R_2 =)	yield[b] (%)
1	C_6H_5	C_6H_5	94 (**9a**)
2	C_6H_5	4-^{i}Pr(C_6H_4)	90 (**9b**)
3	C_6H_5	4-MeO(C_6H_4)	96 (**9c**)
4	C_6H_5	2-MeO(C_6H_4)	95 (**9d**)
5	C_6H_5	4-F(C_6H_4)	82 (**9e**), 4% imine
6	C_6H_5	4-Cl(C_6H_4)	80 (**9f**)
7	4-Me(C_6H_4)	C_6H_5	84 (**9g**), 13% imine
8	4-MeO(C_6H_4)	C_6H_5	90 (**9h**)
9	4-F(C_6H_4)	C_6H_5	80 (**9i**), 15% imine
10	(C_6H_4)CH_2	C_6H_5	74 (**9j**), 14% imine
11	propyl	C_6H_5	91 (**9k**)
12	isopropyl	C_6H_5	96 (**9l**)
13	pentyl	C_6H_5	90 (**9m**)
14	heptyl	C_6H_5	95 (**9n**)
15	C_6H_5	$(CH_2)_2C_6H_5$	82 (**9o**), 11% imine
16	C_6H_5	2-butyl	93 (**9p**), 2% imine
17[c]	pentyl	4-fluorobenzyl	75 (**9q**)
18[c]	heptyl	1-hexyl	86 (**9r**), 6% imine

[a]Conditions: alcohol (0.5 mmol), amine (0.6 mmol), cobalt catalyst **2** (2 mol %), 4 Å MS (0.5 g), and toluene (4 mL) at reflux in a 100 mL Schlenk tube, 48 h. [b]Isolated yields. [c]Yields determined by GC analysis.

aniline. It was noticed that strongly electron-donating 4-methoxy-derived benzylic alcohol was an excellent substrate for the reaction, affording the corresponding product **9h** in 90% yield (entry 8, Table 2), while electron-withdrawing substituents on the benzylic alcohol slightly decreased the yield of the desired *sec*-amine products, yet concomitant with the observation of 15% imine byproduct (entry 9). 2-Phenylethanol was also a suitable substrate, giving the desired *sec*-amine **9j** in reasonable yield, although a minor imine product was also detected (entry 10). Interestingly, several aliphatic alcohols also underwent the N-alkylation reactions with aniline smoothly, affording the desired products in high yields (entries 11−14). In addition, aliphatic amines were found to be suitable substrates for N-alkylation with alcohols including benzylic alcohol and aliphatic alcohols (entries 15−18). For instance, both 2-phenylethylamine and *sec*-butylamine reacted effectively with benzyl alcohol to provide the corresponding products in 82% and 93% yield, respectively, although minor imine byproducts were also present in the resulting reaction mixtures. Moreover, direct N-alkylation occurred between aliphatic alcohols and 4-fluorobenzylamine or 1-hexylamine producing, in the latter case, a *sec*-amine with a long alkyl chain in good yield. The good substrate scope involving aliphatic amines observed here is remarkable as, to the best of our knowledge, such substrates were only previously employed in an iron complex catalyzed N-alkylation through the hydrogen-borrowing process.[13]

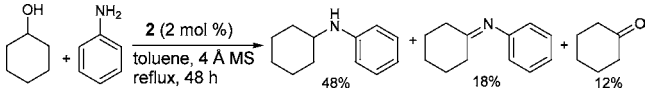
Encouraged by the above findings on a wide substrate scope for the alkylation of amines by alcohols, we performed additional experiments to further assess the ability of cobalt catalyst **2** to promote the reactions of other types of substrates. First, it was noted that *m*-diaminobenzene (0.5 mmol) could also be alkylated with benzyl alcohol (2.0 equiv), and the bis-alkylation product **9s** was isolated in 87% yield under standard conditions (Scheme 3). Second, when cyclohexanol, a secondary alcohol that was not previously utilized in the N-alkylation reaction, was

Scheme 3. N-Alkylation of 1,3-Diaminobenzene with Benzyl Alcohol



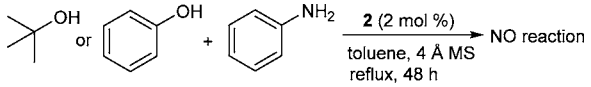
used to react with aniline under the optimal conditions, a mixture of amine, imine and ketone was detected after 48 h, with the expected N-cyclohexylaniline being the major product (48% GC yield, Scheme 4). Despite modest selectivity and yield, this result

Scheme 4. Reaction of Cyclohexanol and Aniline Catalyzed by 2



further indicates the exceptional catalytic activity of the Co^{II} complex **2**, which certainly deserves further investigation in the future. Finally, *tert*-butanol and phenol were tested for the reactions with aniline and, as expected, no coupling reactions were detected, which is consistent with a pathway involving initial alcohol dehydrogenation and supports the hydrogen-borrowing mechanism for the current cobalt-catalyzed N-alkylation reaction (Scheme 5).

Scheme 5. Reactivity Test of *tert*-Butyl Alcohol or Phenol with Aniline



In summary, we have here reported on the selective, direct N-alkylation of both aromatic and aliphatic amines by alcohols catalyzed by a base metal cobalt complex under base-free conditions. The cobalt complex proved to be versatile for both dehydrogenation and hydrogen-transfer reactions by slightly changing the reaction conditions (adding molecular sieves). Our efficient cobalt-catalyzed (2 mol % catalyst loading) N-alkylation can be applied to a wide range of substrates, including even secondary alcohols and aliphatic amines that were scarcely addressed previously. This represents a new breakthrough in cobalt-based catalysis in relation to sustainable chemical synthesis and has implications for future catalyst design based upon earth-abundant elements.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03461.

Experimental procedures and product characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Yang, Q.; Wang, Q.; Yu, Z. *Chem. Soc. Rev.* **2015**, *44*, 2305−2329. (b) Gunanathan, C.; Milstein, D. *Science* **2013**, *341*, 1229712. (c) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681−703. (d) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555−1575. (e) Surry, D. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338−6361. (f) Hartwig, J. F. H. *Acc. Chem. Res.* **2008**, *41*, 1534−1544. (g) Taguchi, K.; Nakagawa, H.; Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2004**, *126*, 72−73. (h) Onodera, G.; Nishibayashi, Y.; Uemura, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3819−3822.

(2) *Catalysis without Precious Metals*; Bullock, R. M., Ed.; Wiley-VCH: Hoboken, NJ, 2010.

(3) (a) Zhou, S.; Fleischer, S.; Junge, K.; Das, S.; Addis, D.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8121−8125. (b) Enthaler, S.; Hagemann, B.; Erre, G.; Junge, K.; Beller, M. *Chem. - Asian J.* **2006**, *1*, 598−604. (c) Enthaler, S.; Erre, G.; Tse, M. K.; Junge, K.; Beller, M. *Tetrahedron Lett.* **2006**, *47*, 8095−8099. (d) Wienhöfer, G.; Sorribes, I.; Boddien, A.; Westerhaus, F.; Junge, K.; Junge, H.; Llusar, R.; Beller, M. *J. Am. Chem. Soc.* **2011**, *133*, 12875−12879. (e) Wienhöfer, G.; Westerhaus, F. A.; Jagadeesh, R. V.; Junge, K.; Junge, H.; Beller, M. *Chem. Commun.* **2012**, *48*, 4827−4829.

(4) (a) Monfette, S.; Turner, Z. R.; Semproni, S. P.; Chirik, P. J. *J. Am. Chem. Soc.* **2012**, *134*, 4561−4564. (b) Casey, C. P.; Guan, H. *J. Am. Chem. Soc.* **2007**, *129*, 5816−5817. (c) Langer, R.; Leitus, G.; Ben-David, Y.; Milstein, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 2120−2124.

(5) Guillena, G.; Ramón, D. J.; Yus, M. *Chem. Rev.* **2010**, *110*, 1611−1641.

(6) *Pharmaceuticals: Classes, Therapeutic Agents, Areas of Application*; McGuire, J. L., Ed.; Wiley-VCH, 2000; Vol. *1*−*4*.

(7) Bahn, S.; Imm, S.; Neubert, L.; Zhang, M.; Nuemann, H.; Beller, M. *ChemCatChem* **2011**, *3*, 1853−1864.

(8) Watanabe, Y.; Tsuji, Y.; Ohsugi, Y. *Tetrahedron Lett.* **1981**, *22*, 2667−2670.

(9) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. *J. Chem. Soc., Chem. Commun.* **1981**, 611−612.

(10) (a) Ruch, S.; Irrgang, T.; Kempe, R. *Chem. - Eur. J.* **2014**, *20*, 13279−13285. (b) Michlik, S.; Hille, T.; Kempe, R. *Adv. Synth. Catal.* **2012**, *354*, 847−862. (c) Michlik, S.; Kempe, R. *Chem. - Eur. J.* **2010**, *16*, 13193−13198. (d) Blank, B.; Kempe, R. *J. Am. Chem. Soc.* **2010**, *132*, 924−925. (e) Blank, B.; Michlik, S.; Kempe, R. *Chem. - Eur. J.* **2009**, *15*, 3790−3799. (f) Blank, B.; Michlik, S.; Kempe, R. *Adv. Synth. Catal.* **2009**, *351*, 2903−2911. (g) Blank, B.; Madalska, M.; Kempe, R. *Adv. Synth. Catal.* **2008**, *350*, 749−758.

(11) Watson, A. J. A.; Williams, J. M. J. *Science* **2010**, *329*, 635−636.

(12) Yan, T.; Feringa, B. L.; Barta, K. *Nat. Commun.* **2014**, *5*, 5602.

(13) Rawlings, A. J.; Diorazio, L. J.; Wills, M. *Org. Lett.* **2015**, *17*, 1086−1089.

(14) Rösler, S.; Ertl, M.; Irrgang, T.; Kempe, R. *Angew. Chem., Int. Ed.* **2015**, *54*, 15046−15050.

(15) Zhang, G.; Scott, B. L.; Hanson, S. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 12102−12106.

(16) Zhang, G.; Vasudevan, K. V.; Scott, B. L.; Hanson, S. K. *J. Am. Chem. Soc.* **2013**, *135*, 8668−8681.

(17) Zhang, G.; Hanson, S. K. *Chem. Commun.* **2013**, *49*, 10151−10153.

(18) Zhang, G.; Hanson, S. K. *Org. Lett.* **2013**, *15*, 650−653.

(19) Xu, R.; Chakraborty, S.; Yuan, H.; Jones, W. D. *ACS Catal.* **2015**, *5*, 6350−6354.

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Organic LETTERS

Letter

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Manganese- and Borane-Mediated Synthesis of Isobenzofuranones from Aromatic Esters and Oxiranes via C−H Bond Activation

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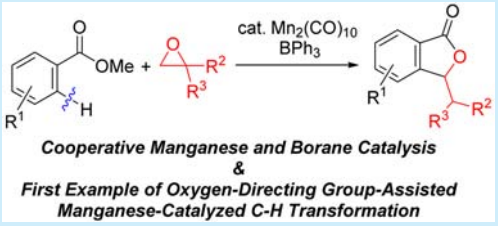
Supporting Information

ABSTRACT: A manganese- and borane-mediated synthesis of isobenzofuranones from esters and oxiranes is developed. The reaction proceeded at aromatic, heteroaromatic, and olefinic C−H bonds with high functional group tolerance. This is the first example of a manganese-catalyzed C−H transformation using an oxygen-directing group. Triphenylborane played an important role in this reaction to cooperatively promote the annulation reaction. Kinetic isotope effect experiments revealed that C−H bond activation of the aromatic rings was the rate-determining step.



Reactions for second- and third-row transition-metal-catalyzed C−H transformations have been reported over the past several decades.[1] Examples of first-row transition-metal-catalyzed C−H transformations,[2] especially manganese-catalyzed reactions,[3,4] however, remain rare. In 2007, we reported a manganese-catalyzed insertion of aldehydes into a C−H bond of aromatic compounds, which was the first example of a manganese-catalyzed C−H transformation.[3a,b] Since 2013, manganese-catalyzed C(sp^2)−H transformations in which the addition of catalytic amounts of secondary amine is essential have been reported by Wang and co-workers.[3c−e] Recently, Ackermann et al. reported manganese-catalyzed synthesis of *cis*-*β*-amino acid esters via C−H bond activation,[3f] and Lei and Li's group reported a manganese and Brønsted acid catalyzed synthesis of substituted alkenylindoles.[3g] All of these transformations utilized nitrogen-directing groups.

In 2008, Nakao and Hiyama et al. reported nickel-catalyzed C−H alkenylation of pyridines.[5a] In this reaction, a zinc or aluminum cocatalyst cooperatively activates the pyridine substrates and facilitates the C-2 selective alkenylation of pyridine derivatives. Cooperative catalytic systems have also been applied to other C−H transformations.[5] Cooperative catalysts have high potential to enable new C−H transformations that could not be achieved by single catalytic systems.

Recently, we reported a palladium-catalyzed C−H alkylation of *N*-methoxybenzamides using oxiranes to give 3,4-dihydroisocoumarins.[6,7] In the course of our studies to develop manganese-catalyzed C−H transformations, we found that isobenzofuranones were obtained by reactions between esters and oxiranes. The manganese-catalyzed synthesis of isobenzofuranones is complementary to that of 3,4-dihydroisocoumarins.

Isobenzofuranones are an important class of organic compounds, and some exist as natural products (Figure 1).[8] Therefore, various methods to synthesize isobenzofuranones have been reported.[9,10] Herein we report a manganese- and borane-mediated synthesis of isobenzofuranones from esters and oxiranes via C−H bond activation. In this reaction, triphenylborane was indispensable to promote the reaction. To our knowledge, this report is the first example of an oxygen-directing group-assisted manganese-catalyzed C−H transformation.

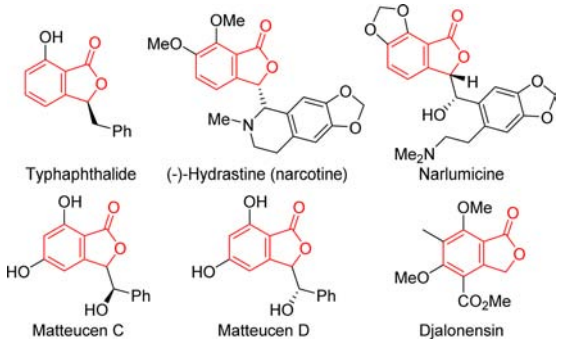


Figure 1. Various naturally occurring isobenzofuranones.

First, various transition metal complexes and solvents were investigated in a reaction of methyl *p*-toluate **1a** with styrene oxide **2a** (Table 1). In a reaction with $MnBr(CO)_5$ and triphenylborane, the desired isobenzofuranone **3a** was not formed (Table 1, entry 1). On the other hand, a dinuclear manganese complex, $Mn_2(CO)_{10}$, and BPh_3 promoted the desired reaction, and **3a** was obtained in 23% yield (Table 1, entry 2). The yield of **3a** was slightly increased when the solvent (chlorobenzene) was changed to 1,2-dichloroethane or hexane (Table 1, entries 3 and 4).[11] The yield of **3a** was further improved by increasing the amounts of the catalyst and equivalents of **2a** (Table 1, entry 5). The reaction in a mixed solvent, 1,2-dichloroethane and hexane (1:1), gave **3a** in 78% yield (Table 1, entry 6). The reactions did not proceed at all without the manganese catalyst (Table 1, entry 7). The desired reaction

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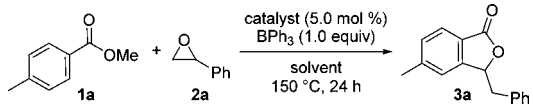
Table 1. Screening of Catalysts and Solvents in Reactions between Methyl *p*-Toluate 1a and Styrene Oxide 2a[a]



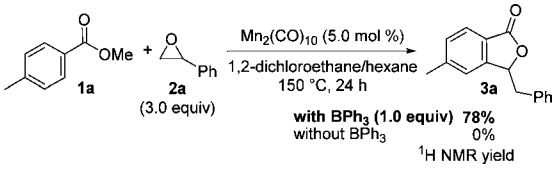
entry	catalyst	solvent	yield (%)[b]
1[c]	$MnBr(CO)_5$	chlorobenzene	0
2[c]	$Mn_2(CO)_{10}$	chlorobenzene	23
3[c]	$Mn_2(CO)_{10}$	1,2-dichloroethane	35
4[c]	$Mn_2(CO)_{10}$	hexane	35
5	$Mn_2(CO)_{10}$	1,2-dichloroethane	54
6	$Mn_2(CO)_{10}$	1,2-dichloroethane/hexane (1:1)	78 (74)[d]
7	none	1,2-dichloroethane/hexane (1:1)	0
8	$ReBr(CO)_5$	1,2-dichloroethane/hexane (1:1)	0
9	$Re_2(CO)_{10}$	1,2-dichloroethane/hexane (1:1)	16
10	$[ReBr(CO)_3(thf)]_2$	1,2-dichloroethane/hexane (1:1)	0
11	$Pd(OAc)_2$	1,2-dichloroethane/hexane (1:1)	4
12	$Ru_3(CO)_{12}$	1,2-dichloroethane/hexane (1:1)	0
13	$RuH_2(CO)(PPh_3)_3$	1,2-dichloroethane/hexane (1:1)	0
14	$Fe(CO)_5$	1,2-dichloroethane/hexane (1:1)	0

[a]**2a** (3.0 equiv). [b]^{1}H NMR yield. [c]Catalyst (2.5 mol %), **2a** (1.5 equiv). [d]Isolated yield.

scarcely proceeded when using rhenium complexes (Table 1, entries 8−10), but other transition metal catalysts, such as palladium, ruthenium, and iron complexes or salts, exhibited almost no catalytic activity (Table 1, entries 11−14).

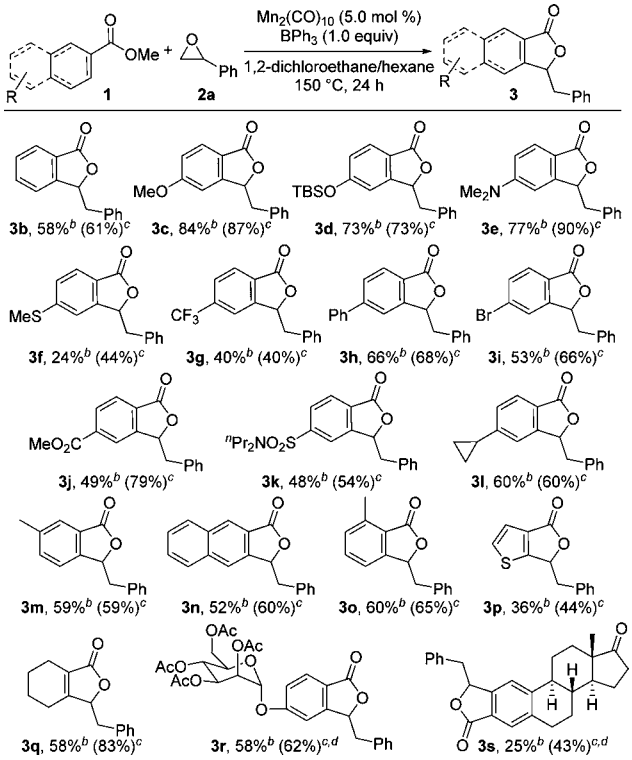
As shown in Table 1, entry 6, the manganese/borane catalysis gave isobenzofuranone **3a** in good yield, but **3a** was not formed without addition of triphenylborane (Scheme 1).[12] These results clearly show that triphenylborane played an important role in this transformation.

Scheme 1. Effect of BPh_3 in Manganese-Catalyzed Synthesis of Isobenzofuranone from Aromatic Ester and Styrene Oxide



The substrate scope of aromatic esters **1** was investigated (Scheme 2). The reaction of methyl benzoate **1b** with styrene oxide **2a** provided isobenzofuranone **3b** in 58% yield. Esters with an electron-donating group, such as a methoxy, *tert*-butyldimethylsilyloxyl, or *N*,*N*-dimethylamino group, **1c**−**1e** gave the corresponding isobenzofuranones **3c**−**3e** in 73%−84% yields. In the case of methyl 4-thiomethylbenzoate **1f**, the desired reaction proceeded even in the presence of a sulfur functional group, which could potentially act as a catalyst poison. Reactions using methyl benzoates bearing an electron-withdrawing group, such as a trifluoromethyl or phenyl group, afforded isobenzofuranones **3g** and **3h** in 40% and 66% yields, respectively. The desired reaction also proceeded in the case of methyl benzoates **1i** and **1j** with a bromine atom or methoxycarbonyl group. In these reactions, the functional groups were tolerated under the reaction conditions and could be used for further transformations. It is notable that the reaction conditions were applicable to a drug derivative, such as probenecid methyl ester **1k** to give **3k** in 48% yield. The reaction of methyl 4-

Scheme 2. Manganese-Catalyzed Synthesis of Isobenzofuranones 3 Using Various Aromatic and Olefinic Esters 1[a]



[a]**2a** (3.0 equiv). [b]Isolated yield. [c]^{1}H NMR yield is reported in the parentheses. [d]dr = 1:1.

cyclopropylbenzoate **1l** gave the corresponding isobenzofuranone **3l** in 60% yield without opening the cyclopropane ring. Methyl *m*-toluate **1m** and methyl 2-naphthalate **1n** provided single regioisomers **3m** and **3n** in 59% and 52% yields, respectively. These reactions occurred at positions with less steric repulsion. Reaction of a sterically hindered ester with a methyl group at the *ortho*-position, **1o**, gave isobenzofuranone **3o** in 60% yield. Based on the results of **3b** and **3o**, the reaction was not inhibited by steric hindrance. Heteroaromatic methyl ester **1p** provided **3p** in 36% yield. The reaction also proceeded at the olefinic C−H bond, and the corresponding cyclic product **3q** was produced in 58% yield. Notably, the reaction of highly functionalized, biologically active esters bearing a protected mannose or estrone moiety gave the corresponding isobenzofuranones **3r** and **3s** in 58% and 25% yields, respectively. In all entries, difunctionalized products were not formed.

The scope of oxiranes **2** was then investigated (Scheme 3). The desired isobenzofuranones bearing an electron-donating group, such as a methyl or methoxy group, **4a** and **4b**, were obtained in 57% and 70% yields, respectively, using oxiranes **2b** and **2c**. The reactions of oxiranes with a halogen atom, **2d**−**2f**, gave the corresponding isobenzofuranones **4c**−**4e** in moderate to good yields. In these cases, the functional group remained unchanged during the reaction. An oxirane with an electron-withdrawing group provided **4f** in 78% yield. The reaction was not affected by steric hindrance from a substituent at the *ortho*-position: oxiranes with a 2-tolyl or 1-naphthyl group produced isobenzofuranones **4g** and **4h** in 58% and 70% yields, respectively. Disubstituted oxirane, 2,2-diphenyloxirane (**2i**), gave the corresponding isobenzofuranone **4i** in 23% yield. In a

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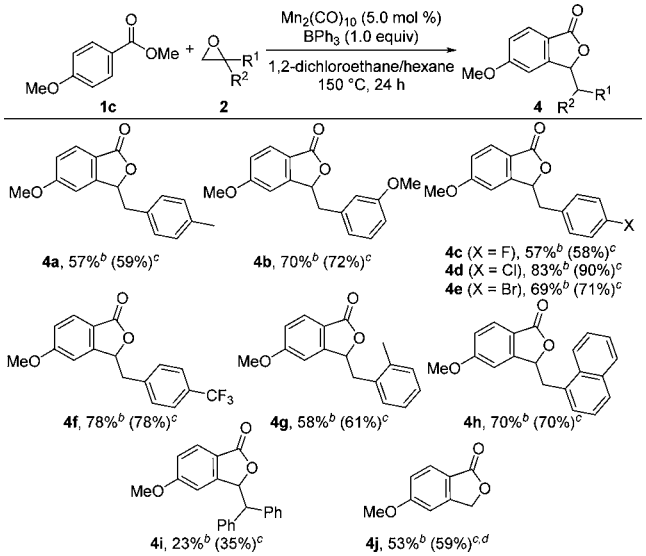
Scheme 3. Manganese-Catalyzed Synthesis of Isobenzofuranones 4 with Various Oxiranes 2[a]

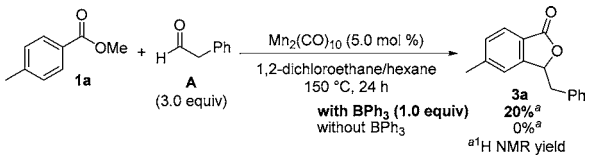


[a]**2** (3.0 equiv). [b]Isolated yield. [c]^{1}H NMR yield is reported in the parentheses. [d]2-(*tert*-Butyl)oxirane **2k** was used as a substrate.

reaction of 2-(*tert*-butyl)oxirane **2k**, isobenzofuranone **4j** was unexpectedly obtained. The product must have been formed from the reaction between methyl *p*-anisate **1c** and formaldehyde, which was generated *in situ* via C−C bond cleavage due to Meinwald rearrangement of **2j**.[13]

To clarify the importance of triphenylborane in the C−H transformation, we investigated a reaction between methyl *p*-toluate **1a** and phenylacetaldehyde **A** under manganese/borane catalysis in 1,2-dichloroethane/hexane at 150 °C. As a result, isobenzofuranone **3a** was produced in 20% yield (Scheme 4). On

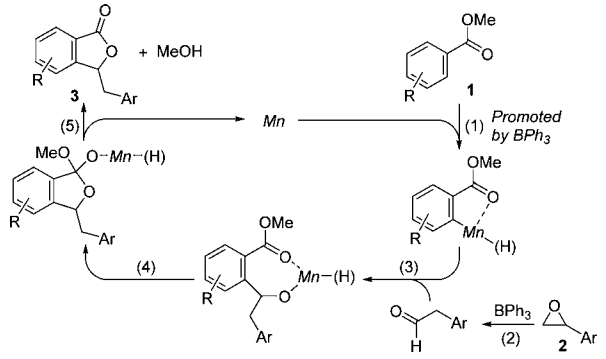
Scheme 4. Effect of BPh_3 in Manganese-Catalyzed Synthesis of Isobenzofuranone from Aromatic Ester and Phenylacetaldehyde



the other hand, **3a** was not formed in the absence of triphenylborane (Scheme 4). These results clearly show that triphenylborane played an important role in the C−H transformation.

The plausible reaction mechanism for the formation of isobenzofuranones **3** is as follows (Scheme 5): (1) oxidative addition of methyl benzoate **1** to a manganese catalyst (C−H bond activation); (2) isomerization of oxirane **2** to an aldehyde under Lewis acidic conditions;[14] (3) insertion of an aldehyde into the formed manganese−carbon bond; (4) intramolecular nucleophilic cyclization; and (5) reductive elimination and elimination of methanol to give isobenzofuranones **3** and regenerate the manganese catalyst. The role of triphenylborane is still ambiguous,[15] but it is clear from the results of Schemes 1 and 4 that the borane was necessary for C−H transformation (steps 1, 3, 4, and/or 5). We also investigated stoichiometric reactions between manganated aryl species and benzaldehyde

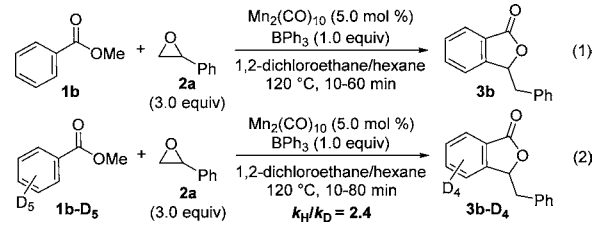
Scheme 5. Plausible Reaction Mechanism for the Formation of Isobenzofuranones 3



(eqs S1 and S2 in the Supporting Information). The results showed that BPh_3 may not be indispensable in steps 3−5, and therefore, BPh_3 may be indispensable in step 1. This is comparable to the fact that step 1 is the rate-determining step in this reaction (see below), and step 1 may be accelerated by BPh_3.

Kinetic studies revealed that the value of the kinetic isotope effect, k_H/k_D, was 2.4 (Scheme 6, eqs 1 and 2). This result indicates that the *ortho*-C−H bond activation (step 1) was the rate-determining step of the reaction.[16]

Scheme 6. Kinetic Studies for Manganese-Catalyzed Synthesis of Isobenzofuranones



In summary, we successfully developed a manganese-catalyzed synthesis of isobenzofuranones from esters and oxiranes in moderate to good yields with high functional group tolerance. The reaction occurred at aromatic, heteroaromatic, and olefinic C−H bonds. This is the first example of manganese-catalyzed C−H transformations using an oxygen-directing group. Triphenylborane is essential for this reaction and promoted the reaction by cooperating with the manganese catalyst. Kinetic isotope effect experiments revealed that C−H bond activation of the aromatic rings is the rate-determining step. We expect that this result will contribute to the development of C−H transformations, and the cooperative catalytic system will provide useful insight into synthetic organic chemistry. Further investigation to disclose the reaction mechanism, especially the role of the borane, is ongoing in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03474.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For several recent reviews of C−H transformations, see: (a) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (b) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885. (c) Kuninobu, Y.; Takai, K. *Chem. Rev.* **2011**, *111*, 1938. (d) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (e) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902. (f) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (g) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (h) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (i) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012**, *41*, 5588. (j) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (k) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236. (l) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369. (m) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (n) Thirunavukkarasu, V. S.; Kozhushkov, S. I.; Ackermann, L. *Chem. Commun.* **2014**, *50*, 29. (o) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74. (p) Tani, T.; Uehara, T. N.; Yamaguchi, J.; Itami, K. *Chem. Sci.* **2014**, *5*, 123. (q) Zhang, X.-S.; Chen, K.; Shi, Z.-J. *Chem. Sci.* **2014**, *5*, 2146. (r) Valyaev, D. A.; Lavigne, G.; Lugan, N. *Coord. Chem. Rev.* **2016**, *308*, 191.

(2) For selected reviews for C−H transformations using first-row transition metal catalysts, see: Fe: (a) Nakamura, E.; Yoshikai, N. *J. Org. Chem.* **2010**, *75*, 6061. (b) Nakamura, E.; Hatakeyama, T.; Ito, S.; Ishizuka, K.; Ilies, L.; Nakamura, M. *Org. React.* **2014**, *83*, 1. (c) Su, B.; Cao, Z.-C; Shi, Z.-J. *Acc. Chem. Res.* **2015**, *48*, 886. Co: (d) Yoshikai, N. *Synlett* **2011**, *2011*, 1047. (e) Yoshikai, N. *Bull. Chem. Soc. Jpn.* **2014**, *87*, 843. (f) Gao, K.; Yoshikai, N. *Acc. Chem. Res.* **2014**, *47*, 1208. (g) Ackermann, L. *J. Org. Chem.* **2014**, *79*, 8948. (h) Yoshikai, N. *ChemCatChem* **2015**, *7*, 732. Ni: (i) Clot, E.; Eisenstein, O.; Jasim, N.; Macgregor, S. A.; Mcgrady, J. E.; Perutz, R. N. *Acc. Chem. Res.* **2011**, *44*, 333. (j) Yamaguchi, J.; Muto, K.; Itami, K. *Eur. J. Org. Chem.* **2013**, *2013*, 19 and current reports are cited therein.

(3) (a) Kuninobu, Y.; Nishina, Y.; Takeuchi, T.; Takai, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 6518. (b) Kuninobu, Y.; Fujii, Y.; Matsuki, T.; Nishina, Y.; Takai, K. *Org. Lett.* **2009**, *11*, 2711. (c) Zhou, B.; Chen, H.; Wang, C. *J. Am. Chem. Soc.* **2013**, *135*, 1264. (d) He, R.; Huang, Z.-T.; Zheng, Q.-Y.; Wang, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 4950. (e) Zhou, B.; Ma, P.; Chen, H.; Wang, C. *Chem. Commun.* **2014**, *50*, 14558. (f) Liu, W.; Zell, D.; John, M.; Ackermann, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 4092. (g) Shi, L.; Zhong, X.; She, H.; Lei, Z.; Li, F. *Chem. Commun.* **2015**, *51*, 7136. (h) Liu, W.; Bang, J.; Zhang, Y.; Ackermann, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 14137.

(4) Manganese-catalyzed or -mediated C−H transformations via radical mechanism are excluded from ref 3.

(5) For selected C−H transformations using cooperative catalysis, see: (a) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448. (b) Tsai, C.-C.; Shih, W.-C.; Fang, C.-H.; Li, C.-Y.; Ong, T.-G.; Yap, G. P. A. *J. Am. Chem. Soc.* **2010**, *132*, 11887. (c) Wu, X.; Zhao, Y.; Ge, H. *J. Am. Chem. Soc.* **2015**, *137*, 4924. For reviews of cooperative catalytic systems including other types of transformations, see: (d) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302. (e) Nakao, Y. *Chem. Rec.* **2011**, *11*, 242. (f) Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 633.

(6) Wang, Z.; Kuninobu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2015**, *137*, 6140.

(7) During the preparation of this manuscript, palladium-catalyzed synthesis of 3,4-dihydroisocoumarins from carboxylic acids and oxiranes via C−H bond activation was reported; see: Cheng, G.; Li, T.-J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 10950.

(8) (a) Okorie, D. A. *Phytochemistry* **1976**, *15*, 1799. (b) Huang, J.-H.; Johnston, G. A. R. *Br. J. Pharmacol.* **1990**, *99*, 727. (c) Tripathi, V. K.; Pandey, V. B. *Phytochemistry* **1992**, *31*, 2188. (d) Shode, F. O.; Mahomed, A. S.; Rogers, C. B. *Phytochemistry* **2002**, *61*, 955. (e) Shao, P.; Zhang, X.; Li, B.; Jiao, W.-H.; Wu, L.-J; Yao, X.-S. *Chem. Pharm. Bull.* **2010**, *58*, 1650. For a review, see: (f) Lin, G.; Chan, S. S.-K.; Chung, H.-S.; Li, S.-L. *Stud. Nat. Prod. Chem.* **2005**, *32*, 611.

(9) (a) Chang, H.-T.; Jeganmohan, M.; Cheng, C.-H. *Chem. - Eur. J.* **2007**, *13*, 4356. (b) Zhang, B.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2009**, *11*, 4712. (c) Omura, S.; Fukuyama, T.; Murakami, Y.; Okamoto, H.; Ryu, I. *Chem. Commun.* **2009**, 6741. (d) Phan, D. H. P.; Kim, B.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 15608. (e) da Penha, E. T.; Forni, J. A.; Biajoli, A. F. P.; Correia, C. R. D. *Tetrahedron Lett.* **2011**, *52*, 6342. (f) Youn, S. W.; Song, H. S.; Park, J. H. *Org. Biomol. Chem.* **2014**, *12*, 2388. (g) Peña-López, M.; Neumann, H.; Beller, M. *ChemCatChem* **2015**, *7*, 865. (h) Mahendar, L.; Satyanarayana, G. *J. Org. Chem.* **2015**, *80*, 7089. For a review, see: (i) Karmakar, R.; Pahari, P.; Mal, D. *Chem. Rev.* **2014**, *114*, 6213.

(10) For synthesis of isobenzofuranones via C−H activation, see: (a) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407. (b) Ackermann, L.; Pospech, J. *Org. Lett.* **2011**, *13*, 4153. (c) Shi, X.; Li, C.-J. *Adv. Synth. Catal.* **2012**, *354*, 2933. (d) Lian, Y.; Bergman, R. G.; Ellman, J. A. *Chem. Sci.* **2012**, *3*, 3088. (e) Nandi, D.; Ghosh, D.; Chen, S.-J.; Kuo, B.-C.; Wang, N. M.; Lee, H. M. *J. Org. Chem.* **2013**, *78*, 3445. (f) Tan, P. W.; Juwaini, N. A. B.; Seayad, J. *Org. Lett.* **2013**, *15*, 5166. (g) Danoun, G.; Mamone, P.; Gooßen, L. J. *Chem. - Eur. J.* **2013**, *19*, 17287. (h) Miura, H.; Tsutsui, K.; Wada, K.; Shishido, T. *Chem. Commun.* **2015**, *51*, 1654. (i) Warratz, S.; Kornhaaβ, C.; Cajaraville, A.; Niepötter, B.; Stalke, D.; Ackermann, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 5513. (j) Jiang, Q.; Zhu, C.; Zhao, H.; Su, W. *Chem. Asian J., in press*, DOI: 10.1002/asia.201500601. (k) Bechtoldt, A.; Tirler, C.; Raghuvanshi, K.; Warratz, S.; Kornhaaß, C.; Ackermann, L. *Angew. Chem., Int. Ed., in press*, DOI:10.1002/anie.201507801.

(11) For details of investigation of other solvents and temperatures, see the Supporting Information.

(12) For details of screening of other boron compounds, see the Supporting Information.

(13) After the reaction, 2-methyl-2-butene was detected by GC in 93% yield. 2-Methyl-2-butene should be generated by the Meinwald rearrangement of **2j**. For details of the migration, see Scheme S2 in the Supporting Information.. Coxon, J. M.; Hartshorn, M. P.; Lewis, A. J.; Richards, K. E.; Swallow, W. H. *Tetrahedron* **1969**, *25*, 4445.

(14) Oxiranes are isomerized to aldehydes under Lewis acidic conditions; see: (a) Jung, M. E.; Marquez, R. *Tetrahedron Lett.* **1999**, *40*, 3129. (b) Angle, S. R.; White, S. L. *Tetrahedron Lett.* **2000**, *41*, 8059.

(15) We investigated NMR and ReactIR experiments to elucidate the role of triphenylborane, but no supportive results were obtained yet.

(16) For details, see Figure S1 in the Supporting Information.

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Organic LETTERS

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Silaborative Carbocyclizations of 1,7-Enynes. Diastereoselective Preparation of Chromane Derivatives

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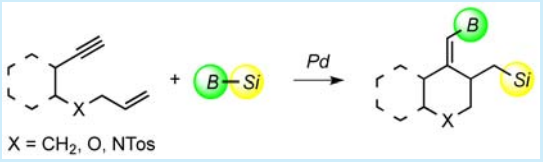
KTH Royal Institute of Technology, Department of Chemistry, Organic Chemistry, SE 10044 Stockholm, Sweden

Supporting Information

ABSTRACT: Palladium(0)-catalyzed carbocyclization of 1,7-enynes mediated by (chlorodimethylsilyl)pinacolborane proceeds with 1,8-addition of the silicon and boron functions to give functionalized cyclohexane derivatives with boron attached to the exocyclic olefin. A variety of chromane dervatives are accessible by this method. In contrast to the analogous reactions with 1,6-enynes, the configuration of the newly formed stereogenic center is controlled by a stereogenic center present in the substrate.



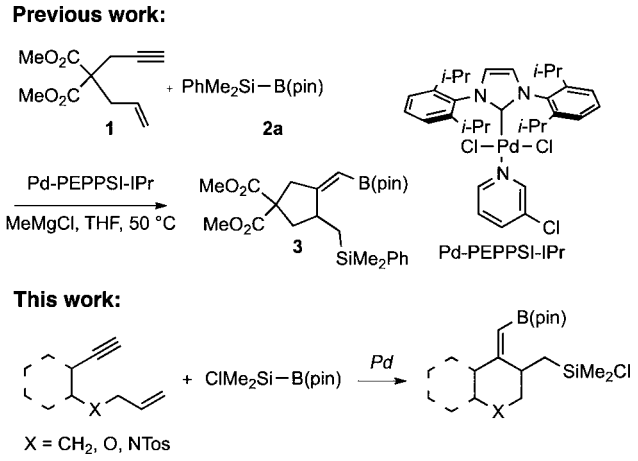
Cyclizations of 1,6-enynes catalyzed by a variety of metal complexes have been extensively studied, and numerous synthetically versatile methods for the construction of substituted five-membered carbocycles and heterocycles have emerged from these studies.[1] In contrast, examples of cycloisomerizations or other types of alkene−alkyne couplings of 1,7-enynes to provide six-membered rings are more rare, and the cyclized products are often obtained in moderate yields.[2]

Bismetallative cyclizations employing interelement compounds,[3] which contain a bond between two main group elements, lead to cyclic products containing two reactive functional groups.[4] Further functional group transformations of the primarily obtained products generate large structural diversity, thereby making bisfunctionalization−cyclizations synthetically powerful processes. Whereas such methods have been explored for 1,6-enynes, using Si−Sn, B−Sn, and B−Si interelement compounds,[5] borastannylative carbocyclization of 1-ethenyl-2-(2-propyn-1-yloxy)benzene is the single example of a bisfunctionalization−cyclization generating a six-membered carbocycle.[6] Instead of the desired cyclic compounds, products from 1,2-addition of the interelement compound to the triple bond[7] are commonly obtained.[6]

Cárdenas and co-workers have also reported cyclizations of 1,7-enynes[8] and dienynes[9] with concomitant introduction of a single reactive group. Boron−boron compounds were used in these reactions, but as a result of the mode of activation, the reactions led to incorporation of only one boron function; with most substrates the product with boron at the terminal alkene carbon atom of the starting enyne was obtained as the sole isomer. A monofunctionalized cyclohexane derivative was also obtained by rhodium-catalyzed silylative cyclization of 4,4-bis(carbomethoxy)oct-7-en-1-yne, using $PhMe_2SiH$, which gave a low yield (34%) of a product from initial addition of Pd−Si to the alkyne and, thus, with the silyl function at the olefinic bond of the product.[10]

Silaborative cyclizations[11] are particularly attractive since the resulting products are nontoxic and possess functions with orthogonal reactivities, which can be transformed in a variety of ways.[12] Our previous work included cyclization of 1,6-enyne **1** using (dimethylphenylsilyl)pinacolborane (**2a**)[13] to give **3** (Scheme 1).[14] Dichloro-*N*,*N*-bis[2,6-(diisopropyl)phenyl]-

Scheme 1. Silaborative Cyclizations



imidazolium (3-chloropyridine) palladium, Pd-PEPPSI-IPr,[15] served as an efficient catalyst for the process, which provided the products in excellent yields with control of regiochemistry as well as olefinic bond configuration, the latter being a consequence of the mechanism of the reaction.

The present work describes the extension of this method to 1,7-enynes. For these studies, (chlorodimethylsilyl)-pinacolborane **2b**,[16] which exhibits higher reactivity than **2a**[17] and which results in products disposed for further transformations,[18] was used (Scheme 2). Reaction of **4** with compound **2b** in the presence of Pd-PEPPSI-IPr did not, however, yield the desired cyclic compound but resulted in 1,2-

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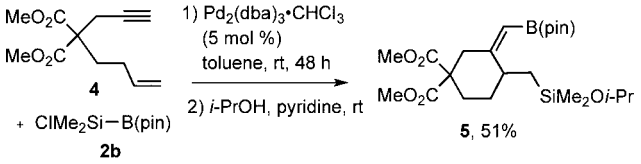
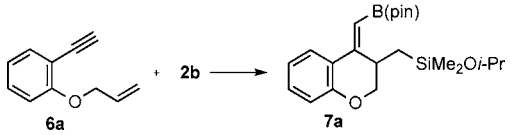
Scheme 2. Silaborative Cyclization of 1,7-Enyne



addition to the triple bond, evidently as a result of reductive elimination being more rapid than insertion of the alkene into the Pd−C bond. In contrast, use of $Pd_2(dba)_3{\cdot}CHCl_3$ gave compound **5**, the product from 1,8-silaboration, as a single diastereomer in a moderate yield of 51%.

Silaborative cyclization of 1-ethynyl-2-(2-propen-1-yloxy)-benzene (**6a**) provided chromane derivative **7a**, also as a single diastereomer. The effect of variation of the reaction conditions was studied using this substrate (Table 1). Best results were

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	Si−B	solvent	temp (°C)	yield (%)
1	Pd-PEPPSI-IPr[b]	**2b**	THF	20	73
2	Pd-PEPPSI-IPr[b]	**2b**	THF	50	76
3	$Pd_2(dba)_3{\cdot}CHCl_3$	**2b**	toluene	20	65
4	$Pd_2(dba)_3{\cdot}CHCl_3/Cy_3P$	**2b**	toluene	50	58
5	$Pd_2(dba)_3{\cdot}CHCl_3/Ph_3P$	**2b**	toluene	50	56
6	$(\eta^3\text{-}C_3H_5)Pd\text{-}(Ph_3P)Cl$	**2b**	toluene	20	60
7	Pd-PEPPSI-IPr[b]	**2a**	THF	50	–
8	$Pd_2(dba)_3{\cdot}CHCl_3$	**2a**	toluene	50	–

[a]Reaction time 48 h, 5 mol % catalyst, ligand/metal 1.2:1, **6a**/**2b** 1.2:1. 2-Propanol and pyridine were added prior to workup. [b]MeMgCl used for reduction of Pd(II).

obtained from reactions catalyzed by Pd-PEPPSI-IPr in THF (entries 1−2); at 50 °C, 76% of cyclized product was isolated. With this substrate, reaction in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ resulted in a lower yield (entry 3). Catalysts prepared from $Pd_2(dba)_3{\cdot}CHCl_3$ and a phosphine ligand or $(\eta^3\text{-}C_3H_5)Pd(PPh_3)Cl$ also gave inferior results (entries 4−6). Even at 50 °C, no cyclized product was obtained from attempted addition of the less reactive silylborane **2a** (entries 7 and 8).

Since chromanes and chromenes[19] display useful biological properties, it was of interest to examine whether substrates functionalized in the aromatic ring underwent the cyclization and at the same time study the influence of substituents on the reactivity. The reactions proceeded smoothly using substrates with both electron-donating and electron-withdrawing substituents to give products **7b−g**; no major impact of the electronic properties on the reactivity was observed (Figure 1).

By use of the same procedure, the *N*-tosyl analogue of **6a**, **8**, afforded hydroquinoline derivative **9** in good yield, and cyclization of enyne **10** produced an isomeric chromane, **11**,[20] employing catalytic $Pd_2(dba)_3{\cdot}CHCl_3$ (Scheme 3).

Attempted cyclizations of 1,7-enynes **12−14** under the conditions specified in Table 1, entry 2, did not result in the desired product; from **13** and **14** the compounds from 1,2-addition to the triple bond were instead obtained as the single

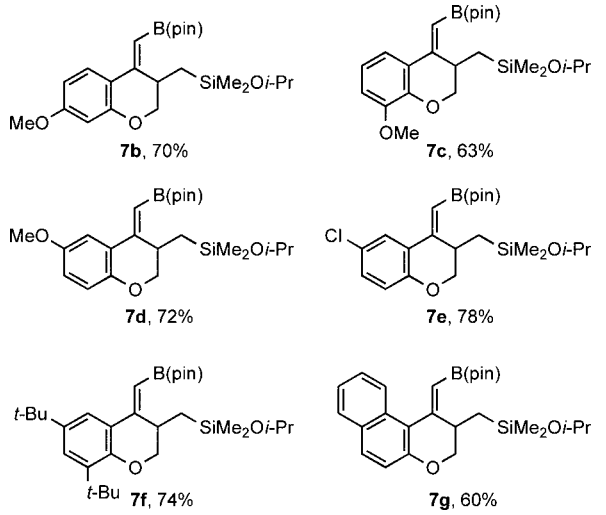
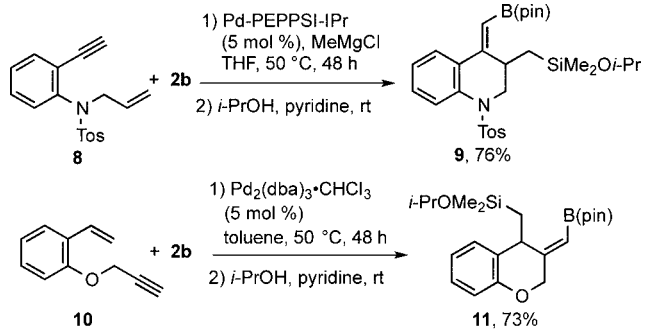
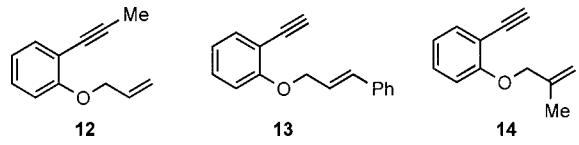


Figure 1. Synthesis of chromane derivatives.

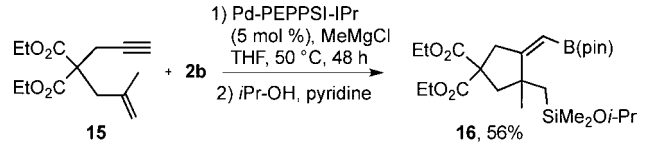
Scheme 3. Preparation of Tetrahydroquinoline and Chromene



products, and from attempted reaction of **12** only starting material was recovered. In analogy to **13**, 1,6-enynes with terminal olefinic substiuents were unreactive, affording low yields of products.[14] In contrast, 1,6-enyne **15** gave a cyclopentane derivative with an all-carbon quaternary center (**16**) in the presence of Pd-PEPPSI-IPr (Scheme 4).



Scheme 4. Cyclization of Substituted 1,6-Enyne



Only a few diastereoselective[2a,c,k,p] or enantioselective[1d,2a,j] cyclizations of 1,7-enynes to cyclohexane derivatives have been reported. We were pleased to observe that the relative configuration of the newly formed center could be controlled by substituents at sp^3-centers of the 1,7-enyne. Thus, cyclization of *rac*-**17** gave a 5:1 diastereomeric mixture of **18** (Scheme 5). Chiral 1,6-enynes reacted with lower selectivity.

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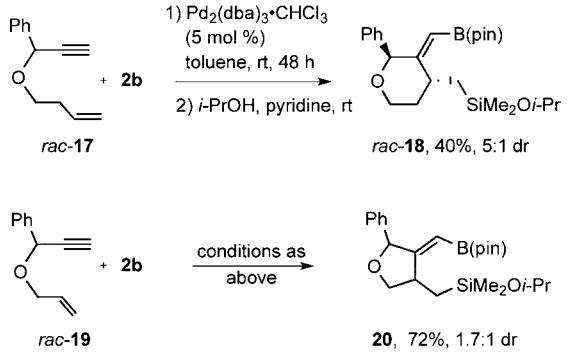
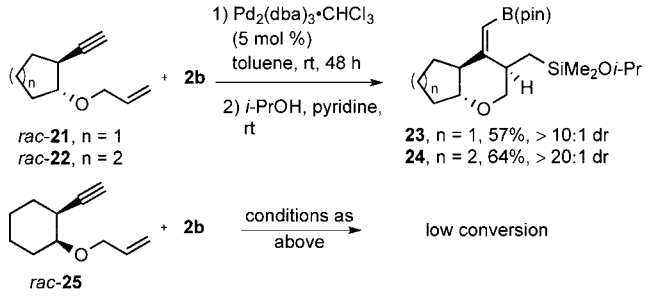
Thus, under the same conditions, *rac*-**19** gave cyclopentane derivative **20** as a 1.7:1 mixture of diastereomers.

Scheme 5. Cyclization of Chiral 1,7- and 1,6-Enynes



The trans-disubstituted enynes (*R**,*S**)-**21** and (*R**,*S**)-**22**, with both substituents in an equatorial position, reacted with high diastereoselectivity to give bicyclic compounds **23** and **24**, respectively, whereas cis isomer (*R**,*R**)-**25**, in which the alkyne substituent according to ^{1}H NMR occupies an axial position, gave a low yield of product when subjected to the same reaction, most likely since addition to the axial alkyne bond is sterically unfavored (Scheme 6).

Scheme 6. Diastereoselective Preparation of Bicyclic Compounds



The relative configurations of **18**, **23**, and **24** were determined by ^{1}H NMR spectroscopy. In **18**, NOE interactions between H_{6a} and H_2 as well as between H_{6a} and the methylene protons adjacent to silicon showed that the substituents are trans oriented with the silicon substituent occupying an axial position as also verified by the coupling constants (Figure 2). In contrast, the corresponding substituents in **23** and **24** were found to be cis, as shown by a NOE interaction between H_a and H_b.

The reaction is assumed to follow a mechanism analogous to that of similar processes, consisting of oxidative addition of the silylborane to Pd(0) followed by addition of PdSi and B to the alkyne and stereochemistry-determining insertion of the alkene into the carbon−palladium bond and final reductive elimination (Scheme 7).

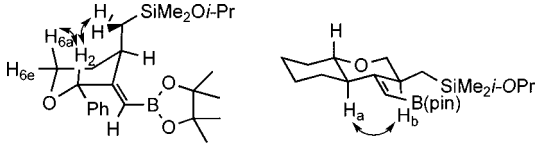
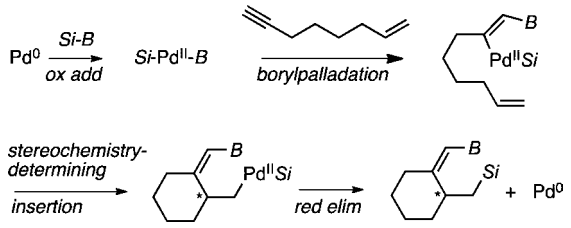


Figure 2. NOE interactions in **18** (left) and **24** (right).

Scheme 7. Mechanism for Silaborative Cyclization



The stereochemistry of products **23** and **24** can be rationalized by assuming a six-membered chair formed transition state (A, Figure 3). Assuming that the phenyl group in **17** is forced into an axial position (B, Figure 3), as a result of steric interaction with the olefinic bond when placed in equatorial position (C, Figure 3), the observed stereochemistry of the product can be explained.

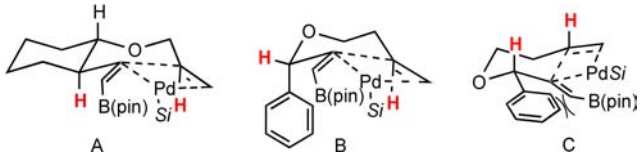


Figure 3. Proposed transition states for stereochemistry-determining migratory insertion.

In conclusion, we have developed an atom economic cyclization of 1,7-enynes, which provides cyclohexane derivatives containing reactive boron and silicon functional groups. With proper reaction conditions, products from 1,2-addition to the alkyne can usually be avoided. Cyclization of chiral substrates proceeds with high diastereoselectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03479.

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Reviews on metal-catalyzed cyclizations of 1,*n*-enynes: (a) Michelet, V.; Toullec, P. Y.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268−4315. (b) Lee, S. I.; Chatani, N. *Chem. Commun.* **2009**, 371−384. (c) Watson, I. D. G.; Toste, F. D. *Chem. Sci.* **2012**, 3,

DOI: 10.1021/acs.orglett.5b03479
Org. Lett. 2016, 18, 308−311

2899−2919. (d) Marinetti, A.; Jullien, H.; Voituriez, A. *Chem. Soc. Rev.* **2012**, *41*, 4884−4908.
(2) (a) Trost, B. M.; Czeskis, B. A. *Tetrahedron Lett.* **1994**, *35*, 211−214. (b) Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049−6050. (c) Trost, B. M.; Li, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6625−6633. (d) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 714−715. (e) Fernández-Rivas, C.; Méndez, M.; Echavarren, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 1221−1222. (f) Fernández-Rivas, C.; Méndez, M.; Nieto-Oberhuber, C.; Echavarren, A. M. *J. Org. Chem.* **2002**, *67*, 5197−5201. (g) Krafft, M. E.; Boñaga, L. V. R.; Wright, J. A.; Hirosawa, C. *J. Org. Chem.* **2002**, *67*, 1233−1246. (h) Chatani, N.; Inoue, H.; Kotsuma, T.; Murai, S. *J. Am. Chem. Soc.* **2002**, *124*, 10294−10295. (i) Harada, K.; Tonoi, Y.; Kato, H.; Fukuyama, Y. *Tetrahedron Lett.* **2002**, *43*, 3829−3832. (j) Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* **2003**, *125*, 4704−4705. (k) Trost, B. M.; Dong, L.; Schroeder, G. M. *J. Am. Chem. Soc.* **2005**, *127*, 10259−10268. (l) Bajracharya, G. B.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 892−897. (m) Miyanohana, Y.; Chatani, N. *Org. Lett.* **2006**, *8*, 2155−2158. (n) Ota, K.; Lee, S. I.; Tang, J.-M.; Takachi, M.; Nakai, H.; Morimoto, T.; Sakurai, H.; Kataoka, K.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 15203−15211. (o) Huang, C.; Kothandaraman, P.; Koh, B. Q.; Chan, P. W. H. *Org. Biomol. Chem.* **2012**, *10*, 9067−9078. (p) Rao, W.; Sally; Koh, M. J.; Chan, P. W. H. *J. Org. Chem.* **2013**, *78*, 3183−3195. (q) Mailyan, A. K.; Krylov, I. M.; Bruneau, C.; Dixneuf, P. H.; Osipov, S. N. *Eur. J. Org. Chem.* **2013**, *2013*, 5353−5363. (r) Kaminsky, L.; Clark, D. A. *Org. Lett.* **2014**, *16*, 5450−5453. (s) Yamashita, K.; Fujii, Y.; Yoshioka, S.; Aoyama, H.; Tsujino, H.; Uno, T.; Fujioka, H.; Arisawa, M. *Chem. - Eur. J.* **2015**, *21*, 17491−17494.
(3) (a) Beletskaya, I.; Moberg, C. *Chem. Rev.* **1999**, *99*, 3435−3461. (b) Suginome, M.; Ito, Y. *Chem. Rev.* **2000**, *100*, 3221−3256. (c) Beletskaya, I.; Moberg, C. *Chem. Rev.* **2006**, *106*, 2320−2354.
(4) Cho, H. Y.; Morken, J. P. *Chem. Soc. Rev.* **2014**, *43*, 4368−4380.
(5) (a) Onozawa, S.-y.; Hatanaka, Y.; Tanaka, M. *Chem. Commun.* **1997**, 1229−1230. (b) Onozawa, S.-y.; Hatanaka, Y.; Choi, N.; Tanaka, M. *Organometallics* **1997**, *16*, 5389−5391. (c) Mori, M.; Hirose, T.; Wakamatsu, H.; Imakuni, N.; Sato, Y. *Organometallics* **2001**, *20*, 1907−1909. (d) Sato, Y.; Imakuni, N.; Mori, M. *Adv. Synth. Catal.* **2003**, *345*, 488−491. (e) Sato, Y.; Imakuni, N.; Hirose, T.; Wakamatsu, H.; Mori, M. *J. Organomet. Chem.* **2003**, *687*, 392−402.
(6) Singidi, R. R.; Kutney, A. M.; Gallucci, J. C.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2010**, *132*, 13078−13087.
(7) Apte, S.; Radetich, B.; Shin, S.; RajanBabu, T. V. *Org. Lett.* **2004**, *6*, 4053−4056.
(8) Pardo-Rodríguez, V.; Buñuel, E.; Collado-Sanz, D.; Cárdenas, D. J. *Chem. Commun.* **2012**, *48*, 10517−10519.
(9) López-Durán, R.; Martos-Redruejo, A.; Buñuel, E.; Pardo-Rodríguez, V.; Cárdenas, D. J. *Chem. Commun.* **2013**, *49*, 10691−10693.
(10) Ojima, I.; Vu, A. T.; Lee, S.-Y.; McCullagh, J. V.; Moralee, A. C.; Fujiwara, M.; Hoang, T. H. *J. Am. Chem. Soc.* **2002**, *124*, 9164−9174.
(11) (a) Ohmura, T.; Suginome, M. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 29−49. (b) Oestreich, M.; Hartmann, E.; Mewald, M. *Chem. Rev.* **2013**, *113*, 402−441.
(12) (a) Si: Denmark, S. E.; Regens, C. S. *Acc. Chem. Res.* **2008**, *41*, 1486−1499. (b) Chang, W.-T. T.; Smith, R. C.; Regens, C. S.; Bailey, A. D.; Werner, N. S.; Denmark, S. E. *Org. React.* **2011**, *75*, 213−745. (c) B: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.
(13) Tanaka and co-workers published one previous example using a different silylborane and obtained the product with inferior yield.
(14) (a) Gerdin, M.; Nadakudity, S. K.; Worch, C.; Moberg, C. *Adv. Synth. Catal.* **2010**, *352*, 2559−2570. See also: (b) Ohmura, T.; Oshima, K.; Taniguchi, H.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 12194−12196.
(15) Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Hadei, N.; Nasielski, J.; O'Brien, C. J.; Valente, C. *Chem. - Eur. J.* **2007**, *13*, 150−157.
(16) Ohmura, T.; Masuda, K.; Furukawa, H.; Suginome, M. *Organometallics* **2007**, *26*, 1291−1294.
(17) Ohmura, T.; Masuda, K.; Suginome, M. *J. Am. Chem. Soc.* **2008**, *130*, 1526−1527.
(18) Zhou, H.; Moberg, C. *J. Am. Chem. Soc.* **2012**, *134*, 15992−15999.
(19) Majumdar, N.; Paul, N. D.; Mandal, S.; de Bruin, B.; Wulff, W. D. *ACS Catal.* **2015**, *5*, 2329−2366.
(20) This compound gave an analogous product by borastannylative cyclization; see ref 6.

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Organic LETTERS

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Modular Approach to Heterogenous Catalysis. Manipulation of Cross-Coupling Catalyst Activity

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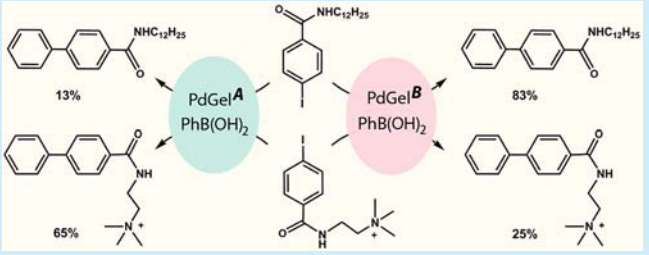
Supporting Information

ABSTRACT: A new type of robust, heterogeneous, modular Pd catalyst with metal embedded in the gel matrix is presented. The regulatory element of its catalytic activity has been introduced via chemical changes in the gel. The concept is illustrated in a series of Suzuki−Miyaura cross-coupling reactions. The demonstrated catalyst activity variations depend on the structure of the gel.



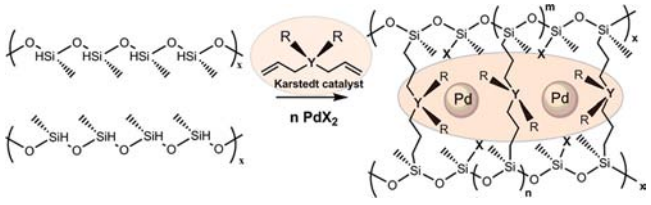
Metal-mediated cross-coupling reactions have been at the center of attention for several decades. From an academically interesting topic, they developed into an indispensable tool without which few chemists could imagine modern organic synthesis.[1] For this reason, much attention has been paid to basic principles of the catalysis and complexes of catalytically active transition metals. The dramatic success of this effort has been illustrated by numerous high-yielding, chemically tolerant protocols which play an important role in the synthesis of complex, highly functionalized chemical entities.[2] The main part in the fine-tuning of the catalytic systems has been traditionally occupied by the ligands which play a paramount role in the reactivity of metallic complexes. Their altering, study, and development can be seen behind every milestone successfully reached on the way to an ideal catalytic system. The downside of this ligand-oriented approach is inherent ligand sensitivity, which must be, in every protocol, addressed. Water and air presence, in particular, are the issues that require scrupulous attention.[3] This is, of course, true mainly for homogeneous catalytic systems, where the metallic complexes are, at least partly, dissolved in the reaction media.[4]

When a catalytic system is "ligandless"/heterogeneous, there are fewer possibilities for catalyst fine-tuning. Although this type of system has its own advantages, it can hardly compete with the multiple options available through ligand alternation and modification.[5,6]

In the present work, we revisit the above notions, connect these scenarios, and introduce a modular concept of a tunable catalyst which would retain the benefits of heterogeneous catalysis while possessing a regulatory handle traditionally reserved for homogeneous catalysis.[7] Polymeric gels were selected as the ideal platform for construction of a new type of metal-containing catalyst. A strength of the macromolecular materials as carriers for the catalytic metal lies in their own spatial structure, which can be modified or otherwise tuned by cross-linking, for example. Our ability to dramatically change their chemical and physical properties on-demand is a crucial point of our concept.

Herein, we illustrate the idea of a tunable heterogeneous catalyst on Pd encased inside chemically tunable polyhydromethylsiloxane (PHMS-based) gels.[8] Besides commercial availability, the main motivation behind the selection of PHMS was its unique chemical reactivity centered around the silicon hydrogen bond. In our synthetic scenario, it serves a double purpose: (1) The active hydrogen can be involved in a hydrosilylation-based cross-linking reaction.[8] (2) The same functionality acts as the reducing agent/activator for palladium.[9] The second crucial element of our concept is a cross-linker, which plays the role of a functional handle for the adjustment of the chemical properties of the desired gel (Scheme 1).

Scheme 1. Encapsulation of Pd in PHMS-Based Gel



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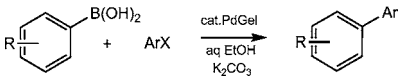
In order to demonstrate the catalytic activity of the new Pd-containing material, a simple 1,5-hexadiene cross-linked PdGel was synthesized and screened as the catalyst in a Suzuki cross-coupling reaction[10] (Table 1).

Table 1. Suzuki–Miyaura Coupling Catalyzed by the Gel-Encapsulated Pd[a]



	R	Ar	X	yield (%)
a	H	phenyl	Br	92
b	4-CH_3	4-formylphenyl	I	96
c	H	4-tolyl	I	99
d	H	4-tolyl	Br	96
e	H	4-formylphenyl	I	95
f	H	4-methoxyphenyl	Br	92
g	2-OCH_3	4-formylphenyl	I	95
h	3-OCH_3	4-methyl-3-nitrophenyl	I	95
i	H	4-nitrophenyl	Br	85
j	4-NO_2	2-tolyl	I	98
k	4-OCH_3	4- formylphenyl	I	98
l	H	4-dimethylaminophenyl	Br	91
m	4-CH═O	1-naphthyl	I	96

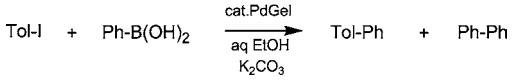
[a]General procedure for a PdGel-catalyzed Suzuki–Miyaura reaction: Haloarene (2.0 mmol), arylboronic acid (3.0 mmol), potassium carbonate (6.0 mmol), 80% aq EtOH (20 mL), PdGel catalyst (50 mg, corresponds to 0.2 mol % of the transition metal, preswelled, 25:1 cross-linking) was stirred at 50 °C under an Ar atmosphere (when bromides are used the temperature is set at 80 °C). Aryl chlorides under the same conditions gave only traces of the desired products.

While various obligatory bases could be used with similar efficacy in the reaction protocol, K_2CO_3 was selected as the base of the choice. Among several solvents which could have been used as the reaction media, a mixture of EtOH/H_2O (4:1) was chosen because of its wide substrate solubility coverage and overall best synthetic perfomance.

In order to address the possibility of the platinum traces influencing the cross-coupling reaction, a blank, palladium-less gel was used instead of PdGel. Not surprisingly, the experiment did not lead to any cross-coupling reaction.[11] Catalytic properties of the PdGel and its efficacy were compared with a series of commercially available and commonly used Pd catalysts in a model Suzuki cross-coupling reaction (see Table 2).

The general procedure for a Pd-catalyzed Suzuki–Miyaura reaction: to 4-iodotoluene (21.8 mg, 0.1 mmol), phenylboronic acid (14.6 mg, 0.12 mmol), and potassium carbonate (27.6 mg, 0.2 mmol) in 80% aq EtOH (2 mL) was added the Pd catalyst (corresponding to 1.0 mol % of the transition metal), and the reaction mixture was stirred at 50 °C. The samples were collected at 60 min and analyzed by GC/MS with internal standard.

Table 2. Comparison of a Catalytic Efficacy of PdGel and Various Commercially Available Pd Catalysts



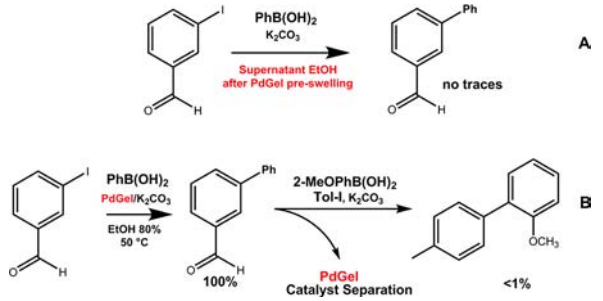
catalyst	Ph-Ph[a] (%)	Tol-Ph[a] (%)
PdGel(40:1)	0	100
$Pd(dba)_2$	16	84
5% Pd/C	3	78
$Pd(OAc)_2$	8	62
$Pd(OAc)_2$ + 0.25 equiv of TPPTS	3	45
$Pd(PPh_3)_4$	0	1

[a]GC yields.

The practical and fundamental importance of metal leaching has been widely recognized. In order to map the issue we combined traditionally used spectroscopic analysis with a set of chemical experiments.

When samples of the supernatant liquid after the PdGel preswelling step (24 h) were analyzed by electrothermal vaporization/inductively coupled plasma/optical emission spectrometry (ETV/ICP/OES),[12] no detectable amount of Pd was observed. The observation was corroborated by chemical means: when the supernatant solvent above was used as the solvent for Suzuki cross-coupling reaction, no cross-coupling product was observed after 2 h at 50 °C (Scheme 2 A). In a different

Scheme 2. Metal-Leaching Determination



experiment, the supernatant liquid after cross-coupling reaction and PdGel separation was subjected to the same chemical test. In this case, 0.2% of the cross-coupling product was observed after 2 h (Scheme 2 B). The result can be attributed to a minor disintegration of the catalytic material during the first coupling reaction.

In order to probe the system further, the PdGel reutilization was also examined. The experimental results showed no reduction in the catalytic activity in a series of consecutive runs under optimized conditions.[13] Less forgiving stirring conditions led, however, to somehow diminished catalytic activity of the reused PdGel in the several consecutive runs. The effect can be explained again by partial disintegration of the gelous material (Scheme 3).

Several control experiments have been carried out to gain extra insight into the present catalytic platform. The study evaluating the swelling of the Pd-containing gels (PdGels) as a parameter in the model cross-coupling reaction clearly show the importance of preswelling in the reaction kinetics (Scheme 4).

The implication of the experimental results above is equally significant: influence of the swelling on the catalytic activity suggests that the location of the active palladium is inside the gel. In this situation, the effect of the cross-linker can arguably be more profound.

After demonstrating the scope of general activity of the PdGel, cross-linker control of the catalytic activity, the main strength of our approach, was investigated. For this purpose, a series of PHMS-based gels were synthesized employing dienes with distinct chemical features as the cross-linkers (Figure 1). Differences in their polarity were of particular importance.

As with a simple hexadiene, the functionalized di(poly)olefins **A**–**F** were utilized as the PHMS cross-linkers via standard

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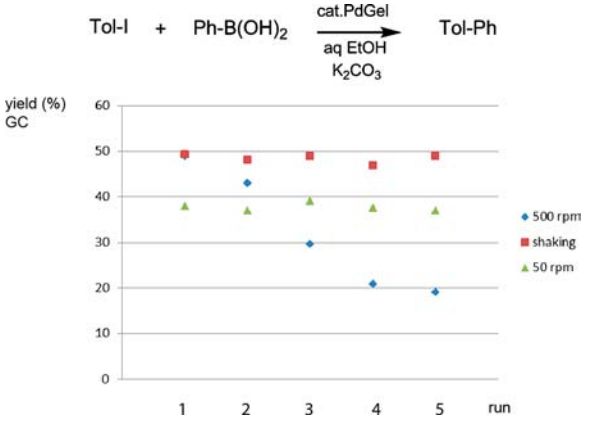
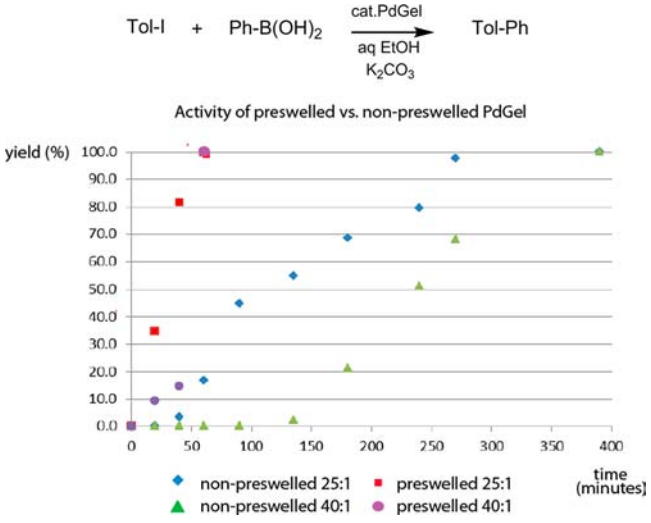
Scheme 3. Effect of the Reaction Mixture Agitation on PdGel Recycling (2 h)[a]



[a]Experimental conditions: PdGel (25:1, 5 mg) was mixed with 80% aq EtOH (0.1 mL) and kept at rt for 2 h without stirring. Then 4-iodotoluene (0.1 mmol), phenylboronic acid (0.12 mmol), 80% aq EtOH (2 mL), and potassium carbonate (0.2 mmol) were added, and the reaction mixture was stirred (50 or 500 rpm) or shaken for 2 h at 50 °C under an Ar atmosphere. The reaction mixture was analyzed (GC/MS) and the gel separated and washed with 80% ethanol. To the wet gel were added the same amounts of reactants and the procedure was repeated four times.

Scheme 4. Effect of PdGel Preswelling on Its Catalytic Activity[a]



[a]Experimental conditions: 4-iodotoluene (0.2 mmol), phenylboronic acid (0.3 mmol), potassium carbonate (0.6 mmol), 80% aq EtOH (2.0 mL), PdGel catalyst (5.0 mg, corresponds to 0.2 mol % of the transition metal, 40:1 or 25:1 cross-linking) was stirred at 50 °C under an Ar atmosphere, and the reaction conversion was followed by GC/MS with internal standard.

chemistry in the preparation of Pd-containing gels. The resultant Pd gels were used after workup and isolation (extraction of unreacted reagents) for comparative studies.

The substrates for the model study were not selected indiscriminately: aryl iodides which show contrasting chemical attributes (e.g., different polarity) and consequently could respond to the cross-linker modified Pd gels while retaining activity under Suzuki cross-coupling conditions were considered the ideal cross-coupling substrates (Figure 2). 4-Iodo-*N*-

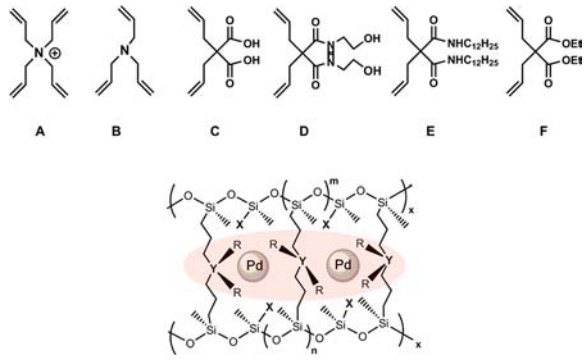


Figure 1. Diene cross-linkers.

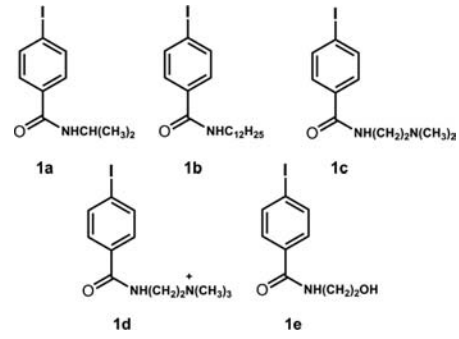
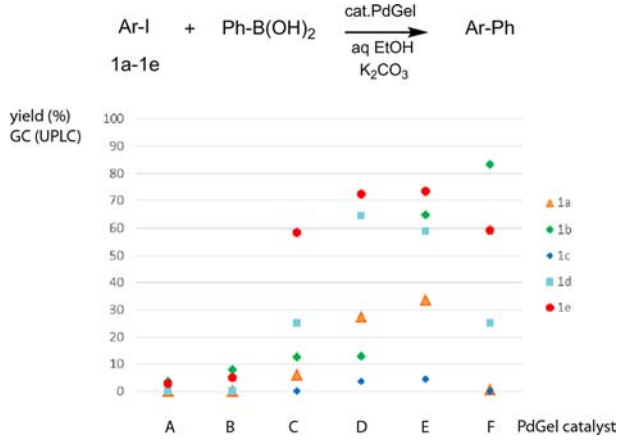


Figure 2. Aryl iodides.

ispopropylbenzamide **1a**, 4-iodo-*N*-dodecylbenzamide **1b**, 4-iodo-2-(*N*,*N*-dimethylamino)ethylbenzamide **1c**, 2-(4-iodobenzamido)-*N*,*N*,*N*-trimethylethan-1-aminium iodide **1d**, and 4-iodo-*N*-(2-hydroxyethyl)benzamide **1e** were eventually selected as the reaction substrates which would act as chemical probes into the catalytic activity of the PdGels. Simple phenylboronic acid acted as the complementary cross-coupling partner.

The above plot of the cross-linker vs the structure of the reaction substrate (Scheme 5) depicts the change of the reaction yield with the modified catalytic gel as the variable factor. The

Scheme 5. Influence of the Functionalized Cross-Linker on the Reaction Yield (Variable Aryl Iodides, 60 min)[a,14]



[a]General procedure for the PdGel catalytic activity screening: Aryl iodide (0.2 mmol), phenylboronic acid (0.3 mmol), potassium carbonate (0.6 mmol), 80% aq EtOH (2.0 mL), PdGel catalyst (5.0 mg - corresponds to 0.2 mol % of the transition metal, preswelled, 40:1 cross-linking) was stirred at 50 °C under an Ar atmosphere for 60 min.

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catalysts are lined up from the left to the right (A–F, Figure 1) according to the assumed declining polarity of the cross-linkers. The visible overall trend of the substrate response to the catalyst thus implies the polarity of the cross-linker as the likely principal factor causing changes in the catalyst activity. Considering the amount of the cross-linker in the polymer matrix and the overall amount of the matrix material in the reaction mixture, the extent of the cross-linker impact over the catalyst activity is fairly remarkable. The close proximity of the reaction center (palladium) and the cross-linker-based functional group may be likely culprit behind the extent of the observed selectivity.[15]

Overall, the concept of a tunable heterogeneous catalyst based on Pd embedded in a polysiloxane matrix is presented and demonstrated in a classical Suzuki–Miyaura protocol. The present type of gelous catalyst, which can be conveniently prepared in a common synthetic laboratory setting, is fairly robust and suffers minimally from metal leakage. Importantly, it permits an effective separation of the catalyst at the end of the process and ultimately allows for catalyst reuse. An additional strength of the introduced PdGel system is the concept of its catalytic activity modulation. Changes in the catalytic activity of the metal are accomplished via alterations in the immediate environment of the metal. These alterations are achieved through the functionalized cross-linkers of the gel matrix. Changes in activity of the novel Pd gel catalyst are illustrated in a series of experiments following the Suzuki–Miyaura protocol with the substrates matching (mismatching) chemophysical properties of the cross-linker. While the overall alteration of the reaction mixture may arguably be (due to a minuscule amount of the modified cross-linker) negligible, a more profound change in the microenvironment of the catalytic metal may explain the observed activity variation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03480.

Technical details, supplementary experiments, and characterization of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: Amsterdam, 2000. (b) Cahiez, G.; Moyeux, A. *Chem. Rev.* **2010**, *110*, 1435. (c) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555. (d) Marion, N.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 1440.

(2) Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177.

(3) Crabtree, R. H. *Chem. Rev.* **2015**, *115*, 127.

(4) For the examples of Pd catalyst with polymer-supported ligand in cross-coupling reactions, see: (a) McNamara, C. A.; Dixon, M. J.; Bradley, M. *Chem. Rev.* **2002**, *102*, 3275. (b) Yang, J.; Li, P.; Wang, L. *Synthesis* **2011**, *2011* (8), 1295. For example of silica-supported Au, see: Shu, X.-Z.; Nguyen, S. C.; He, Y.; Oba, F.; Zhang, Q.; Canlas, C.; Somorjai, G. A.; Alivisatos, A. P.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 7083.

(5) (a) Moreno-Manas, M.; Pleixats, R. *Acc. Chem. Res.* **2003**, *36*, 638. (b) Thomas, J. M.; Raja, R. *Acc. Chem. Res.* **2008**, *41*, 708. (c) Narayanan, R.; El-Sayed, M. A. *J. Phys. Chem. B* **2005**, *109*, 12663.

(6) For examples of supported Pd nanoparticles in cross-coupling catalysis, see: (a) Pagliaro, M.; Pandarus, V.; Béland, F.; Ciriminna, R.; Palmisano, G.; Carà, P. D. *Catal. Sci. Technol.* **2011**, *1*, 736. (b) Firouzabadi, H.; Iranpoor, N.; Ghaderi, A.; Ghavami, M.; Hoseini, S. J. *Bull. Chem. Soc. Jpn.* **2011**, *84*, 100. (c) Han, W.; Liu, Ch.; Jin, Z. *Adv. Synth. Catal.* **2008**, *350*, 501. (d) Zhang, G. *Synthesis* **2005**, *4*, 537.

(7) For a review of microencapsulated metals as catalysts, see: Akiyama, R.; Kobayashi, S. *Chem. Rev.* **2009**, *109*, 594.

(8) For PHMS gels containing Pt and their reactivity in hydrogenation reactions, see: Motoyama, Y.; Kamo, K.; Nagashima, H. *Org. Lett.* **2009**, *11*, 1345.

(9) Chauhan, B. P. S.; Rathore, J. S.; Glloxhani, N. *Appl. Organomet. Chem.* **2005**, *19*, 542.

(10) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(11) Rigorous RFA metal analysis did not show any appreciable amount of Pt in the PdGels. (See the experimental details, SI.)

(12) Sensitivity of ETV/ICP/OES is in the range of ppb.

(13) The reaction mixture was shaken rather than vigorously stirred. The PdGel was isolated and carefully washed after every run.

(14) Without the termination in 60 min, all of the reactions reached quantitative conversion in a few hours.

(15) An important component of the concept is the metal topology: In order to effectively tune the catalytic properties of the catalyst, the metal should be embedded *inside* the polymer matrix. Our findings (the analytical RFA and reactivity studies of the supernatant reaction solvent indicating no loss of the metal to the environment) support this scenario. See the SI for details.

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Organic LETTERS

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Skeletally Diverse Synthesis of Indole-Fused Diazocine and Diazepine Frameworks by One-Pot, Two-Component Cascade Reaction

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Supporting Information

ABSTRACT: An expeditious and novel strategy has been explored for the synthesis of structurally diverse indole-fused diazocine and diazepine derivatives. A substrate-based diversification approach of methyl-3-aminoindole/indoline benzoates coupled with the Pictet−Spengler reaction and three different reaction cascades furnished indolodiazepine and indoloquinoxalines. The formation of indolodiazocines proceeds through an initial condensation followed by intramolecular alkylation.

Indole represents one of the most versatile and important classes of heterocycles which occupy a pivotal position in medicinal and organic chemistry because of their unique structural and interesting biological properties.[1,2] In particular, indoles fused with other heterocycles have shown significant biological applications. Diazepines and diazocines are seven-and eight-membered rings of nitrogen-containing heterocycles found in many natural products. Among those, the indole-fused diazepines act as kinase inhibitors and antidepressant agents.[3,4] Over the years, many medicinal chemists synthesized a variety of compounds by installing various active groups to the indole/indoline moieties through a new synthetic strategy. These heterocycles have potential utility in the fields of biology, pesticides, and medicinal chemistry.[5,6] Some examples of biologically important diazepines and diazocines are shown Figure 1.

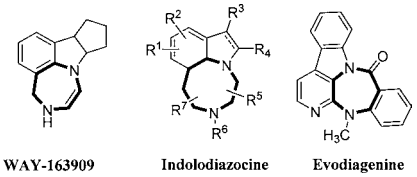

Figure 1. Biologically important compounds containing fused indolodiazepine and indolodiazocine.

Their diverse biological activities and synthetic applications have stimulated substantial interest in the study of these important heterocycles. Surprisingly, the literature contains only a few reports describing the synthesis of indole-fused diazepines. Further, the combination of indoline fused with diazocine is not yet documented. Typical molecular constructions of indole-fused azepine fall into two steps: Pictet−Spengler reaction of tryptamines with pyruvates, followed by skeletal rearrangement via aziridine formation. Kuehne et al. reported the Pictet−Spengler reaction of tryptamine with methylchloro pyruvate for the formation of indoloazepine.[7] Similarly, Flatt and co-workers demonstrated the stepwise synthesis of azepinoindoles through ring expansion of carbolines obtained by the reaction of tryptamine with bromopyruvates.[8] Hence, a convenient and novel strategy for an efficient construction of these scaffolds is highly desirable.

Synthesis of structurally complex and highly functionalized heterocyclic skeletons is a challenging goal in modern organic chemistry. Cascade reactions, which are defined as multiple bond formations in a single step with a sequence of reactions, are one of the most promising approaches.[9] These processes avoid the isolation and purification of intermediates, maximizing the yield of the final product and minimizing solvent waste with high atom-economy. The attractive features of these cascade reactions are the formation of several C−C, C−N bonds for rapid access to fused and complex polycyclic skeletons. In continuation of our earlier work on the synthesis of indole fused nitrogen heterocycles,[10] we aimed to carry out an unconventional Pictet−Spengler reaction on 2-(1*H*-indol-1-yl)aniline/2-(indolin-1-yl)aniline with α-bromo ketones, as shown in Scheme 1. In this present work, we were surprised to find that the reactivity patterns were completely altered by the reaction conditions and substituents on substrates. The tunable reactivity of these scaffolds allowed us to design two different cyclization reactions with α-bromo ketones **2**. It is proposed that indole **6** will undergo cyclization at the C2 position, whereas indoline **1** will cyclize at C7 to create two different, new molecular entities. 2-(1*H*-Indol-1-yl)aniline **6** successfully underwent the Pictet−Spengler cyclization which

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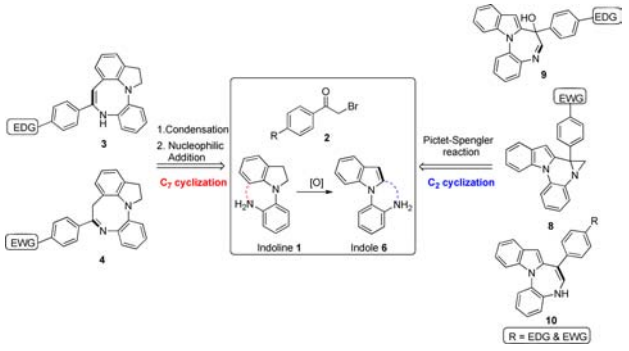
Scheme 1. Synthesis of Skeletally Diverse Indole/Indoline Fused Diazocines and Diazepines



on further reaction to furnish three novel heterocycles under three different reaction conditions. To our surprise, 2-(indolin-1-yl)aniline **1** performed condensation followed by intramolecular C-alkylation to deliver compounds **3** or **4** instead the expected Pictet−Spengler reaction.

The key aspect of our new approach is the construction of quaternary sp^3 carbon atoms in fused ring systems, which disrupts the one-dimensional planarity of the scaffolds. Increasing the saturation may create several conformations which can act as a suitable substrate in drug discovery to design several high affinity ligands by creation of diverse chemical space.[11]

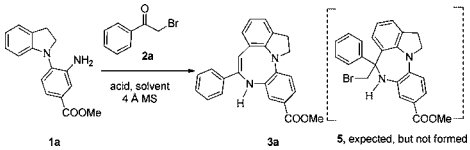
Our studies began with the preparation of a key substrate, methyl 3-amino-4-(indolin-1-yl)benzoate **1a**, from 4-fluoro-3-nitrobenzoic acid by sequential reactions such as esterification, nucleophilic substitution with indoline, and nitro reduction.[10c] Then, we carried out an unconventional Pictet−Spengler reaction on compound **1a** with α-bromo acetophenone **2a** in the presence of TFA (1 equiv) in refluxing chloroform (Table 1, entry 1). To our surprise, the possible Pictet−Spengler product **5** was not observed, and a serendipitous formation of **3a** was isolated in 20% yield with the remaining of starting material **1a**. Careful analysis of the proton NMR reveals the participation of all starting material in the isolated product and the absence of $-CH_2Br$ protons. Similarly, the mass analysis did not show the bromo pattern corresponding to the expected product **5**. Hence, we reasoned that the product **3a** is obtained by stepwise condensation followed by intramolecular C-alkylation. Under these reaction conditions, a high reaction selectivity toward aromatic substitution is observed instead of Pictet−Spengler reaction on imine carbon.

Interestingly, the proton NMR spectra of **3g** shows two conformers which are non-interconverting on the NMR time scale at ambient temperature. This conformational behavior is further supported by varying temperature studies as shown in Figures 3 and 4 (Supporting Information). Although the anticipated product was not obtained, this unprecedented formation of indolo-fused diazocine **3** might be more rewarding, as there are no previous reports on such a convenient one-pot synthesis of new molecules from these readily available starting materials. Hence, we aimed to generalize this outcome by carrying out optimization studies with various acid catalysts and solvents as shown in Table 1. No reaction was observed when TCT (trichlorotriazine) or *p*-TSA was employed as an acid catalyst. A survey of various solvents such as DMSO, DMF, and acetonitrile showed the same results with very little conversion to the desired product. Increasing the amount of TFA (3equiv) in refluxing chloroform improved the reaction yield up to 38%.

However, a higher yield of 88% was obtained when the reaction was carried out in a sealed vessel at 80 °C in chloroform for 4 h (entry 11). Further increase in TFA or temperature did not improve the reaction yield. Thus, we concluded that the optimum conditions for this cyclization is the employment of 3 equiv of TFA in chloroform in a sealed tube at 80 °C for 4 h.

The scope and limitation of the reaction were next studied to understand, in particular, the influence of the substituents presenting on α-bromo acetophenones (Scheme 2). We found that the final outcome of the reaction is significantly dependent

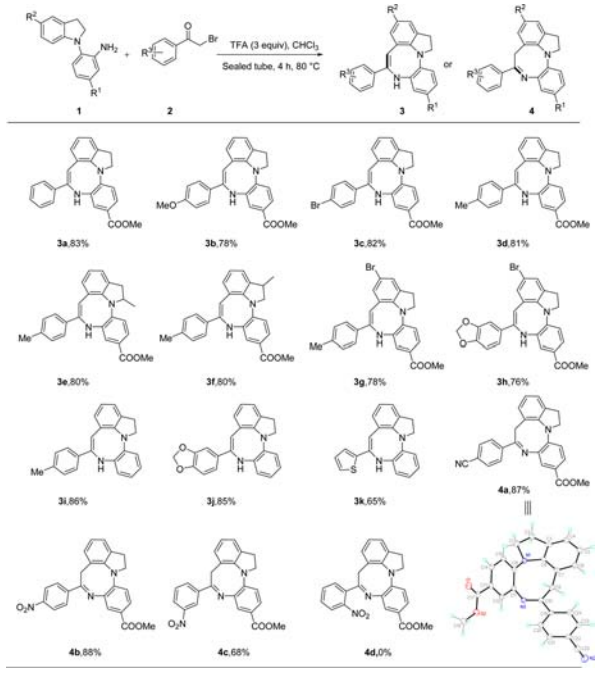
Table 1. Effect of Different Reaction Parameters on the Preparation of Indolodiazocines 3a[a]



entry	acid (equiv)	solvent	temp (°C)	time (h)	yield[b] (%)
1	TFA (1)	$CHCl_3$	reflux	24	20
2	TCT (1)	DMSO	80	24	NR[c]
3	TCT (1)	$CHCl_3$	reflux	24	NR
4	PTSA (1)	$CHCl_3$	reflux	24	NR
5	PTSA (1)	DMF	80	24	NR
6	TFA (3)	DMF	80	24	10
7	TFA (3)	CH_3CN	reflux	24	20
8	PTSA (1)	CH_3CN	reflux	24	NR
9	TFA (3)	$CHCl_3$	reflux	24	38
10	TFA (6)	$CHCl_3$	reflux	12	45
11[d]	**TFA (3)**	**$CHCl_3$**	**80**	**4**	**88**

[a]The reaction was performed in the presence of **1a** (0.25 mmol) and **2a** (0.25 mmol) and acid catalyst in solvent (2 mL). [b]Isolated yield. [c]NR = no reaction. [d]Reaction performed in sealed tube.

Scheme 2. Synthesis of Indolo-Fused Diazocines 3 or 4



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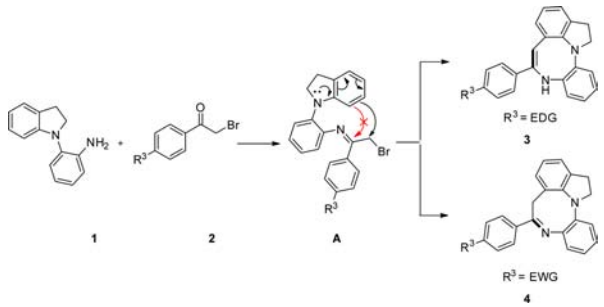
on the electronic nature of substituents attached directly on the aromatic rings of α-bromo acetophenones. Two different types of product formation were observed under these conditions. Aryl rings bearing R^3 electron-donating groups furnished compounds **3a**–**k**, whereas products **4a**–**d** were obtained when the R^3 groups are electron-withdrawing. For example, electron-donating substituents as well as thiophene **3k**, an electron-rich heterocycle, favor the formation of enamines **3**, whereas the electron-deficient cyano and nitro groups favor the formation of **4**. However, α-bromo ketone possessing a nitro substituent at the ortho position did not deliver the product **4d** due to steric effects. In general, all of the substituents are well-tolerated under the same conditions and delivered the products with satisfactory yields. As shown in Scheme 2, the structure of one of the representative compounds **4a** is elucidated by X-ray single-crystal analysis. On the basis of experimental observation, a plausible mechanism is depicted in Scheme 3.

Scheme 3. Plausible Mechanism for the Unexpected Formation 3 or 4

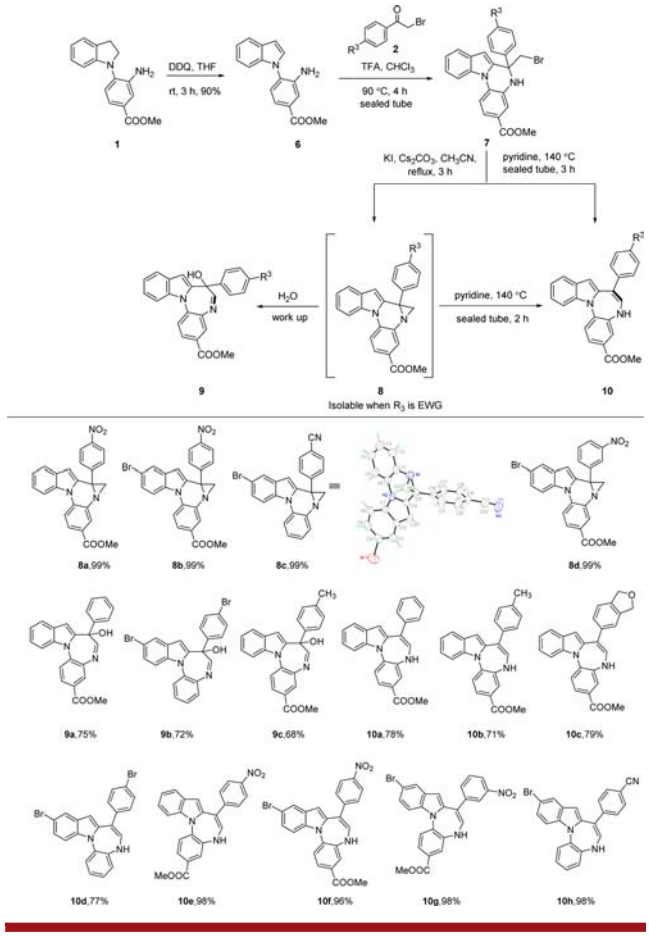


This domino transformation begins with the condensation of 2-(indolin-1-yl)aniline **1** with α-halo ketone **2** to give intermediate **A**, which will undergo intramolecular alkylation at electron-rich C7 to deliver the unexpected indolo-fused diazocine analogues **3** or **4** with respect to the substituents.

Creation of diverse libraries with various molecular scaffolds is an ideal goal in drug discovery research. Hence, the indoline moiety present in compound **1** gave ample opportunity for further diversification. The oxidation of indoline to its corresponding indole **6** was achieved with DDQ as shown in Scheme 4. The obtained 2-(1*H*-indol-1-yl)aniline **6** could act as a suitable substrate for modified Pictet–Spengler reaction with α-bromo ketones under acid conditions to furnish indolo quinoxaline **7** (Scheme 4). The obtained indolo quinoxaline **7** was further treated with potassium iodide and cesium carbonate in acetonitrile under reflux conditions for 3 h. Interestingly, this reaction furnished a new kind of heterocycle **9** possessing hydroxyl group at quaternary carbon (when R^3 = H). The structure of representative compound **9a** is unequivocally confirmed by X-ray crystallography as shown in Figure 2. The compound exhibit attractive 3D-shapes due to the obvious sp^3 character in the skeleton. The indole-fused seven membered diazepine ring is twisted and hence makes the molecule nonplanar.

The formation of **9** can be rationalized by the initial formation of aziridine **8** which undergoes ring-opening reaction on aqueous workup to give indole-fused diazepine **9**. However, addition of water as a cosolvent did not deliver the observed product **9**. In a further study, we tried to isolate the aziridine intermediate **8** to understand the original source of hydroxyl group in compound **9**. Herein, we observed that the electronic

Scheme 4. Synthesis of Indole-Fused Azirinoquinoxalines 8 and Diazepines 9 or 10



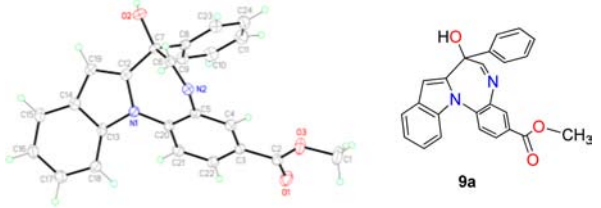


Figure 2. ORTEP diagram of compound **9a**.

nature of R^3 plays a crucial role on the stability of the aziridine intermediate. We were able to isolate the aziridines **8a**–**d** only when the R^3 is an electron-withdrawing substituent. As shown in Scheme 4, the structure of aziridine **8c** is elucidated by X-ray single-crystal analysis. All efforts to isolate compound **8** possessing electron-donating R^3 groups were unsuccessful, and they furnished only compound **9** directly.

In addition, the reaction of isolated aziridine **8a** with water as a cosolvent under the optimized conditions did not proceed to the expected product **9**. Hence, the driving force for the formation of hydroxyl-substituted product could be the substituent-aided stability of the aziridine ring. The presence of an electron-withdrawing group at the para position of the aromatic ring stabilized the highly strained aziridine ring, whereas ring-opening of aziridine was observed during the aqueous workup if there is an electron-donating group at the para position. Treatment of the isolated aziridines **8** in pyridine at 140 °C in a sealed tube for 2 h underwent skeletal

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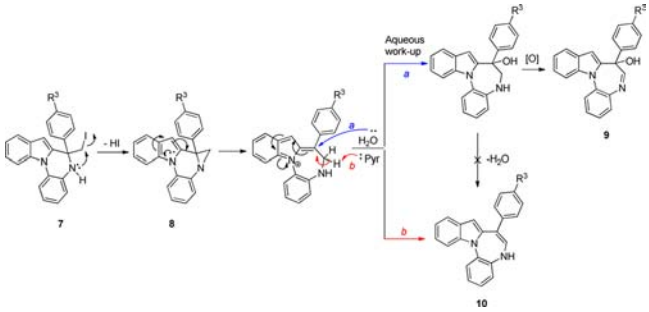
rearrangement to indole-fused diazepines **10**. Delighted with this observation, we evaluated the possibility of performing the whole transformation in a one-pot, two-step domino fashion without isolation of the aziridine intermediate **8**. To our delight, treatment of Pictet− Spengler product **7** with pyridine at 140 °C in a sealed tube for 3 h furnished compound **10** directly. In this transformation, the reaction condition plays a crucial role as both the electron-donating and -withdrawing substituents (R^3) deliver the seven-membered products with satisfactory yields. Hence, three different unique heterocycles were formed exclusively depending on the electronic nature of the substituents and the reaction conditions as depicted in Scheme 4. On the basis of experimental observation, a plausible mechanism is depicted in Scheme 5. To gain insight into the

Scheme 5. Plausible Mechanism for the Formation of Indole Fused Azirinoquinoxalines 8 and Diazepines 9 or 10



reaction mechanism, a few control experiments were conducted. To elucidate the conversion of compound **7** to **10**, a one-pot reaction for the synthesis of **10** was carried out (Scheme 4), and the formation of compound **8** was observed after 1 h.

This experiment strongly confirmed that this cyclization could be rationalized to proceed through an initial intramolecular N-alkylation to generate aziridines **8** followed by ring expansion under basic conditions to diazepines **10**. To confirm further, the isolated intermediate **8** was successfully converted to **10** in refluxing pyridine for 24 h or under a sealed tube at 140 °C for 2 h. To account for the formation of **9**, a tandem aziridine formation followed by a ring-opening mechanism was proposed (Scheme 5). Initial intramolecular N-alkylation of **7** in the presence of KI and Cs_2CO_3 in acetonitrile to furnish aziridine **8**. Further, it underwent ring-opening reaction with the water molecule during the aqueous workup, aided by the electronic effect of the substituent on α-bromo ketones. It is noteworthy to mention that oxidation to imine formation is favored over the dehydration to enamine.

In summary, we have disclosed an efficient method for the construction of several undocumented indole-fused diazepines and diazocines through a substrate-based diversification approach. Employment of four different reactions such as Pictet−Spengler cyclization, aziridine ring formation, skeletal rearrangement, and hydroxylation yielded these novel heterocycles. The selectivity of product formation was dictated by the substituents and reaction conditions. This strategy provides straightforward access to a library of compounds with privileged structures that are of immense interest in drug discovery. Further study on the reaction scope and their biological application is still underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03481.

Experimental details plus spectroscopic and other data for compounds (PDF)
X-ray data for **4a** (CIF)
X-ray data for **8c** (CIF)
X-ray data for **9a** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (b) Fu, P.; Yang, C. L.; Wang, Y.; Liu, P. P.; Ma, Y. M.; Xu, L.; Su, M. B.; Hong, K.; Zhu, M. *Org. Lett.* **2012**, *14*, 2422.
(2) (a) De Sa Alves, F. R.; Barreiro, E. J.; Fraga, C. A. M. *Mini-Rev. Med. Chem.* **2009**, *9*, 782. (b) Sakaki, J.; Konishi, K.; Kishida, M.; Gunji, H.; Kanazawa, T.; Uchiyama, H.; Fukaya, H.; Mitani, H.; Kimura, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4808.
(3) Danilenko, V. N.; Simonov, A. Y.; Lakatosh, S. A.; Kubbutat, M. H. G.; Totzke, F.; Schächtele, C.; Elizarov, S. M.; Bekker, O. B.; Printsevskaya, S. S.; Luzikov, Y. N.; Reznikova, M. I.; Shtil, A. A.; Preobrazhenskaya, M. N. *J. Med. Chem.* **2008**, *51*, 7731.
(4) Putey, A.; Fournet, G.; Lozach, O.; Perrin, L.; Meijer, L.; Joseph, B. *Eur. J. Med. Chem.* **2014**, *83*, 617. (b) Glamkowski, E. J.; Fortunato, J. M. *J. Med. Chem.* **1980**, *23*, 1380.
(5) Gao, H.; Stack, G. P.; Sabb, A. L. WO 2003091257 A1, 2003.
(6) (a) Stansfield, I.; Ercolani, C.; Mackay, A.; Conte, I.; Pompei, M.; Koch, U.; Gennari, N.; Giuliano, C.; Rowley, M.; Narjes, F. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 627. (b) Maeda, M.; Sasaki, S.; Harada, N.; Kimura, J. JP 2000239252A, 2000. (c) Dunlop, J.; Marquis, K. L.; Lim, H. K.; Leung, L.; Kao, J.; Cheesman, C.; Lipson, S. R. *CNS Drug Rev.* **2006**, *12*, 167.
(7) Kuehne, M. E.; Bohnert, J. C.; Bornmann, W. G.; Kirkemo, C. L.; Kuehne, S. E.; Seaton, P. J.; Zebovitz, T. C. *J. Org. Chem.* **1985**, *50*, 919.
(8) Flatt, B.; Martin, R.; Wang, T. L.; Mahaney, P. E.; Murphy, B.; Gu, X. H.; Foster, P.; Li, J.; Pircher, P.; Petrowski, M.; Schulman, I.; Westin, S.; Wrobel, J.; Yan, G.; Bischoff, E.; Daige, C.; Mohan, R. *J. Med. Chem.* **2009**, *52*, 904.
(9) Wasilke, J. C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001.
(10) (a) Barve, I. J.; Dalvi, P. B.; Thikekar, T. U.; Chanda, K.; Liu, Y. L.; Fang, C. P.; Liu, C. C.; Sun, C. M. *RSC Adv.* **2015**, *5*, 73169. (b) Chen, L. H.; Chang, C. M.; Salunke, D. B.; Sun, C. M. *ACS Comb. Sci.* **2011**, *13*, 391. (c) Lai, J. J.; Salunke, D. B.; Sun, C. M. *Org. Lett.* **2010**, *12*, 2174.
(11) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752.

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Organic LETTERS

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Discrete Molecular Recognition Induced Higher-Order Structures: Fibrous Formation Triggered by Melamine Recognition with a Cationic Ethynylpyridine Macrocyclic Host

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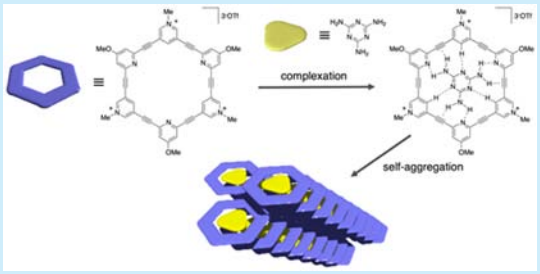
Supporting Information

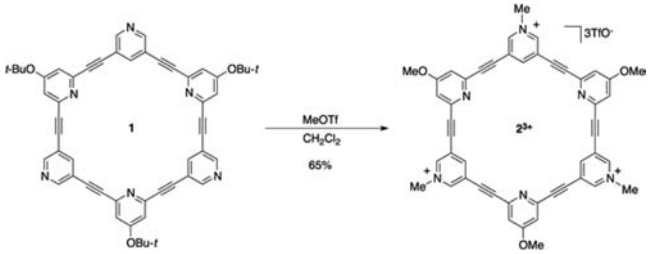
ABSTRACT: A tricationic shape-persistent macrocycle was obtained by methylation on the nitrogen atoms of the three 3,5-pyridylene groups of an alternating 2,6-/3,5-substituted ethynylpyridine macrocycle. The tricationic macrocycle recognized melamine in polar solvents such as DMSO and water, and the host–guest association in water induced a higher-order aggregate confirmed by UV–vis titration and dynamic light scattering experiments. Scanning electron microscopy, transmission electron microscopy, and atomic force microscopy indicated that fibrous network structures resulted from the stacking of the macrocycle and melamine complex.



Shape-persistent macrocycles (SPMs) based on a planar framework with a broad π-surface[1,2] have attracted much attention in the fields of supramolecular chemistry and materials science including liquid crystals,[3] nanoporous materials,[4] and photoconductive materials.[5] To date, SPMs of various frameworks have been developed, and some SPMs self-aggregate by noncovalent interactions such as π-stacking and solvophobic effects.[6] For example, Moore and co-workers reported that a cyclic *meta*-phenylene ethynylene hexamer self-assembled to form a nanofiber.[6a] The size and morphology of the self-assembled structure could be controlled by changing temperature and solvents. Höger et al. investigated phenylene ethynylene macrocycles with flexible long alkyl side chains, and the SPMs showed liquid-crystalline behavior.[3c,d] On the other hand, several kinds of SPMs have been known to accommodate a guest molecule in their cavities.[6f,7] Miljanic and co-workers reported crystal structures of the host–guest complex of phenylene ethynylene macrocycles and fluorinated benzene associating through C–H···F–C interaction.[7c] However, there are few examples of self-aggregation systems triggered by discrete molecular recognition between SPMs and organic guests in their cavity. Yuan et al. investigated an oligoamide-type SPM that recognized an alkylammonium ion in its cavity. The initially resulting complex subsequently self-assembled to form a higher-order structure.[7d] Nevertheless, this type of aggregation is still rare and remains to be widely explored.

Our group also has developed SPMs[8] such as **1**, in which three 2,6-pyridylene and three 3,5-pyridylene units were alternatingly linked by acetylene bonds[9] with D_{3h} symmetry (Scheme 1).[8a] In solid states, the rigid planar structure of **1** took advantage of π-stacking enhanced by the intermolecular dipole–dipole interaction to form self-assemblies. Apart from the self-assembling property, macrocycle **1** has multipoint hydrogen-bonding sites inside and showed an affinity with octyl glucoside in apolar solvent. To give water solubility in the framework, we derivatized **1** by alkylating at the outer nitrogen atoms to produce pyridinium derivatives (Scheme 1). Herein, we report that the water-soluble tripyridinium cation $\mathbf{2}^{3+}$ recognized melamine, and that the discrete host–guest association in water induced self-assembly to form fibrous aggregates observable on the basis of dynamic light scattering (DLS) and various microscopies (Figure 1).

Scheme 1. Preparation of Macrocycle $\mathbf{2}^{3+}\cdot 3\mathrm{TfO}^-$



Precursor **1** was treated with an excess amount of methyl triflate (MeOTf) in CH_2Cl_2 at room temperature (Scheme 1). The reaction gave one major product as a pale yellow solid, which was assigned to trication $\mathbf{2}^{3+}\cdot 3\mathrm{TfO}^-$ based on ^{1}H NMR and ESI-TOF-MS. The ^{1}H NMR spectrum was very simple and showed three kinds of aromatic signals (δ 9.55, 9.32, 6.86 ppm in DMSO-d_6) as well as the case for **1** (δ 8.75, 8.27, 7.14 ppm in $CDCl_3$). In comparison, though the solvents used were different,[10] the two signals on the "outward" pyridine of **1** moved remarkably downfield after the reaction. Thus, in the product, the three nitrogen atoms in the 3,5-pyridylene units

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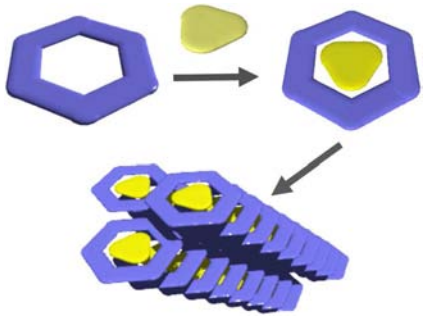

Figure 1. Schematic representation of the aggregation process triggered by molecular recognition of SPM.

were methylated. On the other hand, the "inward" three nitrogen atoms in the 2,6-pyridylene units remained intact. The decreased reactivity was presumably caused by the decreased nucleophilicity, which should be suppressed by the substituents adjacent to the inward nitrogen atoms. The signal of the *tert*-butyl groups of **1** disappeared after the reaction, while two singlets appeared at δ 4.41 and 4.21 ppm, each of which represents nine protons based on the integration. The three *tert*-butyl groups at the 2,6-pyridylene units were replaced with methyl groups by electrophilic substitution on the oxygen atoms. Taking those into account, we concluded that the product of the reaction of **1** with MeOTf must be trication $\mathbf{2}^{3+}$. The counteranion in $\mathbf{2}^{3+}$ proved to be TfO^- as ESI-TOF-MS spectra showed signals of various molecular ions involving $\mathbf{2}^{3+}$ and TfO^- such as $[\mathbf{2}^{3+} + 2TfO^-]^+$ and $[\mathbf{2}^{3+} + 3TfO^- + H]^+$. This salt $\mathbf{2}^{3+}\cdot\mathbf{3TfO}^-$ was soluble in various polar solvents such as H_2O, DMSO, and MeOH.

SPMs consisting of arylene and ethynylene units have been developed as host molecules incorporating guests within their cavities.[6f,7,9] Macrocycle $\mathbf{2}^{3+}$ has three nitrogen atoms facing the cavity, and these were expected to work as convergent hydrogen-bonding acceptors with D_{3h} symmetry. We examined melamine as a guest molecule because melamine appears to just fit in the cavity and has divergent hydrogen-bonding donors in the same planar and D_{3h} symmetric manner as in $\mathbf{2}^{3+}$.[11] High symmetry and rigidity of both the host and the guest would reduce entropic cost that inevitably arises from the host–guest complexation. Geometry optimization of the melamine-incorporated $\mathbf{2}^{3+}$ was carried out using DFT (Figure 2a,b). We predicted the formation of intermolecular hydrogen bonds of the $-NH_2$ groups in melamine (H^a in Figure 2c) with the inward nitrogen atoms of $\mathbf{2}^{3+}$ (N^a in Figure 2c). Unexpectedly, the N–H···π interaction also was indicated between hydrogen

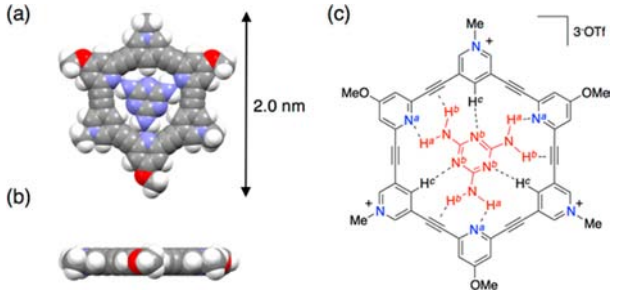

Figure 2. (a) Top and (b) side views of $\mathbf{2}^{3+}\cdot\mathbf{melamine}$ optimized by DFT calculation. Conditions: B3LYP/6-31G. (c) Supposed hydrogen bonds in $\mathbf{2}^{3+}\cdot\mathbf{melamine}$.

atoms of $-NH_2$ groups in melamine (H^b in Figure 2c) and triple bonds of $\mathbf{2}^{3+}$. In addition, the C–H···N interaction was observed for nitrogen atoms in the triazine ring of melamine (N^b in Figure 2c) with 4-hydrogen atoms in the 3,5-pyridylene units of $\mathbf{2}^{3+}$ (H^c in Figure 2c). Overall, the host–guest complex model was stabilized with nine intermolecular hydrogen bonds. The planarity and the D_{3h} symmetry were enforced after the association, thus self-association seems to work well by using the enlarged π-plane in this host–guest complex.

The affinity of host $\mathbf{2}^{3+}$ with melamine in DMSO was studied by UV–vis titration (Figure 3). When melamine was added to a

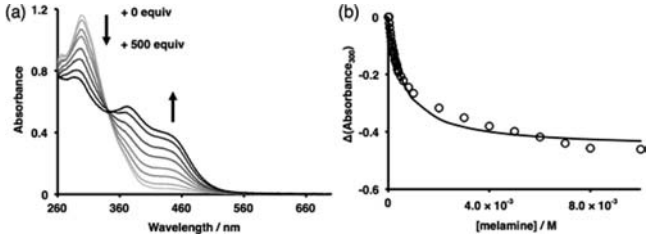

Figure 3. (a) Change of UV–vis spectrum and (b) change of absorbance at 300 nm of $\mathbf{2}^{3+}\cdot\mathbf{3TfO}^-$ in DMSO according to the addition of melamine. Association constant K_a was obtained as $(1.8 \pm 0.3) \times 10^3\ M^{-1}$ by a curve-fitting analysis, and the fitted curve is shown as a solid line. Conditions: $[\mathbf{2}^{3+}\cdot\mathbf{3TfO}^-] = 2.0 \times 10^{-5}$ M, [melamine] = 0 to 1.0×10^{-2} M, DMSO, 25 °C, path length = 10 mm.

DMSO solution of $\mathbf{2}^{3+}\cdot\mathbf{3TfO}^-$ (2.0×10^{-5} M), the absorption band around 300 nm was decreased with a blue shift and that around 450 nm was increased (Figure 3a). An isosbestic point at 344 nm shows the presence of only two kinds of absorptive species, probably $\mathbf{2}^{3+}$ and the complex $\mathbf{2}^{3+}\cdot\mathbf{melamine}$. The absorption band around 450 nm might result from the intramolecular charge transfer between electronically localized 2,6-pyridylene donors and 3,5-pyridylene acceptors in $\mathbf{2}^{3+}$, which should be enhanced by the formation of the rigid framework after the complexation. Indeed, the HOMO in $\mathbf{2}^{3+}$ mainly lies on the 2,6-pyridylene and the LUMO on the 3,5-pyridylene (Figure S1). The titration curve was drawn for the absorbance at 300 nm, and the association constant K_a was obtained as $(1.8 \pm 0.3) \times 10^3\ M^{-1}$ by the curve-fitting analysis based on the assumption of 1:1 association (Figure 3b). Although DMSO was known to strongly interfere with specific hydrogen bonds, $\mathbf{2}^{3+}$ fairly recognized melamine by the multipoint hydrogen bonds even in such highly competitive conditions.

The recognition of melamine by $\mathbf{2}^{3+}$ in H_2O was also studied by UV–vis titration (Figure 4).[12] When melamine was added to a H_2O solution of $\mathbf{2}^{3+}\cdot\mathbf{3TfO}^-$ (2.0×10^{-5} M), the absorption

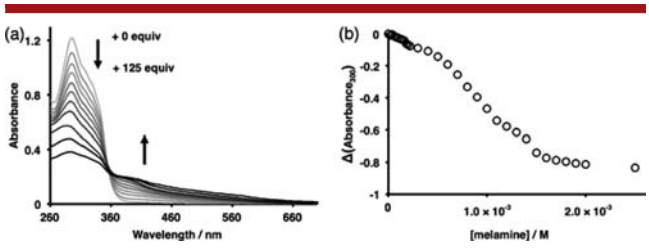

Figure 4. (a) Change of UV–vis spectrum and (b) change of absorbance at 295 nm of $\mathbf{2}^{3+}\cdot\mathbf{3TfO}^-$ in H_2O according to the addition of melamine. Conditions: $[\mathbf{2}^{3+}\cdot\mathbf{3TfO}^-] = 2.0 \times 10^{-5}$ M, [melamine] = 0 to 2.5×10^{-3} M, H_2O, 25 °C, path length = 10 mm.

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band around 295 nm was weakened and a slope appeared around 400−700 nm, accompanying the color change from pale yellow to brown. Melamine is most likely incorporated into the cavity of $\mathbf{2}^{3+}$ because the spectral change resembles that in DMSO. Figure 4b shows the absorbance at 295 nm against the molar concentration of melamine. The shape of the plot, however, was different from that in DMSO and could not fit with any theoretical curve, assuming simple binding models such as 1:1 and 1:2. It was suggested that the combination of $\mathbf{2}^{3+}$ and melamine in H_2O forms some kinds of higher-order aggregates through the $\mathbf{2}^{3+}$**·melamine** host−guest complexation.

To confirm the aggregation, Tyndall scattering was tested using a green-emitting laser pointer (λ_{em} = 532 nm). After a H_2O solution of $\mathbf{2}^{3+}$**·3TfO**$^-$ (2.0×10^{-5} M) was mixed with melamine (1.0×10^{-4} M) in a glass tube, the resulting sample mixture exhibited a clear Tyndall scattering (Figure 5a). On the other hand, H_2O solutions of $\mathbf{2}^{3+}$**·3TfO**$^-$ and melamine alone showed no meaningful Tyndall scattering as well as a DMSO solution of the mixture. The aggregation was quantified by DLS experiments. A sample mixture was prepared from $\mathbf{2}^{3+}$**·3TfO**$^-$ (2.0×10^{-5} M) and melamine (1.0×10^{-3} M) in H_2O and left at 25 °C for 12 h. DLS of the resulting mixture was measured at that temperature, and the mean hydrodynamic diameter of the particles was estimated to be 2.4 μm (Figure 5b). Of course, when DLS was examined for each the aqueous solution of $\mathbf{2}^{3+}$**·3TfO**$^-$ and melamine, no meaningful scattering light could be observed (Table S1).

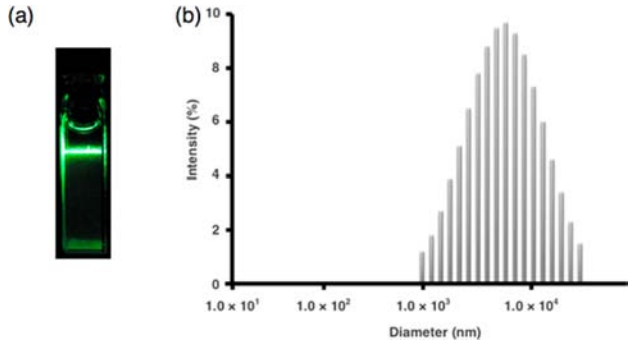

Figure 5. (a) Tyndall scattering of a mixture in H_2O. Conditions: [$\mathbf{2}^{3+}$**·3TfO**$^-$] = 2.0×10^{-5} M, [melamine] = 1.0×10^{-4} M, 25 °C. (b) Hydrodynamic diameter distribution for a sample mixture of $\mathbf{2}^{3+}$**·3TfO**$^-$ and melamine in H_2O measured by DLS. The sample mixture was left at 25 °C for 12 h before DLS measurement. Conditions: [$\mathbf{2}^{3+}$**·3TfO**$^-$] = 2.0×10^{-5} M, [melamine] = 1.0×10^{-3} M, 25 °C.

Annealing experiments for the mixture of $\mathbf{2}^{3+}$**·3TfO**$^-$ and melamine in H_2O gave rise to insoluble materials, which were used to investigate the mesoscopic structure of the aggregates. When the mixture was heated at 45 °C for 5 min and then cooled at 25 °C for 15 min, a fluffy brown precipitate appeared (Figure 6a). This precipitate was analyzed by using various microscopes. As shown in Figure 5, a number of fibril structures were observed by scanning electron microscopy (SEM), transmission electron microscopy (TEM), and atomic force microscopy (AFM). The width of the fiber was estimated as more than 10 nm from all the microscopic images, and this value was much larger than that of one molecule of $\mathbf{2}^{3+}$ predicted by the DFT calculation (Figure 2). Therefore, these observed nanofibers would be some kind of bundles from the several columns that consist of the $\mathbf{2}^{3+}$**·melamine** complex.

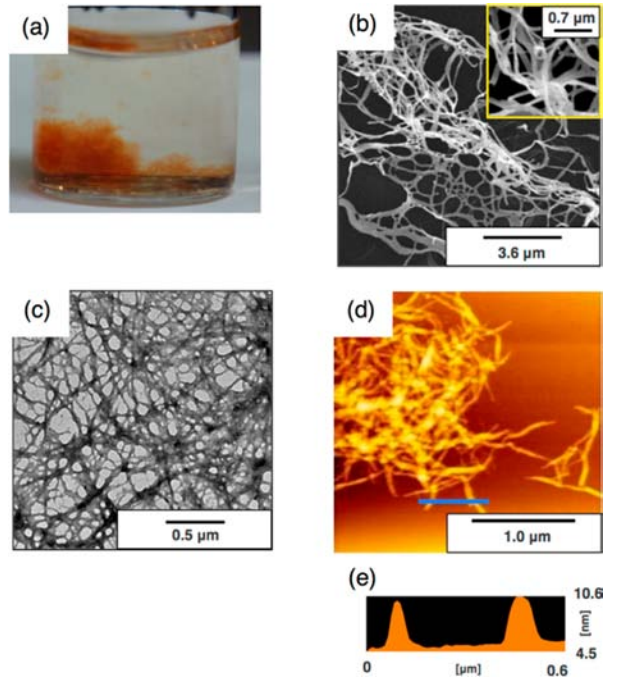

Figure 6. (a) Precipitate appears in a mixture of $\mathbf{2}^{3+}$**·3TfO**$^-$ and melamine in H_2O after annealing treatment: mixture was heated at 45 °C for 5 min and then cooled at 25 °C for 15 min to form the precipitate shown. Conditions: [$\mathbf{2}^{3+}$**·3TfO**$^-$] = 1.0×10^{-4} M, [melamine] = 5.0×10^{-3} M. (b) SEM, (c) TEM, and (d) AFM images of self-aggregated fibril structure of the precipitate. (e) Line scan profile as marked in the AFM image.

Interestingly, the precipitate once yielded was found to never dissolve even in DMSO. This means that the discrete host−guest complex in DMSO would be a kinetic product that fails to self-assemble.

Similar types of SPM-based fibril structures have been reported by Moore, Höger, and other groups.[6] We also reported that precursor **1** self-assembled into stacked structures only in solid states.[8a] Thus, the nanofibers observed in the present study were presumably composed of the columns made of stacked $\mathbf{2}^{3+}$**·melamine**. On the other hand, aqueous solutions of $\mathbf{2}^{3+}$ without melamine showed no self-assembling as mentioned above. Coulomb repulsion would inhibit the self-assembly of $\mathbf{2}^{3+}$ with a large hole inside as an "apo" state of the enzyme. When melamine was incorporated within the "apo-host", the π-surface of the $\mathbf{2}^{3+}$**·melamine** complex became larger than that of $\mathbf{2}^{3+}$. In addition, the rigidity of the framework of $\mathbf{2}^{3+}$ would be enhanced by the formation of the complex. The enlarged and rigidified π-surface would enforce the hydrophobic π-interaction, which should more than make up for the Coulomb repulsion and the entropic loss during the self-assembly (Figure 1).

In summary, we developed a water-soluble pyridine−pyridinium alternating tricationic macrocycle, which recognized melamine in polar solvents such as DMSO and H_2O. The discrete molecular recognition in water induced the stacking of the host−guest complex to give columnar and eventually mesoscopic fibrous structures. This approach could be applied to various discrete host−guest combinations. The resulting higher-order structures are expected to be functional materials of interest, and such projects are now underway.

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■ ASSOCIATED CONTENT

Supporting Information

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Figures S1 and S2, Table S1, experimental details for the preparation of 2^{3+}·3TfO$^-$, details of theoretical analyses for 2^{3+}·melamine, and ^{1}H and ^{13}C NMR spectra for 2^{3+}·3TfO$^-$ (PDF)

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■ REFERENCES

(1) Reviews for shape-persistent macrocycles: (a) Höger, S. *Chem. - Eur. J.* **2004**, *10*, 1320−1329. (b) Zhang, W.; Moore, J. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 4416−4439. (c) Smith, M. K.; Miljanic, O. Š. *Org. Biomol. Chem.* **2015**, *13*, 7841−7845. (d) Höger, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3806−3808. (e) Iyoda, M.; Yamakawa, J.; Rahman, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 10522−10553.

(2) For examples of SPMs, see: (a) Tobe, Y.; Nagano, A.; Kawabata, K.; Sonoda, M.; Naemura, K. *Org. Lett.* **2000**, *2*, 3265−3268. (b) Sonoda, M.; Yamaguchi, Y.; Tahara, K.; Hirose, K.; Tobe, Y. *Tetrahedron* **2008**, *64*, 11490−11494. (c) Henze, O.; Lentz, D.; Schluter, A. D. *Chem. - Eur. J.* **2000**, *6*, 2362−2367. (d) Henze, O.; Lentz, D.; Schafer, A.; Franke, P.; Schluter, A. D. *Chem. - Eur. J.* **2002**, *8*, 357−365. (e) Sun, S. S.; Lees, A. J. *Organometallics* **2001**, *20*, 2353−2358. (f) Campbell, K.; Kuehl, C. J.; Ferguson, M. J.; Stang, P. J.; Tykwinski, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 7266−7267. (g) Campbell, K.; McDonald, R.; Tykwinski, R. R. *J. Org. Chem.* **2002**, *67*, 1133−1140. (h) Yamaguchi, Y.; Kobayashi, S.; Miyamura, S.; Okamoto, Y.; Wakamiya, T.; Matsubara, Y.; Yoshida, Z. *Angew. Chem., Int. Ed.* **2004**, *43*, 366−369. (i) Spitler, E. L.; McClintock, S. P.; Haley, M. M. *J. Org. Chem.* **2007**, *72*, 6692−6699. (j) Miki, K.; Fujita, M.; Inoue, Y.; Senda, Y.; Kowada, T.; Ohe, K. *J. Org. Chem.* **2010**, *75*, 3537−3540. (k) Yamasaki, R.; Shigeto, A.; Saito, S. *J. Org. Chem.* **2011**, *76*, 10299−10305.

(3) (a) Zhang, J.; Moore, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 2655−2656. (b) Mindyuk, O. Y.; Stetzer, M. R.; Heiney, P. A.; Nelson, J. C.; Moore, J. S. *Adv. Mater.* **1998**, *10*, 1363−1366. (c) Höger, S.; Enkelmann, V.; Bonrad, K.; Tschierske, C. *Angew. Chem., Int. Ed.* **2000**, *39*, 2268−2270. (d) Fischer, M.; Lieser, G.; Rapp, A.; Schnell, I.; Mamdouh, W.; De Feyter, S.; De Schryver, F. C.; Höger, S. *J. Am. Chem. Soc.* **2004**, *126*, 214−222.

(4) Chen, T.-H.; Popov, I.; Chuang, Y.-C.; Chen, Y.-S.; Miljanic, O. Š. *Chem. Commun.* **2015**, *51*, 6340−6342.

(5) Luo, J.; Yan, Q.; Zhou, Y.; Li, T.; Zhu, N.; Bai, C.; Cao, Y.; Wang, J.; Pei, J.; Zhao, D. *Chem. Commun.* **2010**, *46*, 5725−5727.

(6) For examples of self-assembly of SPMs see: (a) Li, L. G.; Che, Y. K.; Gross, D. E.; Huang, H. L.; Moore, J. S.; Zang, L. *ACS Macro Lett.* **2012**, *1*, 1335−1338. (b) Datar, A.; Gross, D. E.; Balakrishnan, K.; Yang, X.; Moore, J. S.; Zang, L. *Chem. Commun.* **2012**, *48*, 8904−8906. (c) Li, J.; Zhou, W.; Yang, J.; Lang, X.; Huang, P. *J. Colloid Interface Sci.* **2013**, *395*, 99−103. (d) Balakrishnan, K.; Datar, A.; Zhang, W.; Yang, X.; Naddo, T.; Huang, J.; Zuo, J.; Yen, M.; Moore, J. S.; Zang, L. *J. Am. Chem. Soc.* **2006**, *128*, 6576−6577. (e) Rosselli, S.; Ramminger, A.-D.; Wagner, T.; Lieser, G.; Höger, S. *Chem. - Eur. J.* **2003**, *9*, 3481−3491. (f) Xiao, D.; Zhang, D.; Chen, B.; Xie, D.; Xiang, Y.; Li, X.; Jin, W. *Langmuir* **2015**, *31*, 10649−10655. (g) Lee, S.; Hirsch, B. E.; Liu, Y.; Dobscha, J. R.; Burke, D. W.; Tait, S. L.; Flood, A. H. *Chem. - Eur. J.* **2016**, *22*, 560−569. (h) Tahara, K.; Lei, S.; Mamdouh, W.; Yamaguchi, Y.; Ichikawa, T.; Uji-i, H.; Sonoda, M.; Hirose, K.; De Schryver, F. C.; De Feyter, S.; Tobe, Y. *J. Am. Chem. Soc.* **2008**, *130*, 6666−6667. (i) Tobe, Y.; Utsumi, N.; Kawabata, K.; Nagano, A.; Adachi, K.; Araki, S.; Sonoda, M.; Hirose, K.; Naemura, K. *J. Am. Chem. Soc.* **2002**, *124*, 5350−5364.

(7) For molecular recognition by host molecule based on SPMs, see: (a) Bahr, A.; Droz, A. S.; Puntener, M.; Neidlein, U.; Anderson, S.; Seiler, P.; Diederich, F. *Helv. Chim. Acta* **1998**, *81*, 1931−1963. (b) Anderson, S.; Neidlein, U.; Gramlich, V.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1596−1600. (c) Popov, I.; Chen, T.-H.; Belyakov, S.; Daugulis, O.; Wheeler, S. E.; Miljanic, O. Š. *Chem. - Eur. J.* **2015**, *21*, 2750. (d) He, Y.; Xu, M.; Gao, R.; Li, X.; Li, F.; Wu, X.; Xu, D.; Zeng, H.; Yuan, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 11834−11839.

(8) (a) Abe, H.; Ohtani, K.; Suzuki, D.; Chida, Y.; Shimada, Y.; Matsumoto, S.; Inouye, M. *Org. Lett.* **2014**, *16*, 828−831. (b) Abe, H.; Kurokawa, H.; Chida, Y.; Inouye, M. *J. Org. Chem.* **2011**, *76*, 309−311. (c) Abe, H.; Chida, Y.; Kurokawa, H.; Inouye, M. *J. Org. Chem.* **2011**, *76*, 3366−3371.

(9) Abe, H.; Suzuki, D.; Shimizu, A.; Inouye, M. *Heterocycles* **2014**, *88*, 547−557.

(10) Unfortunately, ^{1}H NMR measurements of the 2^{3+} salt and **1** could not be carried out in solvent of the same kind. Precursor **1** was practically insoluble in H_2O, DMSO, and MeOH.

(11) For examples of supramolecular structures based on melamine, see: (a) Bairi, P.; Roy, B.; Chakraborty, P.; Nandi, A. K. *ACS Appl. Mater. Interfaces* **2013**, *5*, 5478−5485. (b) Bairi, P.; Roy, B.; Nandi, A. K. *Chem. Commun.* **2012**, *48*, 10850−10852. (c) Bairi, P.; Roy, B.; Nandi, A. K. *J. Phys. Chem. B* **2010**, *114*, 11454−11461. (d) Saha, A.; Roy, B.; Garai, A.; Nandi, A. K. *Langmuir* **2009**, *25*, 8457−8461. (e) Makowski, S. J.; Lacher, M.; Lermer, C.; Schnick, W. *J. Mol. Struct.* **2012**, *1013*, 19−25. (f) Lazar, A. N.; Danylyuk, O.; Suwinska, K.; Coleman, A. W. *New J. Chem.* **2006**, *30*, 59−64.

(12) We have also studied the additive effect of melamine on the NMR spectrum of a D_2O solution of 2^{3+}·3TfO$^-$ (5.0×10^{-5} M). Unfortunately, the addition of melamine (10 and 20 equiv) made the sample solution turbid, and the NMR spectrum was significantly broadened, as shown in Figure S2 in the Supporting Information. The chemical shift of pyridinic protons seemed to move upfield, possibly because of host−guest association and/or π-stacking aggregation.

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Organic LETTERS

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Diastereoselective Synthesis of 3,4-Benzomorphan Derivatives via Tandem [5 + 1]/Hemiaminalization of (2-Aminoaryl)divinyl Ketones

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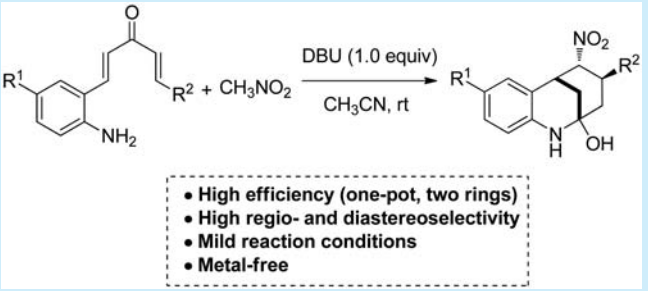
Supporting Information

ABSTRACT: A novel tandem formal [5 + 1]/hemiaminalization reaction based on the readily available (2-aminoaryl)-divinyl ketones and various nucleophiles has been developed. The reaction represents a highly efficient and convenient methodology for the synthesis of 3,4-benzomorphan derivatives with high diastereoselectivity, and three new bonds and two rings are successively formed in one step under mild, metal-free conditions.



The morphan ring system is present in many natural products, such as morphine, and some synthetic compounds with analgesic activity.[1] 3,4-Benzomorphan, a related morphan skeleton with potential biological activity, can also be found in natural products, such as strychnochromine[2] (an unusual alkaloid from *Strychnos gossweileri*) and aspernomine[3] (a cytotoxic anti-insectan metabolite from the sclerotia of *Aspergillus nomius*). Although numerous methods for the synthesis of the morphan structure have been developed,[4,5] only few reports exist in the literature on the construction of 3,4-benzomorphan scaffolds.[2a,6−9] In 2001, Bonjoch's group reported a Pd-mediated intramolecular coupling of aryl iodide with the α-carbon of a carbonyl group to give 3,4-benzomorphan derivatives (Scheme 1, eq 1).[6a] Two years later, a novel rearrangement of 2-(2-bromophenyl)-3-(3-butenyl)-3*H*-indol-3-ol to generate the 3,4-benzomorphan derivative was documented under acidic conditions in McWhorter's work (Scheme 1, eq 2).[7] Very recently, Streuff et al. reported an elegant double-reductive umpolung strategy of quinolones with acrylonitrile to generate the 3,4-benzomorphan derivative in the presence of a titanium(III) catalyst (Scheme 1, eq 3).[8] However, the above methods suffer from drawbacks such as limited substrate scope, lack of readily available precursors, or harsh reaction conditions. Therefore, the development of a new and general methodology for the efficient construction of the 3,4-benzomorphan derivatives from simple starting materials under mild conditions is highly desirable.

Creation of complicated structural molecules from simple substrates,[10] while combining economic aspects,[11,12] constitutes a great challenge in modern organic chemistry. In this context, the one-pot tandem strategy is highly attractive since multiple bonds and stereocenters can be formed in such a single operation without the need to isolate intermediates.[13,14] Recently, we[15−20] and others[21,22] developed a series of new tandem reactions on the basis of divinyl ketones for the efficient construction of structural heterocycles and carbocycles, such as pyrrolizidines,[16] C_2-tethered pyrrole/oxazole pairs,[17] 8-azabicyclo[5.2.1]dec-8-enes,[18] 7-azatetrahydroindoles,[19] and indolizidines.[20] Herein, we report a novel and general tandem [5 + 1]/hemiaminalization reaction of (2-aminoaryl)divinyl ketones with nitroalkanes and activate methylene compounds for the direct and efficient construction of 3,4-benzomorphans in one step under mild conditions (Scheme 1, eq 4). This new general approach allows the formation of two C−C bonds and one C−N bond in a regio- and diastereoselective manner in a single reaction.

In the present study, initially, the reaction of (2-aminoaryl)-divinyl ketone **1a**[23] with nitromethane **2a** was examined carefully to optimize the reaction conditions. As shown in Table 1, the 3,4-benzomorphan derivative **3a** could be obtained in 80% isolated yield from the reaction of (2-aminoaryl)divinyl ketone **1a** (0.30 mmol) with nitromethane **2a** (1.2 equiv, 0.36 mmol) in CH_3CN (5 mL) in the presence of DBU (0.5 equiv, 0.15 mmol) at 25 °C for 9 h, and byproduct quinoline **4a** was produced in 5% yield (Table 1, entry 1). The yield of **3a** was increased to 87% within 8 h by increasing the amount of DBU to 1.0 equiv (0.30 mmol) (Table 1, entry 2). Decreasing the amount of DBU (0.3 or 0.2 equiv) decreased the yield of **3a**. Different bases were also screened, and it was found that NaOH gave a low yield of **3a** with prolonged reaction time (Table 1, entry 5). TMG afforded the desired product **3a** in reduced yield, along with byproduct **4a** in 21% yield (Table 1, entry 6), and when Et_3N was employed, the starting material **1a** was recovered in 99% yield (Table 1, entry 7). The related amidine base DBN showed reaction results similar to those of DBU but with slightly lower yield (Table 1, entry 8). Other solvents, such as THF, DMF, and dichloromethane, gave lower yields of **3a** (Table 1, entries 9−11).

Nitromethane was sometimes found to be unreactive in the double Michael addition with divinyl ketones;[21a,b] however, it is

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Scheme 1. Synthesis of 3,4-Benzomorphan Derivatives

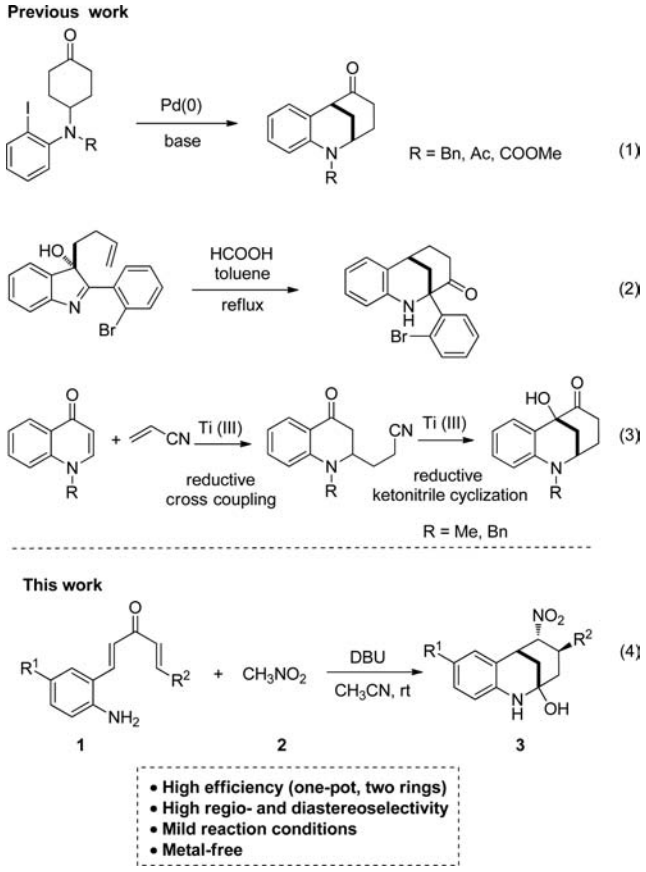
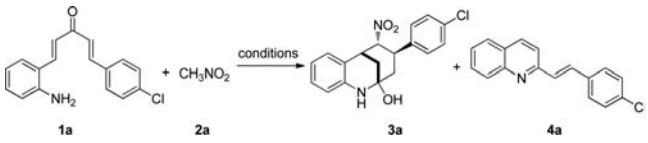


Table 1. Optimization of the Reaction Conditions[a]

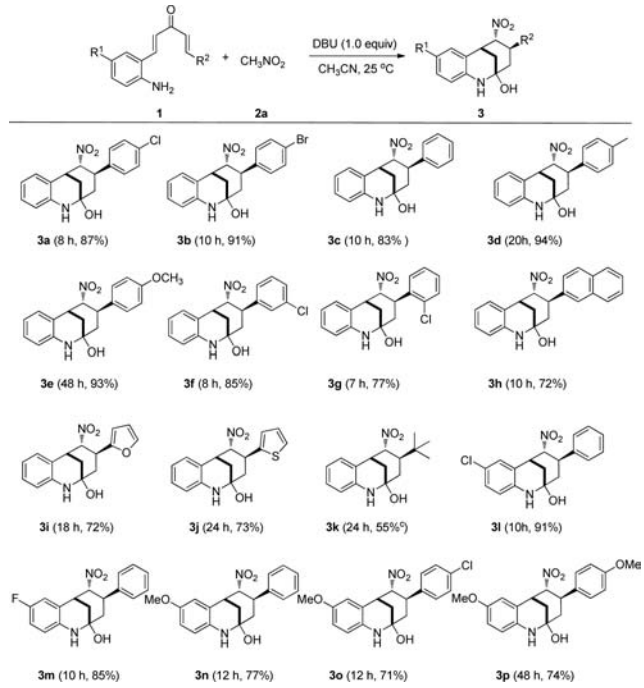


entry	base (equiv)	solvent	temp (°C)	time (h)	3a (%)[b]	4a (%)[b]
1	DBU (0.5)	CH_3CN	25	9.0	80	5
2	***DBU (1.0)***	***CH_3CN***	***25***	***8.0***	***87***	***trace***
3	DBU (0.3)	CH_3CN	25	9.0	72	10
4[c]	DBU (0.2)	CH_3CN	25	72.0	60	10
5	NaOH (1.0)	CH_3CN	25	36.0	45	5
6	TMG (1.0)	CH_3CN	25	5.5	64	21
7[d]	Et_3N(1.0)	CH_3CN	25	72.0	0	0
8	DBN (1.0)	CH_3CN	25	8.0	78	trace
9[e]	DBU (1.0)	THF	25	72.0	17	20
10	DBU (1.0)	DMF	25	6.0	63	5
11	DBU (1.0)	CH_2Cl_2	25	48.0	20	37

[a]Reactions were carried out with **1a** (0.3 mmol), **2a** (0.36 mmol), and DBU (1 equiv) in solvent (5 mL) at 25 °C. [b]Isolated yields. [c]**1a** was recovered in 23% yield. [d]**1a** was recovered in 99% yield. [e]**1a** was recovered in 52% yield.

an active binucleophile in our tandem reactions. To probe the scope of this transformation, reactions of nitromethane with a range of (2-aminoaryl)divinyl ketones were carried out under the optimal conditions (Table 1, entry 2), and the results are summarized in Scheme 2. It was found that the tandem reaction showed broad tolerance for various R^1 and R^2 groups of

Scheme 2. Synthesis of 3,4-Benzomorphan Derivatives 3[a,b]



[a]Reactions were carried out with **1** (0.3 mmol), **2a** (0.36 mmol), and DBU (1 equiv) in CH_3CN (5 mL) at 25 °C. [b]Isolated yields. [c]Byproduct quinoline **4k** was obtained in 40% yield.

substrates **1**. (2-Aminoaryl)divinyl ketones **1** having electron-deficient (**1a,b** and **1f,g**) and electron-rich (**1d,e**) aryl, phenyl (**1c**), *β*-naphthyl (**1h**), heteroaromatic (**1i,j**), and *tert*-butyl (**1k**) R^2 groups can afford the corresponding 3,4-benzomorphan derivatives **3a−i** in good to high yields with high diastereoselectivity. In addition, (2-aminoaryl)divinyl ketones **1** with both electron-donating and electron-withdrawing R^1 groups gave the polysubstituted 3,4-benzomorphans (**3l−p**) in high yields. It is worth mentioning that the tandem reaction of (2-aminoaryl)-divinyl ketones **1** with nitromethane **2a** proceeded in a highly regio- and diastereoselective manner to set four stereocenters in the 3,4-benzomorphan frameworks on the basis of ^1H and ^{13}C NMR spectroscopy data of products **3** (no diastereoisomers of **3a−p** were detected). The configurations of **3a−p** were assigned according to the X-ray diffraction analysis of **3a**.[24]

The tandem process mentioned above represents a concise and highly efficient methodology for the construction of 3,4-benzomorphan derivatives from simple precursors under very mild conditions. To further test the generality of this new reaction, the reactions of (2-aminoaryl)divinyl ketone **1a** with various readily available nucleophiles **2** were investigated. As shown in Scheme 3, under the aforementioned optimal conditions (Table 1, entry 2), the domino reactions of (2-aminoaryl)divinyl ketone **1a** with nitroethane **2b** and nitropropane **2c** proceeded smoothly, affording the corresponding 3,4-benzomorphan derivatives in high yields with diastereoisomers **5b/b′** and **5c/c′** in a ratio of approximately 1:1. Besides nitroalkane, nucleophilic active methylene compounds, such as ethyl cyanoacetate **2d** or ethyl nitroacetate **2e**, also gave high yield of 3,4-benzomorphan derivatives with diastereoismers **5d/5d′** and **5e/5e′**. Malononitrile **2f** and malonates **2g** and **2h** afforded the 3,4-benzomorphan derivatives **5f−h** in good yields, and no other diastereoismers could be detected. The isomers of **5b/b′−5e/e′** were readily isolated with column chromatog-

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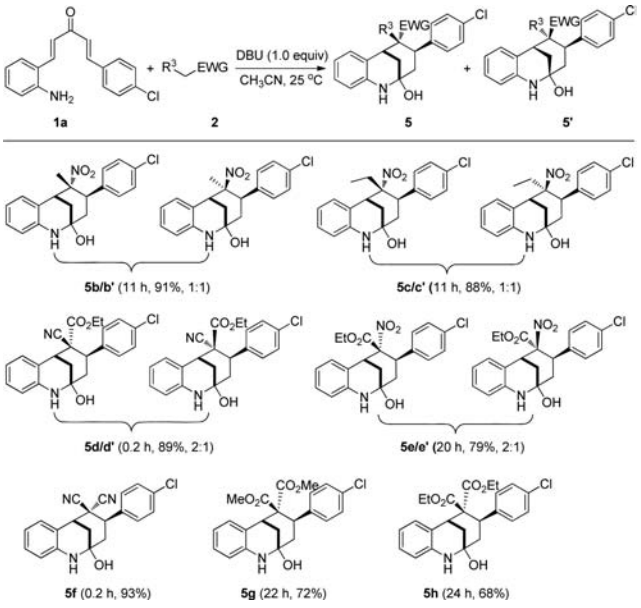
Scheme 3. Synthesis of 3,4-Benzomorphan Derivatives 5[a,b]

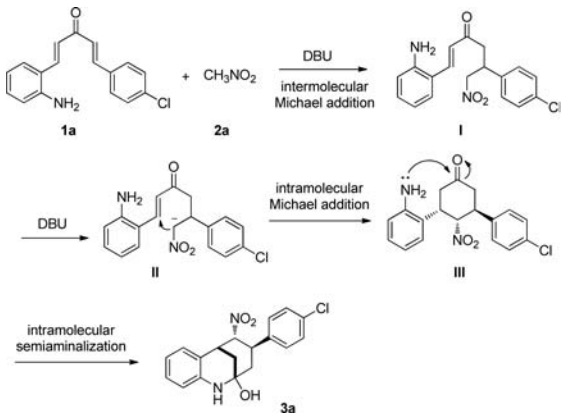


[a]Reactions were carried out with **1a** (0.3 mmol), **2** (0.36 mmol), and DBU (1 equiv) in CH_3CN (5 mL) at 25 °C. [b]Isolated yields.

raphy, and the relative configurations of **5b**/**b′** and **5c**/**c′** were confirmed by NOESY spectroscopy (see Supporting Information). The structure of product **5e** was confirmed by X-ray single-crystal analysis.[24]

With the previous[15−22,25] and present results, a plausible mechanism for the formation of 3,4-benzomorphan derivatives **3** and **5** may involve Scheme 4 (with the transformation of **1a** with

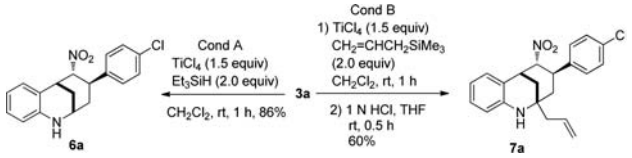
Scheme 4. Proposed Mechanism for Formation of 3,4-Benzomorphan Derivative 3a



2a as an example). The overall process may involve the following steps: (1) a DBU-promoted intermolecular Michael addition of (2-aminoaryl)vinyl ketone **1a** and nitromethane **2a** to provide intermediate **I**; (2) deprotonation of **I** by DBU to form anion intermediate **II**; (3) consecutive intramolecular Michael addition of anion **II** by selectively attacking the less hindered face to generate anti-diastereomer cyclohexanone intermediate **III** in a diastereoselective manner;[15] (4) intramolecular semiaminalization of **III** to furnish 3,4-benzomorphan derivative **3a**. The reason for the diastereoselectivity of this tandem process is not very certain at this stage. Alternatively, thermodynamic control (equilibrium isomerization of one diastereomer into the stable one through the nitronate form of the nitro compounds under basic conditions) is also possible.

To highlight the synthetic potential of this domino process, two possible transformations of the hydroxylation 3,4-benzomorphan derivative **3a** were conducted to form the benzomorphan frameworks, which are found in strychnochromine[2] and aspernomine[3] (Scheme 5). First, the hydroxyl group

Scheme 5. Transformations of 3,4-Benzomorphan Derivatives 3a



of **3a** was readily removed to give the 3,4-benzomorphan derivative **6a** in high yield when **3a** was treated with Et_3SiH (2.0 equiv) and $TiCl_4$ (1.5 equiv). Then, in the presence of allyltrimethylsilane (2.0 equiv) and $TiCl_4$ (1.5 equiv), **3a** was transformed to an allylic 3,4-benzomorphan **7a**, which has a new tetrasubstituted tertiary carbon center.

In conclusion, we have developed a novel domino strategy for the direct and practical synthesis of 3,4-benzomorphan derivatives through (2-aminoaryl)divinyl ketones. The reaction involves a sequential double Michael addition/intramolecular hemiaminalization and allows the diastereoselective construction of 3,4-benzomorphan scaffolds in a single step from easily available substrates in good to high yields under mild metal-free conditions. This strategy shows the highly efficient use of the reactive sites of (2-aminoaryl)divinyl ketones and further expands the synthetic potential of (2-aminoaryl)divinyl ketones in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03506.

Experimental procedures, characterization data for all compounds, and X-ray data of **3a** and **5e** (PDF)

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Notes

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■ REFERENCES

(1) (a) Quirante, J.; Escolano, C.; Merino, A.; Bonjoch, J. *J. Org. Chem.* **1998**, *63*, 968. (b) Quirante, J.; Escolano, C.; Diaba, F.; Bonjoch, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1157. (c) Sato, T.; Okamoto, K.; Nakano, Y.; Uenishi, J.; Ikeda, M. *Heterocycles* **2001**, *54*, 747. (d) Maeng,

DOI: 10.1021/acs.orglett.5b03506
Org. Lett. 2016, 18, 324−327

J. H.; Funk, R. L. *Org. Lett.* **2001**, *3*, 1125. (e) Brummond, K. M.; Lu, J. *Org. Lett.* **2001**, *3*, 1347. (f) Wardrop, D. J.; Zhang, W. *Org. Lett.* **2001**, *3*, 2353. (g) Suzuki, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **2001**, *42*, 3013. (h) Hashimoto, A.; Jacobson, A. E.; Rothman, R. B.; Dersch, C. M.; George, C.; Flippen-Anderson, J. L.; Rice, K. C. *Bioorg. Med. Chem.* **2002**, *10*, 3319. (i) Amat, M.; Pérez, M.; Llor, N.; Escolano, C.; Luque, F. J.; Molins, E.; Bosch, J. *J. Org. Chem.* **2004**, *69*, 8681. (j) Carroll, F. I.; Zhang, L.; Mascarella, S. W.; Navarro, H. A.; Rothman, R. B.; Cantrell, B. E.; Zimmerman, D. M.; Thomas, J. B. *J. Med. Chem.* **2004**, *47*, 281. (k) Brummond, K. M.; Hong, S. *J. Org. Chem.* **2005**, *70*, 907.

(2) (a) Solé, D.; García-Rubio, S.; Vallverdú, L.; Bonjoch, J. *J. Org. Chem.* **2001**, *66*, 5266. (b) Quetin-Leclercq, J.; Angenot, L.; Dupont, L.; Dideberg, O.; Warin, R.; Delaude, C.; Coune, C. *Tetrahedron Lett.* **1991**, *32*, 4295.

(3) (a) Staub, G. M.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *J. Am. Chem. Soc.* **1992**, *114*, 1015. (b) Gloer, J. B. *Acc. Chem. Res.* **1995**, *28*, 343.

(4) For a review of the synthesis of 2-azabicyclo[3.3.1]nonanes, see: (a) Bosch, J.; Bonjoch, J. *Heterocycles* **1980**, *14*, 505. (b) Bonjoch, J.; Diaba, F.; Bradshaw, B. *Synthesis* **2011**, *2011*, 993.

(5) (a) Saito, M.; Kawamura, M.; Hiroya, K.; Ogasawara, K. *Chem. Commun.* **1997**, 765. (b) Thomas, J. B.; Gigstad, K. M.; Fix, S. E.; Burgess, J. P.; Cooper, J. B.; Mascarella, S. W.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. *Tetrahedron Lett.* **1999**, *40*, 403. (c) Aurrecoechea, J. M.; Gorgojo, J. M.; Saornil, C. *J. Org. Chem.* **2005**, *70*, 9640. (d) Solé, D.; Peidró, E.; Bonjoch, J. *Org. Lett.* **2000**, *2*, 2225. (e) Bradshaw, B.; Parra, C.; Bonjoch, J. *Org. Lett.* **2013**, *15*, 2458. (f) Diaba, F.; Martínez-Laporta, A.; Bonjoch, J. *J. Org. Chem.* **2014**, *79*, 9365. (g) Diaba, F.; Martínez-Laporta, A.; Bonjoch, J. *Eur. J. Org. Chem.* **2014**, *2014*, 2371.

(6) (a) Solé, D.; Vallverdú, L.; Bonjoch, J. *Adv. Synth. Catal.* **2001**, *343*, 439. (b) Solé, D.; Vallverdú, L.; Solans, X.; Font-Bardía, M.; Bonjoch, J. *J. Am. Chem. Soc.* **2003**, *125*, 1587.

(7) Liu, Y.; McWhorter, W. W., Jr.; Hadden, C. E. *Org. Lett.* **2003**, *5*, 333.

(8) Bichovski, P.; Haas, T. M.; Kratzert, D.; Streuff, J. *Chem. - Eur. J.* **2015**, *21*, 2339.

(9) Reisman, S. E.; Ready, J. M.; Weiss, M. M.; Hasuoka, A.; Hirata, M.; Tamaki, K.; Ovaska, T. V.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 2087.

(10) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964. (b) Na, R.; Jing, C.; Xu, Q.; Jiang, H.; Wu, X.; Shi, J.; Zhong, J.; Wang, M.; Benitez, D.; Tkatchouk, E.; Goddard, W. A., III; Guo, H.; Kwon, O. *J. Am. Chem. Soc.* **2011**, *133*, 13337. (c) Richers, M. T.; Breugst, M.; Platonova, A. Y.; Ullrich, A.; Dieckmann, A.; Houk, K. N.; Seidel, D. *J. Am. Chem. Soc.* **2014**, *136*, 6123.

(11) Step-economy: (a) Wender, P. A.; Bi, F. C.; Gamber, G. G.; Gosselin, F.; Hubbard, R. D.; Scanio, M. J. C.; Sun, R.; Williams, T. J.; Zhang, L. *Pure Appl. Chem.* **2002**, *74*, 25. (b) Wender, P. A.; Baryza, J. L.; Brenner, S. E.; Clarke, M. O.; Gamber, G. G.; Horan, J. C.; Jessop, T. C.; Kan, C.; Pattabiraman, K.; Williams, T. J. *Pure Appl. Chem.* **2003**, *75*, 143. (c) Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Pham, S. M.; Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 2836. (d) Wender, P. A.; Jeffreys, M. S.; Raub, A. G. *J. Am. Chem. Soc.* **2015**, *137*, 9088. (e) Suzuki, Y.; Seki, T.; Tanaka, S.; Kitamura, M. *J. Am. Chem. Soc.* **2015**, *137*, 9539.

(12) Atom-economy: (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259. (c) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695. (d) Kang, B.; Fu, Z.; Hong, S. H. *J. Am. Chem. Soc.* **2013**, *135*, 11704. (e) Trost, B. M.; Koester, D. C.; Herron, A. N. *Angew. Chem., Int. Ed.* **2015**, *54*, 15863. (f) Modha, S. G.; Greaney, M. F. *J. Am. Chem. Soc.* **2015**, *137*, 1416.

(13) (a) Tietze, L. F.; Kinzel, T.; Brazel, C. C. *Acc. Chem. Res.* **2009**, *42*, 367. (b) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463. (c) Padwa, A. *Chem. Soc. Rev.* **2009**, *38*, 3072. (d) Pellissier, H. *Chem. Rev.* **2013**, *113*, 442. (e) Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev.* **2014**, *114*, 2390.

(14) (a) Huang, S.; Shao, Y.; Zhang, L.; Zhou, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 14452. (b) Burroughs, L.; Eccleshare, L.; Ritchie, J.; Kulkarni, O.; Woodward, S.; Lewis, W. *Angew. Chem., Int. Ed.* **2015**, *54*, 10648. (c) Gao, M.; Li, Y.; Gan, Y.; Xu, B. *Angew. Chem.* **2015**, *127*, 8919. (d) Zhao, D.; Zhang, J.; Xie, Z. *J. Am. Chem. Soc.* **2015**, *137*, 13938. (e) Li, J.; Huang, R.; Xing, Y.; Qiu, G.; Tao, H.; Wang, C. *J. Am. Chem. Soc.* **2015**, *137*, 10124. (f) Gu, Y.; Hu, P.; Ni, C.; Tong, X. *J. Am. Chem. Soc.* **2015**, *137*, 6400. (g) Qiu, J.; Jiang, B.; Zhu, Y.; Hao, W.; Wang, D.; Sun, J.; Wei, P.; Tu, S.; Li, G. *J. Am. Chem. Soc.* **2015**, *137*, 8928.

(15) Zhang, D.; Xu, X.; Tan, J.; Liu, Q. *Synlett* **2010**, *2010*, 917.

(16) Tan, J.; Xu, X.; Zhang, L.; Li, Y.; Liu, Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 2868.

(17) Li, Y.; Xu, X.; Tan, J.; Xia, C.; Zhang, D.; Liu, Q. *J. Am. Chem. Soc.* **2011**, *133*, 1775.

(18) Xu, X.; Li, Y.; Zhang, Y.; Zhang, L.; Pan, L.; Liu, Q. *Adv. Synth. Catal.* **2011**, *353*, 1218.

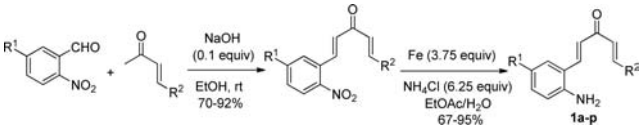
(19) Li, Y.; Xu, X.; Xia, C.; Zhang, L.; Pan, L.; Liu, Q. *Chem. Commun.* **2012**, *48*, 12228.

(20) Xu, X.; Zhang, L.; Liu, X.; Pan, L.; Liu, Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 9271.

(21) Selected representative references on divinyl ketones: (a) Silvanus, A. C.; Groombridge, B. J.; Andrews, B. I.; Kociok-Köhn, G.; Carbery, D. R. *J. Org. Chem.* **2010**, *75*, 7491. (b) Li, X.; Wang, B.; Zhang, J.; Yan, M. *Org. Lett.* **2011**, *13*, 374. (c) Rowland, A. T.; Filla, S. A.; Coutlangus, M. L.; Winemiller, M. D.; Chamberlin, M. J.; Czulada, G.; Johnson, S. D. *J. Org. Chem.* **1998**, *63*, 4359. (d) De Fusco, C.; Lattanzi, A. *Eur. J. Org. Chem.* **2011**, *2011*, 3728. (e) Wu, B.; Chen, J.; Li, M.; Zhang, J.; Xu, X.; Ji, S.; Wang, X. *Eur. J. Org. Chem.* **2012**, *2012*, 1318. (f) Aggarwal, K.; Vij, K.; Khurana, J. M. *RSC Adv.* **2014**, *4*, 13313.

(22) Wu, B.; Liu, G.; Li, M.; Zhang, Y.; Zhang, S.; Qiu, J.; Xu, X.; Ji, S.; Wang, X. *Chem. Commun.* **2011**, *47*, 3992.

(23) Substrates **1a**−**p** were readily prepared in two steps in high overall yields. See Supporting Information.



(24) CCDC 1402478 (**3a**) and CCDC 1425724 (**5e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(25) (a) Bi, X.; Dong, D.; Liu, Q.; Pan, W.; Zhao, L.; Li, B. *J. Am. Chem. Soc.* **2005**, *127*, 4578. (b) Dong, D.; Bi, X.; Liu, Q.; Cong, F. *Chem. Commun.* **2005**, *28*, 3580.

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Organic LETTERS

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Rh(I)-Catalyzed Insertion of Allenes into C−C Bonds of Benzocyclobutenols

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Supporting Information

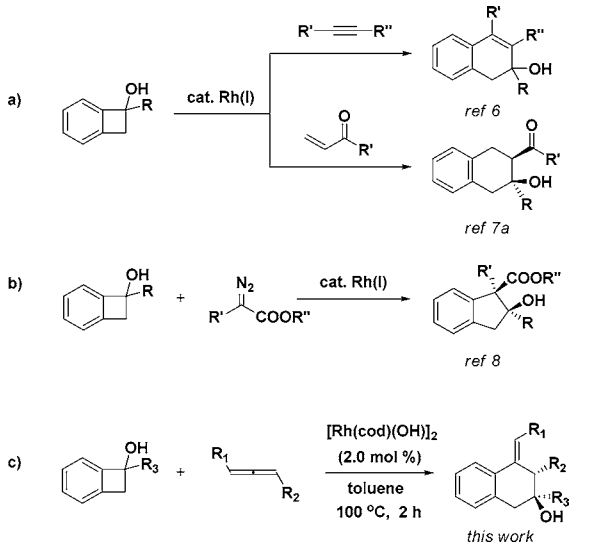
ABSTRACT: Herein we report a Rh(I)-catalyzed two carbon insertion into C−C bonds of benzocyclobutenols by employing symmetrical and unsymmetrical allenes. This reaction provides rapid access to alkylidene tetralins bearing two adjacent stereogenic centers in good yields and diasteroselectivities.

The selective cleavage and functionalization of C−C bonds by transition-metal catalysts is an intriguing process from both mechanistic and synthetic standpoints.[1] As an increasingly sophisticated method, it enables facile assembly of scaffolds[2] that could otherwise be challenging synthetic targets for conventional methods.

One powerful extension of this method involves the insertion of an unsaturated unit after the C−C bond cleavage, which installs new C−C bonds and ring systems in various synthetically meaningful contexts.[3,4] Along this line, benzocyclobutenols have recently attracted considerable attention.[5−8] In 2011, the Orellana group reported the site-selective ring opening of the C(sp^2)−C(sp^3) bond adjacent to the hydroxyl group benzocyclobutenols. This Pd-catalyzed reaction allowed for a tandem C−C bond cleavage/cross-coupling reaction. Since 2012, Murakami and co-workers has pioneered in the rhodium-catalyzed tandem ring-opening/formal cycloaddition reactions featuring alkynes[6] or vinyl ketones[7] surrogates as the two-carbon synthons (Scheme 1a). Notably, the rhodium-catalyzed site-selective ring opening set the stage for the subsequent alkyne or alkene insertion, concluded by an intramolecular aldol condensation to the pedant ketone. In the vinyl ketone reactions, good to excellent diastereoselectivity (8:1 to >20:1 dr) was achieved.[7] In 2014, Wang et al. developed a remarkable rhodium-catalyzed formal carbene insertion into benzocyclobutenols using diazoesters.[8] A wide array of useful indanol derivatives were prepared in high yields with excellent regio- and diastereoselectivity (Scheme 1b).

Allenes as a versatile building block[9] have been widely employed in Rh(I)-catalyzed intramolecular cycloaddition reactions.[10] We thus envisioned that allenes may serve as a two-carbon synthon in Rh(I) catalyzed formal [4 + 2] cycloaddition with benzocyclobutenols (Scheme 1c). This reaction would provide rapid access to the alkylidene tetralin skeleton, which is a privileged scaffold in bioactive molecules[11] and organic synthesis.[12] Importantly, the *exo* alkene should allow for further elaboration of the parent compound through a variety of well-established transformations.

Scheme 1. Rh(I)-Catalyzed Insertion to Benzocyclobutenols with (a) Alkynes and Enones, (b) Carbenes, and (c) Allenes



We commenced our study by employing benzocyclobutenol **1a** and diphenylallene **2a** as the model substrates (Table 1 and Supporting Information). Screening of Rh(I) catalysts revealed that [Rh(cod) (OH)]$_2$ gave the best results (entries 1−5). The reaction could be performed at room temperature with moderate yields in 1,4-dioxane (entry 4) and toluene (entry 5). Other solvents were not as productive. A better yield was obtained at elevated temperature (100 °C). Thus, in the presence of [Rh(cod) (OH)]$_2$ in toluene at 100 °C, tetralin **3a**

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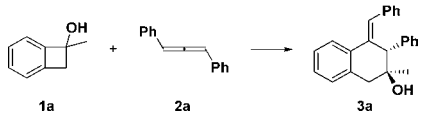
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	catalyst	temp (°C)	solvent	time (h)	yield[b] (%)
1	$[Rh(cod)_2]BF_4$	100	B	2	nd
2	$Rh(PPh_3)_3Cl$	100	B	2	5
3	$[Rh(cod)Cl]_2$	100	B	2	15
4	$[Rh(cod)(OH)]_2$	rt	A	24	57
5	$[Rh(cod)(OH)]_2$	rt	B	24	66
6	$[Rh(cod)(OH)]_2$	100	B	2	80
7	none	160	B	2	nd

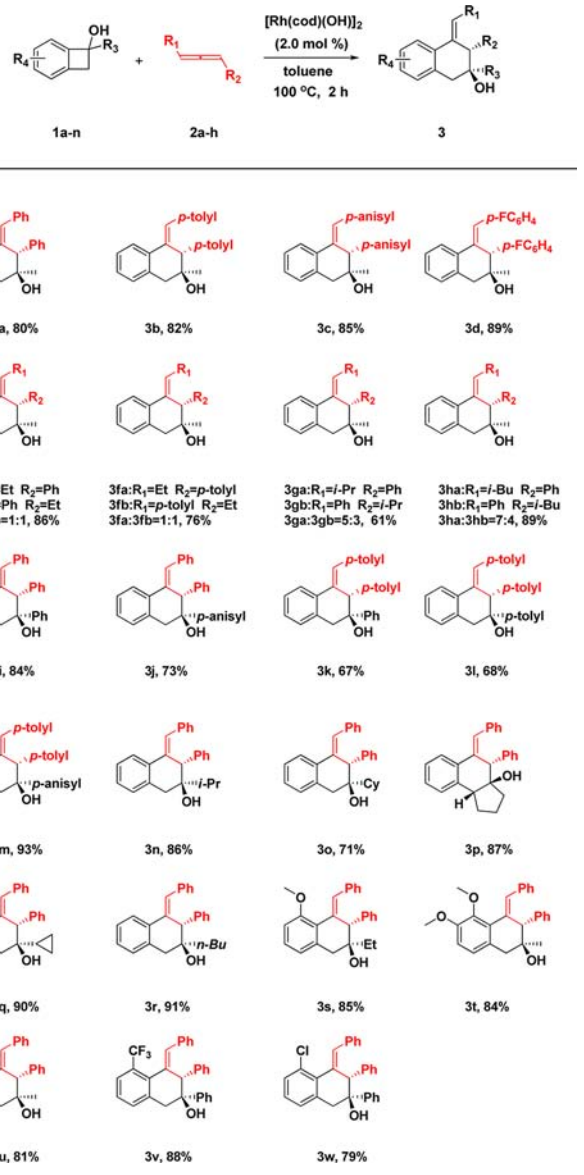
[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.11 mmol), catalyst (2.0 mol %), solvent (0.5 mL). [b]Isolated yields, dr > 19:1. A = 1,4-dioxane, B = toluene; nd = not detected.

was obtained as single product in 80% yield (entry 6). Other possible diastereomeric products were not observed in the crude NMR, underscoring the high regio- and diastereo selectivity. Thermal reaction[13] (i.e., in the absence of $[Rh(cod)(OH)]_2$) did not occur even at 160 °C, suggesting that the reactivity is due to Rh(I) catalysis. During the optimization, it was observed that when 2.0 equiv of allene **2a** was added, the reaction did not proceed. This observation may suggest that disassociation of Rh(I) to allene **2** is a perquisite of the C−C cleavage.

With the optimized conditions in hand, we demonstrated the general applicability of our method with a range of benzocyclobutenols and allenes (Scheme 2). We first evaluated the reaction of different allenes with benzocyclobutenol **1a**. Various allenes bearing *para*-substituted phenyl groups (**2b**, **2c**, **2d**) reacted smoothly to give the desired product in good yields and high diastereoselectivity (dr > 19:1). The nature of the *para*-substitution (electron-donating or -withdrawing) does not seem to affect the reaction. Reaction of unsymmetric allenes bearing an alkyl and an aryl substitution (**2e**, **2f**, **2g**, and **2h**) did not show good regioselectivity, resulting in two separable regioisomers at ratios ranging from 1:1 to 5:3 in 61−89% combined yields. However, the diastereomeric ratios for the individual regioisomeric product remain good, ranging from 10:1 to >19:1. Disappointingly, allenes substituted with two alkyl groups (R_1 = R_2 = isobutyl or *n*-propyl) showed no reactivity toward **1a** even at elevated temperature (120 °C), with both benzocyclobutenol **1a** and allenes being recovered. A similar observation was made with mono-, 1,1-di-, and trisubstituted allenes. As we previously observed that excess **2a** arrested the reaction, we lowered the ratio of allene/Rh(I) to 10:1 without a change in the ratio of **1a**. Under these conditions, the reaction still did not proceed, indicating that the intrinsically strong coordination of Rh(I) to these allenes prevents it from reacting with **1a**.

Benzocyclobutenol with a different group at the R_3 position were then examined. Satisfyingly, various aryl groups such as phenyl (**3i**,**k**), *p*-anisyl (**3j**,**m**), and *p*-tolyl (**3l**) were compatible with the reactions. Larger alkyl groups including isopropyl (**3n**), cyclohexyl (**3o**), cyclopropyl (**3q**), and *n*-butyl (**3r**) were tolerated. The reaction yield seems to increase with smaller R_3 groups (aryl > *n*-alkyl > cyclopropyl > isopropyl > *n*-cyclohexyl). In all these cases, the desired products were obtained in single diastereomeric form, as also evidenced in the crude NMR spectra. Interestingly, the ring-fused benzocyclobutenol **2g** furnished the desired tricyclic tetralin in an excellent yield and with a high diastereoselectivity.

Scheme 2. Reaction Scope[a−c]



[a]Reaction conditions: **1a−n** (0.2 mmol), **2a−h** (0.22 mmol), catalyst (2.0 mol %), toluene (1.0 mL), 100 °C, 2 h. [b]Isolated yields, dr >19:1. [c]for **3ea**, **3fa**, **3ga**, and **3ha**, dr >10:1.

Various substitutions on the phenyl ring of the benzocyclobutenol were tolerated. Electron-donating groups (**3s**,**t**) and electron-withdrawing groups (**3u−w**) did not interfere with the reaction, giving excellent yields of the desired products. Extension of the reaction to unsubstituted benzocyclobutenol (R_3 = R_4 = H) was unsuccessful. A formal retro-aldol reaction occurred, and *o*-methylbenzaldehyde was isolated in high yield.

The structure of **3l** was unambiguously determined by single-crystal X-ray diffraction, which showed that the R_2 and R_3 groups (R_2 = R_3 = tolyl for **3l**) adopted a *cis*-configuration (Figure 1). As a demonstration, Pd/C-catalyzed catalytic hydrogenation of the *exo* olefin in **3l** gave rise to tetralin **4** as one diastereomeric product, featuring three consecutive stereogenic centers (Scheme 3). The newly generated benzylic group was determined to be *syn* to the existing aryl groups, as

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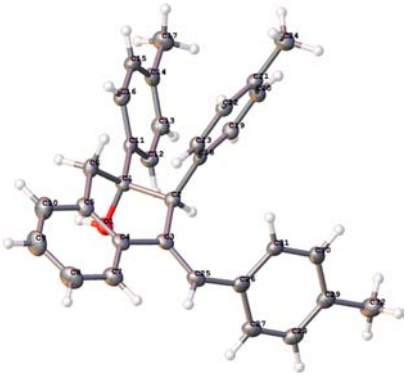
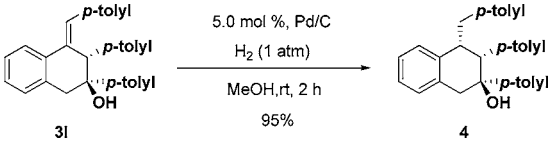


Figure 1. X-ray crystal structure of **3l**.

Scheme 3. Hydrogenation of Tetralin 3l



determined by the coupling constant in ^{1}H NMR (Figure S1, Supporting Information). This is in agreement with the projection that the hydrogen is delivered from the same face as the hydroxyl group, through which the reactant **3l** is absorbed to the Pd catalyst surface.

To probe the reaction mechanism, we employed optically pure allene (*S*)-**2a**[14] in the reaction (Supporting Information).[15] If a stereoselective and stereospecific pathway is assumed, such a reaction would result in chirality transfer from the allene **2a** to the product, thus giving optically pure **3a**. However, racemic **3a** was obtained in numerous trials. We thus monitored the enantiomeric excess of both allene **2a** and product **3a** at different conversions (Table 2). Allene (*S*)-**2a**

Table 2. ee of 2a and 3a at Different Conversions[a]

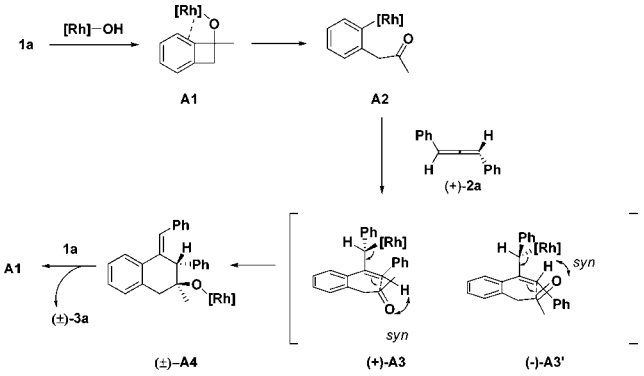
time (h)	conversion of **1a**	**2a** (ee, %)	**3a** (ee, %)
	0	99	
1	17	55	0
4	40	25	0
24	100	0	0

[a]Determined by HPLC analysis on a chiral stationary phase.

was observed to undergo gradual racemization under the reaction conditions. In contrast, when allene (*S*)-**2a** was subjected to the reaction conditions in the absence of substrate **1a**, its ee remained 99% for an extended period of time. This observation suggested that the Ar-Rh (resulted from C−C cleavage) but not the initial Rh(I) caused the racemization of allene **2a**. Such an observation is consistent with the report of Cramer, where they observed that Rh−H induced racemization of chiral allenes.[16] More importantly, the ee of the product **3a** was 0% even at low conversion (17%) when the remaining allene **2a** shows an ee of 55%. Altogether, it could be deduced that the racemic **3a** was not derived from racemic **2a**. Rather, it stemmed from a nonstereospecific reaction pathway.

Based on the above analysis, a tentative mechanism is proposed using **2a** as an example (Scheme 4). First, Rh(I) hydroxide deprotonates **1a**, which then suffers ring opening of benzocyclobutenol through β-carbon elimination, resulting in

Scheme 4. Mechanistic Proposal



the site-selective cleavage of the C(sp^2)−C(sp^3) bond.[6−8,17,18] Insertion of allene **2a** into the Ar−Rh (I) bond in **A2** would give an intermediate of type **A3**. The subsequent intramolecular aldol reaction could happen either by the attack of the (sp3)-C attached to the Rh (as suggested by earlier examples, not shown) or by the attack of the terminal (sp2)-C. The latter pathway not only explains the formation of racemic product **3a** but also accounts for the *E* geometry of the resulted alkene (i.e., not *Z* alkene was observed). However, the diastereoselectivity (i.e., the *cis*-relationship of the methyl and phenyl group) is puzzling. While a *syn* alignment of the C═O and the olefinic H is required to form the diastereomeric product, our inspection of the molecular model does not reveal clear advantage of such a confirmation.

In conclusion, we have developed a Rh(I)-catalyzed insertion of allenes into benzocyclobutenols. This formal [4 + 2] cycloaddition reaction occurred in a site- and diastereoselective manner, providing rapid access to various alkylidene tetralins in good yields. Given the generality, efficiency, and synthetic utility of this method, we expect it to find application in the syntheses of related bioactive compounds. In addition, our preliminary mechanistic study also revealed surprising reactivity of Rh(I) toward allenes that warrants further investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03518.

Experimental procedures, characterization data, X-ray structures, and ^{1}H/^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For selected reviews, see: (a) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610−618. (b) Mack, D. J.; Njardarson, J. T. *ACS Catal.* **2013**, *3*, 272−286. (c) Murakami, M.; Matsuda, T. *Chem. Commun.* **2011**, *47*, 1100−1105. (d) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870−883. (e) Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 7740−7752. (f) Souillart, L.; Cramer, N. *Chem. Rev.* **2015**, *115*, 9410−9464. (g) Van der Boom, M. E.; Milstein, D. *Chem. Rev.* **2003**, *103*, 1759−1792.

(2) For recent examples, see: (a) Evans, P. A.; Inglesby, P. A.; Kilbride, K. *Org. Lett.* **2013**, *15*, 1798−1801. (b) Fan, X.; Tang, M.-X.; Zhuo, L.-G.; Tu, Y. Q.; Yu, Z.-X. *Tetrahedron Lett.* **2009**, *50*, 155−157. (c) Jiao, L.; Lin, M.; Zhuo, L.-G.; Yu, Z.-X. *Org. Lett.* **2010**, *12*, 2528−2531. (d) Xu, T.; Dong, G. *Angew. Chem., Int. Ed.* **2014**, *53*, 10733−10736. (e) Yasui, Y.; Kamisaki, H.; Ishida, T.; Takemoto, Y. *Tetrahedron* **2010**, *66*, 1980−1989. (f) Lu, G.; Fang, C.; Xu, T.; Dong, G.; Liu, P. *J. Am. Chem. Soc.* **2015**, *137*, 8274−8283.

(3) For examples, see: (a) Araya, M.; Gulías, M.; Fernández, I.; Bhargava, G.; Castedo, L.; Mascareñas, J. L.; López, F. *Chem. - Eur. J.* **2014**, *20*, 10255−10259. (b) Gulías, M.; Durán, J.; López, F.; Castedo, L.; Mascarenas, J. L. *J. Am. Chem. Soc.* **2007**, *129*, 11026−11027. (c) Murakami, M.; Ashida, S. *Chem. Commun.* **2006**, 4599−4601. (d) Saya, L.; Fernández, I.; López, F.; Mascareñas, J. L. *Org. Lett.* **2014**, *16*, 5008−5011. (e) Yasukawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 12680−12681. (f) Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 12874−12875.

(4) For C−C bond activation of cyclobutanols, see: (a) Matsuda, T.; Miura, N. *Org. Biomol. Chem.* **2013**, *11*, 3424−3427. (b) Ishida, N.; Shimamoto, Y.; Yano, T.; Murakami, M. *J. Am. Chem. Soc.* **2013**, *135*, 19103−19106. (c) Ishida, N.; Nakanishi, Y.; Murakami, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 11875−11878. (d) Seiser, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 10163−10167. (e) Souillart, L.; Cramer, N. *Chem. Sci.* **2014**, *5*, 837−840. (f) Yada, A.; Fujita, S.; Murakami, M. *J. Am. Chem. Soc.* **2014**, *136*, 7217−7220. (g) Seiser, T.; Cramer, N. *J. Am. Chem. Soc.* **2010**, *132*, 5340−5341.

(5) Chtchemelinine, A.; Rosa, D.; Orellana, A. *J. Org. Chem.* **2011**, *76*, 9157−9162.

(6) Ishida, N.; Sawano, S.; Masuda, Y.; Murakami, M. *J. Am. Chem. Soc.* **2012**, *134*, 17502−17504.

(7) (a) Ishida, N.; Ishikawa, N.; Sawano, S.; Masuda, Y.; Murakami, M. *Chem. Commun.* **2015**, *51*, 1882−1885. (b) Ishida, N.; Sawano, S.; Murakami, M. *Nat. Commun.* **2014**, *5*, 3111−3120.

(8) Xia, Y.; Liu, Z.; Liu, Z.; Ge, R.; Ye, F.; Hossain, M.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2014**, *136*, 3013−3015.

(9) For recent reviews, see: (a) Ma, S. *Acc. Chem. Res.* **2009**, *42*, 1679−1688. (b) Yu, S.; Ma, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074−3112.

(10) For recent examples, see: (a) Haraburda, E.; Lledó, A.; Roglans, A.; Pla-Quintana, A. *Org. Lett.* **2015**, *17*, 2882−2885. (b) Mukai, C.; Ohta, Y.; Oura, Y.; Kawaguchi, Y.; Inagaki, F. *J. Am. Chem. Soc.* **2012**, *134*, 19580−19583. (c) Lainhart, B. C.; Alexanian, E. J. *Org. Lett.* **2015**, *17*, 1284−1287. (d) Ohta, Y.; Yasuda, S.; Yokogawa, Y.; Kurokawa, K.; Mukai, C. *Angew. Chem., Int. Ed.* **2015**, *54*, 1240−1244. (e) Sugikubo, K.; Omachi, F.; Miyanaga, Y.; Inagaki, F.; Matsumoto, C.; Mukai, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 11369−11372.

(11) (a) Koizumi, H.; Yokoshima, S.; Fukuyama, T. *Chem. - Asian J.* **2010**, *5*, 2192−2198. (b) Stork, G.; Yamashita, A.; Adams, J.; Schulte, G. R.; Chesworth, R.; Miyazaki, Y.; Farmer, J. J. *J. Am. Chem. Soc.* **2009**, *131*, 11402−11406. (c) Trost, B. M.; Tang, W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 14785−14803.

(12) (a) Begouin, J.-M.; Capitta, F.; Wu, X.; Niggemann, M. *Org. Lett.* **2013**, *15*, 1370−1373. (b) Novikov, R. A.; Tarasova, A. V.; Korolev, V. A.; Shulishov, E. V.; Timofeev, V. P.; Tomilov, Y. V. *J. Org. Chem.* **2015**, *80*, 8225−8235.

(13) (a) Arnold, B. J.; Sammes, P. G.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 409−414. (b) Choy, W.; Yang, H. *J. Org. Chem.* **1988**, *53*, 5796−5798. (c) Kündig, E. P.; Bernardinelli, G.; Leresche, J. *J. Chem. Soc., Chem. Commun.* **1991**, 1713−1715. (d) Segura, J. L.; Martín, N. *Chem. Rev.* **1999**, *99*, 3199−3246.

(14) (a) Lo, V.K.-Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2008**, *10*, 517−519. (b) Lo, V.K.-Y.; Zhou, C.-Y.; Wong, M.-K.; Che, C.-M. *Chem. Commun.* **2010**, *46*, 213−215.

(15) We thank an anonymous reviewer for suggesting the experiments with optically pure allenes.

(16) Tran, D. N.; Cramer, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 10630−10634.

(17) (a) Nishimura, T.; Katoh, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 4937−4939. (b) Zhao, P.; Hartwig, J. F. *Organometallics* **2008**, *27*, 4749−4757. (c) Zhao, P.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 3124−3125.

(18) (a) Ding, L.; Ishida, N.; Murakami, M.; Morokuma, K. *J. Am. Chem. Soc.* **2014**, *136*, 169−178. (b) Li, Y.; Lin, Z. *J. Org. Chem.* **2013**, *78*, 11357−11365.

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Visible-Light-Promoted and Yb(OTf)$_3$-Catalyzed Constructions of Coumarin-Pyrrole-(Iso)quinoline-Fused Pentacycles: Synthesis of Lamellarin Core, Lamellarin D Trimethyl Ether, and Lamellarin H

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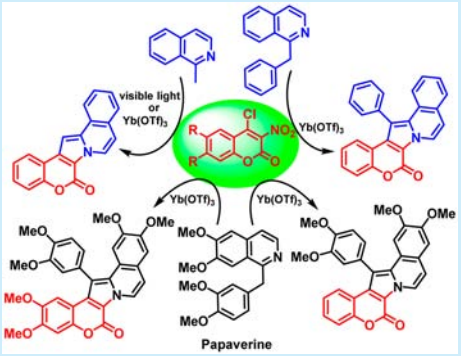
Supporting Information

ABSTRACT: The efficient construction of a coumarin-pyrrole-isoquinoline-fused pentacycle via the visible-light-promoted cyclization of 4-(isoquinolin-1-ylmethyl)-3-nitrocoumarin or Yb(OTf)$_3$-catalyzed coupling of 4-chloro-3-nitrocoumarin and 1-methylisoquinoline is reported. This methodology has further led to the development of the concise synthesis of the lamellarin core in one, two, and three steps, as well as of lamellarin D trimethyl ether in three steps.



Pyrrolo[2,1-*a*]isoquinoline- and coumarin-fused pentacycles constitute the molecular skeleton of the natural products lamellarin alkaloids such as lamellarins D, H, M, N, and α-20-sulfate (Figure 1). These lamellarin alkaloids exhibit a variety of

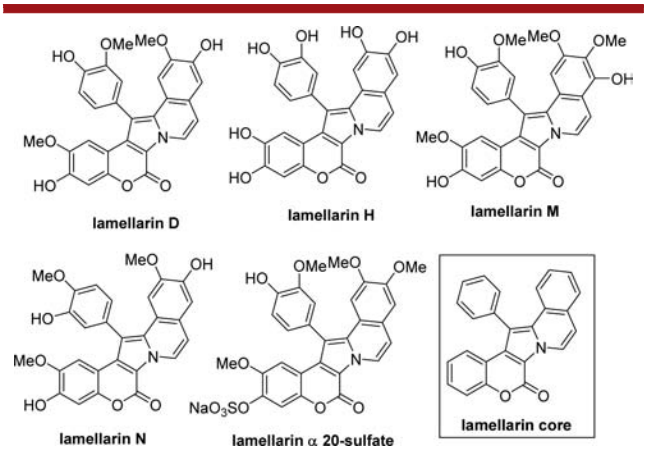
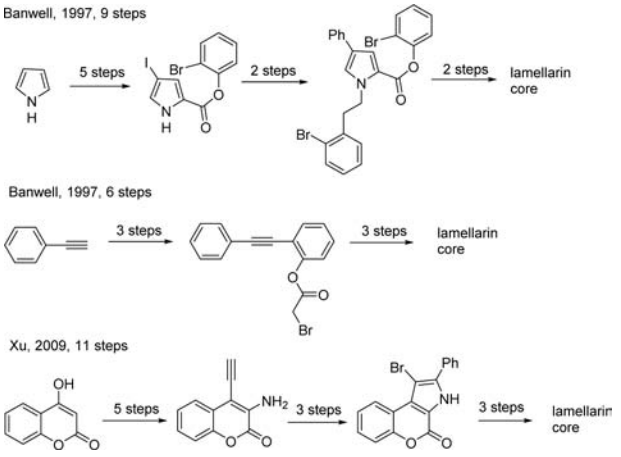


Figure 1. Molecular structures of lamellarins D, H, M, N, and α-20-sulfate.

biological activities.[1] For instance, lamellarin D not only displays strong cytotoxic activity against tumor cell lines[2] but also serves as a potent topoisomerase I inhibitor.[3] Lamellarin H is an effective antiviral agent against the *Molluscum contagiosum* virus.[4] Lamellarin N shows potent inhibition activities against protein kinases,[5] and lamellarin α-20-sulfate is a potent HIV integrase inhibitor.[4,6] In light of their novel structures and intriguing biological properties, the synthesis of the coumarin-pyrrole-isoquinoline-fused pentacycle has become an important and attractive goal for organic chemists. Previous pentacycle syntheses were generally accomplished in two stages by building the pyrrolo[2,1-*a*]isoquinoline core and installing the coumarin moiety onto it (Scheme 1).[7] Direct preparation of the coumarin-pyrrole-isoquinoline-fused pentacyclic system using pre-existing coumarin derivatives, however, has been rarely reported.[8] As a part of our ongoing research on the development of photosensitizer-free, visible-light-mediated

Scheme 1. Previous Synthesis of Lamellarin Core



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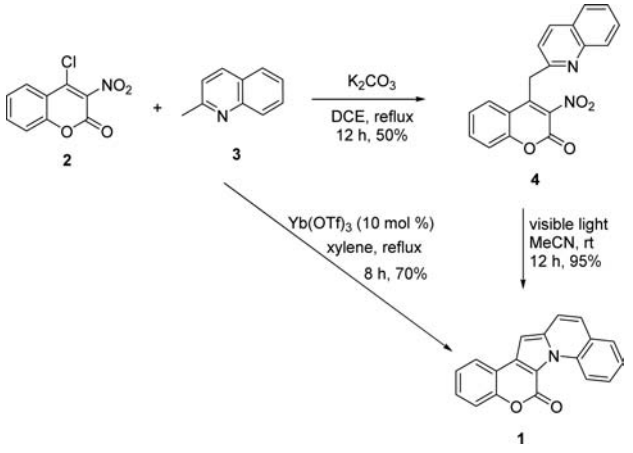
organic reactions,[9] we herein present the synthesis of a coumarin-pyrrole-isoquinoline-fused pentacycle through the cyclization of 4-(isoquinolin-1-ylmethyl)-3-nitrocoumarin under the influence of visible light irradiation or $Yb(OTf)_3$-catalyzed coupling of 4-chloro-3-nitrocoumarin and 1-methylisoquinoline. Further application of this methodology to the synthesis of the lamellarin core, lamellarin D trimethyl ether, and lamellarin H was also explored.

We initiated our study by choosing a coumarin-pyrrole-quinoline-fused pentacycle **1** as the first target (Scheme 2). The

Scheme 2. Synthesis of Compound 1



synthesis of **1** involved K_2CO_3-mediated coupling of commercially available 4-chloro-3-nitrocoumarin (**2**) and 2-methylquinoline (**3**) in 1,2-dichloroethane under reflux conditions to give 3-nitro-4-(quinolin-2-ylmethyl)coumarin (**4**) in 50% yield. During purification of the compound **4**, a new and fluorescent spot on the TLC plate was invariably detected. This observation implied that compound **4** was light-sensitive and slowly converted into a new product under the influence of light. Upon exposure to visible light (23 W fluorescent light bulb or blue LEDs), the compound **4** indeed was found to undergo intramolecular cyclization reaction at room temperature to give the pentacycle **1**, quantitatively. No formation of **1** was observed when the reaction was carried out in the dark. This result confirmed that the cyclization of **4** to **1** was promoted by visible light. As for the solvent effect, among several solvents investigated, acetonitrile gave higher conversion in a shortest time interval. Hence, acetonitrile was used as the solvent for all subsequent visible-light-mediated reactions. The molecular structures of **4** and **1** were confirmed by single-crystal X-ray diffraction analysis as presented in Figure 2.[10] The X-ray crystal structures revealed that the quinoline moiety of **4** is almost orthogonal to the coumarin with the quinoline nitrogen

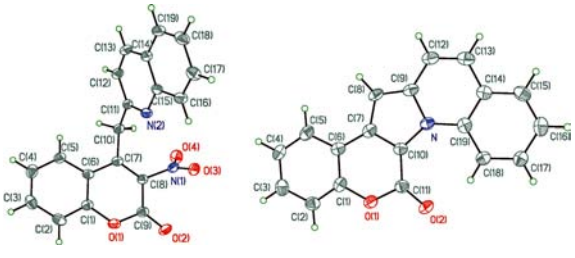


Figure 2. X-ray crystal structures of **4** (left) and **1** (right).

atom pointing toward the nitro group, and the pentacycle **1**, as expected, is virtually planar.

To gain more insight into the mechanism of this visible-light-promoted cyclization, nitrocoumarin **4** was subjected to the EPR measurements. Figure 3 depicts the EPR spectra of **4**

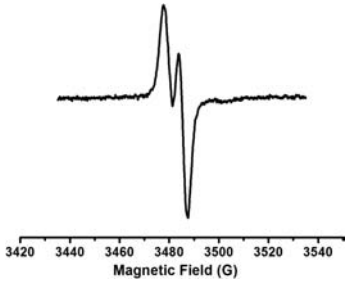
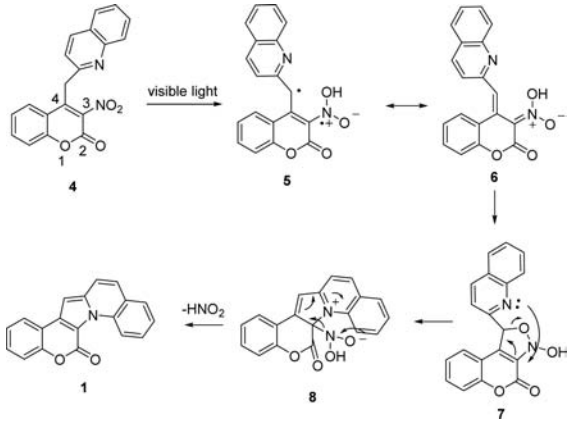


Figure 3. EPR spectra of **4** recorded in degassed CH_3CN solution at room temperature after exposed to visible light.

recorded in degassed CH_3CN solution under visible light irradiation at room temperature. Upon exposure to visible light, strong splitting EPR signals were clearly observed at around 3482−3492 G. This observation provided strong evidence to support that the photochemical reaction of **4** involves, at least in part, a radical species as a transient intermediate.

Based on the EPR experimental results, a plausible mechanism for the formation of **1** from **4** via visible light irradiation is proposed in Scheme 3. Presumably, the

Scheme 3. Proposed Mechanism for the Formation of 1 from 4



photoreaction involves a visible-light-mediated intramolecular hydrogen transfer from the methylene group to the nearby nitro group oxygen to give the biradical species **5**[11] which can delocalize to the 2-oxochroman-3-ylideneazinic acid **6**. The intramolecular cyclization of **6** generates the isoxazol-2(5*H*)-ol derivative **7**. The nucleophilic addition of quinoline nitrogen to the C-3 position of the coumarin ring forms the key carbon−nitrogen bond and subsequently leads to the formation of the quinolinium **8**. Final elimination of nitrous acid from **8** and intermittent aromatization of the pyrrole ring afford the photogenerated pentacycle **1**.

After the synthesis of pentacycle **1** has been successfully realized, we then turned our attention to the preparation of the coumarin-pyrrole-isoquinoline-fused pentacycle **12** and lamellarin core **9** as shown in Scheme 4. The synthesis started with K_2CO_3-mediated coupling of **2** with 1-methylisoquinoline (**10**)

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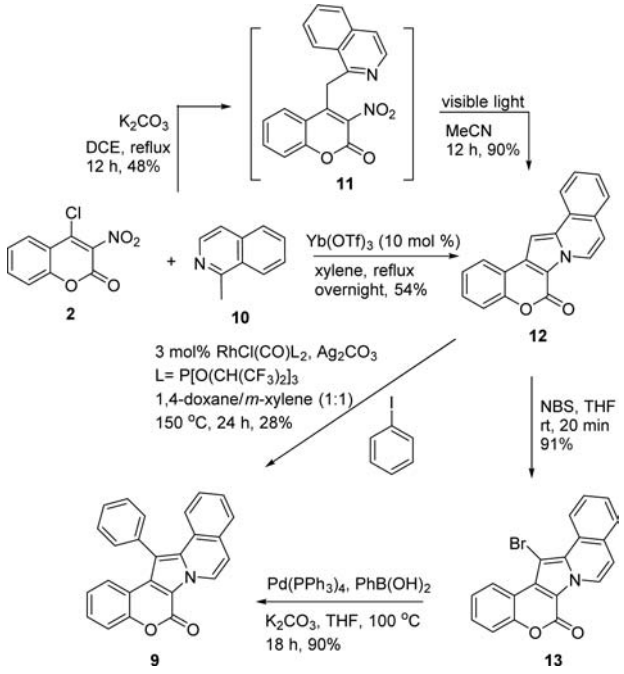
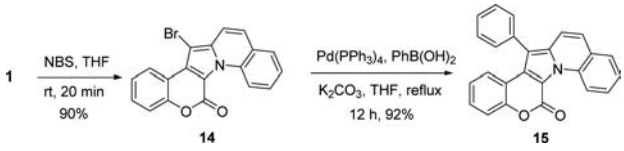
Scheme 4. Synthesis of Compound 12 and Lamellarin Core 9



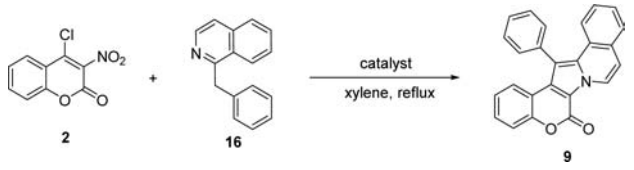
in 1,2-dichloroethane to give 4-(isoquinolin-1-ylmethyl)-3-nitro-2*H*-chromen-2-one (**11**) in 48% yield. Similar to that of **4**, compound **11** was found to be highly sensitive to light and readily undergo intramolecular cyclization reaction which made the isolation of **11** in its pure form difficult. Thus, without further characterization, compound **11** was subjected to visible-light-promoted cyclization in acetonitrile to afford compound **12** in 90% yield. The subsequent Rh-catalyzed coupling[12] of **12** with iodobenzene in 1,4-dioxane/*m*-xylene generated lamellarin core **9** in 28% yield. Alternatively, compound **9** can also be prepared by bromination of **12** with NBS at room temperature to afford **13** and followed by Suzuki coupling of **13** with phenylboronic acid in THF.[7i,8] Similarly, lamellarin core analogue **15** was synthesized from compound **1** to demonstrate the generality of this methodology (Scheme 5). Again, the molecular structures of both **9** and **15**[10] were confirmed by the single-crystal X-ray diffraction analysis (see the Supporting Information).

Scheme 5. Synthesis of Compound 15



In an effort to further shorten the synthetic steps of **9** shown in Scheme 4, we replaced 1-methylisoquinoline (**10**) with 1-benzylisoquinoline (**16**) in which the preinstalled phenyl group on the isoquinoline moiety would be directly introduced to lamellarin core **9**, so that the final metal-catalyzed coupling reaction can be omitted. Unfortunately, all attempts to prepare **9** by reacting **2** with **16** under various basic conditions failed to give the desired product, presumably due to the intrinsic steric hindrance caused by the bulky phenyl group on **16**. Further study, to our delight, indicates that the lamellarin core **9** can be synthesized in one step through Lewis acid catalyzed coupling of **2** and **16** in xylene under reflux conditions. Table 1

Table 1. Optimization of Reaction Parameters for Synthesis of Lamellarin Core 9



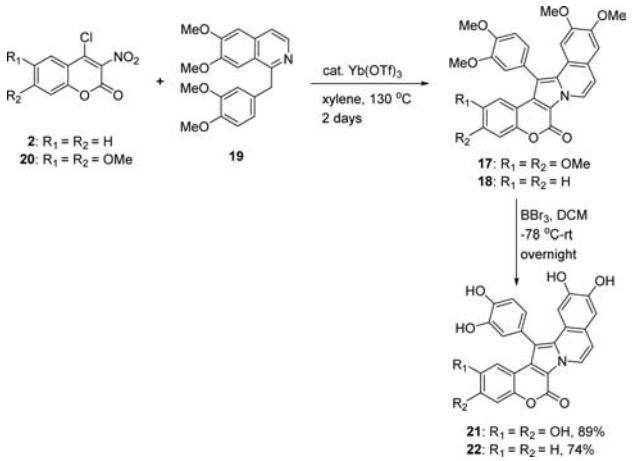
entry	catalyst (10 mol %)	time (h)	yield[a] (%)
1	$AlCl_3$	36	15
2	$FeCl_3$	72	trace
3	$NiNO_3$	72	nr[b]
4	BF_3OEt_2	72	nr
5	$Yb(OTf)_3$	36	17
6	$Sc(OTf)_3$	72	6
7	$Ga(OTf)_3$	72	trace
8	$Bi(OTf)_3$	72	trace

[a]Isolated yield. [b]No reaction.

summarizes the optimization of reaction parameters for the one-step synthesis of lamellarin core **9** from **2** and **16**. According to Table 1, ytterbium triflate was found to be the best Lewis acid with a yield of 17% (entry 5).

The methodology was further utilized in the preparation of lamellarin D trimethyl ether (**17**), its analogue **18**, and lamellarin H as shown in Scheme 6. The $Yb(OTf)_3$-catalyzed

Scheme 6. Preparation of Compounds 17, 18, 21, and 22



coupling of **2** with commercially available papaverine (**19**) in xylene under reflux conditions furnished lamellarin D trimethyl ether analogue **18** in 14% yield. Similarly, lamellarin D trimethyl ether (**17**) was synthesized by coupling 4-chloro-6,7-dimethoxy-3-nitrocoumarin (**20**, prepared from 4-hydroxy-6,7-dimethoxycoumarin in two steps; see the Supporting Information) with **19** in 10% yield (overall yield of 8% in three steps). Subsequent exhaustive demethylation of **17** and **18** using boron tribromide afforded the natural product lamellarin H (**21**) and its analogue **22**. Even though the yield of the coupling step is relatively low, this concise synthesis provides a quick access to the biologically important coumarin-pyrrole-isoquinoline-fused pentacycles and lamellarin D trimethyl ether from commercially available starting materials

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and represents the shortest route to the construction of lamellarin core,[7a,8] lamellarin D trimethyl ether, and lamellarin H[7g,13] ever reported in literature.

This one-step, sequential coupling−cyclization reaction was also utilized to improve the preparation of pentacycles **1** and **12** by reacting **2** directly with **3** and **10** in the presence of a catalytic amount of $Yb(OTf)_3$ in xylene under reflux conditions in 70% and 54% yield, respectively (Schemes 2 and 4). We assumed that the mechanism for the formation of **1** via $Yb(OTf)_3$-catalyzed reaction involves the Lewis acid promoted intramolecular proton transfer (rather than light-promoted hydrogen atom transfer) from the 4-methylene carbon of **4** to the nearby 3-nitro oxygen atom to afford **6**. The remaining mechanistic steps are similar to those of the visible-light-promoted reaction as shown in Scheme 3. Compared to the visible-light-promoted reaction, the $Yb(OTf)_3$-catalyzed route has the advantages of higher overall yield, one less step, and being scalable. Nevertheless, the visible-light-promoted cyclization is more sustainable and environmentally benign and holds the potential for efficient preparation of novel heterocyclic aromatic compounds.

In summary, we have demonstrated that coumarin-pyrrole-isoquinoline-fused pentacycle **12** can be prepared via either visible-light-promoted cyclization of 4-(isoquinolin-1-ylmethyl)-3-nitrocoumarin (**11**) or $Yb(OTf)_3$-catalyzed coupling of 4-chloro-3-nitrocoumarin (**2**) and 1-methylisoquinoline (**10**). The methodology was extended to the one-, two-, and three-step syntheses of lamellarin core **9** with overall yields of 17%, 15%, and 44%, respectively. Moreover, we have successfully implemented this method in the synthesis of lamellarin D trimethyl ether in three steps with an overall yield of 8% and lamellarin H in four steps.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03524.

Synthesis of compounds **1**, **4**, **9**, **11**−**15**, **17**, **18**, and **20**−**22**; experimental details; additional spectra (PDF)
X-ray crystal structure details for **1** (CIF)
X-ray crystal structure details for **4** (CIF)
X-ray crystal structure details for **9** (CIF)
X-ray crystal structure details for **15** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For recent reviews, see: (a) Fukuda, T.; Ishibashi, F.; Iwao, M. *Heterocycles* **2011**, *83*, 491−529. (b) Pla, D.; Albericio, F.; Alvarez, M. *MedChemComm* **2011**, *2*, 689−697. (c) Bailly, C. *Mar. Drugs* **2015**, *13*, 1105−1123.

(2) (a) Kluza, J.; Gallego, M.-A.; Loyens, A.; Beauvillain, J.-C.; Sousa-Faro, J.-M. F.; Cuevas, C.; Marchetti, P.; Bailly, C. *Cancer Res.* **2006**, *66*, 3177−3187. (b) Ballot, C.; Kluza, J.; Lancel, S.; Martoriati, A.; Hassoun, S. M.; Mortier, L.; Vienne, J.-C.; Briand, G.; Formstecher, P.; Bailly, C.; Nevière, R.; Marchetti, P. *Apoptosis* **2010**, *15*, 769−781.

(3) (a) Facompré, M.; Tardy, C.; Bal-Mahieu, C.; Colson, P.; Perez, C.; Manzanares, I.; Cuevas, C.; Bailly, C. *Cancer Res.* **2003**, *63*, 7392−7399. (b) Marco, E.; Laine, W.; Tardy, C.; Lansiaux, A.; Iwao, M.; Ishibashi, F.; Bailly, C.; Gago, F. *J. Med. Chem.* **2005**, *48*, 3796−3807. (c) Khiati, S.; Seol, Y.; Agama, K.; Rosa, I. D.; Agrawal, S.; Fesen, K.; Zhang, H.; Neuman, K. C.; Pommier, Y. *Mol. Pharmacol.* **2014**, *86*, 193−199.

(4) Ridley, C. P.; Reddy, M. V. R; Rocha, G.; Bushman, F. D.; Faulkner, D. J. *Bioorg. Med. Chem.* **2002**, *10*, 3285−3290.

(5) Baunbaek, D.; Trinkler, N.; Ferandin, Y.; Lozach, O.; Ploypradith, P.; Rucirawat, S.; Ishibashi, F.; Iwao, M.; Meijer, L. *Mar. Drugs* **2008**, *6*, 514−527.

(6) (a) Reddy, M. V. R.; Rao, M. R.; Rhodes, D.; Hansen, M. S. T.; Rubins, K.; Bushman, F. D.; Venkateswarlu, Y.; Faulkner, D. J. *J. Med. Chem.* **1999**, *42*, 1901−1907. (b) Yamaguchi, T.; Fukuda, T.; Ishibashi, F.; Iwao, M. *Tetrahedron Lett.* **2006**, *47*, 3755−3757.

(7) (a) Banwell, M. G.; Flynn, B.; Hockless, D. *Chem. Commun.* **1997**, 2259−2260. (b) Banwell, M. G.; Flynn, B. L.; Hockless, D. C. R.; Longmore, R. W.; Rae, D. *Aust. J. Chem.* **1999**, *52*, 755−765. (c) Ruchirawat, S.; Mutarapat, T. *Tetrahedron Lett.* **2001**, *42*, 1205−1208. (d) Cironi, P.; Manzanares, I.; Albericio, F.; Álvarez, M. *Org. Lett.* **2003**, *5*, 2959−2962. (e) Handy, S. T.; Zhang, Y.; Bregman, H. *J. Org. Chem.* **2004**, *69*, 2362−2366. (f) Nyerges, M.; Toke, L. *Tetrahedron Lett.* **2005**, *46*, 7531−7534. (g) Ploypradith, P.; Petchmanee, T.; Sahakitpichan, P.; Litvinas, N. D.; Ruchirawat, S. *J. Org. Chem.* **2006**, *71*, 9440−9448. (h) Su, S.; Porco, J. A., Jr *J. Am. Chem. Soc.* **2007**, *129*, 7744−7745. (i) Ohta, T.; Fukuda, T.; Ishibashi, F.; Iwao, M. *J. Org. Chem.* **2009**, *74*, 8143−8153.

(8) Chen, L.; Xu, M.-H. *Adv. Synth. Catal.* **2009**, *351*, 2005−2012.

(9) (a) Chen, W. Z.; Wei, H. Y.; Yang, D. Y. *Tetrahedron* **2013**, *69*, 2775−2781. (b) Chen, Y. C.; Yang, D. Y. *Tetrahedron* **2013**, *69*, 10438−10444.

(10) Crystallographic data (excluding structure factors) for **1**, **4**, and **15** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Numbers CCDC-1427920, -1427919, and -1436089, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

(11) (a) Yip, R. W.; Sharma, D. K.; Giasson, R.; Gravel, D. *J. Phys. Chem.* **1985**, *89*, 5328−5330. (b) Kammari, L.; Solomek, T.; Ngoy, B. P.; Heger, D.; Klan, P. *J. Am. Chem. Soc.* **2010**, *132*, 11431−11433. (c) Zhao, H.; Sterner, E. S.; Coughlin, E. B.; Theato, P. *Macromolecules* **2012**, *45*, 1723−1736.

(12) Ueda, K.; Amaike, K.; Maceiczyk, R. M.; Itami, K.; Yamaguchi, J. *J. Am. Chem. Soc.* **2014**, *136*, 13226−13232.

(13) (a) Ishibashi, F.; Miyazaki, Y.; Iwao, M. *Tetrahedron* **1997**, *53*, 5951−5962. (b) Dialer, C.; Imbri, D.; Hansen, S. P.; Opatz, T. *J. Org. Chem.* **2015**, *80*, 11605−11610.

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Z-Stereoselective Aza-Peterson Olefinations with Bis(trimethylsilane) Reagents and Sulfinyl Imines

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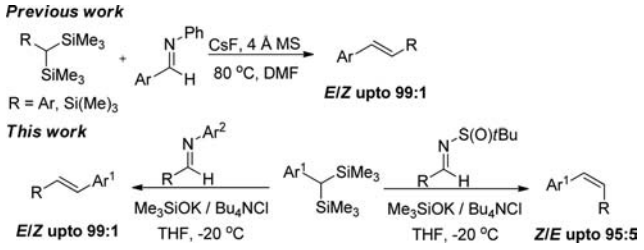
Supporting Information

ABSTRACT: Highly stereoselective aza-Peterson olefinations from bench-stable α,α-bis(trimethylsilyl)toluene reagents and N-substituted imines have been achieved using $TMSO^-/Bu_4N^+$ as Lewis base activator in THF. Remarkably, and for the first time, *N*-*t*-butanesulfinyl imines were utilized for the synthesis of *Z*-stilbenes with excellent selectivities, while *N*-aryl imines generated *E*-stilbenes under identical reaction conditions. The protocol proved general for numerous examples with low molecular weight byproducts formed. The origin of the Z-selectivity is proposed to be a result of diastereoselective addition to *N*-*t*-butanesulfinyl imines followed by *syn*-elimination of an in situ formed hypervalent silicate.

Olefins are ubiquitous structural motifs in biologically relevant entities and serve as versatile precursors for a diverse range of chemical transformations that produce pharmaceutical and industrially important organic compounds.[1] New strategies for the facile synthesis of stereochallenging alkenes remain a considerable focus of research. Selective access to either the *E*- or *Z*-isomer of an alkene is often the decisive factor in the success of any alkene synthesis method. Among the olefin-forming transformations, selective preparation of *E*-isomers has been established the most, while the corresponding methods to access the thermodynamically less favorable *Z*-alkenes remain a challenge.[2,3] Several transformations have been introduced to address this issue, including hydrogenation,[4] alkyne reductive coupling[5] or carbocupration,[6] cross-metathesis,[7] terminal-to-internal olefin isomerization,[8] and photocatalytic *E*-to-*Z* isomerization.[9] A general synthesis of *Z*-olefins is available from the Wittig reaction variant in which *N*-sulfonyl imines are used instead of carbonyl electrophiles.[10]

The Peterson olefination (PO) reaction offers a superior atom economy advantage over the Wittig reaction as it produces noncrystalline low molecular weight silicon byproducts.[11] Yet, stereocontrol has always been the Achilles heel of the PO reaction, especially for direct alkene synthesis (i.e., without isolation of silyl−alcohol intermediates).[1,11] Arguably, this limiting factor, in addition to the necessity to preform α-silyl carbanions using a strong base, has restricted its more widespread use. In an effort to address these limitations, we have recently reported stereoselective aza-PO reactions utilizing bench-stable bis(trimethylsilane) reagents and *N*-phenyl imines to produce thermodynamically favored *E*-alkenes with excellent selectivities (Scheme 1).[12] Despite this success, the significant limitation for silicon-based olefination reactions is that no direct (without β-hydroxysilane isolation) *Z*-selective method currently exists. As such, we were stimulated to identify a *Z*-favoring electrophile, and our attention was drawn to the potential use of *N*-*t*-butanesulfinyl imines (Ellman imines) as substrates for aza-PO reactions.[13] To the best of our knowledge, *t*-butanesulfinyl imines have not been previously utilized for any olefination transformations. They are commonly used in diastereoselective organometallic addition reactions for the synthesis of chiral amines, with high selectivity attributed to either the formation of a metal-chelated closed six-membered ring or open (non-chelating) transition states.[13] We have recently demonstrated diastereoselective addition of benzyltrimethylsilanes to *N*-*t*-butanesulfinyl imines using Me_3SiO^-/Bu_4N^+ in THF to promote the addition reaction.[14,15]

Scheme 1. Stereoselective Aza-Peterson Olefinations



In this work, our motivation for investigating *N*-*t*-butanesulfinyl imines as carbonyl replacement electrophiles was the potential for diastereoselective addition, through a chelating six-membered transition state, brought about by interaction of the silicon of the α-silyl carbanion with the oxygen of the sulfinyl imine (Figure 1). This intramolecular oxygen−silicon activation would induce hypervalency on Si, thereby facilitating an olefin-forming *syn*-elimination step with participation of the six-membered ring guiding the outcome toward the thermodynami-

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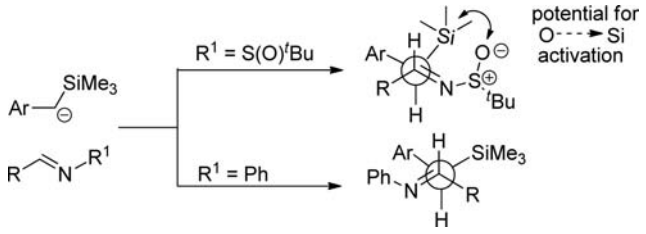


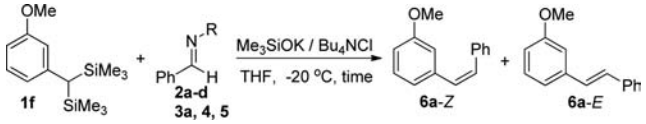
Figure 1. Possible addition profiles when using *N*-*t*-butanesulfinyl imine and *N*-phenyl imine electrophiles.

cally less stable *Z*-isomers. This would contrast with an open nonchelating addition model for the *N*-phenyl imine electrophiles, which delivers the thermodynamically favored *trans*-isomers (Figure 1).

At the outset, the reaction conditions of Me_3SiO^-/Bu_4N^+ in THF were chosen to match those previously successfully used in our addition reactions.[14] As it would be beneficial to have both *E*- and *Z*-isomers accessible from a single set of conditions (and allow direct comparison), these conditions were also applied to a number of *N*-aryl imine reactions, some of which have been previously observed to give high *E*-selectivity using CsF/DMF.[12] In this initial study, 13 bis(trimethylsilane) reagents **1a**−**m**, five *N*-aryl imines **2a**−**e**, and 19 *N*-*t*-butanesulfinyl imines **3a**−**s** were used (for structures, see Figures S1−S3).[16]

Before investigating the *Z*-selectivity, it was first confirmed that changing silicon activation from a fluoride source in DMF to Me_3SiO^- in THF did not impact the high *E*-selectivity with *N*-phenyl-substituted imines. Reaction of ((3-methoxyphenyl)-methylene)bis(trimethylsilane) **1f** and *N*-phenyl imine **2a** in the presence of 1.5 equiv of Me_3SiOK/Bu_4NCl in THF at −20 °C provided the target alkene **6a** in 87% yield with a *Z*/*E* ratio of 1:99, which was consistent with our previous results using CsF in DMF (Table 1, entry 1).[12] To determine the influence, if any, of

Table 1. Imine Stereoeffects on Aza-Peterson Olefinations[a]



entry	R	imine	time (h)	yield[b] (%)	*Z*/*E*[c]
1	Ph	**2a**	3	87	1/99
2	*p*-$MeOC_6H_4$	**2b**	3	76	1/99
3	*p*-$CF_3C_6H_4$	**2c**	3	84	1/99
4	3,5-$(CF_3)_2C_6H_3$	**2d**	3	85	1/99
5	(*R*)-S(O)*t*Bu	**3a**	2	89	95/5
6	(*S*)-S(O)*t*Bu	**3a**	2	88	95/5
7	(±)-S(O)*t*Bu	**3a**	2	86	95/5
8	SO_2Me	**4**	4[d]	51	65/35
9	SO_2*p*-MeC_6H_4	**5**	4[d]	63	45/55

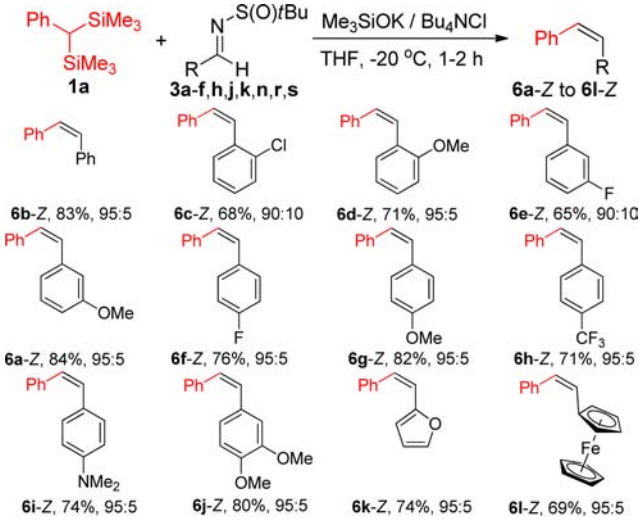
[a]Reaction conditions: bis(silanes) (0.8 mmol), imine (0.4 mmol), and Me_3SiOK/Bu_4NCl (0.6 mmol). [b]Yield of the isolated product after chromatography. [c]Determined by ^1H NMR. [d]Reaction warmed to 0 °C for 2 h.

electronic effects of the *N*-aryl group on the stereochemical outcome of the reaction, *N*-*p*-methoxyphenyl **2b**, *N*-*p*-trifluoromethylphenyl **2c**, and bis(trifluoromethyl)phenyl **2d** substituted imines were used in the reaction with **1f** under the same conditions. In each case, the product *Z*/*E* ratio remained unchanged at 1:99, with only minor variations in yields (entries 2−4). These results pointed toward *N*-aryl sterics influencing the reaction course toward highly selective *E* product.

Next, (*R*)-*N*-benzylidene-2-methylpropane-2-sulfinamide, (*R*)-**3a**, was chosen as electrophile in the reaction with **1a** under identical conditions. To our delight, a complete inversion of the stereo-outcome was obtained, with alkene **6a** obtained in 89% yield with a *Z*/*E* ratio of 95:5 (entry 5). Using either the *S*-isomer or a racemic mixture of sulfinyl imine **3a** had no effect on *Z*/*E* ratio (entries 6 and 7). A survey of the two sulfonyl imines **4** and **5** was next performed to compare their influence on the stereochemical outcome of the reaction. When methylsulfonyl imine **4** was treated with **1f** in the presence of 1.5 equiv of Me_3SiOK/Bu_4NCl in THF, alkene **6a** was formed in 51% yield with a poor *Z*/*E* ratio of 65:35 (entry 8). Employing *p*-toluenesulfonyl imine **5** under the same reaction conditions produced the product alkene **6a** in 63% yield, having little *Z*/*E* selectivity (45:55), which is a comparable result to that seen with benzaldehyde (entry 9).[12] This dramatic difference between sulfinyl and sulfonyl imines is pertinent as *p*-toluenesulfonyl imines are excellent substrates for the formation of *Z*-alkenes in the Wittig reaction.[10c] Together, these initial results indicated that *N*-phenyl imine and *rac*-*N*-*t*-butanesulfinyl imines could be used for *E*- and *Z*-selective olefination, respectively, in the presence of 1.5 equiv of Me_3SiOK/Bu_4NCl at −20 °C in THF.

The established reaction conditions were next evaluated by employing a broad range of aryl **3a**−**f**,**h**,**j**,**k**,**n**, heteroaryl **3r**, and organometallic **3s** *N*-*t*-butanesulfinyl imines with (phenylmethylene)bis(trimethylsilane) **1a** (Scheme 2). *Z*-

Scheme 2. *Z*-Selective PO with *N*-*t*-Butanesulfinylimines[a]



[a]Yield of the isolated product after chromatography; *Z*/*E* determined by ^1H NMR.

Selective olefination of electron-neutral, -rich, and -poor aryl imines having *o*-, *m*-, or *p*-substitution or bisubstitution worked very well, providing the corresponding alkenes *Z*-**6a** to *Z*-**6j** in high yields and with excellent range of *Z*/*E* ratios from 90:10 to 95:5. Pharmaceutically important heteroatomatic furan is also compatible with the protocol to produce the corresponding alkene *Z*-**6k** in 74% yield. Ferrocenyl imine **3s** was utilized for the first time in stereoselective olefination, providing alkene *Z*-**6l** in 69% yield and *Z*/*E* ratio of 95:5 (Scheme 2). Having successfully explored various *N*-*t*-butanesufinyl imines, the influence of diversely substituted bis(trimethylsilane) reagents **1b**,**d**−**f**,**h**,**j**,**k**

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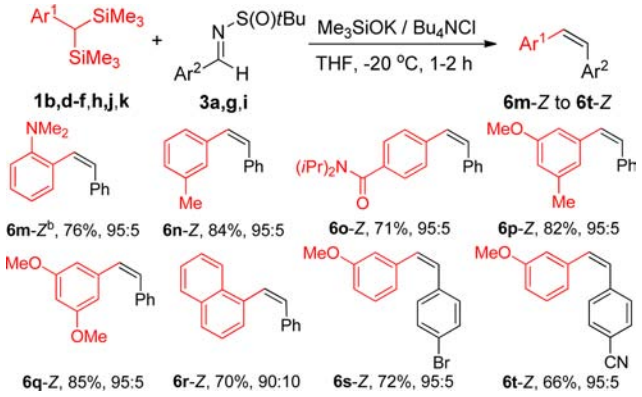
with imines **3a,g,i** was examined (Scheme 3). Pleasingly, each reaction was successful with good *Z*/*E* ratios in spite of the varying substitution patterns.

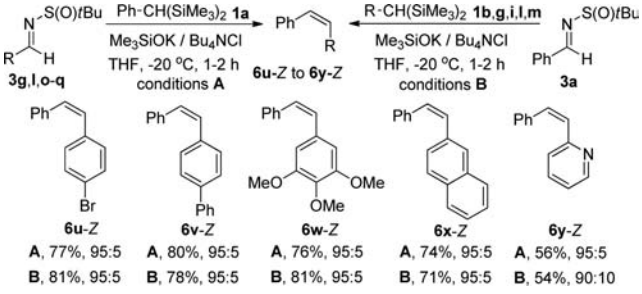
Scheme 3. *Z*-Selective Olefination[a]



[a]Yield of the isolated product after chromatography; *Z*/*E* determined by ^{1}H NMR. [b]Reaction performed at −20 to −10 °C.

An important feature of any new synthetic method is robustness, as its use will often be in the hands of a nonexpert. To showcase the generality of the current method, a dual synthetic strategy was chosen to prepare five representative alkenes **6u−y** (Scheme 4). Under conditions **A**, **1a** was reacted

Scheme 4. Dual Synthetic Strategy[a]

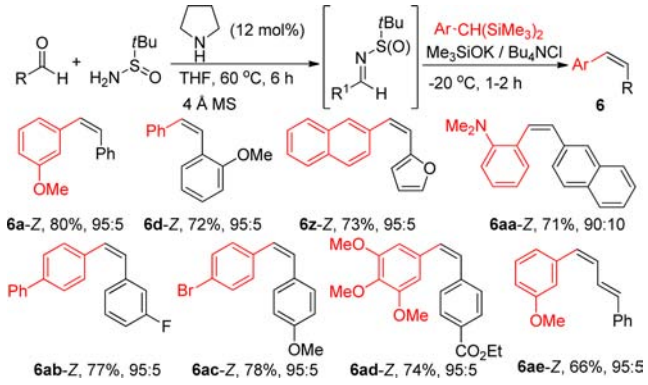


[a]Yield of the isolated product after chromatography; *Z*/*E* determined by ^{1}H NMR.

with five different imines **3g,l,o−q**, providing the corresponding alkenes in good yields with excellent *Z*-selectivities. In dual conditions **B**, five different bis(trimethylsilanes) **1b,g,i,l,m** were employed with **3a** to produce the same alkenes. Yields and *Z*-selectivity for both approaches show comparable results, many of which are within the range of experimental error. Of specific note, bis(trimethylsilane)pyridine derivative **1m** and its *N*-*t*-butanesulfinyl analogue **3q** were both compatible with this process (Scheme 4).

To streamline the *Z*-alkene synthesis from aldehydes, a one-pot approach was adopted (Scheme 5). Reaction of aldehyde and 2-methylpropane-2-sulfinamide in THF with pyrrolidine catalyst generated the sulfinyl imine.[17] Imine formation was monitored by TLC, and upon completion, the temperature was lowered to −20 °C, bis(trimethylsilane) added, and the reaction carried out as previously described. Eight diversely substituted alkenes were produced in good yields while maintaining the excellent *cis*-selectivity (Scheme 5). It could be anticipated that this approach would be of specific importance for library generation of *Z*-

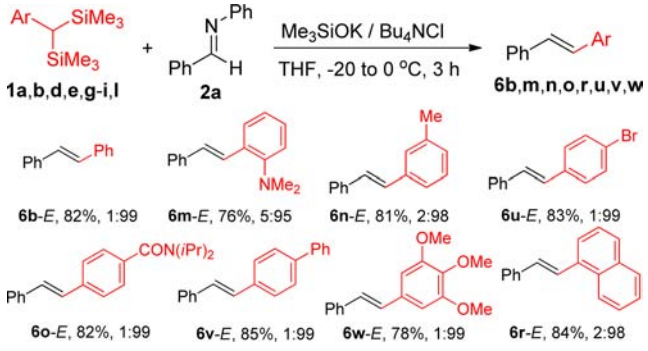
Scheme 5. One-Pot *Z*-Selective Aza-PO from Aldehydes[a]



[a]Reaction conditions: aldehyde (0.4 mmol), sulfinamide (0.44 mmol), bis(silanes) (0.8 mmol), and Me_3SiOK/Bu_4NCl (0.7 mmol); *Z*/*E* determined by ^{1}H NMR.

alkenes via high-throughput synthesis. As it would be a unique advantage to have a single silicon activation to produce both *Z*- and *E*-isomers, the use of Me_3SiO^-/Bu_4N^+ with *N*-phenyl imines was next evaluated. Eight bis(trimethylsilanes) were successfully tested with sulfinyl imine **2a**, providing alkenes **6b,m−o,r,u−w** in high yields and with ratios ranging from 5:95 to 1:99 (Scheme 6).

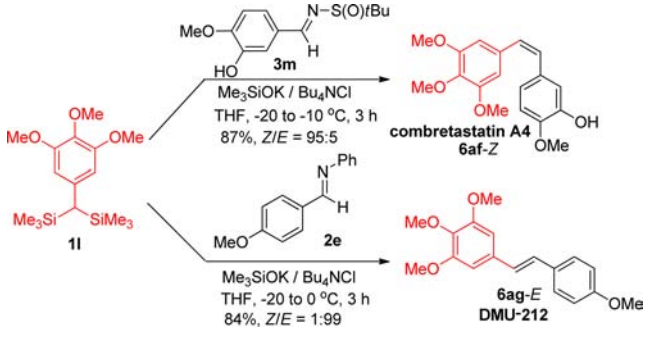
Scheme 6. *E*-Selective Olefination[a]



[a]Yield of the isolated product after chromatography; *Z*/*E* determined by ^{1}H NMR.

These results highlight that phenyl/sulfinyl imine *E*/*Z* stereocontrol is general and achievable under identical reaction conditions. This imine stereocontrolled alkene synthesis has been applied to both *Z* and *E* chemotherapeutics combretastatin A4 and DMU-212 (Scheme 7).[18,19] The reaction of ((3,4,5-

Scheme 7. *Z*-Combretastatin A4 and *E*-DMU-212



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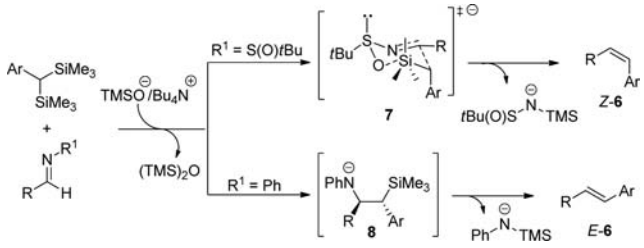
trimethoxyphenyl)methylene)bis(trimethylsilane) **1l** with sulfinylimine **3m** provided the therapeutic *Z*-**6af** in high yield and with excellent geometrical purity. Notably, the phenol group was tolerated, avoiding the need for functional group protection. Moreover, the promising anticancer agent DMU-212 was prepared from **1l** and the *E*-favoring 1-(4-methoxyphenyl)-*N*-phenylmethanimine **2e** (Scheme 7).

Identification of the exact mechanistic pivot point for *N*-sulfinyl- and *N*-phenyl imine *Z*/*E* stereocontrol requires further investigation, but some useful observational conclusions can be drawn at this stage. Based on our previous findings that addition of substituted benzyltrimethylsilanes to sulfinyl imines is highly diastereoselective,[14] it could be anticipated that (arylmethylene)-bistrimethylsilanes **1** would also be, thereby primarily setting the stereochemical outcome of the reaction at the addition step. This poses the question as to whether a four-membered 1-aza-2-silacyclobutane or a six-membered 1,2,3,6-azathiazasilinane intermediate is formed as a result of this addition. Tamao et al. have demonstrated a concerted [2 + 2] cycloreversion mechanism of substituted 1-aza-2-silacyclobutanes with retention of stereochemistry at the carbon atoms in the alkene product.[20] This would indicate that if a concerted [2 + 2] addition (as proposed for PO with carbonyls[21]) of the α-silyl carbanion with sulfinylimine was operating, the stereochemistry fixed at the addition stage would be reflected in the alkene product. Intriguingly, as *Z*-selectivity is observed for sulfinyl but not sulfonyl imines, it is also plausible that a six-membered azathiazasilinane TS (or intermediate) **7** could be operating as a lower energy alternative pathway to the four-membered azasilacyclobutane ring (Scheme 8). For *N*-aryl imines, as the

Scheme 8. Plausible Pathways for Aza-POs



thermodynamic product is being formed, addition to form the acyclic intermediate **8** with subsequent β-elimination could selectively provide the *trans*-product.

In summary, we have demonstrated highly tunable stereoselective aza-Peterson olefinations with bench-stable bis(trimethylsilanes) and imine electrophiles, with silicon activation achieved by trimethylsilyloxide in THF. Stereoselectivity of the product alkene solely depends on the nature of the imine employed. The more challenging Z-selectivity is obtained by the use of *N*-sulfinyl imine electrophiles, potentially through a unique pathway for olefination reactions. Further mechanistic investigation of both the *Z* and *E* reaction pathway(s) is ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03519.

General experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Takeda, T. *Modern Carbonyl Olefination*; Wiley-VCH, 2014.
(2) Oger, C.; Balas, L.; Durand, T. *Chem. Rev.* **2013**, *113*, 1313.
(3) Siau, W.-Y.; Zhang, Y.; Zhao, Y. *Top. Curr. Chem.* **2012**, *327*, 33.
(4) (a) Drost, R. M.; Bouwens, T.; van Leest, N. P.; de Bruin, B.; Elsevier, C. J. *ACS Catal.* **2014**, *4*, 1349. (b) Slack, E. D.; Gabriel, C. M.; Lipshutz, B. H. *Angew. Chem., Int. Ed.* **2014**, *53*, 14051.
(5) Cheung, C. W.; Zhurkin, F. E.; Hu, X. *J. Am. Chem. Soc.* **2015**, *137*, 4932.
(6) Basheer, A.; Marek, I. *Beilstein J. Org. Chem.* **2010**, *6*, 77.
(7) (a) Bronner, S. M.; Herbert, M. B.; Patel, P. R.; Marx, V. M.; Grubbs, R. H. *Chem. Sci.* **2014**, *5*, 4091. (b) Koh, M. J.; Khan, R. K. M.; Torker, S.; Yu, M.; Mikus, M. S.; Hoveyda, A. H. *Nature* **2015**, *517*, 181.
(8) (a) Zhuo, L.-G.; Yao, Z.-K.; Yu, Z.-X. *Org. Lett.* **2013**, *15*, 4634. (b) Chen, C.; Dugan, T. R.; Brennessel, W. W.; Weix, D. J.; Holland, P. L. *J. Am. Chem. Soc.* **2014**, *136*, 945.
(9) (a) Pünner, F.; Schmidt, A.; Hilt, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 1270. (b) Singh, K.; Staig, S. J.; Weaver, J. D. *J. Am. Chem. Soc.* **2014**, *136*, 5275.
(10) (a) Gu, Y.; Tian, S.-K. *Top. Curr. Chem.* **2012**, *327*, 197. (b) Dong, D.-J.; Li, Y.; Wang, J.-Q.; Tian, S.-K. *Chem. Commun.* **2011**, *47*, 2158. (c) Dong, D.-J.; Li, H.-H.; Tian, S.-K. *J. Am. Chem. Soc.* **2010**, *132*, 5018.
(11) (a) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780. (b) Hudrlik, P. F.; Peterson, D. *J. Am. Chem. Soc.* **1975**, *97*, 1464. (c) van Staden, L. F.; Gravestock, D.; Ager, D. J. *Chem. Soc. Rev.* **2002**, *31*, 195. (d) Ager, D. J. *Science of Synthesis* **2010**, *47a*, 85.
(12) Das, M.; Manvar, A.; Jacolot, M.; Blangetti, M.; Jones, R. C.; O'Shea, D. F. *Chem. - Eur. J.* **2015**, *21*, 8737.
(13) (a) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600. (b) Ferreira, F.; Botuha, C.; Chemla, F.; Perez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162.
(14) (a) Das, M.; O'Shea, D. F. *Chem. - Eur. J.* **2015**, *21*, 18717. (b) Das, M.; O'Shea, D. F. *Org. Lett.* **2015**, *17*, 1962.
(15) The addition of organotrimethylsilanes under these conditions may occur via an open transition state; see ref 14b.
(16) Manvar, A.; Fleming, P.; O'Shea, D. F. *J. Org. Chem.* **2015**, *80*, 8727.
(17) Morales, S.; Guijarro, F. G.; Garcia Ruano, J. L.; Cid, M. B. *J. Am. Chem. Soc.* **2014**, *136*, 1082.
(18) Nam, N. H. *Curr. Med. Chem.* **2003**, *10*, 1697.
(19) Ma, Z.; Molavi, O.; Haddadi, A.; Lai, R.; Gossage, R. A.; Lavasanifar, A. *Cancer Chemother. Pharmacol.* **2008**, *63*, 27.
(20) Tamao, K.; Nakagawa, Y.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 218.
(21) Hudrlik, P. F.; Agwaramgbo, E. L. O.; Hudrlik, A. M. *J. Org. Chem.* **1989**, *54*, 5613.

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Organic LETTERS

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Aqueous Compatible Protocol to Both Alkyl and Aryl Thioamide Synthesis

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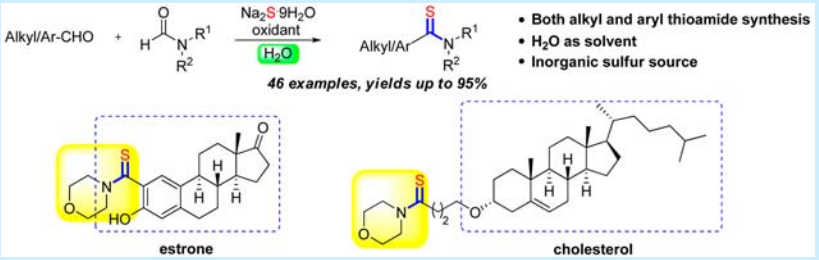
Supporting Information



ABSTRACT: An efficient aqueous synthesis of thioamides through aldehydes, sodium sulfide, and *N*-substituted formamides has been developed. Both alkyl and aryl aldehydes are amenable to this protocol. *N*-Substituted formamides are essential for this transformation. Readily available inorganic salt (sodium sulfide) serves as the sulfur source in water, which makes this method much more practical and efficient. Furthermore, the late-stage modification of bioactive molecules and derivatives through this protocol has been established.

Thioamides are prevalent organic motifs found in vital biological and pharmaceutical molecules, such as closthioamide,[1a] hydroxymethyl thiolactam cyclothialidine,[1b] and *N*-cyclohexylethyl-ETAsV,[1c] etc. (Figure 1). Meanwhile, as

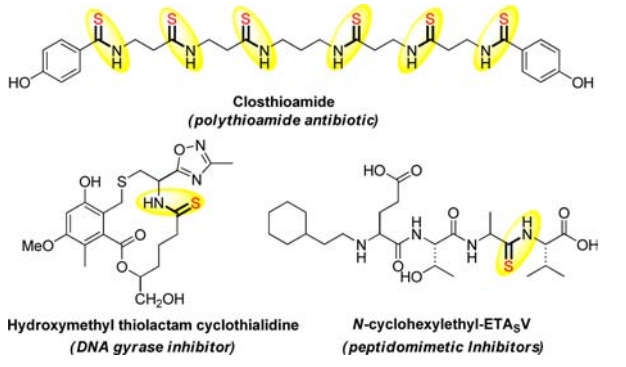
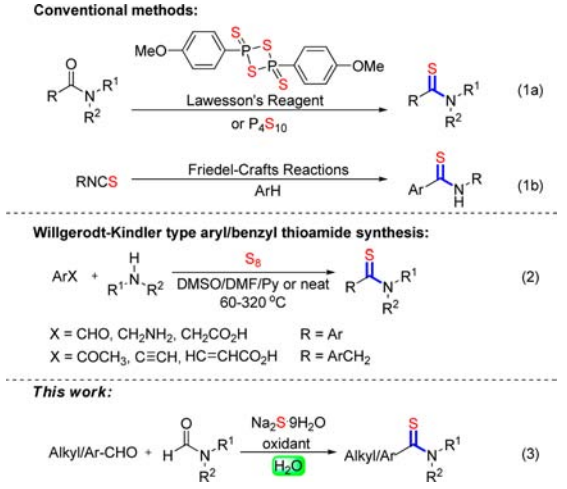


Figure 1. Representative bioactive thioamide scaffolds.

significant building blocks,[2] they are widely applied to construction of many important sulfur-containing heterocycles,[3] such as thiazolins,[3a,e] thiazolinones,[3b] thiazoles,[3c−e] tetrazoles,[3f] etc. Conventionally, Lawesson's reagent and its analogues are applied to the synthesis of thioamides (Scheme 1, eq 1a).[4] Similarly, sulfur−phosphorus-type reagents are also used to afford the thioamides through carboxylic acids[5a] or nitriles.[5b,c] Practically, isothiocyanates are employed for preparing thioamides thesis efficiently under Friedel−Crafts conditions[6]

Scheme 1. Synthetic Methods for Thioamide



(Scheme 1, eq 1b). Moreover, Willgerodt−Kindler reaction[7] is another alternative means to reach thioamides, starting from aryl aldehydes or aryl alkyl ketones. However, only aryl/benzyl thioamides can be afforded even under harsh conditions.[7c] Recently, several excellent approaches have been exploited by the Nguyen,[8a,d] Singh,[8e] and Jiang[8f] groups (Scheme 1, eq 2) that improve the approaches for the synthesis of thioamides by

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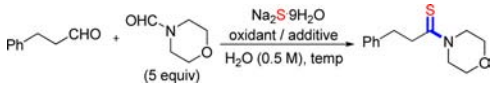
altering different types of starting materials. Therefore, the establishment of an effective, practical, and green strategy,[9] particularly for alkyl thioamides formation, remains highly desirable. Based on the development of sulfur atom transfer reactions in our laboratory,[10] we herein report a new aqueous three-component synthesis of thioamides involving alkyl and aryl aldehydes, sodium sulfide ($Na_2S{\cdot}9H_2O$), and *N*-substituted formamides (Scheme 1, eq 3).

We commenced our study by investigating 3-phenylpropanal and *N*-formylmorpholine in the presence of sodium sulfide. With the assistance of benzoyl peroxide (BPO), the desired product was found in 33% yield (Table 1, entry 1). Then, cosolvents were

Table 1. Optimization of Reaction Conditions



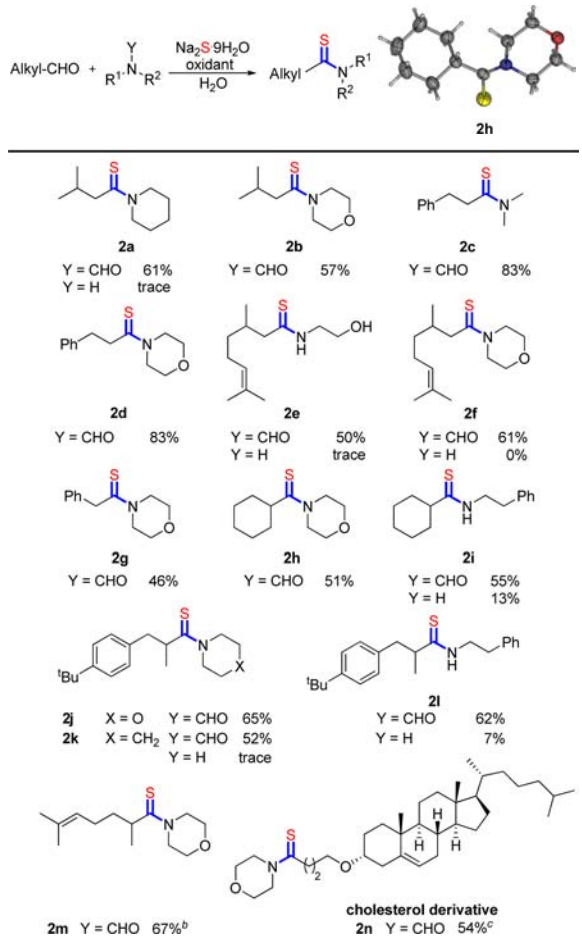
entry	$Na_2S\ 9H_2O$ (equiv)	oxidant (equiv)	additive (equiv)	temp (°C)	yield (%)[a]
1	7	BPO (5)	/	100	33
2	7	BPO (5)	DMSO (5)	100	30
3	7	BPO (5)	1,4-dioxane (5)	100	28
4	7	BPO (5)	NMP (5)	100	37
5	7	BPO (5)	Py (5)	100	42
6	3.5	BPO (2.5)	Py (5)	100	56
7	3.5	BPO (2.5)	Py (5)	100	43[b]
8	3.5	1,4-BQ(2.5)	Py (5)	100	trace
9	3.5	oxone (2)	Py (5)	100	trace
10	3.5	$K_2S_2O_8$ (2)	Py (5)	100	74
11	***3.5***	***$K_2S_2O_8$ (1.8)***	***Py (5)***	***100***	***83***
12	3.5	$K_2S_2O_8$ (1.5)	Py (5)	100	66
13	3.5	$K_2S_2O_8$ (1.8)	Py (5)	60	48
14	3.5	$K_2S_2O_8$ (1.8)	Py (5)	100	trace[c]

[a]Isolated yields. [b]*N*-Formylmorpholine (2 equiv) was used. [c]Morpholine was used instead of *N*-formylmorpholine. BPO = benzoyl peroxide; DMSO = dimethyl sulfoxide; NMP = 1-methylpyrrolidin-2-one; BQ = benzoquinone.

tested to improve the solubility, in which pyridine performed the best in 42% yield (Table 1, entry 2−5). When the amounts of $Na_2S{\cdot}9H_2O$ and BPO were reduced, the yield increased to 56% (Table 1, entry 6). There was no higher transformation when the amount of *N*-formylmorpholine (Table 1, entry 7) was reduced. Different oxidants were estimated (Table 1, entry 8−10), in which potassium persulfate ($K_2S_2O_8$) was found to be the best choice giving 74% yield. The yield was further promoted to 83% by adjusting the amount of $K_2S_2O_8$ to 1.8 equiv (Table 1, entry 11, conditions A). Remarkably, only a trace amount of product could be detected when morpholine was used instead of *N*-formylmorpholine (entry 14).

The readily oxidized alkyl aldehydes, which are big challenges in thioamide synthesis, were widely investigated under conditions A (Table 2). Different formamides and corresponding amines were surveyed under the same conditions. As shown in Table 2, a wide array of primary aldehydes worked well with *N*-substituted formamides to afford the corresponding thioamides in moderate to excellent yields (**2a**−**g**). Notably, a sensitive hydroxyl group could be tolerated in this transformation (**2e**). Moreover, the secondary aldehydes worked commendably under these conditions (**2h**−**m**). The structure was further confirmed by X-ray analysis of **2h**.[11] It is worth noting that naturally occurring aldehydes and cholesterol derivative with carbon−carbon double bonds could realize the late-stage modification[12] through this transformation, such as citronellal (**2e**, **2f**), lily aldehyde (**2j**, **2k**, **2l**), melonal (**2m**), and cholesterol derivative (**2n**), which offered a convenient method for drugs and bioactive

Table 2. Scope of Alkyl Thioamides[a]



[a]Conditions A: alkyl aldehyde (0.3 mmol), $Na_2S{\cdot}9H_2O$ (1.05 mmol), $K_2S_2O_8$ (0.54 mmol), *N*-substituted formamide (1.5 mmol), pyridine (1.5 mmol), H_2O (0.5 M), 100 °C, isolated yields. [b]60 °C. [c]H_2O/glycol = 1/1 (0.3 M).

molecule modification. These results show the excellent substrate compatibility between alkyl aldehydes and formamides.

After the generalities of alkyl aldehydes were studied, aryl aldehydes were further investigated (Table 3). In general, aryl aldehydes could be assembled with both primary formamides (**3a**−**c**) and secondary formamides (**3d**−**h**) to afford the desired products in moderate to excellent yields. Delightedly, the formamides containing sensitive hydroxyl (**3i**) and allylic groups (**3j**) could afford the thioamides in 74% and 75% yields. Meanwhile, aryl aldehydes substituted with electron-rich, -neutral, and -deficient groups (**3k**−**v**) all could afford thioamides in 52%−95% yields. The structure was further confirmed by X-ray crystallographic analysis of **3v**.[13] Thioamide with a strong electron-rich group could be obtained as well in excellent yield through this transformation (**3r**). Moreover, this method could also be applied to condensed groups, and heterocycles, such as naphthalene (**3w**), thiophene (**3x**), pyridine (**3y**), benzofuran (**3z**), benzothiophene (**3aa**), and *N*-benzylindole (**3ab**) could be afforded in excellent yields. Remarkably, bis(carbothioamide) (**3ac**) could be obtained through double thioamidation. 4-Hydroxybenzaldehyde (**3ad**), salicylaldehyde (**3ae**), and estrone derivative (**3af**) containing a free phenolic hydroxyl group could afford the desired thioamides

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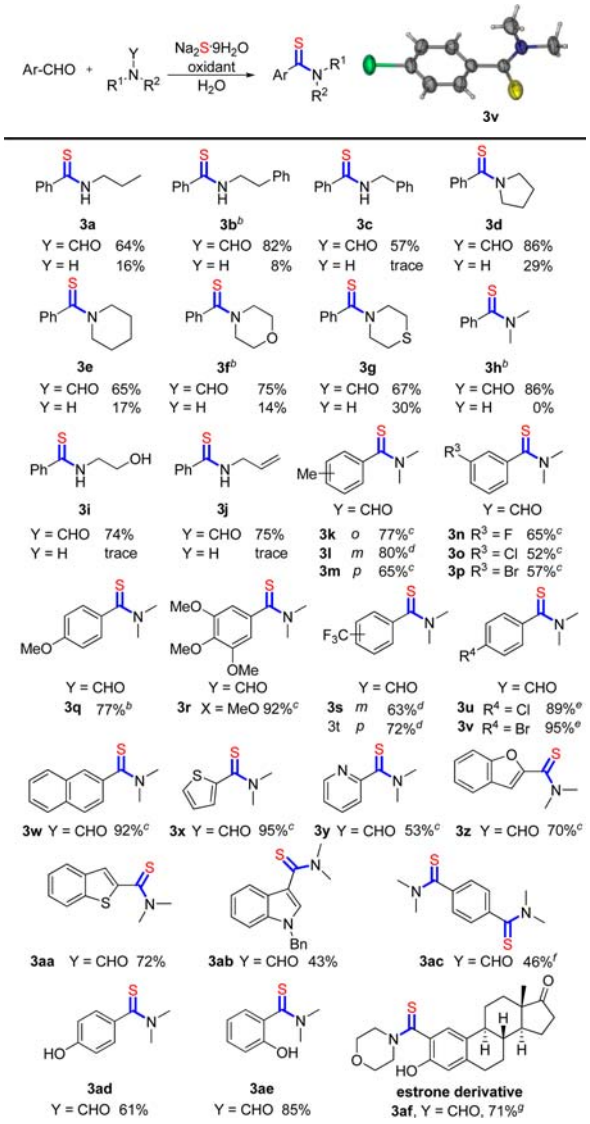
Table 3. Scope of Aryl Thioamides[a]

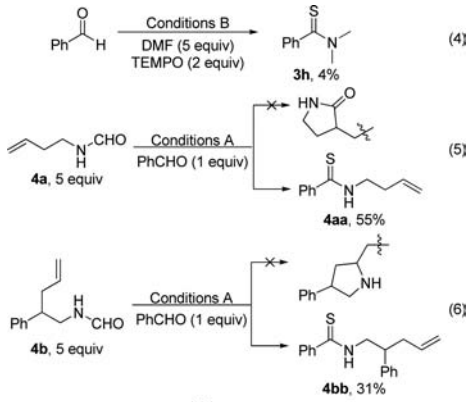


[a]Conditions A, isolated yields. [b]Conditions B: aldehyde (0.5 mmol), $Na_2S·9H_2O$ (1.75 mmol), BPO (1.25 mmol), DMF (2.5 mmol), H_2O (1 M), 100 °C. [c]Conditions B in 60 °C. [d]Aldehyde (0.5 mmol), $Na_2S·9H_2O$ (3.5 mmol), BPO (2.5 mmol), DMF (5 mmol), H_2O (0.5 M), 60 °C. [e]Aldehyde (0.5 mmol),$Na_2S·9H_2O$ (3.5 mmol), BPO (2.5 mmol), DMF (5 mmol), H_2O (0.5 M), 100 °C. [f]Aldehyde (0.3 mmol), $Na_2S·9H_2O$ (2.1 mmol), $K_2S_2O_8$ (1.08 mmol), DMF (3 mmol), pyridine (3 mmol), H_2O (0.3 M), 100 °C. [g]H_2O/glycol = 1/1 (0.3 M).

in excellent yields as well. These results show great substrate compatibility.

In order to gain mechanistic insight into this protocol, radical trapping reagent TEMPO was introduced to the reaction system, in which the formation of desired product **3h** was sharply suppressed (Scheme 2, eq 4). Furthermore, radical clock reactions were examined through designed **4a** and **4b** with benzaldehyde under the standard conditions.[14] However, thioamides (**4aa** and **4bb**) were obtained instead of cyclization products, which excluded the radical pathway to a large extent (Scheme 2, eq 5 and 6). Imine intermediate was another possibility,[8c] which was formed from aldehyde and amine. Then *N*-benzylideneprop-2-en-1-amine (**4c**) was subjected to the standard conditions with only 10% of product formation

Scheme 2. Control Experiments

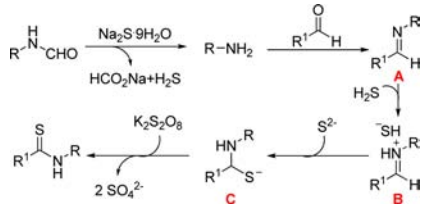


entry	[S] source (equiv)	additive (equiv)	yield of **3j** (%)
1	$Na_2S·9H_2O$ (3.5)	/	10
2	$Na_2S·9H_2O$ (3.5)	$HCO_2Na·2H_2O$ (5)	11
3	$Na_2S·9H_2O$ (3.5)	$NaH_2PO_4·2H_2O$ (3.5)	71
4	$Et_3N·H_2S$ (3.5)	/	trace
5	$Et_3N·H_2S$ (3.5) $Na_2S·9H_2O$ (3.5)	/	72

(Scheme 2, entry 1). Sodium formate was further added, affording the similar result (Scheme 2, entry 2). But when sodium dihydrogen phosphate was added to the system, **3j** was obtained in 71% yield (Scheme 2, entry 3), indicating that hydrogen sulfide generated from sodium sulfide assisting the transformation. To furtherly verify the hypothesis, triethylammonium hydrogen sulfide was examined in the system (Scheme 2, entry 4 and 5), which demonstrated that imine was activated by hydrogen sulfide and then attacked by sodium sulfide.

On the basis of the above results, the possible mechanism is proposed in Scheme 3. Amine release was achieved with the help

Scheme 3. Proposed Mechanism



of sodium sulfide (SI, part III), accompanied by sodium formate and hydrogen sulfide.[15] Imine **A** was formed with aldehyde[16] and then activated by hydrogen sulfide, forming iminium hydrogen sulfide **B**. Sulfide **B** was attacked by sulfur anion, and intermediate **C** was immediately formed, which was further oxidized by potassium persulfate to afford the desired thioamide.

In summary, we have developed an efficient aqueous method for the synthesis of thioamides involving aldehydes, sodium sulfide, and *N*-substituted formamides. Both alkyl and aryl aldehydes are amenable to this protocol with great functional group toleration. *N*-Substituted formamides are superior to the corresponding amines due to the slow release of hydrogen sulfide through the hydrolysis of formamide by sodium sulfide. Readily available inorganic salt (sodium sulfide) serves as sulfur source in water, which makes it more practical and efficient. Further studies on synthetic applications are ongoing in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03541.

Experimental procedure, NMR spectra, and X-ray and analytical data for all new compounds (PDF)
X-ray data for **2h** (CIF)
X-ray data for **3v** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Lincke, T.; Behnken, S.; Ishida, K.; Roth, M.; Hertweck, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 2011. (b) Angehrn, P.; Goetschi, E.; Gmuender, H.; Hebeisen, P.; Hennig, M.; Kuhn, B.; Luebbers, T.; Reindl, P.; Ricklin, F.; Schmitt-Hoffmann, A. *J. Med. Chem.* **2011**, *54*, 2207. (c) Bach, A.; Eildal, J. N. N.; Stuhr-Hansen, N.; Deeskamp, R.; Gottschalk, M.; Pedersen, S. W.; Kristensen, A. S.; Strømgaard, K. *J. Med. Chem.* **2011**, *54*, 1333. (d) Ebert, S. P.; Wetzel, B.; Myette, R. L.; Conseil, G.; Cole, S. P. C.; Sawada, G. A.; Loo, T. W.; Bartlett, M. C.; Clarke, D. M.; Detty, M. R. *J. Med. Chem.* **2012**, *55*, 4683.

(2) For reviews and books, see: (a) Hurd, R.; DeLaMater, G. *Chem. Rev.* **1961**, *61*, 45. (b) Jagodziński, T. S. *Chem. Rev.* **2003**, *103*, 197. (c) Velkov, Z. *Bulg. Chem. Commun.* **2003**, *35*, 227. (d) Moore, J. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier: Amsterdam, 2005; Vol. *5*, pp 519−570. (e) Haughton, E. L. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier: Amsterdam, 2005; Vol. *5*, pp 571−581. (f) Purrello, G. *Heterocycles* **2005**, *65*, 411. (g) Koketsu, M.; Ishihara, H. *Curr. Org. Synth.* **2007**, *4*, 15.

(3) For selected recent examples, see: (a) Downer, N. K.; Jackson, Y. A. *Org. Biomol. Chem.* **2004**, *2*, 3039. (b) Jaseer, E. A.; Prasad, D. J. C.; Dandapat, A.; Sekar, G. *Tetrahedron Lett.* **2010**, *51*, 5009. (c) Murai, T.; Hori, F.; Maruyama, T. *Org. Lett.* **2011**, *13*, 1718. (d) Chaudhari, P. S.; Pathare, S. P.; Akamanchi, K. G. *J. Org. Chem.* **2012**, *77*, 3716. (e) Suzuki, Y.; Iwata, M.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Org. Chem.* **2012**, *77*, 4496. (f) Gopinath, P.; Watanabe, T.; Shibasaki, M. *J. Org. Chem.* **2012**, *77*, 9260. (g) Koduri, N. D.; Scott, H.; Hileman, B.; Cox, J. D.; Coffin, M.; Glicksberg, L.; Hussaini, S. R. *Org. Lett.* **2012**, *14*, 440. (h) Okano, A.; James, R. C.; Pierce, J. G.; Xie, J.; Boger, D. L. *J. Am. Chem. Soc.* **2012**, *134*, 8790. (i) Hwang, J.; Choi, M. G.; Eor, S.; Chang, S. *Inorg. Chem.* **2012**, *51*, 1634. (j) Fukumoto, K.; Sakai, A.; Hayasaka, K.; Nakazawa, H. *Organometallics* **2013**, *32*, 2889. (k) Mukherjee, S.; Verma, H.; Chatterjee, J. *Org. Lett.* **2015**, *17*, 3150.

(4) For reviews, see: (a) Ozturk, T.; Ertas, E.; Mert, O. *Chem. Rev.* **2007**, *107*, 5210. (b) Weng, Z.; Goh, L. Y. *Acc. Chem. Res.* **2004**, *37*, 187. For selected recent examples, see: (c) Curphey, T. J. *J. Org. Chem.* **2002**, *67*, 6461. (d) Coats, S.; Link, J. S.; Hlasta, D. *Org. Lett.* **2003**, *5*, 721. (e) Kaleta, Z.; Makowski, B. T.; Soós, T.; Dembinski, R. *Org. Lett.* **2006**, *8*, 1625. (f) Szostak, M.; Aubé, J. *Chem. Commun.* **2009**, 7122. (g) Bergman, J.; Pettersson, B.; Hasimbegovic, V.; Svensson, P. H. *J. Org. Chem.* **2011**, *76*, 1546. (h) Ray, S.; Bhaumik, A.; Dutta, A.; Butcher, R. J.; Mukhopadhyay, C. *Tetrahedron Lett.* **2013**, *54*, 2164.

(5) (a) Borthakur, N.; Goswami, A. *Tetrahedron Lett.* **1995**, *36*, 6745. (b) Benner, S. A. *Tetrahedron Lett.* **1981**, *22*, 1851. (c) Manaka, A.; Sato, M. *Synth. Commun.* **2005**, *35*, 761. (d) Yadav, A. K.; Srivastava, V. P.; Yadav, L. D. S. *Tetrahedron Lett.* **2012**, *53*, 7113.

(6) (a) Friedmann, A.; Gattermann, L. *Ber. Dtsch. Chem. Ges.* **1892**, *25*, 3525. (b) Tust, K.; Gattermann, L. *Ber. Dtsch. Chem. Ges.* **1892**, *25*, 3528. (c) Jagodzinski, T.; Jagodzinska, E.; Jabłonski, Z. *Tetrahedron* **1986**, *42*, 3683. (d) Jagodzinski, T.; Jagodzińska, E.; Dziembowska, T.; Szczodrowska, B. *Bull. Soc. Chim. Belg.* **1987**, *96*, 449. (e) Jagodzinski, T. *Synthesis* **1988**, *1988*, 717. (f) Varun, B. V.; Sood, A.; Prabhu, K. R. *RSC Adv.* **2014**, *4*, 60798.

(7) (a) Willgerodt, C. *Ber. Dtsch. Chem. Ges.* **1888**, *21*, 534. (b) Kindler, K. *Liebigs Ann. Chem.* **1923**, *431*, 187. (c) Wegler, R.; Kuhle, E.; Schafer, W. *Angew. Chem.* **1958**, *70*, 351. (d) Zbruyev, O. I.; Stiasni, N.; Kappe, C. O. *J. Comb. Chem.* **2003**, *5*, 145. (e) Priebbenow, L. D.; Bolm, C. *Chem. Soc. Rev.* **2013**, *42*, 7870.

(8) (a) Nguyen, T. B.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2012**, *14*, 4274. (b) Qu, Y.; Li, Z.; Xiang, H.; Zhou, X. *Adv. Synth. Catal.* **2013**, *355*, 3141. (c) Xu, H.; Deng, H.; Li, Z.; Xiang, H.; Zhou, X. *Eur. J. Org. Chem.* **2013**, 7054. (d) Nguyen, T. B.; Tran, M. Q.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2014**, *16*, 310. (e) Guntreddi, T.; Vanjari, R.; Singh, K. N. *Org. Lett.* **2014**, *16*, 3624. (f) Sun, Y.; Jiang, H.; Wu, W.; Zeng, W.; Li, J. *Org. Biomol. Chem.* **2014**, *12*, 700.

(9) (a) Loh, T.-P.; Li, X.-R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 980. (b) Herrerías, C.; Yao, X.; Li, Z.; Li, C.-J. *Chem. Rev.* **2007**, *107*, 2546. (c) Simon, M.; Li, C.-J. *Chem. Soc. Rev.* **2012**, *41*, 1415. (d) Li, B.; Dixneuf, P. *Chem. Soc. Rev.* **2013**, *42*, 5744. (e) Kobayashi, S. *Pure Appl. Chem.* **2013**, *85*, 1089.

(10) For selected recent examples, see: (a) Qiao, Z.; Liu, H.; Xiao, X.; Fu, Y.; Wei, J.; Li, Y.; Jiang, X. *Org. Lett.* **2013**, *15*, 2594. (b) Qiao, Z.; Wei, J.; Jiang, X. *Org. Lett.* **2014**, *16*, 1212. (c) Li, Y.; Pu, J.; Jiang, X. *Org. Lett.* **2014**, *16*, 2692. (d) Zhang, Y.; Li, Y.; Zhang, X.; Jiang, X. *Chem. Commun.* **2015**, *51*, 941. (e) Xiao, X.; Feng, M.; Jiang, X. *Chem. Commun.* **2015**, *51*, 4208. (f) Qiao, Z.; Ge, N.; Jiang, X. *Chem. Commun.* **2015**, *51*, 10295. (g) Li, Y.; Xie, W.; Jiang, X. *Chem. - Eur. J.* **2015**, *21*, 16059. For reviews, see: (h) Liu, H.; Jiang, X. *Chem. - Asian J.* **2013**, *8*, 2546.

(11) CCDC-1429371 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(12) (a) Tang, P. P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 12150. (b) Wang, D.; Yu, J. *J. Am. Chem. Soc.* **2011**, *133*, 5767. (d) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369. (e) Kang, T.; Kim, Y.; Lee, D.; Wang, Z.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 4141.

(13) CCDC-1429370 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(14) (a) Elad, D.; Rokach, J. *J. Org. Chem.* **1964**, *29*, 1855. (b) Elad, D.; Rokach, J. *J. Org. Chem.* **1965**, *30*, 3361. (c) Rokach, J.; Elad, D. *J. Org. Chem.* **1966**, *31*, 4210. (d) Rosenthal, I.; Elad, D. *J. Org. Chem.* **1968**, *33*, 805. (e) Elad, D.; Sperling, J. *J. Am. Chem. Soc.* **1971**, *93*, 967. (f) Beckwith, A. L. J.; Blair, I.; Phillipou, G. *J. Am. Chem. Soc.* **1974**, *96*, 1613. (g) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. (h) Čeković, Z.; Ilijev, D. *Tetrahedron Lett.* **1988**, *29*, 1441. (i) Brown, C. E.; Neville, A. G.; Rayner, D. M.; Ingold, K. U.; Lusztyk, J. *Aust. J. Chem.* **1995**, *48*, 363. (j) Litwinienko, G.; Beckwith, A. L. J.; Ingold, K. U. *Chem. Soc. Rev.* **2011**, *40*, 2157.

(15) (a) Lockhoff, O. *Angew. Chem., Int. Ed.* **1998**, *37*, 3436. (b) Simon N. H. US 2003225069 (A1), 2003. (c) Werner, D.; Jocelyn, F.; Lisa, G.; Reinhard, K. WO 2006079504 (A2), 2006.

(16) (a) Bowman, R. K.; Johnson, J. S. *J. Org. Chem.* **2004**, *69*, 8537. (b) Jafarpour, M.; Rezaeifard, A.; Haddad, R.; Gazkar, S. *Transition Met. Chem.* **2013**, *38*, 31.

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Organic LETTERS

Addition/Correction

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Correction to "Auxiliary-Directed Pd-Catalyzed γ-C(sp^3)–H Bond Activation of α-Aminobutanoic Acid Derivatives"

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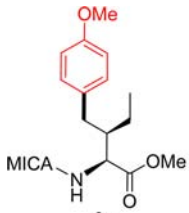
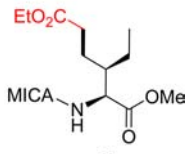
Supporting Information

In Table 2, the configuration of C3 of the two L-isoleucine-derived compounds **6a** and **6b** were drawn incorrectly. The correct structural drawings should be

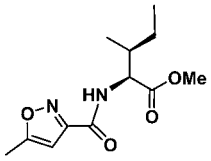


6a

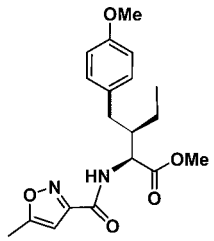


6b

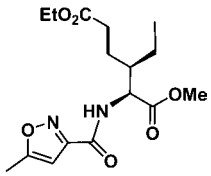
Similarly, in the Supporting Information, the configuration of C3 for all L-isoleucine-derived compounds **6**, **6a**, and **6b** were also drawn incorrectly, and the correctly drawn structures should be



6



6a



6b

Correspondingly, the configuration for C3 in the names of these compounds in the Supporting Information should also be corrected to (2*S*,3*S*)-methyl 3-methyl-2-(5-methylisoxazole-3-carboxamido)pentanoate (**6**), (2*S*,3*R*)-methyl 3-(4-methoxybenzyl)-2-(5-methylisoxazole-3-carboxamido)pentanoate (**6a**), and (2*S*,3*R*)-6-ethyl-1-methyl-3-ethyl-2-(5-methylisoxazole-3-carboxamido)hexanedioate (**6b**).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03650.

Revised file with corrected compound configurations (PDF)

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