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Metal-Free Microwave-Assisted Decarboxylative Elimination for the Synthesis of Olefins

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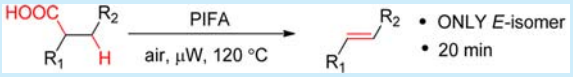
Supporting Information

ABSTRACT: A metal-free efficient synthesis of olefins via microwave-assisted direct decarboxylative elimination of arylacetic acids is described. This reaction, using commercially available reagent PIFA as oxidant, readily provides a variety of desired products in moderate to good yields.

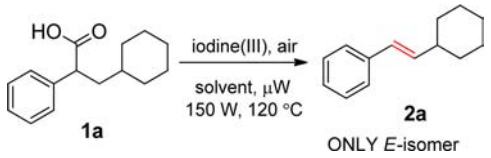


Direct decarboxylative transformations of carboxylic acids, which are usually considered as readily available, bench stable, and inexpensive feedstocks, provide a useful approach for chemical synthesis. In particular, decarboxylative couplings using transition-metal catalysts, such as Pd,[1] Ag,[2] Rh,[3] Cu,[4] and Ni,[5] have received significant attention. Recently, the utility of photoredox reagents including iridium complex[6] and Fukuzumi acridinium photooxidant[7] has emerged as an alternative strategy for direct decarboxylative functionalization of carboxylic acids.

Hypervalent iodine reagents are extensively used in organic synthesis as oxidants mainly due to their benign environmental quality, commercial availability, and easy handling. Although the efficient generation of a carbon-centered radical from a carboxylic acid is not easy, several methods for decarboxylative coupling reactions have been developed recently using iodine(III) derivatives, in combination with transition-metal[2d,8] or photoredox catalysis,[9,10] especially, Ag-catalyzed[2d] and photoinduced[10] decarboxylative alkynylation. Moreover, the iodine(III) dicarboxylate intermediates were produced in the photoredox system,[10d] followed by the formation of carbon-centered radicals. However, via a direct decarboxylative elimination of fatty acids to form olefins, there are only a few reports in which a transition-metal catalysis was employed.[11] Herein, we would like to report on metal-free direct decarboxylative elimination of arylacetic acids for the synthesis of olefins using iodine(III) reagents under microwave heat conditions.

We began by investigating the reaction parameters (Table 1). In the presence of air, commercially available iodine(III) reagents and organic solvents were screened under microwave irradiation conditions. In terms of chemical yield (only *E*-isomer found), PIFA ($PhI(OCOCF_3)_2$, phenyliodine bis(trifluoroacetate)) was determined as the best one with acetonitrile as the solvent (entries 1−6). The addition of acid or base did not improve the chemical yields (entries 7−9). When shortening the reaction time from 30 to 20 min, the chemical yield did not drop (entry 10). However, microwave irradiation for 10 min, no microwave heat, lower or higher reaction temperature, led to lower yields (entries 11−14).

Table 1. Optimization of Reaction Conditions[a]



entry	iodine(III)	solvent	*t* (min)	yield (%)[b]
1	PhIO	CH_3CN	30	<5
2	$PhI(OAc)_2$	CH_3CN	30	<5
3	PIFA	CH_3CN	30	85
4	PIFA	$PhCH_3$	30	10
5	PIFA	AcOEt	30	29
6	PIFA	DCE	30	52
7[c]	PIFA	CH_3CN	30	84
8[d]	PIFA	CH_3CN	30	40
9[e]	PIFA	CH_3CN	30	<5
10	**PIFA**	**CH_3CN**	**20**	**85**
11	PIFA	CH_3CN	10	63
12[f]	PIFA	CH_3CN	30	13
13[g]	PIFA	CH_3CN	20	<5
14[h]	PIFA	CH_3CN	20	79

[a] **1a** (0.20 mmol), iodine(III) (0.24 mmol), solvent (2 mL). [b] Isolated yield. [c] CF_3COOH (0.40 mmol). [d] *t*-BuOK (0.40 mmol). [e] K_2CO_3 (0.40 mmol). [f] Oil bath heat. [g] 100 °C. [h] 140 °C.

With the optimized reaction condition established, we first explored the substrate scope of aryl/diphenylacetic acids. As depicted in Figure 1, the reaction exhibited a broad generality, readily affording a variety of different aryl/diphenylvinyls in moderate to good yields. It should be noted that the direct decarboxylative elimination generated the sole *E*-olefins, which could be the thermodynamic products (**2b−2r**). Moreover, substituents or functional groups on the aromatic ring (**2b−2i**) or side chain (**2o−2r**) were well tolerated. We also observed that thienyl group (**2h**) or hydroxyl group (**2q**) led to a sharp

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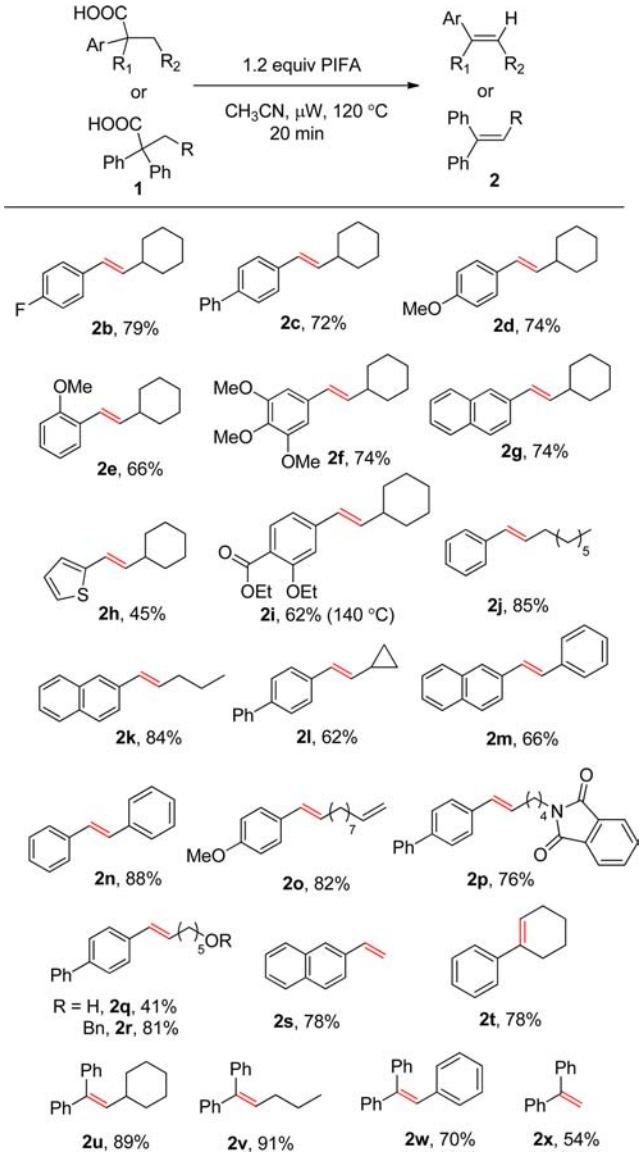
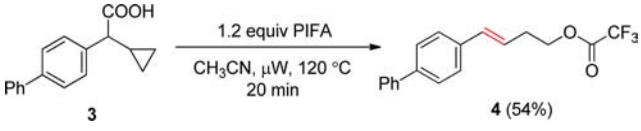


Figure 1. Substrate scope of aryl/diphenylacetic acids.

decrease of the yield. Higher reaction temperature was required to achieve olefin **2i**. When treating diphenylacetic acids with the same reaction condition, it also furnished the desired products in satisfactory yields (**2u**−**2x**).

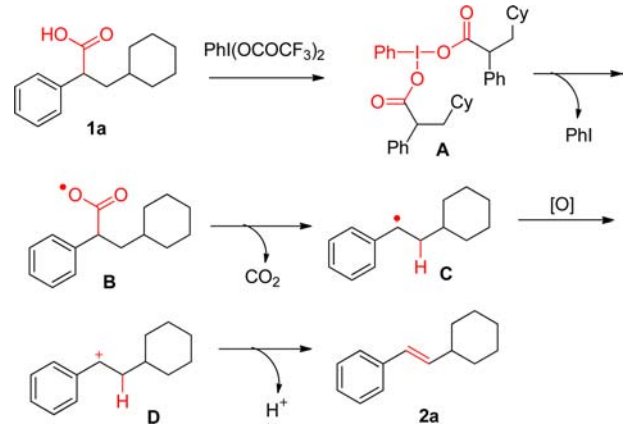
To probe the mechanism of this decarboxylative elimination, arylacetic acid **3** with a cyclopropyl group was subjected to the optimized condition (Scheme 1). This reaction gave a

Scheme 1. Reaction of Cyclopropyl Acid 3



cyclopropyl ring opening product **4**, suggesting that a radical-mediated process was involved. On the basis of the above results, a postulated mechanism is depicted in Scheme 2. The reaction of **1a** and PIFA provides iodine(III) dicarboxylate intermediate A,[9a,10d] which is liable to furnishing carboxylic radical **B**, followed by generating the corresponding carbon

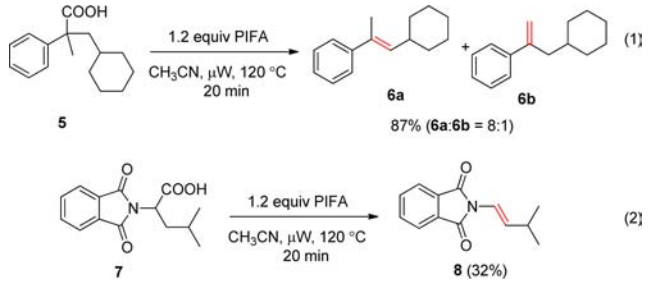
Scheme 2. Proposed Mechanism



radical C and the release of CO_2. Subsequent oxidation[8] and elimination give corresponding olefin **2a**.

In addition, we conducted the decarboxylative elimination of substrate **5**, which could be subject to proton leaving at the methyl site or methylene site (Scheme 3, eq 1). As expected,

Scheme 3. Reactions of 5 and 7



this reaction afforded an inseparable mixture of **6a** and **6b** with fair regioselectivity. Using phthalimide-protected amino acid instead of arylacetic acid as the substrate (Scheme 3, eq 2) also afforded the desired olefin **8**.

In conclusion, we have developed the first example of a metal-free direct decarboxylative elimination for the synthesis of olefins under microwave irradiation conditions. The reaction, in the presence of commercially available PIFA, readily afforded a variety of aryl/diphenylvinyls in moderate to good yields. Preliminary mechanistic investigations suggested a radical process could be involved in the decarboxylative elimination reaction.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03069.

Experimental details, characterizations, and copies of ^1H and ^{13}C NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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One-Pot Synthesis of (*S*)-Baclofen via Aldol Condensation of Acetaldehyde with Diphenylprolinol Silyl Ether Mediated Asymmetric Michael Reaction as a Key Step

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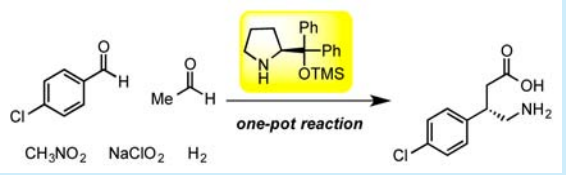
Supporting Information

ABSTRACT: An efficient asymmetric total synthesis of (*S*)-baclofen was accomplished via a one-pot operation from commercially available materials using sequential reactions, such as aldol condensation of acetaldehyde, diphenylprolinol silyl ether mediated asymmetric Michael reaction of nitromethane, Kraus–Pinnick oxidation, and Raney Ni reduction. Highly enantioenriched baclofen was obtained in one pot with a good yield over four reactions.

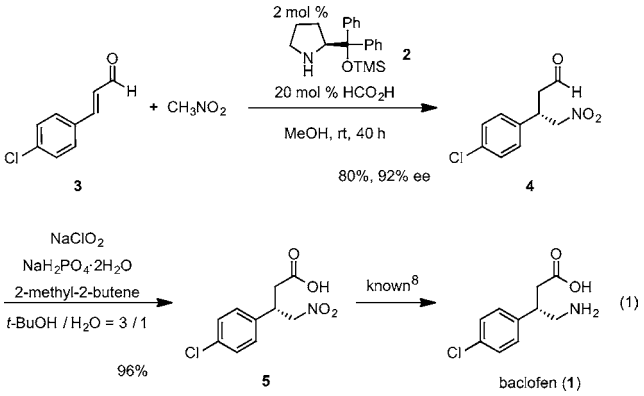


One-pot operations are effective methods for both carrying out several transformations and forming several bonds in a single pot, while at the same time cutting out several purifications, minimizing chemical waste generation, and saving time. Thus, a one-pot reaction can be not only efficient but also green and environmentally friendly, and "pot economy"[1] should be one of the important economies in the synthesis of molecules. However, one-pot reactions are challenging because subsequent reactions have to be conducted in the presence of the products generated in the previous reactions, which might interfere with the desired successive reactions.[2]

We have a continuing interest in making natural products and drugs via one-pot procedures, and we previously accomplished a one-pot synthesis of (−)-oseltamivir,[3] one-pot synthesis of ABT-341,[2] and three-pot synthesis of prostaglandin A_1 and E_1 methyl esters,[1c] all of which use the organocatalyst mediated asymmetric Michael reaction as a key step. It is a synthetic challenge to make a drug with a chiral center via a one-pot operation from readily available materials.

Baclofen (**1**) is a potent $GABA_B$ receptor agonist used for the treatment of spinal cord injury induced spasm.[4] Although the racemic compound is used in clinical practice, the *R*-enantiomer is the actual active species, the synthesis of which has been actively investigated.[5] A two-pot synthesis of baclofen was reported using organic–inorganic hybrid catalysts with moderate enantioselectivity (70% ee).[6] Recently, Kobayashi and co-workers reported an excellent asymmetric synthesis of rolipram, which has a similar structure to baclofen, via a one-flow method.[7]

We have previously reported the formal asymmetric synthesis of baclofen based on an organocatalyst mediated asymmetric reaction[8] (eq 1). The asymmetric Michael reaction of nitromethane with 3-(*p*-chlorophenyl)propenal (**3**) catalyzed by diphenylprolinol silyl ether **2**, which has been independently developed by our group[9] and Jørgensen's group,[10] afforded γ-nitroaldehyde **4** with excellent enantioselectivity. Oxidation of aldehyde **4** provided carboxylic acid **5**, a known intermediate of baclofen (**1**).



There are two key concerns in preparing (*S*)-baclofen from the commercially available materials via a one-pot operation. (1) Is there a method for the synthesis of α,β-unsaturated aldehydes that is suitable for the first step of the one-pot reaction? (2) Does each subsequent reaction proceed in the one-pot procedure with the same efficiency as the reaction using isolated starting material?

The first problem is a transformation of *p*-chlorobenzaldehyde into 3-(*p*-chlorophenyl)propenal with two-carbon homologation. Many methods are known for this basic chain extension,[11] such as the Horner–Wadsworth–Emmons reaction of phosphonate imine,[12] phosphonate hydrazone,[13] aldol reaction using a combination of vinyl acetate and $Ba(OH)_2$,[14] reaction with C-silylated imines,[15] and a Peterson-type reaction using silyl aldimines.[16] Starting from ethoxy acetylene, vinyl lithium,[17] vinyl Zr,[18] and vinyl Zn[19] reagents have been

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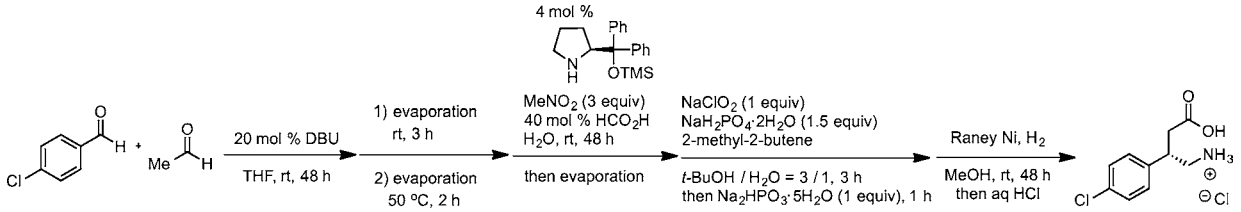
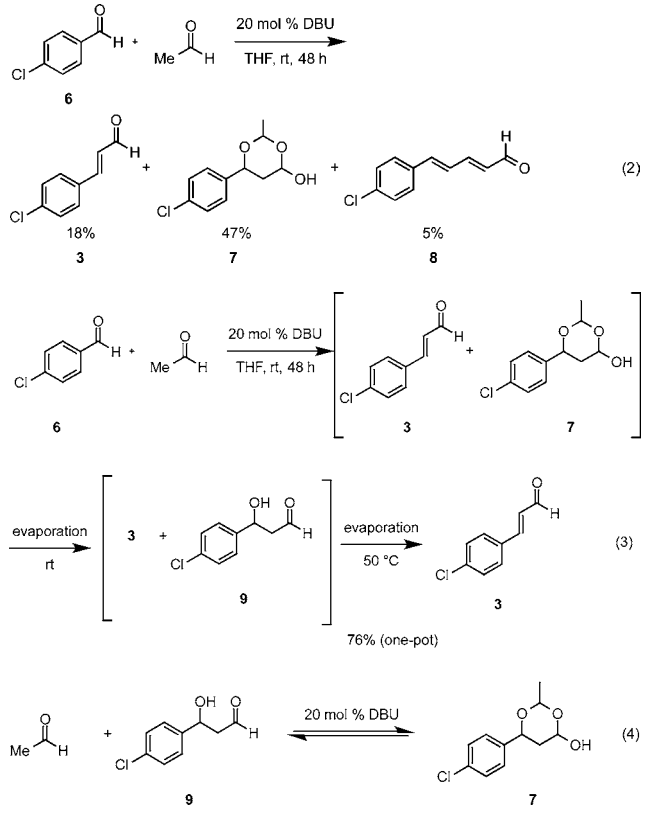
Scheme 1



successfully employed for this transformation. None of these methods, however, are applicable to the first reaction of a one-pot operation because aqueous workup is necessary, or generated byproducts or remaining reagents would interfere with subsequent reactions. In particular, the subsequent reaction is a catalytic asymmetric reaction, and there is a possibility that even a small amount of byproduct or remaining reagents would decrease the enantioselectivity.

We thought that an ideal method would be aldol condensation of acetaldehyde because an equivalent amount of water is the only byproduct. However, this is a difficult reaction, as the obtained product also possesses a formyl moiety, which reacts further with the other nucleophile. Only aqueous NaOH is known to promote this reaction as far as we were aware.[20]

We have reported that amines such as diarylprolinols promote the asymmetric aldol reaction of acetaldehyde,[21,22] which indicates that an amine catalyst would promote the aldol condensation. A range of amine catalysts were screened: pyrrolidine, which is a basic skeleton of diarylprolinol, gave a complex mixture. While no reaction proceeded in the presence of pyridine, DABCO, DMAP, and K_2CO_3, the desired product **3** was obtained in DBU along with acetal **7** and dienal **8** (eq 2). Although Et_3N and *i*-Pr_2NEt also afforded the product, the reaction was slow. Solvent screening (THF, DMF, toluene, MeOH, and CH_2Cl_2) indicated that THF was the preferred solvent. Although we could not obtain the desired *α,β*-enal **3** in good yield because of the generation of acetal **7**, the successful conversion of acetal **7** into **3** would make the one-pot synthesis of *α,β*-enal **3** possible. After extensive experimentation, we were pleased to find the following conditions (eq 3): aldol reaction was performed in the presence of DBU (20 mol %) to afford *α,β*-enal **3** and acetal **7**. Two evaporations, first at room temperature then at 50 °C, gave desired *α,β*-enal **3** in good yield (76%) in one pot. The reaction proceeds as follows. The aldol product **9**, acetaldehyde, and acetal **7** were under equilibration (eq 4). While acetaldehyde was removed under the reduced pressure at the first evaporation at room temperature, this equilibration shifts to the left with retro-acetalization to convert acetal **7** into **9**. Dehydration from aldol product **9** proceeds at 50 °C in the presence of DBU to provide the desired *α,β*-enal **3** in good yield. If the evaporation was carried out at 50 °C from the beginning without doing it at room temperature, a second aldol reaction of *α,β*-enal **3** with acetaldehyde also proceeded to provide a substantial amount of dienal **8**.



The next step was the asymmetric Michael reaction of nitromethane (Scheme 1). Because we used DBU in THF in the first reaction, the next asymmetric Michael reaction had to be conducted in the presence of DBU, which might interfere with the asymmetric reaction because DBU is a stronger base than diphenylprolinol silyl ether. Moreover, the solvent should be optimized because a protic solvent such as MeOH is the best solvent in the asymmetric Michael reaction.[8] After thorough optimization of reaction conditions, the reaction was found to proceed efficiently without sacrificing enantioselectivity, using formic acid as an additive, which reduced the basicity of the DBU by the protonation, in a mixture of THF and water.[23] That is, after the first aldol condensation reaction of acetaldehyde using DBU (20 mol %) for 48 h, nitromethane (3 equiv), diphenylprolinol silyl ether (4 mol %), HCO_2H (40 mol %), and water were added to the reaction vessel, and the asymmetric Michael reaction proceeded at room temperature for 48 h to afford the Michael product **4**. The enantioselectivity was found to be 95% when the reaction was stopped.

Subsequent transformations were also performed in the same flask. After removal of solvent and nitromethane under reduced pressure, Kraus−Pinnick oxidation[24] was successfully performed in aqueous *t*-BuOH to afford carboxylic acid **5**. After addition of $Na_2HPO_3·5H_2O$ to reduce unreacted $NaClO_2$, the reduction of the nitro group to the amine was carried out using

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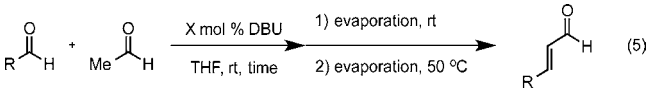
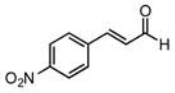
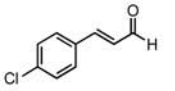
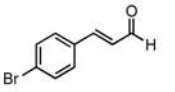
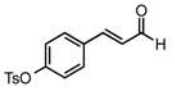
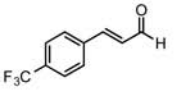
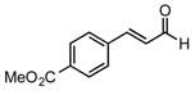
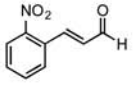
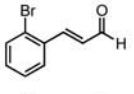
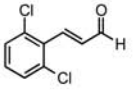
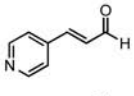
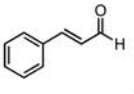
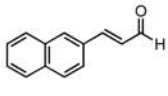
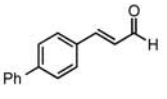
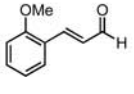
Table 1. One-Pot Synthesis of α,β-Unsaturated Aldehydes via Two-Carbon Homologation[a]



entry	product	X (mol %)[b]	time (h)[c]	yield (%)[d]
1		10	19	82
2		20	48	76
3		20	20	70
4		20	33	62
5		20	60	65
6		20	33	74
7		20	21	71
8		20	29	76
9		20	46	80
10		10	15	60
11		20	48	63
12		20	14	75
13		20	20	53
14		20	100	53

[a]Unless otherwise noted, the reaction was performed by employing aldehyde (0.5 mmol), acetaldehyde (2.5 mmol), and DBU (0.1 mmol) in THF (0.5 mL) at room temperature for the indicated time. See Supporting Information for details. [b]Amount of DBU. [c]Reaction time for the first aldol reaction. [d]Isolated yield.

Raney Ni under a H_2 atmosphere to provide the baclofen hydrochloride salt by the addition of HCl.

All of the transformations can be carried out in a one-pot operation to afford the product in 31% total yield (93% ee) over four steps (75% per step), starting from 3 g of *p*-chlorobenzaldehyde.

Because the first aldol condensation reaction of acetaldehyde for the synthesis of α,β-enal is synthetically useful, the generality of the reaction was investigated (Table 1). The reaction is effective, with aromatic aldehydes containing electron-deficient substituents; *p*-nitro-, *p*-chloro-, *p*-bromo-, *p*-toluenesulfonyloxy-, *p*-trifluoromethyl-, and *p*-methoxycarbonyl-substituted benzaldehyde are all suitable substrates to afford α,β-unsaturated aldehydes in good yields (entries 1−6). Benzaldehyde derivatives with an electron-deficient substituent at the *o*-position, such as *o*-nitrobenzaldehyde and *o*-bromobenzaldehyde, afforded α,β-enals in good yields (entries 7 and 8). The reaction proceeded efficiently in the reactions of 2,6-dichlorobenzaldehyde and heteroaromatic aldehydes such as pyridine-4-carbaldehyde (entries 9 and 10). Aromatic aldehydes without an electron-deficient substituent, such as benzaldehyde, 2-naphthaldehyde, and 4-biphenylcarbaldehyde, can also be used as suitable electrophiles (entries 11−13). An aromatic aldehyde with an electron-donating substituent is not a good substrate. The desired product was obtained in 53% yield after 100 h in the reaction of *o*-anisaldehyde (entry 14), and no reaction proceeded in the case of *p*-anisaldehyde. A self-aldol reaction proceeded in the case of an aliphatic aldehyde such as 3-phenylpropanal.

In summary, an efficient asymmetric synthesis of (*S*)-baclofen was accomplished via a one-pot operation with a total yield of 31% on a gram scale. All of the reagents are commercially available and cheap. It is one of the most efficient methods for the preparation of (*S*)-baclofen. The synthesis has several noteworthy features. Aldol condensation of acetaldehyde catalyzed by DBU is a straightforward and efficient method for the preparation of α,β-unsaturated aldehydes from the corresponding aldehydes. Asymmetric Michael reaction of nitromethane catalyzed by diphenylprolinol silyl ether is robust and is not interfered with in the presence of a strong base such as DBU by the addition of formic acid. Kraus−Pinnick oxidation and Raney Ni reduction in the same pot proceeded smoothly despite the presence of several byproducts that were generated in the previous reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02839.

Experimental procedures and analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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(*R*)-baclofen was changed to (*S*)-baclofen in the text and Supporting Information on December 14, 2015.

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Intermolecular Cyclopropanation of Styrenes Using Iodine and Visible Light via Carbon–Iodine Bond Cleavage

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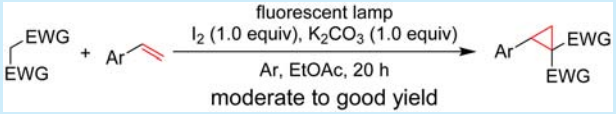
Supporting Information

ABSTRACT: The intermolecular cyclopropanation of aromatic olefins with activated methylene compounds using iodine and visible light irradiation was described. This reaction proceeds under rare-metal-free conditions. Styrenes with various substituted groups (alkyl and electron-withdrawing groups) provided corresponding cyclopropanes in moderate to good yields.

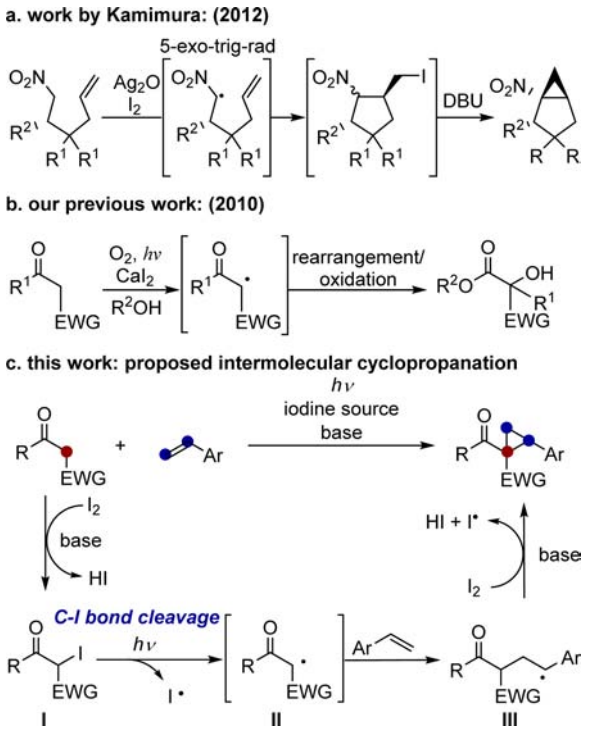


Functionalized cyclopropanes are an important class of organic compounds because of their unique biological activities[1] and physical properties.[2] They have also been applied as important synthetic intermediates in cyclopentannulation via metal-catalyzed ring-opening reactions.[3] Therefore, the development of methods for the synthesis of members of this class is highly important. Hence, a large number of synthesis methods to access fused cyclopropanes have been developed.[4] Furthermore, the total synthesis of naturally occurring products containing cyclopropanes, such as Solanoeclepin A[5] and Mycorrhizin,[6] has been achieved. To prepare cyclopropane units, chemists can employ commonly developed methods, including transition metal catalyzed carbene[7] insertion into alkenes,[8] Simmons–Smith reactions,[9] Corey–Chaykovsky reactions,[10] Kulinkovich–de Meijere reactions,[11] and Michael-initiated ring-closure (MIRC) reactions.[12] In 2012, a silver- and iodine-mediated radical pathway was reported by Kamimura for the intramolecular construction of cyclopropanes from nitromethane derivatives (Scheme 1a).[13] This reaction proceeds with an unconjugated alkene. However, no conditions that produce intermolecular reaction products have yet been found. There we have speculated on the ability to realize the intermolecular cyclopropanation with a radical pathway.

In our laboratory, a unique photo-oxidative approach based on the ability of iodine, which led to the formation of tartaric acids from β-ketoesters via tandem oxidation/rearrangement reaction, has been introduced (Scheme 1b).[14] Visible light irradiation of the iodinated intermediate induced homolytic carbon–iodine bond cleavage, allowing access to radical species under moderate conditions. This reactivity enabled the development of light-driven cyclopropanation of active methylene compounds using styrenes, a process that could not be realized under thermal activation (Scheme 1c).

Herein, we investigate the intermolecular cyclopropanation of styrenes with active methylene compounds, mediated by molecular iodine. This study demonstrates that a radical intermediate (II), generated upon photoinduced homolytic carbon–iodine bond cleavage of an iodinated starting material I, can serve as a suitable precursor (III) for cyclopropanation resulting from radical addition of II to styrenes.

Scheme 1. Proposed Photomediated Construction of Cyclopropanes



We examined the reaction of ethyl cyanoacetate (**1a**) with styrene (**2a**) in ethyl acetate under visible light irradiation. Only a trace amount of the cyclopropanated product (**3a**) was detected when **1a** and **2a** were reacted in the presence of calcium iodide or magnesium iodide (Table 1, entries 1 and 2). Fortunately, in the presence of iodine, the reaction occurred and gave the desired cyclopropane in 66% yield (entry 3). Changing the amount of iodine drastically decreased the yield

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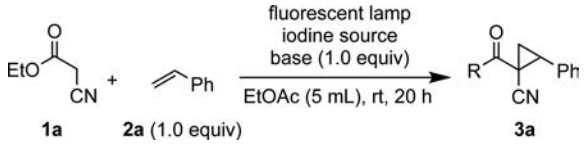
Table 1. Optimization of the Reaction Conditions



entry	iodine source (equiv)	base	solvent	yield (%)[a]	dr[b]
1	CaI_2 (1.0)	K_2CO_3	EtOAc	trace	–
2	MgI_2 (1.0)	K_2CO_3	EtOAc	0	–
3	I_2 (1.0)	K_2CO_3	EtOAc	66	4.5:1
4	I_2 (0.2)	K_2CO_3	EtOAc	12	4.5:1
5	I_2 (2.0)	K_2CO_3	EtOAc	46	6:1
6	I_2 (1.0)	Cs_2CO_3	EtOAc	66	6.5:1
7	I_2 (1.0)	KOH	EtOAc	58	5.5:1
8	I_2 (1.0)	CsOAc	EtOAc	trace	–
9	I_2 (1.0)	pyridine	EtOAc	17	4:1
10	I_2 (1.0)	Et_3N	EtOAc	trace	–
11	–	K_2CO_3	EtOAc	0	–
12	I_2 (1.0)	–	EtOAc	0	–
13	I_2 (1.0)	K_2CO_3	^{n}Hexane	31	4:1
14	I_2 (1.0)	K_2CO_3	$CHCl_3$	10	5:1
15	I_2 (1.0)	K_2CO_3	MeCN	52	7:1
16	I_2 (1.0)	K_2CO_3	DMF	45	6:1
17[c]	**I_2 (1.0)**	**K_2CO_3**	**EtOAc**	**80 (86)**	**5:1**

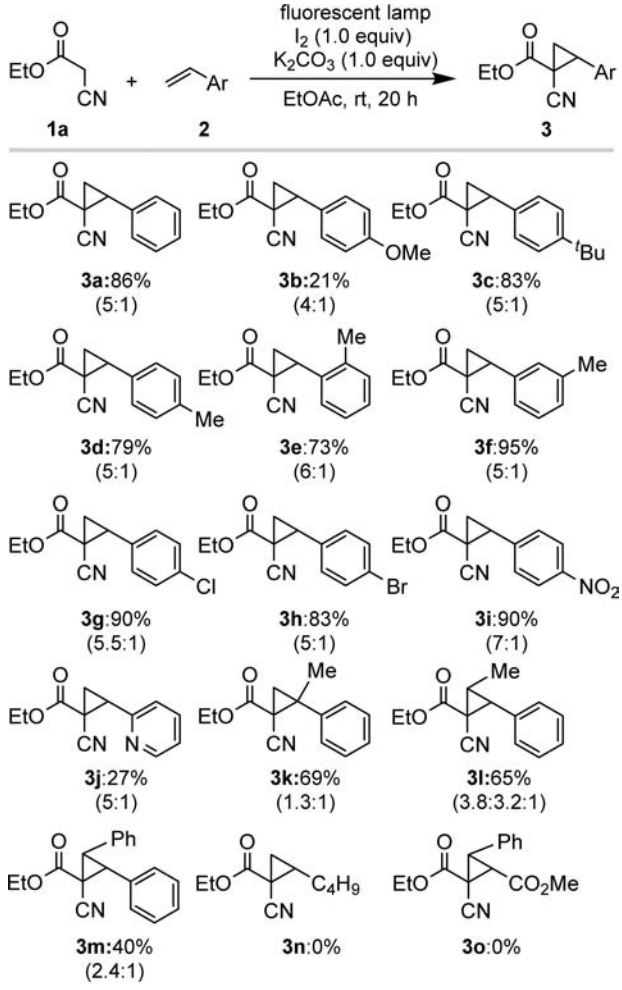
[a]Yield was determined by ^{1}H NMR analysis of the crude reaction mixture. The number in parentheses is the isolated yield. [b]The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Reaction carried out with 3 mL of EtOAc and 3 equiv of styrene.

of the desired product (entries 4 and 5). Among the different bases examined, K_2CO_3 was found to be the best base (entries 6–10). Conversely, performing the reaction in the absence of either iodine or base led to no detectable product (entries 11 and 12). Subsequent screening for the best solvent showed EtOAc to be the best solvent (entries 13–16). Finally, fine-tuning the ratio of **1a** and **2a** as well as the concentration of the solvent proved to give the best results, giving the product (**3a**) in 86% isolated yield (entry 17).

After obtaining optimized reaction conditions, we then explored the reaction scope and limitations. First, we investigated a variety of styrenes (**2**) to assess their ability to react with ethyl cyanoacetate (**1a**) (Scheme 2). Styrenes with an electron-donating group showed poor reactivity and gave the cyclopropanated product (**3b**) in 21% yield. Styrenes bearing alkyl groups at the ortho, meta, and para positions reacted well with **1a** to give the corresponding cyclopropanes (**3c–3f**) in good yield. Higher yields of cyclopropanes **3g–3i** were obtained when various styrenes substituted with electron-withdrawing groups were employed in this transformation. However, the product yields dropped drastically when 2-vinylpyridine was used as the starting material. Alpha or beta substituted styrenes gave corresponding cyclopropanes (**3k–3m**) in moderate yields. An attempt to extend this reaction system to olefin-bearing alkyl substituents was not successful; no cyclopropanated product (**3n**) was observed for a 1-hexene substituted styrene. Also, cinnnamate did not react with **1a** and only starting material was observed.

Diverse active methylene compounds (**1**) were next examined to study the scope of this methodology (Scheme 3). At the outset, active methylene compounds possessing a nitrile group and other electron-withdrawing groups were

Scheme 2. Synthesis of Cyclopropanes (3) Using Various Styrenes (2)[a]



[a]General conditions: **1a** (0.30 mmol), **2** (0.90 mmol), I_2 (0.3 mmol), and K_2CO_3 in EtOAc (3 mL) at rt for 20 h under an Ar atmosphere and visible light irradiation. Yields refer to the isolated yield. Numbers in parentheses refer to the diastereomeric ratio, and the ratios were determined by ^{1}H NMR analysis of the crude reaction mixture.

employed to evaluate the ability of our method. Methyl cyanoacetate provided the desired product (**3p**) in good yield. When acyloyl acetonitriles were investigated as the substrates for this reaction, all the cyclopropanated products (**3q–3s**) were obtained in good yield. Moreover, this reaction could be applied to other active methylene compounds, such as malononitrile and dimethyl malonate, providing the corresponding cyclopropanes **3t** and **3u** in 75% and 51% yield, respectively. However, the reaction of styrene (**2a**) with 2-nitroacetophenone resulted in a lower yield. In addition, the reaction of benzyl cyanide with styrene (**2a**) was unsuccessful, leading to a complex mixture, and no desired product (**3w**) was obtained.

To further investigate the primary reaction mechanism, several controlled experiments were performed (Scheme 4). First, we attempted the reaction of ethyl cyanoacetate (**1a**) with styrene (**2a**) under dark reaction conditions, and a significantly lower yield of the desired product (**3a**) was observed (Scheme 4, eq 1). Second, when TEMPO (1.0 equiv) was added under the optimized reaction conditions, the reaction could not produce **3a**, possibly due to the fact that the radical

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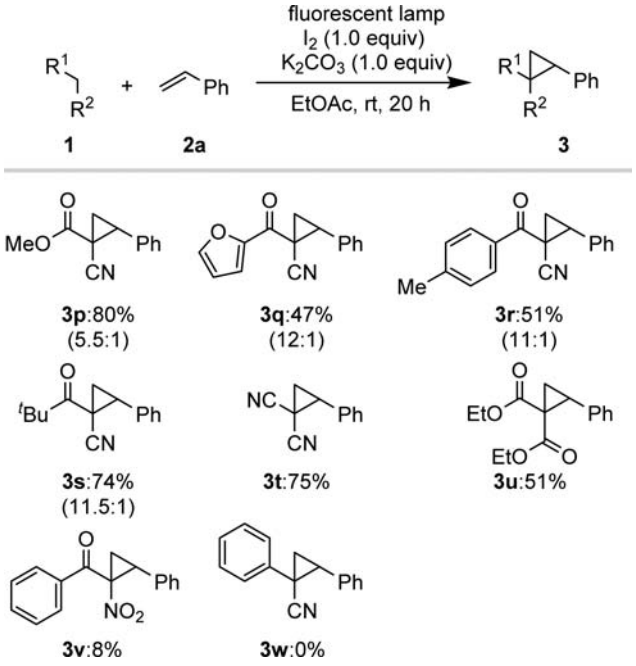
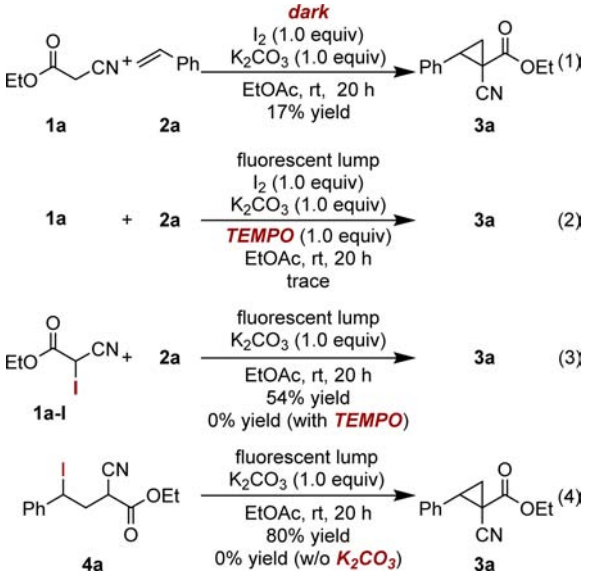
Scheme 3. Synthesis of Cyclopropanes (3) Using Various Active Methylene Compounds (1)[a]



[a]General conditions: **1** (0.30 mmol), **2a** (0.90 mmol), I_2 (0.3 mmol), and K_2CO_3 in EtOAc (3 mL) at rt for 20 h under an Ar atmosphere and visible light irradiation. Yields refer to the isolated yield. Numbers in parentheses refer to the diastereomeric ratio, and the ratios were determined by ^{1}H NMR analysis of the crude reaction mixture.

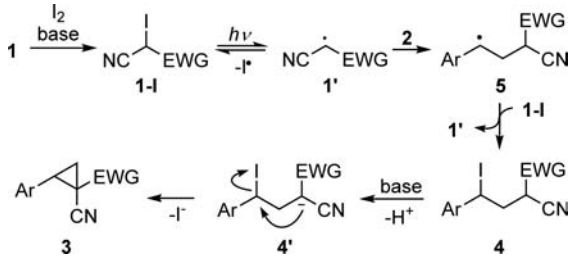
Scheme 4. Controlled Experiments



intermediate that formed was blocked by the TEMPO and, thus, could not aid cyclization (Scheme 4, eq 2). The above-mentioned results clearly indicated that the visible light irradiation played a significant role in forming the radical intermediate and that the reaction proceeded via a radical pathway. Moreover, we prepared iodinated ethyl cyanoacetate (**1a−I**) and performed the photoinduced cyclopropanation of **1a−I** with **2a** under our optimized reaction conditions without iodine; a 54% yield of the desired product (**3a**) was observed (Scheme 4, eq 3). Furthermore, the reaction of **2a** with TEMPO under our reaction conditions could not furnish the desired product. These experiments suggested that the homolytic carbon−iodine bond cleavage to form the radical intermediate could be involved in the transformation under standard conditions. To gain insight into the cyclization mechanism of this reaction, an iodinated precursor (**4a**) was used under the standard conditions (Scheme 4, eq 4). The results indicated that no cyclization product was formed when the reaction was performed without potassium carbonate. Unfortunately, precursor **4** was not observed under the standard condition in all cases.

From the above-mentioned experimental results, we proposed a possible reaction mechanism that involved a photoinduced homolytic carbon−iodine bond cleavage process (Scheme 5). First, a radical intermediate **1′** was formed by the

Scheme 5. Plausible Reaction Mechanism for the Cyclopropanation



base-assisted iodination of **1**, followed by the photoinduced homolytic carbon−iodine bond cleavage of **1−I**. The generated carbon radical then attacks the alkene, producing intermediate **5**, which abstracts the I atom from **1−I** to generate radical **1′** and intermediate **4** in a chain reaction. Finally, 3-exo-tet cyclization of **4** occurs to form the desired cyclopropane (**3**).

In conclusion, we have successfully developed a highly efficient photoinduced intermolecular reaction of active methylene compounds with styrenes, mediated by iodine for the straightforward synthesis of cyclopropanes, which are important and useful intermediates in organic chemistry. A general reaction mechanism has been proposed involving the generation of a radical intermediate via photoinduced homolytic carbon−iodine bond cleavage, which could be further applied for various types of reactions. Moreover, the corresponding cyclopropane products could be obtained under rare-metal-free conditions, constituting a green chemistry approach for the synthesis of cyclopropane derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02957.

General experimental procedure and compound characterization data (PDF)

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Organic LETTERS

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Chiral 2 + 3 Keto-Enamine Pseudocyclophanes Derived from 1,3,5-Triformylphloroglucinol

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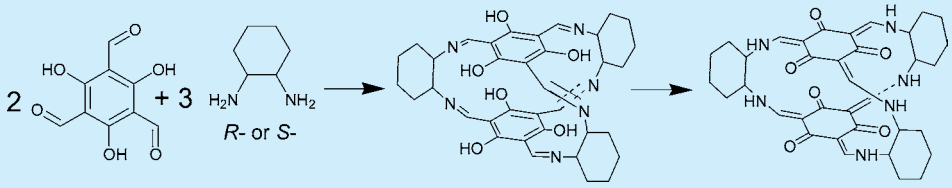
Supporting Information



ABSTRACT: The reactions of 1,3,5-triformylphloroglucinol with (1*R*,2*R*)-1,2-diaminocyclohexane, (1*R*,2*R*)-1,2-diphenylethylenediamine, or (*R*)-2,2′-diamino-1,1′-binaphthyl result in the formation of enantiopure [2 + 3] keto-enamine condensation products, in contrast to analogous reactions of 1,3,5-triformylbenzene, where [4 + 6] Schiff base cages are formed. The X-ray crystal structure of the diaminocyclohexane 2 + 3 derivative as well as modeled structures of other compounds of this type show cyclophane-like molecules with close contact between the phloroglucinol rings. Density Functional Theory (DFT) calculations confirm that there is a sizable $\pi-\pi$ interaction between these rings influencing the conformation of these molecules.

The condensation of 1,3,5-triformylbenzene with (1*R*,2*R*)-1,2-diaminocyclohexane or other chiral diamines results in interesting [4 + 6] cage imines,[1−3] such as compound **1** (Figure 1), that exhibit unique guest binding and gas sorption properties,

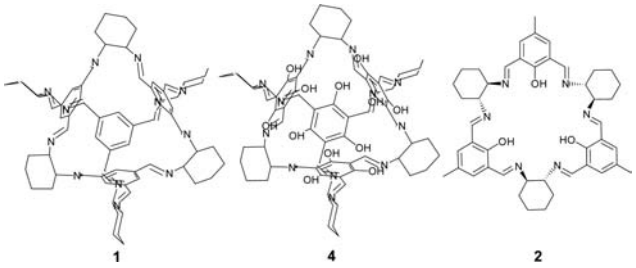


Figure 1. Structures of the [4 + 6] cage **1**, a putative [4 + 6] cage **4** and the [3 + 3] macrocycle **2**.

as demonstrated by Cooper et al.[2,3] On the other hand, the condensation of aromatic dialdehydes with the same chiral diamines often leads to [3 + 3] imine macrocycles, which, together with their amine counterparts, act as hosts for metal ions as well as organic molecules.[4,5] In particular the condensation of 2,6-diformylphenols with chiral diamines results in the formation of [3 + 3] Schiff bases such as **2**. These macrocycles and their amine counterparts form interesting trinuclear metal complexes.[5] In contrast, the [4 + 6] cage **1** seems to be a relatively poor ligand for polychelate binding of metal ions. To date, no metal complexes of these imine cages have been reported, while a reduced amine-type [4 + 6] cage derived from 1,3,5-triformylbenzene and ethylenediamine forms a metal−organic framework (MOF) coordination polymer with zinc(II) clusters.[6]

Inspired by the elegance of the [4 + 6] cages derived from 1,3,5-triformylbenzene, we have envisaged that the introduction of additional coordinating groups to **1** will create an organic molecule that will allow for "three-dimensional" extension of "two-dimensional" coordination chemistry of [3 + 3] macrocycles (Figures 1, 2). For this purpose we have chosen 1,3,5-

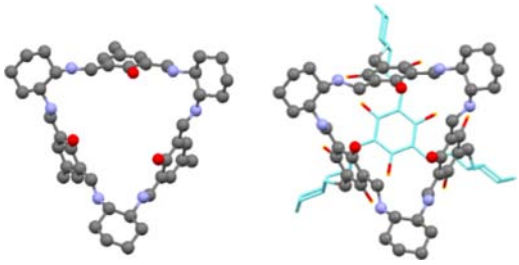


Figure 2. Comparison of the X-ray crystal structure[7] of macrocycle **2** (left) with one of the faces of the modeled structure of the putative cage **4** (right).

triformylphloroglucinol **3** as the starting carbonyl compound for the synthesis of a hypothetical compound **4** and similar cages. In these new molecules, each face of the tetrahedral cage would correspond to a [3 + 3] triphenolic macrocycle. In particular, the modeled structure of the [4 + 6] condensation product **4** based on **3** and (1*R*,2*R*)-1,2-diaminocyclohexane **5** shows a tetrahedral cage, where each face very closely corresponds to a [3 + 3]

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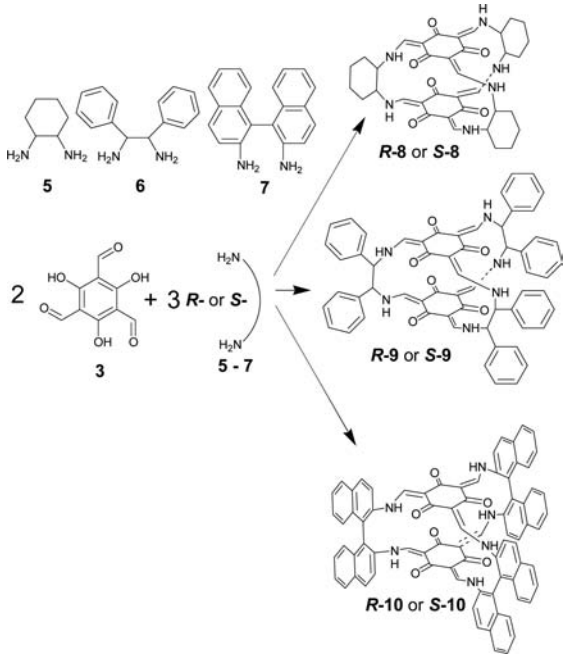
macrocycle **2** previously studied by us (Figure 2, Figure S25, Supporting Information (SI)).[7]

Trialdehyde **3** is an interesting substrate for the formation of [1 + 3] condensation products with various amines, which have been studied in the context of proton tautomerism, metal binding, liquid crystal properties, and helicity inversion;[8] **3** has been also condensed with aromatic diamines in a 2:3 ratio to give 2-D planar covalent polymers.[9]

In this report we present the characterization of condensation products of **3** with (1*R*,2*R*)-1,2-diaminocyclohexane ***R*-5**, (1*S*,2*S*)-1,2-diaminocyclohexane ***S*-5**, (1*R*,2*R*)-1,2-diphenylethylenediamine ***R*-6**, (1*S*,2*S*)-1,2-diphenylethylenediamine ***S*-6**, (*R*)-2,2′-diamino-1,1′-binaphthyl ***R*-7**, and (*S*)-2,2′-diamino-1,1′-binaphthyl ***S*-7**. We show that the [2 + 3] condensation products are formed instead of the expected [4 + 6] cages (Scheme 1). This result is in contrast to the recent finding of the

Scheme 1. Formation of the [2 + 3] Keto-enamines 8−9



odd−even alteration between [2 + 3] and [4 + 6] imine cages formed from 1,3,5-triformylbenzene and diamines of various chain length.[10] Thus, in the case of condensation of 1,3,5-triformylbenzene and diamines with an even number of carbon atoms (including **5** and **6**) [4 + 6] products were formed, while in the case of diamines with an odd number of carbon atoms [2 + 3] products were observed.

The reaction of enantiopure diamine ***R*-5** or ***S*-5** with **3** in refluxing ethanol resulted in formation of precipitate ***R*-8** or ***S*-8** that can also be obtained from methanol, chloroform, or pyridine (see SI for experimental details and spectroscopic characterization). The formation of the 2 + 3 product is confirmed by an ESI MS spectrum. The integration of ^{1}H NMR signals (e.g., signals **a** and **c**; see Figures 3 and 4 for labeling) of ***R*-8** confirms the 2:3 ratio of 1,3,5-trisubstitued phloroglucinol to diaminocyclohexane which, together with the observation of five diaminocyclohexane signals, indicate formation of a symmetric cage product. The condensation of trialdehyde **3** with diamine results in formation of keto-enamine rather than a Schiff base product (Figure 3), as indicated by the COSY spectrum (Figure 4) and disappearance of the ^{1}H NMR signal at 10.49 ppm after

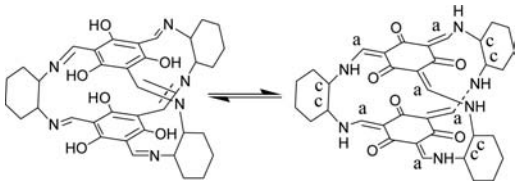


Figure 3. Structures of the two extreme tautomers of **8**.

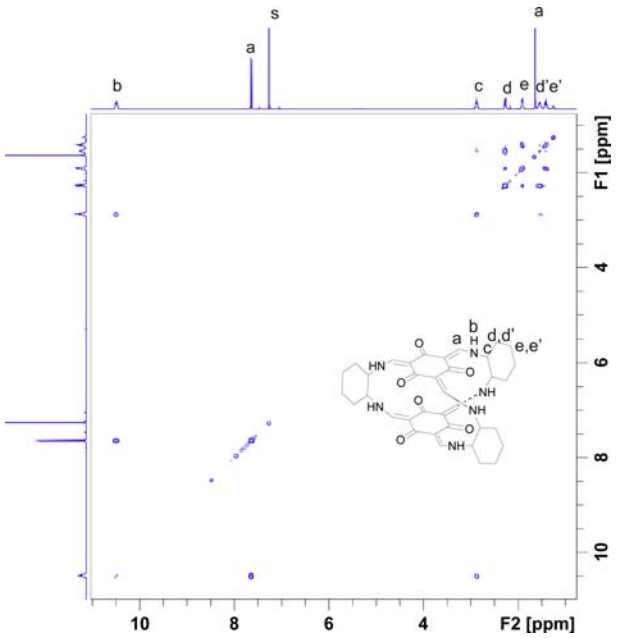


Figure 4. COSY spectrum (500 MHz, $CDCl_3$) of ***R*-8** showing the correlations between the signals of protons a and b as well as between b and c, which are characteristic for the keto-enamine tautomer.

addition of CD_3OD, confirming the presence of an exchangeable NH proton (Figure S3, SI). The COSY spectrum shows correlation of the cyclohexane signal **c** to the NH signal **b**, which in turn is correlated to the vinylic doublet **a**.

The formation of 2 + 3 products is also confirmed by the X-ray crystal structures of ***R*-8** and ***S*-8** (Figure 5, Figures S26−S33, SI)

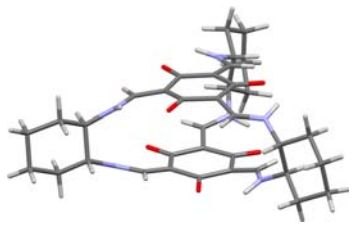


Figure 5. X-ray molecular structure of ***R*-8**.

showing a propeller shaped molecule. These structures indicate that **8** can be regarded as chiral [6.6.6] azacyclophane.[12] Although the two 6-membered rings derived from the phloroglucinol fragments in the keto-enamine product **8** are not formally aromatic, their close parallel arrangement observed in the X-ray molecular structure suggests attractive $\pi-\pi$ stacking interactions in analogy to cyclophanes. The π orbitals responsible for these interactions are characterized computationally in the SI.

The role of $\pi-\pi$ interactions was modeled by a series of Density Functional Theory (DFT) calculations for a keto-enamine tautomer of **8** (see SI for computational details and the

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discussion of stability preferences for the keto-enamine vs enol-imine and [2 + 3] vs [4 + 6] cages). Two DFT functionals, B3LYP and TPSS, and empirical dispersion correction scheme D3, were used.[13] The distance between the ring centroids in the X-ray structure is 3.500 Å. After structure optimization, this distance was 3.838 Å for TPSS and 3.463 Å for TPSS-D3. Similarly, values of 3.871 Å for B3LYP and 3.529 Å for B3LYP-D3 were obtained. DFT lacks the ability to reproduce dispersion consistently. Our results (inclusion of D3 dispersion correction is required for proper estimation of the ring spacing) show that the $\pi-\pi$ interactions are an important factor in explaining the closeness of the ring planes, which tend to stack even without the cyclohexane linkers (for an isolated molecule the diaminocyclohexane linkers can readily tilt to accommodate a range of interplanar distances). This is shown in the Figure 6a:

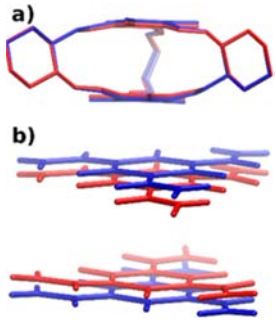

Figure 6. Results of the DFT modeling without dispersion (blue, B3LYP) and dispersion-corrected (red, B3LYP-D3): (a) molecules of **8** (hydrogens not shown for clarity); (b) dimers formed by central unconnected fragments of **8**.

superposition of the B3LYP and B3LYP-D3 structures shows that the difference between the two is restricted to the arrangement of the rings. Even more significant is the result of the optimization of a dimer constructed from **8** by removing the cyclohexane units and capping the amine nitrogen atoms with either −H or −Me (see SI for details). This leads to stable structures with an interaction energy close to −13 to −19.5 kcal/mol at the DFT-D3 level, with an intermonomer separation of 3.36 to 3.39 Å (see Figure 6b). When the dispersion correction is not present, the structures are not stable (interaction energies of ca. −0.9 to 0.3 kcal/mol) with the ring−ring distance of over 4.16 Å, and in case of the capping with methyl groups, the structures diverge and are no more planar (Figures S36, S37, SI).

The reaction of **3** with excess ***R*-5** results in a [1 + 3] condensation product. The NMR spectra of this product again indicate formation of a keto-enamine tautomer (Figures S13−S18, SI). Unlike the case of ***R*-8**, this time the formation of two isomers[8] ***R*-11** and ***R*-12** (differing in the orientation of the C═NH−C arms, Figure 7) is observed.

Similarly to ***R*-5**, refluxing ***R*-6** or ***S*-6** with **3** in a 3:2 ratio in ethanol for 8 h resulted in the formation of precipitate ***R*-9** or ***S*-9**. The same product can be also obtained from methanol or chloroform. In contrast, the reaction of ***R*-7** or ***S*-7** and **3** in ethanol, chloroform, or toluene resulted in complicated mixtures; however the condensation product **10** can be obtained using pyridine as a solvent. As in the case of **8**, correlations characteristic for the keto-enamine tautomers were found in the COSY spectra of ***R*-9** and of ***R*-10** (Figures S6 and S10, SI). Reactions of **3** with simple achiral diamines such as ethylenediamine or 1,3-diamino-2-hydroxypropane resulted in formation of precipitates practically insoluble in common solvents.

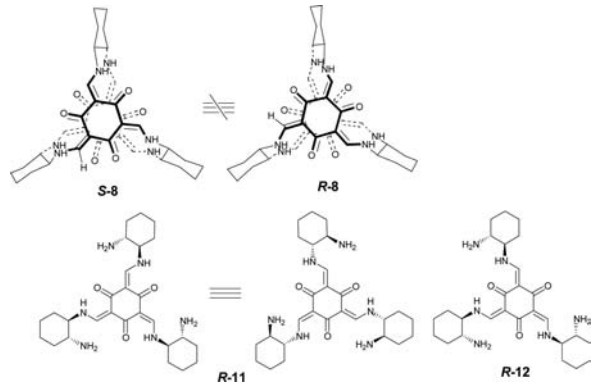

Figure 7. Clockwise and anticlockwise arrangement of the C═C−NH−C fragments in ***S*-8** and ***R*-8** and the structures of the geometric isomers ***R*-11** and ***R*-12**.

The chiral nature of the discussed products is reflected in the mirror-like CD spectra of the respective enantiomers (Figures S22−S24, SI). The rigid nature of the 2 + 3 keto-enamines **8**−**10** in combination with the chiral nature of the diamine results in a fixed sense of the helical arrangement of diamine fragments and the sense of rotation of the C═C−NH−C arms. It should be mentioned that these are higher-order stereogenic centers; their presence would result in enantiomeric structures of the analogous derivatives of the achiral ethylenediamine. Thus, the presence of *R*,*R*-diamine determines the anticlockwise arrangement of the C═C−NH−C fragments in ***R*-8** and the *S*,*S*-diamine results in a clockwise arrangement in ***S*-8** (Figure 7, Figure S32, SI). In the case of 1 + 3 product **11**, there is no clear distinction between the "top" and the "bottom" of the system due to easy rotation of the cyclohexane fragments; thus, the switch between the clockwise and anticlockwise orientation of arms simply corresponds to the rotation of the molecule (Figure 7).

Some of the [2 + 3] products obtained from the condensation of trialdehydes with diamines are large enough to be regarded as cages.[13] In contrast, the crystal structure as well as MM+ modeled structures of **8** show a packed conformation with close contact between the two phloroglucinol rings. The gap between the phloroglucinol rings is somewhat larger for the modeled structure of **10** (Figure S34, SI). Interaction of the latter compound with the racemic mandelic acid results in enantiodifferentiation of the mandelic acid signals; the effect is however small, suggesting rather hydrogen bond formation on the periphery and not the binding of the mandelic acid guest inside the 2 + 3 cage.

Although the pure products **8**−**10** were isolated in moderate 27−65% yields, the ^{1}H NMR spectra of crude reaction mixtures indicate that they are formed in ca. 70−90% yields (Figure S19, SI) so they are the preferred thermodynamic products. The formation of [2 + 3] products **8** and **9** from 1,3,5-triformylphloroglucinol contrasts strongly with the formation of [4 + 6] products from 1,3,5-triformylbenzene and the same diamines. Similarly, formation of [2 + 3] product **10** contrasts with the formation of [4 + 6] product from 1,3,5-triformylbenzene and 1,4-diaminobutane, which has the same number of carbon atoms connecting the two amine groups as diamine **7**. Thus, the outcome of the reaction not only is dependent on the length of the carbon chain but also is influenced by the additional substitution of the benzene ring by oxygen and formation of

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keto-enamine instead of imine derivatives. The different preference for [2 + 3] vs [4 + 6] type of products in the reactions of 1,3,5-triformylphloroglucinol and 1,3,5-triformylbenzene may originate from different energies of $\pi-\pi$ interactions of the respective six-membered rings, but other factors, such as the entropic contribution related to different reaction conditions, insufficient "error correction," and incomplete reversibility of keto-enamine formation, may also play a role (see SI for Figures S19, S20 and a more detailed discussion that follows).

In summary we have demonstrated that the introduction of three hydroxyl substituents to the 1,3,5-triformylbenzene drastically changes the course of the condensation reaction with chiral diamines. Instead of [4 + 6] imine condensation products, [2 + 3] keto-enamines are obtained. The X-ray crystal structures of these products as well as theoretical calculations indicate formation of [*n.n.n*] cyclophane-type products with the two phloroglucinol derived fragments interacting via $\pi-\pi$ interactions. The binding of small aromatic guests by **10** and similar more extended [2 + 3] cyclophanes, as well as the coordinating properties of these compounds, will be the subject of further studies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02989.

Experimental details for the macrocycle synthesis and characterization, crystallographic data, details of DFT calculations, Figures S1−S37 (^{13}C and ^{1}H NMR spectra, CD spectra, views of molecular structures) (PDF)

X-ray crystallographic information (CIF)

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Notes

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Direct, Regioselective *N*-Alkylation of 1,3-Azoles

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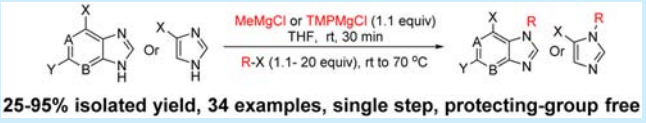
Supporting Information

ABSTRACT: Regioselective *N*-alkylation of 1,3-azoles is a valuable transformation. Organomagnesium reagents were discovered to be competent bases to affect regioselective alkylation of various 1,3-azoles. Counterintuitively, substitution selectively occurred at the more sterically hindered nitrogen atom. Numerous examples are provided, on varying 1,3-azole scaffolds, with yields ranging from 25 to 95%.



25-95% isolated yield, 34 examples, single step, protecting-group free

The concept of protecting-group-free (PGF) synthesis has gained prominence in the synthetic organic chemistry community over the past decade.[1] A successful PGF synthesis of a target molecule is advantageous for a number of reasons; it eliminates time-consuming and tedious manipulation of protecting groups and increases efficiency with respect to atom economy, loss of material, waste production, and synthetic design.[2]

Numerous biologically interesting natural products and medicinally important small molecules contain 1,3-azoles (e.g., imidazole, benzimidazole, imidazopyridine, and purine) (Figure 1). One challenge for the synthesis of 1,3-azole-containing molecules is the ambident nature of the azole toward *N*-alkylation chemistry.[3] A particularly challenging situation arises when the more sterically hindered nitrogen of the unsymmetrical azole is the target for alkylation. Under conventional conditions, alkylation favors the less sterically encumbered site.[4] In many instances, the desired reverse selectivity could be achieved through protection of the less hindered position followed by alkylation of the desired position and then deprotection.[5,6] A PGF alternative to this less efficient process would therefore be desirable.

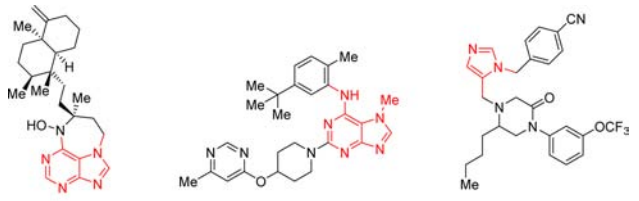
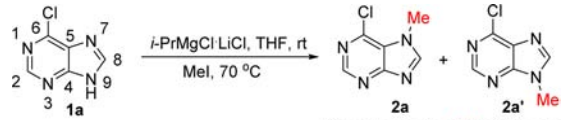


Figure 1. Selected examples of natural and biologically active compounds that contain 1,3-azoles.

Recently, a large quantity of N^7-methyl-6-chloropurine (**2a**) was required as an intermediate toward the scale-up of a medicinal chemistry lead for in vivo studies.[7] Unfortunately, the only method known for the production of **2a** utilized a strategy that relied upon a reduction/oxidation as well as a protection/deprotection process, which was nonideal for the preparation of large quantities of material.[5g] In order to facilitate the rapid synthesis of **2a**, conditions to reverse the inherent selectivity for alkylation of the N^9 over the N^7 position were investigated. It was discovered that deprotonation of 6-chloropurine with *i*-PrMgCl·LiCl followed by alkylation with methyl iodide furnished the desired regioisomer with 9:1 selectivity (**2a**/**2a**′) in 70% yield. Using this unoptimized method, 30 g of **2a** was prepared in a single reaction (Scheme 1).[8]

Scheme 1. Chemoselective Methylation of 6-Chloropurine



A thorough literature search revealed that the selective alkylation of the more hindered position of 1,3-azoles was uncommon. The only examples of direct N^7 alkylation of purine utilized a cobalt complex as a transient protecting group.[9] However, difficult access to the cobalt complexes, long reaction times, and a narrow substrate scope limit the potential applications for this method. Due to the lack of literature precedent for direct regioselective alkylation of the more hindered position of 1,3-azoles, we decided to investigate this transformation more rigorously.

Starting from our original conditions (Scheme 1), optimization was directed toward maximizing selectivity and conversion. A range of various bases including organomagnesium, organozinc, and lithium reagents were examined in the methylation of 6-chloropurine in THF at room temperature.[10] *i*-PrMgCl·LiCl and *s*-BuMgCl·LiCl gave similar N^7/N^9 selectivity (25:1 and 26:1, respectively) with a slightly higher conversion in the former case (Table 1, entries 1 and 2). Use of the non-nucleophilic Knochel–Hauser base TMPMgCl·LiCl (2,2,6,6-tetramethylpiperidinylmagnesium lithium chloride complex) resulted in lower selectivity with fair conversion (entry 3). Interestingly, use of *i*-

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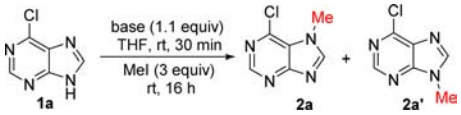
Table 1. Base Screen for the Methylation of 6-Chloropurine



entry	base	conv[a] (%)	2a:2a'[b]
1	*i*-PrMgCl·LiCl	64	25:1
2	*s*-BuMgCl·LiCl	50	26:1
3	TMPMgCl·LiCl	50	15:1
4	*i*-PrMgCl	65	>99:1
5	MeMgCl	73	>99:1
6	MeMgBr	<5	21:1
7	MeMgI	<5	20:1
8	TMPMgCl	65	72:1

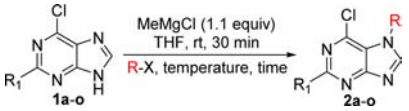
[a]Conversion determined by LC−MS. [b]Product ratio determined by ^{1}H NMR spectroscopy.

PrMgCl without LiCl complexation improved the N^7/N^9 selectivity to >99:1, with good conversion at ambient temperature (entry 4). Encouraged by this result, MeMgCl was tested and provided similar selectivity and improved yield in this transformation (entry 5). Interestingly, when the counterion of the Grignard reagent was changed from chloride to bromide or iodide, the conversion and the selectivity dramatically decreased (entries 6 and 7). Additionally, TMPMgCl could be employed in this method, with good selectivity (entry 8).[11,12] The non-nucleophilic nature of this base, relative to MeMgCl, allows for application of this strategy in the presence of sensitive functional groups.[13,14]

After MeMgCl was identified as the optimal base, alkylation of 6-chloropurine with a variety of alkylating reagents was studied (Table 2, entries 1−9). As anticipated, the N^7-substituted regioisomer was obtained irrespective of the aliphatic alkylating reagent employed in this transformation. Alkylation using unactivated electrophiles was sluggish even at elevated temperatures and with excess alkylating reagent. For example, *n*-butyl iodide required refluxing temperatures for 3 days to deliver a 25% yield of alkylated material (entry 4). The product selectivity was diminished with more reactive electrophiles. Decreased N^7 selectivity was observed for phenacyl bromide at room temperature; however, the product ratio could be improved (N^7/N^9 = 5:1) through slow addition of phenacyl bromide to the reaction mixture at low temperature (entry 9). The present conditions were also found to be amenable to the regioselective alkylation of 2,6-dichloropurine, a common building block used in medicinal chemistry (entries 10−15).[3b] A small amount of N^9-substituted products were observed in these cases (<10% detected by ^{1}H NMR analysis of reaction mixtures) albeit in good to excellent isolated yields for the N^7-regioisomer (72−90%).

To understand whether the selectivity in this transformation was a result of electronic or steric effects, purine derivatives with various substituents at the C^6 position were investigated (Table 3). TMPMgCl was utilized for the alkylation of 6-bromopurine and 6-cyanopurine at room temperature. The use of MeMgCl as a base for these substates resulted in the formation of dehalogenated and methyl addition byproducts (entries 5 and 6). While selectivity was not affected by the electronic nature of the substituent on the purine, the yields were influenced by the electronic nature of the substituent at the C^6 position (entries 1 and 2). These observations suggest that steric effects govern the selectivity in this transformation with respect to this substitution pattern.

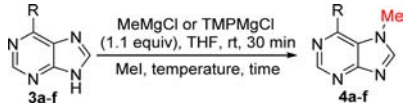
Table 2. Alkylation of 6-Chloropurine and 2,6-Dichloropurine



entry	2	R^1	alkylating reagent (equiv)	temp (°C)	time (h)	yield[a] (%)
1	**a**	H	MeI (3.0)	50	5	95
2	**b**	H	EtI (3.0)	70	16	81
3	**c**	H	*n*-PrI (20.0)	70	16	85
4	**d**	H	*n*-BuI (20.0)	70	72	25
5	**e**	H	BnBr (3.0)	50	20	88
6	**f**	H	CH_2=$CHCH_2Br$ (20.0)	70	16	90
7	**g**	H	$CH{\equiv}CCH_2Br$ (3.0)	70	16	72
8	**h**	H	$CF_3CH_2SO_3CF_3$ (2.0)	70	16	82
9[b]	**i**	H	$C_6H_5COCH_2Br$ (1.1)	−78 to rt	8	69
10	**j**	Cl	MeI (3.0)	50	16	90
11	**k**	Cl	EtI (3.0)	70	16	72
12	**l**	Cl	BnBr (3.0)	70	16	77
13	**m**	Cl	CH_2=$CHCH_2Br$ (3.0)	70	16	74
14	**n**	Cl	$CH{\equiv}CCH_2Br$ (3.0)	70	16	81
15	**o**	Cl	$CF_3CH_2SO_3CF_3$ (2.0)	70	16	74

[a]Isolated yield of the desired regioisomer.[15] [b]See text for details.

Table 3. Methylation of Purine Derivatives



entry	4	R	MeI (equiv)	temp (°C)	time (h)	yield[a] (%)
1	**a**	NMe_2[b]	10.0	25	16	25[d]
2	**b**	OMe[b]	10.0	25	22	57[d]
3	**c**	SMe[b]	3.0	70	16	80
4	**d**	Me[b]	3.0	70	30	77
5	**e**	Br[c]	3.0	25	20	80
6	**f**	CN[c]	1.5	70	24	78

[a]Isolated yield of desired regioisomer.[15] [b]MeMgCl as the base. [c]TMPMgCl as the base. [d]Overmethylation of desired prouduct caused reduced yield in these reactions.

Gratifyingly, this method could also be effectively applied to various other bicyclic 1,3-azoles (Scheme 2). The methylation of 4-chloro-2-methyl-1*H*-benzo[*d*]imidazole gave the more sterically hindered regioisomeric product **6d** in 88% yield. 7-Substituted 1*H*-imidazo[4,5-*b*]pyridines provided the desired N^1-methylated products in good yields (**6c** and **6g**). Similarly, 4-substituted-3*H*-imidazo[4,5-*c*]pyridine afforded the desired N^3-methylation under standard conditions (**6e** and **6f**). However, a benzimidazole substrate with a chloride (EWG) or methoxide (EDG) at C^6 rather than at the C^7 position provided a 1:1 ratio of regioisomeric products (**6a**−**b**). In order to reduce the steric component, we moved the substituent to a remote position (C^6). If the regiochemistry was influenced by electronics, we would expect to observe some selectivity; however, the electronic character of the substituent had no effect on the regiochemistry of the products. This observation provides further evidence that

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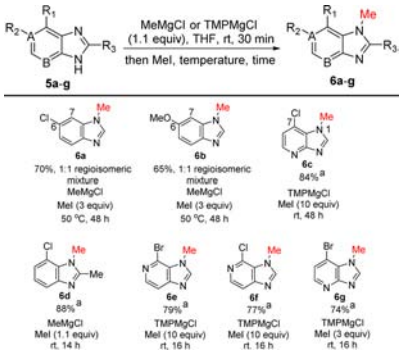
Scheme 2. Methylation of 1,3-Azoles[a]

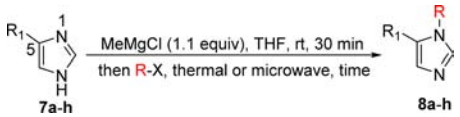


[a]Isolated yield of desired regioisomer.[15]

the alkylation is dictated by steric effects rather than by electronics. In addition, the presence and position of a nitrogen atom in the 6-membered ring does not affect the regioselectivity of 1,3-azole methylation. However, a C^7 substituent adjacent to the site of alkylation is required to differentiate the steric environment of the two reactive nitrogen atoms in the 1,3-azole ring.

Encouraged by the excellent selectivity of various bicyclic 1,3-azoles, we set out to extend this methodology to the alkylation of unsymmetrical imidazoles. To our delight, the expected N^1 substituted imidazole was the major product under standard reaction conditions (Table 4). Bromide and cyano groups were

Table 4. Alkylation of Imidazoles



entry	8	R_1	alkylating reagent (equiv)	base	temp (°C)	time (h)	yield[b] (%)
1	a	Ph	MeI (1.1)	MeMgCl	25	48	76
2	b	*t*-Bu	MeI (1.1)	MeMgCl	25	48	87
3	c	Me	MeI (1.5)	MeMgCl	70	20	64
4	d	Cl	MeI (1.5)	MeMgCl	70	20	69
5	e	Br	MeI (1.5)	TMPMgCl	70	20	69
6	f	CN	MeI (1.5)	TMPMgCl	70	20	74
7[a]	g	Ph	CH_2=$CHCH_2Br$ (1.5)	MeMgCl	120	2	42
8[a]	h	Ph	CH≡CCH_2Br (1.1)	MeMgCl	70	10	35

[a]Microwave irradiation. [b]Isolated yield of desired regioisomer.[15]

tolerated using TMPMgCl as the base and afforded a good yield of the N^1 regioisomeric products (entries 5 and 6). Electrophiles other than methyl iodide showed poor reactivity at ambient temperature (Table 4, entries 7 and 8).[15,16]

In conclusion, the direct, protecting-group free alkylation of the more sterically encumbered position of a wide range of 1,3-azoles has been demonstrated. High yields and regioselectivity were achieved using commercially available alkylmagnesium reagents or easily prepared TMPMgCl. It was observed that selectivity was not affected by the electronic nature of the substituents on the purine; however, the yields were influenced by the electronic character of the substituents. This transformation may also be useful for the simplified preparation of 1,3-azole-containing biologically active compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02994.

Synthetic methods, analytical methods, condition opimization, and full characterization of materials (PDF)

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Notes

The authors declare no competing financial interest.

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(15) The identification of the regiochemistry was determined by the use of ^{1}H, ^{13}C, HSQC, and HMBC spectra. There exists clear evidence in the long-range ^{1}H−^{13}C HMBC data as to what side of the molecule the methyl group has added. The carbon chemical shifts of the two bridge carbons are quite distinct from each other. We were able to use the long-range ^{1}H−^{13}C HMBC data to correlate the methyl protons to each of the bridge carbons and determine connectivities. Therefore, the regiochemistry of methylation could be determined (see the Supporting Information, for example).

(16) Attempts to accelerate the reaction rate with excess alkylating reagent or elevated temperature led to the formation of undesired overalkylated imidazolium salts.

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Enantioselective Synthesis of Four Stereoisomers of Sulfinyl Ferrocenyl Quinones with Central, Planar, and Helical Chirality

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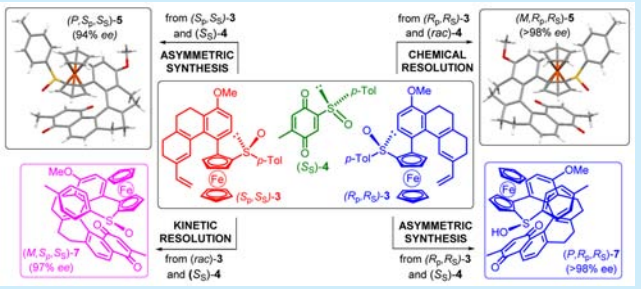
Supporting Information

ABSTRACT: Four stereoisomers of sulfinyl ferrocenyl-substituted helicenequinones having central, planar, and helical elements of chirality were stereoselectively formed, in one step, from reaction between enantiopure sulfinyl ferrocenyl dienes and a sulfinyl quinone. Asymmetric synthesis, kinetic resolution, or chemical resolution processes occurred in sequential cycloaddition, sulfoxide elimination, and partial aromatization steps.



The development of chiral molecules that show strong chiroptical properties may lead to new multifunctional molecular materials.[1] In this context, helicenes, nonplanar polycyclic systems that consist of *ortho*-fused aromatic rings displaying helical chirality,[2] show great potential because, owing to their extended π-conjugated twisted backbone, they combine huge chiroptical properties[3] with other ones such as absorption, emission, and redox activity.[4] The potential use of helicene derivatives in these applications depends greatly on the facility of generating different frameworks to modulate and optimize their properties.[3,4] Although remarkable progress has been made in helicene chemistry,[5] a straightforward access to novel well-defined molecular helical structures, as well as an understanding of the factors controlling their structures and properties, are crucial to the development of [*n*]helicenes toward functional materials and still remains a challenge to synthetic chemists.

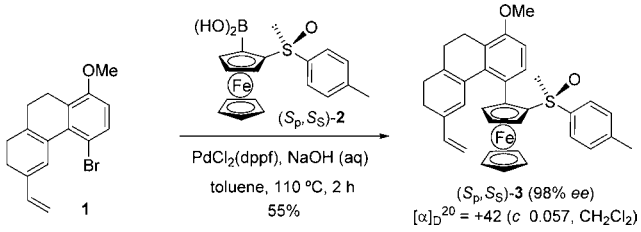
Recently, organometallic helicenes in which a transition metal is included within the helical π-framework have emerged as highly promising candidates for optoelectronic applications, owing to the presence of the metal center.[6] Coordination of the polycyclic aromatic molecules to metal atoms may alter the electronic density distribution and significantly change their properties. In this context, the switching of chiral metal-based systems has great potential,[7] due to the possibility of reversibly modifying the molecule by changing the properties of the metal center (geometry, redox state). Therefore, it has been considered attractive to explore the chemistry of these kinds of complexes.

During last years, we have succeeded in a short synthesis of enantiopure helicenequinones[8] based on the efficient transfer of chirality from a homochiral sulfoxide to the helical structure. The strategy stems on the asymmetric domino Diels–Alder reaction/pyrolytic sulfoxide elimination/aromatization process occurring when vinyl dihydroaromatic derivatives, acting as dienes, react with enantiopure sulfinyl quinones. More recently, we achieved the enantioselective synthesis of a condensed ferrocene-[4]-helicenequinone showing planar and helical elements of chirality.[8b] The study of its chiroptical properties revealed the presence of an efficient intramolecular charge transfer between the donor planar–chiral ferrocene and the acceptor helical–chiral quinone, which could be evidenced by circular dichroism (CD).

We now report the application of our asymmetric approach to the synthesis of [5]helicenequinones with a ferrocene substituent at the most hindered C-14 position, showing central and planar elements of chirality, by introducing a sulfinyl ferrocenyl moiety. We have synthesized four stereoisomers of the eight possible of such organometallic helical quinones, in a highly stereoselective way by applying asymmetric synthesis, kinetic resolution, and chemical resolution processes. We also describe their electronic and chiroptical properties.

The asymmetric Diels–Alder approach required the ferrocene diene (S_p,S_S)-**3**, which was prepared in one step by Suzuki coupling between known enantiopure sulfinyl ferrocenyl boronic acid (S_p,S_S)-**2**[9] and tricyclic bromoaromatic derivative **1**[8c] (Scheme 1). Thus, the reaction between (S_p,S_S)-**2** and **1** in the presence of $PdCl_2$(dppf) and NaOH in refluxing toluene for 2 h[9] led to sulfinyl ferrocenyl diene (S_p,S_S)-**3**, with planar and central

Scheme 1. Synthesis of Diene (S_p,S_S)-3



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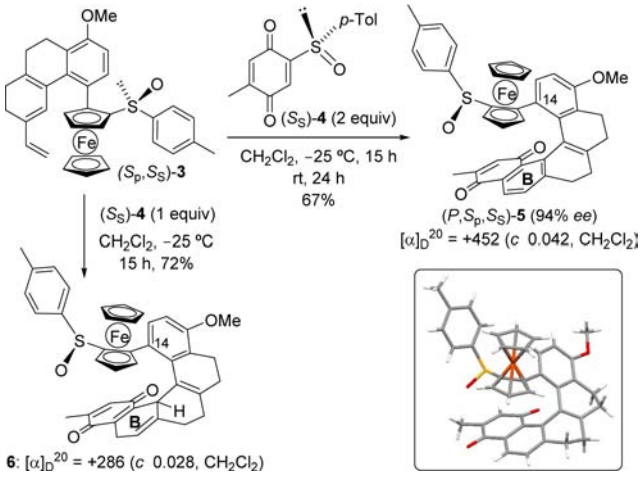
elements of chirality in a defined configuration, in 55% yield and 98% *ee*,[10] after flash chromatography.

With sulfinyl ferrocenyl diene (S_p,S_S)-**3** in hand, we performed its reaction with 2 equiv of enantiopure 2-(*p*-tolylsulfinyl) quinone (S_S)-**4**.[11,12] When the reaction was carried out in CH_2Cl_2 at −25 °C for 15 h and at rt for additional 24 h (Scheme 2), a unique product, characterized as 14-(2-*p*-tolylsulfinyl)-

Scheme 2. Asymmetric Synthesis of Enantiomer (P,S_p,S_S)-5 from the Domino Process between (S_p,S_S)-3 and (S_S)-4



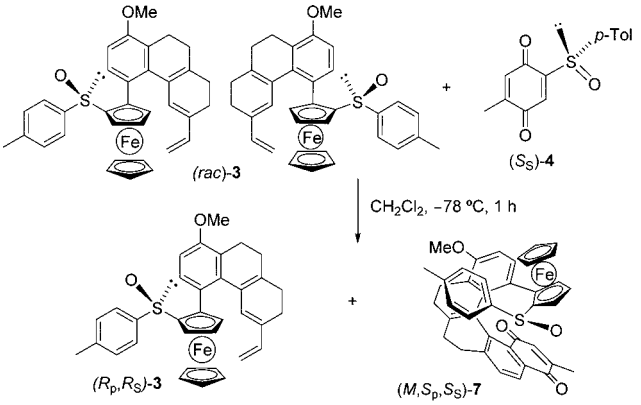
ferrocenyl-tetrahydro-[5]-helicenequinone (P,S_p,S_S)-**5**, with helical, planar, and central elements of chirality, was isolated in 68% yield and 94% *ee*[10] {$[\alpha]^{20}_D$ = +452 (*c* 0.042, CH_2Cl_2)}. This product resulted from a domino process comprising asymmetric Diels−Alder reaction with the first equiv of (S_S)-**4**, sulfoxide elimination and aromatization of the B ring effected by the second equiv of (S_S)-**4**. The absolute (*P*) configuration of the helix in **5** was determined after an X-ray diffraction study of a racemic sample, taking into account the known absolute configuration of the sulfinyl ferrocenyl boronic acid (S_p,S_S)-**2**, used to prepare diene (S_p,S_S)-**3** (Scheme 1).

When the same reaction was carried out with 1 equiv of (S_S)-**4** at −25 °C for 15 h (Scheme 2), the only compound isolated was the hexahydroaromatic derivative **6** showing the nonaromatized B ring. Compound **6** was formed after asymmetric Diels−Alder reaction with (S_S)-**4** and sulfoxide elimination of the nonisolated initial adduct.

Taking into account our precedent work,[8] where we had observed the kinetic resolution of a planar−chiral ferrocene diene upon reaction with sulfinylquinones, we decided to perform the reaction of enantiopure (S_S)-**4** with racemic diene *rac*-**3**, hoping for an efficient kinetic resolution.[12] Initially, reaction of *rac*-**3** was carried out with 0.5 equiv of (S_S)-**4** (CH_2Cl_2, −78 °C, 1 h). Under these conditions (Scheme 3), we could isolate, after flash chromatography, a 45% yield of unreacted enantioenriched diene (−)-(R_p,R_S)-**3**, which showed a 33% *ee*,[10] together with a 36% of 14-[2-(*p*-tolylsulfinyl)-ferrocenyl]-tetrahydro-[5]-helicenequinone (M,S_p,S_S)-**7**, with a good 81% *ee*.[10]

This result indicated that a kinetic resolution of the starting racemic diene **3** had taken place. The more reactive (S_p,S_S) enantiomer of **3** had preferably reacted with enantiopure sulfinyl quinone (S_S)-**4**, but surprisingly, the product obtained after the domino process was not the hexahydroaromatic derivative **6** nor the B-ring aromatized tetrahydro-[5]-helicenequinone (P,S_p,S_S)-

Scheme 3. Kinetic Resolution of (*rac*)-3 with (S_S)-4 To Give Enantiomer (M,S_p,S_S)-7

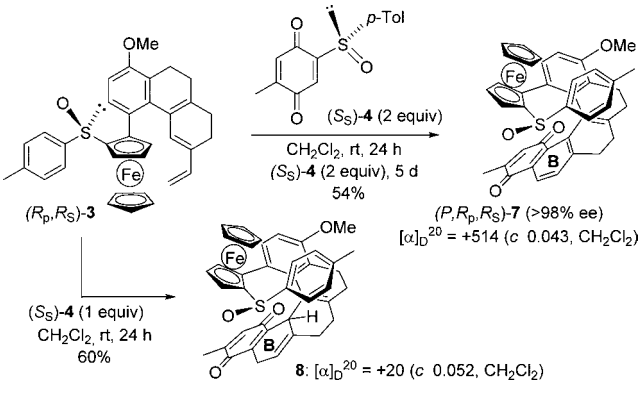


(S_S)-4 (equiv)	(R_p,R_S)-3 % yield / % *ee* / $[\alpha]_D^{20}$	(M,S_p,S_S)-7 % yield / % *ee* / $[\alpha]_D^{20}$
0.5	45 / 33 / −7 (*c* 0.107, CH_2Cl_2)	36 / 81 / −429 (*c* 0.007, CH_2Cl_2)
0.41	**49 / 70 / −21 (*c* 0.051, CH_2Cl_2)**	**25 / 97 / −530 (*c* 0.032, CH_2Cl_2)**

5 (Scheme 2), resulting upon reaction with enantiopure (S_p,S_S)-**3**, but the diastereomer (M,S_p,S_S)-**7**, showing the opposite (*M*) absolute configuration at the helix.[13] After some experimentation varying the amount of sulfinyl quinone (S_S)-**4**, the best results of the kinetic resolution process were obtained from reaction of diene (*rac*)-**3** with 0.41 equiv of (S_S)-**4** in CH_2Cl_2 at −78 °C for 1 h (Scheme 3). Under these conditions, a 49% yield of unreacted diene (−)-(R_p,R_S)-**3** showing a good 70% *ee*,[10] together with a 25% yield of the tetrahydro-[5]-helicenequinone (M,S_p,S_S)-**7** {$[\alpha]^{20}_D$ = −530 (*c* = 0.032, CH_2Cl_2)}, which showed an excellent 97% *ee*,[10] could be isolated. This result is noteworthy both in terms of optical (97%) and chemical yields (25%) of tetrahydro-[5]-helicenequinone (M,S_p,S_S)-**7**, taking into account that the maximum global yield would be 41% for a domino process comprising four steps: kinetic resolution of the racemic diene **3**, Diels−Alder reaction, sulfoxide elimination, and partial aromatization. Moreover, the synthesis of the two helical epimers from the same starting material is also remarkable.

Next, we studied the same reaction of sulfinylquinone (S_S)-**4** with the (R_p,R_S) enantiomer of sulfinylferrocenyl diene **3** with the aim of evaluating the possible different stereochemical course of the overall process (Scheme 4).

Scheme 4. Asymmetric Synthesis of Enantiomer (P,R_p,R_S)-7 from the Domino Process between (R_p,R_S)-3 and (S_S)-4



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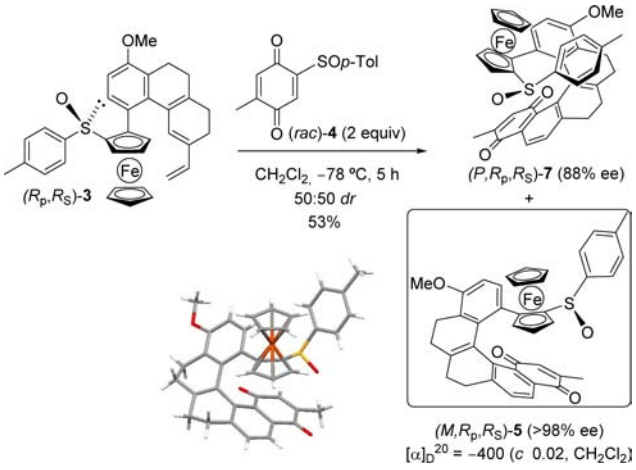
As expected on the base of the above observed kinetic resolution, when the reaction between diene (R_p,R_S)-**3**, prepared from sulfinyl ferrocenyl boronic acid (R_p,R_S)-**2** in a similar way as indicated in Scheme 1, and 2 equiv of (S_S)-**4** was conducted at −25 °C in CH_2Cl_2, no evolution was observed at all. It was necessary to increase the temperature to rt for 24 h, followed by a second addition of sulfinylquinone (S_S)-**4** and continue the reaction for 5 days, to observe the completion of the domino process.[14] Under these conditions, the diastereomeric 14-sulfinylferrocenyl-tetrahydro-[5]-helicene quinone (P,R_p,R_S)-**7**,[15] bearing helical, planar, and central elements of chirality, was obtained in 54% yield and >98% *ee* {$[\alpha]^{20}_D$ = +514 (*c* = 0.043, CH_2Cl_2)},[10] after flash chromatography. It was also possible to isolate the corresponding hexahydro-[5]-helicene-quinone **8**, with the nonaromatized B ring, when the reaction of diene (R_p,R_S)-**3** was performed with 1 equiv of (S_S)-**4** at rt for 24 h (Scheme 3). Under these conditions, compound **8** was obtained in 60% yield, after flash chromatography.

Having synthesized three stereoisomers of 14-(*p*-tolylsulfinyl)-ferrocenyl-tetrahydro-[5]-helicenequinones (P,S_p,S_S)-**5**, (P,R_p,R_S)-**7**, and (M,S_p,S_S)-**7**, showing helical, planar, and central elements of chirality, we decided to carry out the reaction between enantiopure diene (R_p,R_S)-**3** and racemic sulfinyl quinone **4** with the aim of obtaining a new steroisomer (M,R_p,R_S)-**5** from a chemical resolution process (Scheme 5).

Scheme 5. Chemical Resolution of (*rac*)-4 with (R_p,R_S)-3 To Give Enantiomer (M,R_p,R_S)-5



When we performed the reaction between enantiopure diene (R_p,R_S)-**3** and 2 equiv of sulfinyl quinone (*rac*)-**4** in CH_2Cl_2 at −78 °C for 5 h, we could obtain, after flash chromatography, in 53% global yield, an equimolecular mixture of separable diastereoisomers (P,R_p,R_S)-**7** (88% *ee*),[10] previously obtained as indicated in Scheme 3, and the new stereoisomer (M,R_p,R_S)-**5** {$[\alpha]^{20}_D$ = −400 (*c* = 0.02, CH_2Cl_2)}, showing an excellent >98% *ee*.[10] The absolute (M) configuration of the helix present in (M,R_p,R_S)-**5** was determined after an X-ray diffraction study of a racemic sample (Scheme 5), taking into account the known absolute configuration of the starting sulfinyl ferrocenyl boronic acid (R_p,R_S)-**2**, used to prepare diene (R_p,R_S)-**3**.

The UV/vis spectra of ferrocenyl helicenequinones **5** and **7** are shown in Figure 1a. As can be seen, they are dominated by the intense sulfoxide absorption at λ = 250 nm. The bands in the region of λ < 350 nm can be due to the ferrocene−cyclopentadiene charge transfer [Fe (e2g) → Cp (eg1)]

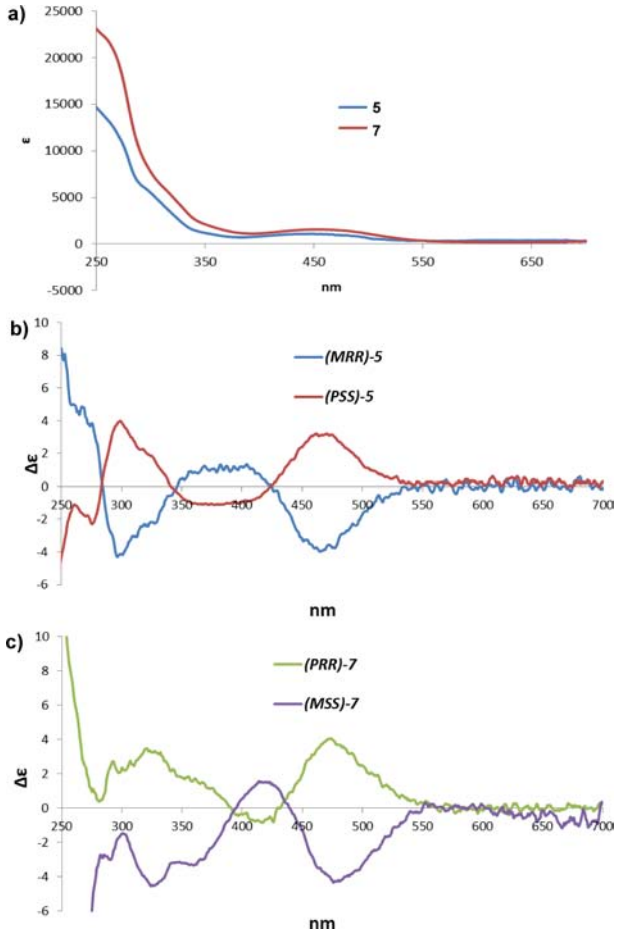


Figure 1. (a) UV/vis spectra of **5** and **7**. (b) CD spectra of (P,S_p,S_S)-**5** and (M,R_p,R_S)-**5**; (c) CD spectra of (P,R_p,R_S)-**7** and (M,S_p,S_S)-**7**.

absorption and the quinone transitions. The absorptions centered at ca. 465 nm ($\varepsilon \approx 1550$ cm^{-1} M^{-1}) could be attributed to a symmetry forbidden Fe (a1g) → Fe (e2g) transition as well as to a weak intramolecular charge transfer transition from the ferrocene donor to the π-conjugated aromatic system. An interaction between the ferrocene substituent and the quinone moiety is not evident, probably due to the interrupted conjugation between the naphthoquinone (AB rings) and the ferrocenyl substituted naphthalene fragment (DE) due to the hydroaromatic C ring of the pentacyclic system.

The CD spectra of (+)-(P,S_p,S_S)-**5** and (−)-(M,R_p,R_S)-**5** (Figure 1b) and (+)-(P,R_p,R_S)-**7** and (−)-(M,S_p,S_S)-**7** (Figure 1c) evidenced their opposite absolute configurations. Apart from the intense Cotton effect of the sulfoxide at λ = 250 nm, and the absorption at ca. 300 nm attributed to the ferrocene, the band at ca. 360 nm is evidencing the chirality of the quinone. The band appearing at 470 nm is significantly intense. This is reflecting an effective intramolecular transfer of chirality within the planar−chiral ferrocene and the helicenequinone, which could also be associated with the intramolecular charge transfer dπ−π* transitions.

In summary, we have achieved the enantioselective synthesis of four stereoisomers of 14-(*p*-tolylsulfinyl)ferrocenyl-substituted [5]helicenequinones **5** and **7** using a strategy based on double asymmetric induction Diels−Alder reactions between planar−chiral sulfinylferrocenyl tricyclic diene **3** and sulfinyl *p*-benzoquinone **4**. Upon reaction of enantiopure (S_p,S_S)-**3** with (S_S)-**4**, helicenequinone (P,S_p,S_S)-**5** was exclusively formed.

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Kinetic resolution of *rac*-3 with (S_S)-**4** gave rise to helical epimer (M,S_p,S_S)-**7**, while enantiopure (R_p,R_S)-**3** reacted much more slowly with (S_S)-**4** leading to (P,R_p,R_S)-**7**. Finally, stereoisomer (M,R_p,R_S)-**5**, together with an equimolecular amount of (P,R_p,R_S)-**7**, resulted in a chemical resolution process occurring between enantiopure (R_p,R_S)-**3** and *rac*-**4**. The CD spectra of derivatives **5** and **7** showed the opposite absolute configuration of the enantiomers as well as a significantly intense chiroptical response of the band at 470 nm, which was poorly intense in the UV/vis spectrum.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03029.

Synthetic procedures, characterization data, copies of ^{1}H- and ^{13}C NMR spectra (PDF)
X-ray data for (*rac*)-**5** (CIF)

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Notes

The authors declare no competing financial interest.

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(13) The (M) absolute configuration at the helix of derivative (M,S_p,S_S)-**7** was initially assigned on the basis of the negative sign of its optical rotation (see, Laarhoven, W. H.; Prinsen, W. J. *Top. Curr. Chem.* **1984**, *125*, 63 and references 2d and 3) and later confirmed by comparison of its CD spectrum with that of enantiomer (P,R_p,R_S)-**7** (see Figure 1b).

(14) In this case, the lower reactivity of diene (R_p,R_S)-**3** compared with that of diene (S_p,S_S)-**3** face to enantiopure (Ss)-**4**, made necessary the use of an excess of (S_S)-**4** and a higher temperature to effect the asymmetric Diels−Alder step of the domino process. A second addition of 2 equiv of (S_S)-**4** and 5 days of reaction were also necessary to complete the aromatization of the B ring of the initially formed intermediate **8**.

(15) The (P) absolute configuration at the helix of derivative (P,R_p,R_S)-**7** was initially assigned on the basis of the positive sign of its optical rotation (see, Laarhoven, W. H.; Prinsen, W. J. *Top. Curr. Chem.* **1984**, *125*, 63 and references 2d and 3) and later confirmed by comparison of its CD spectrum with that of compound (P,S_p,S_S)-**5** (see Figure 1).

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Molecular Iodine-Mediated Chemoselective Synthesis of Multisubstituted Pyridines through Catabolism and Reconstruction Behavior of Natural Amino Acids

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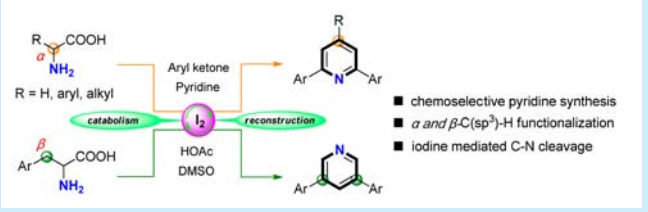
Supporting Information

ABSTRACT: A new process has been developed for the selective construction of 2,6-disubstituted, 2,4,6-trisubstituted, and 3,5-disubstituted pyridines based on the catabolism and reconstruction behaviors of amino acids. Molecular iodine was used as a tandem catalyst to trigger the decarboxylation−deamination of amino acids and to promote the subsequent formation of the pyridine products.



Amino acids hold an important place in the annals of ligand chemistry,[1] chiral catalysis,[2] and total synthesis.[3] They have also been used to develop an interesting array of synthetic methodologies, with the majority of these studies being focused on C−C bond-forming reactions via a decarboxylative coupling process.[4] However, nature is much more effective at affecting the chemical transformations of amino acids. These compounds are used in nature for many other reactions besides decarboxylative coupling reactions since amino acids are some of the most basic and versatile synthons available to living organisms. During the biosynthesis of alkaloids, amino acids can be catabolized into smaller fragments, which are subsequently used as building blocks to reconstruct the core skeletons of alkaloids under enzymatic conditions.[5] A representative example of this process is the biosynthesis of haouamine A, which is a pyridine-based alkaloid that is widely believed to be biogenetically derived from four identical tyrosine congeners[6] (Figure 1). The catabolism of these

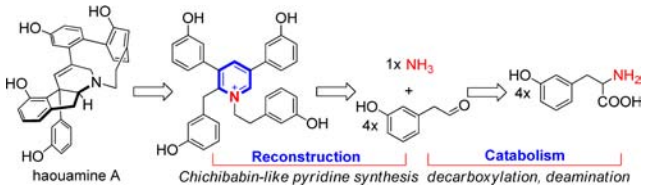


Figure 1. Biosynthesis protocol of haouamine **A**.

tyrosine derivatives through sequential decarboxylation and deamination reactions is thought to lead to the formation of the corresponding phenylacetaldehyde derivatives and ammonia, which might undergo a Chichibabin-type reaction to produce a pyridinium core.[7] To the best of our knowledge, there have been no reports concerning the use of the catabolism and reconstruction behaviors of natural amino acids as a leading strategy for the development of novel synthetic methodologies.

Pyridine is one of the most common N-containing aromatic ring systems[8] and can be found in a wide range of natural products, pharmaceuticals, and functional materials.[9] Pyridine rings are traditionally prepared from aldehydes and amines via multicomponent reactions[10] or transition-metal-catalyzed cycloaddition processes.[11] However, the application of these reactions can sometimes be limited by their requirements for the use of toxic aldehydes or the need for extensive workup procedures to remove residual metals. To address these limitations, research efforts have recently been directed toward the construction of pyridine skeletons via the oxidative cleavage of the C−N bonds of amine derivatives[12] (Figure 2, Column 1, left side). Herein, we report an unprecedented I_2-mediated reaction for the in situ cleavage of the unreactive C−N bonds[13] of natural amino acids to catabolize to the corresponding aldehydes and amines, which subsequently undergo a reconstruction process to afford 2,6-disubstituted, 2,4,6-trisubstituted, and 3,5-disubstituted pyridines in a single step. Given that the construction of pyridines from natural amino

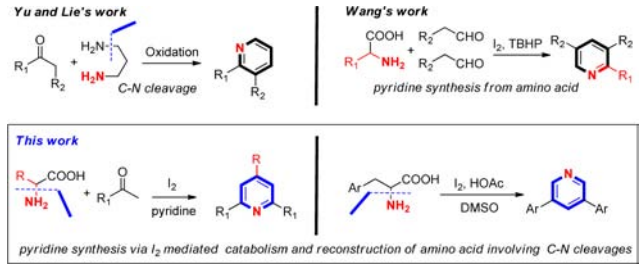


Figure 2. Selected examples of pyridine synthesis and a brief introduction of this work.

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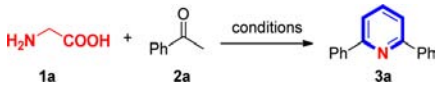
acids under mild condition represents a rare transformation[14] (Figure 2, Column 2, right side), this new method for the selective synthesis of multisubstituted pyridines from different kinds of amino acids will be of considerable practical value (Figure 2, Column 2).

We initially investigated the reaction of glycine (**1a**) with acetophenone (**2a**) as a model reaction in the presence of 1.0 equiv of I_2 at 100 °C in DMF. Several bases were screened against this transformation to optimize the reaction conditions (for optimization details, please see Supporting Information (SI)). The results of these screening experiments showed that pyridine was critical to the success of the transformation (Table 1, entry 1). When the solvent was switched from DMF to pyridine, the yield of the desired product 2,6-diphenylpyridine (**3a**) increased significantly (Table 1, entry 2). Several other bases were also evaluated but found to be ineffective (Table 1, entries 3−7). The optimal temperature for this reaction was determined to be 120 °C (Table 1, entry 9). Notably, decreasing or increasing the loading of I_2 led to a reduction in the yield of the product, indicating that a loading of 1.0 equiv was optimal.

Table 1. Optimization of the Reaction 1[a]



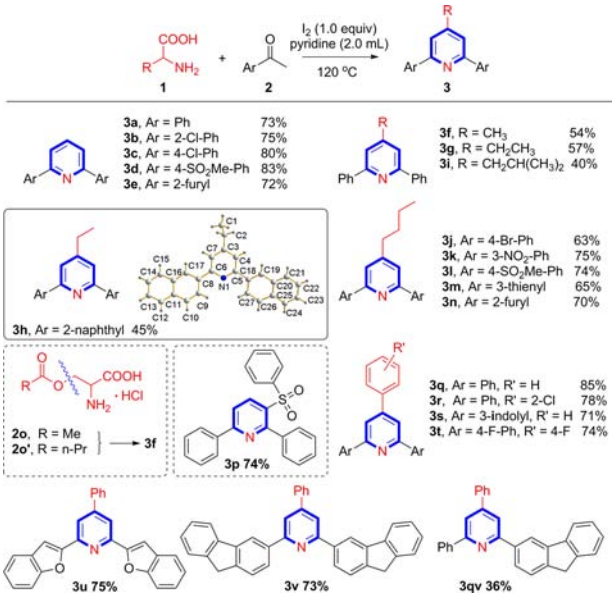
1a 2a 3a

entry	solvent	I_2 (equiv)	additive (equiv)	temp (°C)	yield[b] (%)
1	DMF	1.0	Pyridine (2.0)	100	31
2	Pyridine	1.0	–	100	61
3	Pyridine	1.0	DBU (2.0)	100	trace
4	Pyridine	1.0	DMAP (2.0)	100	36
5	Pyridine	1.0	Cs_2CO_3 (1.0)	100	trace
6	Pyridine	1.0	K_2CO_3 (1.0)	100	23
7	Pyridine	1.0	KOH (2.0)	100	27
8	Pyridine	1.0	–	110	65
9	**Pyridine**	**1.0**	–	**120**	**73**
10	Pyridine	0.2	–	120	24
11	Pyridine	0.5	–	120	41
12	Pyridine	1.5	–	120	27

[a]Reaction conditions: **1a** (2.0 mmol, excessive dose), **2a** (2.0 mmol), additive, solvent (2.0 mL) for 12 h. [b]Isolated yields based on **2a**. Reactions were carried out in a pressure vessel.

With the optimized conditions in hand, we proceeded to examine the scope of the reaction using a variety of different substrates (Scheme 1). Several alkyl-branched amino acids, including alanine (**3f**), 2-aminobutanoic acid (**3g**, **3h**), leucine (**3i**), and 2-aminohexanoic acid (**3j**−**n**), all reacted smoothly under the optimized conditions to produce the corresponding 2,4,6-trisubstituted pyridines in moderate yields. Unfortunately, the use of *O*-acetyl-L-serine hydrochlorideas (**2o**) or *O*-butyryl-L-serine hydrochlorideas (**2o′**) as substrates failed to provide the desired products. The unexpected cleavage of C−O bonds led to 4-methyl-2,6-diphenylpyridine (**3f**) being the major product. Furthermore, a wide range of acetophenones were screened under the optimized conditions. Acetophenones bearing an electron-withdrawing group on their phenyl ring reacted well and produced the desired pyridine products in good yields (e.g., **3d**, **3k**, **3l**). Acetophenone substrates bearing a halogen substituent on their benzene ring (e.g., 2-Cl, 4-Cl, 4-Br: **3b**, **3c**, **3j**) were well tolerated. Notably, 2-naphthyl methyl ketone also reacted smoothly to give the desired product (**3h**) in moderate yield (45%) which was unambiguously confirmed by X-ray crystallography (please see SI). The optimized conditions were also successfully applied to a wide variety of heteroaryl ketones, including furanyl, thienyl, indolyl, and benzofuryl methyl ketones, which generated the corresponding heterocyclic substituted pyridines in good yields (**3e**, **3n**, **3m**, **3s**, **3u**, respectively). It is noteworthy that the reaction of glycine with 1-phenyl-2-(phenylsulfonyl)ethan-1-one under the optimized conditions led to the unexpected cleavage of one of the two sulfonylbenzene groups and the formation of 2,3,6-trisubstituted pyridine (**3p**) as the main product in 74% yield. Several non-natural α-aromatic amino acids, such as 2-amino-2-phenylacetic acid and related derivatives, were found to be especially good substrates for this transformation (**3q**−**t** with good yields in most cases) because of the electron-withdrawing effect of their aromatic rings. Sterically hindered substituents were also employed, and the results were satisfactory (**3u** and **3v**). Cross-trapping product **3qv** could be obtained using **2a** (1.0 mmol) together with 1-(9*H*-fluoren-3-yl)ethanone (1.0 mmol) as substrates.

Scheme 1. Scanning of Substrate Scope of Reaction 1[a,b]



[a]Reaction conditions: **1** (2.0 mmol), **2** (2.0 mmol), I_2 (2.0 mmol), pyridine (2.0 mL), 120 °C for 12 h. [b]Isolated yields. Reactions were carried out in a pressure vessel.

Having evaluated the scope of this new method, we turned our attention to the reaction of phenylalanine (**4a**) with acetophenone (**2a**). However, this reaction did not generate any of the desired product under the optimized conditions, but it did result in the formation of a small amount of 3,5-diphenylpyridine. Further investigation revealed that acetophenone did not participate in this transformation and that the 3,5-diphenylpyridine product was therefore formed as a consequence of the catabolism and homoreconstruction of phenylalanine through a C−N cleavage process. Because of this unusual transformation, we screened a variety of different solvents with the aim of improving the yield of the 3,5-diphenylpyridine product (for the optimization details, please see SI). Only DMSO gave a relatively meaningful yield (Table 2, entry 1). The optimal temperature for the reaction was determined to be 115 °C (Table 2, entry 2). The loading of I_2 was also examined. Addition of 0.2 equiv of I_2 led to a 20%

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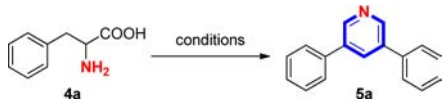
Table 2. Optimization of the Reaction 2[a]



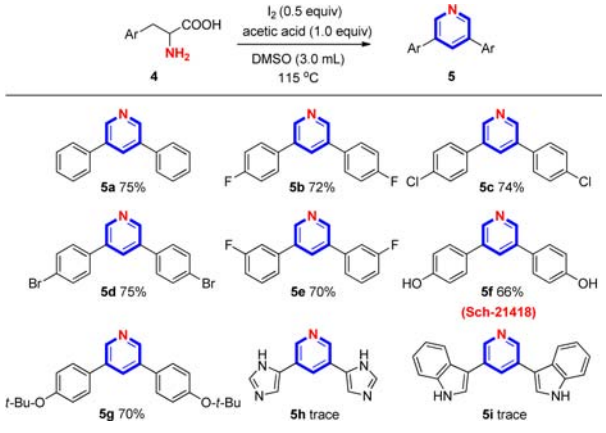
entry	I_2 (equiv)	additive (1.0 equiv)	temp (°C)	yield[b] (%)
1	1.0	–	100	31
2	1.0	–	115	46
3	0.2	–	115	20
4[c]	0.2	–	115	65
5	0.4	–	115	25
6	0.5	–	115	61
7	1.0	–	115	33
8	1.5	–	115	trace
9	0.5	K_2CO_3	115	25
10	0.5	NaOAc	115	trace
11	**0.5**	**HOAc**	**115**	**75**
12	0.5	acetic anhydride	115	70

[a]Reaction conditions: **4a** (1.0 mmol), I_2, additive, DMSO (3.0 mL) for 6 h. [b]Isolated yields. [c]Reaction time extented to 24 h. Reactions were carried out in a pressure vessel.

yield of the product (Table 2, entry 3). However, extension of the reaction time to 24 h lead to a 65% yield which means I_2 could be recycled by DMSO as a catalyst. The best result could be achieved when using 0.5 equiv of I_2 (Table 2, entry 6). An increased dose of I_2 lead to a dramatic reduction of desired product. Additives such as acids and bases have been scanned, and acetic acid was found to be optimal in reducing byproducts and improving the yield of **5a** (Table 2, entry 11).

Given that the yield of 3,5-diphenylpyridine achieved by this reaction was pleasing compared with that of "abnormal" *Chichibabin* pyridine synthesis,[15] we proceeded to investigate the scope of this conversion using a variety of phenylalanine derivatives bearing sensitive halogen substituents (4-F, 4-Cl, 4-Br, and 3-F; Scheme 2). All of these compounds gave the desired products in good yields. It is noteworthy that the reaction of tyrosine with a free hydroxyl group successfully furnished the interleukin-6 inhibitor Sch-21418[16] (**5f**) in 66% yield. The use of tyrosine derivatives bearing a *t*-Bu protecting group on their hydroxyl functionality gave **5g** (70%), which was

Scheme 2. Scanning of Substrate Scope of Reaction 2[a,b]

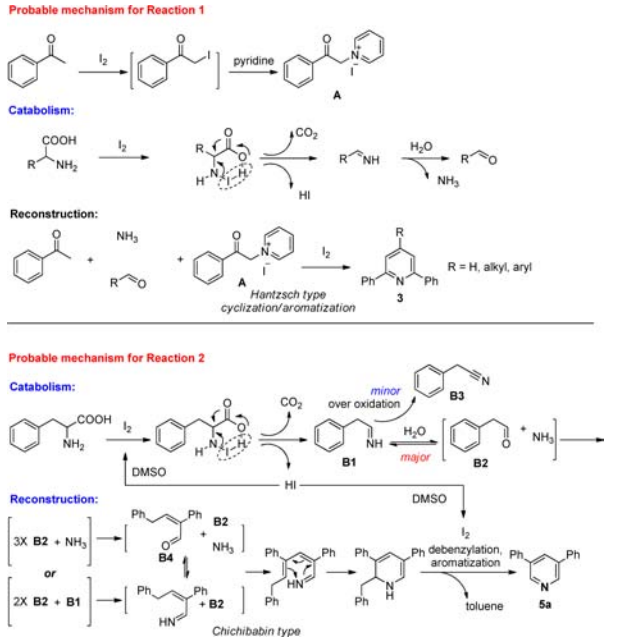


[a]Reaction conditions: **4** (2.0 mmol), HOAc (2.0 mmol), I_2 (1.0 mmol), DMSO (3.0 mL), 115 °C for 6 h. [b]Isolated yields. Reactions were carried out in a pressure vessel.

visualized as a white fluorescent dot by TLC. Unfortunately, histamine and tryptophan did not react in the same way.

The following control experiments were performed to provide some insight into the mechanisms of these reactions (for a detailed graphic, please see SI). For reaction 1, acetophenone was treated with 1.0 equiv of I_2 in the absence of an amino acid in pyridine under the standard conditions for 6 h. This reaction produced 1-(2-oxo-2-phenylethyl)pyridin-1-ium iodide (**A**) as a undissolved product in excellent yield. Given that the generation of the pyridinium ylide equivalent **A** would be an inevitable part of this reaction and pyridine was found to be critical to the success of this transformation, it seemed reasonable to assume that a pyridinium ylide was formed as a crucial intermediate during this reaction. The formation of **3q** in 71% yield from the reaction of amino acid **1q** with **A** in the absence of acetophenone provided further proof of this idea. However, the yield of this reaction was lower than that of the reaction shown in Scheme 3, which indicated

Scheme 3. Probable Mechanisms



that acetophenone played another role in the transformation. The subsequent reaction of **1q** with equal amounts of **A** and **2v** under the standard conditions gave the symmetrical products **3q** and **3v** in 7% and 34% yields, respectively. The cross-trapping product **3qv** was also obtained, as predicted, in a 45% yield. For reaction 2, we repeated the first reaction using 2-phenylethan-1-amine instead of phenylalanine (**4a**). However, this reaction failed to produce any trace of the desired product **5a** under standard conditions. This result suggests that the driving force for this reaction was the decarboxylation of the amino acid. The absence of a carboxyl group would make it difficult to activate the C−N bond at the α position, therefore preventing its oxidative cleavage by I_2. This result also suggests that this efficient I_2-mediated catabolism process is unique to amino acids. Furthermore, 2-phenylacetonitrile (**B3**), 2,4-diphenylbut-2-enal (**B4**), and toluene could be detected by GC-MS as intermediates.

Based on the results described above and previous research, we have proposed a plausible mechanism (Scheme 3). For

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reaction 1, the acetophenone substrate would be initially converted to 2-iodo-1-phenylethan-1-one, which would be trapped by pyridine to afford 1-(2-oxo-2-phenylethyl)pyridin-1-ium iodide (**A**). At the same time, I_2 would trigger the sequential decarboxylation and oxidation reactions of the amino acid substrate to generate the corresponding imine species, which would undergo a rapid hydrolysis reaction to give ammonia and the corresponding aldehyde. The ammonia, aldehyde, **A**, and residual acetophenone would converge via a Kröhnke type pyridine synthesis[17] to reconstruct the desired 2,6-disubstituted or 2,4,6-trisubstituted pyridine product in the presence of I_2. A similar mechanism would also occur for reaction 2 (with phenylalanine as an example). Followed by decarboxylation of carboxyl group, I_2 promoted the oxidation of the C−N bond to afford the unstable intermediate 2-phenylethan-1-imine (**B1**). After hydrolysis, phenylalanine catabolized to corresponding ammonia and 2-phenylacetaldehyde (**B2**). The combination of 3 equiv of **B3** with 1 equiv of ammonia (or 2 equiv of **B3** with 1 equiv of **B1**) would allow for the construction of the pyridine core in situ via a *Chichibabin*-type pyridine synthesis. Finally, the 3,5-disubstituted pyridine product could be obtained by a debenzylation/aromatizition process.[10a] This process would allow for the regeneration of a catalytic equivalent of I_2 in the presence of DMSO.

In summary, we have developed a novel method for the chemoselective synthesis of 2,6-disubstituted, 2,4,6-trisubstituted, and 3,5-disubstituted pyridines from natural amino acids. These transformations featured a catabolism and reconstruction reaction model including an unprecedented I_2-mediated oxidative cleavage of unreactive C−N bonds. In addition to the inherent value offered by this reaction as a biomimetic process, one of the main advantages of this environmentally benign method is that it avoids the direct use of toxic aldehydes and harsh conditions. Moreover, the transformation of biomass materials into synthetically valuable scaffolds is ecologically and economically beneficial.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03037.

Experimental procedures, product characterizations, crystallographic data, and copies of the ^{1}H and ^{13}C NMR spectra (PDF)

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

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Notes

The authors declare no competing financial interest.

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Dearomatization of Indoles via Palladium-Catalyzed Allylic C−H Activation

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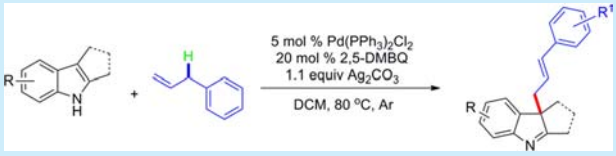
Supporting Information

ABSTRACT: The first Pd-catalyzed allylic dearomatization of substituted indoles triggered by C−H bond activation is reported. The presence of a catalytic amount of 2,5-DMBQ is proven to be a key factor for the high yield. This one-pot tandem allylic C−H activation/dearomatization sequence provides a straightforward access to 3,3-disubstituted indolines.



The dearomatization process has been widely recognized as a powerful strategy for the construction of cyclic or heterocyclic frameworks from simple starting materials.[1,2] Therefore, a great deal of effort has been devoted to dearomatization reactions, and various methods have been established in alkylative and arylative dearomatizations.[3] Among them, transition-metal-catalyzed dearomatization of indoles derivatives attracts much more attention for its extensive application in the synthesis of different indole alkaloids. In general, the classical and efficient dearomatization reactions of indoles have been made with electrophiles containing a leaving group.[4] However, from a step- and atom-economic point of view, the dearomatization reactions triggered by a simple C−H bond activation[5] would be a more straightforward and advanced alternative. Very recently, Luan's group and You's group independently reported the dearomatization of naphthols via transition-metal-catalyzed C−H functionalization.[6a−c] The Tanaka group successfully developed a gold-catalyzed dearomatization of 1-aminonaphthalene derivatives with an intramolecular C−H functionalization.[6d] Despite this progress, transition-metal-catalyzed direct dearomatization via C−H bond functionalization remains rare and sluggish.

It is well-known that transition-metal-catalyzed allylic C−H activation is potentially a more efficient and complementary process to the conventional Tsuji−Trost-type reactions.[7] Though allylic C−H bond activation studies have made significant advancements recently,[8−11] application of this strategy to the dearomatization of indoles has not yet been described. Previous strategies for the allylic dearomatization of indoles mainly employed allylic halides or esters (Scheme 1, path A).[12] As a result of our endeavors, a new method for the dearomatization of indoles triggered by a Pd(II)-catalyzed allylic C−H activation was developed (Scheme 1, path B). Compared with existing allylic dearomatization of indoles, our reaction combines allylic C−H activation with dearomatization of indoles and provides a rapid and concise route to the synthesis of polysubstituted indolines.

Scheme 1. Strategies for Dearomatization of Indoles

At the outset of this study, we chose 2,3-dimethylindole (1a) and allylbenzene (2a) as model substrates to optimize suitable reaction conditions. We screened a number of conditions including palladium sources, oxidants, solvents, and additives (Table 1). After consulting previous reports of allylic C−H activations, we selected $Pd(PPh_3)_2Cl_2$ (5 mol %) as the catalyst, Ag_2CO_3 (1.1 equiv) as the oxidant as well as the base, and benzoquinone (BQ) (1.1 equiv) as an additive. A series of solvents were then evaluated at 80 °C in the reaction of allylic C−H activation and dearomatization of indoles. Gratifyingly, we found that $Pd(PPh_3)_2Cl_2$ could catalyze the reaction and that dichloromethane (DCM) is the best solvent (entries 1−7); the desired product was obtained in 23% yield. Encouraged by this result, we further optimized the reaction conditions. Subsequently, control experiments indicated that Ag_2CO_3 and BQ were essential to the reaction (entries 8 and 9). A screening of different palladium catalysts showed that $Pd(PPh_3)_2Cl_2$ is still the best choice in this transformation (entries 10−14). It is well-known that BQ is pivotal in many Pd-catalyzed allylic functionalization reactions and often serves as the oxidant and ligand.[13] Therefore, various BQ derivatives such as additives 2−8 on an equivalent scale were examined. When substituted electron benzoquinones such as 2-methylbenzoquinone, 2,6-dimethylbenzoquinone, and 2,5- dimethylbenzoquinone (2,5-DMBQ),

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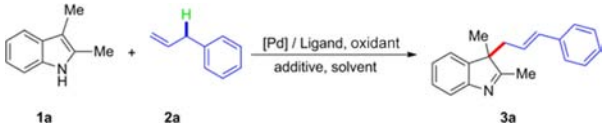
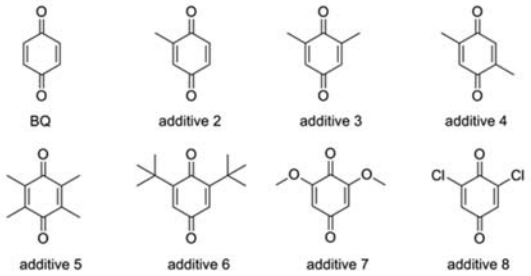
Table 1. Reaction Conditions Screening[a]



1a 2a 3a

entry	[Pd] +ligand	oxidant	additive	solvent	yield (%)[b]
1	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	BQ	toluene	20
2	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	BQ	DCM	23
3	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	BQ	DCE	19
4	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	BQ	THF	20
5	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	BQ	MTBE	23
6	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	BQ	DMSO	0
7	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	BQ	$CHCl_3$	21
8	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3		DCM	0
9	$Pd(PPh_3)_2Cl_2$		BQ	DCM	<5
10	$Pd(OAc)_2$ +PPh_3	Ag_2CO_3	BQ	DCM	<5
11	$PdCl_2$ +PPh_3	Ag_2CO_3	BQ	DCM	<5
12	$Pd(TFA)_2$ +PPh_3	Ag_2CO_3	BQ	DCM	<5
13	$[Pd(C_3H_5)Cl]_2$	Ag_2CO_3	BQ	DCM	<5
14	$Pd(PCy_3)_2Cl_2$	Ag_2CO_3	BQ	DCM	12
15	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	additive 2[e]	DCM	42
16	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	additive 3[e]	DCM	58
17	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	additive 4[e]	DCM	93
18	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	additive 5[e]	DCM	<5
19	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	additive 6[e]	DCM	<5
20	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	additive 7[e]	DCM	<5
21	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	additive 8[e]	DCM	<5
22[c]	**$Pd(PPh_3)_2Cl_2$**	**Ag_2CO_3**	**additive 4[e]**	**DCM**	**93**
23[d]	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	additive 4[e]	DCM	31
24[c]	$Pd(PPh_3)_2Cl_2$	$K_2S_2O_8$	additive 4[e]	DCM	<5
25[c]	$Pd(PPh_3)_2Cl_2$	oxone	additive 4[e]	DCM	10
26[c]	$Pd(PPh_3)_2Cl_2$	AgOAc	additive 4[e]	DCM	<5
27[c]	$Pd(PPh_3)_2Cl_2$	Ag_2O	additive 4[e]	DCM	34
28[c]	$Pd(PPh_3)_2Cl_2$	DICP	additive 4[e]	DCM	21

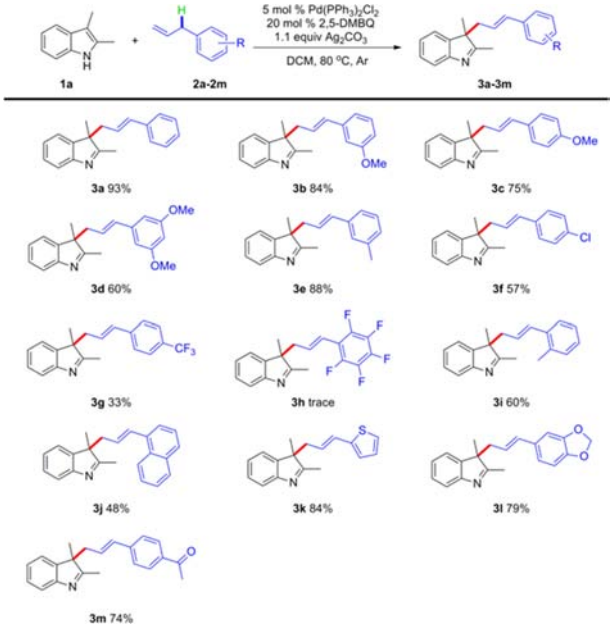


[a]The reactions were carried out by using **1a** (0.20 mmol), **2a** (0.44 mmol), palladium (5 mol %), ligand (10 mol %), oxidant (1.1 equiv), and additive (1.1 equiv) in solvent (1.5 mL) at 80 °C for 16 h under argon. [b]Isolated yields. [c]Additive (20 mol %). [d]Additive (10 mol %). [e]Additive 2 = *p*-toluquinone; additive 3 = 2,6-dimethyl-1,4-quinone; additive 4 = *p*-xyloquinon; additive 5 = duroquinone; additive 6 = 2,6-di-*tert*-butyl-*p*-benzoquinone; additive 7 = 2,6-dimethoxy-1,4-benzquinone; additive 8 = 2,6-dichloro-1,4-benzquinone.

were examined, the yield of the desired product improved (entries 15−17). The 2,5-dimethylbenzoquinone (2,5-DMBQ) gave an excellent yield of 93% (entry 17). Owing to the electronic and steric effects, duroquinone, 2,6-di-*tert*-butyl-*p*-benzoquinone, and 2,6-dimethoxyquinone only provided lower yields (entries 18−20). Moreover, electron-poor 2,6-dichlorobenzoquinone also was unfavored for this reaction (entry 21). Next, decreasing the amount of 2,5-dimethylbenzoquinone (2,5-DMBQ) to 20 mol % left the yield of product completely unchanged (entry 22). A further decrease of the amount of 2,5-dimethylbenzoquinone (2,5-DMBQ) is not beneficial to the reaction (entry 23). Finally, we also investigated other oxidants, but no improvements were obtained (entries 24−28). Thus, the optimal reaction conditions were obtained by using $Pd(PPh_3)_2Cl_2$ (5 mol %) as the catalyst, 2,5-dimethylbenzoquinone (2,5-DMBQ) (20 mol %) as additive, 1.1 equiv Ag_2CO_3 as the base as well as the oxidant in 1.5 mL of DCM for 0.2 mmol of **1a** with 0.44 mmol of allylbenzene at 80 °C under an argon atmosphere (entry 22).

Having discovered optimized conditions for the allylic dearomatization reaction of 2,3-disubstituted indole, we wished to demonstrate the generality of this straightforward transformation. We first investigated the compatibility of the olefin partners (Scheme 2). Indeed, electron-rich allylbenzene such as

Scheme 2. Substrate Scope of Alkenes[a,b]



[a]The reaction was carried out with $Pd(PPh_3)_2Cl_2$ (5 mol %), 2,5-DMBQ (20 mol %), Ag_2CO_3 (1.1 equiv), **1a** (0.20 mmol), and **2a−m** (0.44 mmol) in DCM (1.5 mL) at 80 °C for 16 h under argon. [b]Yield of isolated product.

m-methoxyallylbenzene, *p*-methoxyallylbenzene, and 3,5-dimethoxyallylbenzene afforded the desired products in 84%, 75%, and 60% yields, respectively (**3b−d**). 3-Methylallylbenzene furnished the desired product with 88% yield (**3e**). Unfortunately, the electron-poor allylbenzenes such as 4-Cl- and 4-CF_3-substituted allylbenzene delivered the desired products in 57% and 33% yield, respectively (**3f,g**). The allylpentafluorobenzene only gave trace amounts of the desired product (**3h**). Meanwhile, possibly due to a steric effect, 2-methylallylbenzene gave the corresponding product in 60% yield (**3i**), and 2-naphthylpropene gave the corresponding product in 48% yield (**3j**). Notably, heteroaryl-substituted propenes such as 2-allylthiophene and 5-allylbenzo[*d*][1,3]dioxole also produced the desired products in good yields (**3k**, 84%; **3l**, 79%). Moreover, the 4-acetylallylbenzene afforded the desired product in 74% yield (**3m**). Nonactivated alkenes such as 1-decene or 1-octene are not compatible in this reaction.

Next, various substituted indoles were examined (Scheme 3). Both electron-donating group (5-OMe) and electron-withdrawing groups (5-Cl, and 5,7-di-Cl) on the indoles were well-tolerated and gave the corresponding products in moderate to good yields (**4b−d**). Moreover, carbon-cycle-fused indoles were also proven to be suitable for this transformation. For example, the 1,2,3,4-tetrahydrocarbazole and indolo(2,3-B)cycloheptene afforded dearomatizated products in 88% and 67% yields (**4e** and **4f**). 3-Monosubstituted indoles were then studied. 3-methylindole delivered the desired product **4g** in 56% yield. Tryptophol

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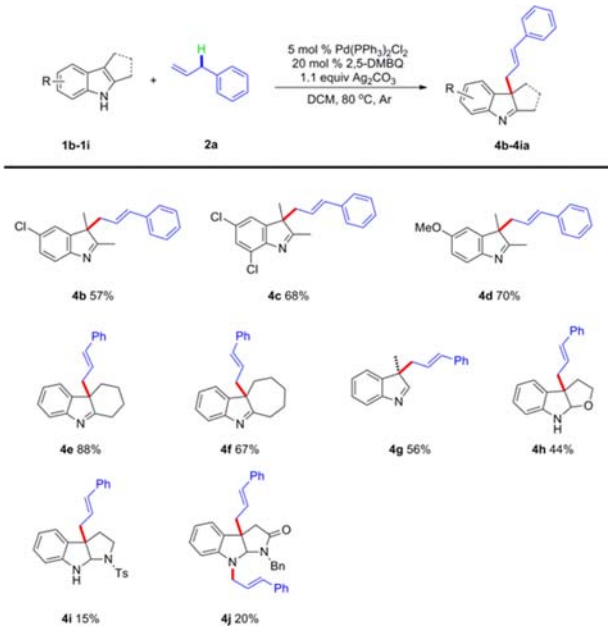
Scheme 3. Substrate Scope of Indoles[a,b]

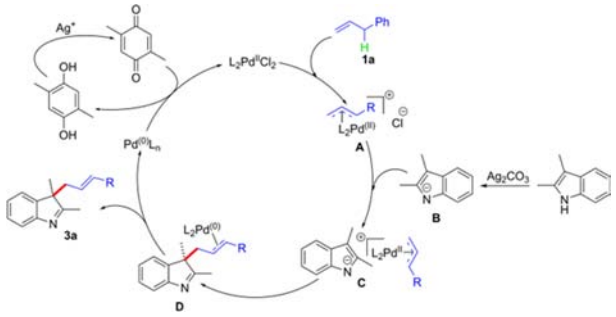


[a]The reaction was carried out with $Pd(PPh_3)_2Cl_2$ (5 mol %), 2,5-DMBQ (20 mol %), Ag_2CO_3 (1.1 equiv), **1b−i** (0.20 mmol), and **2a** (0.44 mmol) in DCM (1.5 mL) at 80 °C for 16 h under argon. [b]Yield of isolated product.

gave the corresponding furanoindoline product in 44% yield (**4h**). When *N*-tosyltryptamine was used, the corresponding product was observed in lower yield (**4i**), and the allylic amination product was obtained as byproduct concomitantly. Moreover, indolylcarboxyamide gave the double allylic substituent product at the C-3 and N-1 positions in 20% yield (**4j**), and meanwhile, the C−H bond amination product was also produced.

In accordance with the experimental results (see the Supporting Information) and by referring to the leading literature,[13] the mechanism is proposed in Scheme 4. The

Scheme 4. Proposed Mechanism of Allylic C−H Activation/Dearomatization of Indoles



catalytic cycle was initiated via an electrophilic allylic C−H activation by Pd(II) catalyst, and π-allylpalladium complex **A** was formed.[14] At the same time, Ag_2CO_3 worked as the base for deprotonation of substituted indole to afford nucleoplilic reagent **B**, which then accepted the π-allylpalladium complex attack and produced the dearomatization to form the complex **D**. Then, complex **D** released the product **3a** and formed the L_2Pd^0, followed by a redox reaction with 2,5-DMBQ to generate $L_2PdIICl_2$ and 2,5-dimethylbenzene-1,4-diol to complete the catalytic cycle. Meanwhile, 2,5-dimethylbenzene-1,4-diol was oxidized by Ag_2CO_3 to regenerate the 2,5-DMBQ. In this reaction, we also could not exclude that 2,5-DMBQ performed as the ligand and prompted the reductive elimination to proceed with a swing.

In conclusion, we have developed the first general example of direct palladium-catalyzed C3-allylic dearomatization of substituted indoles through C−H activation/dearomatization tandem processes. This Pd-catalyzed transformation is effective for indoles and allylbenzenes containing sterically and electronically diverse substituents and affords the C3-phenylpropenyl indolenine products in good yield.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03053.

Experimental details, characterization data, and copies of NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(14) The ESI/MS showed peaks at *m*/*z* 745.1602, 746.1613, 747.1606, 748.1637, 749.1598, 750.1630, 751.1612, 752.1637, which corresponds to a cation of complex A (for detailed information, see the Supporting Information).

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Thermodynamic Control of Isomerizations of Bicyclic Radicals: Interplay of Ring Strain and Radical Stabilization

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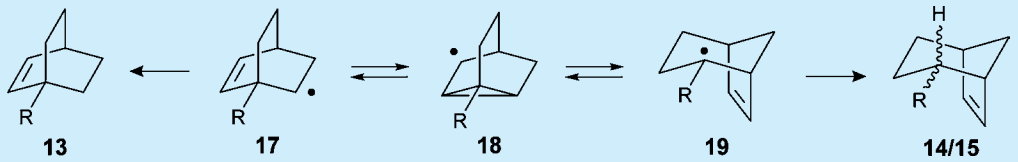
Supporting Information



ABSTRACT: The rearrangements of 4-substituted bicyclo[2.2.2]oct-5-en-2-yl radicals, generated from the corresponding Diels–Alder adducts with phenylseleno acrylates by radical-induced reductive deselenocarbonylations, give the 2-substituted bicyclo[3.2.1]oct-6-en-2-yl radicals with some substituents, e.g., alkoxy and phenyl, but not for silyloxymethyl or benzyl substituents. Theoretical calculations with DFT give the thermodynamics of these reactions and the origins of these processes.

Recently, we reported the development of phenylseleno acrylate **1** as an "ethylene equivalent" in Diels–Alder reactions.[1] Thus, heating **1** with various dienes **2** gave the expected cycloadducts **3**, which could be reduced cleanly using tris(trimethylsilyl)silane **4**, the Chatgilialoglu reagent,[2] to give the desired formal cycloadducts of ethylene **5** (Figure 1).

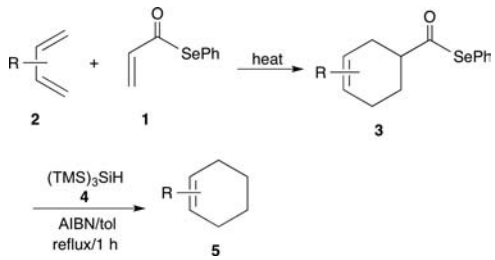
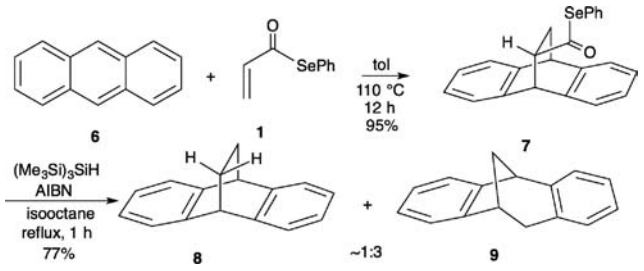


Figure 1. Use of **1** as an ethylene equivalent in Diels–Alder reactions.

The majority of substrates were reduced under the normal conditions without any rearrangement of the generated radicals.[3] However, we reported that the adduct **7**, prepared by the Diels–Alder reaction of anthracene **6** with the dienophile **1**, underwent significant rearrangement to give a 1:3 mixture of the expected dibenzobicyclo[2.2.2]octane product **8** and the rearranged dibenzobicyclo[3.2.1]octane product **9** (Scheme 1).[1] This was attributed to the well-known homoallyl–cyclopropyl carbinyl radical rearrangement pathway leading to a more stable radical.[4] This specific transformation is also known as a neophyl rearrangement.[5] We now report that this rearrangement is general and proceeds for all systems in which the radical in the new bicyclo[3.2.1]octyl ring system is more stable than the radical in the original bicyclo[2.2.2]octyl ring system. We observe an interesting result, namely that a secondary bicyclo[2.2.2]oct-5-en-2-yl radical is more stable than a tertiary bicyclo[3.2.1]oct-6-en-2-yl radical. Theoretical

Scheme 1. Rearrangement of Anthracene Adduct 7



calculations show the interplay of ring strain and relative stabilities of these substituted radical systems.

The substrates for the radical rearrangement studies were all prepared by the Diels–Alder reaction of the freshly prepared 1-substituted 1,3-cyclohexadienes **10**[6] with the phenylseleno acrylate **1**, which were carried out in refluxing toluene for 14 h (Table 1). The cycloadducts were obtained in yields of 55–97% as mixtures of endo and exo isomers **11** and **12**. In all cases, the endo isomers **11** were the major products, with the endo/exo ratio varying from 3.3–8 to 1.[7]

With the Diels–Alder products **11** and **12** in hand, we next examined their reductive decarbonylation to produce the reduced products. A mixture of the endo and exo esters was treated with tris(trimethylsilyl)silane and AIBN in refluxing benzene for several hours to give the reduction products (Table 2). The reduction of the parent unsubstituted compound **11a**/**12a** gave predominately the expected bicyclo[2.2.2]octene **13a**, with very little rearranged products (>20:1). However, the behavior of the substituted analogues was quite different. Reduction of the 4-methoxy esters **11b**/**12b** afforded only a minor amount of the unrearranged product **13b** and gave

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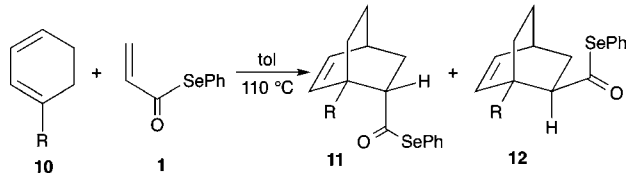
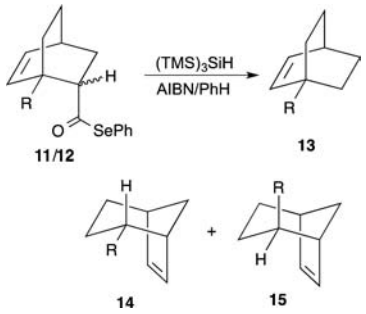
Table 1. Diels–Alder Reaction of 1-Substituted Dienes 10 and Phenylseleno Acrylate 1



entry	compd	R	yield (%)	ratio **11**:**12**[a]
1	**a**	H	97	8:1
2	**b**	OMe	87	5.1:1
3	**c**	OTBS	76	3.4:1
4	**d**	Ph	66	4.4:1
5	**e**	CH_2OTBS	83	3.3:1
6	**f**	CH_2Ph	88	4.1:1

[a]The ratios of all products were determined by careful integration of the appropriate peaks in the ^1H NMR spectra.[7]

Table 2. Reduction of Bicyclo[2.2.2]oct-2-enyl-5-selenophenyl Esters 11 and 12



entry	compd	R	ratio **13**:**14** + **15**	ratio **14**:**15**[a]
1	**a**	H	>20:1	NA
2	**b**	OCH_3	1:5.6	2.6:1
3	**c**	OTBS	1:2.5	2.5:1
4	**d**	Ph	1:10	2.4:1
5	**e**	CH_2OTBS	7:1	2.9:1
6	**f**	CH_2Ph	7:1	3.8:1

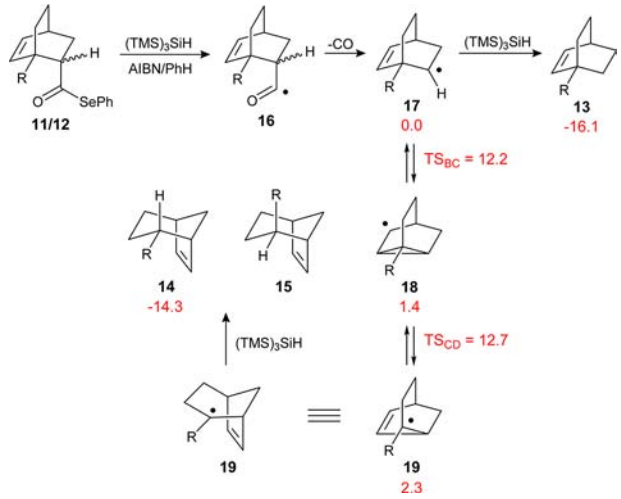
[a]The ratios of all products were determined by careful integration of the appropriate peaks in the ^1H NMR spectra.[8]

mainly the rearranged 2-methoxybicyclo[3.2.1]oct-6-enes **14b** and **15b**, with the ratio of unrearranged to rearranged product being 1:5.6.[8]

The proposed mechanism for the reduction is shown in Scheme 2. Treatment of the selenophenyl esters **11** and **12** with tris(trimethylsilyl)silane generates the acyl radicals **16**, which undergo decarbonylation to give the secondary radicals **17**.[9] Reduction of **17** by the silane affords the unrearranged bicyclo[2.2.2]octene product **13**. However, in competition with this reduction, the radical **17** can rearrange via the cyclopropyl carbinyl radical **18** to give the bicyclo[3.2.1]oct-6-en-2-yl radical **19**. Reduction of this radical by the silane gives a mixture of the equatorial and axial products **14** and **15**.

The prevalence of the rearranged products **14b**/**15b** is not surprising since intermediate **19b**, leading to the bicyclo[3.2.1]-octene product, has a radical adjacent to a methoxy group. In contrast, intermediate **17b**, leading to the bicyclo[2.2.2]octene product, has a simple secondary radical (Scheme 2). As expected, the more substituted radical is more stable. In a like manner, the 4-silyloxy analogue **11c**/**12c**, upon similar

Scheme 2. Proposed Mechanism of Reduction of Selenophenyl Esters[a]



[a]Relative computed Gibbs free energies for the parent compound (R = H) are given in red.

treatment, gave the rearranged products **14c** and **15c** as the major products in a 2.5:1 ratio with the unrearranged product **13c**. Again, the stability of the intermediate radical leading to the rearranged product would be expected to be greater than that of the unrearranged product. The 4-phenyl analogue **11d**/**12d** behaved similarly and afforded the rearranged products **14d** and **15d** in a 10:1 ratio with the unrearranged product **13d**. Here the bicyclo[3.2.1]octenyl radical **19d** is tertiary and benzylic and, therefore, is much more stable than the secondary homobenzylic radical in **17d**. On the basis of these foregoing results, the reduction of the 4-silyloxymethyl analogue **11e**/**12e** seems surprising, since in this case the unrearranged product **13e** predominated, formed in a 7:1 ratio with the rearranged products **14e** and **15e**. This implied that the bicyclo[2.2.2]-octenyl intermediate leading to **13e**, containing a secondary radical, is more stable than the rearranged bicyclo[3.2.1]octenyl intermediate with a tertiary radical. We also reduced the 4-benzyl analogue **11f**/**12f**, and the unrearranged product **13f** was formed preferentially over the rearranged products **14f** and **15f**, again in a ratio of 7:1.

To further investigate these varying product ratios, we performed density functional calculations at the M06-2X/6-311G(d,p)//B3LYP/6-31G(d) level of theory using the Gaussian09 program.[10] Activation free energies for the homoallyl–cyclopropyl carbinyl radical rearrangement of **17a**–**18a** and **18a**–**19a** were also computed.

Figure 2 shows the relative energies of radicals, transition states for rearrangement, and products for the parent system (R = H). The bicyclo[2.2.2]octene, **13a**, is 1.8 kcal/mol more stable than the bicyclo[3.2.1]octene **14a**. The corresponding radicals **17a** and **19a** differ in energy by 2.3 kcal/mol in the same direction. This results from the greater strain of the bicyclo[3.2.1] skeleton. The low activation barriers for $\mathbf{TS}_{17-18}$ and $\mathbf{TS}_{18-19}$ are consistent with the proposed equilibrium between radical species **17** and **19**.

Table 3 shows the computed energy differences between substituted radical species **17** and **19**, along with the corresponding equilibrium ratios from these energies. The energy differences are in good accord with the expected energies of radical stabilization by these substituents.[11]

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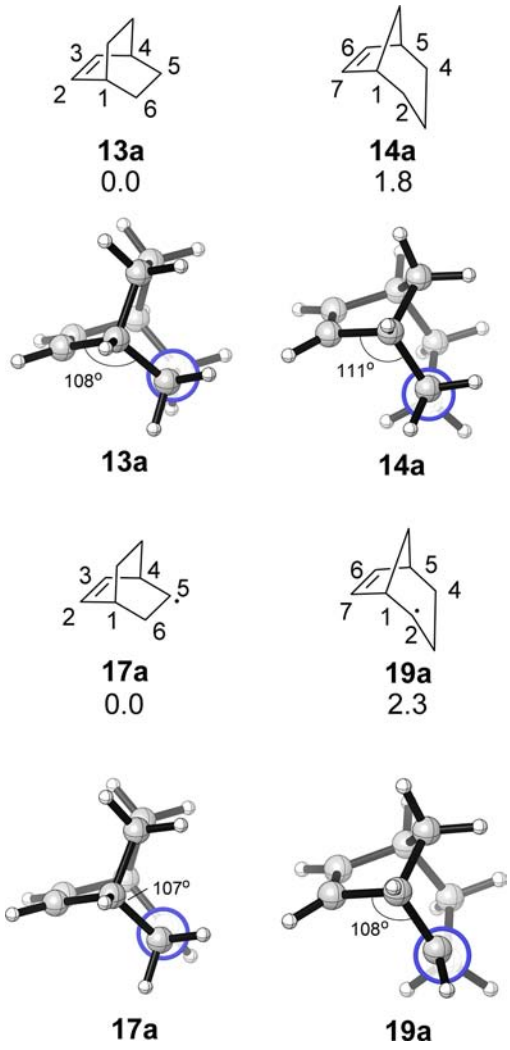

Figure 2. Structures of bicyclo[2.2.2]oct-2-ene **13a**, bicyclo[3.2.1]oct-6-ene **14a**, and their radicals **17a** and **19a**, with relative M06-2X/6-311G(d,p)//B3LYP/6-31G(d) Gibbs free energies in kcal/mol.

Table 3. Computed Radical Stabilities and Equilibrium Ratios of Bicyclic Compounds with Various Substituents

entry	R	$\Delta\Delta G_{17-19}$ (kcal/mol)	predicted ratio **17:19**	experimental ratio **13:14 + 15**
1	H	2.3	48:1	>20:1
2	OCH_3	−1.0	1:5	1:5.6
3	Ph	−6.7	$1:>8 \times 10^4$	1:10
4	CH_3	1.2	8:1	7:1[a]

[a]Experimental value for the CH_2OTBS and CH_2Ph substituents.

Comparing these computed ratios with those observed experimentally confirms our initial assumptions that radical-stabilizing substituents promote the ring rearrangement—methoxy and phenyl substituents favor formation of the bicyclo[3.2.1]octene system, while a methyl substituent, although also stabilizing, prefers to remain unrearranged as the [2.2.2] system.

Furthermore, in the rearranged 2-substituted bicyclo[3.2.1]-oct-6-ene products, the equatorial product **14** is always favored over the axial, **15**, and the ratio of **14**/**15** varies from a low of 2.3:1 to a high of 3.8:1. The radical is only slightly nonplanar, as shown in Figure 3, to minimize eclipsing between the bonds to

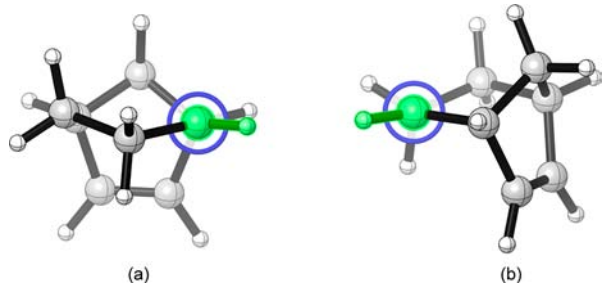

Figure 3. Newman projections for **19a**, viewing from (a) C2−C1 and (b) C2−C3.

the radical center and the attached carbon. Moreover, this preference is reinforced in the transition states in order to minimize eclipsing with the newly forming bond, a well-known phenomenon in C−C bond-forming reactions, sometimes referred to as torsional steering.[12] For instance, in Figure 3, hydrogen abstraction from silane will occur from the top of the radical center of **19a** to avoid torsional strain from eclipsing bonds. This favors formation of product **14** over **15**.

In conclusion, we have found that the in situ generated [2.2.2] radicals are generally more stable than the corresponding [3.2.1] rearrangement counterparts, but radical-stabilizing substituents can reverse this preference. The relative stabilities of these radicals control the product ratios, while torsional effects control the stereochemistry of hydrogen transfer from silane to the alkyl radicals.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03112.

Experimental methods, NMR spectra, and analytical data for all new products (PDF)

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Notes

The authors declare no competing financial interest.

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(8) The mixture of diastereomers could not be separated, but their stereochemistry was assigned by analysis of the crude NMR spectra. The proton α to the R group in **14** always exhibited a very large coupling constant (J = 9.0−12.0) due to the axial−axial coupling, whereas that large coupling was absent from the isomeric compounds **15**.

(9) The acyl radical **A** can also be reduced before decarbonylation, and indeed small amounts of aldehydes are occasionally isolated from these reductions.

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Organic LETTERS

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Asymmetric Organocatalytic Reductive Coupling Reactions between Benzylidene Pyruvates and Aldehydes

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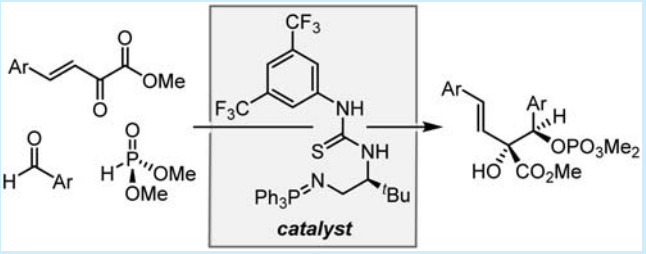
Supporting Information

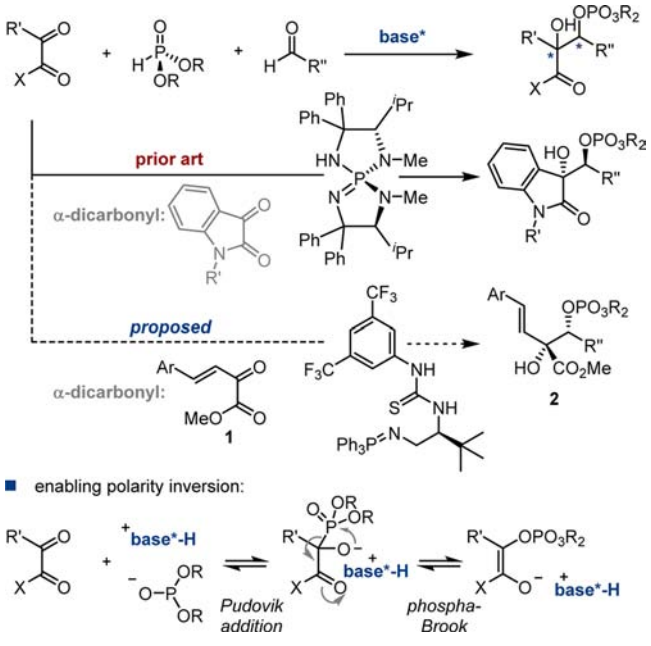
ABSTRACT: An organocatalytic three-component reductive coupling reaction between dimethyl phosphite, benzylidene pyruvates, and aldehydes is reported. A chiral triaryliminophosphorane catalyst promotes Pudovik addition, which is followed by phospha-Brook rearrangement to transiently generate enolates that are trapped stereoselectively by aldehydes. This reductive coupling provides vicinal polyfunctionalized stereocenters from readily available prochiral starting materials with excellent diastereoselectivity, enantioselectivity, and yield.



The reductive union of two prochiral starting materials into products bearing vicinal stereogenic centers builds molecular complexity and as such is an actively sought transformation in chemical synthesis. Pinacol-type reductive coupling reactions deliver vicinal diols,[1−5] but drawbacks remain. Commonly used single-electron transfer methods rely on stoichiometric amounts of low-valent metal,[3n−r] and stereocontrol can be challenging.[5b,c] In the methodologies that have successfully achieved selectivity in the reductive coupling reaction, there is still the issue of making the vicinal alcohols react orthogonally in downstream transformations.[3g] Some of these issues were recently addressed through the use of a base-catalyzed, phosphite-mediated asymmetric reductive coupling of two different carbonyls.[6,7] In this mechanistic manifold, a Pudovik addition of a dialkylphosphite to an isatin triggers phospha-Brook rearrangement and subsequent catalyst controlled trapping of the resultant enolate with an aldehyde.[6−9] Herein, we extend this reaction framework and report a highly stereoselective phosphite-mediated reductive coupling reaction between benzylidene pyruvates and aryl aldehydes (Scheme 1).

Our goal of introducing a higher level of functionality into the product carries with it challenges not faced in our prior work (Scheme 2). In order to achieve a stereoselective cross-coupled product from ambident benzylidene pyruvates and aryl aldehydes, it is necessary to be able to control (a) the chemoselectivity of the phosphite addition (pyruvate vs aldehyde),[10] (b) the regioselectivity of the phosphite addition (1,2- vs 1,4-addition),[11] (c) the nucleophilicity of the nascent enolate (α- vs γ-trapping),[12] (d) the chemoselectivity of the enolate trap (pyruvate vs aldehyde),[12,13] and (e) the stereoselectivity of the enolate addition into the aryl aldehyde. Fortunately, the relative electron deficiency of the benzylidene pyruvates made the chemo- and regioselectivity issues manageable. Furthermore, the chiral triaryliminophosphoranes developed by Dixon and co-workers[14] guided the stereo-

Scheme 1. Asymmetric Reductive Multicomponent Coupling Reactions



defining C−C bond construction with excellent levels of diastereo- and enantiocontrol.

Initially, we studied the dimethyl phosphite mediated reductive coupling of benzylidene pyruvate **1a** with *para*-bromobenzaldehyde (Table 1). Using 10 mol % KO^{t}Bu at 0 °C, the reaction was complete in minutes and hydroxy phosphate **2a** was formed exclusively (dr 1.2:1). Having found that the enolate formed by the Pudovik−phospha−Brook sequence was

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Scheme 2. Chemoselectivity Issues

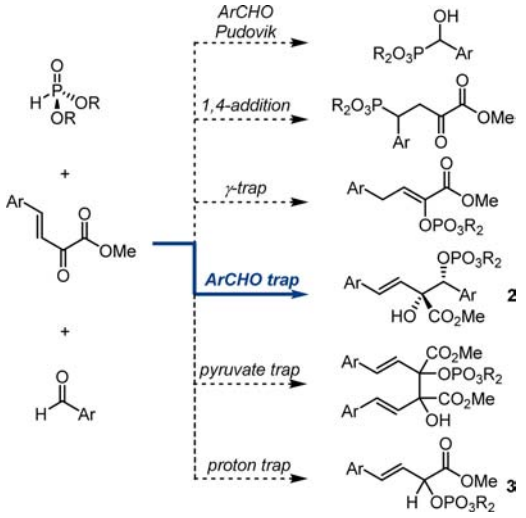
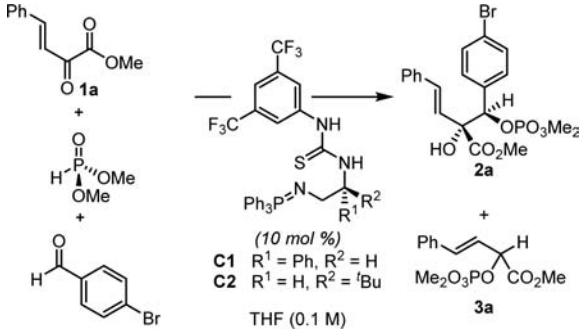


Table 1. Reaction Optimization



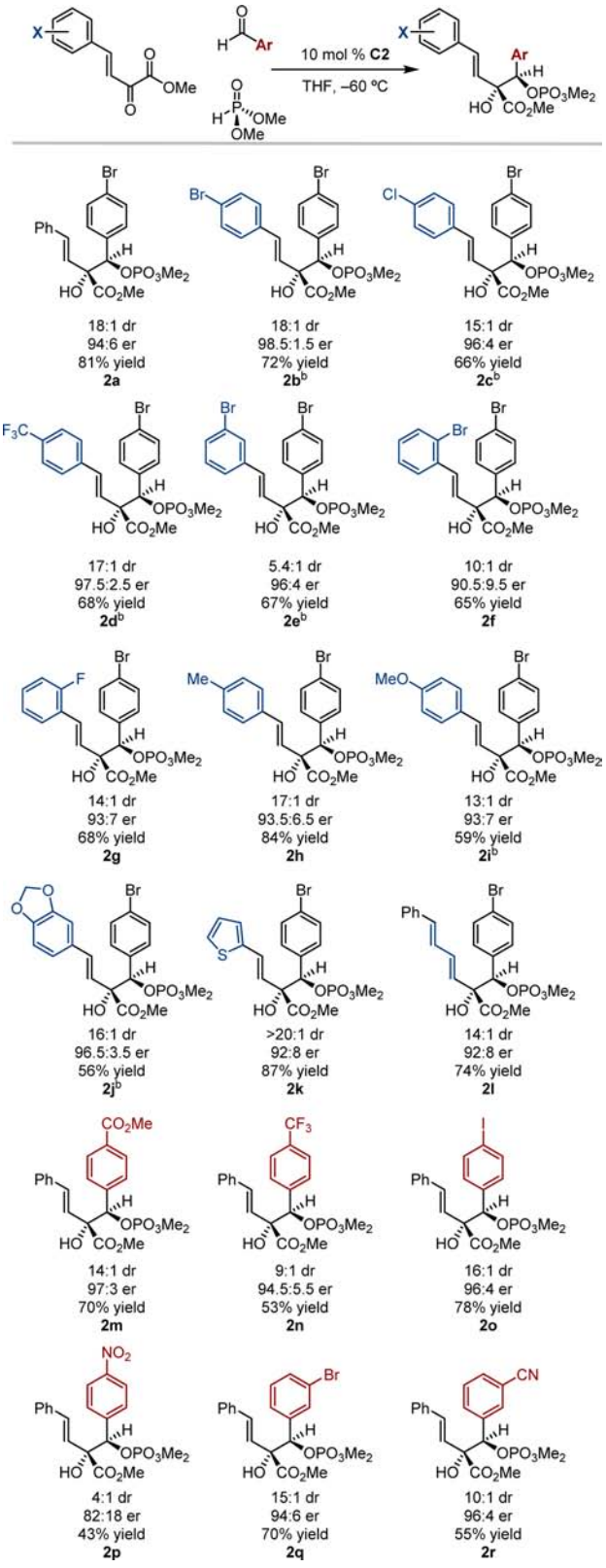
entry	temp (°C)	catalyst	dr	er	2a:3a
1[a]	0	KO^{t}Bu	1.2:1	50:50	100:0
2[b]	−60	C1	13:1	9:91	6:1
3[b]	−60	C2	17:1	97:3	>20:1

[a]Reaction was conducted on 1.0 mmol scale, using 1.1 equiv of dimethylphosphite and 5.0 equiv of ArCHO; reaction was complete in minutes. [b]Reactions were conducted on 0.2 mmol scale, using 1.1 equiv of dimethylphosphite and 5.0 equiv of ArCHO. Reactions were run for 24 h.

both nucleophilic at the correct position and capable of being trapped by aryl aldehydes, we turned our attention to the development of the asymmetric variant. In our previous experience with this type of reductive coupling reaction, we demonstrated through crossover experiments that a stereoablative retro aldol process becomes possible somewhere in the cryogenic range;[7] therefore, we sought to carry out the reactions at as low a temperature as possible. We observed that cinchona alkaloid-derived thiourea catalysts were not basic enough to permit the reaction to proceed at cryogenic temperatures, which caused us to move toward other catalyst families. The evaluation of chiral triaryliminophosphorane **C1** revealed that, after 48 h at −60 °C, the starting material was completely consumed and a 6:1 ratio of products was obtained arising from aldehyde trapping (**2a**) relative to proton trapping (**3a**), the former with a diastereomer ratio of 13:1. This encouraging result led us to synthesize and evaluate catalyst **C2**, which gave a >20:1 ratio of **2a**:**3a**, with >20:1 dr and 97:3 er.

The application of catalyst **C2** to a broader range of reaction partners was then undertaken (Scheme 3). The reaction

Scheme 3. Asymmetric Reductive Coupling Reactions[a,b]



[a]All reactions were conducted on 0.1 mmol scale, using 1.1 equiv of dimethyl phosphite and 5.0 equiv of ArCHO. % yields refer to isolated yields. All dr, er, and % yields are the averages of two trials. [b]Reaction time = 48 h.

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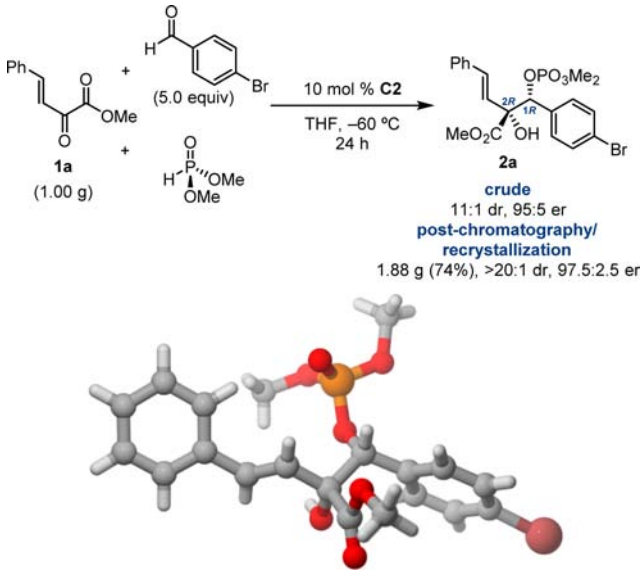
proceeds with electron-withdrawing groups on the benzylidene pyruvate; placing the electron-withdrawing group on the *ortho* (**2f**, **2g**) or *para* (**2b**–**2d**) positions on the benzylidene pyruvate led to comparable yields and stereoselectivities to the unsubstituted case, but we found that using a *meta*-bromo benzylidene pyruvate gave only 5.4:1 dr. Additionally, while substrates with *meta* and *para* electron-withdrawing groups gave upward of 96:4 er, we observed enantioselectivities of 90.5:9.5 for **2f** and 93:7 for **2g** (*o*-bromo and *o*-fluoro, respectively). Using a 4-methyl substituted benzylidene pyruvate we observed that the reaction was complete in 24 h (**2h**), though, with stronger electron-donating groups on the ring, the reaction is slower likely due to depressed rate of Pudovik addition (**2i**–**2j**). Using the 2-thienylidene pyruvate gave **2k** in >20:1 dr, with 87% yield and 92:8 er, but extending the conjugation of the starting material as in **2l** gave 14:1 dr and 92:8 er, with a 74% yield. The reaction was found to proceed with other electron-deficient aryl aldehydes as well (**2m**–**2r**), either in the *para* or *meta* position, although there was a noticeable drop in stereoselectivity with *para*-nitrobenzaldehyde. We attempted to use benzaldehyde as a coupling partner, but observed that the major product formed in that reaction was **3**.[15]

The asymmetric reductive coupling reaction on gram scale works comparably to those reactions conducted on smaller scale. Figure 2 illustrates the conversion of 1 g of **1a** to 1.88 g of the derived coupled product **2a** with >20:1 dr and 97.5:2.5 er after a single recrystallization. An X-ray diffraction study of this material revealed the absolute configuration of the coupled product to be (*1R*,*2R*) (Scheme 4).[16]

Scheme 4. Asymmetric Reductive Coupling Reaction on Gram-Scale and X-ray Diffraction Study of 2a[a]



[a]The reaction was conducted using 1.1 equiv of dimethyl phosphite and 5.0 equiv of ArCHO. % yield refers to isolated yield. Reaction was run for 24 h.

The work described here expands on organic reductant-based organocatalytic reductive coupling. The title process exhibits high levels of chemo- and stereoselectivity in the face of multiple potential reaction pathways. Specifically, this work presents new possibilities for the coupling partners that can participate in this reaction. Research into potential applications of these new motifs is 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.5b03127.

Crystallographic data for **2a** (CIF)
Experimental procedures, characterization, spectral data for all compounds (PDF)

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Notes

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Organic LETTERS

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Synthesis of Chiral β-Amino Nitroalkanes via Rhodium-Catalyzed Asymmetric Hydrogenation

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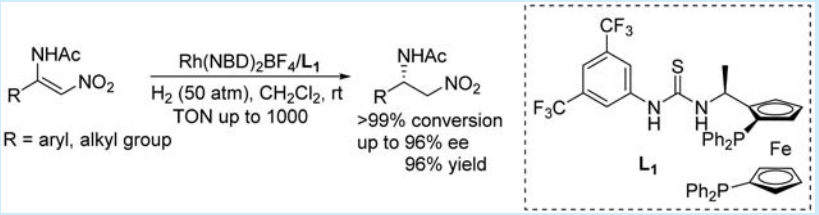
Supporting Information



ABSTRACT: The asymmetric hydrogenation of β-amino nitroolefins has been successfully achieved by rhodium/bis(phosphine)-thiourea $\mathbf{L_1}$ with excellent enantioselectivities and yields (up to 96% ee, 96% yield, >99% conversion, TON up to 1000) under mild conditions. Chiral β-amino nitroalkane products and their derivatives are versatile intermediates in organic synthesis.

Optically active β-amino nitroalkanes are important chiral synthetic intermediates and easily converted into other useful organic molecules. For example, chiral 1,2-diamines and α-amine acids can be obtained via the well-known Nef reaction[1] or nitro reduction.[2] In addition, their derivative structural motifs were widely distributed in many pharmaceuticals (Figure 1), such as ostltamivir,[3] GR-205171A,[4] (+)-CP-99, 994,[4] and asimadoline.[5]

Owing to the great significance of chiral β-amino nitroalkanes, much more attention is paid to developing excellent methodologies to approach them. Asymmetric aza-Henry reactions[6] and aza-Michael additions of amines to nitroalkenes[7] worked as the primary and direct ways to prepare chiral β-amino nitroalkanes. In addition, Sun and co-workers developed another important route through asymmetric hydrosilyation of β-amino nitroalkenes catalyzed by a bifunctional catalyst *N*-sulfinyl urea with high enantioselectivities.[8] Until now, catalytic asymmetric hydrogenation of functionalized olefins was regarded as one of the most environmentally friendly methodologies to access chiral molecules.[9] Recently, our group developed an efficient method to afford various chiral β-amino nitroalkanes through asymmetric hydrogenation of β-amino nitroolefins catalyzed by Rh/TangPhos.[10] Subsequently, Hou and co-workers also reported excellent enantioselective hydrogenation of β-amino nitroolefins via Ir/spiro-Phos to provide chiral β-amino nitroalkanes[11] (Scheme 1).

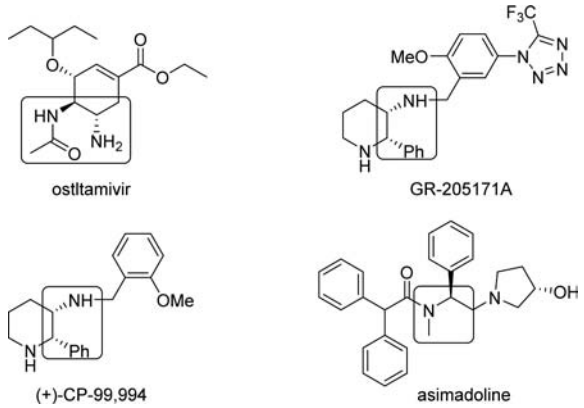


Figure 1. Related chiral pharmaceuticals containing key chiral structural motifs.

Most recently, we were devoted to developing a series of novel chiral bifunctional ligands based upon the synergistic activation strategy via cooperating transition-metal catalysis and organocatalysis, such as bisphosphine-thiourea ligands.[12−14] We successfully applied these bifunctional bisphosphine-thiourea ligands into the rhodium-catalyzed asymmetric hydrogenation of nitroalkenes[12] and unprotected NH imines[13] with excellent results, which respectively made use of hydrogen-bonding and anion-binding interaction between the thiourea scaffold and the functional groups of substrates. Since thioureas have been approved for the activation of the nitro group through hydrogen-bonding interaction, we believe that the asymmetric hydrogenation of β-amino nitroolefins should provide excellent

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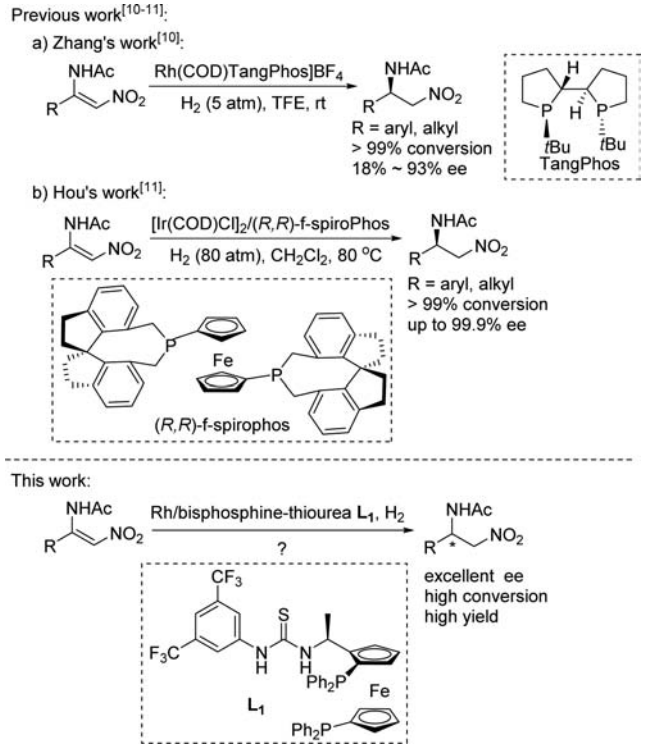
Scheme 1. Synthesis of Chiral *β*-Amino Nitroalkanes *via* Asymmetric Hydrogenation

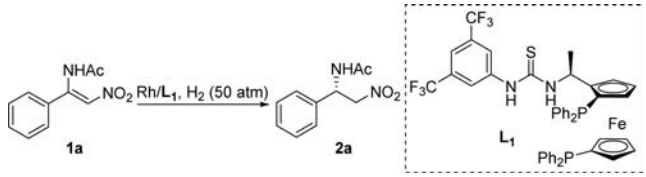


results with our bifunctional bisphosphine-thiourea ligands. Herein, this novel synergistic activation strategy proved to be very efficient in this rhodium-catalyzed asymmetric hydrogenation of *β*-amino nitroolefins (up to 96% ee, >99% conversion, 96% yield, TON up to 1000).

We began the initial investigations with the hydrogenation of model substrate (*Z*)-N-(2-nitro-1-phenylvinyl) acetamide **1a** to optimize the reaction conditions, the results are summarized in Table 1. We examined the catalytic activity of $\mathbf{L_1}$ with different rhodium sources (Table 1, entries 1−4). To our delight, $Rh(NBD)_2BF_4$ afforded the best result with full conversion and excellent enatioselectivity (>99% conversion, 96% ee, Table 1, entry 2). And we found that the solvents played an important role in this catalytic transformation (Table 1, entries 5−11). We obtained excellent results in CH_2Cl_2 and toluene (Table 1, entries 2, 10). But the substrate **1a** did not resolve well in toluene. CH_2Cl_2 was chosen as the best solvent, while a slight decrease in enationselectivities were observed when using ethanol, ethyl acetate and CF_3CH_2OH as the solvents (Table 1, entries 6, 9, 11). Moderate enationselectivities were obtained when the reactions were performed in the ^{i}PrOH, MeOH and THF (Table 1, entries 5, 7, 8).

Encouraged by these promising results, another chiral ligand $\mathbf{L_2}$ was employed and obtained lower enantioselectivity (Table 2, entry 2). It was shown that the CF_3 group on the 3,5-(trifluoromethyl)-phenyl ring played an important role. The ligand $\mathbf{L_3}$ without the thiourea scaffold provided a poor result (Table 2, entry 3); this control experiment exhibited that the thiourea motif activated the substrate efficiently and worked excellently in a directing role. Subsequently, we decreased the catalyst loading from 12 to 1 mol % resulting in similar results with high activity (97% conversion, 96% ee, Table 2, entry 1 vs entry 4).

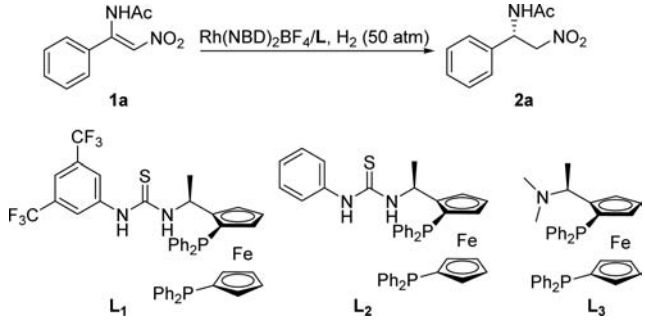
Table 1. Metal Source and Solvent Screening for Asymmetric Hydrogenation of (*Z*)-*N*-(2-Nitro-1-phenylvinyl)-acetamide 1a[a]



entry	metal source	solvent	conversion (%)[b]	ee (%)[c]
1	$[Rh(COD)Cl]_2$	CH_2Cl_2	>99	91
2	$Rh(NBD)_2BF_4$	CH_2Cl_2	>99	96
3	$Rh(COD)_2CF_3SO_3$	CH_2Cl_2	0	NA
4	$Rh(COD)_2BF_4$	CH_2Cl_2	>99	88
5	$Rh(NBD)_2BF_4$	^{i}PrOH	>99	77
6	$Rh(NBD)_2BF_4$	EtOH	>99	91
7	$Rh(NBD)_2BF_4$	MeOH	>99	81
8	$Rh(NBD)_2BF_4$	THF	>99	77
9	$Rh(NBD)_2BF_4$	EA	>99	90
10	$Rh(NBD)_2BF_4$	toluene	>99	96
11	$Rh(NBD)_2BF_4$	CF_3CH_2OH	>99	85

[a]Unless otherwise noted, all reactions were carried out with a Rh/ligand/substrate (0.1 mmol) ratio of 12:13.2:100 in 1.0 mL of CH_2Cl_2 at room temperature under hydrogen (50 atm) for 24 h. [b]Conversion was determined by ^{1}H NMR. [c]Ee was determined by HPLC analysis using a chiral stationary phase. COD = 1,5-cyclooctadiene, NBD = 2,5-norbornadiene, NA = Not Available, EA = ethyl acetate.

Table 2. Ligand and Catalyst Loading Screening for Asymmetric Hydrogenation of (*Z*)-*N*-(2-Nitro-1-phenylvinyl)-acetamide 1a[a]



entry	ligand	catalyst loading (mol %)	conversion (%)[b]	ee (%)[c]
1	$\mathbf{L_1}$	12	>99	96
2	$\mathbf{L_2}$	12	>99	85
3	$\mathbf{L_3}$	12	NR	ND
4	$\mathbf{L_1}$	1	97	96

[a]Unless otherwise noted, all reactions were carried out with a $Rh(NBD)_2BF_4$/ligand/substrate (0.1 mmol) ratio of 12:13.2:100 or 1:1.1:100 in 1.0 mL of CH_2Cl_2 at room temperature under hydrogen (50 atm) for 24 h, NR = No Reaction. [b]Determined by ^{1}H NMR. [c]Determined by HPLC analysis using a chiral stationary phase.

With the optimized conditions in hand ($Rh(NBD)_2BF_4/\mathbf{L_1}$/$CH_2Cl_2/H_2$ (50 atm)/room temperature), we turned our attention to the scope of this asymmetric hydrogenation. As summarized in Scheme 2, a variety of *β*-acylamino nitroolefins were hydrogenated smoothly to afford the corresponding products in high yields and excellent enantioselectivities. To our delight, the desired product **2a** was obtained in 97% yield and 95% ee when the catalyst loading was reduced to 0.1 mol %

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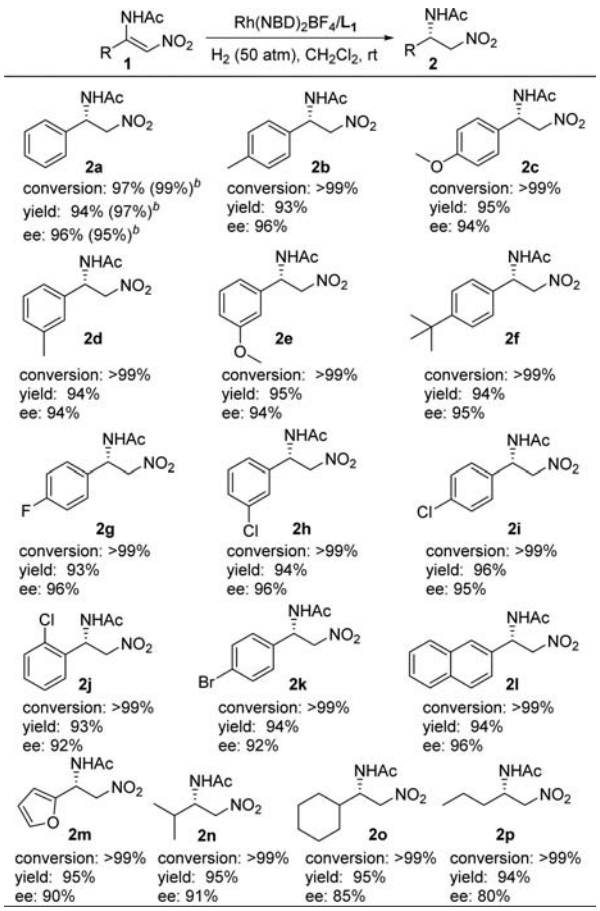
Scheme 2. Asymmetric Hydrogenation of β-Amino Nitroolefins 1 Catalyzed by Rhodium/L_1[a]



[a]The reactions were carried out with a $Rh(NBD)_2BF_4/L_1$/substrate (0.1 mmol) ratio of 1:1.1:100 (**1a**−**1c**, **1g**−**1i**, **11**) or 4:4.4:100 (**1d**−**1f**, **1j**−**1k**, **1m**−**1p**) in 1.0 mL of CH_2Cl_2 at room temperature under hydrogen (50 atm) for 24 h. The conversion was determined by ^1H NMR. The yield was isolated yield. The ee was determined by HPLC analysis using a chiral stationary phase. [b]The reaction was carried out with a $Rh(NBD)_2BF_4/L_1$/substrate (0.5 mmol) ratio of 1:1.1:1000 (S/C = 1000) in 0.5 mL of CH_2Cl_2 at room temperature under hydrogen (90 atm) for 72 h.

(S/C = 1000) at this scale. The electronic properties of the substituents on the phenyl group of the substrates had little influence on the reactions. The substrates bearing electron-donating (**1b**−**1f**) and electron-withdrawing groups (**1g**−**1k**) on the phenyl ring performed well with excellent enantioselectivities (92−96% ee). Although the *meta*-methyl (**1d**), methoxyl (**1e**), *para*-*tert*-butyl (**1f**), *orth*-Cl (**1j**), or *para*-Br (**1k**) group on the phenyl ring resulted in a little lower conversion, and a 4 mmol % loading of catalyst was introduced to achieve full conversion. The 2-naphthyl substituted nitroolefin **1l** also afforded an excellent result (>99% conversion, 96% ee) when the 4 mmol % loading of catalyst was applied. In addition, the heteroaromatic 2-furyl substrate **1m** reacted smoothly to provide a high conversion and enantioselectivity (>99% conversion, 90% ee). Noticeably, the less reactive isopropyl and *n*-propyl β-acylamino nitroolefins (**1n**, **1p**) obtained good to excellent enantioselectivities (>99% conversion, 80%−91% ee). More sterically hindered cyclohexyl β-acylamino nitroolefins (**1o**) converted well into the corresponding products with good enantioselectivity (>99% conversion, 85% ee).

In conclusion, we successfully developed the highly efficient asymmetric hydrogenation of β-amino nitroolefins catalyzed by rhodium/bis(phosphine)-thiourea L_1 with excellent enantioselectivities and yields (up to 96% ee, 96% yield, >99% conversion, TON up to 1000). Further studies on the extension of this novel catalytic system and reaction mechanism are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03158.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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Access to Difluoromethylated Arenes by Pd-Catalyzed Reaction of Arylboronic Acids with Bromodifluoroacetate

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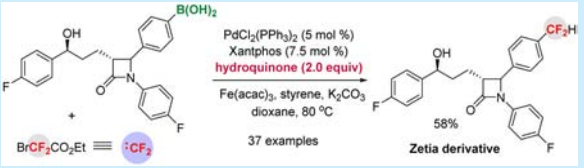
Supporting Information

ABSTRACT: An unprecedented example of Pd-catalyzed difluoromethylation of aryl boronic acids with bromodifluoroacetate is described. The reaction proceeds under mild reaction conditions with hydroquinone and $Fe(acac)_3$ as additives. Preliminary mechanistic studies reveal that a difluorocarbene pathway is involved in the reaction, which is unusual compared to the most traditional approaches. This reaction has advantages of high efficiency and excellent functional group compatibility, even toward bromide and hydroxy group, thus providing a useful protocol for drug discovery and development.

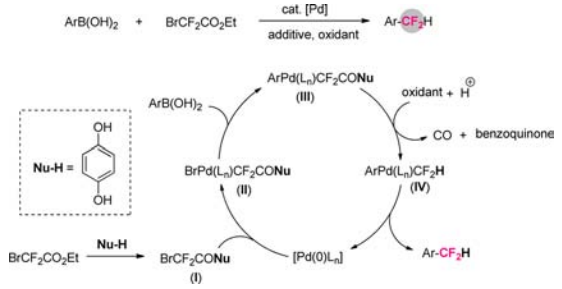


The demand for discovery of new bioactive compounds and advanced functional materials has triggered considerable efforts in the introduction of fluorinated functional groups into organic molecules.[1] It has become an intensive topic of organosynthetic chemistry. Among the organofluorinated compounds, difluoromethylated arenes constitute a type of distinct compound because of the unique properties of the difluoromethyl group (CF_2H)[2] and important applications of difluoromethylated arenes in pharmaceuticals and agrochemicals.[3] To date, however, compared to trifluoromethylation of arenes,[4] strategies for the introduction of CF_2H into an aromatic ring remain limited and have been less explored.[5] Although CF_2H can be prepared through deoxyfluorination of aldehydes with SF_4 or dialkylaminosulfur trifluorides (i.e., DAST or DeoxoFluor),[6] these reactions suffer from important functional group incompatibility and the need for expensive and/or toxic fluorinated reagents.

Recently, some new strategies for the use of difluoroalkylated reagents as fluorine sources to access such a fluorinated structural motif have been developed.[7−10] Despite the importance of these methods, the development of new strategies and efficient methods to access difluoromethylated arenes remains a requirement for drug discovery and development. We envisioned that the transition-metal-catalyzed difluoromethylation of aryl metals with electrophilic difluoromethylated reagents, such as difluoroalkyl halides, would be an attractive alternative. To date, however, such a transformation is a longstanding challenge and has not been reported because some difluoromethyl transition-metal complexes are unstable.[11] To the best of our knowledge, the palladium complex $[HCF_2Pd(L_n)X]$ (X = halides) has not been documented thus far. As part of a systematic study on the transition-metal-catalyzed direct introduction of fluorinated functional groups into organic molecules,[12] we herein disclose an unprecedented example of Pd-catalyzed difluoromethylation of arylboronic acids with low-cost ethyl bromodifluoroacetate.[13] Preliminary mechanistic studies reveal that a difluorocarbene pathway is involved in the reaction, which is unusual compared to the traditional reactions.

We began our studies on the basis of the hypothesis that if an active species **I** could be generated in situ by the reaction of ethyl bromodifluoroacetate **2** with a nucleophile **Nu-H** (i.e., hydroquinone) the formation of difluoromethylated arenes would be possible through the catalytic cycle illustrated in Scheme 1.

Scheme 1. Hypothesis for Pd-Catalyzed Difluoromethylation of Arylboronic Acids with Bromodifluoroacetate



We envisioned that once the intermediate **I** was formed, the oxidative addition of the C−Br bond to $Pd(0)L_n$ would produce the palladium complex **II**, which would subsequently deliver an active palladium complex **III** via transmetalation. The key step to realize the hypothesized reaction is to generate the key intermediate $[ArPd(L_n)CF_2H]$ **IV**. We considered that with the aid of an oxidant, if the −CO**Nu** group (Nu = OPh-*p*-OH) of the complex **III** could be removed through a redox pathway to release CO and benzoquinone, the formation of **IV** would be possible; as a result, the reductive elimination of **IV** would give

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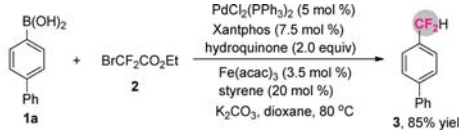
the difluoromethylated arenes and regenerate $Pd(0)L_n$ simultaneously.

Accordingly, our initial studies focused on the Pd-catalyzed cross-coupling of bromodifluoroacetate **2** with arylboronic acid **1a** in the presence of hydroquinone[14] and a variety of oxidants (for details, see Tables S1−S8 in the Supporting Information). After extensive efforts, we found that an optimal yield of **3** (85% upon isolation) could be obtained with utilization of $PdCl_2(PPh_3)_2$ (5 mol %), Xantphos (7.5 mol %), hydroquinone (2.0 equiv), $Fe(acac)_3$ (3.5 mol %), and styrene (20 mol %) in dioxane at 80 °C (eq 1). Styrene is used because of its beneficial



(1)

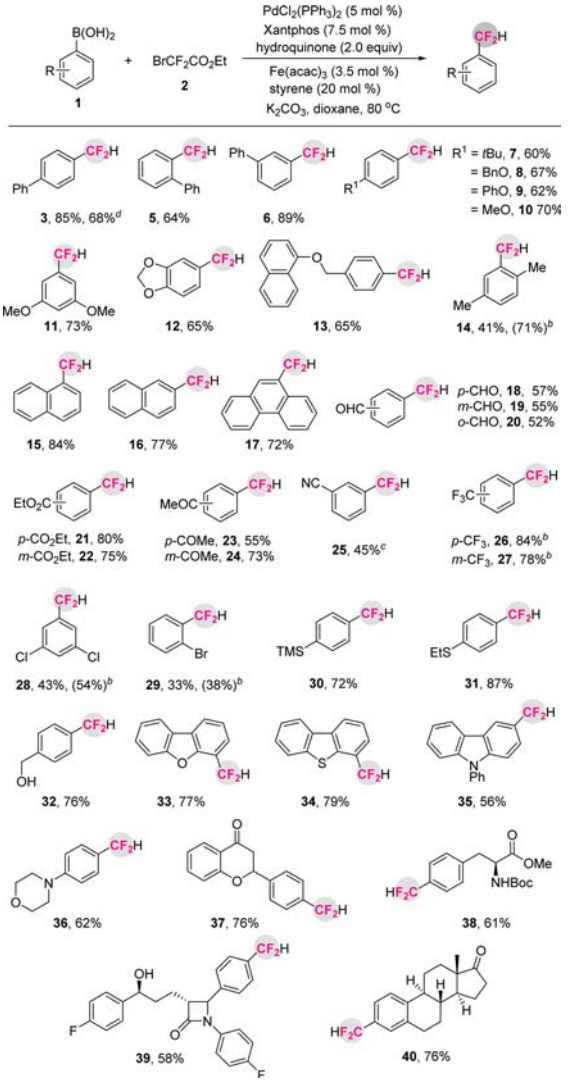
effect on the reaction efficiency. We reasoned that this is probably because styrene can coordinate with iron species and improve the reactivity of the iron complexes.[15,16] Any absence of other reaction factors, such as hydroquinone, $Fe(acac)_3$, and styrene, all led to no or lower yields of **3** (see Table S8 in the Supporting Information). No product **3** was observed without the palladium or Xantphos, thus demonstrating that the Pd/Xantphos do play an essential role to promote the reaction.

A wide range of arylboronic acids could be difluoromethylated with **2** through this method (Scheme 2). Many versatile functional groups, including base or nucleophile-sensitive moieties, such as formyl, alkoxycarbonyl, enolizable ketone, cyano, siyl, thioether, and amine, were tolerated quite well (**18**−**25**, **30**, **31**, and **36**). Most remarkably, chloride, bromide, and free hydroxy group containing aryl boronic acids are also suitable substrates (**28**, **29**, and **32**). This is in sharp contrast to previous results,[7,9,10c] in which aryl halides and/or free proton-containing substrates were incompatible with their reaction conditions. Furthermore, heteroaromatic rings, such as dibenzo[*b*,*d*]furan and -thiophene, and carbazole-derived boronic acids all underwent difluoromethylation smoothly (**33**−**35**). However, pyridine-containing boronic acids were not suitable substrates. Additionally, the difluoromethylated arene **3** could also be synthesized on a 1 g scale with good yield (68%).

The utility of this method can also be demonstrated by late-stage difluoromethylation of different bioactive molecules (**37**−**40**). As shown in Scheme 2, good yields were obtained when the flavanone and estrone derived arylboronic acids were employed (**37** and **40**). The difluoromethylation of tyrosine-derived arylboronic acid also proceeded smoothly with 61% yield (**38**). The most significant example is the direct difluoromethylation of Zetia, a drug famous for the treatment of high blood cholesterol, without protecting the free hydroxy group (**39**), thus providing an useful tool for the medicinal chemistry.

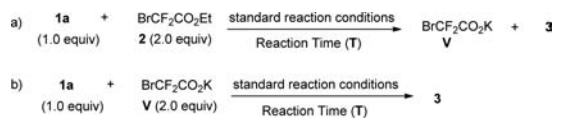
To probe the reaction mechanism illustrated in Scheme 1, we conducted a kinetic study of the reaction of **1a** with **2** (Scheme 3a), and the yield of **3** was plotted against time (Figure 1b, black line). It was found that a new species $BrCF_2CO_2K$ (**V**) instead of 4-hydroxylphenyl difluoroacetate ($BrCF_2O_2Ph$-*p*OH, **I**) was generated at the beginning of the reaction and the production of **3** at initial stage required formation of a large amount of **V** (Figure 1a, black line), thus indicating the critical role of **V** in promotion of the reaction. This finding was further confirmed by the kinetic study of the reaction of **V** with arylboronic acid **1a** under standard reaction conditions, in which a similar kinetic profile was also observed (Scheme 3b, Figure 1b, red line).

Scheme 2. Pd-Catalyzed Difluoromethylation of Arylboronic Acids 1 with Bromodifluoroacetate 2[a]



[a]Reaction conditions (unless otherwise specified): **1** (0.3 mmol), **2** (2.0 equiv), K_2CO_3 (4.0 equiv), dioxane (2.5 mL) for 24 h. All reported yields are isolated yields. [b]Determined by ^{19}F NMR using fluorobenzene as an internal standard. [c]**1** (0.6 mmol) and dioxane (3.0 mL). [d]Reaction carried out on a gram scale.

Scheme 3. Cross-Coupling of 1a with 2 or V



Additionally, the ^{19}F NMR and GC−MS analysis of the reaction showed no **I** was formed during the reaction process. Thus, these results imply that the hypothesized mechanism illustrated in Scheme 1 is less likely.

To rule out the possibility that the formation of difluoromethylated arenes arises from the decarboxylation of difluoroacetylated arene, the reaction of compound **4** or **4′** with hydroquinone under standard reaction conditions was conducted (eq 2). However, no difluoromethylated arene **3** was observed during the reaction, thus clearly indicating that an intriguing mechanism is involved in the reaction.

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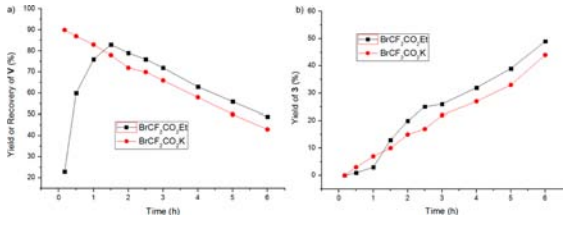
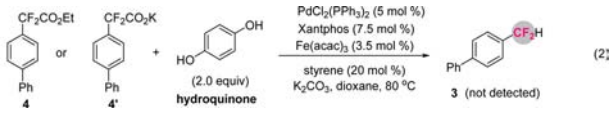
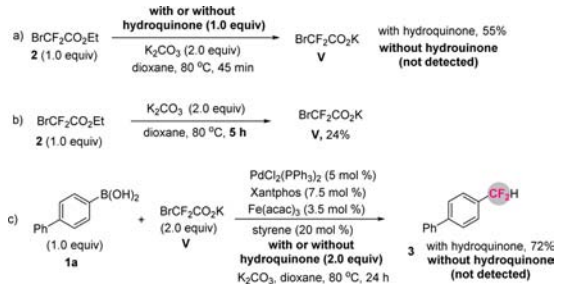


Figure 1. (a) Yield (black line) or recovery of **V** (red line) and (b) yield of **3** with $BrCF_2CO_2Et$ (black line) or $BrCF_2CO_2K$ (red line) as a starting material.



To further understand the role of hydroquinone, several experiments were performed (Scheme 4). It was found that when

Scheme 4. Roles of Hydroquinone for the Reaction

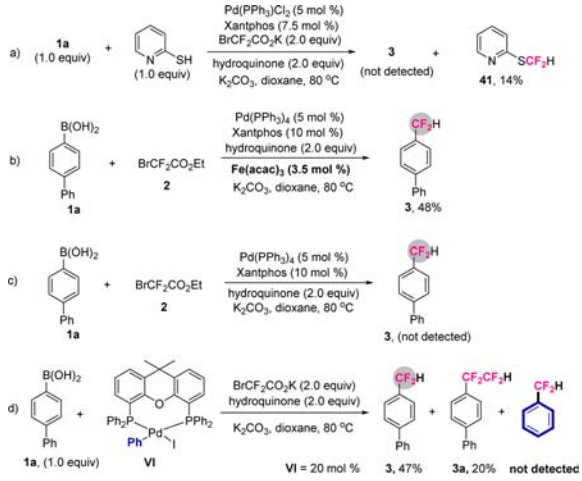


bromodifluoroacetate **2** was treated with K_2CO_3 (2.0 equiv) in the presence of hydroquinone, 55% yield of **V** (determined by ^{19}F NMR) was formed after the reaction was stirred for only 45 min (Scheme 4a). However, the absence of hydroquinone led to no **V** (Scheme 4a), while prolonging the reaction time to 5 h could afford **V** in 24% yield (determined by ^{19}F NMR, Scheme 4b). Thus, these results clearly demonstrate that the hydroquinone has a beneficial effect on the formation of **V**, but it is not essential. On the contrary, the hydroquinone plays an essential role for the generation of difluoromethylated arenes, as no product **3** was observed in the absence of hydroquinone (Scheme 4c). In addition, the comparison of reaction of **1a** with **2** or **V** in the presence of hydroquinone with or without $Fe(acac)_3$ (Schemes S4 and S5 and Figures S2 and S3 in the Supporting Information) reveals that the iron species is not essential for the reaction, but it can facilitate the transformation of **V** into final product **3**.

It has been demonstrated that $BrCF_2CO_2K$ can serve as a precursor of difluorocarbene.[17] This inspired us to surmise that a difluorocarbene may be generated in situ from **V** and a palladium catalytic cycle via a difluorocarbene pathway may be involved in the reaction. To identify whether a difluorocarbene is involved in the reaction, a difluorocarbene scavenger pyridine-2-thiol[18] was added to the reaction by using **V** as a coupling partner (Scheme 5a). It was found that the difluoromethylthiopyridine **41** instead of **3** was produced, thus indicating that a difluorocarbene is involved in the reaction.

In addition, given the fact that a 48% yield of **3** could be provided when **1a** was treated with **2** in the presence of $Pd(PPh_3)_4$ (5 mol %), hydroquinone and $Fe(acac)_3$ (Scheme 5b), but no **3** was produced in the absence of $Fe(acac)_3$ or other

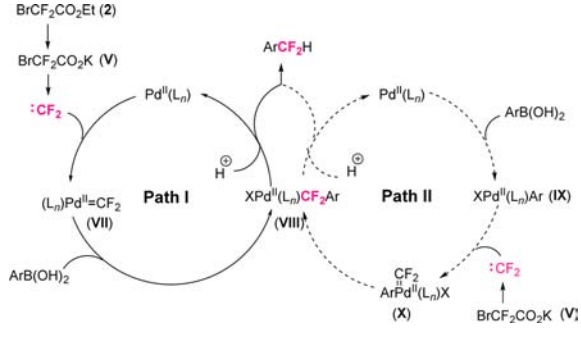
Scheme 5. Mechanistic Studies



oxidants (Scheme 5c), we envisioned that probably only the Pd^{II} species was involved for the formation of difluoromethylated arenes. This was further confirmed by the X-ray photoelectron spectroscopy (XPS) analysis of the reaction, in which only Pd^{II} was found (Scheme S9 and Figure S4, Supporting Information). What is more, when we used a catalytic amount of palladium complex [PhPd(Xantphos)I] **VI** (20 mol %) as a catalyst, compound **3** (47% yield) was indeed generated (Scheme 5d). However, it is worthy to note that no difluoromethylbenzene was generated during the reaction process, even when 50 mol % of **VI** was used (for details, see Scheme S7b , Supporting Information). Thus, these results clearly indicate that the aryl group of the difluoromethylated arene does not derive from [ArPd(Xantphos)X]. In the meantime, a difluorocarbon elongated tetrafluoroethylated **3a** was produced in 20% yield (Scheme 5d). These findings confirm that a difluorocarbene species is involved in the reaction, as it has been demonstrated that an elongated difluorocarbon can be produced by the insertion of a difluorocarbene into fluoroalkylmetal species.[19]

Therefore, on the basis of above results, the hypothesized mechanism illustrated in Scheme 1 can be ruled out, and a plausible mechanism through a the Pd^{II}-involved difluorocarbene pathway is proposed (Scheme 6). The reaction was initiated by

Scheme 6. Proposed Reaction Mechanism



the reaction of $Pd^{II}(L_n)$ with difluorocarbene which was generated in situ from **V** (path I). Subsequently, the resulting palladium(II) difluorocarbene species (**VII**) was trapped by arylboronic acid to produce the key intermediate [$XPd^{II}(L_n)$-CF_2Ar] (**VIII**). Finally, protonolysis of **VIII** afforded difluoromethylated arenes and regenerate $Pd^{II}(L_n)$ simultaneously. In

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the overall catalytic cycle, the hydroquinone is essential for promotion of the reaction. However, the exact role of hydroquinone remains elusive at this stage. As for the role of $Fe(acac)_3$ in the overall catalytic cycle, one possibility is that a Fe-based difluorocarbene species[20] may be generated in the reaction, which is being subsequently transferred onto Pd to produce **VII**. What is more, taking into account the fact that the aryl group of difluoromethylated arene does not derive from the palladium complex $[ArPd(L_n)X]$ (**IX**), the proposed mechanism illustrated in path II[21] for the current reaction can be excluded.

In conclusion, we have demonstrated an unprecedented example of Pd-catalyzed difluoromethylation of arylboronic acids with low-cost ethyl bromodifluoroacetate. The significant features of this reaction are its high efficiency, broad substrate scope, and excellent functional group compatibility, even toward bromide and hydroxyl groups. Applications of the reaction led to difluoromethylated biologically relevant molecules with high efficiency, thus providing a useful protocol for drug discovery and development. Preliminary mechanistic studies reveal that a palladium catalytic cycle via a difluorocarbene pathway is involved in the reaction. To the best of our knowledge, this is the first example of a transition-metal-catalyzed carbon−difluorocarbon single bond ($C-CF_2$) formation via a difluorocarbene pathway. We believe that it will not only prompt the research in the field of transition-metal difluorocarbene chemistry but also be useful for related chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Informationis also is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03206.

Detailed experimental procedures and characterization data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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Organic LETTERS

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Pd(II)-Catalyzed Alkylation of Tertiary Carbon via Directing-Group-Mediated C(sp^3)−H Activation: Synthesis of Chiral 1,1,2-Trialkyl Substituted Cyclopropanes

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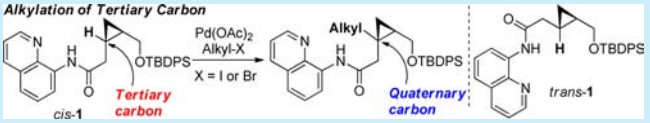
Supporting Information

ABSTRACT: A Pd(OAc)$_2$-catalyzed alkylation reaction of the tertiary carbon of chiral cyclopropane substrates with alkyl iodides and bromides via C(sp^3)−H activation has been developed. This is an elusive example of a C−H activation-mediated alkylation of tertiary carbon to effectively construct a quaternary carbon center. The alkylation proceeded with various alkyl halides, including those of functional groups, to provide a variety of chiral *cis*- and *trans*-1,1,2,-trialkyl substituted cyclopropanes of medicinal chemical importance.



Directing-group-mediated C−H functionalization is one of the most useful transformations in organic synthesis because it allows regio- and stereoselective functionalizations and alternative synthetic routes that are different from conventional transformations via prefunctionalization of the C−H bond, such as halogenation and/or metalation.[1] Thus, these C(sp^3)−H functionalizations have been effectively used in the synthesis of a variety of complex molecules.[2] Considerable effort has been devoted to the functionalizations of C(sp^3)−H as well as C(sp^2)−H bonds, and many primary or secondary C(sp^3)−H bond activation examples are known. In contrast, only a few examples of tertiary C(sp^3)−H functionalization have been reported, probably because sterically hindered tertiary carbons are less reactive than primary and secondary carbons.

In our continuing studies using cyclopropanes as key conformational restriction units,[3] we needed to prepare a variety of chiral 1,1,2-trisubstituted cyclopropane structures with a quaternary carbon (Figure 1). To construct such

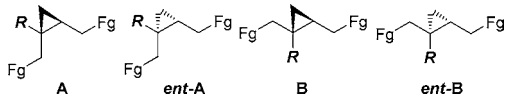
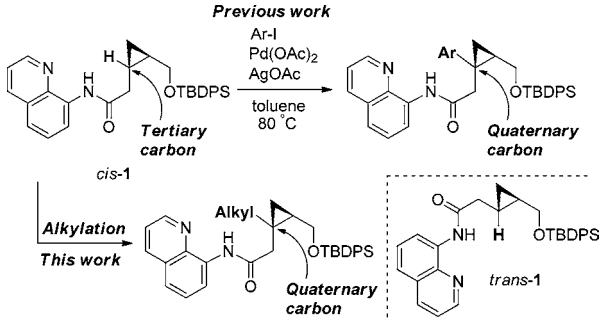


Figure 1. Target chiral 1,1,2-trisubstituted cyclopropanes.

structures,[4] directing-group-mediated substitution via transition-metal-catalyzed direct C−H activation can be the most attractive strategy because it regio- and stereoselectively provides a wide range of compounds via a short synthetic route.[1] In fact, we successfully developed tertiary C(sp^3) arylation on chiral cyclopropanes with aryl iodides via Pd(II)-catalyzed chelation-assisted C(sp^3)−H activation, using *cis*-cyclopropane substrate *cis*-**1** as well as *trans*-substrate *trans*-**1** (Scheme 1).[5]

Scheme 1. Functionalization of Tertiary C(sp^3)−H Bond on Cyclopropanes



Furthermore, we were required to obtain chiral 1,1,2-trialkylsubstituted cyclopropanes. For their synthesis, we considered that the directing-group-mediated alkylations of C(sp^3) would be very effective, which might allow us to construct the quaternary carbon center while preparing a wide variety of chiral 1,1,2-trialkyl-substituted cyclopropanes. Again, *cis*-**1** as well as *trans*-**1** would be effective substrates (Scheme 1).

Although directing-group-mediated alkylations of C(sp^3) have recently been studied intensively by Dauglis,[6] Shi,[7] Chen,[8] and Ge,[9] alkylation of tertiary C(sp^3) has not yet been reported. However, we hypothesized that, when chiral cyclopropane substrates *cis*-**1** and *trans*-**1** are employed, the tertiary C(sp^3) alkylation forming the quaternary carbon center

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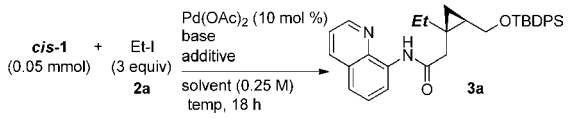
might proceed owing to the following characteristic features of cyclopropane: (i) the tertiary carbon of cyclopropanes is less sterically hindered compared with the usual ones due to the small and rigid ring structure, (ii) the ring carbons forming the cyclopropane structure are unusually sp^2-like-hybridized, and (iii) the C(sp^3)−H activation may be potentially promoted due to conformational restriction of the directing group attached to the rigid cyclopropane ring.[10]

Here, we report Pd(II)-catalyzed tertiary C(sp^3) alkylation via a directing-group-mediated C−H activation by employing chiral cyclopropane substrates.[11] To the best of our knowledge, this is the first example of tertiary C(sp^3) alkylation via metal-catalyzed C−H activation with a directing group, although the arylations of tertiary C(sp^3) have been reported.[1]

We first examined the tertiary C(sp^3) alkylation of chiral cyclopropane *cis*-**1** with EtI (**2a**) as an electrophile. As a result, we found that the reaction under our conditions previously optimized for the arylation using **2a** instead of an aryl iodide—i.e., **2a** (3 equiv), $Pd(OAc)_2$ (10 mol %), AgOAc (1.5 equiv), in toluene at 100 °C, 12 h—actually produced the desired alkylated quaternary cyclopropane product **3a**, although the yield was very low (17%) (Table 1, entry 1). K_2CO_3, a

Table 1. Optimization of Reaction Conditions



entry	conditions: solvent (temp)	base (equiv)	additive (equiv)	yield (%)[b,c]
1	toluene (100)	AgOAc (1.5)	---	17 (83)
2	toluene (100)	K_2CO_3 (1.5)	---	1 (99)
3	toluene (100)	AgOAc (1.5)	PivOH (0.3)	20 (78)
4	toluene (100)	AgOAc (1.5)	$TsNH_2$ (0.3)	9 (63)
5	toluene (100)	AgOAc (1.5)	$(BnO)_2P(O)OH$ (0.3)	31 (31)
6	toluene (100)	AgOAc (1.5)	$(PhO)_2P(O)OH$ (0.3)	12 (88)
7	toluene (100)	AgOAc (1.5)	$BnOP(O)(OH)_2$ (0.3)	10 (89)
8	dioxane (100)	AgOAc (1.5)	$(BnO)_2P(O)OH$ (0.3)	18 (81)
9	CF_3CF_2OH (100)	AgOAc (1.5)	$(BnO)_2P(O)OH$ (0.3)	6 (44)
10	*t*-AmylOH (100)	AgOAc (1.5)	$(BnO)_2P(O)OH$ (0.3)	50 (42)
11	*t*-BuOH (100)	AgOAc (1.5)	$(BnO)_2P(O)OH$ (0.3)	58 (42)
12	*t*-BuOH (100)	Ag_3PO_4 (1.5)	$(BnO)_2P(O)OH$ (0.3)	5 (65)
13	*t*-BuOH (100)	AgOTf (1.5)	$(BnO)_2P(O)OH$ (0.3)	complex mix
14	*t*-BuOH (100)	Ag_2CO_3 (1.5)	$(BnO)_2P(O)OH$ (0.3)	66 (31)
15	*t*-BuOH (100)	Ag_2CO_3 (1.5)	$(BnO)_2P(O)OH$ (1.3)	75 (25)
16[a]	*t*-BuOH (100)	Ag_2CO_3 (1.5)	$(BnO)_2P(O)OH$ (1.3)	85 (0)
17[a]	***t*-BuOH (50)**	***Ag_2CO_3 (1.3)***	***$(BnO)_2P(O)OH$ (1.3)***	***95 (0), 92[d]***
18[a]	*t*-BuOH (50)	Ag_2CO_3 (1.3)	$(BnO)_2P(O)OH$ (0.6)	82 (9)
19[a]	*t*-BuOH (50)	Ag_2CO_3 (0.6)	$(BnO)_2P(O)OH$ (1.3)	54 (32)
20[a]	*t*-BuOH (50)	Ag_2CO_3 (1.1)	$(BnO)_2P(O)OH$ (1.3)	78 (5)
21[a]	*t*-BuOH (50)	$(BnO)_2P(O)OAg$ (1.3)	---	56 (10)
22[a]	*t*-BuOH (50)	$(BnO)_2P(O)OAg$ (1.3)	K_2CO_3 (1.1)	58 (8)
23[a]	*t*-BuOH (50)	$(BnO)_2P(O)OAg$ (1.3)	$KHCO_3$ (1.1)	80 (8)

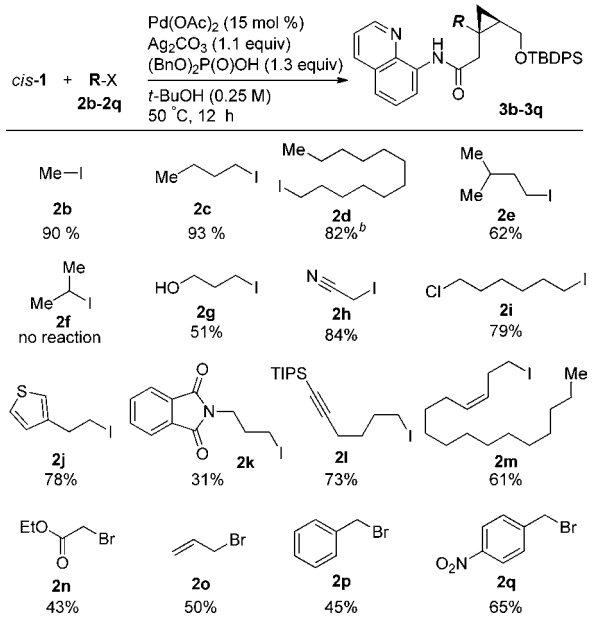
[a] $Pd(OAc)_2$ (15 mol %), for 12 h. [b] Yields were estimated by ^1H NMR using anthracene as an internal standard. [c] Numbers in parentheses are remaining *cis*-**1**. [d] Isolated yield.

nonsilver salt, was also tested, but the reaction did not proceed at all (entry 2). We then tested various additives together with AgOAc. Addition of PivOH (0.3 equiv) or $TsNH_2$ (0.3 equiv) was not effective in improving the yield (entries 3 and 4). Addition of $(BnO)_2P(O)OH$ (0.3 equiv), which was reported to be effective for C(sp^3)−H alkylation by the Chen group,[8] somewhat improved the yield (31%, entry 5). We also examined other phosphate additives; however, addition of $(PhO)_2P(O)OH$ or $BnOP(O)(OH)_2$ was ineffective (entries 6 and 7). Next, we examined the reaction solvent. Although dioxane and CF_3CF_2OH were not suitable solvents (entries 8 and 9), the use of *t*-AmylOH or *t*-BuOH as the solvent clearly improved the yield (50%, entry 10; 58%, entry 11). Next, we screened the silver salts. The use of Ag_2PO_4 or AgOTf instead of AgOAc significantly decreased the yield (entries 12 and 13); however, the switch to Ag_2CO_3 provided the product **3a** in 66% yield (entry 14). Thus, we fine-tuned the reaction conditions with Ag_2CO_3 as a base. The use of 1.3 equiv of $(BnO)_2P(O)OH$ increased the yield to 75% (entry 15). When we examined the alkylation in the presence of $Pd(OAc)_2$ (15 mol %), *cis*-**1** was effectively consumed to produce **3a** in 85% yield (entry 16). Even at a lower temperature (50 °C), the reaction proceeded smoothly to give **3a** in 95% yield (entry 17). When the amount of Ag_2CO_3 or $(BnO)_2P(O)OH$ was reduced, the reaction was not completed (entries 18−20). As described, we found that the ethylation at the tertiary C(sp^3) of chiral cyclopropane *cis*-**1** efficiently occurred and that the optimized reaction conditions were those in entry 17.

To gain information about the effect of Ag_2CO_3 and $(BnO)_2P(O)OH$, we examined the alkylation using $(BnO)_2P(O)OAg$ instead of the combination of Ag_2CO_3/$(BnO)_2P(O)OH$. As a result, we obtained **3a** in 56% yield (entry 21). Addition of K_2CO_3 to the reaction system did not improve the yield (58%, entry 22). When $KHCO_3$ was added to the reaction system, however, the yield effectively increased to 80% (entry 23). These results suggest that $(BnO)_2P(O)OAg$ might be formed in situ and that the bicarbonate ion ($^-HCO_3$) plays an important role in promoting the alkylation.[12−14]

With the optimized reaction conditions in hand, we investigated the reactions of *cis*-**1** with various alkyl iodides and bromides. The results are summarized in Scheme 2.[15] The reaction with low molecular weight primary alkyl iodides, i.e., methyl iodide (**2b**) and butyl iodide (**2c**), afforded the corresponding products in high yields. Fatty dodecyl iodide (**2d**) and branched 3-methylbutyl iodide (**2e**) were also suitable electrophiles, and they gave the corresponding alkylated product in 82% yield and 62% yield, respectively. However,

Scheme 2. Substrate Scope of *cis*-1[a]



[a] All reactions were carried out using *cis*-**1** (0.05 mmol) and R−I or R−Br (3 equiv). [b] Yield of 0.5 mmol (250 mg) scale reaction was 86%.

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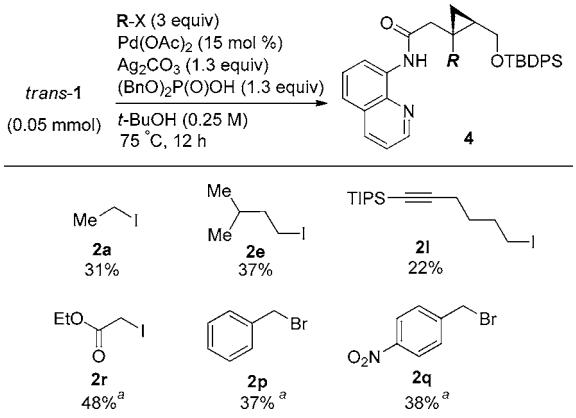
the reaction with secondary isopropyl iodide (**2f**) did not proceed at all. Next, we tested alkyl iodides with functional groups, i.e., 3-iodopropanol (**2g**), iodoacetonitrile (**2h**), and 1-chloro-6-iodohexane (**2i**).

These functional groups tolerated the alkylation to provide the corresponding coupling products, while the yields were moderate. Alkyl iodides with thiophene (**2j**) and phthalimide (**2k**) were also good coupling partners. The reactions with a TIPS-protected terminal alkyne (**2l**) and *cis*-olefin (**2m**) proceeded smoothly. We next examined the reaction with alkyl bromides. When the reaction was carried out with EtBr, only a trace of the desired coupling product was obtained. However, the reactions with active alkyl bromides, such as ethyl bromoacetate (**2n**) and allyl bromide (**2o**), proceeded to give the corresponding alkylated products in 43% and 50% yield, respectively. Benzyl bromide (**2p**) and 4-nitrobenzyl bromide (**2q**) were also effective electrophiles for the alkylation.

We next investigated the alkylation of *trans*-**1**, which was a more challenging substrate than *cis*-**1** because its tertiary C(sp^3)−H bond to be activated was significantly sterically hindered due to the adjacent *cis*-substituent. In fact, only a 21% yield of the coupling product **4a** was obtained under the reaction conditions optimized for *cis*-**1** and EtI (Supporting Information Table S1, entry 1). We conducted the alkylation under various conditions and found that the reaction at higher temperature (75 °C) made the yield slightly higher, obtaining **4a** in 31% yield (Supporting Information Table S1, entry 2).[16,17]

The reaction results of *trans*-**1** with various alkyl halides are summarized in Scheme 3. The reaction with a simple alkyl

Scheme 3. Substrates Scope for *trans*-1



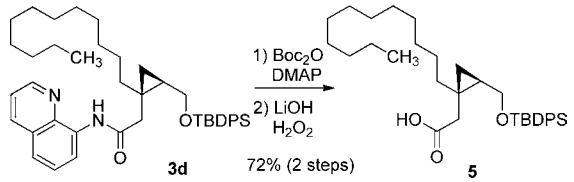
Reactions were carried out at 50 °C.

iodide **2a**, branched alkyl iodide **2e**, TIPS-protected terminal alkyne **2l**, and ester **2r** provided the corresponding alkylated product in 22%−48% yields. Activated alkyl bromides **2p** and **2q** also worked as coupling partners.

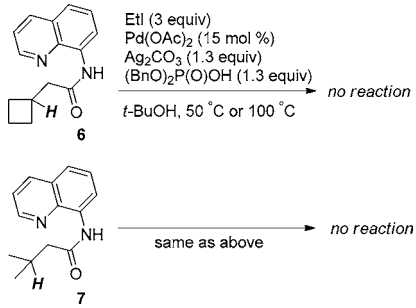
We then examined the transformation of the 8-aminoquinoline moiety. A two-step sequence was employed: (i) Boc introduction at the amide and (ii) hydrolysis of the resulting secondary amide with LiOH and H_2O_2. This gave the carboxylic acid **5** in 72% yield from **3d** (Scheme 4).

We also examined the tertiary C(sp^3) alkylation with noncyclopropane substrates, i.e., cyclobutane substrate **6** and acyclic substrate **7** (Scheme 5). When **6** or **7** was treated with EtI under the optimized reaction conditions for *cis*-**1**, the ethylation did not proceed at all, even under the higher

Scheme 4. Transformation of the 8-Aminoquinoline Moiety



Scheme 5. C(sp^3)−H Alkylation of Non-cyclopropane Substrates 6 and 7



temperature at 100 °C. These results suggest that the characteristic steric and hybridization property of cyclopropane enables the tertiary C(sp^3) alkylation of cyclopropane substrates to proceed, as we hypothesized.

In conclusion, we successfully developed the directing-group-mediated tertiary C(sp^3) alkylation of chiral cyclopropanes with alkyl iodides and activated alkyl bromides in the presence of $Pd(OAc)_2$. This is the elusive example of tertiary C(sp^3) alkylation via C(sp^3)−H activation, and it allows us to prepare a variety of chiral 1,1,2-trialkylcyclopropanes of medicinal chemical importance. The results of the control experiments with noncyclopropane substrates suggested that the tertiary C(sp^3) alkylation effectively occurs due to the characteristic structural and hybridization feature of the cyclopropane ring.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03229.

Experimental data, characterization data for new compounds, and chiral HPLC chart (PDF)

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Notes

The authors declare no competing financial interest.

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(15) For determination of the optical purity of **3d**, see the Supporting Information.

(16) See the Supporting Information for the details of optimization of the reaction conditions.

(17) The reaction of *cis*-**1** with $Pd(TFA)_2$ instead of $Pd(OAc)_2$ under the optimized conditions (entry 17) provided the desired product **3a** in 56% yield and recovered *cis*-**1** in 18% yield.

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Organic LETTERS

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Hydroalkylation of Alkenes Using Alkyl Iodides and Hantzsch Ester under Palladium/Light System

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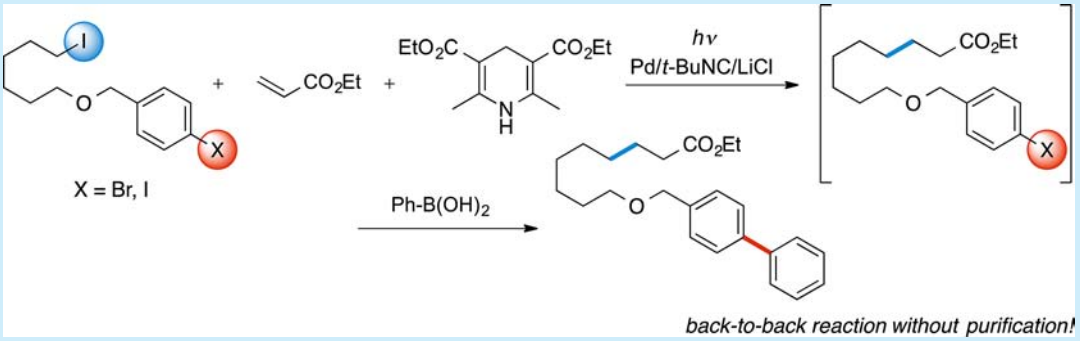
Supporting Information



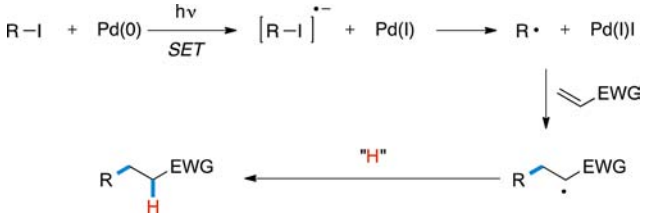
ABSTRACT: The hydroalkylation of alkenes using alkyl iodides with Hantzsch ester as a hydrogen source occurred smoothly under a Pd/light system, in a novel, tin-free Giese reaction. A chemoselective reaction at C(sp^3)−I in the presence of a C(sp^2)−X (X = Br or I) bond was attained, which allowed for the stepwise functionalization of two types of C−X bonds in a one-pot procedure.

The addition of radicals to alkenes is among the most basic of radical reactions. The Kharasch[1] and Giese reactions[2−4] both proceed with a radical chain composed of radical addition to alkenes followed by S_H2 reaction delivering halogen and hydrogen, respectively. There has been a recent renewal of interest in palladium-assisted radical reactions using alkyl iodides[5−7] whereby a SET (single electron transfer) process from Pd(0) to alkyl iodides is typically proposed for the generation of alkyl radicals/PdI radical pair as a first event. Based on this concept, we previously developed a series of cascade carbonylation reactions using alkyl iodides, CO, and coupling reagents using a Pd/light combined system[6] in which CO trapping by alkyl radicals ultimately leads to the formation of acylpalladium intermediates.[8]

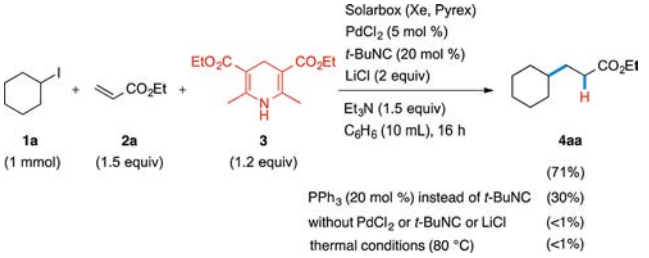
We expected that such a Pd/light combined system would be applicable even to a tin-free Giese reaction, as outlined in Scheme 1. A key issue here was deciding what reagent would work as a hydrogen source in the presence of a Pd complex. We focused on the use of Hantzsch ester, which has been used successfully in radical reductions[9] and glycosylations[10] based on photoredox catalysts such as $Ir(ppy)_3$ and $[Ru(bpy)_3](BF_4)_2$. In this paper, we report that a palladium/light system worked well to achieve the Giese-type reaction of alkyl iodides with electron-deficient alkenes by introducing Hantzsch ester as a hydrogen source.

As expected, under photoirradiation (SolarBox; 1500 W of xenon lamp in a box, for details see the Supporting Information) the reaction of iodocyclohexane **1a**, ethyl acrylate **2a**, and Hantzsch ester **3** in benzene in the presence of Et_3N and a catalytic amount of $PdCl_2$ and PPh_3 proceeded to give the desired Giese addition product **4aa** in a 30% yield (Scheme 2). Without Hantzsch ester **3**, the Giese product would not form.

Scheme 1. Concept: Pd/Photoirradiation System for Tin-Free Giese Reaction



Scheme 2. Photoinduced Reductive Radical Addition of Iodocyclohexane 1a to Ethyl Acrylate 2a



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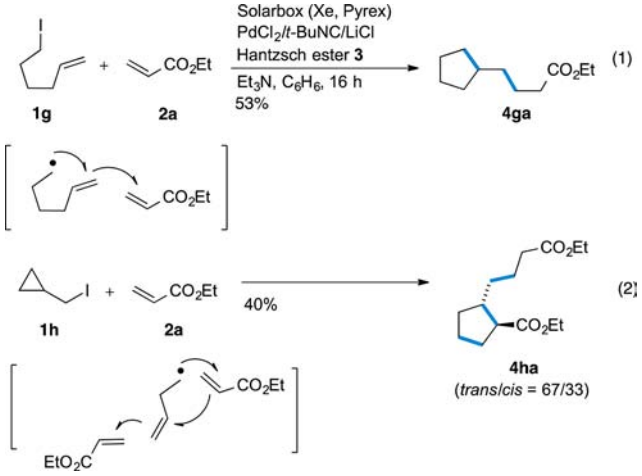
Changing the ligand from PPh_3 to *t*-BuNC[11] in benzene improved the yield of **4aa** to 71%. In the absence of a Pd catalyst, *t*-BuNC, or LiCl, only a trace amount of **4aa** was observed. No reaction took place under thermal conditions (80 °C).

Table 1 demonstrates the general nature of the present reductive alkylation of alkenes **2** by iodoalkanes **1** and Hantzsch ester **3**. A series of substituted α,β-unsaturated esters **2b**−**f** were examined (entries 2−6). The reaction of **1a** with ethyl crotonate **2b**, dimethyl maleate **2d**, and Me- and Ph-substituted ethylidene malonate **2e** and **2f** gave the corresponding addition products **4ab**−**af** in moderate to good yields. In contrast, the reaction of **1a** with methyl methacrylate **2c** gave **4ac** in a rather poor yield of 38% (entry 3). Other alkenes with an electron-deficient group, such as ethyl vinyl ketone **2g**, acrylonitrile **2h**, and phenyl vinyl sulfone **2i**, also gave the alkylation products **4ag**−**ai** in good yields (entries 7−9). The reaction of **1a** with cyclohexenone **2j** gave the desired product **4aj** in a modest yield of 48% (entry 10). Irrespective of whether the alkyl moiety of RI **1** was primary, secondary, or tertiary, the reaction worked quite well (entries 11−16).

To confirm the intervention of radical species,[12] radical cascade reactions were examined (Scheme 3). The reaction of

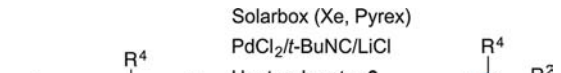
Scheme 3. Radical Cascade Reactions Using 6-Iodo-1-hexene 1g and (Iodomethyl)cyclopropane 1h

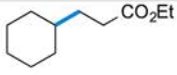
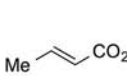
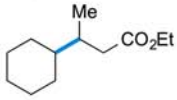
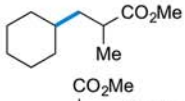
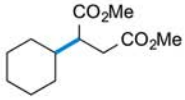
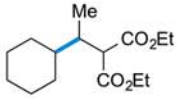
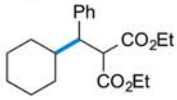
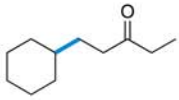
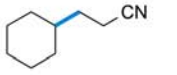
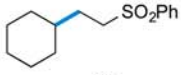
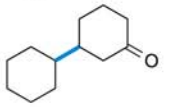
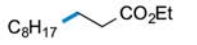
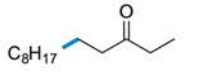
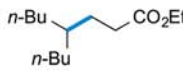
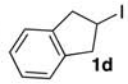
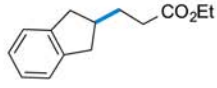
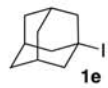
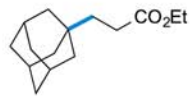
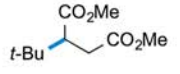


6-iodo-1-hexene **1g** and **2a** gave ethyl 4-cyclopentylbutanoate **4ga** in 53% yield by way of 5-*exo* radical cyclization (Scheme 3, eq 1). (Iodomethyl)cyclopropane **1g** reacted with **2a** to give 1,2-disubstituted cyclopentane **4ha** in a 40% yield. In this reaction, an initially formed cyclopropylcarbinyl radical undergoes ring-opening to give a homoallyl radical,[13] which then adds to **2a** to form an α-carbonyl radical. The 5-*exo* cyclization and the addition of the resultant radical to the second molecule of **2a** followed by hydrogen abstraction from Hantzsch ester gives the product **4ha** (Scheme 3, eq 2). The *syn*/*anti* ratio of **4ha** was nearly the same as that of a previously established radical cyclization.[4c]

We then examined the chemoselectivity of the reaction using alkyl iodides **1i** and **1j** with a haloaryl moiety (Scheme 4). The alkylation reactions of **1i** or **1j** with **2a** proceeded chemoselectively at the C(sp^3)−I bond, leaving C(sp^2)−X bonds for the next functionalization (Scheme 4, eq 3). The crude products **4ia** and **4ja** were exposed to the standard conditions of Suzuki−Miyaura raection without additional Pd, which gave the

Table 1. Reaction of Alkyl Iodides 1 and Alkenes 2 under the Pd/*hν* System



entry	1	2	4	yield (%)
1	 1a	 2a		4aa 71%
2	1a	 2b		4ab 55%
3	1a	 2c		4ac 38%
4	1a	 2d		4ad 72%
5	1a	 2e		4ae 73%
6	1a	 2f		4af 64%
7	1a	 2g		4ag 75%
8	1a	 2h		4ah 77%
9	1a	 2i		4ai 88%
10	1a	 2j		4aj 48%
11	 1b	2a		4ba 67%
12	1b	2g		4bg 61%
13	 1c	2a		4ca 60%
14	 1d	2a		4da 62%
15	 1e	2a		4ea 68%
16	t-Bu−I 1f	2d		4fd 66%

[a]Reaction conditions **1** (1 mmol), **2** (1.5 equiv), **3** (1.2 eqiuv), $PdCl_2$ (5 mol %), *t*-BuNC (20 mol %), LiCl (20 mol %), Et_3N (1.5 equiv), C_6H_6 (10 mL), 16 h, *hν* (SolarBox (Xe, 1000 W/m^2), Pyrex).

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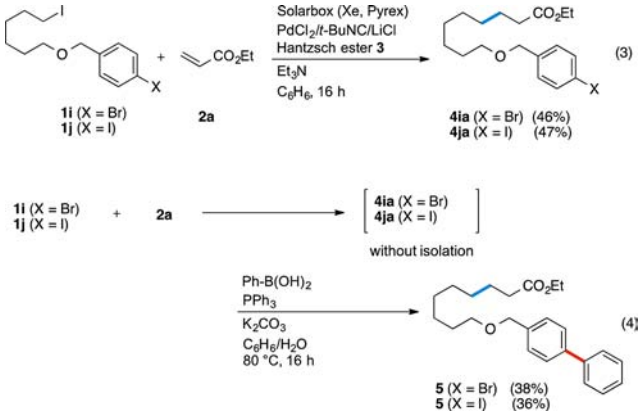
Scheme 4. Chemoselective Reaction of 1i and 1j with Alkyl−I and Aryl−X Moieties (X = Br, I)



arylated products **5ia** and **5ja**, respectively (Scheme 4, eq 4). Although the chemoselective reaction was achieved, moderate yields of **4ia** and **4ja**, which are due to the side reactions of key alkyl radicals to add to two molecules of ethyl acrylate and H-abstraction from α-position to ether oygen, requires further optimization of the reaction conditions. On the other hand, it should be noted that GC−MS analysis of the crude reaction mixture indicated that the reduction of the yields of **5** is partly because of Pd-catalyzed aromatic reduction of **4ia** and **4ja** with Hantzch ester remaining in the one-pot procedure.

Whereas an appreciable byproduct of the reaction of **1b** with **2a** (Table 1, entry 11) was diester **7** (>10%), which incorporated two molecules of ethyl acrylate **2a**, octane **6**, a simple reduction product, was detected in only a trace amount (Figure 1). This suggests that while a reduction of the adduct α-carbonyl radical by Hantzsch ester is sluggish, that of the parent octyl radical is far more sluggish.[10a]

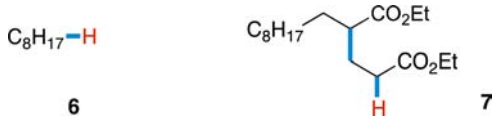
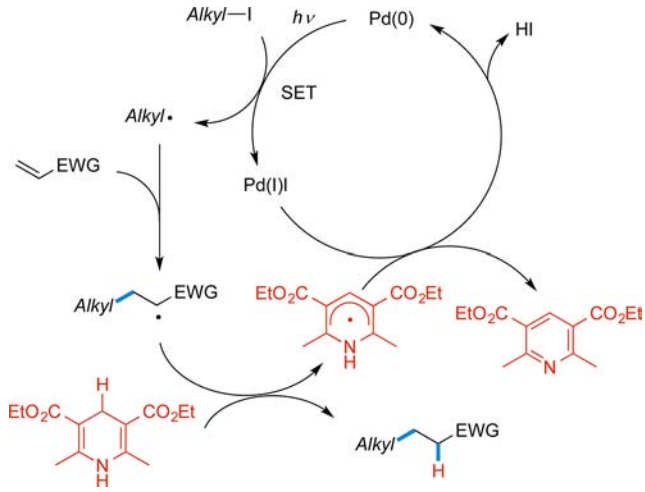


Figure 1. Byproducts.

A plausible reaction mechanism is illustrated in Scheme 5. First, alkyl radicals are generated by the reaction of alkyl iodides and Pd(0) under photoirradiation via a SET process, which is then added to olefins. The resultant radicals abstract hydrogen at the 4-position of Hantzsch ester to give the products and a dienyl radical, which reacts with the Pd(I) species to give Pd(0), HI, and a pyridine derivative.

In summary, we have demonstrated a new protocol for the Giese-type reductive alkylation of alkenes by alkyl iodides, which uses Hantzsch ester as a hydrogen source and a Pd/photoirradiation system to promote radical generation. The reaction can be applied to cascade reactions involving 5-*exo* cyclization and the ring opening of a cyclopropylcarbinyl radical. Unlike the original tin hydride conditions reported by Giese, a chemoselective reaction is possible in spite of the C(sp^2)−X (X = Br, I) bonds. Further synthetic applications of this new combination of a Pd/light system with Hantzsch ester are currently underway in this laboratory.

Scheme 5. Proposed Reaction Mechanism



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03238.

Typical experimental procedure and characterization for all products (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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Organic LETTERS

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Acid-Promoted Cross-Dehydrative Aromatization for the Synthesis of Tetraaryl-Substituted Pyrroles

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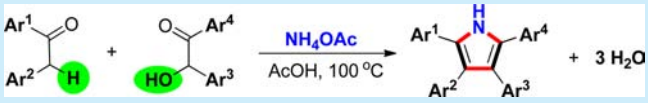
Supporting Information

ABSTRACT: Tetraaryl-substituted pyrroles are one important class of luminophores. In this work, an acid-promoted cross-dehydrative aromatization between benzoin and deoxybenzion was developed. This transformation provides an efficient and straightforward path for the synthesis of various aryl group substituted tetraarylpyrroles. Good to excellent yields were obtained through the easy operation with acetic acid and ammonium acetate.



Aromatic rings are important building blocks existing in numerous pharmaceuticals, natural products, and functional materials.[1] Among various aromatic compounds, five- and six-membered aromatic rings are the most common system in the chemical world. Tremendous efforts have been devoted to construct aromatic rings during the past decades.[2] Normally, six-membered aromatic cycle can be constructed through cyclotrimerization of alkyne or nitrile or the Dies–Alder reaction followed by aromatization.[3] A five-membered aromatic cycle can usually be built via the classic Paal–Knorr synthesis or transition-metal-catalyzed cycloisomerization-type or cycloaddition-type reactions.[4] The Paal–Knorr synthesis is a typical dehydrative aromatization process with H_2O as the side product.[5] However, it usually requires uneasily accessible 1,4-dione as the precursor.[6]

Pyrroles are one of the most frequently appearing five-membered rings in many important molecules.[7] Recently, with the development of electroluminescent materials, some tetraarylpyrroles were discovered to have remarkable fluorescence, which shows potential application in organic electronic devices.[8] However, until now, most of the reported synthetic methods could only selectively afford symmetric tetraaryl-substituted pyrroles, which restrict further application of those types of molecules in materials chemistry.[4,9] In 1938, Davidson successfully prepared a symmetric tetraphenylpyrrole from benzoin.[10] It is known that benzoin is a proper precursor of desoxybenzoin.[11] Inspired by these results, we deduced that whether the direct cross-condensation of benzoin and desoxybenzoin could construct important tetraaryl pyrroles with four different aryl groups. Herein, we demonstrated an acid-promoted cross-dehydrative aromatization for the synthesis of unsymmetrical tetraaryl-substituted pyrroles (Scheme 1).

In our initial attempt, 1,2-diphenylethan-1-one (**1a**) and 4,4′-bis(trifluoromethyl)benzoin (**2c**) were selected as the substrates in the presence of ammonium acetate in AcOH at 120 °C to prepare the unsymmetric tetraaryl-substituted pyrrole **3ac**. To our delight, the desired product **3ac** was successfully obtained in 70% yield. When the temperature was decreased to 100 °C and the amount of **2c** was increased to 1.33 equiv, the unsymmetrical tetraaryl-substituted pyrrole **3ac** was obtained in 98% yield (Scheme 2).

Scheme 1. Approach To Access Tetraaryl-Substituted Pyrrole

Scheme 2. Initial Attempt To Access Unsymmetrical Tetraaryl-Substituted Pyrrole

Amount of 2c	Temp	Yield of 3ac
1.0 equiv	120 °C	70%
1.33 equiv	100 °C	98%

Furthermore, the reaction conditions were applied to the synthesis of other unsymmetrical tetraaryl-substituted pyrroles. First, different benzoins were tested as substrates to react with **1a** (Scheme 3). Both electron-donating and electron-withdrawing substituents on the benzene ring of benzoin were well tolerated under the current conditions (Scheme 3, **3ab**, **3ac**). Even the cyano group was also well tolerated (Scheme 3, **3ad**). Benzoin substituted with halogens such as F, Cl, and Br afforded the corresponding products in excellent yields (Scheme 3, **3ae–ag**). It is worthy of noting that functional groups such as cyano, fluoro always show the potential of improving the photovoltaic

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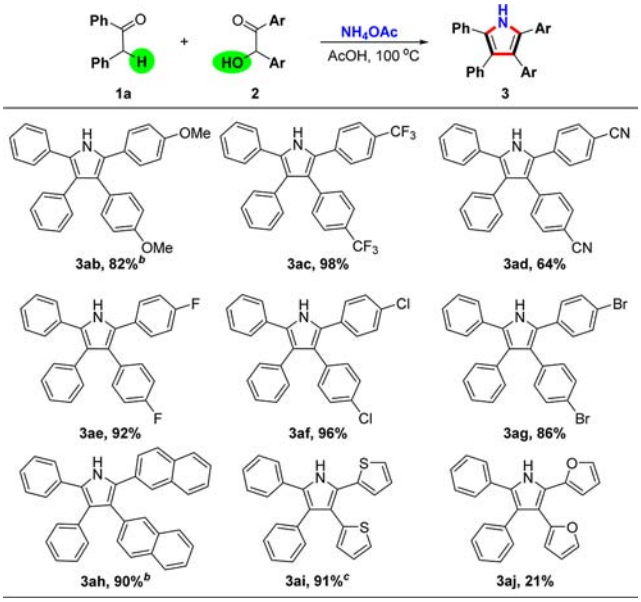
Scheme 3. Acid-Promoted Cross-Dehydrative Aromatization of 1a with Different Benzoins[a]



[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.4 mmol), NH_4OAc (4.5 mmol), AcOH (2.0 mL), 100 °C, 12 h. The products were obtained in isolated yields. [b]The reaction was conducted under 120 °C. [c]**2** (0.5 mmol) was used.

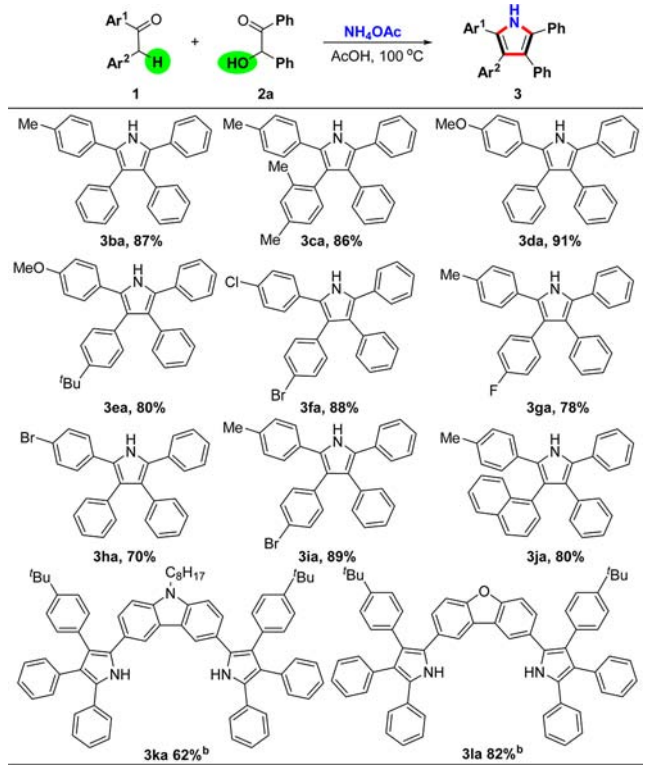
properties of materials. Moreover, the halogens such as Br and Cl, usually provide possibilities for further functionalization. Some benzoin that the phenyl groups were replaced by other aryl cycles were also investigated. Benzoins with naphthalene and thiophene substituents were able to furnish the desired products in good yields (Scheme 3, **3ah** and **3ai**), while 2,2′-furoin only afforded the target product in 21% yield, which might due to its instability under the standard conditions (**3aj**).

In the next step, a series of 1,2-diarylethan-1-ones were investigated to extend the substrate scope (Scheme 4). The reactions of desoxybenzoin with *p*- and *o*-methyl substitutents showed good reaction efficiency in this acid-promoted cross-dehydrative aromatization reaction (Scheme 4, **3ba** and **3ca**). Electron-rich substituents on the benzene ring were also well compatible (Scheme 4, **3da** and **3ea**). The desoxybenzoins with halide substituents such as F, Cl, and Br afforded the corresponding products in good yields (Scheme 4, **3fa**–**ia**). Ethanone substituted with α-naphthyl groups was also suitable in this transformation (Scheme 4, **3ja**). Carbazole and dibenzofuran are also important structure motifs in material chemistry because of their stability and special properties. Interestingly, unsymmetrical tetraaryl-substituted pyrroles containing the block of carbazole or dibenzofuran were synthesized successfully by adding 1.0 mL of toluene as a cosolvent to increase the solubility (**3ka**, **3la**).

At last, the synthesis of tetraaryl-substituted pyrrole with four different aromatic substituents was also explored through this acid-promoted cross-dehydrative aromatization transformation. 4-Chlorobenzoin was used to react with desoxybenzoin bearing two different aryl substituents. The desired pyrroles with four different aryl substitutents were obtained with two regioisomers due to the tautomerism of benzoin as expected (Scheme 5).

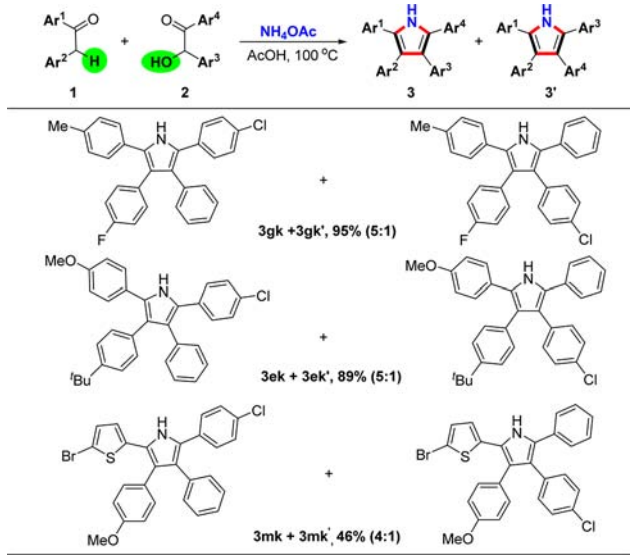
It is obvious that Ar^1 and Ar^2, respectively, bound to the C1 and C2 positions of the produced pyrrole. However, due to the tautomerism of benzoin, it is not clear that whether the Ar group

Scheme 4. Acid-Promoted Cross-Dehydrative Aromatization of Different 1,2-Diarylethan-1-ones with 2a[a]



[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.4 mmol), NH_4OAc (4.5 mmol), AcOH (2.0 mL), 100 °C, 12 h. The products were obtained in isolated yields. [b]**1** (0.15 mmol), **2a** (0.4 mmol), PhMe (1.0 mL) was added.

Scheme 5. Synthesis of Tetraaryl-Substituted Pyrrole with Four Different Substituents via Cross-Dehydrative Aromatization



Reaction conditions: **1** (0.3 mmol), **2** (0.4 mmol), NH_4OAc (4.5 mmol), AcOH (2.0 mL), 100 °C, 12 h. Isolated yields.

bound to the carbonyl goes to the C4 position of the product pyrrole. To confirm this, **2k** and **2l** were, respectively, subjected to reaction with **1a** (Scheme 6). Both reactions resulted in the

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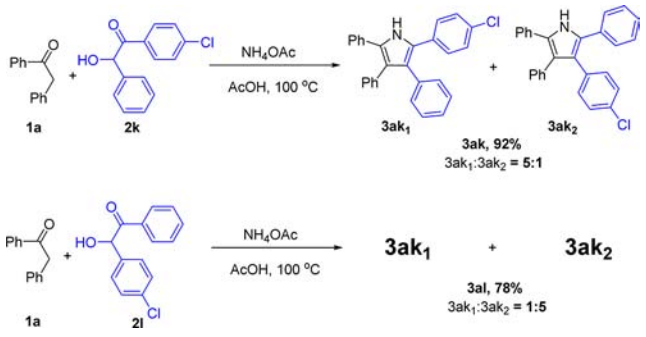
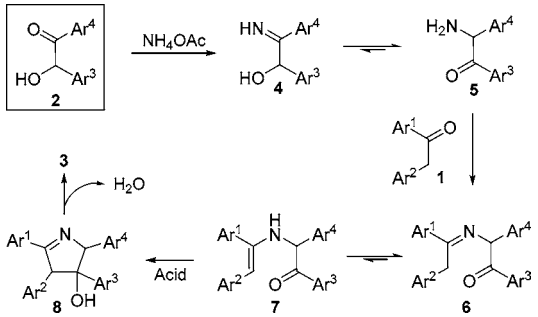
Scheme 6. Comparison Experiments



same products $\mathbf{3ak_1}$ and $\mathbf{3ak_2}$, yet with different ratios. When **2k** was applied as the substrate (*p*-Cl phenyl was bound to the carbonyl), $\mathbf{3ak_2}$ was the major product, in which the *p*-Cl phenyl was at the C4 position. When **2l** was applied as the substrate (Ph was bound to the carbonyl), $\mathbf{3ak_2}$ was the major product, in which the Ph group was at the C4 position. Those results indicated that the carbonyl carbon of **2** became the C4 carbon of the produced pyrrole and the tautomerism of benzoin derivatives led to the minor product of the isomers.

On the basis of those results, a tentative reaction pathway was proposed in Scheme 7. Benzoin **2** initially reacts with NH_4OAc to

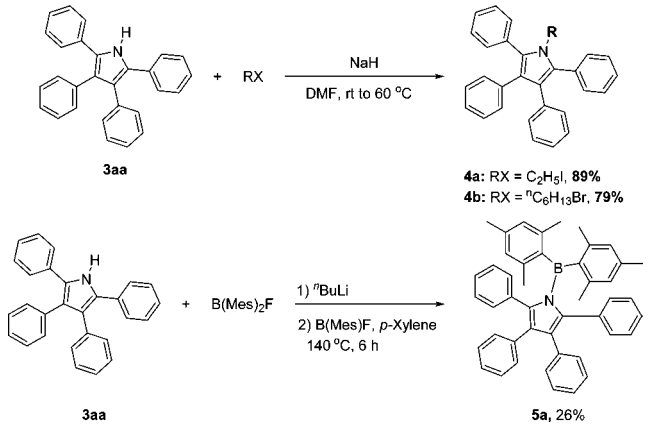
Scheme 7. Tentative Reaction Pathway



result in **4**, which could be isomerized into α-amino ketone **5**. Further condensation of **5** with **1** results in imine **6** followed by a tautomerism to enamine **7**. An intramolecular cyclization via an electrophilic addition to the carbonyl group forms **8**. Then, an acid promoted dehydrative aromatization of **8** releases the desired pyrrole **3**. The isomerized product might result from the initial tautomerism of benzoin **2**.

Author: Next, it is known that the N−H bond of the tetraaryl-substituted pyrroles seem to be too active to be implemented on photoelectric devices directly.[12] Both *N*-alkylation and borylation are important methods for modifying the tetraaryl-substituted pyrrole to the desired molecular materials. *N*-Alkylation can stabilize the molecule and improve the photovoltaic properties of materials to some extent.[13] The alkylation reaction of **1aa** with iodoethane and bromohexane all proceeded smoothly (Scheme 8). Furthermore, boron is a strong electron-withdrawing atom. Formation of an N−B bond can greatly change the photovoltaic property of tetraaryl-substituted pyrrole.[14] *N*-Borylpyrroles showed larger stocker shift and better fluorescence efficiency in PL spectra compared with *N*-alkylpyrroles. The *N*-borylation reaction of **3aa** was also explored. A 26% yield of the desired product **5a** was obtained with $B(Mes)_2F$ as the boron source (Scheme 8).

Scheme 8. Applications of the Obtained Tetraaryl Pyrroles



In summary, we have developed a facile and highly efficient approach for the construction of unsymmetrical tetraaryl-substituted pyrroles via acid-promoted cross-dehydrative aromatization. In this strategy, two monocarbonyl compounds, instead of the difficult-to-synthesize 1,4-diketone, were used as substrates to construct tetraaryl-substituted pyrroles with H_2O as the side product. Various functional groups and heterocycles were tolerated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03240.

Experimental details and spectral data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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Organic LETTERS

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Alkynylation of Thiols with Ethynylbenziodoxolone (EBX) Reagents: α- or β- π-Addition?

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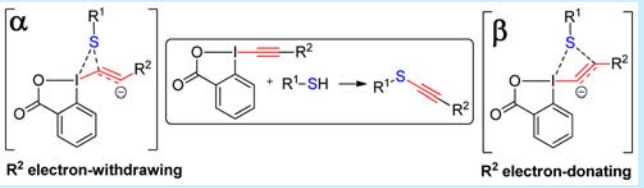
Supporting Information

ABSTRACT: The alkynylation of thiols with EthynylBenziodoXolone (EBX) reagents is a fast and chemoselective method for the synthesis of thioalkynes. Combined experimental and computational studies are reported, which led to the identification of a new mechanism for this reaction, proceeding via an initial sulfur−iodine interaction followed by β-addition, α-elimination, and a 1,2-shift. Depending on the substituent on the alkyne, this mechanism can be favored over the previously disclosed concerted α-addition pathway.

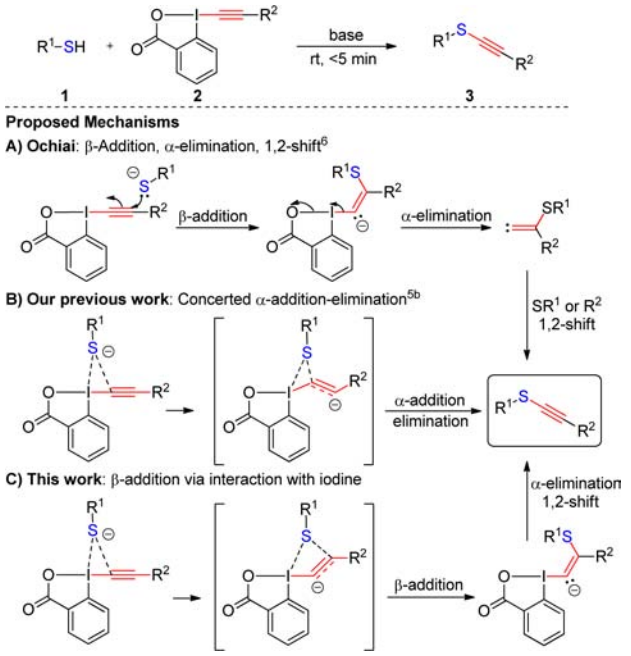


Alkynes are among the most versatile building blocks in synthesis due to their interesting structural properties and the numerous methods available for their transformation.[1] Additionally, they have found a multitude of applications in chemical biology and materials science. Heteroatom-substituted alkynes, such as ynamides and thioalkynes, are particularly interesting owing to their enhanced reactivity.[2] Whereas important breakthroughs have recently been realized in the efficient synthesis of ynamides, most methods for accessing thioalkynes require multiple steps and/or the use of highly reactive intermediates, such as lithium acetylides.[3] Recently, milder metal-catalyzed methods for the alkynylation of thiols have emerged.[4] Our group developed a metal-free alternative approach based on the use of EthynylBenziodoXolone (EBX) hypervalent iodine reagents.[5] Originally limited to the transfer of silyl alkynes, the method was later extended to the synthesis of aryl and alkyl acetylenes and was also applied to the functionalization of cysteines in proteins in the living cell.

Most reactions of nucleophiles with alkynyliodonium salts involve a conjugate addition, α-elimination, and 1,2-shift pathway (Ochiai's mechanism, Scheme 1A).[6] Based on Density Functional Theory (DFT) computations, we proposed in 2014 an unprecedented concerted α-addition mechanism proceeding via a low energy three-atom transition state for the alkynylation of thiols with EBX reagents (Scheme 1B).[5b] Herein, we present further computational results which reveal a third unexpected mechanism, resulting from the shift of a van der Waals complex characterized by a favorable sulfur−iodine interaction directly to a low lying transition state for β-addition (Scheme 1C). Computations predict that either α- or β-addition can be favored depending on the reagent substituents, as supported by a ^{13}C-labeling experiment.

In our previous studies, we demonstrated that thiols could be alkynylated in high yields with both silyl- and alkyl-substituted EBX reagents.[5b] DFT computations led to the discovery of a new concerted α-addition pathway, which was 12.2 kcal/mol lower in energy than β-addition for the alkynylation of benzylthiol **1a** with the commercially available TIPS-EBX reagent **2a** (Scheme 2). However, for Me-EBX **2b** we were able to isolate a side product **4** coming from a β-addition pathway. Computations indeed showed that the difference in energy between the two pathways was smaller for methyl than silyl substituents (4.7 instead of 12.2 kcal/mol). Nevertheless, the α-addition pathway was still significantly lower in energy and the isolation of **4** was therefore intriguing.

Scheme 1. Alkynylation of Thiols and Proposed Mechanisms



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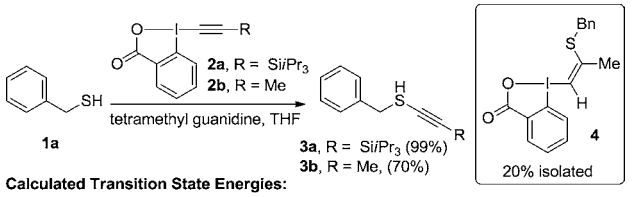
Scheme 2. Alkynylation of Benzyl Thiol 1a and Computed Transition State Energies



Consequently, we conducted additional computations for the alkynylation with EBX reagents (at the PBE0-dDsC/TZ2P//M06-2X/def2-SVP theoretical level; see computational details in the Supporting Information for additional information).[7] Thiophenol **1b** was used as a substrate, rather than the previously employed benzylthiol, to minimize conformational freedom (Figure 1). Lower energy pathways involving direct β-addition of thiophenolate **1b′** on the triple bond could not be identified. In fact, all these attacks involve a nonfavorable van der Waals interaction with the β-position of the alkyne ($\mathbf{b_0}^{old}$). However, when we reinvestigated pathways starting from the more favorable van der Waals interaction complex $\mathbf{a_0}$ between the sulfur and the iodine atom, which was previously identified as the entry point for the concerted α-addition ($\mathbf{a_{TS1}}$), a new low energy pathway proceeding via transition state $\mathbf{b_{TS1}}$ was found. This corresponds to a direct attack of the sulfur atom on the alkyne β-position and is lower in energy than the α-addition pathway (9.3 vs 10.1 kcal/mol). In this new transition state, the sulfur atom attacks at a trajectory 180° to the arene ring, rather than 90° as in the previously identified β-addition pathway.[8] After formation of vinyl intermediate $\mathbf{b_1}$, elimination of iodine occurs readily via transition state $\mathbf{b_{TS2}}$, followed by a barrierless 1,2-silicon shift to give the observed product **5a** and 2-iodobenzoate (**6**).

The new reaction pathway was also computed for Me-EBX **2b** (Figure 2). In this case, β-addition via transition state $\mathbf{b_{TS1}}$ was favored by 5.8 kcal/mol. Furthermore, the obtained vinyl intermediate $\mathbf{b_1}$ was more stable, with a barrier of 12.2 kcal/mol for carbon−iodine bond cleavage. Interestingly, intermediate $\mathbf{b_2}$, corresponding to a vinylidene carbene, could also be identified, as the sulfur shift was significantly slower than the silicon shift. Finally, a relatively facile (8.4 kcal/mol activation energy) 1,2-sulfur shift gives the observed product **5b**.

An important difference between silyl and alkyl reagents in the β-addition pathway is the identity of the migrating group: silicon vs sulfur.[9] In the case of TIPS-EBX **2a**, introducing a ^{13}C label onto the alkyne would unambiguously differentiate the two pathways. Indeed, when thiophenol **1b** was reacted with ^{13}C-labeled reagent **2c**,[10] a 1:1.2 mixture of products labeled in the α- and β-positions to silicon was obtained (products **5a′** and **5a″**; Scheme 3). This result supports the coexistence of the two reactions pathways and agrees well with the small energy difference (0.8 kcal/mol) obtained by computation.

In order to better understand the factors determining the relative energies of the two possible reactions pathways, we computed the reaction of EBX reagents with systematically varied heterocyclic cores (**2**, **7**−**9**) and alkynyl substituents (Figure 3).[11]

From these computations, it appears that the structure of the hypervalent iodine heterocycle has only a marginal effect on the energy of the transition state (Figure 4). In contrast, the substituent on the alkyne had a strong influence on the transition state energy. With an electron-withdrawing substituent, such as an ester, α-addition is favored, as the resulting partial negative charge is stabilized. With silyl and phenyl substituents, both pathways are competitive. Finally, electron-donating groups make the α-pathway less favorable and at the same time lower the energy for the transition state of the β-pathway.[12] Interestingly, alkynes bearing either a highly electron-rich or an electron-withdrawing substituent are expected to react faster with nucleophiles (activation energy around 5 kcal/mol). Unfortunately, to date we have been unable to synthesize reagents bearing a methoxy or an ester group for experimental verification. It is also worth mentioning that alkynyliodonium salts, such as **9**, displayed very similar behavior to EBX reagents, although they cannot be used for the

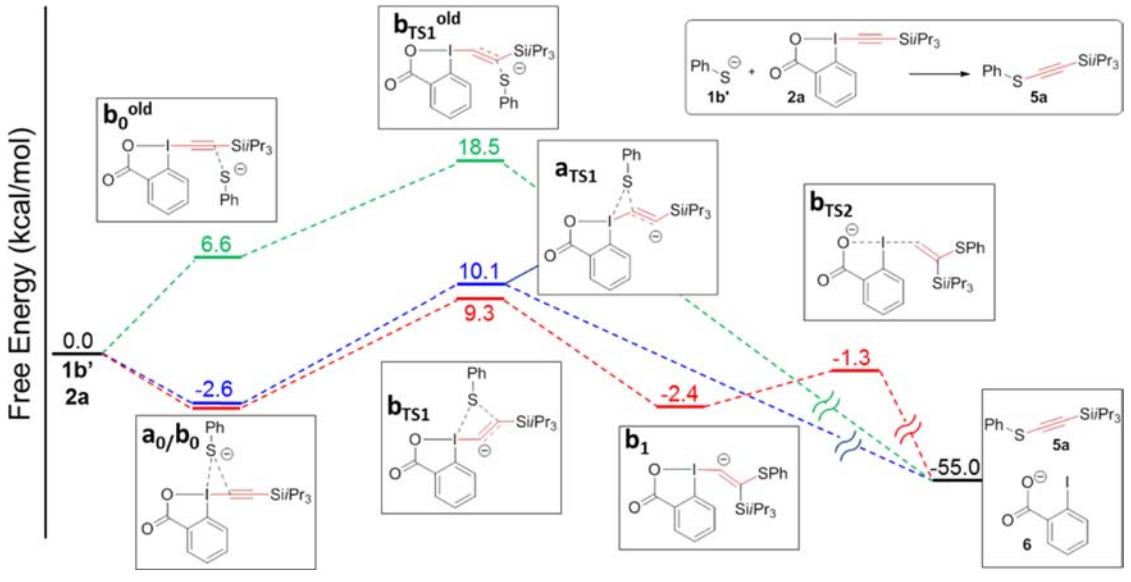


Figure 1. Reaction free energy profile [PBE0-dDsC/TZ2P//M06-2X/def2-SVP level in implicit THF solvent (COSMO-RS)] for the three possible mechanistic pathways **a** (blue), $\mathbf{b}^{old}$ (green), and **b** (red) for the reaction of TIPS-EBX **2a** with thiolate **1b′**.

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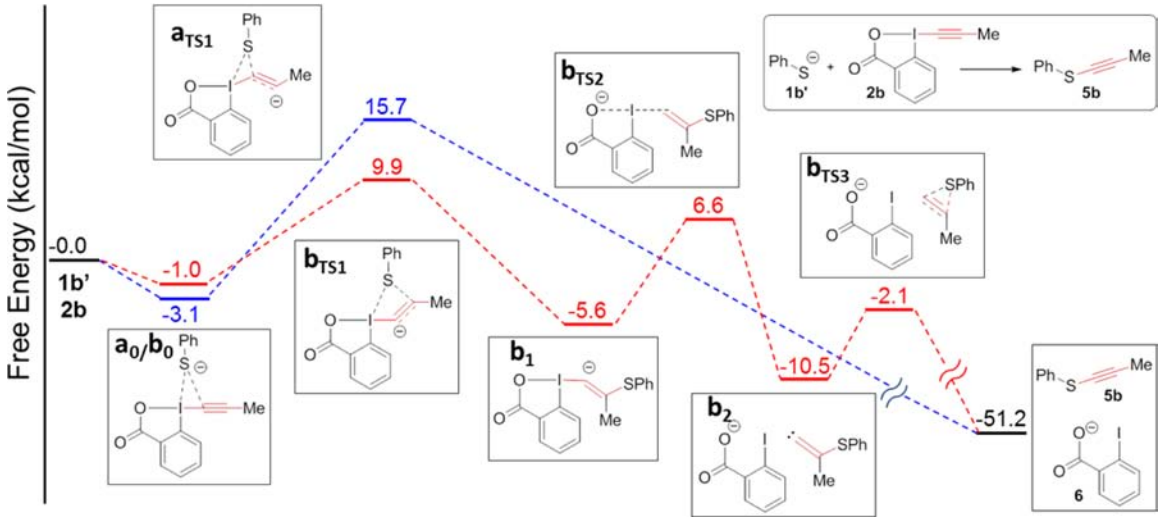
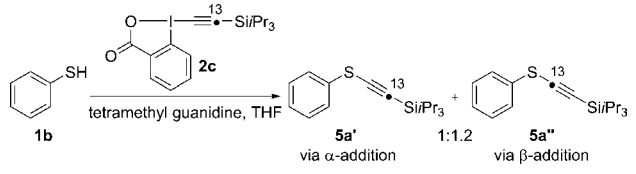
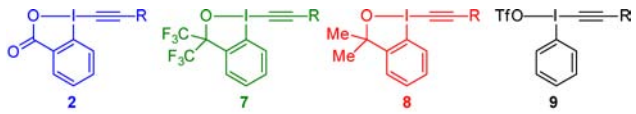


Figure 2. Reaction free energy profile [PBE0-dDsC/TZ2P//M06-2X/def2-SVP level in implicit THF solvent (COSMO-RS)] for the two possible mechanistic pathways **a** (blue) and **b** (red) for the reaction of Me-EBX **2b** with thiolate **1b**′.

Scheme 3. Reaction of thiophenol 1b with ^{13}C-labelled reagent 2c





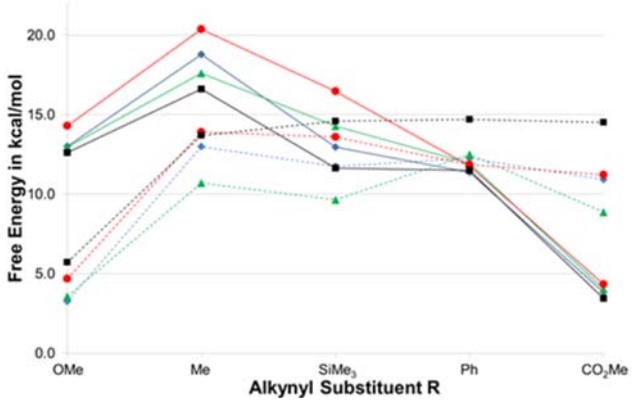


Figure 3. Transition state energies for α (full lines) and β (dotted lines) pathways for EBX reagents depending on the R group and heterocyclic core **2** (blue diamond), **7** (green triangle), **8** (red circle), and **9** (black square).

alkynylation of thiols due to the formation of disulfides as major products.[5a] The superiority of EBX reagents, therefore, can be assigned not to a faster alkynylation of thiols, but to a slower oxidation to disulfides.

In conclusion, further in-depth computational studies prompted discovery of a new mechanism for the alkynylation of thiols with EBX reagents proceeding via an initial sulfur–iodine interaction followed by a concerted β-addition. This mechanism is favored in the presence of electron-donating

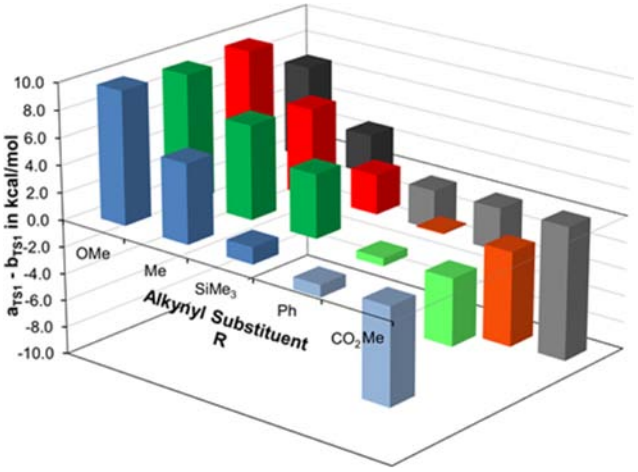


Figure 4. Energy difference $a_{TS1}-b_{TS1}$ depending on the R group and heterocyclic core **2** (blue), **7** (green), **8** (red), and **9** (black).

groups on the alkyne, whereas the previously reported α-addition pathway dominates in the presence of electron-withdrawing groups. With the commercially available reagent TIPS-EBX **2a**, both pathways are accessible, as supported by a labeling experiment. With this study, a more complete picture of the mechanism of the alkynylation of thiols has emerged, which will be highly useful for the design of new transformations using the versatile EBX reagents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03241.

Experimental procedures and analytical data for the labeling experiments and computational details (energies) (PDF)

Cartesian coordinate .xyz files (ZIP)

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(8) See Figure S1 in Supporting Information for the computed structures.

(9) A methyl shift is much higher in energy and was not observed by computation.

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(11) Preliminary computations were also performed with phenolate and tolyl anions as nucleophiles. For the case of the oxygen nucleophile, pathways corresponding to α and β addition could also be identified and were close in energy. For the carbon nucleophile, the β addition pathway via preliminary interaction with the iodine atom could not be easily located and requires further study.

(12) The fact that the transition state energy of the α pathway is lower for methoxy than methyl could be tentatively explained by the inductive effect of the oxygen atom.

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Organic LETTERS

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Lewis Acid Mediated Vinylogous Additions of Enol Nucleophiles into an α,β-Unsaturated Platinum Carbene

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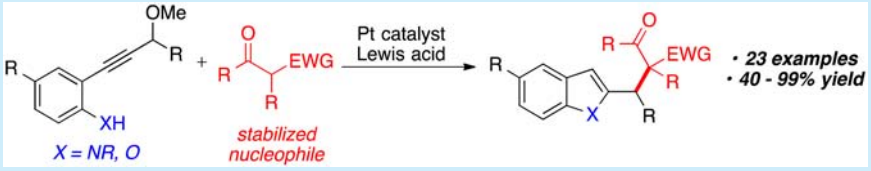
Supporting Information

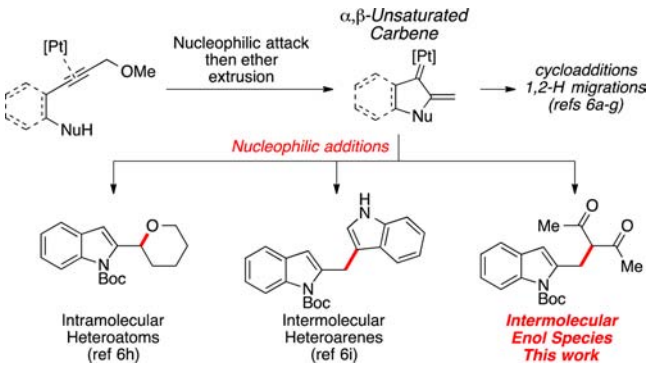


ABSTRACT: A variety of substituted indoles and benzofurans are accessed via a platinum catalyzed annulation and vinylogous addition of enol nucleophiles. Several β-dicarbonyl compounds participate in the reaction, as do α-nitro and α-cyano carbonyl species. Subjecting the indole products to acidic conditions results in the formation of fused heterocycles.

Substituted indoles continue to prove their worth as privileged molecules. This structural motif is present in a wide variety of natural products and pharmaceuticals,[1] and its utility as an important chemical building block is highlighted by the rich chemistry describing its elaboration to more complex molecular architectures.[2] Numerous approaches have been developed over the years to facilitate indole formation,[3] with many recent efforts utilizing metal catalysis to promote the ring formation.[4] Among these, methods that use indole formation as part of a multicomponent coupling process are particularly appealing due to their ability to synchronize the formation of multiple bonds during a single reaction.[5]

We envisioned a process where initial indole formation would be linked to the intermolecular addition of a carbon nucleophile, providing ready access to diversely substituted heterocyclic products. We and others have been investigating the use of platinum catalysis to generate α,β-unsaturated carbene intermediates via an intramolecular nucleophilic addition into alkynes bearing propargylic ethers (Scheme 1).[6] These carbenes have been demonstrated to undergo cycloadditions,[6a−d] hydrogen migrations,[6e−g] and vinylogous nucleophilic additions.[6h,i] In the latter systems, both heteroatom nucleophiles and electron-rich heterocycles have been shown to be competent reactants. Inspired by the demonstration that enol nucleophiles can achieve vinylogous additions into rhodium and gold carbenes generated from diazo species,[7] we became curious whether this class of nucleophiles would be participatory within this catalytic platinum reaction manifold. Herein, we demonstrate that the nucleophilic interception by these enol species can indeed be coupled to indole formation, yielding heterocyclic products that feature synthetically attractive structural motifs (e.g., all-carbon quaternary carbon centers, functionality poised for subsequent manipulations).

Scheme 1. α,β-Unsaturated Carbene Generation/ Nucleophilic Attack



We began our studies using *N*-Boc-aniline **1a** and 3-ethyl-2,4-pentanedione as our enol nucleophile (Table 1). Using similar conditions to those we had developed for the vicinal bisheterocyclizations, we observed minimal nucleophilic addition (entry 1, 8% yield of **3aa**). We suspected that the poor reactivity was due to the PPh_3 ligand rendering the metal carbene too electron rich to induce the double-addition process. Indeed, switching the phosphine ligand to $P(C_6F_5)_3$ produced the desired reactivity, generating indole **3aa** in 58% yield (entry 2). Added base suppressed the reaction (entries 3 and 4), but several Lewis acid additives were beneficial to the overall process. Given its boost in reactivity and relatively low cost, we determined $MgCl_2$ was the optimal Lewis acid for further studies. Reducing the equivalents of enol source to 2.0 or 1.1 resulted in diminished reactivity (entries 10 and 11). Interestingly, exclusion of the phosphine ligand had no adverse effect on the reaction overall (entry 12), suggesting that the phosphine was merely an inhibitor when electron rich and not influential when electron deficient. Other Lewis acids without phosphine additives showed comparable results (entries 13–

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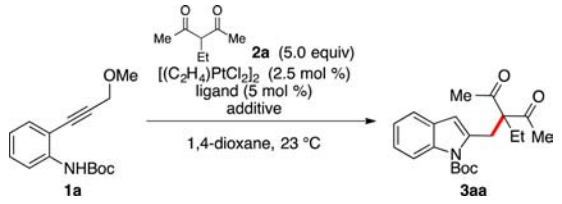
Table 1. Optimization of the Reaction Conditions



entry	ligand	additive (mol %)	time (h)	yield **3aa**[a] (%)
1	PPh_3	none	5	8
2	$P(C_6F_5)_3$	none	3	58
3	$P(C_6F_5)_3$	Na_2CO_3 (100)	5	0
4	$P(C_6F_5)_3$	Na_2CO_3 (10)	5	18
5	$P(C_6F_5)_3$	$MgCl_2$ (5)	2	72
6	$P(C_6F_5)_3$	$La(OTf)_3$ (5)	2	73
7	$P(C_6F_5)_3$	$CuSO_4$ (10)	4	68
8	$P(C_6F_5)_3$	$CeCl_3$ (5)	0.5	65
9	$P(C_6F_5)_3$	$Sc(OTf)_3$ (5)	0.5	30
10	$P(C_6F_5)_3$	$MgCl_2$ (5)	2	50[b]
11	$P(C_6F_5)_3$	$MgCl_2$ (5)	2	30[c]
12	none	$MgCl_2$ (5)	3	72 (70)[d]
13	none	$CuSO_4$ (20)	6	61
14	none	$La(OTf)_3$ (5)	2	71
15	none	none	2	59

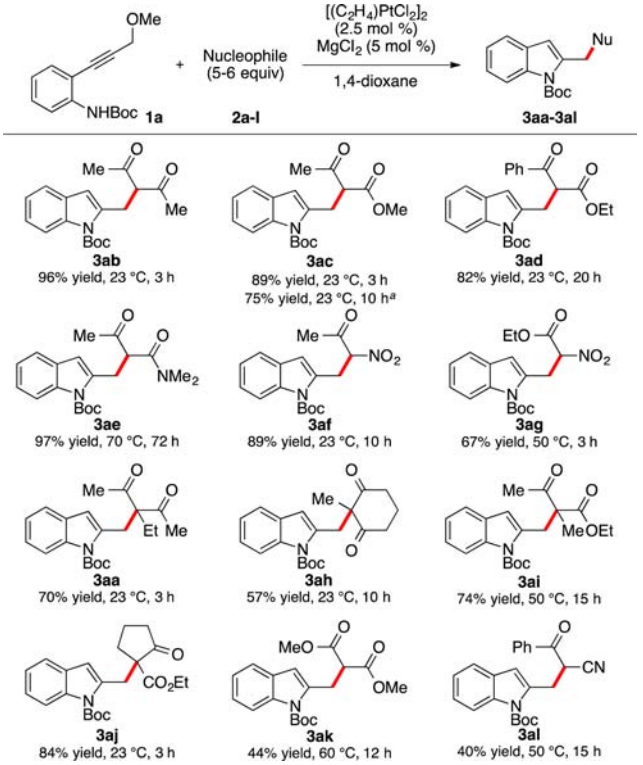
[a]Determined by ^1H NMR using dibenzyl ether as an internal standard. [b]Used 2.0 equiv of diketone **2a**. [c]Used 1.1 equiv of diketone **2a**. [d]Isolated yield in parentheses.

14). As a control experiment, we also ran the reaction without a Lewis acid and observed a measurable decrease in yield (entry 15), confirming our hypothesis that the efficiency of the addition process is loosely correlated to the concentration of the enol nucleophile.[8,9]

With the optimized conditions in hand (2.5 mol % Zeise's dimer, 5 mol % $MgCl_2$, no ligand), we set out to establish the generality of this reaction. A variety of β-dicarbonyl compounds were evaluated using *N*-Boc aniline **1a** as our carbene precursor (Scheme 2). Overall, this process generated the desired substituted indoles in high yields. β-Diketones, ketoesters, and ketoamides all successfully added into the platinum carbene intermediate. The nucleophile stoichiometry could be reduced, albeit generating indole **3ac** in lower relative yield and requiring longer reaction times (75% in 10 h with 1.1 equiv vs 89% in 3 h with 5 equiv). α-Nitro carbonyl compounds proved to be competent nucleophiles, forming indoles **3af** and **3ag** in good yields. Of particular interest is indole **3ag**, which represents a modular method of constructing an isomeric tryptophan motif with the side chain connected to the 2-position of the indole ring.[10] Similar to the product formed in reaction optimization (**3aa**), nucleophiles with an additional α-substituent could be utilized in this transformation to generate the formation of all-carbon quaternary centers (**3ah**−**aj**). Nucleophiles that form less of the enol species in equilibrium (malonates, ketonitriles) were less reactive in this catalytic manifold.

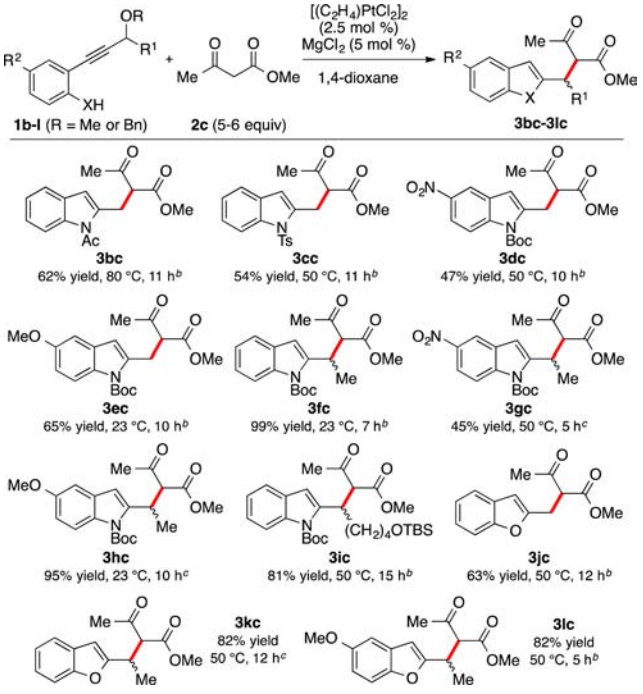
Having demonstrated a broad tolerance for a variety of enol nucleophiles, we next explored the effects of substitution on the carbene precursor (Scheme 3). The starting materials were easily accessed, generally via Sonogashira coupling of *o*-iodoanilines with the desired alkyne.[11] Both acetyl- and toluenesulfonyl-protected anilines were successful (**3bc** and **3cc**), although with lower yields than obtained when the

Scheme 2. Examination of Enol Nucleophiles on the Coupled Annulation/Vinylogous Addition Reaction



[a]Using 1.0 equiv of methyl acetoacetate.

Scheme 3. Examination of Substitution on the Coupled Annulation/Vinylogous Addition Reaction[a]



[a]Diastereoselectivity ranged from 1 to 2:1; see the Supporting Information for details. [b]Starting material is Me ether. [c]Starting material is Bn ether.

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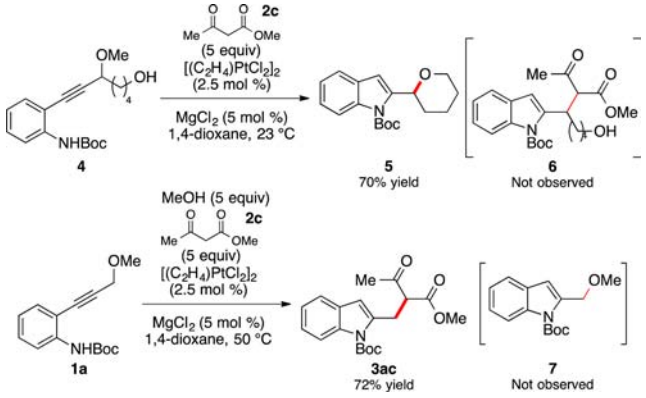
corresponding *N*-Boc aniline was used. The presence of electron-withdrawing ($-NO_2$) and electron-donating ($-OMe$) groups could be incorporated into the carbene precursor. Secondary propargylic ethers were also tolerated, forming indoles **3fc**–**ic** in good yields; diastereoselectivity, however, was not controlled in this process. A variety of phenol substrates also reacted as hoped, generating benzofuran products **3jc**, **3kc**, and **3lc** in good yields.

In our prior work,[6h] we had demonstrated that heteroatom nucleophiles could intramolecularly intercept the putative carbene intermediate at the β position. To evaluate the efficacy and the selectivity of the dicarbonyl nucleophile, we performed two tests (Scheme 4). In the first case, substrate **4** was

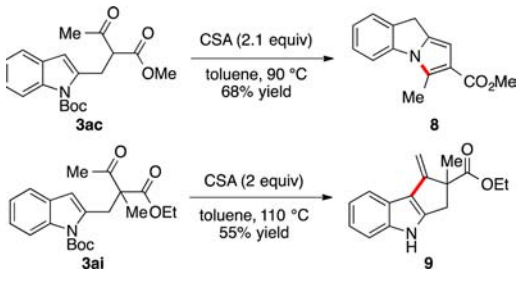
Scheme 4. Nucleophile Competition Experiments



combined with ketoester **2c** under the catalytic conditions. Bisheterocycle **5** was the only observed product, illustrating that intramolecular trapping by the hydroxyl group was faster than dicarbonyl nucleophile incorporation. This experiment also agrees with our proposed mechanistic rationale, implicating the nucleophilic addition at the β position of a platinum carbene. An alternative mechanism involving addition to an indolyl cation that originates from ether ionization[12] would suggest that compound **6** would be observed in the reaction via eventual conversion of **5**. The second experiment represented a competition between two external nucleophiles. For this case, addition of the ketoester was completely selective, as only indole **3ac** was observed.[13]

The coupling of a dicarbonyl group to an indole moiety with this relative connectivity enables direct routes to fused heterocyclic compounds. Illustrated in Scheme 5, indoles **3ac** and **3ai** were subjected to acidic conditions (CSA, toluene, heat). In the case of indole **3ac**, Boc removal and condensation with the methyl ketone occurred to afford the pyrrolo[1,2-*a*]indole skeleton in compound **8** in good yield.[14] This fused

Scheme 5. Elaboration of the Indole Products



heterocyclic motif is of interest due to its structural relationship to the mitomycins.[15] Indole **3ai**, meanwhile, underwent an orthogonal ring closure at C3, and heterocycle **9** was formed.[16] The straightforward conversion of the products that arise from these vinylogous carbene additions to higher order heterocycles is demonstrative of the overall utility of this method.

Catalytic transition metal carbenes continue to be proven invaluable in synthetic chemistry due to their capacity to promote a variety of bond-forming reactions. The results described herein highlight the ability to generate platinum carbenes under mild conditions, enabling the intermolecular construction of carbon–carbon bonds with a variety of enol sources. The addition of Lewis acidic $MgCl_2$ was important to encourage sufficient nucleophilicity across this range of enol species. The regioselectivity of addition to the putative vinyl platinum carbene intermediate parallels the observed vinylogous additions of nucleophiles in vinyl rhodium and gold carbenes.[7] This reactivity mode offers an opportunity to introduce species β to the carbene center and represents a unique coupling process with concomitant ring closure. Further investigations into this reactivity profile and applications are underway 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.5b03246.

Experimental procedures, compound characterization data, and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(13) We believe this outcome simply illustrates that an enol nucleophile is faster at reacting with the metal carbene than an alcohol in an intermolecular sense. It likely does not indicate the necessity of an anionic/metal-complexed nucleophile, as demonstrated by the outcome in Table 1, entry 15.

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(16) We have not detected the products arising from the opposite regioselectivity of cyclization in either case. It is not clear a priori why cyclization selectivity occurs with N vs C3 preferences based on α-substitution. Potentially, the aromatization of compound **8** provides a thermodynamically favored tricycle that cannot be obtained using indole **3ai**. Further investigations would be required to determine all of the factors that govern cyclization regioselectivity.

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Rh(III)-Catalyzed C−H Cyclization of Arylnitrones with Diazo Compounds: Access to *N*-Hydroxyindolines

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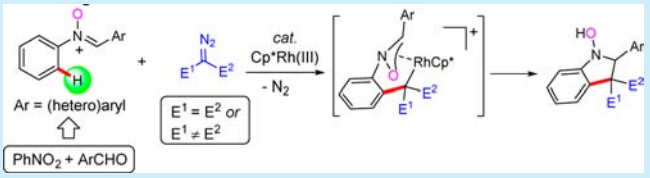
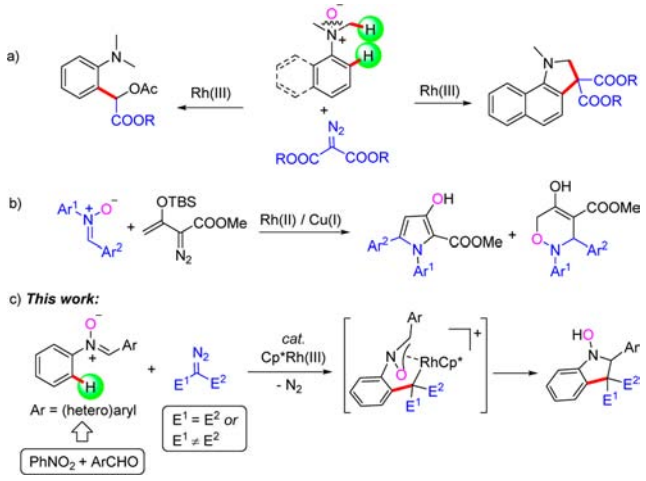
Supporting Information

ABSTRACT: We have developed the Cp*Rh(III)-catalyzed cyclization reaction of arylnitrones with diazo compounds to obtain *N*-hydroxyindoline products under mild conditions. The substrate scope and functional group compatibility were examined with the demonstration of synthetic utility.



Indolines are an important structural motif present in numerous alkaloid compounds[1] displaying interesting biological and pharmaceutical properties.[2] Their facile preparation, as a result, has drawn much attention, thus leading to the development of indolines and various derivatives bearing synthetically valuable functional groups. Especially noteworthy among those are a CuH-catalyzed route to 2,3-disubstituted indolines[3] and a Pd-catalyzed C−C coupling procedure involving unactivated methylenes.[4,5] A more direct approach using redox-neutral C−H functionalization has been demonstrated to be fruitful for the synthesis of broad types of heterocycles.[6] For example, Zhou et al. reported a Rh(III)-catalyzed C−H functionalization of arylamine *N*-oxides in reaction with diazo compounds.[7a] While this annulation works efficiently with polyaromatic amine *N*-oxides to give 1*H*-benzo[*g*]indolines (Scheme 1a, right side), aniline *N*-oxides afford acyclic aminomandelic acids via an O atom transfer pathway (Scheme 1a, left side). Doyle et al. reported a cooperative catalytic reaction of nitrones with substituted vinyl diazoacetates to give functionalized 3-hydroxypyrroles (Scheme 1b).[8]

Scheme 1



Metal-mediated transformations of nitrone compounds can lead to the development of facile synthetic methods.[9] The fact that we can take advantage of the nitrone moiety as a reacting site as well as a directing group may allow an additional opportunity to form heterocyclic products of structural diversity.[6] Indeed, in continuation of our efforts on C−H functionalizations,[10] we recently reported an efficient Rh(III)-catalyzed redox-neutral cyclization reaction of arylnitrones to afford indolines via C−H bond activation and a subsequent oxygen atom transfer pathway.[11] This development was inspired by the recent advances in Rh-carbene chemistry[12] contributed by Rovis,[13] Glorius,[14] Yu,[15] and others.[16] Along this line, we herein report the Rh(III)-catalyzed C−H cyclization of nitrones in reaction with diazo compounds leading to *N*-hydroxyindoline products under mild conditions (Scheme 1c). It should be mentioned that, during the preparation of this manuscript, Zhou et al. reported an analogous transformation using a similar catalytic system.[7b]

We commenced our studies by examining the reaction parameters in a reaction of a nitrone species **1a** with dimethyl 2-diazomalonate **2a** (Table 1). The well-established combination of $[RhCp^*Cl_2]_2$ (3 mol %) and $AgSbF_6$ (12 mol %) in 1,4-dioxane resulted in the poor yield of the desired indoline product **3a** (entry 1). Decomposition of the diazo reactant **2a** was observed to occur slowly over time under these conditions. The cyclization efficiency was significantly improved by the addition of acid additives.[17] Among those acids screened, pivalic acid (2.0 equiv) was especially effective and the indoline product could be isolated in 89% yield (entry 2). The structure of indoline **3a** was unambiguously confirmed by X-ray crystallographic analysis. A satisfactory product yield was obtained still with a lower catalyst loading (73% with 1 mol % of Cp*Rh catalyst, entry 3). While a lower loading of pivalic

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Table 1. Optimization of Reaction Conditions[a]

entry	catalyst/[Ag] salt	additive (equiv)	t (h)	yield (%)[b]
1	$[RhCp^*Cl_2]_2/AgSbF_6$	none	24	13
2	**$[RhCp^*Cl_2]_2/AgSbF_6$**	**PivOH (2)**	**12**	**93 (89)**[c]
3[d]	$[RhCp^*Cl_2]_2/AgSbF_6$	PivOH (2)	24	73
4	$[RhCp^*Cl_2]_2/AgSbF_6$	PivOH (0.5)	12	67
5	$[RhCp^*Cl_2]_2/AgSbF_6$	AcOH (2)	12	68
6	$[RhCp^*Cl_2]_2/AgSbF_6$	$PhCO_2H$ (2)	15	61
7	$[RhCp^*Cl_2]_2/AgSbF_6$	CF_3CO_2H (2)	12	36
8	$[RhCp^*Cl_2]_2/AgSbF_6$	*p*-TsOH (2)	15	29
9	$[RhCp^tCl_2]_2/AgSbF_6$	PivOH (2)	12	78
10	$[IrCp^*Cl_2]_2/AgSbF_6$	PivOH (2)	12	<1
11	$[Ru(p\text{-cymene})Cl_2]_2/AgSbF_6$	PivOH (2)	10	<1
12	$[RhCp^*Cl_2]_2/AgNTf_2$	PivOH (2)	10	63
13[e]	$[RhCp^*Cl_2]_2/AgSbF_6$	PivOH (2)	24	42
14[f]	$[RhCp^*Cl_2]_2/AgSbF_6$	PivOH (2)	24	44

[a]Reaction conditions: **1a** (0.11 mmol), **2a** (0.10 mmol), catalyst (3.0 mol %), [Ag] salt (12 mol %), molecular sieves (4 Å), and additive (2.0 equiv) in 1,4-dioxane (0.5 mL) at 25 °C. [b]NMR yield of the crude reaction mixture (internal standard: 1,3,5-trimethylbenzene). [c]Isolated yield. [d]1.0 Mol % of Rh catalyst and 4.0 mol % [Ag] salt were used. [e]In 1,2-dichloroethane. [f]In toluene.

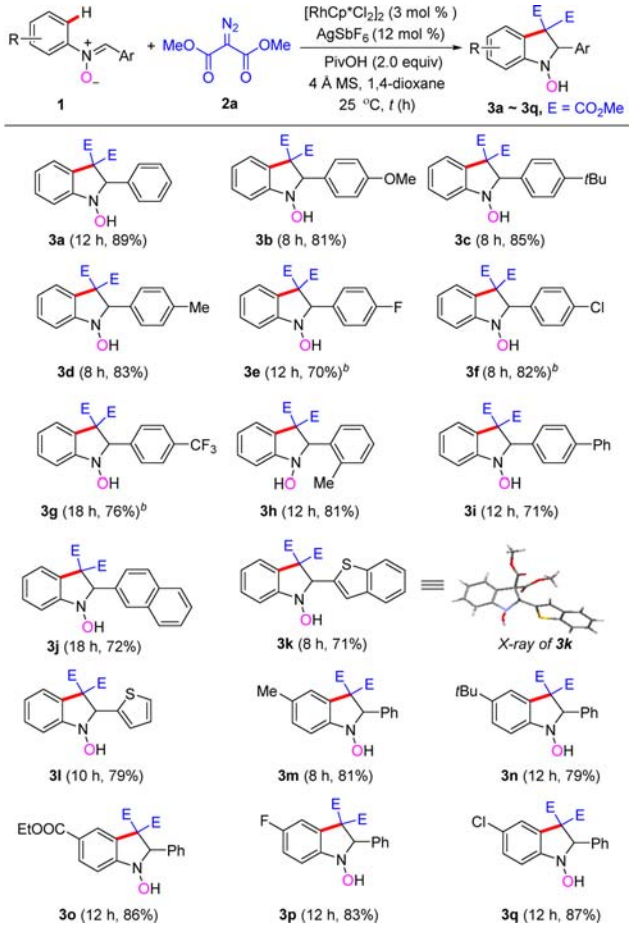
acid gave decreased efficiency (entry 4), other Brønsted acid additives (AcOH, $PhCO_2H$, TFA, or TsOH) were less effective when compared to PivOH (entries 5−8).

A rhodium catalyst derivative replacing Cp* with (1,3-di-*tert*-butyl)cyclopentadienyl (Cp^t)[18] was slightly less effective (entry 9). Interestingly, different catalytic systems (Ru or Ir), also known to promote the C−H functionalization,[10d,f] did not display reactivity (entries 10−11). Palladium catalysts were also ineffective (see the Supporting Information for details). The use of $AgNTf_2$ instead of $AgSbF_6$ afforded **3a** in moderate yield (entry 12). Solvents other than 1,4-dioxane were less effective (entries 13−14).

With the optimal conditions in hand, we scrutinized the scope of the arylnitrones in reactions with dimethyl 2-diazomalonate **2a** (Scheme 2). To our delight, high efficiency was observed over a wide range of substrates irrespective of the structural variation of nitrones to furnish the desired indolines in good to excellent yields. Phenylnitrones bearing methoxy, *tert*-butyl, and methyl groups at the 4-position of the phenylimino moiety underwent the cyclization smoothly at room temperature to give the corresponding products (**3b−3d**) in 81−85% yields. Substrates bearing electron-withdrawing groups such as fluoro, chloro, or trifluoromethyl underwent the desired reaction efficiently albeit at a slightly higher temperature (40 °C) leading to satisfactory yields (**3e−3g**). Reaction of a nitrone substrate having an *ortho*-methyl group at the phenylimino moiety was smooth without difficulty (**3h**).

When nitrones bearing biphenyl- or naphthylimino groups were subjected to the standard conditions, the corresponding indoline products (**3i** and **3j**, respectively) were obtained in reasonable yields. Heterocyclic substituents were compatible with the present procedure as demonstrated by the facile formation of **3k** (benzothiophene) and **3l** (thiophene). The structure of product **3k** was unambiguously confirmed by X-ray

Scheme 2. Substrate Scope of Arylnitrones[a]



[a]**1** (0.11 mmol) and **2a** (0.10 mmol) in 1,4-dioxane (0.5 mL) at 25 °C. [b]At 40 °C.

crystallographic analysis. In addition, the present cyclization could be expanded to include nitrones bearing substituents at the N-aryl moiety. Interestingly, the efficiency was maintained at a high level with nitrones substituted with either electron-donating or -withdrawing groups on that side. Indeed, the product yields of **3m−3n** were comparable to those of **3o−3q**. It is worth mentioning that the present reaction conditions are compatible with various functional groups such as halides, heteroarenes, or esters.

The scope of the diazo reactants was subsequently examined (Scheme 3). Symmetrical diazo compounds with di-*n*-butyl, di(2,2,2-trifluoroethyl), and diphenyl esters underwent the reaction efficiently (**3r−3t**). Diazo esters bearing readily removable dibenzyl groups were facile for this cyclization (**3u−3v**). Pleasingly, *unsymmetrical* diazo esters underwent the cyclization in satisfactory efficiency. In fact, diazo compounds bearing both ester and ketone groups were reacted with a nitrone (**1a**) to afford the corresponding indoline products (**3w−3y**) as single diastereomers in each case, determined by NMR analysis (see the Supporting Information for details).

The synthetic utility of the obtained 1-hydroxyindoline product (**3a**) was briefly examined (Scheme 4). Reduction of a *N*-hydroxy group was readily carried out using iron filings in acetic acid to afford N−H indoline compound **4** in 73% yield.[19] Considering the fact that C-7 substituted indolines exhibit interesting biological activities such as antibacterial, antiviral,

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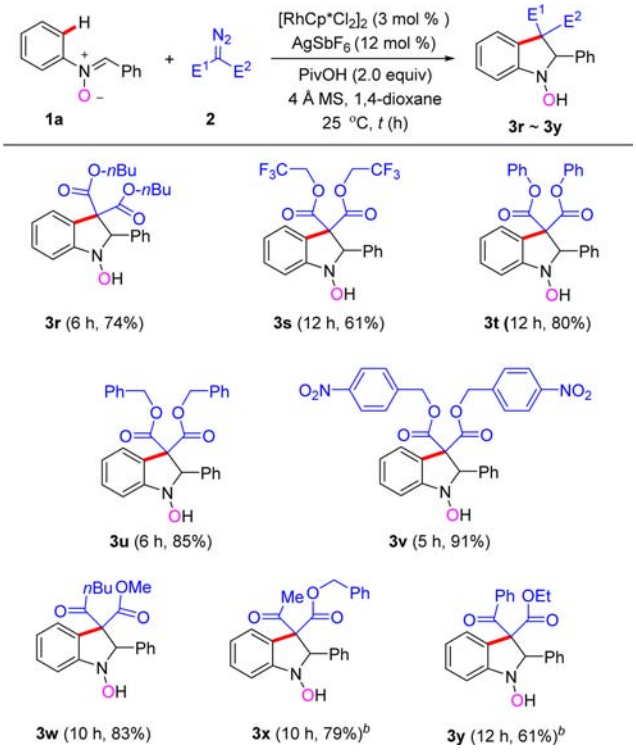
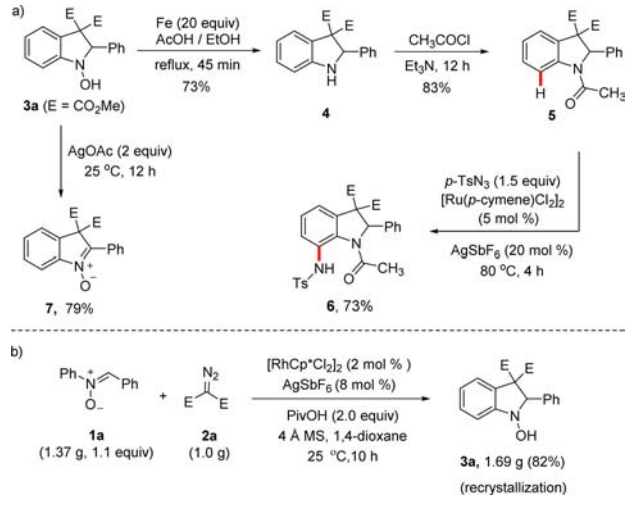
Scheme 3. Scope of Diazo Compounds[a]



[a]**1a** (0.11 mmol) and **2** (0.10 mmol) in 1,4-dioxane (0.5 mL) at 25 °C. [b]At 40 °C.

Scheme 4. Synthetic Utilities of Indoline Products

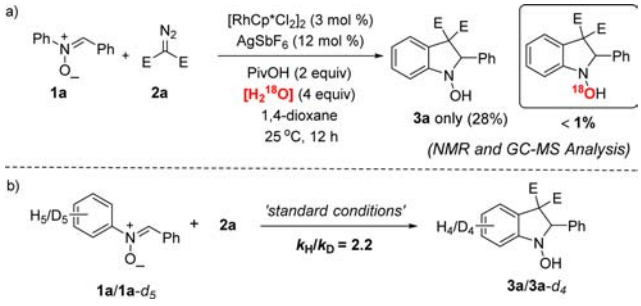


and antidiabetic properties,[20] thus making them a versatile pharmacophore, we wondered if direct introduction of functional groups would be plausible at the C-7 position of indolines.

Pleasingly, under the conditions previously developed by us,[10d] direct C−H amidation of *N*-acetylindoline **5** with tosyl azide was readily achieved to furnish **6** by the action of a ruthenium catalyst. Oxidation of 1-hydroxyindoline **3a** was facilitated by silver acetate (2.0 equiv) to afford 3*H*-indole-*N*-oxide **7** under mild conditions. In addition, the present cyclization procedure was convenient to perform in a gram scale reaction, and the desired product was isolated in good yield after recrystallization (Scheme 4b).

In order to obtain mechanistic insights, preliminary experiments were briefly carried out (Scheme 5). A reaction in the

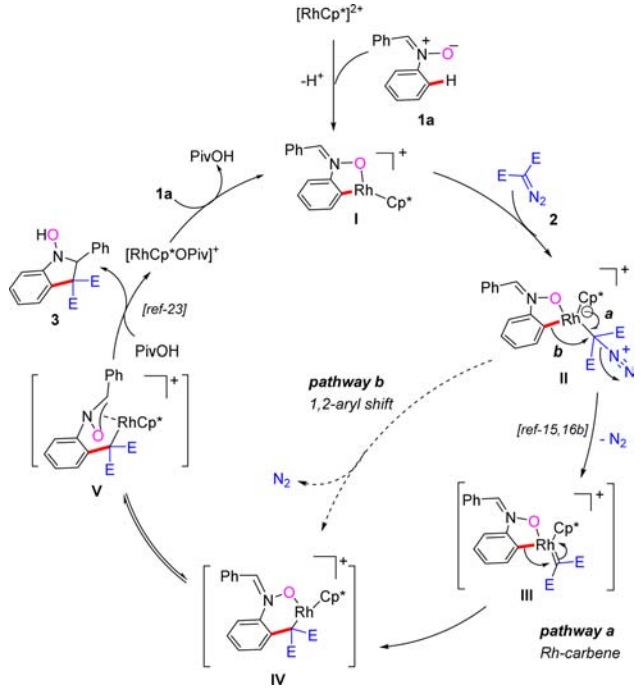
Scheme 5. Preliminary Mechanistic Studies



presence of $H_2{}^{18}O$ revealed that the obtained product **3a** was not incorporated with the ^{18}O atom (Scheme 5a).[21] This result implies that the cyclization does not proceed via the N−O bond cleavage in nitrone **1a**, thereby indicating that no oxygen atom transfer occurs throughout the reaction progress. In addition, a notable kinetic isotopic effect was measured (k_H/k_D = 2.2), suggesting that C−H bond cleavage may be involved in the rate-limiting step (Scheme 5b).[22]

On the basis of the preliminary mechanistic studies and precedent literature,[11,15,16b,23] a mechanistic proposal is depicted in Scheme 6. At the first step, the Rh(III)-mediated

Scheme 6. Proposed Mechanism



ortho C−H bond cleavage occurs to form a five-membered rhodacycle **I** followed by coordination of a diazo compound leading to **II**.[11] In the subsequent diazo insertion step, as reported independently by Yu[15] and Lee,[16b] two pathways would be plausible. Extrusion of N_2 from **II** delivers a Rh-carbene species **III** that undergoes a migratory insertion to afford a six-membered rhodacycle **IV** (pathway a). Alternatively, direct intramolecular 1,2-migratory insertion of **II** may also deliver the same intermediate **IV** without an intervening

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rhodium carbenoid species (pathway b). Cyclization is assumed to proceed through a redox-neutral pathway presumably via **V**, the protonation of which by pivalic acid providing the desired product **3** with regeneration of a catalytically active Rh species.[23]

In summary, we have developed a highly efficient synthetic route to *N*-hydroxyindolines by the Rh(III)-catalyzed C−H cyclization of arylnitrones with diazo compounds. The scope of the nitrone substrates and diazo reactants was sufficiently broad to deliver structurally diverse indoline products in high yields under mild conditions. This study will allow a new point of entry to enrich nitrone chemistry, especially toward the direct C−H functionalization approach.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03273.

Experimental details and spectra for important compounds (^{1}H, ^{13}C NMR spectra) (PDF)
Crystallographic data for **3a** (CIF)
Crystallographic data for **3k** (CIF)

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Notes

The authors declare no competing financial interest.

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Copper-Catalyzed Trifluoromethylation of Polysubstituted Alkenes Assisted by Decarboxylation

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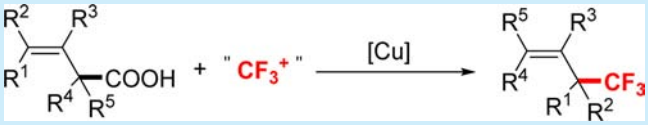
Supporting Information

ABSTRACT: An efficient copper-catalyzed trifluoromethylation of polysubstituted alkenes assisted by decarboxylation of β,γ-unsaturated carboxylic acids has been achieved. The reaction provides a general method to construct allylic and vinylic CF_3-substituted compounds under mild conditions.



Molecules bearing trifluoromethyl group(s) have been widely applied in modern pharmaceuticals, agrochemicals, and materials.[1,2] For instance, the selective incorporation of a trifluoromethyl group into drug candidates often significantly alters their metabolic stability, lipophilicity, and biopotency.[1,3] Hence, it has been of great synthetic interest to develop efficient methods for the incorporation of the CF_3 group into organic molecules.[4] During the past years, trifluoromethylations of aryl, vinyl, and allyl halides,[5] organoboron reagents,[6] and terminal alkynes[7] employing catalytic or stoichiometic amounts of copper species have been developed. In particular, transition-metal-catalyzed methods for the trifluoromethylation of $C(sp^2)-H$ and $C(sp^2)-X$ (X = halogen) bonds have attracted great attention.[8,9] Moreover, trifluoromethylation of alkenes have been studied intensively recently.[10]

Recently, the groups led by Buchwald,[11] Liu,[12] and Wang[13] independently reported Cu(I)-catalyzed trifluoromethylation of alkenes with electrophilic trifluoromethylating agents to construct the allylic $C-CF_3$ bonds. Qing and co-workers aslo reported that the allylic CF_3 product could be obtained from Cu(I)-catalyzed oxidative trifluoromethylation of alkenes with $TMSCF_3$.[14] However, these processes were shown to be effective only with linear terminal alkenes, while the branched terminal alkenes and the internal alkenes were found to be unsuitable substrates for the reaction.[11,12,14] Although the scope of the alkenes was expanded to cyclic alkenes in Wang's process, the yields were rather low.[13] Moreover, Wang's process was found to be not amenable to the linear internal alkenes and substituted cyclic alkenes.[13] Sodeoka[15] and Gouverneur[16] also independently reported the Cu(I)-catalyzed trifluoromethylation of allylsilanes, but the scope of substrates was limited. Therefore, a new protocol for catalytic trifluoromethylation of polysubstituted alkenes is highly desired.

Previously, we reported the copper-catalyzed decarboxylative fluoroalkylation of α,β-unsaturated carboxylic acids with Togni-type electrophilic fluoroalkylating agents, which provides a rapid access to various organofluorine compounds bearing di- and trifluoromethyl groups at vinylic positions.[17a] We also reported copper-catalyzed decarboxylative difluoromethylation of β,γ-unsaturated carboxylic acids with Togni-type electrophilic fluoroalkylating agents.[17b] Herein, we report a Lewis acid ($CuCl_2\cdot 2H_2O$)-catalyzed decarboxylative trifluoromethylation of β,γ-unsaturated carboxylic acids. This new synthetic protocol acts as a powerful strategy for allylic trifluoromethylation that nicely complements the aforementioned methods.[11−16]

At the onset of our investigation, we chose the reaction between Togni's reagent (**1a**)[18] and 3-(*p*-tolyl)-3-butenoic acid (**2a**) as a model reaction to survey the reaction conditions. We screened the different combinations of catalyst, solvent, and reaction temperature. As shown in Table 1, when a mixture of **1a** (1.0 equiv) and **2a** (2.0 equiv) in 1,4-dioxane/H_2O (4:1 v/v) was heated to 110 °C (temperature of oil bath), the desired product **3a** was formed only in 3% yield (entry 1) with **1a** being completely decomposed. Then we screened a series of Lewis acids to activate **1a** (entries 2−11). We found that Lewis acids $Zn(OAc)_2\cdot 2H_2O$[18c,19] and $FeCl_2\cdot 4H_2O$[6f,19] showed very low catalytic activity for the reaction (entries 2 and 4), and $Sc(OTf)_3$,[19] $Ce(OTf)_3$, $Sm(OTf)_3$,[19] $La(OTf)_3$, and $Ga(NO_3)_3$ showed no catalytic activity (entries 5−9). Other Lewis acids such as $Pd(OAc)_2$, CuCl,[6f,19] and $CuCl_2\cdot 2H_2O$[19] exhibited higher activity to catalyze this reaction, among which $CuCl_2\cdot 2H_2O$ showed the highest catalytic potency (entries 3 and 10, 11). However, the yield of product **3a** was only moderate (53%) when 2.0 equiv of **2a** were used (entry 11). When the amount of **2a** was increased to 4.0 equiv, the product **3a** was formed in 80% yield (entry 17). It was found that the product yield was not significantly influenced by the solvent system, and the reaction in 1,4-dioxane/H_2O (4:1 v/v) gave the highest yield (entries 11−15). The 1.6 mol % catalyst loading was found to be optimal, since both lower (1.0 mol %) and higher (3.2 mol %) loadings led to decreased yields (entries 17−19). The yields were also found to be sensitive to the reaction temperature. Initially, we thought that the yield could be improved by lowering the temperature, which could decrease the tendency of decomposition of **1a**. However, the product **3a**

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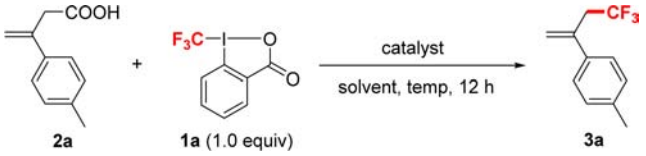
Table 1. Optimization of Reaction Conditions[a]



entry	2a (equiv)	solvent (v/v)	catalyst (equiv)	temp (°C)	yield (%)[b]
1	2.0	dioxane/H_2O (4:1)	–	110	3
2	2.0	dioxane/H_2O (4:1)	$Zn(OAc)_2{\cdot}2H_2O$ (0.016)	110	9
3	2.0	dioxane/H_2O (4:1)	$Pd(OAc)_2$ (0.016)	110	23
4	2.0	dioxane/H_2O (4:1)	$FeCl_2{\cdot}4H_2O$ (0.016)	110	5
5	2.0	dioxane/H_2O (4:1)	$Sc(OTf)_3$ (0.016)	110	0[c]
6	2.0	dioxane/H_2O (4:1)	$Ce(OTf)_3$ (0.016)	110	0[c]
7	2.0	dioxane/H_2O (4:1)	$Sm(OTf)_3$ (0.016)	110	0[c]
8	2.0	dioxane/H_2O (4:1)	$La(OTf)_3$ (0.016)	110	0[c]
9	2.0	dioxane/H_2O (4:1)	$Ga(NO_3)_3$ (0.016)	110	0[c]
10	2.0	dioxane/H_2O (4:1)	CuCl (0.016)	110	48
11	2.0	dioxane/H_2O (4:1)	$CuCl_2{\cdot}2H_2O$ (0.016)	110	53
12	2.0	DME/H_2O (4:1)	$CuCl_2{\cdot}2H_2O$ (0.016)	110	44
13	2.0	DMF/H_2O (4:1)	$CuCl_2{\cdot}2H_2O$ (0.016)	110	48
14	2.0	DMSO/H_2O (4:1)	$CuCl_2{\cdot}2H_2O$ (0.016)	110	43
15	2.0	dioxane	$CuCl_2{\cdot}2H_2O$ (0.016)	110	41
16	3.0	dioxane/H_2O (4:1)	$CuCl_2{\cdot}2H_2O$ (0.016)	110	69
17	4.0	dioxane/H_2O (4:1)	$CuCl_2{\cdot}2H_2O$ (0.016)	110	80[d]
18	4.0	dioxane/H_2O (4:1)	$CuCl_2{\cdot}2H_2O$ (0.010)	110	76
19	4.0	dioxane/H_2O (4:1)	$CuCl_2{\cdot}2H_2O$ (0.032)	110	70
20	4.0	dioxane/H_2O (4:1)	$CuCl_2{\cdot}2H_2O$ (0.016)	90	64
21	4.0	dioxane/H_2O (4:1)	$CuCl_2{\cdot}2H_2O$ (0.016)	60	41[e]

[a]Typical reaction conditions: Togni reagent **1a** (1.0 equiv, 0.8 mmol), H_2O (1 mL), 1,4-dioxane (4 mL). [b]Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as internal standard. [c]Reagent **1a** was decomposed completely probably due to the strong Lewis acidity of the catalyst. [d]74% of **2a** (based on the amount of **2a** added) was recovered, and 95% of 2-iodobenzoic acid was obtained as byproduct. [e]38% of **1a** was found to remain unreacted.

was only formed in 64% yield at 90 °C, although Togni's reagent was fully consumed (entry 20). When we decreased the temperature to 60 °C, the yield decreased to 41%, and reagent **1a** was partially (38%) unreacted after 12 h (entry 21). Finally, the optimal yield (80%) of product **3a** was obtained when Togni's reagent **1a** and substrate **2a** (molar ratio **1a**/**2a** = 1:4) were stirred in 1,4-dioxane/H_2O (4:1 v/v) in the presence of $CuCl_2{\cdot}2H_2O$ (1.6 mol %) at 110 °C for 12 h (entry 17). Notably, most of the unreacted substrate **2a** (74% based on the amount of **2a** added) could be easily recovered, and the byproduct 2-iodobenzoic acid could be isolated in 95% yield (entry 17). It is also noteworthy to mention that the reaction was found to be insensitive to air.

By using the optimized reaction conditions (Table 1, entry 17) as a standard, we examined the substrate scope of the present copper-catalyzed trifluoromethylation reaction. The results are summarized in Scheme 1. The reactions with terminal alkenes bearing aryl (or alkyl) groups proceeded smoothly to afford the corresponding products in moderate to excellent yields (such as **3a**–**j**, **3k**–**m**). The present trifluoromethylation was found to tolerate various functional groups, such as ester, hydroxyl, and alkynyl groups, which makes this trifluoromethylation protocol attractive for many synthetic applications. Notably, the aldehyde functional group, which is usually fragile under oxidative conditions, remained intact in the reaction (in the case of **3f**). Trisubstituted alkenes, including cyclic alkenes and the linear internal ones, could also react under the same reaction conditions to give the corresponding trifluoromethylated products in moderate to excellent yields (such as **3n**–**s**). It is worthwhile mentioning that the endo double bond of the substrate **2n** [2-(3,4-dihydronaphthalen-1-yl)acetic acid] could be transformed into an exocyclic double bond in product **3n**. Moreover, the unreacted substrate **2n** could be mostly recovered (79% yield based on the **2n** added). In addition, the tetrasubstituted alkenes **2t** could also react smoothly to afford the products in moderate yields (**3ta** and **3tb**) featuring exocyclic double bonds. The formation of double-trifluoromethylated product **3tb** is probably due to the high reactivity of **3ta**, which could further react with Togni's reagent **1a**. It is remarkable that the 3,4-allenoic acid **4** could also be readily trifluoromethylated using the same protocol to give 2-trifluoromethylated 1,3-diene compound **5a** in 70% yield (Scheme 2).

To gain some mechanistic insights into the current decarboxylative trifluoromethylation reaction, we examined the reaction between **1a** and *p*-benzoquinone (**6**) under the standard reaction conditions and found that the product **7** was not detected by ^{19}F NMR and GC-MS, while **1a** decomposed completely (Scheme 3), which was different from the results reported by Wang.[20] Moreover, when reagent **1a** reacted with **2a** in the presence of a stoichiometric amount of **6** under the same reaction conditions, the product **7** was still not detected by ^{19}F NMR and GC-MS, and the trifluoromethylated product **3a** was obtained in 65% yield (Scheme 3). These experimental results indicate that, in our reaction system, a CF_3 radical is not likely involved as a reactive species in the reaction mechanism.

Based on these results, we speculate that the present trifluoromethylation reaction may proceed through cationic

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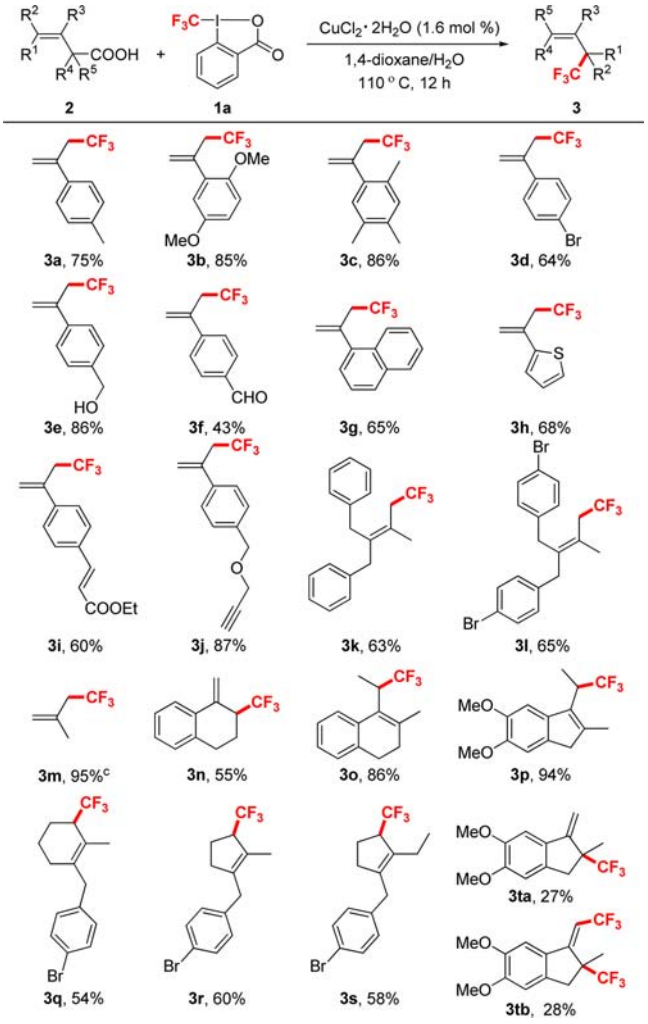
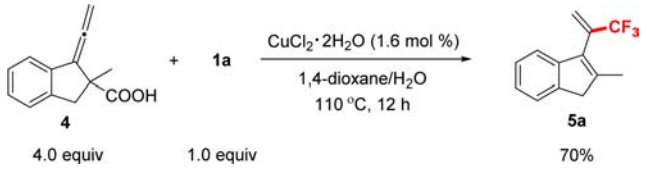
Scheme 1. Trifluoromethylation of Polysubstituted Alkenes 2 with Reagents 1a[a,b,c]



[a]The reaction conditions were as follows: **1a** (0.8 mmol), **2** (3.2 mmol), $CuCl_2·2H_2O$ (0.0125 mmol), 1,4-dioxane (4 mL), and H_2O (1 mL) were stirred at 110 °C for 12 h. [b]Isolated yield. [c]Yields were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as internal standard.

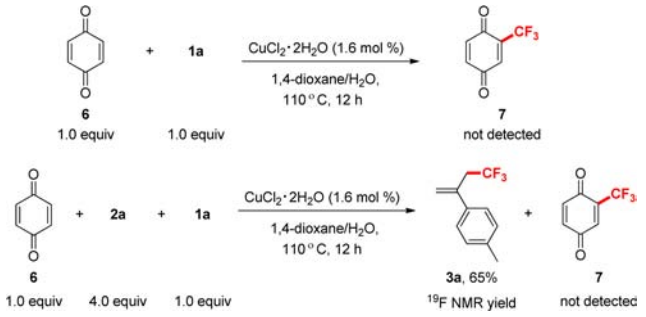
Scheme 2. Trifluoromethylation of 3,4-Allenoic Acid 4 with Reagents 1a



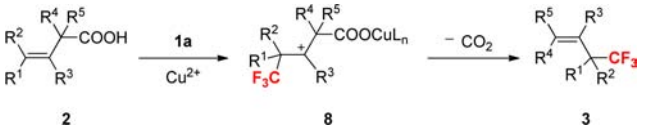
intermediates.[21] As illustrated in Scheme 4, the substrate **2** should react with reagent **1a** in the presence of $CuCl_2·2H_2O$ to generate intermediate **8**, and the intermediate **8** further undergoes decarboxylation to give the desired product **3**.

In summary, we have developed a new strategy for allylic trifluoromethylations; that is, Lewis acid ($CuCl_2·2H_2O$)-catalyzed and decarboxylation-assisted trifluoromethylation enables the efficient transfer of the CF_3 group into polysubstituted alkenes. This new strategy nicely complements the previous trifluoromethylation methods for alkenes.[10−14]

Scheme 3. Attempted Capture of the Trifluoromethyl Radical by *p*-Benzoquinone



Scheme 4. Possible Reaction Pathway



Our present trifluoromethylation method has a wide ranging scope of substrates and shows good tolerance for various functional groups. More importantly, this new method tolerates oxygen and water and, thus, significantly simplifies the operation. Furthermore, 3,4-allenoic acids could also be successfully trifluoromethylated by using this protocol to afford the 2-trifluoromethyl-1,3-diene product in high yield. Further investigations of the reaction mechanism and the application of the current strategy in other fluoroalkylations/fluorinations 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.5b03290.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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Organic LETTERS

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Synthesis of *Mycobacterium tuberculosis* Sulfolipid-3 Analogues and Total Synthesis of the Tetraacylated Trehaloglycolipid of *Mycobacterium paraffinicum*

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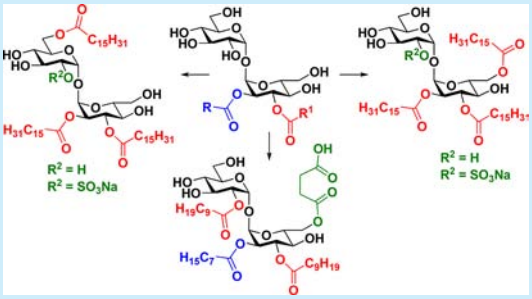
Supporting Information

ABSTRACT: A novel methodology for the regioselective O6 acylation of the 2,3-diacyl trehaloses to access *Mycobacterium tuberculosis* sulfolipid SL-3 and related 2,3,6-triester glycolipid analogues is reported for the first time. The methodology was successfully extended to achieve the first total synthesis of the tetraacylated trehalose glycolipid from *Mycobacterium paraffinicum*. The corresponding 2,3,6′-triesters trehalose glycolipids were also synthesized starting from the common 2,3-diacyl trehalose. These synthetic glycolipids are potential candidates for serodiagnosis and vaccine development for tuberculosis.



The resurgence of tuberculosis (Tb) and its rapid spread around the globe is alarming.[1] Due to the emergence of the multidrug resistant strains and its coinfection with HIV, Tb remains a top killer infectious disease worldwide.[2] Thus, effective vaccines, new drugs and methods for quick diagnosis of Tb are highly warranted to stop the spread of the disease. In this regard, sulfoglycolipids (SLs) and polyacyl-glycolipids present on the outer coat of the virulent strains of *Mycobacterium tuberculosis* (MTb) are promising candidates for vaccine development.[3−11]

Among the various glycolipids expressed on the surface of MTb, the tetraacyl-sulfotrehalose glycolipid SL-1[3−6] and diester Ac_2SGL[5d,7] have received much attention from synthetic chemists as well as biologists. In contrast, the corresponding triester, 2′-*O*-sulfated 2,3,6-triacyl trehalose glycolipid termed SL-3 **1** (Figure 1), has been explored to a much lesser extent.[3,6] Although studies have confirmed the antigenic nature of SL-3 **1**,[6] chemical synthesis of **1** or its simplified analogues (e.g., **2**) has not been reported to date. Likewise, the nonsulfated 2,3,6-triesters of trehalose have been isolated from MTb[9] and other mycobacterial strains.[10] Due to their microheterogeneous nature, the exact structures of these glycolipids still remain obscure, but biological studies have highlighted their importance for serodiagnosis of tuberculosis.[11] On the basis of the observed 2,3,6-acylation pattern and the isolated side chain acids, a possible structure **3** has been proposed for a MTb glycolipid which is composed of an octadecanoyl ester at the 2- and 6-positions and a mycolipenoyl ester at the 3-position.[9b] The chemical synthesis of **3** or its simplified analogues such as **4** is not reported. Also, it would be interesting to access the corresponding 2,3,6′-triacyl trehalose derivatives **5** and **6** to study the effect of the acylation site (O6- versus O6′-positions) on the biological activity. In fact, the 2′-*O*-sulfated 2,3,6-triester and 2,3,6′-triester of trehalose are shown to be intermediates in the biosynthesis of SL-1.[4] Yet another structurally related glycolipid **7** is a novel 2,3,6,2′-tetraacyl trehalose derivative isolated from *Mycobacterium paraffinicum*.[12] Compound **7** is an acidic glycolipid characterized as 2-*O*-octanoy1-3,2′-di-*O*-decanoy1-6-*O*-succinoyl-α,α-D-trehalose. Synthesis of such sulfated/nonsulfated triesters or tetraesters would require an efficient strategy for the monoesterification of the 2,3-diacyl trehalose at O6/O6′-position, which to the best of our knowledge is unexplored. In continuation of our studies on

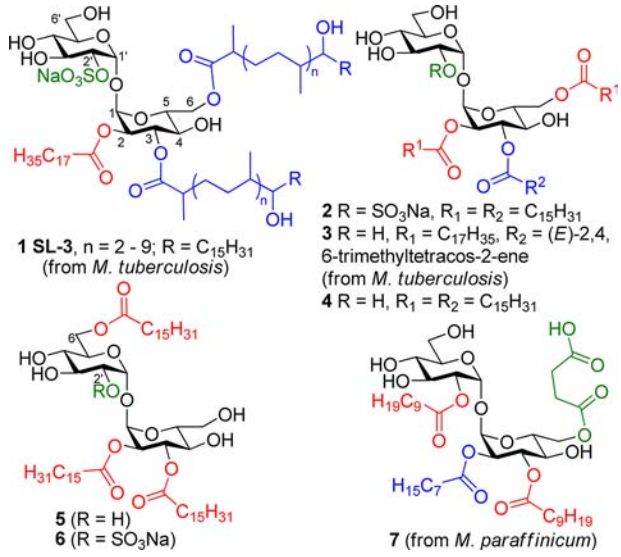


Figure 1. Mycobacterial trehaloglycolipids and their analogues.

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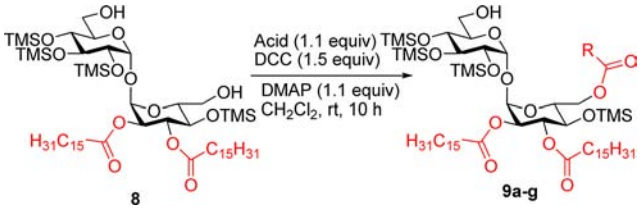
the synthesis of trehalose glycoconjugates,[5d,13] herein we report a novel methodology for the regioselective O6 acylation of the 2,3-diacyl trehaloses to access SL-3 and related 2,3,6-triester glycolipid analogues **2** and **4**, respectively. The methodology was successfully extended to achieve the first total synthesis of tetraacylated trehalose glycolipid **7**. The 2,3,6′-triesters **5** and **6** were synthesized via regioselective hydrolysis of dicyclohexylidene acetals followed by acylation at O6′.

It was envisioned that an appropriately protected 2,3-diacyl trehalose derivative[5d,14] could be a valuable intermediate for the synthesis of trehalose glycolipids requiring functionalization at 2,3 and 6-positions. Regioselective 6-*O*-monoacylation of the 2,3-diester would give access to the 2,3,6-triester **4** and its analogues, whereas synthesis of its 2′-*O*-sulfated SL-3 analogue **2**, and the 2′-*O*-acylated tetraester **7**, would require further regioselective functionalization at 2′-*O*-position. Likewise, the synthesis of 2,3,6′-acylated derivatives could be achieved starting from the same 2,3-diacyl trehalose. We hypothesized that the presence of both the O2- and O3-acyl functionalities on the same D-glucose ring should induce a difference in the reactivity of the two primary 6- and 6′-OH groups, and this difference can be tuned to direct the incoming acyl group to one of the primary positions.

To test this hypothesis, we decided to explore the regioselective monoacylation of the 6,6′-diol **8**, which can be conveniently prepared from trehalose in five steps and 41% overall yield on a multigram scale following our earlier reported strategy.[5d] As shown in Table 1, the regioselective acylation of

Table 1. Regioselective Acylation of Diol 8



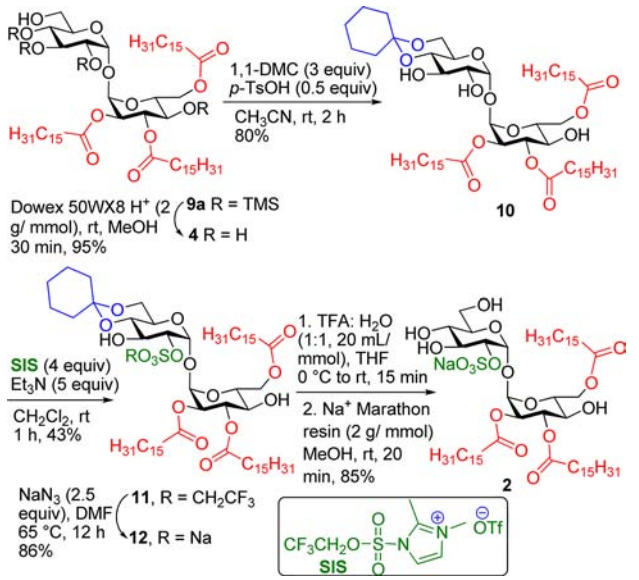
entry	acid	**9a-9g** (%)	**8** (%)
1	$C_{15}H_{31}CO_2H$	68	16
2	$C_{17}H_{35}CO_2H$	68	17
3	$C_{11}H_{23}CO_2H$	64	18
4	$C_9H_{19}CO_2H$	62	17
5	$C_7H_{15}CO_2H$	59	18
6	$C_{10}H_{19}CO_2H$	60	18
7	$C_{17}H_{33}CO_2H$	67	18

compound **8** was performed by cannulating a premixed solution of palmitic acid (1.1 equiv), DCC (1.5 equiv), and DMAP (1.1 equiv) in CH_2Cl_2 into the solution of diol **8** in CH_2Cl_2 at rt and stirring for 10 h. The major product was isolated and characterized as 2,3,6-tri-*O*-palmitoyl trehalose (**9a**) in 68% yield, along with a recovery of 16% unreacted diol **8**. We also obtained a small amount of the 2,3,6,6′-tetra-*O*-palmitoyl derivative; however, the other regioisomer, i.e., 2,3,6′-triester, was not observed. The regioselectivity of monopalmitoylation reaction was confirmed by observing a downfield shift of two C6 protons in ^{1}H NMR and their correlation in the ^{1}H−^{1}H COSY as well as ^{1}H−^{13}C HSQC and HMBC spectra (see the Supporting Information). The reason behind this regioselectivity is not clear. We believe that the incoming fatty acid may get associated with the lipid chains of **8** and is slowly delivered to the proximal hydroxyl group on the same sugar.

With such exciting results in hand, we proceeded to study the substrate scope of the reaction with fatty acids of different chain length and unsaturation. DCC-mediated esterification of diol **8** with stearic acid also afforded the monoesterified product **9b** in 68% yield (entry 2). When compound **8** was reacted with dodecanoic acid under the optimized conditions, monododecanoyl ester **9c** was obtained in 64% yield (entry 3). Similarly, reaction with decanoic acid and octanoic acid furnished the corresponding triesters **9d** and **9e** in 62% and 59% yields, respectively (entries 4 and 5). Monoacylation of diol **8** with unsaturated fatty acid viz. undecenoic acid (60%) and oleic acid afforded **9f** (60%) and **9g** (67%), respectively (entries 6 and 7). In all of these reactions, 16−18% of starting material **8** was recovered. The O6 regioselectivity observed in the monoacylation of the 2,3-diacyl trehalose 6,6′-diol provided unprecedented access to the 2,3,6-functionalized trehalose glycolipids and SL-3 analogues.

Scheme 1 delineates our strategy for the synthesis of 2,3,6-tri-*O*-palmitoyl trehalose **4** and SL-3 analogue **2**. The TMS

Scheme 1. Synthesis of Triester 4 and SL-3 Analogue 2



groups in compound **9a** were removed by acid-promoted hydrolysis using Dowex 50WX8 H^+ acidic resin to obtain 2,3,6-tri-*O*-palmitoyl trehalose **4** in 95% yield. For the synthesis of 2′-sulfated derivative **2**, the free 4′- and 6′-hydroxyl groups in **4** were protected as a cyclohexylidene acetal using 1,1-dimethoxycyclohexane (1,1-DMC) and a catalytic amount of *p*-TsOH to obtain compound **10** in 80% yield. Regioselective 2′-*O*-sulfation of triol **10** was performed using sulfuryl imidazolium salt (SIS)[15] reagent, employing Et_3N as a base[5d] to obtain compound **11** in moderate yields of 43%, along with 35% recovery of the starting material **10**. Use of excess of SIS reagent or changing the base from Et_3N to 1,2-dimethylimidazole or DMAP did not improve the yields of the sulfation reaction. The trifluoroethyl (TFE) group in compound **11** was removed smoothly by heating with NaN_3 (**12**, 86%), followed by acid hydrolysis of the cyclohexylidene acetal to furnish SL-3 analogue **2** in 85% yield.

Next, we turned our attention to the synthesis of 2,3,6′-triesters **5** and **6**. Since the regioselective acylation of 6,6′-diol **8** favored the O6-position, we needed a different strategy for the

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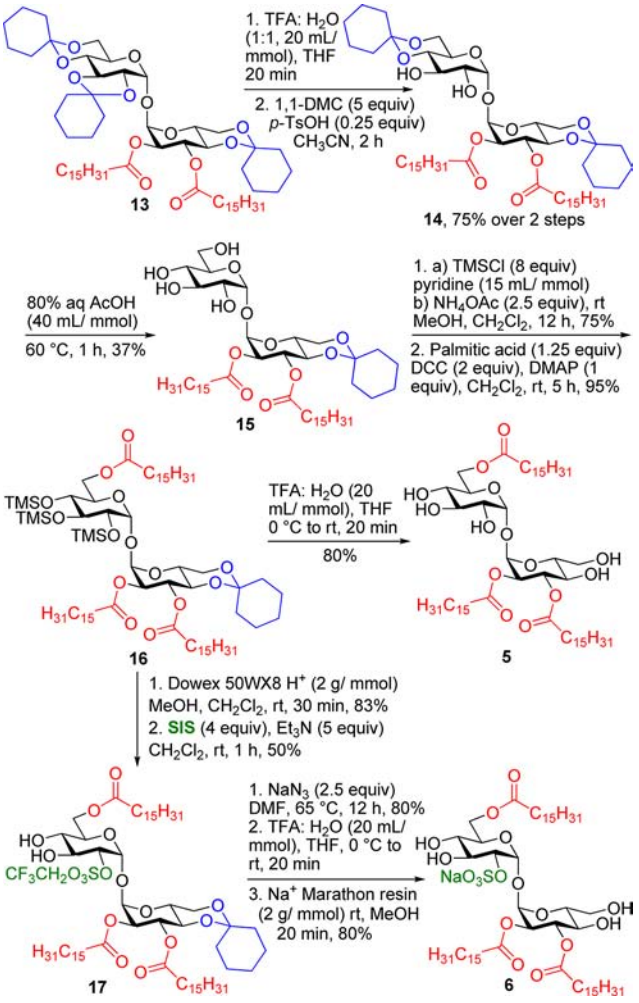
synthesis of 2,3,6′-tri-*O*-palmitoyl trehalose derivatives **5** and **6** (Scheme 2). Therefore, we started with the easily accessible

Scheme 2. Synthesis of Sulfated and Nonsulfated 2,3,6′-Tri-*O*-palmitoyl Trehaloses 5 and 6



tricyclohexylidene-protected 2,3-di-*O*-palmitoyl trehalose **13**.[5d] It was envisaged that if we could selectively remove two cyclohexylidene acetals (2′,3′ and 4′,6′) from the same D-glucose unit of **13** we could then use the so-obtained 4,6-monoacetal derivative for the synthesis of **5** and **6**. For this purpose, compound **14**, which was prepared earlier by us in 50% yield by AcOH hydrolysis of **13**, was procured in an improved yield by performing the reaction in two steps. First, all the three cyclohexylidene acetals were completely removed using TFA-mediated hydrolysis, and then 4,6,4′,6′-dicyclohexylidenation was performed with 1,1-DMC (5 equiv) and *p*-TsOH at rt to obtain **14** in 75% yield. Subsequent selective removal of the 4′,6′-acetal in **14** turned out to be a very difficult task since both the acetals are in 6-membered chair form and their reactivity should be nearly same. However, the diacyl functionalities were expected to disarm one of the rings and thereby affect the rates of acetal hydrolysis. When we performed the hydrolysis reaction using 80% AcOH at elevated temperature (60 °C), the reaction offered the desired monoacetal **15**, albeit in a moderate 37% yield, along with the other regioisomer 4,6-diol (20%) and di-*O*-palmitoyl trehalose (25%). Our attempts to improve the yield of the hydrolysis reaction by performing it at lower temperature and by changing the acid did not offer better results. Nevertheless, both byproducts could be recycled back to the starting material **14** by carrying out cyclohexylidenation, thereby increasing the effective yield of the transformation.

With compound **15** in hand, we proceeded further to synthesize glycolipids **5** and **6**. The free hydroxyl groups in compound **15** were protected as TMS ethers, and the O6′-TMS group was selectively removed by using NH_4OAc[16] to afford the corresponding 6′-OH derivative (75% yield over two steps), which upon DCC-mediated coupling with palmitic acid furnished 2,3,6′-triester **16** in 95% yield. Aqueous TFA-promoted hydrolysis of TMS and cyclohexylidene protecting groups afforded 2,3,6′-tri-*O*-palmitoyl trehalose **5** in 80% yield. In order to synthesize compound **6**, the TMS groups in **16** were removed selectively by stirring it with Dowex 50WX8 H^+ resin to obtain an intermediate 2′,3′,4′-triol (83%), which upon regioselective sulfation with SIS reagent employing Et_3N as a base offered 2′-*O*-sulfated product **17** (50%), along with a recovery of the starting material (30%). The TFE protecting group was removed by heating **17** with NaN_3 in DMF at 65 °C for 12 h (80%), and finally, removal of the cyclohexylidene acetal by TFA hydrolysis afforded compound **6** in 80% yield. We did not observe acyl migration in any of these reactions.

Synthesis of monosuccinoyl tetraester **7**, isolated from *M. paraffinicum*,[12] has not been reported. Based on the trehalose functionalization pattern in **7** we envisaged that the strategy we used for the regioselective 2,3,6,2′-functionalization of **2** could be extended for the synthesis of compound **7**. Accordingly, we began the synthesis from trehalose tricyclohexylidene acetal **18**[5d,14] (Scheme 3). Regioselective 2-*O*-acylation of **18** with octanoic acid via a DCC-mediated coupling furnished the monoacylated intermediate in good yield (78%). The remaining 3-OH was acylated with decanoic acid to obtain compound **19** in 97% yields. Hydrolysis of cyclohexylidene acetals in **19** using aq TFA furnished 2-octanoyl-3-decanoyl trehalose **20** in 85% yield. The free hydroxyl groups in **20** were protected as TMS ether and the primary TMS groups were removed by treatment with NH_4OAc to afford 6,6′-diol **21** with 75% yield over two steps. Regioselective DCC-mediated monoacylation at O6-position with monobenzyl succinic acid[17] under earlier optimized conditions (Table 1) offered monosuccinoyl derivative **22** in 58% yields. With the desired triester **22** in hand, we proceeded further to complete the synthesis of **7**. The TMS groups in **22** were removed by using Dowex 50WX8 H^+ resin (91%) and the free 4′- and 6′-OH groups were protected as a cyclohexylidene acetal by reaction with 1,1-DMC/*p*-TsOH conditions to obtain compound **23** in 65% yields. Regioselective 2′-*O*-acylation of compound **23** via a DCC-mediated coupling with decanoic acid afforded compound **24** (76%). Finally, removal of the cyclohexylidene acetal in **24** using aq TFA (79%) followed by debenzylation of the intermediate under catalytic hydrogenation conditions afforded the desired tetraester **7** in 90% yield. All of the synthesized target glycolipids were purified by silica gel chromatography and characterized thoroughly using ^1H, ^{13}C, and in-depth 2D analysis (see the Supporting Information).

In conclusion, we have established efficient conditions for the regioselective O6-monoacylation of the 6,6′-diol of 2,3-dipalmitoyl trehalose via DCC-mediated coupling with fatty acid acyl chains. The reaction proceeds with excellent regioselectivity and affords good yields of the desired monoacylation products and works well for fatty acids with

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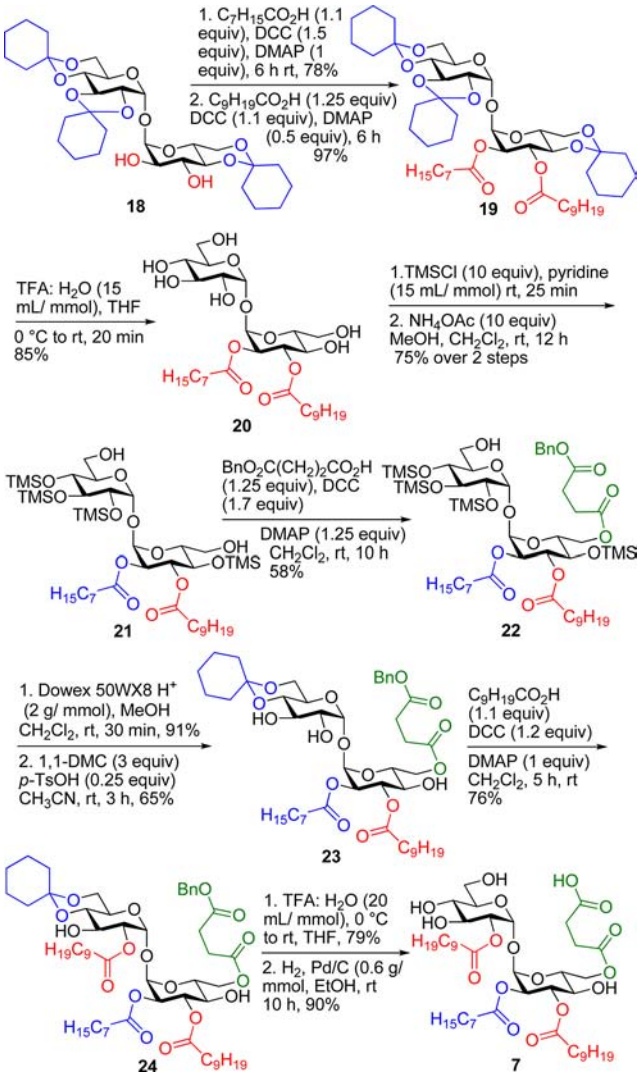
Scheme 3. Synthesis of Tetraester 7



different chain lengths and unsaturation. This strategy allowed unprecedented access to compounds **2** and **4**, the analogues of trehalose-based glycolipid SL-3 from *M. tuberculosis*. The nonsulfated and sulfated triesters (**5** and **6**) having a palmitoyl group at O6′-position were also prepared starting from 2,3-di-*O*-palmitoyl trehalose. The regioselective O6 acylation strategy was extended to accomplish the first total synthesis of the trehalose-based tetraester **7** from *M. paraffinicum*. The various trehaloglycolipids synthesized during our studies, which are structurally well characterized and homogeneous materials, are now available for evaluation of their antigenic activity to test their utility as serodiagnostic markers and vaccine candidates for *M. tuberculosis*.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03300.

^{1}H and ^{13}C NMR spectra for all compounds and ^{1}H−^{1}H COSY spectra for all new compounds (PDF)

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Notes

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Organic LETTERS

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Enantioselective Bromo-oxycyclization of Silanol

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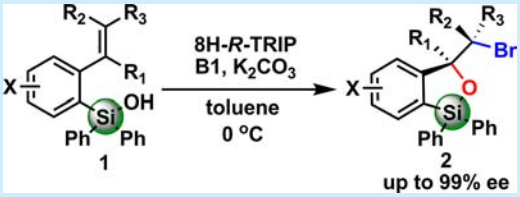
Supporting Information

ABSTRACT: Relying on the nucleophilicity of silanol for building up silicon-incorporated scaffold with an enantiopure tetrasubstituted carbon center remains elusive. In this report, asymmetric bromo-oxycyclization of olefinic silanol by using chiral anionic phase-transfer catalyst is described. This protocol provided a facile entry to a wide arrangement of enantiopure benzoxasilole in moderate to excellent enantioselectivities depending on the unique reactivity of bromine/*N*-benzyl-DABCO complex.



Organosilicon has undoubtedly occupied a unique position in organic chemistry, as shown by its wide applications in synthetic chemistry,[1a,b] material chemistry,[1c,d] and pharmaceutical chemistry.[1e] Therefore, an enormous endeavor has been dedicated to the incorporation of silicon into an organic scaffold, particularly into the enantiopure molecules, as the resulting organosilicon could be employed to construct diversely valuable chemical bonds (e.g., C−C, C−O, C−X bonds).[2] In this regard, although silanol is easily accessible and widely employed in synthetic chemistry (e.g., for the synthesis of siloxane,[1c] cross-coupling[2d]), harnessing the nucleophilicity of silanol for organic transformations is not well investigated, presumably due to its instability (easy to dehydrate to form siloxanes) and weak nucleophilicity of hydroxyl.[3] In this account, catalytic asymmetric reactions by directly taking advantage of silanol as oxygen source are scarce.[4] Only iridium- and palladium-catalyzed asymmetric allylic etherification of silanol has been reported by Hartwig and Xu respectively (Figure 1).[4a,b] However, silanol is only used as a water surrogate in those reactions, and the synthetic potential of silicon could not be fully utilized for constructing other chiral scaffolds in subsequent transformations. To this end, construction of an asymmetric tetrasubstituted carbon center directly based on the nucleophilicity of silanol represents a big challenge in the chemistry of silanol, which to the best of our knowledge has not been described to date.

Recently, asymmetric electrophilic halo-functionalization of unsaturated C−C bonds has witnessed great advances.[5,6] In this context, asymmetric halo-oxycyclization of olefinic alcohol has been extensively studied for giving easy access to enantiopure halogenated tetrahydrofuran and tetrahydropyran (Figure 1).[6] Furthermore, by employing tethered nucleophiles other than alcohol, asymmetric halo-oxycyclization has also emerged as

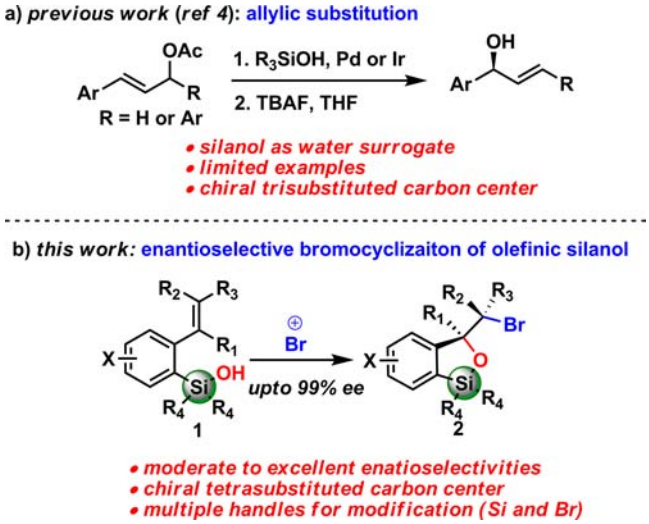


Figure 1. Enantioselective reactions directly relying on the nucleophilicity of silanol.

powerful strategy for construction of other functionalized chiral heterocycles.[6g−l] Despite the significant progress in asymmetric halo-oxycyclization reactions, synthetic applications of those enantiopure halogenated products are mainly limited to the derivatization of halogen. Therefore, incorporation of other orthogonally versatile functionality (e.g., Si, B) via asymmetric halogenation reaction is still highly desirable. In continuation of our work on asymmetric halogenation reactions,[7] herein we report our preliminary results on the first enantioselective

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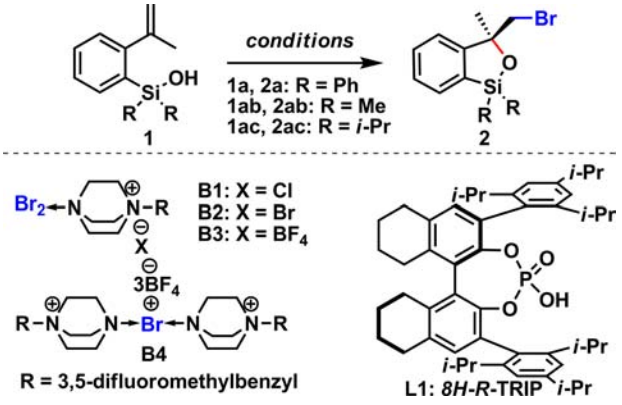
bromo-oxycyclization of olefinic silanol,[3b] which enables access to chiral benzoxasilole in moderate to excellent enantioselectivities.

The reaction condition optimization commenced with asymmetric bromocyclization of silanol **1a** using chiral anionic phase-transfer catalyst,[8] and selected results are listed in Table 1. Encouragingly, benzoxasilole **2a** was initially obtained in 82%

Table 1. Screening of Reaction Conditions for Enantioselective Bromo-Cycloetherification of Olefinic Silanol 1a[a]



entry	cat.	Br+	base	solvent	time (h)	yield[b] (%)	ee[c] (%)
1	L1	B1	$NaHCO_3$	toluene	6	81	92
2	L1	B2	$NaHCO_3$	toluene	12	64	81
3	L1	B3	$NaHCO_3$	toluene	12	40	75
4	L1	B4	$NaHCO_3$	toluene	12	0	NR
5	L1	B1	$NaHCO_3$	hexane	20	53	93
6[d]	L1	B1	$NaHCO_3$	bezene	4	61	91
7	L1	B1	$NaHCO_3$	Et_2O	5	66	91
8	L1	B1	Na_2CO_3	toluene	4	81	95
9	L1	B1	K_2CO_3	toluene	4	87	95.5
10[d]	L1	B1	K_3PO_4	toluene	4	77	94
11[e]	L1	B1	K_2CO_3	toluene	20	80	94
12[f]	L1	B1	K_2CO_3	toluene	4	91	72
13[g]	L1	B1	K_2CO_3	toluene	4	89	68

[a]The reaction was carried out by addition of silanol **1a** (0.1 mmol) in toluene (1 mL) to a mixture of catalyst (0.01 mmol), brominating reagent (0.13 mmol), and base (0.40 mmol) in toluene (1 mL) at 0 °C. [b]Isolated yield. [c]Determined by HPLC on a Chiralpak AD-H column. [d]The reaction was carried out at rt. [e]The reaction was conducted at −20 °C. [f]Silanol **1ab** as substrate. [g]Silanol **1ac** as substrate.

yield and 92% ee under our previous optimal conditions for asymmetric bromocyclization of tryptamine[7a] (entry 1). Subsequent evaluation of different bromine/*N*-benzyl-DABCO complexes showed that enantioselectivity of this reaction greatly depended on the counteranion of those complexes. **B1** with chloride as counteranion was superior to other bromine complexes in terms of yield and enantioselectivity (entries 2 and 3). To our surprise, bromonium salt **B4**[8d] was ineffective for this reaction even after the reaction time was extended (entry 4). This could be ascribed to the reduced reactivity of bromine by double complexation with *N*-benzyl-DABCO. Next, a survey of different chiral phosphoric acids revealed that 8*H*-*R*-TRIP **L1** was the catalyst of choice (see the Supporting Information). Solvent screening showed that inferior results were produced using nonpolar solvents other than toluene (entries 5−7). Among bases tested for this reaction, K_2CO_3 gave the best outcome, leading to **2a** in 95.5% ee (entries 8−10). Furthermore, reducing the temperature was detrimental to the reaction (entry 11). Two phenyls on silicon were indispensible for this reaction, as putting other substituents (e.g., Me, *i*-Pr) on silicon only led to the corresponding benzoxasiloles in moderate enantioselectivities (**2ab**, **2ac**, entries 12 and 13).

With optimal reaction conditions being set up, we turned our attention to examine the substrate scope of this reaction. Electron-donating or electron-withdrawing groups on phenyl have little impact on this reaction, leading to the corresponding benzoxasilole in excellent enantioselectivities (Figure 2, 92−97% ee, **2a**−**g**). However, presumably due to steric repulsion, introducing substituents adjacent to silicon dramatically reduced enantioselectivity of this reaction, leading to **2h** and **2i** only in 75% ee and 84% ee, respectively. On the other hand, substituents on olefin have complicated effect on enantioselectivities. Replacement of the olefinic methyl with other alkyl groups (e.g., Et, *i*-Pr) resulted in decreased enantioselectivities (87% for **2j** and 59% ee for **2k**). Only *6-endo*-bromooxycylization was detected when this methyl group was removed from the substrate, delivering benzoxasiline **2′l**[9] and **2′m** in moderate enantioselectivities. Substituents on the

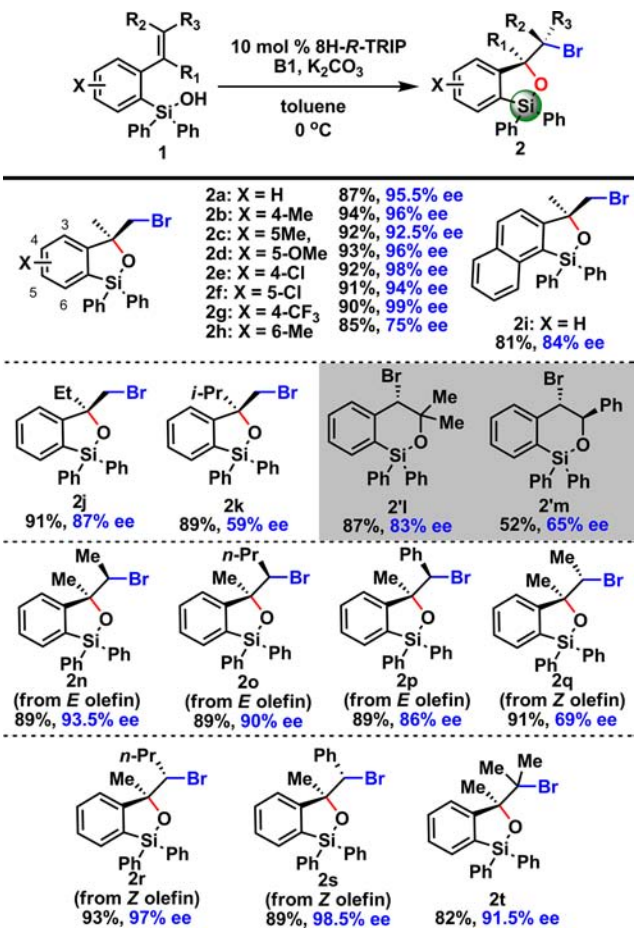


Figure 2. Substrate scope of enantioselective bromo-cycloetherification of olefinic silanols. Key: (a) The reaction was carried out by addition of silanol (0.1 mmol) in toluene (1 mL) to a mixture of 8*H*-*R*-TRIP (0.01 mmol), **B1** (0.13 mmol), and K_2CO_3 (0.40 mmol) in toluene (1 mL) at 0 °C.

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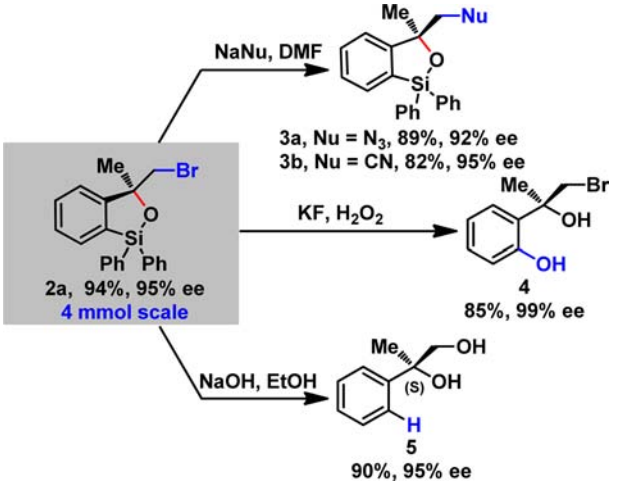
terminal olefin were also tolerated, while enantioselectivities depended on the configuration of alkene. As shown in Figure 2, lower enantioselectivities were obtained when the more bulky group was present on *E*-olefins (93% ee for **2n** to 86% ee for **2p**), while a reverse trend was observed for *Z*-olefins (69%ee for **2q** to 98.5% ee for **2s**). Finally, even tetrasubstituted olefin could be smoothly transferred to benzoxasilole **2t** in 91% ee.

To display the synthetic application of the resulting chiral benzoxasilole, synthesis of **2a** on a 4 mmol scale was first implemented to afford benzosilole in comparable enantioselectivity (Scheme 1). Its subsequent transformations by taking

Scheme 1. Synthetic Transformations of Benzoxasilole 2a

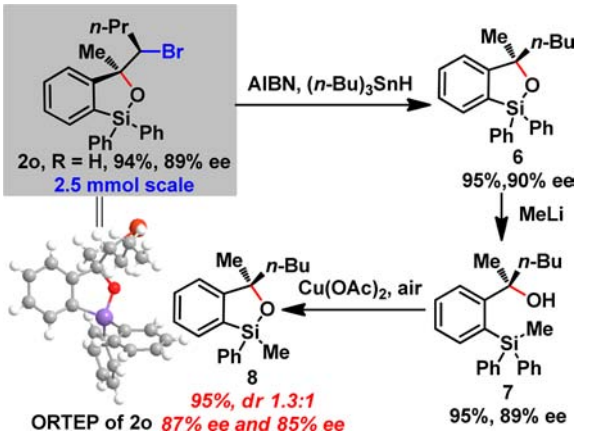


advantage of bromine and silicon were tested, respectively. Halogen as a handle for introduction of other functionality was routinely achieved by substituting of bromide with azide and cyanide, respectively, affording the corresponding benzosiloles **3a** and **3b** in high enantiopurities. For transformation of silicon, Tamao−Fleming oxidation of **2a** smoothly furnished phenol **4** with retention of bromine. Protonation of silicon concurrently with displacement of bromine with H_2O could be readily realized by heating **2a** in NaOH/EtOH, affording the known diol **5**, which established absolute configuration of **2a** to be *S*.[10]

Although benzoxasilole has emerged as an efficient transfer reagent for reactive organometallic reagents for cross-coupling reactions,[11] diastereoselective transmetalation of substituents on silicon for construction of stereogenic silicon is not well explored.[12] To this end, synthesis of **2o** on a 2.5 mmol scale enabled us to obtain a good crystal of **2o** for X-ray analysis, which confirmed its absolute configuration (Scheme 2).[13] Removal of bromine with AIBN/Bu_3SnH followed by ring opening of benzoxasilole with methyllithium generated silane **7** in excellent yields. Selective transfer of one phenyl of **7** proved to be challenging owing to the competitive transfer of methyl under previous cross-coupling conditions[11c,d] (see the Supporting Information). After extensive optimization (see the Supporting Information), transfer of methyl could be totally suppressed using CuI-catalyzed oxidative homodimerization of silane **7**.[14] Disappointingly, only poor diastereoselectivities resulted, and initial attempts employing achiral or chiral ligands proved to be fruitless (see the Supporting Information).

In conclusion, the generation of a chiral tetrasubstituted carbon center by directly utilizing the nucleophilicity of silanol is described. The reaction was realized by employing bromine/*N*-benzyl-DABCO complex under chiral anionic phase-transfer

Scheme 2. Selective Transmetalation of Phenyl on Silicon



catalyst. Structurally diverse benzosiloles were obtained in moderate to excellent enantioselectivities, which mainly depended on the substituents and configuration of alkene. Selective transfer of the phenyl of silane derived from chiral benzoxasilole was enabled by copper-catalyzed oxidative dimerization, albeit with no diastereoselectivity on the silicon stereogenic center.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03303.

Experimental procedures, spectral data, and copies of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(10) The optical rotation of diol **5** ($[\alpha]^D$ = 11.4 (*c* 0.4, $CHCl_3$)) is in agreement with reported data of the (*S*)-isomer ($[\alpha]^D$ = 9.8 (*c* 0.4, $CHCl_3$)); see: Gaul, C.; Scharer, K.; Seebach, D. *J. Org. Chem.* **2001**, *66*, 3059 The rationale for the observed stereoselectivity was also proposed in the Supporting Information..

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Mechanistic Information from Nonstationary Points

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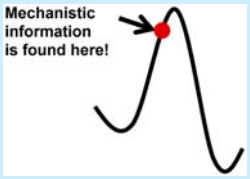
Supporting Information

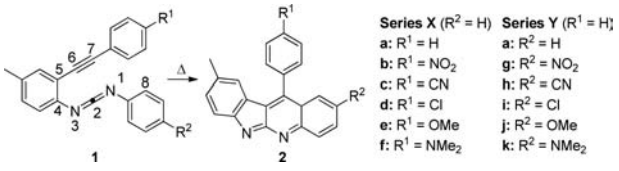
ABSTRACT: The thermal cyclization of enyne−carbodiimides substituted at both the alkyne and carbodiimide terminus showed two curved Hammett correlations (log k/k_0 against σ_p) that were fully reproduced by DFT (density functional theory) computational results. The latter suggest a concerted mechanism, but the transition state (TS) analysis failed to reveal any mechanistic insight about the reason for a curved Hammett correlation. Instead a *preTS* inspection, i.e., examination of the electronic and steric details on route between reactant and TS, furnished a detailed picture of the mechanism.



The meticulous inspection of stationary points along the potential energy surface (PES) to identify mechanistic information has a long and triumphant history, in particular for physical organic chemistry after teaming up with computational investigations.[1] A large amount of attention is typically given to the rate-determining step with its preceding minimum, the transition state (TS), and the corresponding product because agreement between computed and experimental kinetic data, e.g., see kinetic isotope effects,[2] provides a solid base for any mechanistic hypothesis derived therefrom. Here, we show that at the concerted vs stepwise boundary[3] the mechanistic information is not necessarily revealed from a review of the stationary points. Instead, the examination of nonstationary points between reactant(s) and rate-determining TS, a *preTS inspection*, provides the important clues.

Over many years, the C^2−C^6 diradical cyclization of enyne−allenes has been investigated by numerous authors.[4,5] For the cyclization of the related enyne−carbodiimides **1** (Scheme 1), we

Scheme 1. Thermal Cyclization of Enyne−carbodiimides 1a−k with Polar Substituents at Either Terminus



proposed in 1998 a stepwise mechanism involving a diradical intermediate[6] based on MR-CI + Q computations (DZP basis set) and experimental kinetic data, which showed an onset temperature difference of only 21 °C between **1a** and **3** (Figure 1).[6] A notable solvent dependence suggested some polar contributions in the TS of **1**, a phenomenon well-known at the boundary of diradicals and zwitterions.[7] To elucidate the polar effects, a detailed kinetic study was thus undertaken in 2008 by studying two groups of enyne−carbodiimides (Scheme 1), one substituted at the alkyne (series X) and the other at the carbodiimide terminus (series Y).[8] The relative rates of each series nicely correlated with the substituent constants σ_p

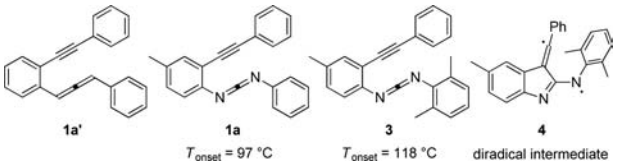


Figure 1. Comparison of the onset temperatures in the thermal cyclization of **1a** and **3**.

furnishing a curved Hammett relationship that separated electron-donating and -withdrawing groups (Figure 2). At the

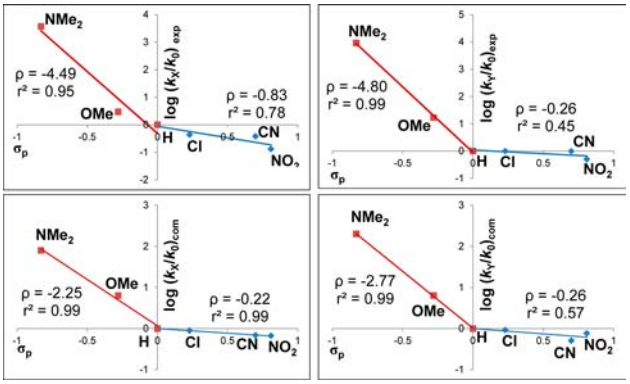


Figure 2. Hammett plots of rate constants for **1a−k** vs σ_p (Table S1). Experimental (top)[8] and computed (bottom) data. Subscripts X and Y stand for series X (left) and Y (right).

time, the curvature was explained by a changeover from a coarctate mechanism[9] involving a carbene intermediate (with X, Y = EWG) to a zwitterion (with X, Y = NMe_2, OMe) mechanism, with the carbene intermediate indirectly supported by isolation of product **8**[8] (Scheme 2) and the latter by the notable rate accelerations in polar solvents.

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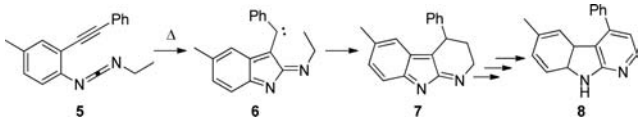
Scheme 2. Formation of Product 8 Indirectly Suggested Involvement of the Carbene Intermediate 6



To better resolve the putative mechanistic changeover in the thermolysis of **1** as reflected by the curved Hammett relationship, we decided to undertake a computational study. For that reason, we computed the PES for **1a** by varying the C^2–C^6 and C^7–C^8 bond distances at BLYP/6-31G* level of theory (Figure 3).

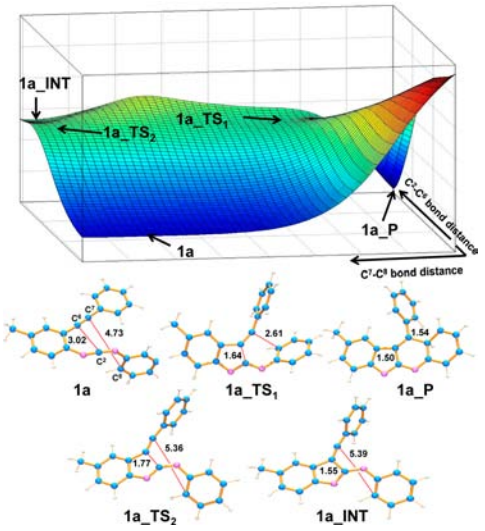


Figure 3. Potential energy surface (BLYP/6-31G*; grid: 30 × 30; smoothed) for the thermal cyclization of **1a**. The numerical values represent the respective bond distances in Å.

Against our expectations, we could not locate any intermediate along the reactive reaction coordinate; rather, we identified the singlet diradical **1a_INT** as a dead end with no direct exit route to the product. By comparison with experimental data, the 6-31+G* basis set gave better results than 6-31G*. Hence, we reoptimized all stationary points on the PES at BLYP/6-31+G* level and searched for the presence of any reactive diradical intermediate. Again, we could not find any productive intermediate on the PES, suggesting a concerted mechanism for the thermal cyclization of **1a**.

The calculated free energy barriers for the cyclization of enyne–carbodiimides **1b–k**, all operating via a concerted mechanism, are in very good agreement with the experimental kinetic data (Table 1). Hammett correlations with the calculated rate constants revealed exactly the same curvature like the experimental kinetic results (Figure 2). As an interim conclusion one has to state that the C^2–C^6 cyclization of enyne–carbodiimides seems to follow a concerted pathway with no intermediate, quite in contrast to earlier claims.[8]

The premise of a concerted mechanism, however, requires that equally all other pieces of evidence for a stepwise mechanism collected over the years, such as the low barrier for *ipso*-cyclization of **3** and the formation of **8** from **5**, have to be reconsidered. Notably, the parent **1a** and the sterically encumbered enyne–carbodiimide **3** exhibit a computed free energy barrier difference $\Delta\Delta G^{\ddagger}$ of only 2.2 kcal mol^{-1} for the concerted pathway, which is in rather good agreement with the

Table 1. Computations at the BLYP/6-31+G* Level and Experimental Free Energy of Activation for 1 at 120 °C

compd **1**	computed free energy of activation $\Delta G^{\ddagger}_{120}$ (kcal mol^{-1})	experimental free energy of activation[a] $\Delta G^{\ddagger}_{120}$ (kcal mol^{-1})
a	28.2	27.9
b	28.5	29.5
c	28.5	28.6
d	28.3	28.5
e	26.8	27.0
f	24.8	21.5
g	28.4	28.4
h	28.8	27.9
i	28.3	27.9
j	26.8	25.7
k	24.1	20.8

[a]Experimental free energies of activation were derived from experimental rate constants[8]

experimentally found onset temperature difference (97 vs 118 °C). This unexpectedly small $\Delta\Delta G^{\ddagger}$ may be ascribed to a ground-state destabilization of **3** by 4.3 kcal mol^{-1} (Figures S4 and S5) and a different C^7–C^8 distance in the TS (2.50 and 2.64 Å for **1a** and **3**). Equally, formation of **8** from **5** may be explained by a competitive pathway (SI) that does not involve the postulated carbene trapping as depicted in Scheme 2.

But what is the reason for the curvature in the Hammett plots of **1** if there is no change in mechanism? Curved Hammett correlations[10] have been previously observed in substitution, elimination, acyl-transfer, and oxidation reactions.[11] The traditional explanation for such phenomena is attributed to (a) a change in mechanism, (b) a single mechanism with a different extent of bond formation and cleavage or a change of the charge character in the TS, and (c) a different balance of polar and resonance effects by different substituents in the TSs.[12] Option (a) can be eliminated due to the full agreement of experimental and computational data and the computational evidence for a concerted mechanism for **1**. To evaluate option (b), we calculated (i) the asynchronicity (Δd) at the TS (Figure 4),

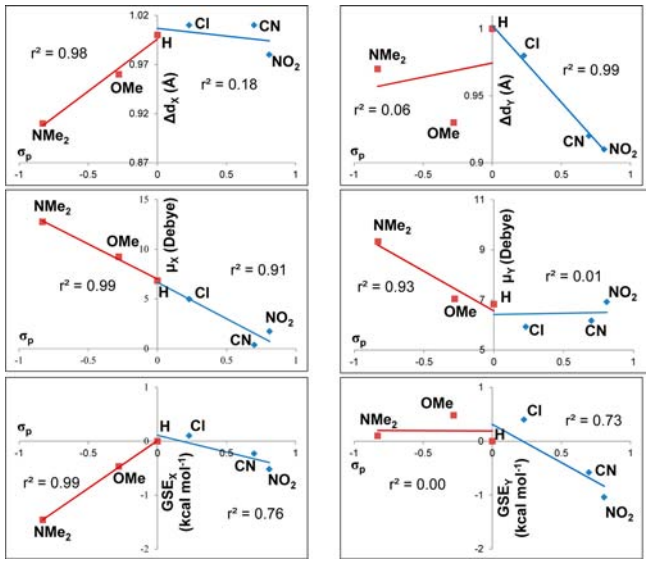


Figure 4. Correlations (subscripts X and Y stand for the series X and Y) of asynchronicity Δd at TS, dipole moment μ at TS, and ground-state stabilization energy (GSE) of **1** all vs σ_p.

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(ii) TS σ-contraction,[13] (iii) Mulliken and natural bond orbital (NBO) charges, and (iv) the dipole moment at the TS (Figure 4), but none of them would correlate with σ_p in an analogous manner as the rate constants for both series X and Y (Figure 2).

To check the balance of polar and resonance effects, i.e., option (c), Yukawa–Tsuno diagrams of $\log(k/k_0)$ vs $\sigma_p + r^+(\sigma_p^+ - \sigma_p)$ and $\sigma_p + r^-(\sigma_p^- - \sigma_p)$ were plotted by varying $r = 0-1$, which, however, did not lead to any linear correlation (Table S2). All known reasons for curvature in Hammett correlations were thus met with failure.

Furthermore, no correlations were detected with aromaticity in the TS as measured by the nucleus-independent chemical shift (NICS) or the harmonic oscillator model of aromaticity (HOMA) index (Table S6). Houk's[14] distortion/interaction model (see the SI) also failed to rationalize our findings. Finally, the impact of ground-state stabilization[10f] on the starting material was considered by checking isodesmic reactions, such as **1a** + $PhNMe_2$ → **1f** + PhH (Figure 4).

After failing to find a reason for the curvature by inspection of both the TS and reactant, we decided to compare qualitatively the energy profiles of enyne–carbodiimide (concerted) and enyne–allene (stepwise) cyclizations. From a large battery of studies,[4,5] it has become evident over the years that enyne–allenes follow the stepwise pathway in their thermal cyclization. The idealized reaction coordinate (Figure 5) shows a rate-determining C^2–C^6 bond formation (first step) that is followed by the closure of the C^7–C^8 bond (second step). A projection of typical reaction coordinates for enyne–allene (blue curve) and for enyne–carbodiimide cyclizations (red curve) on top of each other suggests that in the concerted TS of the latter the C^2–C^6 binding has merged with the C^7–C^8 bond formation. As a result, the contributions of the initial C^2–C^6 binding are obscured in the TS. This insight suggested to search in the *preTS* region of the concerted carbodiimide reaction as there we expected to see the changeover, like that of enyne–allenes, from the C^2–C^6 to the follow-up C^7–C^8 bond formation.

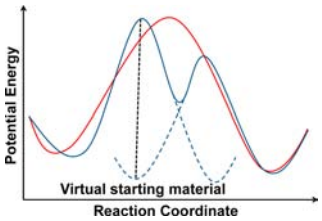

Figure 5. Two idealized reaction coordinates. The solid blue curve represents the thermal cyclization of enyne–allenes and the red one that for enyne–carbodiimides.

To find this nonstationary point (represented roughly by the vertical line in Figure 5, i.e., the starting point for the virtual second step, i.e., C^7–C^8 bond formation) on the PES, we decided to critically consider all steps in the cyclization of **1a** from the starting material to the TS. By decreasing the C^2–C^6 bond distance stepwise by 0.025 Å from the reactant to the TS, leaving the C^7–C^8 free to optimization, we obtained the graph depicted in Figure 6 (left). Upon decreasing the C^2–C^6 bond distance, both carbodiimide C═N bonds elongate although they are perpendicular to each other. Once the C^2–C^6 bond distance approaches the one of the TS the structure collapses (after the 57th point) to the product region because of an unimpeded approach of C^7 and C^8. At point 57, i.e., prior to the collapse, the C^2–C^6 bond distance is 1.64 Å, which is almost the same as in the real TS. The electronic energy gap between the real TS and that at the 57th point is only 0.02 kcal mol^{-1}. All these facts reflect how close one can approach the real TS of **1** by scanning one bond distance only.

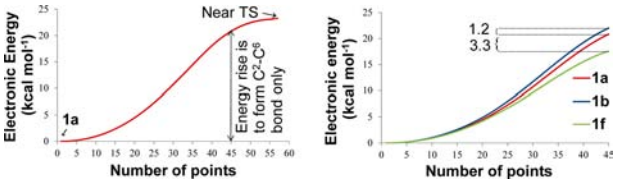

Figure 6. (Left) Scanning of C^2–C^6 bond distance by 0.025 Å from **1a**. (Right) Comparison of scan results of **1a**, **1b**, and **1f**.

For mechanistic insight, all molecular orbitals were analyzed beginning from the reactant at five-step intervals. The 45th point is the first point where some electron density, found in the HOMO−1 (Figure S1), arises between C^7 and C^8. At that point, the C^2–C^6 bond formation is well progressed (1.94 Å), while the C^7–C^8 bond distance is still at 3.37 Å.

Thereafter, the same analysis was performed for all other enyne–carbodiimides **1b–k**. A representative comparison of **1a**, **1b**, and **1f** (Figure 6, right) shows that at the 45th point the electronic energy of all three compounds is already well pronounced, so that an inspection at this point may shed some light on the cause for the curvature in the Hammett plots.

An in depth NBO analysis at the 45th point showed four major stabilizing orbital interactions, i.e., $\pi_1 \rightarrow \pi_2^*$, $\pi_1 \rightarrow \pi_3^*$, $\pi_2 \rightarrow \pi_1^*$, and $\pi_3 \rightarrow \pi_1^*$, to be relevant in the cyclization of enyne–carbodiimides **1a–k** (Figure 7). Their individual contribution to the interaction energy as a function of σ_p is shown in Figure 8, right. The addition of all four interaction energies furnishes the total stabilizing interaction energy, which correlates with σ_p (Figure 8, left) for both series in exactly the same manner as do the experimental and computational kinetic data (Figure 2). Thus, the information provided by the orbital interactions is the one that is relevant for the kinetics from a mechanistic point of view.

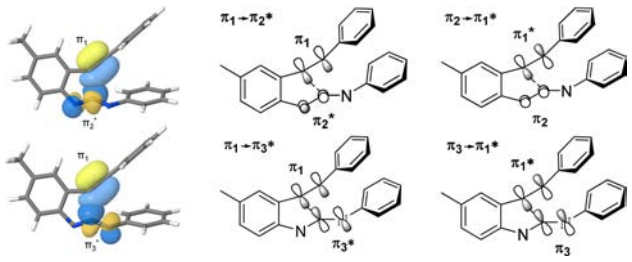

Figure 7. Colored structures: Two orbital interactions contributing to the stability of **1a** at the 45th point. Black and white structures: The four relevant orbital interactions at the 45th point of **1a**.

An analysis of the individual contributions for series X, i.e., compounds **1a–f** (Figure 8, top right), indicates that for donor substitution the $\pi_1 \rightarrow \pi_3^*$ interaction dominates, while for neutral and EWG substituents the $\pi_3 \rightarrow \pi_1^*$ and $\pi_1 \rightarrow \pi_2^*$ interactions almost cancel. For series Y, i.e., **1a,g–k** (Figure 8, bottom right), the situation is somewhat more complicated; the interaction analysis shows that donor-substituted cases are dominated by several interactions ($\pi_1 \rightarrow \pi_2^*$, $\pi_1 \rightarrow \pi_3^*$, $\pi_3 \rightarrow \pi_1^*$) that add up almost pari passu. On the side of neutral and EWG substituents for **1a,g–k**, the sum of all four interaction cancels mostly. This complexity prevents us from drawing a

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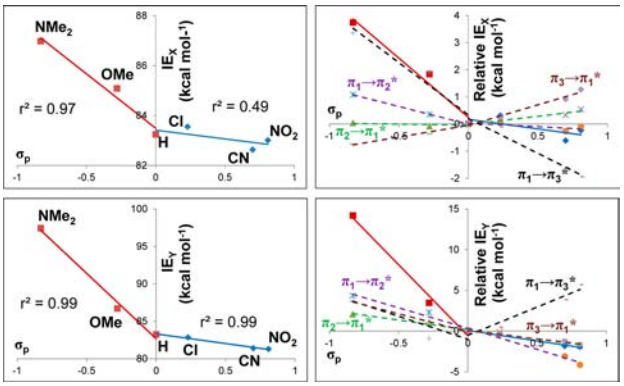

Figure 8. (Left) Correlation of the total orbital interaction energies (IEs) of **1** against σ_p. (Right) The individual (dashed lines) and the total IEs (solid red and blue line) are plotted against σ_p (reference R = H is set to zero). Subscripts X and Y stand for the series X (top) and Y (bottom).

simple electron push−pull mechanisms for the true rate-determining process in the thermal cyclization of **1a**−**k**.

Why are those interactions not visible at the real TSs? For comparison, a reaction profile for the thermal cyclization of enyne−allene **1a**′ was computed at the same DFT level. Interestingly, all of the interactions depicted for enyne−carbodiimide **1a** at the 45th point are present in the C^2−C^6 TS of enyne−allene **1a**′ as well, but they vanish as the system moves on to the diradical intermediate and C^7−C^8 TS. Thus, in the course of further structural and electronic changes the original interactions become invisible. By the same token, the relevant interactions in the enyne−carbodiimide cyclization, as illustrated in Figure 7, already become invisible in the TS due to the second bond formation.

Is there a hidden transition state (hTS)[15] at or near the 45th point? Actually, the analysis by IRC gradient norm fails to detect a hTS, thus lending even more importance to a *preTS* inspection! The current finding suggests that many concerted reactions with highly asynchronous bond formations, in which the first bond-forming process has the predominant influence on the rate, may benefit from a *preTS* analysis.

Our study reveals that a concerted, but highly asychronous, mechanism is operative for the thermal cyclization of enyne−carbodiimides **1a**−**k**. Due to the asynchronicity, a TS inspection does not reveal the orgin of the rate changes and of the curved Hammett correlation. Rather, *preTS* inspection at the nonstationary point just prior to formation of the second bond reveals the various underlying interactions that guide the rate and as a result the curved Hammett correlation.

In summary, the traditional heuristics using mechanistic information from the analysis of stationary points fails in our system. A strategy is presented that uses the analysis of nonstationary points (*preTS* inspection).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03310.

Full list of calculations, optimized geometries, and number of imaginary frequencies (PDF)

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Notes

The authors declare no competing financial interest.

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Organic LETTERS

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One-Pot, High-Yielding, Oxidative Cyclodehydrogenation Route for N-Doped Nanographene Synthesis

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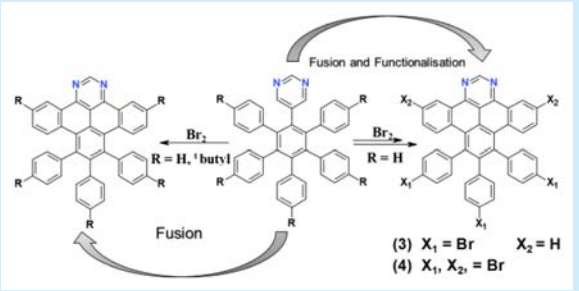
Supporting Information

ABSTRACT: An intramolecular oxidative cyclodehydrogenation via a one-pot process is described, which induces selective C−C bond formation and bromine functionalization. The application of this new route gives rise to a novel family of partially fused, selectively brominated N-doped pyrimidine graphenes.



Interest in the synthesis of N-containing polycyclic hydrocarbons (PAHs), particularly from a materials chemistry perspective, is growing exponentially.[1] The realization of multiple inter- and intramolecular bond fusions in halogenated polyphenylenes, catalyzed by Au(111),[2] Pt(111),[3] and Cu(111)[4] surfaces,[5−7] has prompted this revived research attention. Such processes offer low-energy routes to N-doped graphene nanoribbons and nanofragments, via single-source precursors.[5,6,8] Synthetic work is required, however, to improve the yield and purity of the N-doped halogenated precursors and to optimize the selectivity of their coupling reactions.

Oxidative cyclodehydrogenation in solution (the Scholl reaction) is understood to require a Lewis acid and oxidant and to occur either by a radical cation (electron transfer) or by an arenium cation (proton transfer) mechanism.[9,10] In N-containing materials, the extent of ring fusion is highly catalyst- and dopant- dependent. For one polyphenylene precursor, 1,2-dipyrimidyl-3,4,5,6-tetra(4-*tert*-butylphenyl)benzene, fully fused materials were previously obtained using $AlCl_3/CuCl_2$ as Lewis acid and oxidant, whereas a variety of incomplete ring closures are produced when $FeCl_3$ is used.[11,12] Increasing the number of N dopant atoms causes a decrease in reactivity, even in the presence of resonance-stabilizing methoxy substituents.[13] Such a lack of specificity and control has given rise to the search for alternative catalytic reagents.

The authors have an established interest in the bottom-up fabrication of N-doped graphene fragments.[12,14,15] Prompted by this and the drive to develop and test new routes to N-doped fused and partially fused materials, they decided to revisit the earlier findings of Gourdon et al. into the cyclodehydrogenation of diaza-substituted polyphenylenes.[16] This work had shown that cyclodehydrogenations using $AlCl_3/CuCl_2$ or $MoCl_5$ gave rise to insoluble polychlorinated products and had led the authors to conclude that *para* unsubstituted pendant phenyl rings promote uncontrolled oligomerization.

Using elemental bromine under controlled conditions, this new work demonstrates that it is possible to induce intramolecular bond formation at the pyrimidine rings in diaza-substituted polyphenylenes. Furthermore, it shows that controlled bromination is achievable at the *para* positions of pendant unsubstituted phenyl rings, giving a range of brominated pyrimidine-fused PAHs. Figure 1 shows the mass spectrum of the reaction mixture, comprising 1-pyrimidyl-2,3,4,5,6-pentaphenylbenzene (**1**) and elemental bromine after 10 min. At room

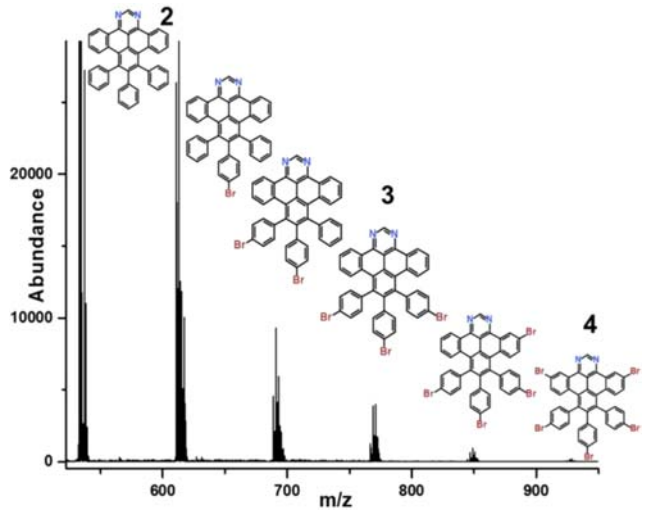


Figure 1. Mass spectrum of a sample of the reaction mixture of 1-pyrimidyl-2,3,4,5,6-pentaphenylbenzene polyphenylene (**1**) and bromine after 10 min in an open vessel at room temperature.

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temperature, no remaining uncyclized polyphenylene is observed after a reaction time of 10 min. By controlling the time and temperature of the reaction, the degree of substitution can be optimized to yield 8,9,10-tris(4-bromophenyl)-tribenzoperimidine (**3**) and 5,13-dibromo-8,9,10-tris(4-bromophenyl)tribenzoperimidine (**4**) in 80 and 50% yields, respectively.

Inspired by the one-pot reaction conditions employed by Rathore to generate hexakis(4-bromophenyl)benzene,[17] we used a 1×10^{-8} M solution of polyphenylene **1** in $CDCl_3$, with 100 equiv of reagent grade bromine. Despite the fact that the excess bromine would cause significant shifting of the NMR signals of the products, a study of the crude reaction mixture was undertaken, using in situ ^{1}H NMR spectroscopy. From this, it was possible to gain an insight into the time scale of each step of the reaction as it proceeded. The spectroscopic study, over the course of 25 min, documented the almost instantaneous nature of the cyclization between the pyrimidine ring and its neighboring phenyl rings, the stepwise bromination of the pendant phenyl rings, and finally the bromination of the fused pyrimidine core. The information garnered from the resulting ^{1}H NMR spectra (S15) suggested how we might vary the reaction conditions (reaction time, temperature, solvent, vessel conditions (open or closed)) to separately optimize the formation of each of the products.

Initially, **1** was reacted in neat bromine at room temperature for varying reaction times (5 min to 5 h) to yield different proportions of **2**, **3**, and **4**. Column chromatography using dichloromethane as eluent, followed by recrystallization from dichloromethane/methanol, allowed the isolation of each highly pure fraction. Subsequently, more direct routes to two of the major products were successfully obtained. Changing to pressure tube conditions in toluene resulted in the formation of only **2** in quantitative yields. The pure product could be crystallized directly from the reaction mixture without the need for any additional purification. Refluxing in chloroform was successful in driving the reaction to higher yields of the pentabrominated **4**. The evolution of HBr was observed in all cases. Figure 2 presents the individual spectra of the isolated materials.

^{1}H NMR spectroscopy was the primary tool for characterizing the new products. A comparison of the spectra is presented in Figure 2. Taking the spectrum of the starting material as a reference, the most dramatic change occurs upon the initial cyclization to give **2**, whereupon the resonance of proton (H1) in the pyrimidine ring of **1** shifts from 8.6 ppm to a peak at 9.8 ppm. Once this ring is fused (as in **2**, **3**, and **4**), the chemical shift of this signal remains essentially constant. The signal at 8.2 ppm (H2) in the starting material (corresponding to both protons, α to nitrogen) is now absent. From the in situ experiment, a plot was generated of the integrations of the pyrimidyl signals (e.g., H1 and H2) and their variation with reaction time. The plot is consistent with the rapid formation of the C−C intramolecular bonds (complete within 4 min). Fusion results in the significant deshielding of protons (H4) (from the multiplet at 6.9 ppm in **1**) to a doublet at 9.4 ppm in the ^{1}H NMR spectra of **2** and **3** (Figure 2). This doublet then becomes a singlet in **4** after the final bromination takes place.

Fortunately, single-crystal X-ray diffraction was possible for most of the isolated products and gave data that were consistent with those arising through spectral characterization techniques. Diffusion of 5-(4′,5′,6′-triphenyl-[1,1′:2′,1″-terphenyl]-3′-yl)-pyrimidine into toluene solutions allowed the growth of single crystals of **2**, suitable for single-crystal X-ray diffraction

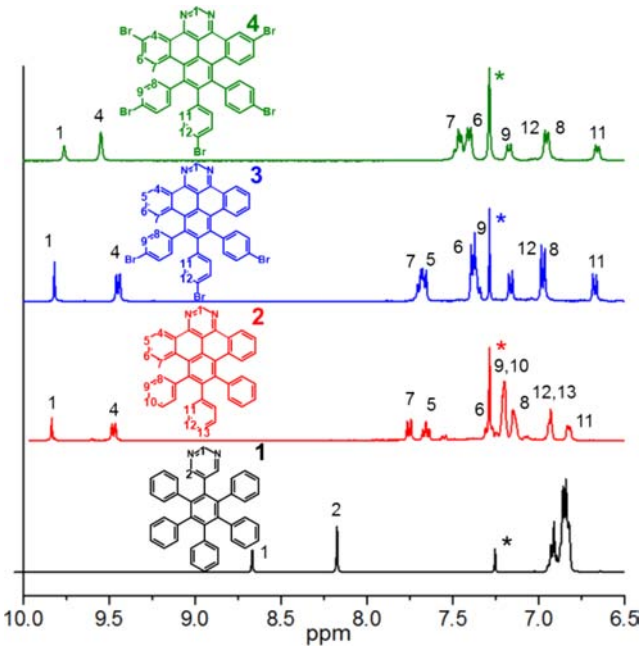

Figure 2. ^{1}H NMR spectra of **1** and the isolated products **2**, **3**, and **4** in $CDCl_3$ (solvent signal marked with an asterisk).

measurements. The molecule crystallized in the $P\bar{1}$ space group with two molecules per unit cell. Solvent molecules found in the voids could not be modeled to an acceptable level, and therefore, SQUEEZE was applied.

As a result of the ring closure, the fused phenyl and pyrimidine rings now form part of a significantly curved bowl-like structure. The strained nature of this pyrimidine section results in a curve of 20° at the extremities, relative to the plane of the central ring. The molecules pack in a head-to-tail fashion, with $\pi-\pi$ interactions between the aromatic cores resulting in intermolecular distances of 3.538 Å. Analysis of the single-crystal X-ray structure of the tribrominated **3** shows that the bromine atoms present result in only minimal changes to the molecular structure. The dimeric lateral overlap of the fused aromatic portions, however, was very much enhanced in **3**, possibly due to the presence of two dichloromethane molecules in the void, as seen in Figure 3b.

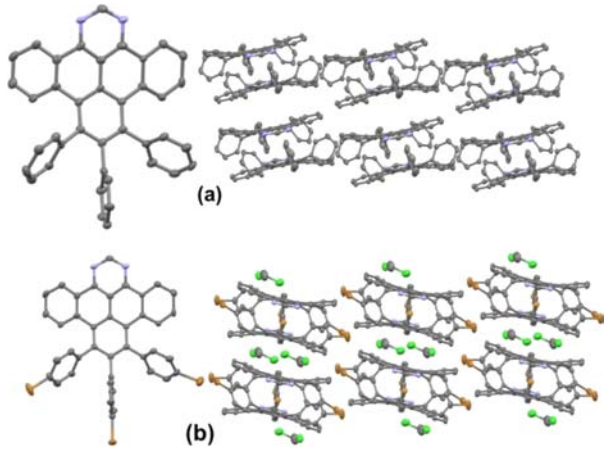

Figure 3. (a) Asymmetric unit and packing motif of **2**; (b) asymmetric unit and packing motif of **3**. Displacement ellipsoids shown at 50%. Hydrogen atoms omitted for clarity.

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At this point, it was decided to explore the generality of the new method and to apply it to the more challenging 4N-containing polyphenylene 1,2-dipyrimidyl-3,6-bis(4-*tert*-butylphenyl)-4,5-bis(4-bromophenyl)benzene **5**. This precursor was chosen for comparison with a system previously studied by Draper et al.[15] The difference in this case is that two *t*-butyl groups are present to block two of the *para* positions on the pendant phenyls. On heating dipyrimidyl polyphenylene precursor **5** in toluene with Br_2 for 45 min, the half-cyclized product **6** was isolated in 70% yield (Figure 4). This was a positive improvement on the reported yields of similar half-cyclized analogues that were generated by the traditional $FeCl_3$ route (e.g., 32%).[12]

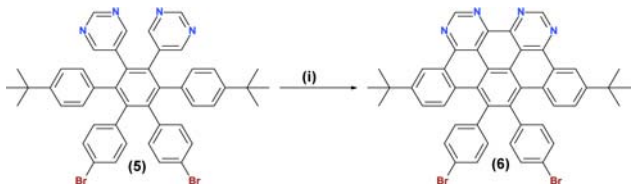

Figure 4. Schematic of the reaction to generate a fused dipyrimidyl analogue (**6**) from polyphenylene precursor (**5**): (i) Br_2, toluene, 90 °C, 1 h.

Recrystallization of **6** from CH_2Cl_2/MeOH yielded the product as a crystalline yellow solid. After filtering, no further purification was necessary, and on diffusing the product in a methanol solution, twinned crystals suitable for X-ray diffraction studies were genereated. The data were refined as a two-component twin using PLATON and HKLF 5 and were successfully integrated using a triclinic unit cell. The unit cell contains 6 H_2O molecules, which were treated as a diffuse contribution to the overall scattering without specific atom positions by SQUEEZE/PLATON. The packing motif (Figure 5) shows the head-to-tail stacking between alternating molecules, with very small interplanar distances of 3.365 and 3.349 Å.

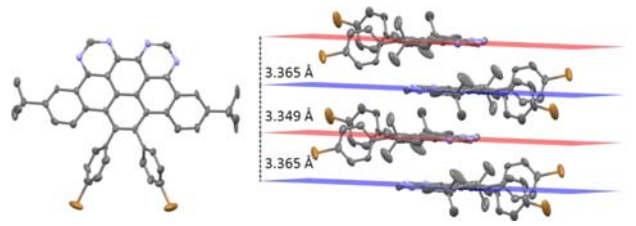

Figure 5. Asymmetric unit and packing motif of **6**. Displacement ellipsoids shown at 50%. Hydrogen atoms omitted for clarity.

For all-carbon systems, cyclodehydrogenation is not seen to occur by the route presented here. All carbon hexaphenylbenzenes are seen to only undergo *para* bromination, while precursors blocked at these sites show no reaction at all. Increasing the number of pyrimidine rings has a direct influence on the total number of C−C bond formations achieved. This can be limited, ultimately, at higher degrees of closure, at which point the twisted nature of the increasingly fused molecule possibly inhibits any further reaction. It is likely that, in the presence of nitrogen atoms, cyclodehydrogenation progresses via an arenium cation mechanism. This could be rationalized by protonation of the pyrimidine ring, thereby generating a cation at the adjacent carbons, *ortho* to both nitrogen atoms. Evidence for this is seen in the fact that cyclodehydrogenation never occurs with adjacent phenyl rings bearing electron-withdrawing substituents, such as Br. This new work supports the general consensus that for bond formation to occur, via electrophilic attack, a sufficiently electron-rich contiguous ring is required.

In summary, a gateway reaction has been demonstrated that offers an unprecedented and one-step process to partially fused and bromo-functionalized N-doped polyaromatics. These are suitable for chemical functionalization and/or further aromatization using existing routes. The work impacts recent publications that mark the point of convergence between top-down and bottom-up synthetic routes to doped nanoribbons. The arrival of an alternative reagent to brominated precursors with precise substitution patterning will provide new opportunities for the control of the symmetry and edge characteristics of graphene materials and the broadening of their potential application in electronic devices. Under the right conditions, such materials can be intermolecularly stitched to form a patchwork holey graphene sheet or nanoribbon. The new selective fusion and bromination of highly aromatic di- and tetra-aza PAHs also introduces a high-yielding methodology to deliver novel ligands. The systems isolated to date are relevant to making orthometalated or N-coordinated transition metal complexes with interesting photophysical applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03312.

Additional experimental details and figures (PDF)

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Notes

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Organic LETTERS

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Asymmetric Synthesis of 1,2-Diamines bearing Tetrasubstituted Centers from Nonstabilized Azomethine Ylides and *N*-Sulfinylketimines under Brønsted Acid Catalysis

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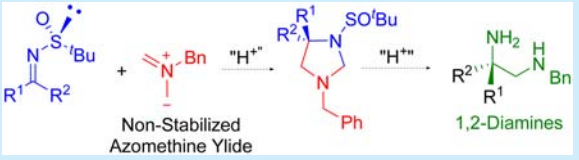
Supporting Information

ABSTRACT: The first asymmetric cycloaddition of nonstabilized azomethine ylide and *N*-sulfinylimines is presented. In reactions with aryl−alkyl and heteroaryl−alkyl ketimines, excellent diastereoselectivities and good yields are obtained in all cases, regardless of the electronic character of the substituents at the aromatic rings. Moreover, the cycloadducts obtained can easily be deprotected in acid media, giving access to free 1,2-diamines which are prevalent in many natural and pharmaceutical products.



1,2-Diamine, containing one tetrasubstituted center and an unsubstituted CH_2 ($N-CR_2-CH_2-N$), is a highly relevant privileged moiety because it is present in the structure of compounds exhibiting pharmacological properties. These properties have important biological effects such as antitumor, anti-infective, anti-inflammatory, antidiabetic, and cardiovascular agents, as well as enzyme inhibitors and immune agents, among others. These 1,2-diamines usually form part of a large family of heterocycles. The homochiral tetrasubstituted centers are one of the keys to their biological role. Because of the importance of these structures, the search for synthetic methods able to produce them in an optically pure form is extremely important. Figure 1 shows examples of these compounds with important biological effects, such as imidazolines, pyrrolidines, piperazines, or platinum complexes.

The two main asymmetric strategies used in the synthesis of this type of 1,2-diamine involve two steps. The first one, the creation of the tetrasubstituted center, is based on the highly efficient asymmetric Strecker[1] or aza-Henry[2] reaction, yielding

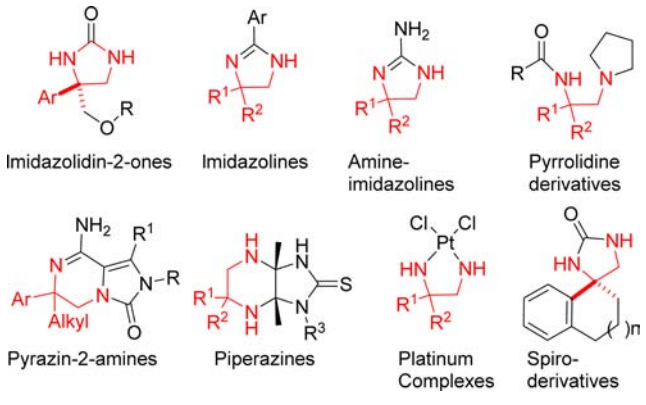
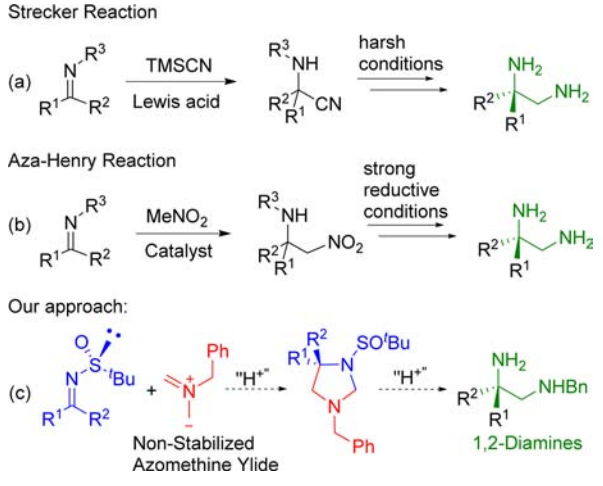


Figure 1. Biologically important 1,2-diamines containing the $N-CR_2-CH_2-N$ fragment.

aminonitrile and aminonitroderivative intermediates, respectively (equations a and b, Scheme 1). These must be further

Scheme 1. Approaches for the Asymmetric Synthesis of 1,2-Diamines Containing the $N-CR_2-CH_2-N$ Fragment



transformed into the diamines required. However, the second step involves a change in the oxidation state, usually requiring strong conditions such as harsh acidic reagents for hydrolyzing nitriles, which sometimes provoke retro-Strecker reactions, and strong agents to reduce the NO_2 group, which are not compatible with many functional groups. This is the main handicap limiting the applicability of these methods.[3] Thus, the synthesis of optically pure compounds containing the $N-CR_2-CH_2-N$ fragment still remains a unresolved problem in asymmetric synthesis, which presents an important challenge in the search for new procedures that avoid the drawbacks described above.

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It is well-known that imidazolidines can be transformed into 1,2-diamines using hydrolytic procedures.[4] On this basis, we reasoned that by finding a good method for obtaining optically pure imidazolidines with the N−CR_2−CH_2−N fragment we could easily achieve the desired diamines. However, the stereoselective synthesis of these heterocycles is not a trivial task. Despite one of the most straightforward methods for the asymmetric synthesis of pyrrolidines being the 1,3-dipolar cycloaddition of olefins with stabilized azomethine ylides,[5] there are very few references concerning their reactions with imines to obtain imidazolidines.[6] Moreover, to obtain the heterocycles bearing the asymmetric tetrasubstituted center of our desired 1,2-diamines, we needed to start from ketimines, whose reactions with azomethine ylides have never been reported (refs 6a and b only concern asymmetric examples with *N*-sulfinylaldimines). On the other hand, reactions yielding the CR_2−CH_2 moiety require the use of nonstabilized azomethine ylides, which are much less explored in asymmetric cycloadditions due to their usually low stereoselective control (only the addition to different electrophiles in racemic versions has been described).[7]

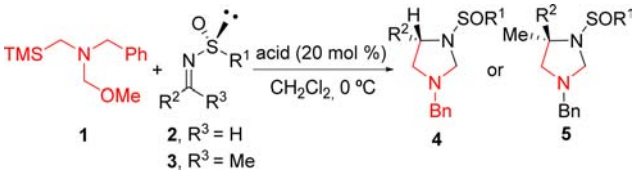
In this work, we present a general procedure for preparing the desired 1,2-diamines based on the asymmetric 1,3-dipolar reaction of nonstabilized azomethine ylides with *N*-sulfinylketimines (equation c, Scheme 1) and a further transformation of the resulting imidazolidines. In addition, we will present the results obtained with some *N*-sulfinylaldimines.

We started our exploration of the reactions of aldimines[8] with a nonstabilized dipole generated from **1** in catalytic acid media, which to date has never been studied. Reactions with Ellman's *t*-butyl-*N*-sulfinylimine **2a**[8c] were performed in the presence of a catalytic amount of different conventional acids such as TFA, benzoic acid, and *ortho*-fluorobenzoic acid (*o*-FBA), with the results shown in Table 1 (entries 1−3). They were improved by using diphenyl phosphate (20 mol %) as the acid; this resulted in a 91:9 mixture of inseparable diastereoisomers (**4a** and **4a′**) in 72% isolated yield after 12 h (entry 4). Other solvent concentrations and temperatures were also studied (see Supporting Information), but the diastereomeric ratio could not be improved. As expected from a steric point of view, the reactions with *N*-tolylsulfinylaldimine **2b** (R^1 = Tol) under TFA and DPP catalysis (entries 5 and 6) required lower reaction times (2 h) and the stereoselectivity was slightly lower. We then studied the influence of the electronic effect of the substituents in the aromatic ring on the stereoselectivity (see entries 7 and 8). The electron-withdrawing groups (EWGs, i.e., *p*-CN) improved the dr, whereas electron-donating groups (EDGs, i.e., *p*-MeO) decreased the final diastereomeric ratio.

The behavior of the *N*-sulfinylketimines **3a** and **3b** (precursors of the tetrasubstituted centers) in these reactions (entries 9−11) was then explored. Davis' ketimine **3b** did not react, and no trace of the expected adduct **5b** could be detected after 24 h, under conditions similar to those used with aldimines (entry 9). Other conditions were also studied (see SI) with analogous negative results. Surprisingly, the bulkier Ellman's ketimine **3a** yielded **5a** in 26% yield under mild conditions after 18 h (entry 10), and this yield could be improved by up to 86% in 2 h by increasing the amount of **1** (4 equiv, entry 11).

Once the optimal conditions had been determined, we studied the reactions with different methyl aryl ketimines **3** (Table 2).

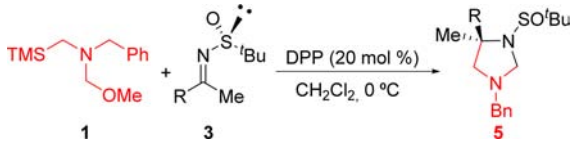
Table 1. Initial Exploration of the Addition of Nonstabilized Ylide Derived from 1 to *N*-Sulfinylimines 2a−c and 3a,b[a]



entry	R^1	R^2	acid	dr[b]	yield (%)[c]
1	^{t}Bu-**2a**	Ph	TFA	69:31	63 (**4a**/**4a′**)
2	^{t}Bu-**2a**	Ph	BzOH	87:13	70 (**4a**/**4a′**)
3	^{t}Bu-**2a**	Ph	*o*FBA	81:19	80 (**4a**/**4a′**)
4	^{t}Bu-**2a**	Ph	DPP	91:9	72 (**4a**/**4a′**)
5	Tol-**2b**	Ph	TFA	80:20	51 (**4b**/**4b′**)
6	Tol-**2b**	Ph	DPP	87:13	82 (**4b**/**4b′**)
7	^{t}Bu-**2c**	*p*-$MeOC_6H_4$	DPP	80:20	78 (**4c**/**4c′**)
8	^{t}Bu-**2d**	*p*-CNC_6H_4	DPP	>98:2	87 (**4d**)
9	Tol-**3b**	Ph	DPP		NR[e]
10	^{t}Bu-**3a**	Ph	DPP	>98:2[f]	26 (**5a**)
11[d]	^{t}Bu-**3a**	Ph	DPP	>98:2[f]	86 (**5a**)

[a]All reactions were carried out with **1** (0.2 mmol) and **2** or **3** (0.1 mmol) and 20 mol % of the catalyst indicated in 0.2 mL of dichloromethane. [b]Determined by ^{1}H NMR. [c]Combined yield. [d]Reaction carried out with 0.4 mmol of **1**. [e]No reaction. [f]Amine center with opposite configuration (ddp = diphenyl phosphate, *o*FBA = *ortho*-fluorobenzoic acid, TFA = trifluoroacetic acid).

Table 2. Scope of the Reaction between Ketimines 3 and 1 in the Presence of Catalytic DPP[a]



entry	R	time (h)	dr[b]	yield (%)
1	C_6H_5 (**3a**)	2	>98:2	86 (**5a**)
2[c]	C_6H_5 (**3a**)	8	>98:2	83 (**5a**)
3	*p*-MeC_6H_4 (**3c**)	2	>98:2	97 (**5c**)
4	*p*-CNC_6H_4 (**3d**)	2	>98:2	89 (**5d**)
5	*p*-$NO_2C_6H_4$ (**3e**)	3	>98:2	87 (**5e**)
6	*o*-FC_6H_4 (**3f**)	3	>98:2	57 (**5f**)
7	2-naphthyl (**3g**)	2	>98:2	84 (**5g**)
8	*m*-$MeOC_6H_4$ (**3h**)	2	>98:2	94 (**5h**)
9	2-furyl (**3i**)	10	>98:2	92 (**5i**)
10	2-thienyl (**3j**)	12	>98:2	87 (**5j**)

[a]All reactions were carried out with **1** (0.4 mmol) and **3** (0.1 mmol) in 0.2 mL of dichloromethane. [b]Determined by ^{1}H NMR. [c]Reaction carried out with 5.3 mmol of **1**.

The result of the reaction of **3a** under conditions of entry 11 in Table 1 was repeated in entry 1 of Table 2. This reaction could be scaled up to 5.3 mmol without any erosion in the yield and the diastereoselectivity (entry 2). The reaction tolerated EDGs and EWGs in the aryl moiety. This reactivity was only slightly sensitive to the electronic character of the ring, with longer reaction times for substrates bearing electron-rich rings (entries 9 and 10) and similar reaction times with electron-poor ones (entries 4 and 5). Bulkier aromatic rings like 2-naphthyl or *ortho*-fluorophenylketimines (entries 6 and 7) had a mild influence on the reactivity. Stereocontrol is very efficient in all cases (dr > 98:2), and the yields are usually very good.

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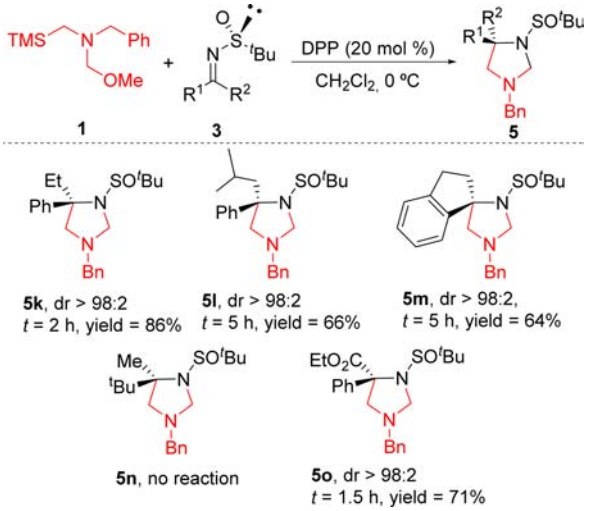
We then examined the influence of other ketimines (**3k**−**3o**) on the dipolar reaction with the nonstabilized dipole (Scheme 2).

Scheme 2. Scope of the Reaction between *N*-Sulfinylalkylketimines 3k−3o and 1 in the Presence of Catalytic DPP[a]



[a]All reactions were carried out with **1** (0.4 mmol) and **3** (0.1 mmol) and 20 mol % of DPP in 0.2 mL of dichloromethane. The diastereomeric ratio was determined by ^{1}H NMR.

The reactions of phenylalkylketimines **3k** (R^2 = Et) and **3l** (R^2 = *s*-Bu) produced the corresponding imidazolidines **5k** and **5l** as single diastereoisomers in good yields (86 and 66%, respectively), whereas the dialkylketimines which contained the bulky *t*-Bu group did not give fruitful results (**5n** was not detected). Two interesting examples illustrate the synthetic possibilities of this reaction. The first is the spiranic compound **5m**, which was obtained diastereomerically pure in 64% yield and illustrates the behavior of *N*-sulfinylimines derived from cyclic arylketones. It is relevant because of the importance of the spiranic structures containing the fragment NCR_2CH_2N,[9] which are accessible from the adducts obtained. The second example is the derivative **5o**, also obtained with complete control of the stereoselectivity in the reaction of a sulfinylimine derived from an α-ketoester, which could provide an interesting route for the preparation of optically pure tetrasubstituted α-amino acids derived from 1,2-diamines.

The absolute configuration of imidazolidine **5d** was unequivocally assigned as *R*,*R* (left, Figure 2) by X-ray crystallographic analysis.[10] We assigned the same configuration to all imidazolidines derived from ketimines **3** and obtained as unique diastereoisomers. Analogously, the absolute configuration of **4d** was assigned as *S*,*R* (right, Figure 2). This was also

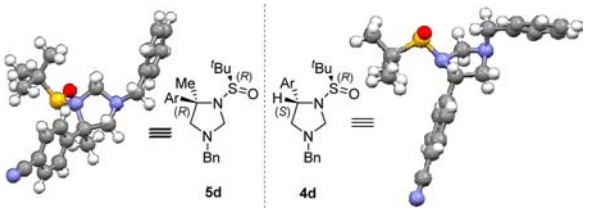


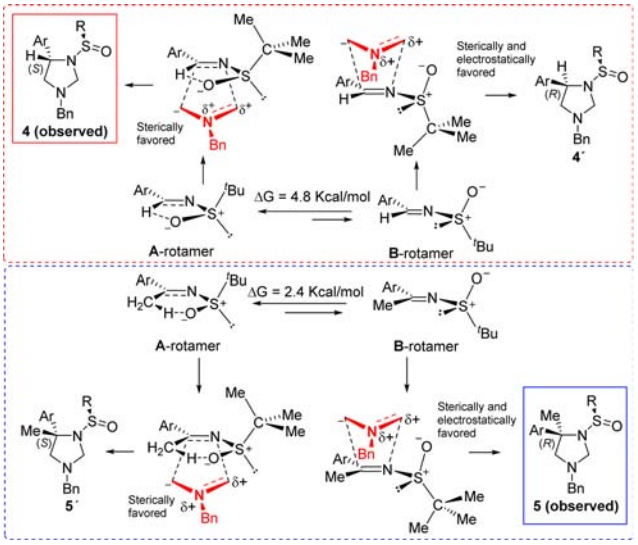
Figure 2. Absolute configuration of the imidazolidine **5d** and **4d** (Ar = *p*-CNC_6H_4).

assumed for the major diastereoisomer obtained for the other aldimines **2a**−**2c** studied. Thus, the predominant configuration is different for both types of substrates.

As the configuration at carbon starting from aldimines is the opposite of that resulting from ketimines, the factors controlling the stereoselectivity in both reactions should be different. The conformational stability of the different rotamers of the ketimine **3a** around the N−S bond was studied previously by DFT calculations.[11]

Analogously, this question was also studied in the *N*-phenylsulfinylimine derived from acetaldehyde,[12] which will be used here as a model of the behavior of *N*-sulfinylaldimines. In both cases, **A** rotamers, with the sulfinyl oxygen in a *s-cis* arrangement with respect to the C−N bond, is more stable than the **B** rotamer, with the lone electron pair at sulfur adopting the *s-cis* arrangement (Scheme 3). This is presumably due to the

Scheme 3. Stereochemical Course for Aldimines and Ketimines



minimization of the dipolar moment and the significant contribution of the stabilizing hydrogen bond of the sulfinyl oxygen with H ($d_{O\cdots H}$ = 2.33 Å) in aldimines or with the CH_3 in **3a** ($d_{O\cdots H-C}$ = 2.17 Å). The shifting of the equilibrium, and therefore the predominance of rotamers **A**, is much higher for aldimines (ΔG = 4.8 kcal/mol) than for ketimines (2.4 kcal/mol in **3a**), as would be expected from the steric repulsions involving the sulfinyl oxygen in both cases (O/H in aldimines < O/Me in **3a**). According to these data, **B** rotamers must be scarcely populated in aldimines. However, they will be small, but significant, in ketimines such as **3a**.[13] Due to their relative reactivity, steric factors predict a similar reactivity for **A** and **B** rotamers, being favored in both cases by the approach of the dipole to the face, avoiding interactions with a bulky *t*-butyl group (pro-*R* in **A** and pro-*S* in **B**). However, electrostatic factors determine the higher reactivity of the **B** rotamers due to the favorable formation of compounds **5**, with the *R* configuration at carbon. On this basis, we have explained the stereochiral results obtained as follows. In the case of the ketimines, the population of the **B** rotamers is low but significant. Higher reactivity of the **B** rotamers compared to **A** rotamers determines the exclusive formation of compounds **5** (Curtin−Hammett principle). Nevertheless, the stereoselectivity control is not complete in the case of aldimines, and compound **4′**, resulting from an attack

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of the dipole to the **B** rotamers of compound **2a**, can be detected (91:9 mixtures of **4a**/**4a**′, Table 1). The influence of the substituents supports this explanation. Thus, the presence of an EWG (such as CN in **2b**) will increase the acid characteristics of the aldiminic hydrogen and therefore the strength of the hydrogen bond and the ΔG value. Thus, the population of **B** decreases, and the stereoselectivity increases (only **4b** was detected), whereas an EDG (such as OMe in **2c**) produces the opposite result, decreasing the diastereomeric ratio (80:20 mixture of **4c**/**4c**′, Table 1).

Finally, we studied different transformations of the imidazolidine **5** (Scheme 4). Desulfinylation into imidazolidines **7a** and

Scheme 4. Selective Deprotection to Different Diamine Derivatives

7f can be performed in high yields with HCl in a mixture of dioxane/MeOH (7:1), whereas the desired open chain 1,2-diamines **6a** and **6e**, containing the N−CR_2−CH_2−N fragment, can be obtained only using methanol as solvent.

In conclusion, we have developed the first asymmetric cycloaddition of nonstabilized azomethine ylides and *N*-sulfinylimines, with almost complete control of the stereoselectivity. The cycloadducts obtained from ketimines can be deprotected in acid media, providing easy access to 1,2-diamine derivatives containing tetrasubstituted centers, which are prevalent structures in natural and pharmaceutical products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03251.

Complete screening tables, experimental details, and NMR spectra of all new compounds (PDF)
X-ray structure of **4d** (CIF)
X-ray structure of **5d** (CIF)

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Notes

The authors declare no competing financial interest.

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(13) These assumptions are reinforced, taking into account that theoretical calculations indicate that ΔG values decrease in the presence of solvents (see ref 11).

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Organic LETTERS

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Divergent Reactivity of Amino Acid Alkyl Ester Hydrochlorides with 2-Oxoaldehydes: Role of Selenium Dioxide To Promote Regioselective Synthesis of Imidazoles

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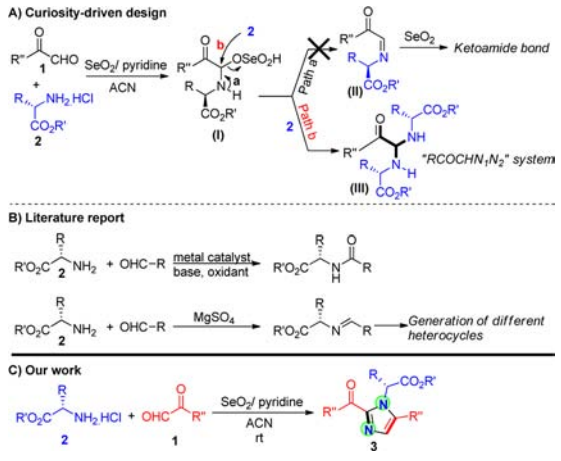
Supporting Information

ABSTRACT: Novel amino acid substituted imidazoles engendered from amino acid alkyl ester hydrochlorides and 2-oxoaldehydes as a result of selenium dioxide promoted unconventional reaction in a basic environment is presented for the first time. Despite the nature of the 2-oxoaldehydes/amino acids used, the imidazoles generated had a functional core structure, and all of the reactions meticulously retained regioselectivity. The imperative feature of these reactions was the uniqueness of selenium dioxide in fixing two nitrogen atoms from amino acids through an in situ generated $ArCOCHN_1N_2$ system.

2-Oxoaldehydes (OAs) have proven to be versatile building blocks for a variety of chemical transformations.[1] The application of OAs toward the generation of different exigent products/chemistry is the current interest of our group.[2] The differing behavior of the aldehyde group in OA is primarily due to the presence of an electron-withdrawing ketone group.[1] Although reactions through the aldehydic group of OA with different nucleophiles are well explored in diverse directions, the reactivity through the in situ generated hypothesized system ($RCOCHN_1N_2$) is not well explored. To develop applications for such a system, we recently established a novel method for the synthesis of 6-aminophenanthridines.[2a] Therein, benzotriazoles were used as nucleophiles against an in situ generated 2-oxoiminium ion. However, with amino acid alkyl esters, the reactivity was not possible due to the tendency of 2-oxoiminium to oxidize to α-ketoamides.[2h,j] In an effort to develop such a system with amino acids, we designed our reaction against amino acids in the presence of selenium dioxide (Scheme 1A). In our previous observation regarding the conversion of α-carbonylimines to α-carbonylamides, we efficiently developed an oxidative amidation approach against weak nucleophilic amines (anilines, benzamides, and sulfonamides).[2f] However, such reactions, when tested against primary aliphatic amines, failed to produce any reaction. For these observations, we presume that, due to the low nucleophilicity of WNA, the intermediate **I** undergoes an elimination reaction to the 2-oxoimine **II** intermediate (path a) that ultimately undergoes oxidation to an amide bond. However, the behavior of such a reaction against amino acids alkyl esters bearing primary nucleophilic amine with the β-ester group was never explored. Herein, we assume that due to moderate nucleophilicity of amino acid alkyl esters between secondary and weak nucleophilic amines it would preferably go through path b and result in the generation of an $RCOCHN_1N_2$ system **III** that ultimately results in the synthesis of imidazoles in a regioselective manner (Scheme 1C).

Scheme 1. Summary of Work



Imidazole derivatives are well known for their diverse pharmacological applications.[3] In addition, imidazole is part of histidine and histamine, and their derivatives are the core fragments in different natural products.[4] Thus, our method could

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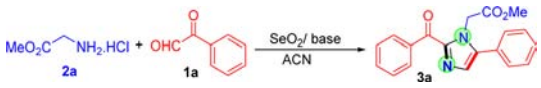
be a novel, alternative, economical, and imperative method for their regioselective synthesis. Amino acids are always considered to be an attractive class of chiral reactants/reagents used for the generation of different complex organic compounds.[5] While the reaction of amino acids with aldehydes has been successfully employed for the generation of amide bonds[6] and different heterocycles through reaction of in situ generated imine with different reagents (Scheme 1B),[7] they have never been directly utilized as reagents for the synthesis of different imidazoles (Scheme 1C). In this regard, our method highlights an unconventional tendency of selenium dioxide to promote the synthesis of imidazoles in a regioselective manner through a $RCOCHN_1N_2$ system in a basic environment. The beauty of the reaction lies in the fixing of two nitrogens from the amino acid in manner similar to the method of Hashemi et al. for the synthesis of imidazoles.[8]

In our initial investigations, we ventured to examine the nature of product obtained on reacting phenylglyoxal **1a** (1 mmol) and glycine methyl ester hydrochloride **2a** (1 mmol) in ACN under a basic environment (1 mmol) with selenium dioxide (1 mmol) as the reagent at 100 °C. To our delight, the reaction produced an unexpected product **3a** in 33% yield (Table 1, entry 1).

Table 1. Optimization of the Reaction[a]



entry	**2a** (mmol)	base (mmol)	SeO_2/ oxident (mmol)	temp (°C)	**3a** (yield[b])/ time (h)
1	1	pyridine (1)	1	100	33/4
2	1	pyridine (1)	1	50	32/4
3	1	pyridine (1)	1	rt	30/4
4	1	pyridine (1.3)	1	rt	50/4
5	1	pyridine (1.5)	1	rt	52/4
6	1	pyridine (1.7)	1	rt	52/4
7	1.1	pyridine (1.5)	1	rt	56/4
8	1.2	pyridine (1.5)	1	rt	61/4
9	**1.2**	**pyridine (1.5)**	**1.2**	**rt**	**67/4**
10	1.2	pyridine (1.5)	1.5	rt	67/12
11	1.5	pyridine (1.5)	1.2	rt	67/12
12	1.2	TEA (1.5)	1.2	rt	30/24
13	1.2	KOH (1.5)	1.2	rt	25/24
14	1.2	NaOH (1.5)	1.2	rt	28/24
15	1.2	$NaHCO_3$ (1.5)	1.2	rt	18/24
16	1.2	$KHCO_3$ (1.5)	1.2	rt	21/24
17	1.2	pyridine (1.5)	MnO_2 (1.2)	rt	0/24
18	1.2	pyridine (1.5)	IBX (1.2)	rt	0/24
19	1.2	pyridine (1.5)	TBHP (1.2)	rt	0/24
20	1.2	pyridine (1.5)	Oxone (1.2)	rt	0/24
21	1.2	pyridine (1.5)	DIB (1.2)	rt	0/24

[a]Reaction conditions: **1a** (1 mmol), **2a** (1.2 mmol), pyridine (1.5 mmol), selenium dioxide (1.2 mmol), and ACN (3 mL). [b]Isolated yields.

Compound **3a**, when examined in HRMS, surprisingly generated a mass of 321.1235 that formulated a structure formula of $C_{19}H_{17}N_2O_3$. This perhaps could be possible if two molecules of OA **1a** reacted with two molecules of amino acid **2a** in an unprecedented manner. In this regard, detailed NMR analysis was performed to reach a structure of **3** (for details, see the Supporting Information, page S14). The structure was finally fortified by single-crystal X-ray diffraction studies of the best crystallizable

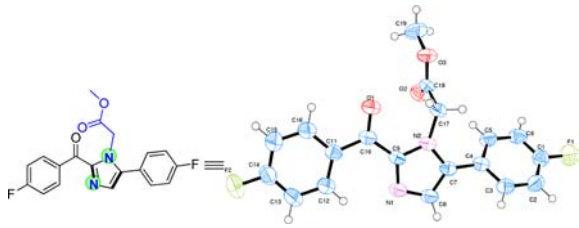


Figure 1. ORTEP diagrams of compound **3e**.

compound **3e**, generated by reacting 2-(4-fluorophenyl)-2-oxoacetaldehyde **1e** (1 mmol) and glycine methyl ester hydrochloride **2a** (1 mmol) under the above-mentioned conditions (Figure 1; for details, see the Supporting Information).

Following the promising results achieved with the above method, the reaction conditions, particularly the change in concentrations, temperature, and base, were thoroughly investigated (Table 1). Under the conditions comparable to those perceived above, a survey of change in temperature (entry 1−3) intimated that there was no predominant effect of temperature on the yields (entry 3). Besides, screening of our reaction at different concentrations of pyridine was also performed (entries 3−6). We observed that better yields of desired product were observed at 1.5 equivalence of pyridine (entry 5). A further increase in the concentration of pyridine had no promising effect (entry 6). Later, screening about the change in amino acid concentration (entries 6−8) generated best results when taken at 1.2 equiv (entry 8). In addition, our reaction when tested with different concentrations of selenium dioxide (entries 8−10) indicated best results at 1.2 mmol (entry 9). Furthermore, we tested our reaction under different bases (entries 12−16). Finally, different reactions were tested against different oxidants to confirm the unanimous role of SeO_2 to promote our reaction (entries 17−21). After extensive studies, we observed that the best conditions for the reaction were when 1 mmol of **1a** was treated with 1.2 mmol of **2a** and 1.2 mmol of SeO_2 in 3 mL of ACN in the presence of 1.5 mmol of pyridine at rt (entry 9).

Having observed that SeO_2 catalyzed the unprecedented addition of glycine methyl ester **1a** with 2-oxoaldehyde **2a** under the above optimized conditions in a highly regioselective manner, we then decided to examine the substrate scope of this process. As compiled in Tables 2 and 3, a variety of amino acid alkyl esters **1** were tested against 2-oxoaldehydes **2** with diverse steric and electronic properties (entries **3a**−**ad**). We were gratified to find that in all reactions tested the desired products **3** were produced in good yields (60−89%). In general, we classified these reactions in two different sets of experiments. In one set of experiments, different reactions were conducted between different 2-oxoaldehydes **1** and glycine methyl ester hydrochloride **2a** (entries **3a**−**h**). It was observed that both electron-rich and electron-deficient OA could be smoothly transformed into the desired product. In addition, different experiments were performed between different representative amino acids **2** and phenylglyoxal **1a** (entries **3i**−**l**). In this case as well, yields were good for all the reactions conducted. Further, to check the reproducibility of our reaction against different ester protected amino acids, we conducted a few experiments against ethyl-protected glycine (entries **3m**−**o**). In all reactions, we found no effect of the change in yields to that extent.

Another set of experiments was conducted between different OAs and amino acid hydrochlorides in order to check for a broad substrate scope (Table 3). In general, substituents at different positions of the arene group and their electronic nature in OA do

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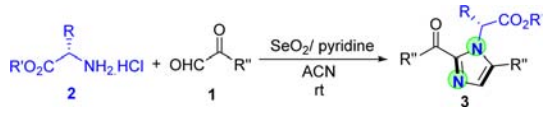
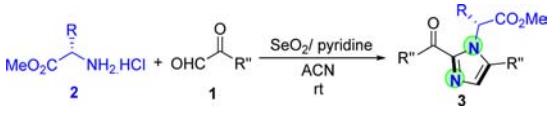
Table 2. Scope of the Reaction[a]



entry	R	R′	R″	yield[b] (%)/time (h)
3a	H	Me	Ph	67/4
3b	H	Me	4-MePh	68/4
3c	H	Me	3-MePh	66/4
3d	H	Me	4-MeOPh	69/4
3e	H	Me	4-FPh	62/4
3f	H	Me	4-ClPh	64/4
3g	H	Me	4-BrPh	65/4
3h	H	Me	4-HOPh	60/4
3i	Me	Me	Ph	84/3.5
3j	benzyl	Me	Ph	83/3
3k	isopropyl	Me	Ph	81/2.5
3l[c]	ethyl(methyl)sulfane	Me	Ph	79/2.5
3m	H	Et	4-Me	66/4
3n	H	Et	4-F	61/4
3o	H	Et	4-Br	60/4

[a]Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), pyridine (1.5 mmol), selenium dioxide (1.2 mmol), and ACN (3 mL). [b]Isolated yields. [c]*d*-isomer.

Table 3. General Substrate Scope of the Reaction[a]



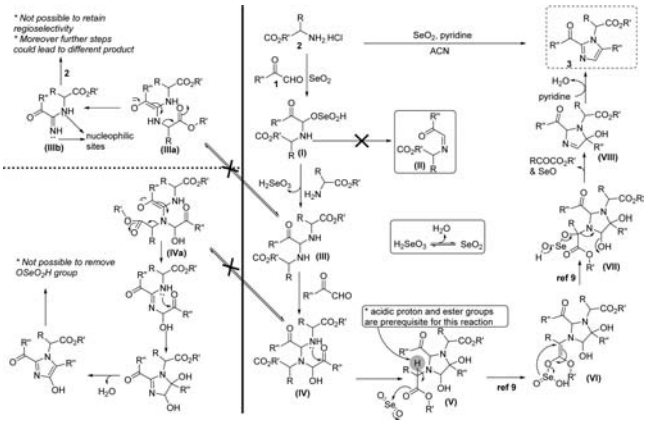
entry	R	R″	yield[b] (%)/time (h)
3p	Me	3-MePh	85/3.5
3q	Me	4-MePh	86/3.5
3r	Me	4-MeOPh	88/3.5
3s	Me	4-FPh	84/3.5
3t	benzyl	4-MePh	82/3
3u	isopropyl	3-MePh	85/2.5
3v	isopropyl	4-MePh	86/2.5
3w	isopropyl	4-FPh	81/2.5
3x	isopropyl	4-ClPh	83/2.5
3y	isopropyl	4-BrPh	82/2.5
3z	isopropyl	4-MeOPh	89/2.5
3aa[c]	ethyl(methyl)sulfane	4-MePh	82/2.5
3ab	H	5-methylthiophene-2-yl	64/4
3ac	Me	5-methylthiophene-2-yl	86/3
3ad	H	4-NO_2Ph	0/24

[a]Reaction conditions: **1**(1 mmol), **2** (1.2 mmol), pyridine (1.5 mmol), selenium dioxide (1.2 mmol), and ACN (3 mL). [b]Isolated yields. [c]*d*-isomer.

not affect the efficiency of the reaction (**3a**–**ac**). However, reactions with nitro-substituted OA failed to produce any reaction (entry **3ad**). In addition, we found that in the case of amino acids yields were good despite the nature of the isomer being used (*d* or *l*); however, variation in the R group in amino acids affects the overall yields to some extent. For glycine, the yields were slightly less than other amino acids.

Since such reactions on amino acid alkyl esters **2** and 2-oxoaldehydes **1** are possible with selenium dioxide only, we currently anticipate a plausible mechanism that can justify the generation of imidazole regioselectively (Scheme 2). In this

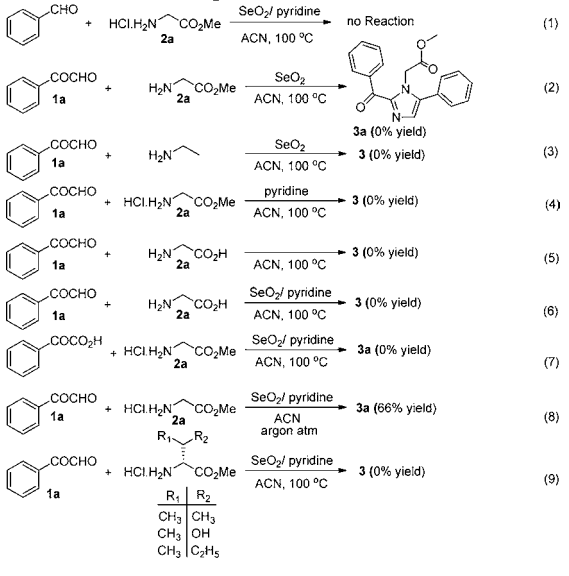
Scheme 2. Plausible Mechanism



mechanism, OA reacts with the amino acid in the presence of SeO_2 to generate intermediate **I**. Intermediate **I** avoids generation of 2-oxoimine **II**, undergoes elimination of selenonic acid on reacting with a second amino acid **2**, and generates intermediate **III**. Intermediate **III** can either undergo tautomerism to **IIIa** that ultimately can undergo N−C bond cleavage to **IIIb** or can undergo addition of another OA molecule to **IV**. Since intermediate **IIIa** cannot justify regioselectivity, we propose a mechanism through **IV**. Intermediate **IV** can also tautomerize to **IVa**. However, different transformation through **IVa** could result in the generation of different product. Therefore, we presume that **IV** undergoes cyclization to **V**, ultimately through different steps eliminates SeO, and generates intermediate **VIII**. Intermediate **VIII** on aromatization generates the required product **3**. The mechanism was supported by LC−ESI−MS analysis experiments performed between **1a** and phenylalanine methyl ester **2**. We could easily trap the mass of intermediate **III** "$RCOCHN_1N_2$ system" (for details, see the Supporting Information).

In addition to the reaction mechanism, different control experiments were conducted to gain insight into the significance of different groups/reagents toward our reaction (Scheme 3). For example, we observed no reaction under the optimized conditions for coupling of benzaldehyde with **2a** (experiment 1). This

Scheme 3. Control Experiment



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observation clearly indicated the importance of the 2-oxo group in performing the reaction. Our reaction, when performed in the absence of pyridine, failed to produce the desired product (experiment 2). This result demonstrates that besides neutralization of amino acid alkyl ester hydrochloride, pyridine act as the catalyst as well. Failure of reaction with primary amines (experiment 3) proves the importance of the β-ester group. Experiment no. 4, obviously justifies the role of SeO_2 in performing the reaction. However, experiments 5 and 6 clearly rule out the possibility of the Maillard-based mechanism[10] for the generation of imidazoles. In experiment 7, the absence of **3a** clearly justifies that our mechanism is not through 2-oxoacid. In addition, the reaction between **1a** and **2a** under optimized conditions under argon atmosphere also generated the desired product **3a** in comparable yields (experiment 8). It clearly rules out the role of air assistance in our reaction. Finally, failure of valine, threonine, and isoleucine to generate desired product justifies that rearrangement of **VI** to **VIII**/elimination of SeO is difficult with sterically hindered amino acids (experiment 9).

In conclusion, we revealed an efficient novel synthetic method for the generation of amino acid substituted imidazoles from amino acid alkyl esters **2** and 2-oxoaldehydes **1** via selenium dioxide promoted unconventional reaction in a basic environment. Despite variation in the nature of 2-oxoaldehydes/amino acids, the imidazoles generated had a functional core structure with fixed regioselectivity. The imperative feature of these reactions was the uniqueness of selenium dioxide in fixing two nitrogen atoms from amino acids through an in situ generated $ArCOCHN_1N_2$ system and generation of optically pure compounds. Further investigations, including detailed mechanistic studies, expansion of the substrate scope to different natural/nonprotein amino acids, and peptides, and application toward the development of novel IDO inhibitors[11]/peptidomemitics,[12] are currently 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.5b03321.

Experimental procedures, ^1H and ^{13}C NMR spectra, LC−ESI−MS data, and characterization of all compounds (PDF)

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

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Notes

The authors declare no competing financial interest.

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Organic LETTERS

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LC–UV-Guided Isolation and Structure Determination of Lancolide E: A Nortriterpenoid with a Tetracyclo[5.4.0.0^{2,4}.0^{3,7}]undecane-Bridged System from a "Talented" *Schisandra* Plant

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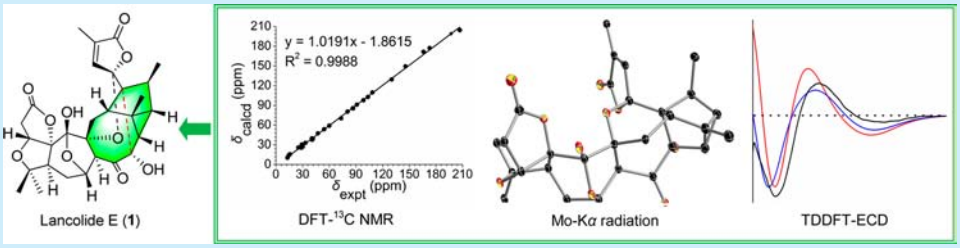
Supporting Information



ABSTRACT: Lancolide E (**1**) featuring a complex tetracyclo[5.4.0.0^{2,4}.0^{3,7}]undecane-bridged system that is constructed by an eight-, a three-, and two five-membered carbon rings in a sterically congested region was obtained in trace amounts from a "talented" schinortriterpenoid producer *Schisandra lancifolia*. Its structure was fully characterized by combining 2D NMR spectroscopy, theoretical calculations, and X-ray diffraction analysis. The biogenetic pathway of **1** was proposed to involve a Prins cyclization.

Since the discovery of the first schinortriterpenoid (SNT) from *Schisandra micrantha* in 2003,[1] plants of the Schisandraceae family, an important medicinal taxon, have become famous for their ability to produce highly oxygenated, rearranged nortriterpenoids. Their underlying biogenetic pathways are thought to originate from 3,4:9,10-disecocycloartanes, which show intriguing terpenoid oxidation and cyclization reactions occurring in nature.[2] Such complex chemical reactions generate tremendous structural variety that the skeletal repertoire is far more diverse than initially thought. In this context, enormous efforts directed toward the total synthesis of these challenging molecules have been ongoing for more than 10 years in several research groups,[2,3] and recently, the complete syntheses of schindilactone A,[3a] rubriflordilactone A,[3c,h] schilancitrilactones B and C,[3f] and propindilactone G[3g] have been accomplished successively, providing a cornucopia of reports on synthetic strategies and tactics.

In our search for new SNTs from plants of the Schisandraceae family, we attempted to identify new architectures in a structure-guided isolation approach. HPLC–UV screening enables simple, rapid, and direct identification of the structural features of SNTs, which is based on our long-established SNTs library. By using this approach, we recently discovered several SNTs bearing unusual scaffolds from *S. lancifolia* collected in the Nujiang prefecture such as schilancitrilactones A–C,[4] lancolides A–D,[5] and lancifonins E and F.[6] Meanwhile, inspecting the isolates and the data from HPLC analysis, we noticed that almost all SNTs from this species showed a maximum UV absorption band in the range of 270–300 nm with slight differences in peak shapes, which is an attribute of the $\alpha,\beta,\gamma,\delta$-unsaturated-$\gamma$-lactone moiety in the side chain or exocyclic position.[2b] Therefore, if there is an exception to the aforementioned cases in *S. lancifolia*, it allows us to assume that the structural feature may have changed and thus a new compound appears to be prospective. As a part of our ongoing research for structurally fascinating SNTs from such a "talented" producer using UV screening approach, a minor SNT (1.3 mg) with a λ_{max} at 204 nm featuring a complex tetracyclo[5.4.0.0^{2,4}.0^{3,7}]undecane-bridged system, termed lancolide E (**1**), was isolated (Figure 1). Herein, we report the isolation, identification by using 2D NMR spectroscopy, theoretical calculations, X-ray diffraction analysis, and biogenetic pathway of **1**.

Lancolide E (**1**) was obtained as white amorphous powder. Its molecular formula was determined as $C_{29}H_{32}O_{10}$ by the positive ESIMS (*m*/*z* 563 [M + Na]$^+$) and HREIMS (*m*/*z* 540.1998 [M]$^+$, calculated 540.1995), indicating 14 degrees of unsaturation. The ^{1}H NMR spectrum of **1** (Table S1, Supporting Information) recorded in acetone-d_6 showed one secondary

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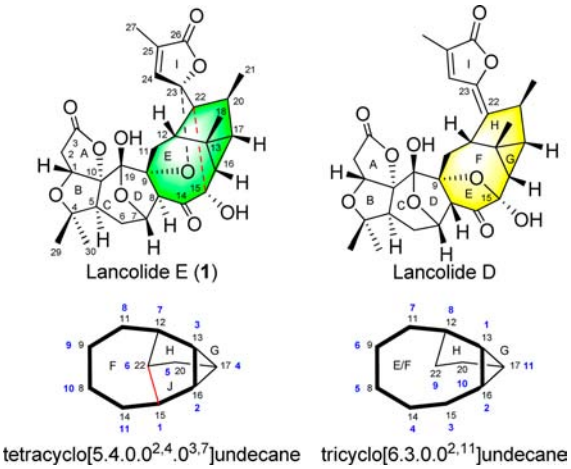

Figure 1. Structures of lancolides D and E (**1**) and their respective nomenclatures of the unique bridged systems (numbering in blue).

methyl at δ_H 1.04 (d, J = 7.0 Hz) and four tertiary methyls at δ_H 1.19 (s), 1.25 (s), 1.26 (s), and 1.96 (br s). An olefinic proton resonance at δ_H 7.28 (d, J = 1.6 Hz) suggested the existence of a trisubstituted double bond. In the lower-field region, four resonances at δ_H 4.23 (br s), 4.39 (s), 4.83 (dd, J = 5.1, 2.5 Hz), 4.97 (d, J = 6.0 Hz), and 6.25 (s) were ascribed to either methines or exchangeable hydroxyl groups. Its ^{13}C NMR and DEPT spectra (Table 1) exhibited 29 carbon resonances, including five methyls, three methylenes, nine methines (one olefinic and two oxygenated carbons), and 12 quaternary carbons (one keto carbonyl, two ester groups, one olefinic carbon, and six oxygenated carbons). By analysis of the HSQC spectrum, all proton resonances were unambiguously assigned to their respective carbons except for the two singlets at δ_H 4.39 (s) and 6.25 (s), which indicated that these two proton resonances were from hydroxyl groups. These observations occupied 4 out of 14 degrees of unsaturation, indicative of an SNT with a decacyclic structure for **1**.

Extensive analysis of the 1D (Table 1) and 2D (Figure 2) NMR data demonstrated that **1** possessing rings A–D and G shared partially structural similarities with lancolide D, a 12,22-cyclopreschisanartane-type SNT that was isolated from this species previously,[5] but the analysis also revealed some significant functional group and structural distinctions between them. The resonances of the C-22/C-23/C-24/C25 conjugated double bond (δ_C 139.6, 141.4, 135.9, and 127.0) and the characteristic C-15 hemiketal carbon resonance (δ_C 106.7) in lancolide D were absent. Instead, a trisubstituted double bond (δ_C 149.3 and 129.4) and three anomalous quaternary carbon resonances (δ_C 109.6, 91.1, and 53.6) were observe in **1**. Additionally, the UV spectrum of lancolide D showed a λ_{max} at 304 nm that was contributed by the exocyclic $\alpha,\beta,\gamma,\delta$-unsaturated γ-lactone moiety,[5] while the λ_{max} of **1** was blue-shifted to 204 nm indicating a rupture in the $\alpha,\beta,\gamma,\delta$-unsaturated γ-lactone but yet suggestive of an α,β-unsaturated-γ-lactone moiety.[7]

The aforementioned differences allowed us to postulate that the tricyclo[6.3.0.0^{2,11}]undecane-bridged system involving the exocyclic conjugated double bond in lancolide D is rearranged in **1**. This assumption was confirmed by detailed analysis of HMBC and ^{1}H–^{1}H COSY data recorded in acetone-d_6 as well as in pyridine-d_5 (Figure 2). The hemiketal C-15 resonance (δ_C 106.7) in lancolide D had been replaced by an oxygenated quaternary carbon resonance at δ_C 91.1 in the eight-membered

Table 1. Experimental and Calculated ^{13}C (150 MHz) NMR Data of Lancolide E (1) (δ in ppm)

	expt		calcd	
no.	δ_C, type[a]	δ_C, type[b]	δ_C[c]	$\Delta\delta_C$[d]
1	80.5, CH	80.8, CH	80.6	0.1
2	39.8, CH_2	40.4, CH_2	40.3	0.5
3	177.2, C	178.1, C	173.0	4.2
4	85.7, C	85.8, C	86.5	0.8
5	47.4, CH	47.4, CH	47.2	0.2
6	33.0, CH_2	32.8, CH_2	33.2	0.2
7	70.2, CH	70.2, CH	73.3	3.1
8	59.0, CH	59.9, CH	60.0	1.0
9	85.3, C	85.6, C	86.8	1.5
10	97.8, C	98.5, C	98.4	0.6
11	25.5, CH_2	26.4, CH_2	28.6	3.1
12	37.6, CH	37.8, CH	40.7	3.1
13	27.2, C	27.3, C	30.3	3.1
14	204.3, C	206.3, C	206.9	2.6
15	91.1, C	91.2, C	91.0	0.1
16	27.0, CH	27.6, CH	29.2	2.2
17	28.5, CH	28.5, CH	29.3	0.8
18	13.9, CH_3	14.0, CH_3	14.4	0.5
19	102.7, C	103.0, C	103.5	0.8
20	39.4, CH	39.5, CH	41.6	2.2
21	15.6, CH_3	16.0, CH_3	15.7	0.1
22	53.6, C	53.8, C	54.3	0.7
23	109.6, C	109.8, C	108.5	1.1
24	149.3, CH	149.6, CH	145.8	3.5
25	129.4, C	129.6, C	130.3	0.9
26	171.5, C	172.5, C	166.1	5.4
27	10.3, CH_3	10.3, CH_3	13.0	2.7
29	25.8, CH_3	26.0, CH_3	25.2	0.6
30	30.4, CH_3	30.7, CH_3	29.1	1.3

[a]Recorded in acetone-d_6. [b]Recorded in pyridine-d_5. [c]Calculated in acetone-d_6. [d]$\Delta\delta_C = |\delta_{calcd} - \delta_{expt}|$, MAE = 1.6 ppm, and CMAE = 2.2 ppm.

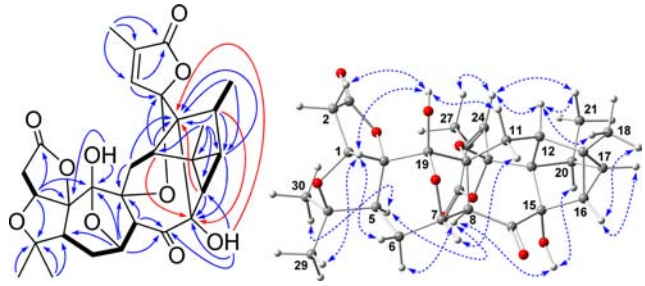

Figure 2. Key HMBC (H → C), ^{1}H–^{1}H COSY(−), and ROESY correlations of **1**.

carbon ring (ring F) of **1**, which was judged by the HMBC correlations (recorded in acetone-d_6) from the hydroxyl group resonance at δ_H 4.39 (HO-15) to C-14 (δ_C 204.3), C-15 (δ_C 91.1), and C-16 (δ_C 27.0) together with the correlations (recorded in pyridine-d_5) from H-16 (δ_H 1.97, d, J = 5.5 Hz) and H-17 (δ_H 1.18, d, J = 5.5 Hz) to C-15 (δ_C 91.2). Although the chemical shift of C-9 in **1** was almost identical with that in lancolide D, the disappearance of a hemiketal resonance in ring F of **1** indicated a cleavage of the oxa bridge formed between C-9 and C-15. The quaternary carbon resonance at δ_C 53.6 was assigned to C-22 in ring H because it showed HMBC correlations (recorded in acetone-d_6) with H-11α (δ_H = 2.48, ddd,

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J = 14.6, 11.1, 1.0 Hz), H-12 (δ_H = 2.31, dd, J = 11.1, 6.2 Hz), H-20 (δ_H = 2.67, m), and Me-21 (δ_H = 1.04, d, J = 7.0 Hz). Most notably, HMBC correlations (recorded in acetone-d_6) from HO-15 and H-16 to C-22 and from H-12 to C-15 together with correlation (recorded in pyridine-d_5) from H-20 to C-15, which were not presented in lancolide D, were observed in **1**, and thus, this set of HMBC correlations required that there was a carbon−carbon linkage between C-15 and C-22, which formed a five-membered carbon ring (ring J) containing C-15, C-16, C-17, C-20, and C-22. Therefore, a complex, sterically congested tetracyclo[5.4.0.0^{2,4}.0^{3,7}]undecane-bridged system constructed by an eight-, a three-, and two five-membered carbon rings was established. Subsequently, analysis of the HMBC correlations (recorded in acetone-d_6) from a tertiary methyl (δ_H 1.96) to two olefinic carbon resonances (δ_C 149.3 and 129.4) and an ester group (δ_C 171.5) and from an olefinic proton resonance (δ_H = 7.28, d, J = 1.6 Hz) to the ester group and a quaternary carbon resonance (δ_C 109.6) demonstrated the existence of an α,β-unsaturated γ-lactone moiety (ring I) containing C-23, C-24, C-25, and C-26. In addition, linkage of rings H and I by a carbon−carbon single bond could be deduced from the HMBC correlation (recorded in acetone-d_6) from H-12 to C-23. Considering the molecular formula and the remaining one degree of unsaturation unaccounted for, C-9 and C-23 should be attached to the oxygen atom left to form a six-membered oxygen-containing ring (ring E) that was connected to ring I in a spirocyclic manner at C-23, thus completing the planar structure of **1** (Figure 1).

The rigidity of **1** facilitated the assignment of the relative configuration. The relative configuration of chiral centers in rings A−D was determined to be the same as those in lancolide D by the similar ROESY correlations (Figure 2) and carbon (Table 1) and proton (Table S1, Supporting Information) chemical shifts of both compounds, except that H-8 in **1** was assigned to be α-orientated via the ROESY correlations of H-8 (δ_H = 4.23, br s) with H-5 (δ_H = 2.64, m) and H-6α (δ_H = 1.94, m). The observation of ROESY correlations of HO-15 with H-8 and H-20 indicated that HO-15 and H-20 were α-orientated. Moreover, the ROESY correlations of H-12 with Me-18 and Me-21; and of H-16 (δ_H = 1.59, d, J = 5.4 Hz) with H-17 (δ_H = 1.20, overlap) and Me-18 were observed as well, thus leading to assignments of a β-orientation to H-12, H-16, H-17, Me-18, and Me-21. The R* configuration for C-23 in the spiro lactone was determined by the ROESY correlations of H-24 with H-12 and Me-21. Thus, the relative configuration of **1** was determined as 1R*, 5S*,7S*,8S*,9R*,10R*,12S*,13S*,15S*,16S*,17R*,19S*,20S*, 22S*,23R*.

A computational method was carried out to confirm the planar structure and relative configuration of **1** through comparison of its experimental and calculated ^{13}C NMR data due to the initially unsuccessful attempts to obtain single crystals of **1**. The MMFF conformational search resulted in seven conformers in a 30 kJ/mol energy window. The conformational geometries optimization of these conformers at the B3LYP/6-31G(d) level in vacuo afforded one conformer accounting for more than 99% (Table S3, Supporting Information), suggesting that compound **1** presented as a structurally rigid polycyclic construct. In regard to calculation of ^{13}C chemical shifts, nuclear shielding constants were calculated using the GIAO method[8] at the MPW1PW91-SCRF/6-31G(d,p) level in acetone with PCM, and the shieldings so obtained were converted into chemical shifts by referencing to TMS at 0 ppm ($\delta_{calcd} = \sigma_{TMS} - \sigma_{calcd}$). The correlation coefficient (R^2) between calculated and experimental data obtained by linear regression analysis was 0.9988 (Figure 3), and the mean absolute error (MAE) and the corrected mean absolute error (CMAE) were 1.6 and 2.2 ppm (Table 1), respectively, thus supporting the structure furnished by 1D and 2D NMR data.

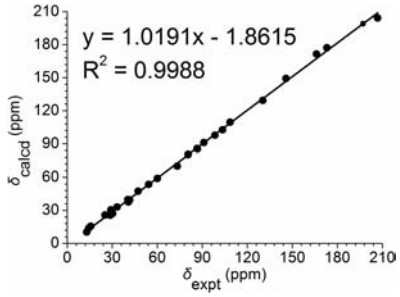

Figure 3. Regression analysis of experimental versus calculated ^{13}C NMR chemical shifts of **1**; linear fitting was shown as a line.

Various recipes and solvent systems were employed to address the issue of growing suitable single crystals for X-ray diffraction experiment so as to provide solid evidence of the structure of **1**. Slow evaporation, slow cooling, and solvent diffusion methods with single and binary solvent systems were first used. However, the evaporation rate was carefully controlled but amorphous powders rather than crystals were obtained. The vapor diffusion method was then tried, yet slow diffusion of poor solvents, i.e., chloroform, petroleum ether, 2-propanol, and ethyl acetate, into the clear solutions of methanol, acetone, or pyridine containing **1**, respectively, led to the formation of noncrystalline powders as well. Fortunately, when water was used as a poor solvent to slowly diffuse into a solution of methanol containing **1** at room temperature, suitable crystals of **1** in the form of colorless prisms were ultimately obtained. The X-ray diffraction analysis using Mo Kα radiation revealed that **1** crystallized in the monoclinic chiral P21 space group and its asymmetric unit contained two crystallographically independent molecules with same configurations (Figure S1, Supporting Information). Further investigation indicated that **1** exhibited twinning, and therefore, the structure was refined employing the TWIN and BASF instructions in SHELXL-97,[9] generating the final BASF value of 0.217. Thus, the structure and relative configuration of **1** were successfully established (CCDC 1427792, Figure 4).

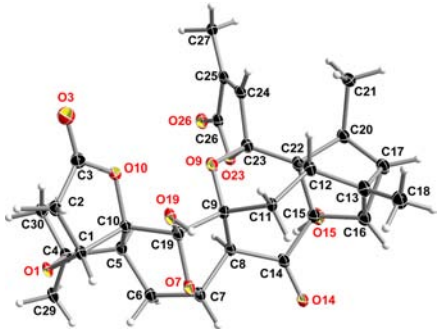

Figure 4. ORTEP representation of crystal structure of **1**.

The absolute configuration of **1** was assigned as 1R,5S,7S,8S, 9R,10R,12S,13S,15S,16S,17R,19S,20S,22S,23R based on the conservation of the absolute stereochemistries of the western

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hemisphere of SNTs. Subsequently, time-dependent density-functional theory (TDDFT) method[10] at the CAM-B3LYP/TZVP level in the gas phase and in methanol with PCM was employed to simulate the electronic circular dichroism (ECD) spectra of **1**. Close agreement was found in the calculated and experimental curves (Figure 5). Molecular orbital (MO) analysis (Figure S3, Supporting Information) at the same level in methanol revealed that the weak Cotton effect (CE) in the experimental curve at 301 nm could be ascribed to the negative rotatory strength at 288.6 nm that was generated by the electronic transitions from MO143 to MO145 in the cyclopropyl moiety and the carbonyl group; the experimental positive CE at 248 nm could be assigned to the positive rotatory strength at 235.6 nm that was contributed by the electronic transitions from MO137 to MO144; the diagnostic negative CE at 213 nm could be ascribed to the negative rotatory strength at 209.6 nm from MO139 to MO144 involving a $\pi \rightarrow \pi^*$ transition of in the α,β-unsaturated-γ-lactone moiety. Therefore, the absolute configuration of **1** was defined to be 1*R*,5*S*,7*S*,8*S*,9*R*,10*R*,12*S*,13*S*,15*S*,16*S*,17*R*,19*S*,20*S*,22*S*,23*R*.

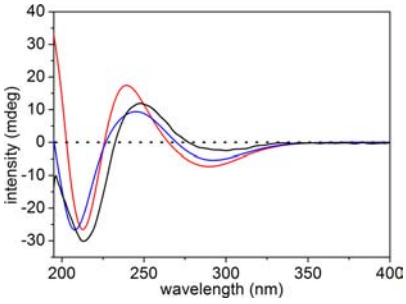
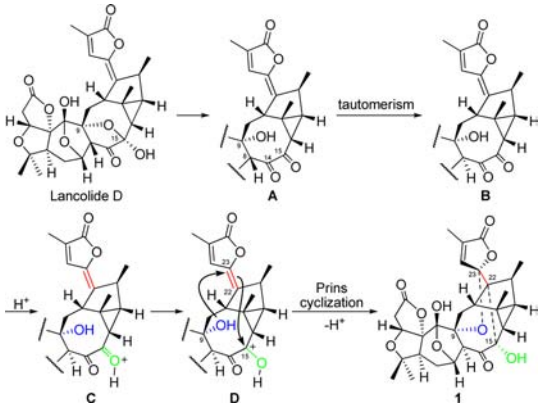


Figure 5. Experimental and calculated ECD spectra of **1** (black, experimentally observed in methanol; blue, calculated in the gas phase; red, calculated in methanol).

In the structural elucidation of lancolide E (**1**), we became aware of a biogenetic relationship between lancolides D and E (**1**) (Scheme 1). It is likely that a cleavage of the hemiketal in lancolide D affords intermediate A that forms intermediate B, a C-8 epimer, via a keto−enol tautomerism. A subsequent Prins cyclization catalyzed by organic acids[11] of intermediate B is as a key step to constructing the C-15/C-22 carbon bond and the oxa bridge between C-9 and C-23. Due to sample quantity limitations, bioactivity evaluation of **1** was not feasible.

Scheme 1. Proposed Biogenetic Pathway for 1



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03334.

Detailed experimental procedures, physical−chemical properties, 1D and 2D NMR, MS, UV, and ECD spectra, and computational data of compound **1** (PDF)

X-ray data of **1** (CIF)

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Notes

The authors declare no competing financial interest.

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Organic LETTERS

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Cobalt-Catalyzed Carbonylative Cyclization of Pyridinyl Diazoacetates for the Synthesis of Pyridoisoquinolinones

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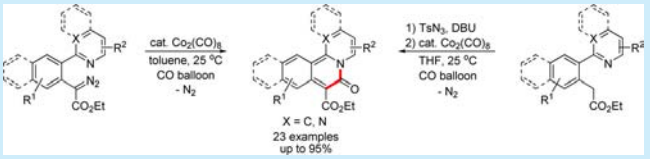
Supporting Information

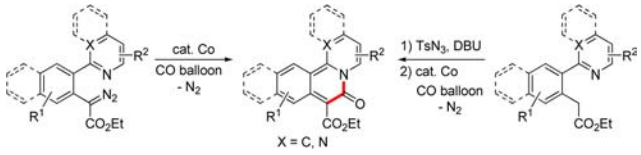
ABSTRACT: Dicobalt octacarbonyl-catalyzed carbonylative cyclization of pyridinyl diazoacetates is developed for the synthesis of pyridoisoquinolinones under mild conditions (room temperature) in a carbon monoxide atmosphere. Moreover, a synthetic method for various pyridoisoquinolinones from ethylpyridinyl aryl acetates is demonstrated through diazotization using TsN_3 and DBU followed by Co-catalyzed carbonylation to generate ketene intermediates, which can subsequently undergo intramolecular cyclization under mild conditions in a carbon monoxide atmosphere in a semi-one-pot fashion.



Transition-metal-catalyzed carbonylation using carbon monoxide is one of the significant methods to prepare a variety of carbonyl compounds.[1] In particular, Pd-catalyzed carbonylative cross-coupling is an important method for the synthesis of a large number of compounds having the carbonyl functional group. However, the carbonylation of metal carbenes is rarely reported due to the limitations of substrate scope and harsh conditions, such as the high pressure of carbon monoxide, high reaction temperature, and stoichiometric processes. Moreover, because the carbonylation of metal carbene furnishes ketenes, which are very important in organic synthesis, the development of streamlined synthetic methods to overcome these shortcomings is still highly attractive and challenging.

Recently, Ungváry[2] and Wang[3] reported the transition-metal-catalyzed carbonylation of metal carbenes derived from diazo compounds with carbon monoxide for the preparation of ketenes and the intermolecular addition of ketenes with nucleophiles such as alcohols and amines, resulting in the formation of a variety of carbonyl derivatives.[4] However, we are not aware of any reported examples of the transition-metal-catalyzed carbonylation of diazo compounds and sequential intramolecular cyclization. More recently, we demonstrated a robust synthetic method for a wide range of pyridoisoindoles from pyridinyl aryl diazoacetates under Cu-catalytic or metal-free conditions.[5] Inspired by our previous work, we envisioned that treatment of diazoacetate possessing a nucleophilic pyridinyl moiety with a transition-metal carbonyl catalyst, under a CO atmosphere or not, would result in the carbonylation of metal carbene to afford pyridinyl aryl-substituted ketene, which can be applicable in intramolecular cyclization reactions to provide pyridoisoquinolinones.[6] Herein, we report dicobalt octacarbonyl catalyzed carbonylative cyclization of pyridinyl diazoacetates for the synthesis of pyridoisoquinolinones under mild conditions (room temperature) in a carbon monoxide atmosphere (Scheme 1).

Scheme 1. Co-Catalyzed Carbonylative Cyclization for the Synthesis of Pyridoisoquinolinones



Moreover, a useful synthetic method for a number of pyridoisoquinolinones from pyridinyl aryl acetates is demonstrated through diazotization using TsN_3 and DBU followed by Co-catalyzed carbonylation and the intramolecular cyclization of ketene with a tethering pyridinyl moiety under mild conditions in a carbon monoxide atmosphere in a semi-one-pot fashion.[7]

First, we investigated the scope and limitation of transition-metal carbonyl catalyzed carbonylative cyclization of pyridinylaryl diazoacetate **1a** as the substrate under a CO atmosphere (Table 1). A variety of pyridinylaryl diazoacetates were easily prepared from Rh-catalyzed alkylation[8] of 2-arylpyridines with Meldrum's acid and the diazotization reaction[9] of the corresponding pyridinyl aryl acetates (see the Supporting Information). Although $Cr(CO)_6$, $Mo(CO)_6$, $W(CO)_6$, and $Fe_3(CO)_{12}$ (2.0 mol % each) were completely ineffective (entries 1−4), $Co_2(CO)_8$ (2.0 mol %) successfully produced pyridoisoquinolinone in 95% isolated yield in toluene at 25 °C under a CO atmosphere after CO bubbling for 2 min (entry 5). When $Co_2(CO)_8$-catalyzed carbonylative cyclization was carried out under a CO atmosphere without CO bubbling or under a N_2 atmosphere without CO bubbling, the cyclization reaction did not go to completion, and the desired product **2a** was obtained in 61% and 19% yields, respectively, along with

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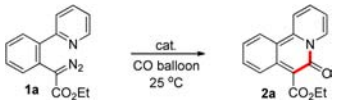
Table 1. Reaction Optimization[a]



entry	cat. (mol %)	solvent	time (h)	yield[b] (%)
1	$Cr(CO)_6$ (2.0)	toluene	12	0
2	$Mo(CO)_6$ (2.0)	toluene	12	0
3	$W(CO)_6$ (2.0)	toluene	12	0
4	$Fe_3(CO)_{12}$ (2.0)	toluene	12	0
5	$Co_2(CO)_8$ (2.0)	toluene	5	97 (95)[c]
6[d]	$Co_2(CO)_8$ (2.0)	toluene	5	61 (35)[e]
7[f]	$Co_2(CO)_8$ (2.0)	toluene	5	19 (70)[e]
8	$Co_2(CO)_8$ (1.0)	toluene	24	56
9	$Co_2(CO)_8$ (2.0)	DCE	12	57
10	$Co_2(CO)_8$ (2.0)	CH_3CN	12	30
11	$Co_2(CO)_8$ (2.0)	THF	5	88

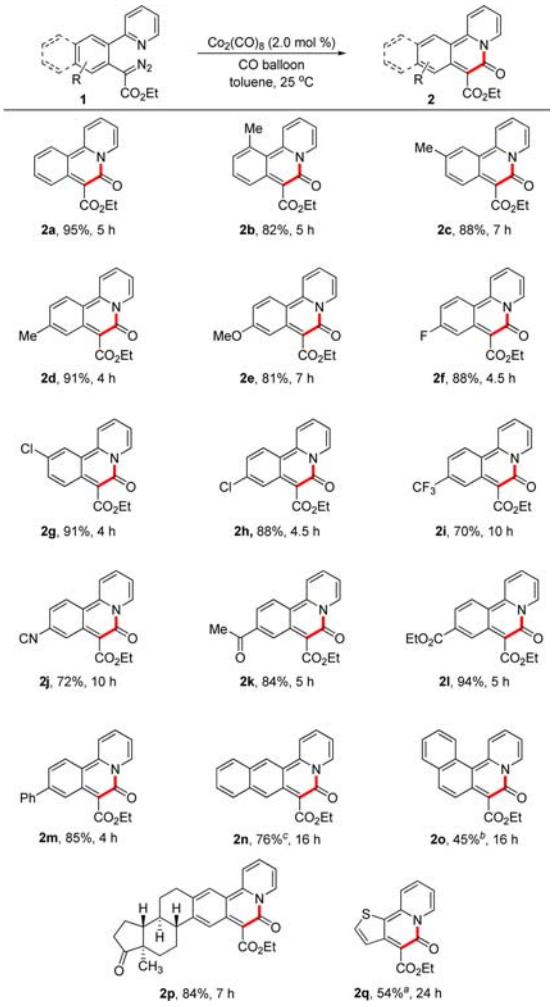
[a]Reactions were carried out with **1a** (0.2 mmol) and metal carbonyl (1.0–2.0 mol %) in solvent (1.25 mL) at 25 °C. After CO bubbling for 2 min, the reaction mixture was stirred under CO atmosphere. [b]NMR yield using dibromomethane as an internal standard. [c]Isolated yield. [d]Under CO atmosphere without CO bubbling. [e]Recovery yield of **1a**. [f]Under N_2 atmosphere without CO bubbling.

recovery of **1a** (entries 6 and 7). These results indicate that the CO bubbling and atmosphere are essential for the carbonylative cyclization. The use of 1.0 mol % of $Co_2(CO)_8$ gave inferior results compared to 2.0 mol % (Table 1, entries 5 and 8). Toluene gave the best result among the solvents (DCE, CH_3CN, and THF; entries 9–11). Screening of a series of Pd and Rh catalysts did not give satisfactory results (see the Supporting Information).

Next, the scope of substrates in this carbonylative cyclization reaction was examined with pyridinyl aryl diazoacetates (**1**) possessing a wide range of substituents on the aryl groups under the optimal conditions (Scheme 2). Electronic modification of the substituents at the aryl moiety of **1** had little effect on the reaction efficiency. The substrates possessing both electron-donating groups (R = Me and MeO) and electron-withdrawing groups (R = F, Cl, CF_3, CN, CH_3CO, and EtO_2C) on the aryl moiety were well tolerated under the reaction conditions and provided the corresponding products **2b–l** in good to excellent yields ranging from 70% to 94%. When 2,3-naphthyl-substituted pyridinyl diazoacetate (**1n**) underwent the Co-catalyzed carbonylative cyclization, the desired benzopyridoisoquinolinone **2n** was produced in 76% yield. However, 1,2-naphthyl-substituted pyridinyl diazoacetate (**1o**) was cyclized to **2o** in 45% yield. This decreased efficiency was attributed to the steric congestion of the bent polycyclic aromatic compound. When pyridinyl diazoacetate (**1p**) possessing an estrone moiety was employed as the substrate, the carbonylative cyclization product **2p** was satisfactorily obtained in 84% yield. Moreover, the arene is not limited to a benzene skeleton. Heteroaromatic diazoacetate **1q** obtained from (thiophene-2-yl)pyridine was applied to the present Co-catalyzed carbonylative cyclization, affording **2q** in 54% yield.

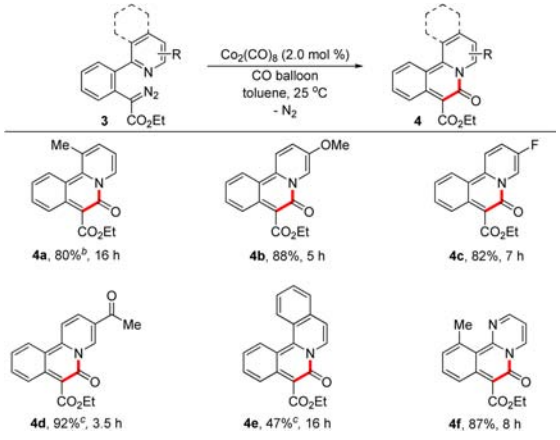
In addition, modification of a wide range of substituents (R = Me, MeO, F, and CH_3CO) on the pyridine moiety was tolerated without notably affecting the catalytic effectiveness (Scheme 3, **4a–d**). Diazoacetate (**3e**) possessing an isoquinoline moiety showed moderate reactivity in this transformation due to the steric congestion arising from the intramolecular cyclization. Pyrimidine-substituted diazoacetate (**3f**) is appli-

Scheme 2. Scope of Aryl Groups[a]



[a]Reactions were carried out with **1** (0.2 mmol, 1.0 equiv) and $Co_2(CO)_8$ (2.0 mol %) in toluene (1.25 mL) at 25 °C under CO atmosphere after CO bubbling. [b]$Co_2(CO)_8$ (5.0 mol %) was used. [c]$Co_2(CO)_8$ (15.0 mol %) was used.

Scheme 3. Scope of Pyridyl Groups[a]



[a]Reactions were carried out with **3** (0.2 mmol) and $Co_2(CO)_8$ (2.0 mol %) in toluene (1.25 mL) at 25 °C under CO atmosphere after CO bubbling. [b]$Co_2(CO)_8$ (15.0 mol %) was used. [c]$Co_2(CO)_8$ (5.0 mol %) was used.

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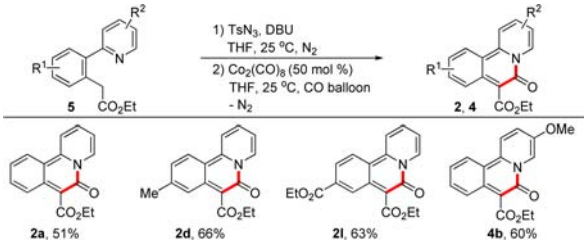
cable to the present transformation, providing the corresponding cyclic product (**4f**) in 87% yield.

Subsequently, because pyridinyl aryl diazoacetates (**1** and **3**) were easily obtained from the diazotization reaction of the corresponding pyridinyl aryl acetates,[9] we envisioned that this carbonylative cyclization for the synthesis of pyridoisoquinolinones could be achieved directly through diazotization followed by the Co-catalyzed carbonylative cyclization from pyridinyl aryl acetates in a one-pot fashion (Scheme 4). First, after

Scheme 4. Synthesis of Pyridoisoquinolinones from Pyridinyl Aryl Esters in a Semi-One-Pot Fashion[a]



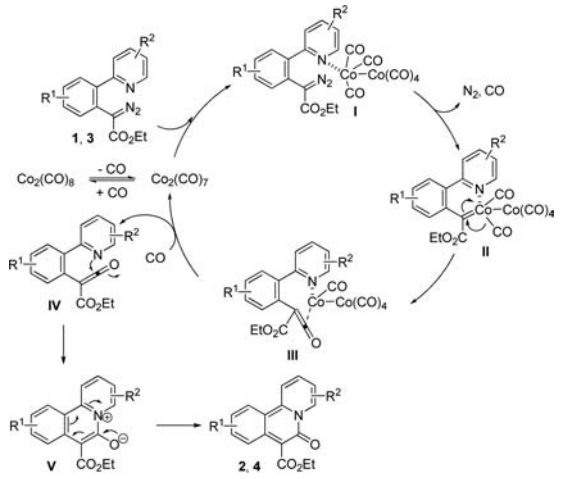
[a]Reactions were carried out with **5** (0.2 mmol, 1.0 equiv), TsN_3 (0.4 mmol), and DBU (0.4 mmol) in THF at 25 °C for 12 h. After the reaction mixture was filtered through a short pad of silica, $Co_2(CO)_8$ (50.0 mol %) in THF was added to filtrate at 25 °C for 6 h under CO atmosphere.

pyridinyl aryl diazoacetate **5a** was treated with TsN_3 and DBU in THF at 25 °C for 12 h, $Co_2(CO)_8$ catalyst (2.0 mol %) was added to the reaction mixture for carbonylative cyclization. However, because the remaining DBU in the reaction mixture deactivated the Co catalyst, the corresponding cyclic product **2a** was not produced. Accordingly, we attempted the synthesis of the pyridoisoquinolinone (**2** and **4**) in a two-step, semi-one-pot procedure.[7] After pyridinyl aryl diazoacetate **5a** was treated with TsN_3 and DBU in THF for 12 h, the reaction mixture was filtered through a short pad of silica, and the filtrate was used as the starting material in the following Co-catalyzed carbonylative cyclization at 25 °C under a CO atmosphere, leading to the formation of **2a** in 51% yield. Likewise, pyridinyl aryl diazoacetates (**5**) possessing a variety of substituents (R^1 = Me and EtO_2C, R^2 = MeO) on the aryl and pyridinyl groups are applicable in this modified method, providing the corresponding pyridoisoquinolinones (**2d**, **2l**, and **4b**) in good yields ranging from 60% to 63%.

Because pyridoisoquinolinones (**2** and **4**) are fluorescent, their optical properties in CH_2Cl_2 solution were examined (see the Supporting Information). The pyridoisoquinolinone fluorophores displayed Stokes shifts ranging from 41 to 75 units. The extinction coefficients were variable from 67264 to 245677 $M^{-1}\cdot cm^{-1}$. The pyridoisoquinolinone (**2q**) affords high quantum yields and extinction coefficients, which are an attractive property for biological probes.[6]

Although the mechanism of the present reaction has not been completely established, a feasible reaction pathway is illustrated in Scheme 5. Coordination of the cobalt catalyst to the nitrogen atom in pyridinyl diazoacetate **1** and **3** results in the formation of the intermediate **I**, which is converted to a cobalt ethoxycarbonyl carbene complex **II** through dinitrogen extrusion. Migration of a CO from the Co carbene **II** affords the metal-complexed ketene intermediate **III**, which is followed by decomplexation to furnish ethoxycarbonyl ketene **IV** with regeneration of the cobalt catalyst.[2a,b,j−l] Subsequent intra-

Scheme 5. Proposed Mechanism



molecular cyclization of the ketene group with the pyridinyl moiety in **IV** provides pyridinium enolate **V**, which is in resonance with pyridoisoquinolinone **2** and **4**. The elucidation of the detailed reaction mechanism must wait further study.

In conclusion, we have successfully developed a dicobalt octacarbonyl catalyzed carbonylative cyclization of pyridinyl diazoacetates for the synthesis of pyridoisoquinolinones under a carbon monoxide atmosphere. Moreover, a useful synthetic method for a wide range of pyridoisoquinolinones from pyridinyl aryl acetates has been demonstrated through diazotization using TsN_3 and DBU followed by Co-catalyzed carbonylation and intramolecular cyclization of ketene with a tethering pyridinyl moiety under a carbon monoxide atmosphere in a semi-one-pot procedure. These transformations are attractive due to the use of an inexpensive and commercially available Co catalyst and an easily accessible starting material and the release of harmless N_2 under mild conditions (room temperature).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03340.

Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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DEDICATION

This paper is dedicated to Professor Barry M. Trost (Stanford University) on the occasion of his 75th birthday.

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Organic LETTERS

Letter

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Iodine(III)-Mediated Oxidative Hydrolysis of Haloalkenes: Access to α-Halo Ketones by a Release-and-Catch Mechanism

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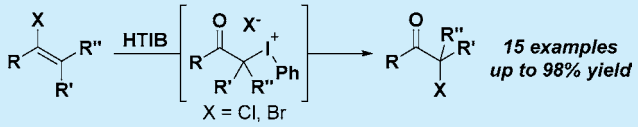
Supporting Information

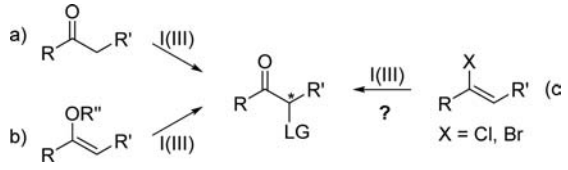
ABSTRACT: An unprecedented iodine(III)-mediated oxidative transposition of vinyl halides has been accomplished. The products obtained, α-halo ketones, are useful and polyvalent synthetic precursors. There are only a handful of reported examples of the direct conversion of vinyl halides to their corresponding α-halo carbonyl compounds. Insights into the mechanism and demonstration that this synthetic transformation can be done under enantioselective conditions are reported.



Although hypervalent iodine reagents have been known for over a century, they have recently become a subject of growing and keen interest in the field of chemistry.[1] In addition to being mild, selective, eco-friendly, and versatile oxidants, iodine(III) and iodine(V) reagents have also proven their utility in performing synthetically relevant transformations, such as phenolic dearomatizations[2] and various other oxidative rearrangements.[3] They can also act as safer alternatives to some toxic metal-based oxidants, such as thallium.[4] Lately, there have been numerous efforts in the development of stereoselective methods involving these reagents.[5]

The iodine(III)-mediated synthesis of functionalized ketone derivatives has been a particularly active area of research.[6] This is not surprising considering the ubiquitous nature of α-functionalized ketones in natural and synthetic compounds. One particularly useful approach exploits iodine(III) chemistry to introduce by oxidation a leaving group at the α position of the carbonyl (Scheme 1a). If performed under enantioselective

Scheme 1. Concept of the Described Research



conditions, the resulting products are versatile chiral precursors for stereoselective synthesis. In this context, our group has been interested in the synthesis of chiral nonracemic α-tosyloxy ketone derivatives. For more than 15 years, the published methods involved the direct α-tosyloxylation of ketones.[7] Recently, we have raised the issue that the probable mechanism involved for the direct α-tosyloxylation of ketones could prevent achievement of high enantioselectivities.[8] In an effort to solve this issue, we have developed reaction conditions that have given access to the desired α-tosyloxy ketones from their corresponding enol esters (Scheme 1b, R″ = Ac), with unprecedented levels of enantioselectivities (up to 90% *ee*).[9]

We envisioned that other vinylic substrates having the same oxidation state as enol derivatives, such as vinyl halides, could thus serve as α-substituted ketone precursors (Scheme 1c). Only scarce examples are found in the literature for the direct conversion of vinyl halides to their corresponding α-halo ketone derivatives.[10] In analogy to α-tosyloxy ketones, the α-halo ketones families have the same versality and are common and useful building blocks in synthetic chemistry.[11]

Accessing these products from the vinyl halides family is particularly interesting in this regard, due to the numerous synthetic methods to access them from nonketonic precursors.[12] We report herein the oxidation of vinyl halides to their corresponding α-halo ketones in high yields and mild conditions.

To evaluate the reactivity of the described compound family, we elected to use vinyl halides **1a** and **1b**, derived from octanophenone, for the low volatilities of the substrates and final products. For the sake of simplicity, these substrates were obtained directly from the ketone.[13] The results of the optimization are described in Table 1. The reaction of **1a** with [hydroxy(tosyloxy)iodo]benzene (HTIB) did not result in the formation of the α-tosyloxy ketone product, but instead its chloro analog (**2a**). The formation of acid derivatives **3** in small amounts was observed as a consequence of 1,2-aryl migration. Isolated yields of **3** compounds could not be obtained due to their partial and continuous hydrolysis over the course of the purification by flash chromatography on silica gel.

The effect of adding $TsOH{\cdot}H_2O$ in increasing amounts was studied to determine if this additive could accelerate the reaction rate, as it was previously observed for the reaction of HTIB with enol esters.[14] It was found to furnish a great acceleration effect, while not affecting the relative **2a**/**3**

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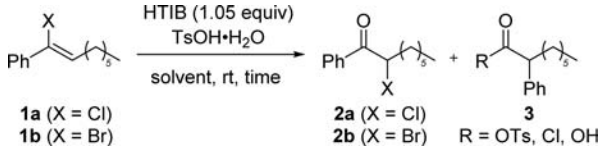
Table 1. Conditions Screening[a]



entry	TsOH (equiv)	solvent	time (h)	**2** [%][b]	**3** [%][c]
1	0	MeCN	20	69	15
2	0.1	MeCN	5	77	18
3	0.5	MeCN	2	79	21
4	1	MeCN	1.5	80	20
5	0.1	MeCN[d]	6	97	<2
6	0.1	MeCN/H_2O (1:1)	24	76	<2
7	0.1	H_2O	72	29	<2
8	0.1	CH_2Cl_2	48	68	20
9	0.1	CH_2Cl_2[d]	26	70	30
10	0.1	EtOAc	72	46	<2
11	0.1	THF	1	53	<2
12[e]	0.1	MeCN[d]	17	86	<2
13[e]	0.1	MeCN	17	98	<2

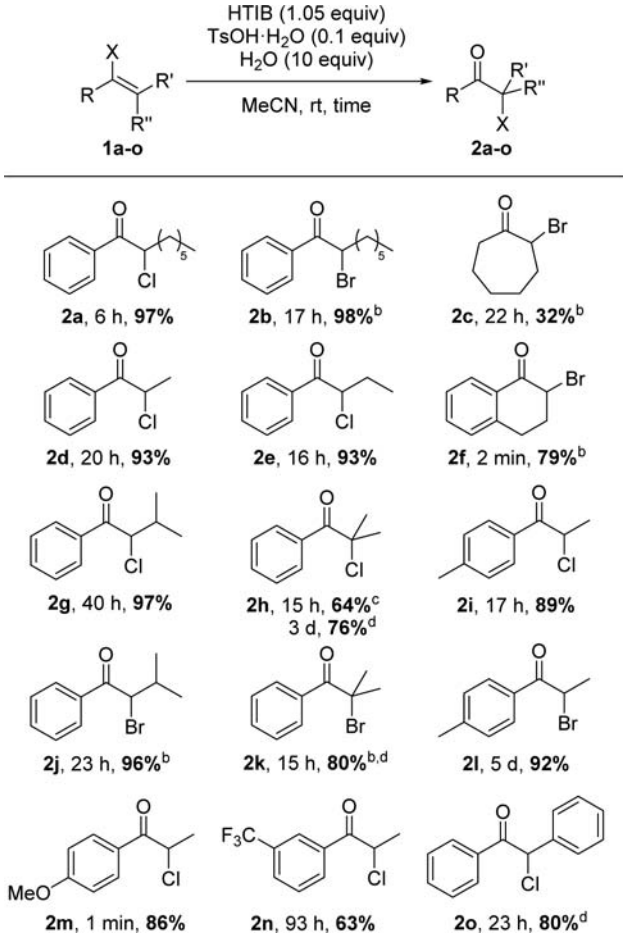
[a]Unless otherwise stated, **1a** was used. [b]Isolated yield. [c]Yield determined by ^{1}H NMR of the crude mixture, with respect to isolated **2**. [d]10 equiv of water were added to the reaction. [e]Reaction performed with **1b**.

formation ratio (entries 2–4). Since the concentration of TsOH increases as HTIB is reduced during the reaction process, a substoichiometric loading (0.1 equiv) of TsOH is sufficient to achieve noticeable overall acceleration, and was used for the remainder of the optimization. As hydrolysis is most probably involved in the reaction process, the effect of water was next evaluated. Addition of 10 equiv of water resulted in no acceleration, but in a very clean conversion of **1a** to **2a**, with no detectable aryl migration products **3** (entry 5). Attempts to perform the reaction in either equivolumic MeCN/water solution or directly in water resulted in lower yields of **2a**, but no observable formation of phenyl migration products (entries 6–7). Other solvents (entries 8–11) were tested, but only resulted in lower yields and side products formation. The addition of 10 equiv of water in dichloromethane did not prevent the formation of migration products **3**. The optimized conditions were evaluated on vinyl bromide **1b**; a lower yield and no migration products were observed (entry 12). The presence of the α-hydroxy ketone in the crude mixture suggested susceptibility of **2b** toward hydrolysis. The reaction was thus was performed without the addition of water; the α-bromo product **2b** was obtained in essentially quantitative yield, with no noticeable migration products (entry 13).

With these optimized conditions in hand, the scope of this new transformation was investigated with various vinyl chlorides and bromides. The results are summarized in Scheme 2. The transformation is efficient on styrene analogs (R = aromatic), with excellent yields in most cases. It is important to point out that it does however proceed with some success on fully aliphatic substituted vinyl bromide **1c**, affording product **2c** with 32% yield. Conversion of **1c** was complete, with the formation of numerous unidentified side products.

The method supports variation on the other portion of the styrene derivatives (R′, R″). For example, vinyl chloride and bromide **1g** and **1j**, respectively, were converted in almost quantitative yields to their respective α-halo ketone products.

Scheme 2. Reaction Scope[a]



[a]Isolated yields reported. [b]No water was added in the reaction. [c]Reaction performed at 55 °C. [d]Reaction performed at 40 °C.

The reaction can even proceed on tetrasubstituted vinyl halides (**1h** and **1k**), although higher reaction temperatures (40–55 °C) are required to obtain complete conversion. Cyclic vinyl bromide **1f** afforded the desired product **2f** in a very fast reaction. In the last three cases, the lower yield is attributed to partial formation of the enone products. These results are in stark contrast with the behavior observed for the corresponding enol ester analogs, which afforded mainly the formation of the corresponding enones in low yield.[13,14] The electronic properties of the aromatic group of the styrene derivatives greatly affect the reactivity. Vinyl halide **1m**, bearing a *p*-methoxy phenyl group, is converted almost instantly to product **2m**. The lower yield is attributed to numerous unidentified side products, but aryl migration products **3** are observed in higher quantities in the crude mixture. In contrast, almost 4 days of reaction are required to achieve complete conversion of substrate **1n**, bearing a *p*-trifluoromethyl phenyl group. The described methodology demonstrates a larger scope than the known methods to directly convert vinyl halides to α-halo ketones.

During the optimization process, the observation of the aryl migration products **3** prompted the investigation of the reaction mechanism. These products point toward a potential internal transposition of the halogen atom in the reaction process. To assess the feasibility of the latter versus an external halide attack manifold, a scrambling experiment was performed.

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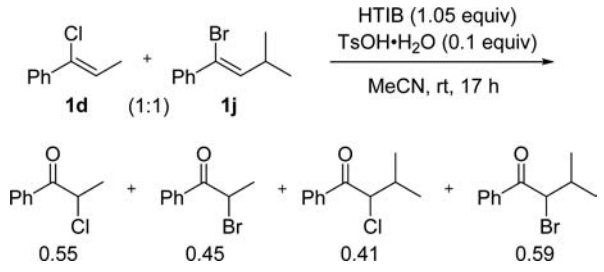
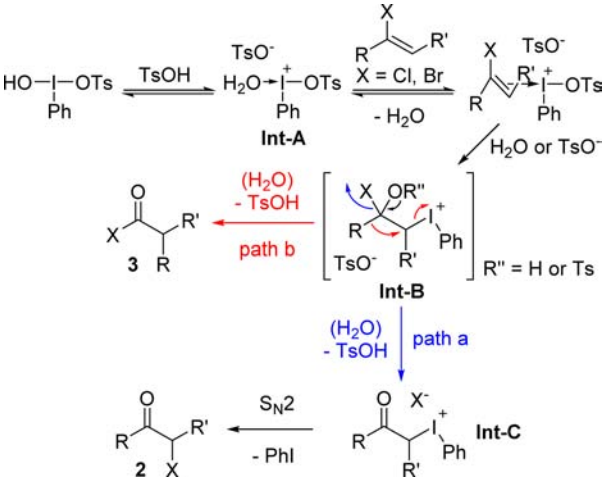
An equimolar mixture of substrates **1d** and **1j** was subjected to the optimized reaction conditions. The outcome is presented in Scheme 3.

Scheme 3. Scrambling Experiment



Starting from an equimolar mixture of vinyl halides **1d** and **1j**, the four possible α-halo ketone products were observed in almost equimolar quantities. The slight variance in ratio could be explained by either the different rates of conversion of **1d** and **1j** or competing mechanisms. It is clear however that the main reaction pathway does not consist of an internal halide migration, but an external halide attack. Addition of 10 equiv of water did not change noticeably the scrambling outcome. The possibility of the formation of the α-tosyloxy ketone product and subsequent S_N2 by a halide was infirmed; a displacement reaction with HCl in similar reaction conditions was found to be very slow (35% conversion in 36 h) in a control experiment.[13] Additionally, the α-tosyloxy ketone products were not observed in the crude reaction mixtures, even if the reactions were stopped prior to completion. With these experimental clues in hand, we proposed at the moment the mechanism illustrated in Scheme 4.

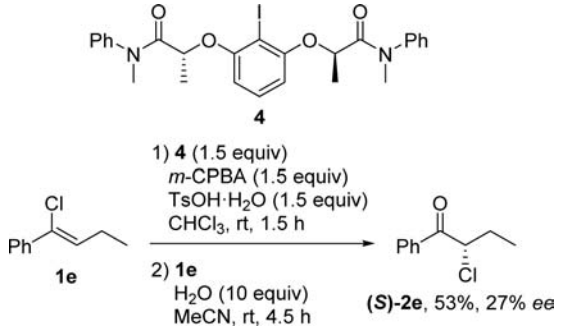
Scheme 4. Proposed Mechanism



As observed for the enol esters, the acceleration in the presence of TsOH is attributed to the formation of the phenyl tosyloxy iodonium intermediate **Int-A**, which is suggested to be the reactive iodine(III) species. Association of the vinyl halide and attack of a nucleophile (TsO^- or H_2O) lead to the formation of intermediate iodonium **Int-B**. At this point, depending on the rate of halide expulsion and migratory aptitude of the R group, there can be competing internal aryl migration through a semipinacolic displacement of PhI. In the case of vinyl chloride substrates, addition of water is necessary to accelerate expulsion of the chloride anion, through better solvation, and prevent formation of products **3**. In the case of vinyl bromides, the bromide anion is a better leaving group, and the competing aryl migration is not observed. No α-tosyloxy ketone is observed as the conjugate base of the strongest acid (HCl and HBr vs TsOH) will be the counterion of the iodonium intermediate **Int-C** and lead, by S_N2 substitution, to the final product. We refer to this pathway as a "release-and-catch" mechanism.

This unusual mechanism would have strong implications on the stereochemical aspects of this reaction. We thus tested preliminary enantioselective conditions to determine if this transformation would only furnish racemic products. The result is illustrated in Scheme 5.

Scheme 5. Enantioselective Conditions



While the enantioselectivity observed is modest, the fact that the product is not racemic is very promising for the development of an enantioselective variant of this new transformation. The sense of induction was found to be the same as that obtained with enol esters using chiral iodoarene **4**,[9] suggesting a similar reaction process. To the best of our knowledge, this is the first example of an enantioselective conversion of a prochiral vinyl halide to a corresponding chiral nonracemic α-halo ketone.

In summary, this new iodine(III)-mediated transformation shows high potential to serve as a very useful synthetic tool. This methodology will be of great interest for the synthetic community considering the variety of methods to synthesize vinyl halides and the utility of α-halo ketone derivatives. The results described herein also raise numerous interesting questions for the field of hypervalent iodine chemistry. It is clear from the control experiments and the results obtained under enantioselective conditions that several aspects of the mechanism will need to be investigated in order to fully exploit this highly promising process. Joint computational/experimental investigations are currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and NMR spectra for all new compounds (PDF)

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Notes

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Organic LETTERS

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Synthetic Studies on Amphirionin-5: Stereochemical Assignment/Reassignment of the C1−C9 Portion through Stereodivergent Synthesis

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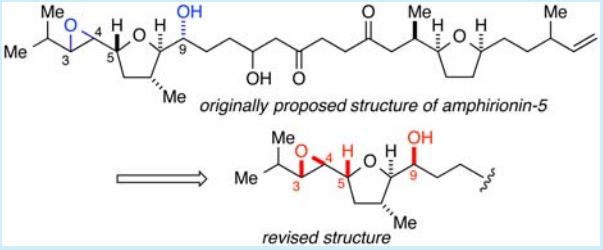
Supporting Information

ABSTRACT: Synthesis of four diastereomers of the C1−C12 fragment of amphirionin-5 has been achieved in a convergent and stereodivergent manner. Detailed comparison of the ^{1}H and ^{13}C NMR data of each compound with those reported for the natural product led to not only the stereochemical assignment of the relative configuration of the C4/C5 stereogenic centers but also reassignment of the proposed relative configuration at C9 of amphirionin-5.



Dinoflagellates of the genus *Amphidinium* are an enormously rich source of structurally diverse secondary metabolites of complex molecular architecture with potent biological activities. In particular, a number of potent cytotoxic macrolides, amphidinolides and iriomoteolides, have been isolated from *Amphidinium* sp. to date.[1] Recently, novel complex tetrahydrofuran-containing linear polyketide natural products with intriguing biological activities have been isolated from *Amphidinium* sp. by Tsuda and co-workers.[2−4] Of these, amphirionin-5 (**1**, Figure 1) was isolated in 2014 by Tsuda and co-workers from cultivated algal cells of the benthic dinoflagellate *Amphidinium* sp. (KCA09053 strain) collected off the coast of Iriomote Island, Okinawa Prefecture, Japan.[2] The gross structure and partial stereochemical assignment of amphirionin-5 was elucidated on the basis of 2D-NMR data and *J*-based configurational analysis[5] and found to consist of a linear polyketide skeleton containing two tetrahydrofuran rings, a *trans*-epoxide, and 11 stereogenic centers. However, despite extensive NMR studies, the relative configurations of the C4/C5 stereogenic centers and the stereochemistry of the two isolated stereogenic centers at C12 and C26 could not be resolved, and the absolute configuration has also remained undefined. These stereochemical problems can only be addressed efficiently using a synthetic approach.

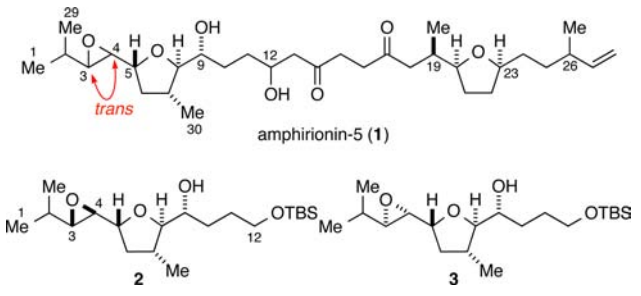


Figure 1. Structures of amphirionin-5 (**1**) and two possible diastereomeric C1−C12 fragments **2** and **3**.

Interestingly, this linear polyketide natural product was found to exhibit potent proliferation-promoting activity on murine bone marrow stromal ST-2 cells (282%) and murine osteoblastic MC3T3-E1 cells (320%) at a dose of 10 ng/mL, whereas it did not induce cellular differentiation or cellular morphological changes at a dose range of 0.001−1000 ng/mL and also exhibited no cytotoxicity at high doses (1−10 μg/mL).[2]

As part of our program toward the total synthesis and complete stereochemical assignment of amphirionin-5, we herein report the stereodivergent synthesis of four diastereomeric C1−C12 fragments and comparison of their NMR data with those reported for the natural product. This has led both to an assignment of the relative configuration of the C4/C5 stereogenic centers and a reassignment of the proposed relative configuration at C9 of amphirionin-5.

Our stereochemical-determination strategy for establishing the relative configuration of the C4/C5 stereogenic centers of amphirionin-5 relied on the synthesis of two possible diastereomers of the epoxide-containing C1−C12 fragments **2** and **3** (Figure 1). Comparison of their NMR spectroscopic data with those of the natural product would assign the relative configuration of C4/C5.[6−8] Our retrosynthetic plan for the C1−C12 fragments **2** and **3** is depicted in Scheme 1. We envisioned that the 2,5-*trans*-substituted tetrahydrofuran ring of **2** and **3** would be constructed through a domino Sharpless asymmetric dihydroxylation (SAD)[9]/stereospecific cyclization of mesylates **4** and **5**, respectively.[10] The two requisite diastereomeric epoxides **4** and **5** would be derived by branching from allylic alcohol **6** by Katsuki−Sharpless asymmetric epoxidation[11] using (+)- or

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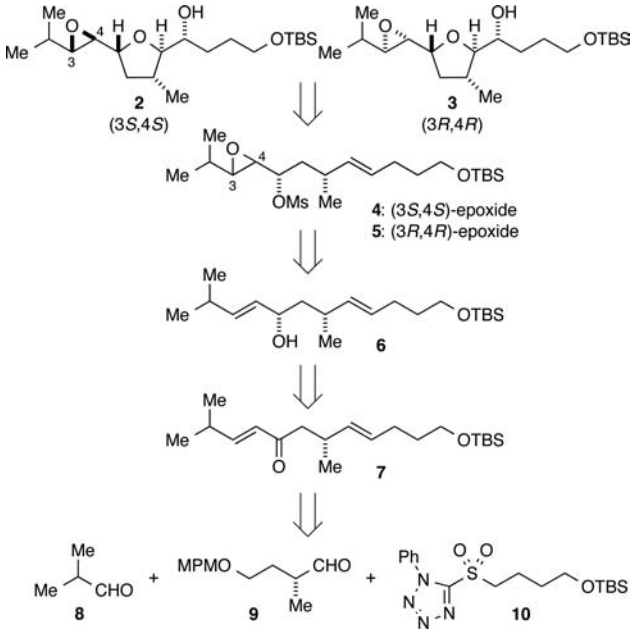
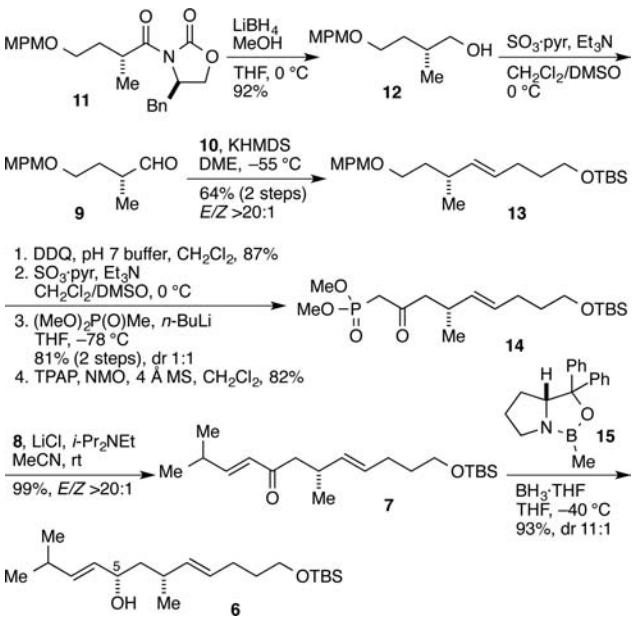
Scheme 1. Retrosynthesis of Two Diastereomeric C1−C12 Fragments 2 and 3



(−)-tartrate ester. Compound **6** would be accessed by means of Corey−Bakshi−Shibata (CBS) reduction[12] of enone **7**, which in turn would be assembled from three fragments, isobutyraldehyde (**8**), aldehyde **9**, and sulfone **10**, through Julia−Kocienski olefination[13] and Horner−Wadsworth−Emmons (HWE) reaction, in a convergent manner.

The synthesis of allylic alcohol **6** started with the known imide **11**.[14] Reductive removal of the chiral auxiliary in **11** with $LiBH_4$ (MeOH, THF, 0 °C)[15] afforded alcohol **12** in 92% yield (Scheme 2). Parikh−Doering oxidation[16] of **12** provided aldehyde **9**, which was then coupled with the known sulfone **10**[17] through Julia−Kocienski olefination (KHMDS, DME, −55 °C)[13] to give (*E*)-alkene **13** in 64% yield from alcohol **12** (*E*/*Z* > 20:1). The *p*-methoxyphenylmethyl (MPM) group of **13** was oxidatively removed with DDQ (87%), and the resultant primary alcohol was oxidized to the corresponding aldehyde. Treatment of the aldehyde with lithiated dimethyl methylphosphonate, followed by oxidation with tetra-*n*-propylammonium perruthenate (TPAP)/*N*-methylmorpholine *N*-oxide (NMO),[18] provided *β*-keto phosphonate **14** (66% yield for the three steps). HWE reaction of **14** with isobutyraldehyde (**8**) under Masamune−Roush conditions (*i*-Pr_2NEt, LiCl, MeCN)[19] led to (*E*)-enone **7** in 99% yield as a single stereoisomer (*E*/*Z* > 20:1). Finally, CBS reduction[12] of enone **7** using (*R*)-2-methyl-CBS-oxazaborolidine **15** provided the desired allylic alcohol **6** in 93% yield with an 11:1 diastereomer ratio.[20] The absolute configuration of the C5[21] stereogenic center was unambiguously established by a modified Mosher analysis.[22]

Scheme 2. Synthesis of Allylic Alcohol 6



Katsuki−Sharpless asymmetric epoxidation[11] of allylic alcohol **6** using (+)-diisopropyl tartrate (DIPT) as a chiral ligand delivered epoxy alcohol **16**[23] in 90% yield with high diastereoselectivity (dr ca. 23:1) (Scheme 3). Alcohol **16** was converted to the corresponding mesylate **4** (MsCl, Et_3N), which was then subjected to SAD using AD-mix-*β*.[9] Diastereoselective dihydroxylation and concomitant stereospecific cyclization proceeded smoothly to form a tetrahydrofuran ring, and the desired C1−C12 fragment **2** was obtained in 90% yield for the two steps. The 2,5-*trans* configuration of the tetrahydrofuran ring in **2** was confirmed by means of HMBC spectra and NOE data, and the absolute configuration of the C9 stereogenic center was unambiguously established by a modified Mosher analysis.[22,23]

The diastereomeric fragment **3** was prepared in a similar fashion from allylic alcohol **6** via epoxy alcohol **17** (Scheme 3). In this case, Katsuki−Sharpless asymmetric epoxidation of **6**[24] with (−)-DIPT is a typical "mismatched" pair[11b,c] and thus resulted in a 1.4:1 mixture of epoxides **17** and **16**, which were readily separated by flash column chromatography on silica gel. Epoxide **17** was advanced by employing the sequence described in the conversion of **16** to **2** to furnish **3** (86% yield, two steps).[23]

The ^1H and ^{13}C NMR chemical shifts in the C1−C9 region of the two diastereomeric C1−C12 fragments **2** and **3** were compared in detail with those of the corresponding moiety of the natural product.[25] As shown in Figure 2, the ^{13}C NMR chemical shifts in the C1−C6 region of fragment **2** matched with those reported for the natural product within ±0.7 ppm, while the diastereomer **3** displayed obviously different chemical shifts. In particular, the observed ^{13}C NMR chemical shifts for C5 and C6 of **3** distinctively deviated from those of the natural product ($\Delta\delta$ > 1.0 ppm). These results strongly suggested that natural amphirionin-5 has the (3*S**,4*S**,5*R**)-configuration shown for structure **2**. In contrast, there were large and similar discrepancies in the ^{13}C NMR chemical shifts for C7, C9, and C30 in the right-hand region of both compounds **2** and **3**. From these significant deviations in the NMR data between the synthetic fragments **2**/**3** and the natural product, we inferred that the C9 stereogenic center of amphirionin-5 might be misassigned and that the most likely configuration of the C1−C9 portion of amphirionin-5 is represented by the revised structure **18** (see Scheme 4).

Thus, inversion of the C9 hydroxy group of **2** and **3** was performed using modified Mitsunobu conditions (*p*-$NO_2C_6H_4CO_2H$, Ph_3P, diethyl azodicarboxylate (DEAD), THF)[26] followed by methanolysis (K_2CO_3, MeOH) to afford alcohols **18** and **19**, respectively, as shown in Scheme 4. Their NMR data were again compared with those of the natural product (Figure 3). Clearly, the ^{13}C NMR chemical shifts in the C1−C9 region of diastereomer **18** were virtually identical to

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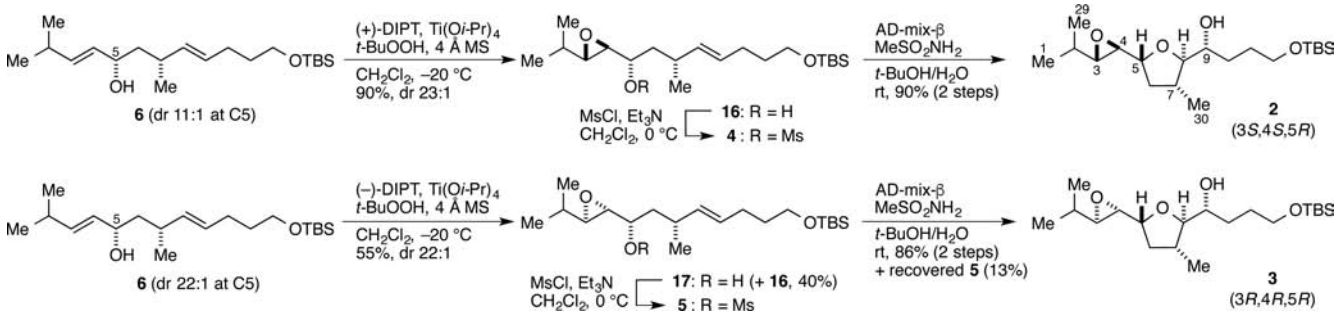
Scheme 3. Synthesis of the Diastereomeric C1−C12 Fragments 2 and 3



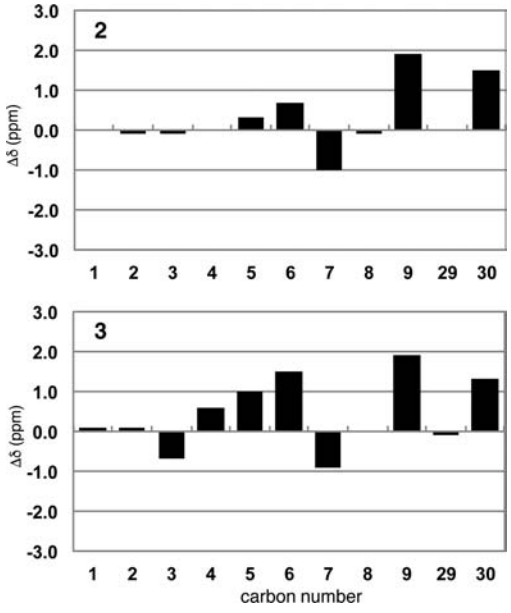


Figure 2. Differences in ^{13}C NMR chemical shifts between amphirionin-5 (125 MHz) and synthetic fragments **2** and **3** (150 MHz). $\Delta\delta = \delta$ (natural product) − δ (synthetic fragment) in ppm ($CDCl_3$).

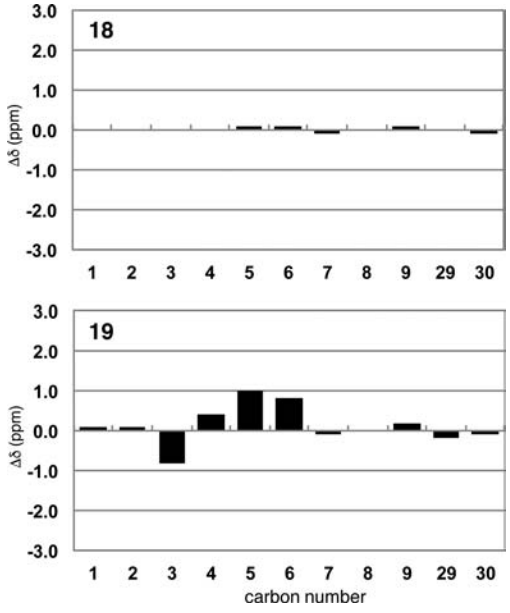
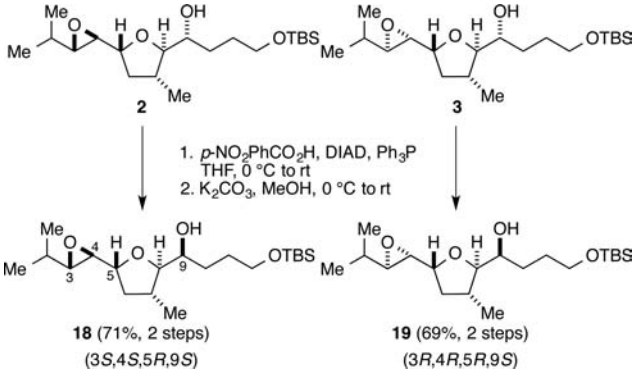


Figure 3. Differences in ^{13}C NMR chemical shifts between amphirionin-5 (125 MHz) and synthetic fragments **18** and **19** (150 MHz). $\Delta\delta = \delta$ (natural product) − δ (synthetic fragment) in ppm ($CDCl_3$).

Scheme 4. Synthesis of Diastereomers 18 and 19



those reported for the natural product.[25] In contrast, as with the case of compound **3**, distinct differences were observed in the ^{13}C NMR chemical shifts of the diastereomer **19** and the natural product in the C3−C6 region. Furthermore, $^3J_{H,H}$ data of the C1−C9 portion of **18** correspond well to the data of amphirionin-5.[25] These results convincingly defined the relative configuration of the C1−C9 portion of amphirionin-5 as that represented by structure **18** with the (3*S**,4*S**,5*R**,9*S**)-stereochemistry.

In conclusion, four diastereomers C1−C12 fragments of amphirionin-5 have been synthesized in a stereodivergent manner. The key features of the synthesis route include (1) convergent synthesis of the common intermediary allylic alcohol by employing Julia−Kocienski olefination, Horner−Wadsworth−Emmons reaction, and Corey−Bakshi−Shibata reduction and (2) efficient construction of the 2,5-*trans*-substituted tetrahydrofuran ring by a domino Sharpless asymmetric dihydroxylation/stereospecific cyclization. Comparison of the NMR data of the four diastereomers with those of the natural product allowed not only assignment of the relative configuration of the C4/C5 stereogenic centers but also reassignment of the proposed configuration at C9 of amphirionin-5. Further studies aimed at the complete stereochemical assignment and total synthesis of amphirionin-5 are underway 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.5b03346.

Experimental procedures, characterization data for all new compounds, stereochemical assignments for selected compounds, comparison of the NMR data of compounds

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2, **3**, **18**, and **19** with the data of amphirionin-5, and ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(25) See the Supporting Information for details.

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Letter

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Asymmetric α,γ-Regioselective [3 + 3] Formal Cycloadditions of α,β-Unsaturated Aldehydes via Cascade Dienamine−Dienamine Catalysis

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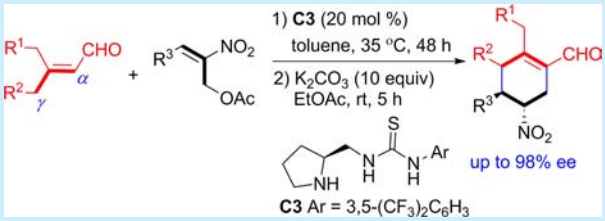
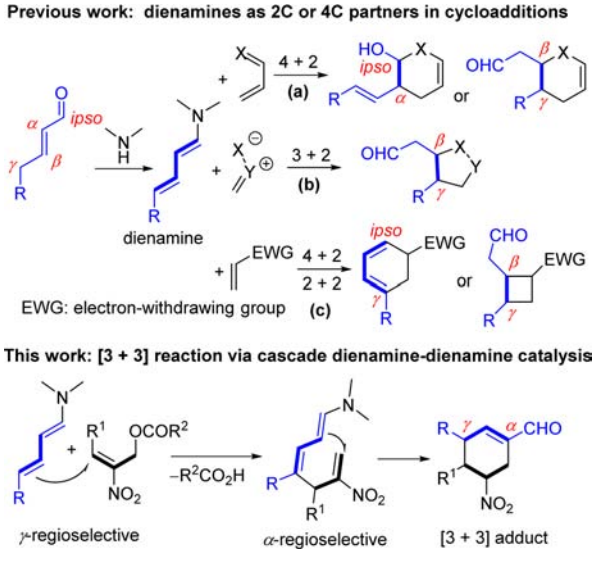
Supporting Information

ABSTRACT: Asymmetric α,γ-regioselective [3 + 3] formal cycloadditions of α,β-unsaturated aldehydes and 2-nitroallylic acetates have been developed for the first time. These reactions proceeded through a domino Michael addition−Michael addition sequence via an unusual cascade dienamine−dienamine catalysis of a chiral secondary amine, and multifunctional cyclohexene derivatives were generally constructed in moderate yields with excellent stereoselectivity after simple treatment with K_2CO_3.



α,β-Unsaturated aldehydes are readily available bifunctional starting materials and have been extensively utilized in a variety of catalytic reactions. In particular, they can form iminium ions with lower LUMO energy in the presence of an amine catalyst; thus, a number of α,β- and *ipso*,β-regioselective pericyclic or stepwise cycloaddition reactions have been fruitfully developed.[1] On the other hand, the γ-CH becomes more acidic when the iminium ions are formed and can be removed generating the corresponding HOMO-raised dienamine species, which could facilitate more versatile regioselective cycloaddition reactions with diverse electrophilic reagents.[2] As outlined in Scheme 1, both *ipso*,α- and β,γ-regioselective inverse-electron-demand Diels−Alder cycloaddition reactions have been realized by combining in situ generated dienamines with electron-deficient dienes (path a).[3] In contrast to α,β-regioselective pericyclic 1,3-dipolar cyclioadditions,[4] a β,γ-regioselective formal [3 + 2] reaction could occur between the dienamines and electrophilic 1,3-dipoles (path b).[5] Moreover, the dienamines could perform as electron-rich dienes in *ipso*,γ-regioselective normal-electron-demand Diels−Alder-type reactions with activated alkenes, producing 1,3-cyclohexadiene scaffolds.[6] In addition, a few β,γ-regioselective [2 + 2] cycloadditions to access cyclobutanes have also been presented via cascade dienamine−iminium catalysis (path c).[7,8]

Scheme 1. Diverse Cycloaddition Reactions via Dienamine Catalysis



The above-mentioned examples demonstrated that the dienamine species from α,β-unsaturated aldehydes have multiple reactive sites, which supply high potential in developing diverse regioselective cycloaddition reactions. Nevertheless, it has rarely been reported that such dienamines could serve as α,γ-regioselective 3C partners for constructing cyclic skeletons.[9] In fact, the dienamine intermediates possess two nucleophilic α- and γ-sites,[10] thus an α,γ-regioselective [3 + 3] formal cycloaddition[11] reaction would be expected when assembled with suitable 1,3-biselectrophilic substances via an unusual cascade dienemine−dienamine catalytic addition sequence.[12] We envisaged that 2-nitroallylic acylates[13] might be the model components, as the initial Michael addition could efficiently generate the required second acceptors through the elimination of a molecule of acid, favoring the subsequent Michael addition to furnish the cyclohexene structures (Scheme 1).[14]

Although a [2 + 2] cycloaddition to access a cyclobutane has been previously reported between 2-hydroxymethylnitrostyrene and α,β-unsaturated aldehyde via dienamine catalysis,[7b] it was

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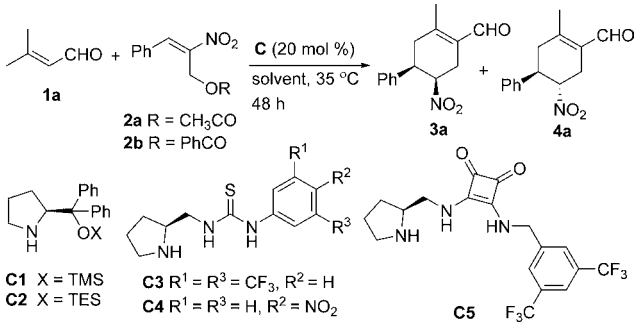
found that the reaction of the corresponding acetate **2a** and 3-methylcrotonaldehyde **1a** proceeded in a different pattern in toluene by the catalysis of chiral amine **C1** and benzoic acid **A1**. The desired α,γ-regioselective [3 + 3] formal cycloaddition occurred smoothly through the above-mentioned cascade catalysis, producing *cis*-product **3a** and its *trans*-diastereomer **4a** in a low ratio (2:1) due to the poor diastereoctontrol in the protonation step. Both diastereomers had the same ee value (85%), indicating that the enantiocontrol was determined in the first γ-regioselective Michael addition step. The yield was fair because a few unidentified byproducts were also observed (Table 1, entry 1). Comparable results were obtained by using

Table 1. Screening Studies of [3 + 3] Formal Cycloaddition of Enal 1a and 2-Nitroallylic Acetate 2a[a]



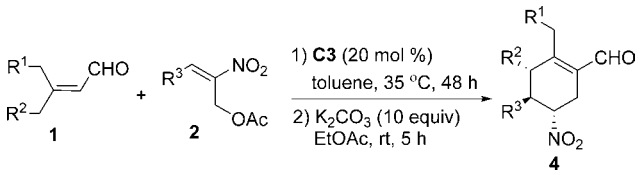
entry	cat.	acid	solvent	yield/%[b]	ee/%[c]
1	**C1**	BA	toluene	49	85
2	**C1**	BA	*o*-xylene	45	81
3	**C1**	BA	mesitylene	46	86
4	**C1**	BA	DCM	42	48
5	**C1**	Me_3BA	mesitylene	45	88
6	**C2**	Me_3BA	mesitylene	45	90
7	**C3**	Me_3BA	mesitylene	44	97
8[d]	**C3**	Me_3BA	mesitylene	45	92
9[e]	**C3**	Me_3BA	mesitylene	45	96
10	**C3**	–	mesitylene	58	98
11	**C4**	–	mesitylene	72	92
12	**C5**	–	mesitylene	66	94
13	**C3**	–	toluene	68	97

[a]Unless noted otherwise, reactions were performed with enal **1a** (0.2 mmol), acetate **2a** (0.1 mmol), amine **C** (20 mol %), and acid **A** (20 mol %) in solvent (1.0 mL) at 35 °C for 48 h. [b]Combined yield of isolated diastereomers; dr values around 2:1 to 2.5:1 by ^{1}H NMR analysis. [c]Determined by HPLC analysis on chiral stationary phase (for major *cis*-**3a**). [d]**2b** was used. [e]NaOAc (0.1 mmol) was added.

other aromatic solvents (entries 2 and 3), but the enantioselectivity was reduced significantly in DCM (entry 4). It was found that using bulkier 2,4,6-trimethylbenzoic acid (Me_3BA, entry 5) or amine **C2** (entry 6) could slightly improve the enantiocontrol in mesitylene. An excellent ee value was attained by the aid of amine **C3** with a bifunctional thiourea group,[15] though the yield was still unsatisfactory (entry 7). In addition, using benzoate **2b** as the substrate could not improve the yield (entry 8). As AcOH would be generated, the attempt to enhance the reaction efficiency by adding some AcONa to the mixture still resulted in no success (entry 9). The reaction proceeded more efficiently without any additive, retaining remarkable enantioselectivity (entry 10). Thiourea **C4** and squaramide **C5** were investigated, giving better yields but with slightly reduced enantioselectivity (entries 11 and 12). Finally, a comparable yield with an excellent ee value was produced in toluene in the presence of bifunctional **C3**, but still with a similarly low dr value (entry 13, **3a**:**4a** = 2.5:1).

As a mixture of diastereomers with low ratios was always obtained in the asymmetric [3 + 3] formal cycloadditions, we treated the diastereomers with diverse bases in order to epimerize the chiral center adjacent to the NO_2 group. It was found that the major *cis*-**3a** could be efficiently converted to *trans*-**4a** in EtOAc in the presence of excess K_2CO_3 at ambient temperature;[16] thus, we can smoothly isolate the pure *trans*-diastereomer **4a** in a moderate yield in two steps (Table 2, entry 1). The similar results could be smoothly obtained at a larger scale (data in parentheses). As a consequence, we explored the substrate scope and limitations through a sequential [3 + 3] formal cycloaddition and epimerization process. The results are summarized in Table 2. First, a number of 2-nitroallylic acetates with diverse substitutions were explored in the reactions with 3-methylcrotonaldehyde **1a**. In general, the substrates with either electron-withdrawing or -donating aryl groups could be well tolerated, affording the corresponding *trans*-products **4b**–**4j** in moderate yields with excellent enantioselectivity after epimerization treatment (Table 2, entries 2–10). 1-Naphthyl, heteroaryl, and 2-styryl-substituted ones could be smoothly utilized, and products **4k**–

Table 2. Substrate Scope and Limitations of [3 + 3] Formal Cycloadditions[a]



entry	R^1, R^2	R^3	yield/%[b]	ee/%[c]
1	H, H	Ph	**4a**, 56 (55)	97 (96)[d]
2	H, H	4-FC_6H_4	**4b**, 52	97
3	H, H	2-ClC_6H_4	**4c**, 54	98
4	H, H	3-BrC_6H_4	**4d**, 54	97
5	H, H	4-BrC_6H_4	**4e**, 53	95
6	H, H	2-F-4-BrC_6H_3	**4f**, 54	97
7	H, H	3,4-$Cl_2C_6H_3$	**4g**, 61	97
8	H, H	3-MeC_6H_4	**4h**, 54	91
9	H, H	4-MeC_6H_4	**4i**, 51	96
10	H, H	4-$MeOC_6H_4$	**4j**, 56	97
11	H, H	1-naphthyl	**4k**, 51	95
12	H, H	2-furyl	**4l**, 53	94[e]
13	H, H	2-thienyl	**4m**, 52	94
14	H, H	2-styryl	**4n**, 52	95
15	H, H	chexyl	**4o**, 41	88
16	H, Me	3,4-$Cl_2C_6H_3$	**4p**, 56	96
17	H, Et	3,4-$Cl_2C_6H_3$	**4q**, 43	96
18	$-(CH_2)_2-$	3,4-$Cl_2C_6H_3$	**4r**, 44	97
19	$-(CH_2)_3-$	3,4-$Cl_2C_6H_3$	**4s**, 51	95

[a]Unless noted otherwise, reactions were performed with enal **1** (0.2 mmol), 2-nitroallylic acetate **2** (0.1 mmol), amine **C3** (20 mol %) in toluene (1.0 mL) at 35 °C for 48 h. Then the isolated diastereomers were treated with excess K_2CO_3 in EtOAc at rt for 5 h. [b]Yield of isolated pure diastereomer for two steps. [c]Determined by HPLC analysis on chiral stationary phase; dr >19:1 by ^{1}H NMR analysis. [d]Data in parentheses were obtained at 0.5 mmol scale. [e]The absolute configuration of **4l** was determined by X-ray analysis; see the Supporting Information. The other products were assigned by analogy.

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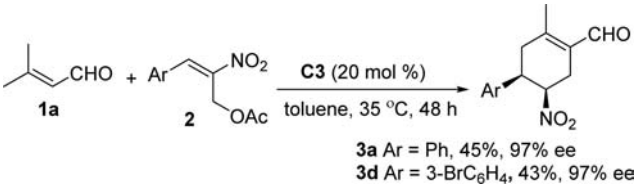
4n were produced with good results (entries 11−14). Nevertheless, a branched alkyl-substituted substrate showed lower reactivity, and product **4o** was obtained in a fair yield but with high enantioselectivity (entry 15). On the other hand, the substitution patterns of enal substrates were investigated in the reactions with the 2-nitroallylic acetate bearing a 3,4-dichlorophenyl group. It was noteworthy that γ,γ-unsymmetrically substituted enals showed high regioselectivity, favoring the formation of thermally stable dienamine species to deliver products **4p** and **4q** with three contiguous chiral centers, respectively (entries 16 and 17). Moreover, chiral bicycles **4r** and **4s** were also obtained in excellent enantioselectivity, albeit in fair to modest yields (entries 18 and 19). However, the linear enals without γ,γ-disubstitutions failed to participate in this type of [3 + 3] formal cycloaddition reactions.

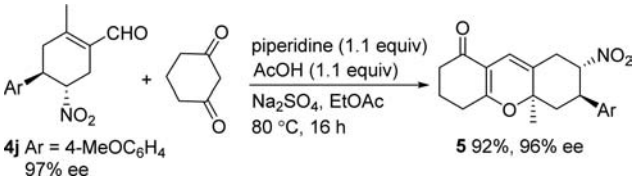
Since *cis*-diastereomers were produced as the major one in the previous [3 + 3] reaction, simple flash chromatography was applicable to isolate these isomers, thus enriching the stereogenic diversity of the chiral products. As outlined in Scheme 2, both *cis*-**3a** and -**3d** were obtained with outstanding enantioselectivity, albeit in fair yields.

Scheme 2. Isolation of *cis*-[3 + 3] Products



The remaining α,β-unsaturated aldehyde moiety of **4j** could undergo another [3 + 3] formal cycloaddition reaction with cyclohexane-1,3-dione, efficiently delivering a tetracyclic product **5** containing a quaternary chiral center in exclusive diastereoselectivity (Scheme 3).[17] Thus, the multifunctional products obtained from these [3 + 3] formal cycloadditions would find more applications in organic synthesis and medicinal chemistry.

Scheme 3. Synthetic Transformations of Cycloadduct 4j



In conclusion, we have developed an asymmetric [3 + 3] formal cycloaddition reaction of α,β-unsaturated aldehydes and 2-nitroallylic acetates under the catalysis of a chiral bifunctional secondary amine-thiourea substance. This reaction exhibited high α,γ-regioselectivity and excellent enantioselectivity, proceeding through a domino Michael addition−Michael addition sequence through a less explored cascade dienamine−dienamine catalytic pattern. Moreover, diastereopure cyclohexene derivatives were efficiently obtained with excellent enantioselectivity after simple treatment with K_2CO_3, which allowed further transformation to access chiral skeletons with high molecular complexity. Additional results 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.5b03355.

Complete experimental procedures and characterization of new products, NMR spectra, and HPLC chromatograms (PDF)

Crystallographic data for enantiopure product **4l** (CIF)

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Notes

The authors declare no competing financial interest.

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Callistrilones A and B, Triketone–Phloroglucinol–Monoterpene Hybrids with a New Skeleton from *Callistemon rigidus*

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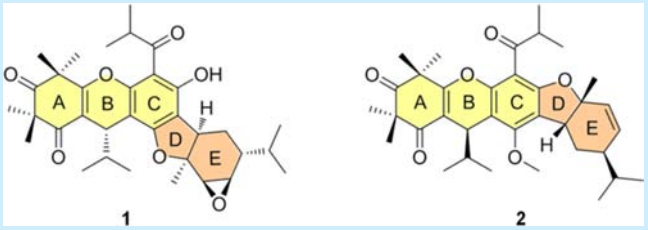
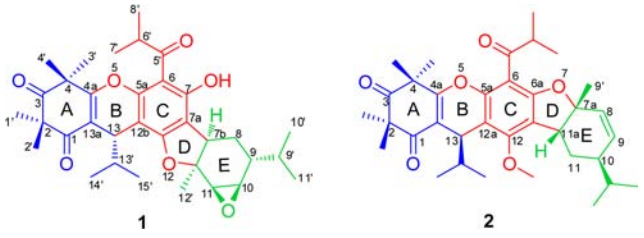
Supporting Information

ABSTRACT: The first triketone–phloroglucinol–monoterpene hybrids, callistrilones A and B (**1** and **2**), along with a postulated biosynthetic intermediate (**3**) were isolated from the leaves of *Callistemon rigidus*. Compounds **1** and **2** featured a new carbon skeleton with an unprecedented [1]benzofuro[2,3-*a*]xanthene or [1]benzofuro[3,2-*b*]xanthene pentacyclic ring system composed of three kinds of building blocks. Their structures and absolute configurations were elucidated by spectroscopic analysis, X-ray diffraction, and electronic circular dichroism (ECD) calculations. A plausible biogenetic pathway for the new compounds is also proposed. Compound **1** exhibited moderate antibacterial activity against Gram-positive bacteria including multiresistant strains.



Many plants of the family Myrtaceae have been used as folk medicine due to their significant antimicrobial, antitumor, and anti-inflammatory properties.[1−3] Phytochemical investigations revealed that these plants possess a series of cyclic triketones, phloroglucinols, and terpenes.[4−7] Interestingly, these constituents are also found as building blocks to construct more complex bioactive natural products, such as antibacterial triketone–phloroglucinols,[8] antiviral phloroglucinol–monoterpenes,[9] cytotoxic phloroglucinol–sesquiterpenes,[10] and insecticidal triketone–monoterpenes.[11] Recently, a rearranged triketone–phloroglucinol–triketone adduct with two kinds of building blocks was isolated from *Myrtus communis*, which was considered to be a new inhibitor of reactive oxygen species (ROS) generation.[12] Due to their complex structural features and diverse biological effects, these natural products have become attractive targets for organic chemists.[13,14]

In our continuing studies on structural unique and bioactive phloroglucinol derivatives,[10,15] the first triketone–phloroglucinol–monoterpene hybrids (**1** and **2**) along with a postulated biosynthetic intermediate (**3**) (Scheme 1) were isolated from the plant *Callistemon rigidus* (Myrtaceae). Compounds **1** and **2** represent a new carbon skeleton with an unprecedented [1]benzofuro[2,3-*a*]xanthene or [1]benzofuro[3,2-*b*]xanthene pentacyclic ring system composed of three kinds of building blocks, which were combined via two different coupling patterns to form pyran (ring B) and dihydrofuran (ring D) rings. Moreover, **1** exhibited moderate activity against Gram-positive bacteria including multiresistant strains. In this paper, we describe the structural elucidation, hypothetical biogenetic pathway, and antibacterial activities of **1**−**3**.



The molecular formula of **1** was established as $C_{34}H_{44}O_7$ by its HR-ESI-MS (*m*/*z* 565.3177 $[M + H]^+$, calcd for $C_{34}H_{45}O_7$: 565.3160). The UV spectrum of **1** displayed absorption maxima at 206, 219, and 302 nm. The IR spectrum showed characteristic absorptions for aromatic ring (1623, 1461 cm^{-1}), hydroxyl group (3437 cm^{-1}), and carbonyl groups (1719, 1653 cm^{-1}). The ^1H NMR spectrum of **1** suggested the presence of five tertiary methyls, two isopropyl moieties, an isobutyryl unit, and two oxygenated methines. The ^{13}C NMR and DEPT spectra of **1** exhibited 34 carbon signals including those for a benzene ring, an olefinic bond, and three carbonyl groups.

A comparison of the 1D and 2D NMR data of **1** (Table 1) with those of myrtucommulone C[16] suggested the presence of an isobutyl syncarpic acid unit (**1a**) and an isobutyryl phloroglucinol moiety (**1b**) in **1** (Figure 1). The HMBC cross peaks between H-13 and C-1/C-4a/C-12a/C-5a revealed the substructures **1a** and **1b** were connected through a C-12b and C-13 bond. The remaining 10 aliphatic carbon atoms could be attributable to a monoterpene moiety. The $^1H-^1H$ COSY

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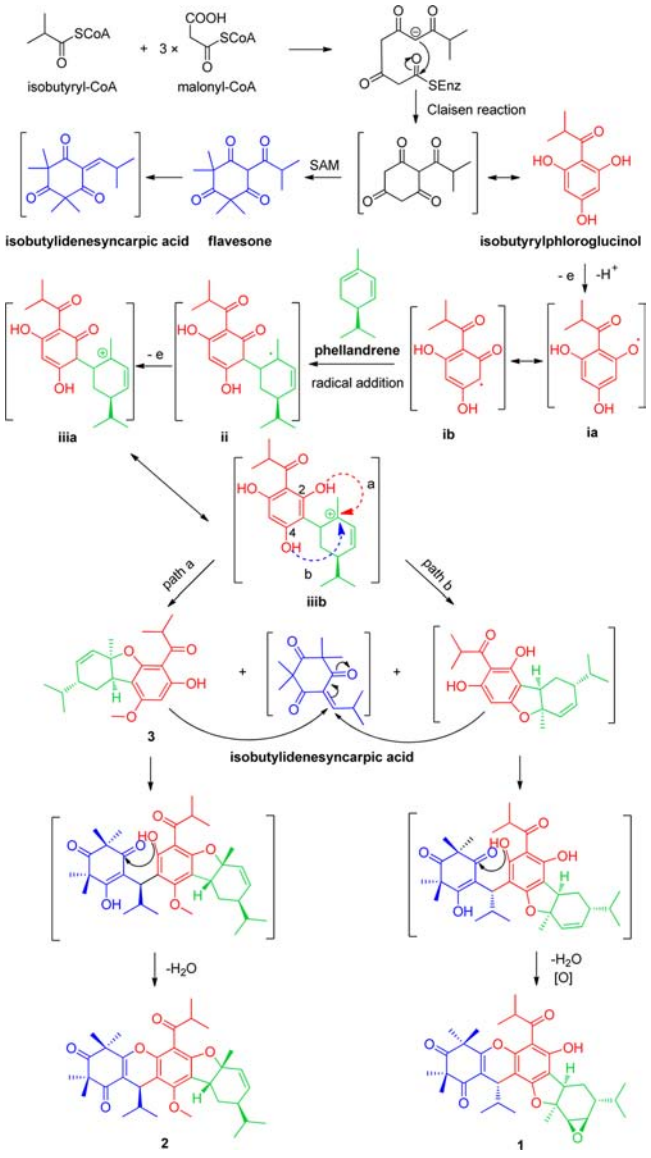
Scheme 1. Plausible Biosynthetic Pathways of 1−2



spectrum of **1** revealed the presence of three spin systems as shown in Figure 1. In addition, the HMBC cross peaks between H-10′/H-11′ and C-9 and between H-9/H-12′ and C-11/C-7b suggested the presence of a 2,3-epoxy-*p*-menthane moiety (**1c**) in **1**. The HMBC correlations between H-7b and C-12a/C-7 indicated the connection of the monoterpene and phloroglucinol units via a C-7a and C-7b bond. Based on the molecular formula information and the sole hydroxyl proton that involved in hydrogen bond (δ_H 13.31, 7-OH), the forming modes of the pyran ring (ring B) and the dihydrofuran ring (ring D) were deduced as via C-4a−O−C-5a and C-11a−O−C-12a bonds, respectively (Figure 1).

The relative stereochemistry of **1** could be elucidated by a NOESY experiment. The NOE correlations between H-12′ and H-7b/H-11/H-9′/H-15′, between H-1′ and H-3′/H-14′, as well as between H-4′ and H-2′/H-6′ established the relative configuration of **1** (Figure 2). The complete structure and stereochemistry of **1** were further established by X-ray diffraction analysis. Crystals suitable for X-ray diffraction were grown in methanol solution. The final refinement of the Cu Kα data resulted in a small Flack parameter of −0.02(16), allowing

Table 1. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR Data of 1 and 2 in $CDCl_3$ (δ, ppm; *J*, Hz)[a]

no.	1		2	
	δ_C	δ_H	δ_C	δ_H
1	197.3	–	198.1	–
2	56.4	–	56.1	–
3	212.3	–	213.0	–
4	47.4	–	47.8	–
4a	167.7	–	168.9	–
5a	154.1	–	149.8	–
6	104.3	–	110.8	–
6a	–	–	157.1	–
7	160.4	–	–	–
7a	113.6	–	87.6	–
7b	40.5	3.03 dd (12.4, 5.9)	–	–
8	23.6	2.12 ddd (14.1, 5.9, 2.7)	129.2	5.64 dd (10.3, 2.0)
		1.58 m		
9	39.3	1.82 m	134.7	5.87 dd (10.3, 3.3)
10	56.1	3.45 dd (4.1, 3.3)	38.5	1.91 m
11	55.1	3.29 d (4.1)	27.4	2.02 m, 1.77 m
11a	88.6	–	44.6	3.50 dd (7.0, 4.5)
11b	–	–	117.8	–
12	–	–	156.0	–
12a	161.9	–	110.3	–
12b	99.3	–	–	–
13	32.6	4.15 d (3.6)	32.7	4.28 d (3.6)
13a	112.6	–	109.0	–
1′	23.9	1.38 s, CH_3	25.2	1.39 s, CH_3
2′	25.4	1.37 s, CH_3	25.3	1.49 s, CH_3
3′	25.1	1.56 s, CH_3	24.5	1.33 s, CH_3
4′	25.4	1.40 s, CH_3	24.9	1.38 s, CH_3
5′	209.2	–	204.6	–
6′	39.7	3.87 m	41.4	3.26 m
7′	18.0	1.20 d (7.0), CH_3	18.3	1.13 d (6.9), CH_3
8′	21.2	1.22 d (6.6), CH_3	18.1	1.11 d (6.9), CH_3
9′	28.5	1.62 m	26.7	1.53 s, CH_3
10′	22.1	1.09 d (6.5), CH_3	31.7	1.60 m
11′	21.5	1.08 d (6.5), CH_3	20.2	0.92 d (6.7), CH_3
12′	26.3	1.48 s, CH_3	20.3	0.92 d (6.7), CH_3
13′	34.7	1.86 m	36.0	1.80 m
14′	18.0	0.69 d (6.9), CH_3	18.2	0.70 d (6.9), CH_3
15′	20.1	0.85 d (6.9), CH_3	20.1	0.76 d (6.9), CH_3
16′	–	–	60.6	3.91 s, OCH_3
7-OH	–	13.31 s	–	–

[a]Overlapped signals are reported without designating multiplicity.

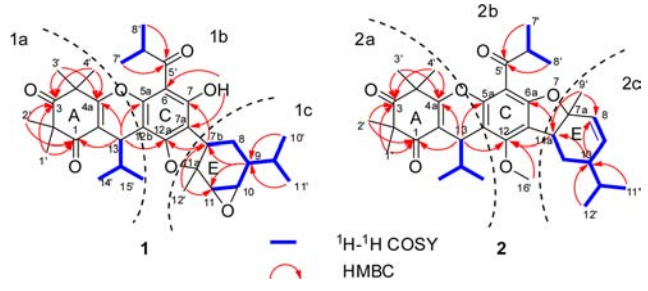


Figure 1. Key ^{1}H−^{1}H COSY and HMBC correlations of **1** and **2**.

the assignment of the absolute configuration of **1**. The rings A−D in **1** are nearly planar. The six-membered ring E is in an envelope conformation due to the presence of an epoxy group

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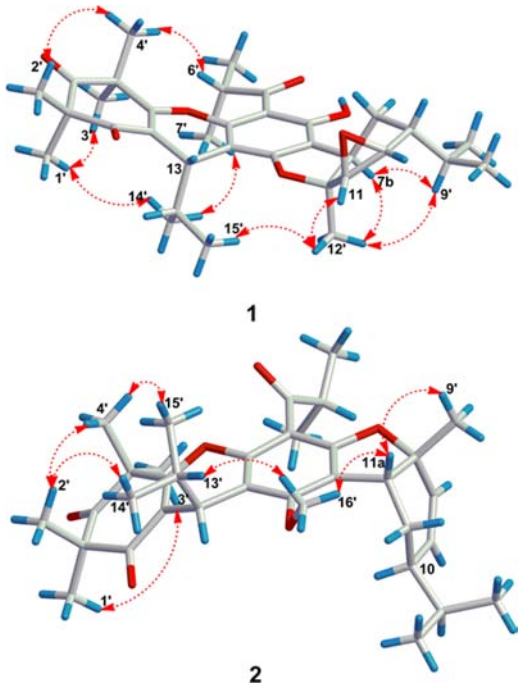

Figure 2. Optimized structures and key NOESY correlations of **1** and **2**.

(Figure 3). Moreover, the quantum-chemical ECD calculation method was used to further confirm the absolute configuration

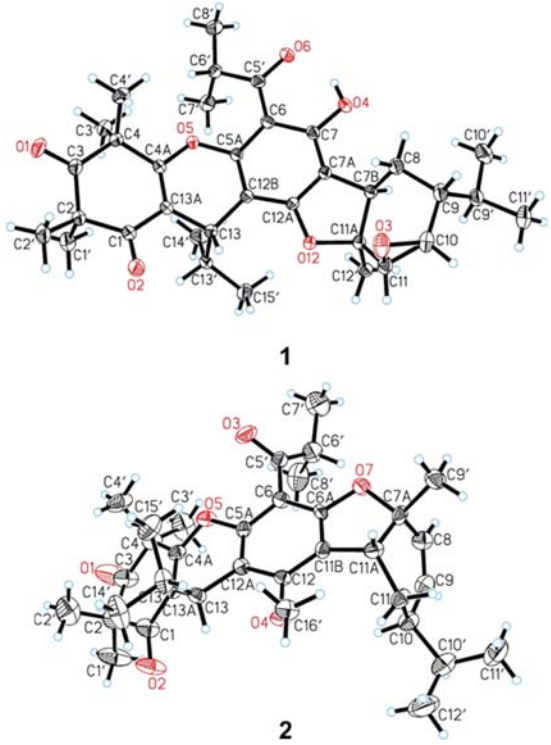

Figure 3. X-ray ORTEP drawings of **1** and **2**.

of **1**. The ECD spectra calculation for (7b*R*,9*R*,10*R*,11*R*,11a*S*,13*S*)-**1** and its enantiomer (7b*S*,9*S*,10*S*,11*S*,11a*R*,13*R*)-**1** using the TDDFT method was performed (see the Supporting Information). The experimental ECD spectrum of **1** exhibited a negative Cotton effect at 321 ($\Delta\varepsilon$ − 35.9) nm as well as positive Cotton effects at 290 ($\Delta\varepsilon$ + 17.1) and 249 ($\Delta\varepsilon$ + 27.4) nm, which were similar to those of the calculated spectrum for the isomer with 7b*R*,9*R*,10*R*,11*R*,11a*S*,13*S* configurations (Figure 4). Hence, the absolute configuration of **1** was elucidated as 7b*R*,9*R*,10*R*,11*R*,11a*S*,13*S*.

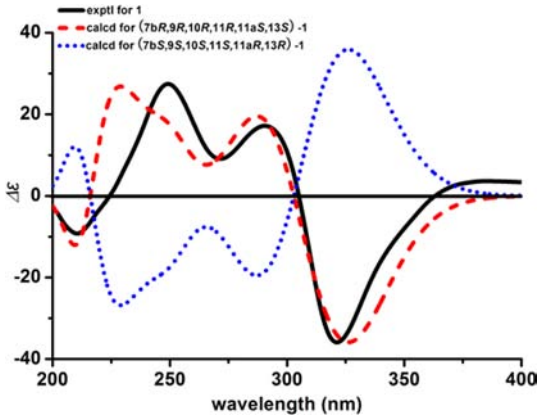

Figure 4. Calculated and experimental ECD spectra of **1**.

The molecular formula of **2** was deduced as $C_{35}H_{46}O_6$ by the quasimolecular ion at *m*/*z* 563.3382 $[M + H]^+$ (calcd for $C_{35}H_{47}O_6$: 563.3367) in its HR-ESI-MS. The UV absorption maxima at 205, 225, 265, 287 nm as well as the IR bands at 1696, 1649, 1602, 1465 cm^{-1} implied the presence of a carbonyl group and an aromatic ring. Comparison of the ^{13}C NMR data of **2** with those of **1** revealed that their chemical shifts for rings A, B, and C were similar, except the signals for the epoxy carbons (δ_C 56.1, 55.1) of monoterpene part in **1** were replaced by olefinic carbons (δ_C 134.7, 129.2) as well as the presence of one more methoxyl signal (δ_C 60.6) in **2**. The HMBC correlations between H-16′ and C-12 suggested the methoxyl was attached at C-12 position (Figure 1). The spin systems (H-8 to H-11a and H-10 to H-11′/H-12′) observed in the $^1H-^1H$ COSY spectrum (Figure 1) as well as the HMBC correlations between H-9′/H-10 and C-8/C-11a, and between H-11′/H-12′ and C-10 revealed the presence of 2-menthene unit (**2c**). Furthermore, the HMBC correlations between H-11a and C-12/C-6a, as well as the upfield shift of C-6a (δ_C 157.1) and downfield shift of C-7a (δ_C 87.6) led to the construction of dihydrofurane ring (ring D) via monoterpenoid and phloroglucinol units.

In the NOESY spectrum of **2**, the correlations between H-2′ and H-4′/H-14′, between H-15′ and H-4′, between H-1′ and H-3′, between H-16′ and H-13′/H-11a, as well as between H-9′ and H-11a confirmed the relative configurations of C-7a, C-11a, and C-13 (Figure 2). However, the configuration of C-10 could not be deduced by the NOESY data. Fortunately, crystals suitable for single-crystal X-ray diffraction were obtained. The Flack parameter of 0.01(15) of **2** allowed unambiguous assignment of the absolute configuration as 7a*R*,10*R*,11a*R*,13*R* (Figure 3).

A plausible biosynthetic pathway for compounds **1** and **2** is proposed as shown in Scheme 1. It has been reported that isobutyrylphloroglucinol and flavesone are two major components of *Callistemon* plants, derived from the Claisen reaction between malonyl CoA and isobutyryl CoA.[17] Oxidation of isobutyrylphloroglucinol could lead to the radicals **ia** and **ib**.[17] The latter could be combined with the conjugated diene of

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phellandrene, a common monoterpene of *Callistemon* plants, to form a reactive intermediate (**ii**). Further oxidation of **ii** could form the cations **iiia** and **iiib**. The intramolecular cyclization between 2-OH and the carbocation of **iiib** could lead to the formation of biosynthetic intermediate (**3**), which was further coupled with the precursor isobutylidenesyncarpic acid via Michael and intramolecular nucleophilic additions to yield a linear framework compound **2**.[18,19] On the other hand, the cyclization between 4-OH and carbocation, followed by the procedures similar to those of **2**, could give **1**.

In order to confirm that compounds **1**−**3** are indeed natural products, the crude methanol extract of the fresh leaves of *C. rigidus* was analyzed by HPLC−HRESIMS (see the Supporting Information). The ion peaks in accord with those of **1**−**3** were detected, which confirmed the natural occurrence of these compounds.

Compounds **1**−**3** were tested for their antibacterial effect against five Gram-positive and four Gram-negative strains (see the Supporting Information). Among them, only **1** exhibited moderate antibacterial activity against all Gram-positive bacteria with MIC values ranging from 16 to 32 μg/mL. Furthermore, compound **1** showed more potent antibacterial activity against multiresistant strains *Staphylococcus aureus* ATCC33591, *S. aureus* Mu50, and *Enterococcus faecium* 13-01 than positive control oxacillin (MIC 256−512 μg/mL).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03360.

Detailed description of the experimental procedure; UV, IR, MS, and NMR spectra for compounds **1**−**3**; ECD calculation for **1**; HPLC−HRMS analyses of the methanol extract of the fresh leaves of *Callistemon rigidus*(PDF)

X-ray data for **1** (CIF)

X-ray data for **2** (CIF)

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

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Organic LETTERS

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Regioselective Rhodium-Catalyzed Addition of 1,3-Dicarbonyl Compounds to Terminal Alkynes

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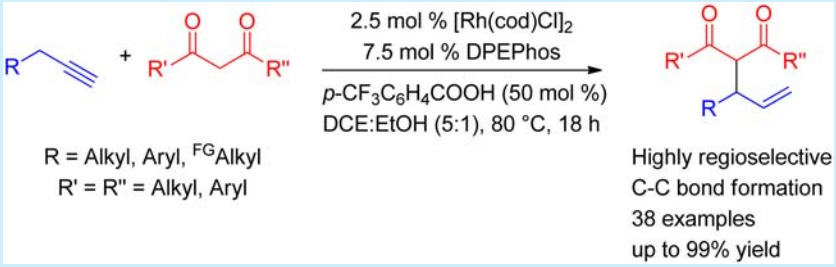
Supporting Information



ABSTRACT: A new method for the rhodium-catalyzed regioselective C−C bond formation using terminal alkynes and 1,3-dicarbonyl compounds to achieve valuable branched α-allylated 1,3-dicarbonyl products is reported. With a Rh(I)/DPEphos/p-CF_3-benzoic acid as the catalyst system, the desired products can be obtained in good to excellent yields and with perfect regioselectivity. A broad range of functional groups were tolerated, and first experimental insights of a plausible reaction mechanism were obtained.

Recently, we reported on a series of rhodium-catalyzed addition of different pronucleophiles to allenes[1] and terminal alkynes,[2] which can be regarded as an atom economic alternative to the transition metal-catalyzed allylic substitution[3−7] and the palladium-catalyzed allylic oxidation.[8,9] Although terminal allenes[10] displayed in many cases higher reactivity, the isomeric terminal alkynes[11] are much easier accessible substrates and thus synthetically more appealing starting materials.

Unfortunately, the reactivity of terminal alkynes is so far restricted to the additions of carboxylic acids furnishing allylic esters (C−O bond formation)[2a,c] as well as to the addition of sulfonylhydrazides furnishing allylic sulfones (C−S bond formation).[2b]

However, the addition of carbon nucleophiles would be synthetically very attractive since this allows for further carbon skeleton extension. Mechanistic investigations indicated that the reaction of terminal alkynes and carboxylic acids proceed via a σ-allyl rhodium complex as the resting state.[12] We speculated that a suitable carbon nucleophile such as a 1,3-dicarbonyl species could serve to trap this σ-allyl complex by a C−C bond formation.

We herein report on the successful realization of this concept achieving a regioselective rhodium-catalyzed addition of 1,3-dicarbonyl compounds to terminal alkynes as an efficient method for the formation of valuable branched α-allylated 1,3-dicarbonyl compounds (Scheme 1).

Our studies emanated by employing 1-dodecyne (**1**, 2.0 equiv) and acetylacetone (**2**, 1.0 equiv) as model system (Table 1).[13] After first reactivity assays[14] we were pleased to find that applying $[Rh(COD)Cl]_2$ (2.5 mol %) and DPEphos (**3**, 7.5 mol %) as catalyst and benzoic acid (100 mol %) as an additive in DCE at 80 °C led to the desired branched product **4** in 64% yield (Table 1, entry 1). In the absence of benzoic acid, only traces of product could be observed (entry 2) demonstrating its importance for the title reaction. Studying different *para* substituted benzoic acid

Scheme 1. Proposed Pathway for Carbon−Carbon Bond Formation from Terminal Alkynes

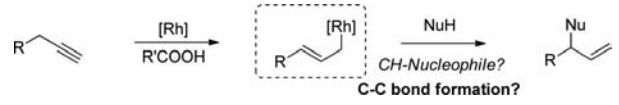
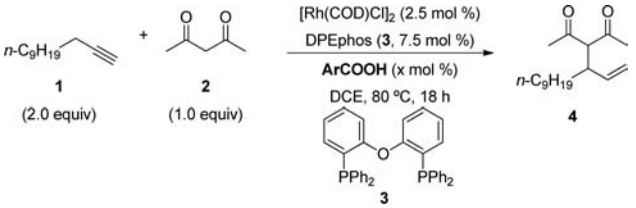


Table 1. Ligand Screening and Optimizations



entry	Ar	x (mol %)	yield[a] (%)
1	Ph	100	64
2	Ph	0	traces
3	p-$CF_3C_6H_4$	100	93
4[b]	**p-$CF_3C_6H_4$**	**50**	**97**

[a]Isolated yield of the branched product **4**. [b]Reaction performed in DCE/EtOH (5:1).

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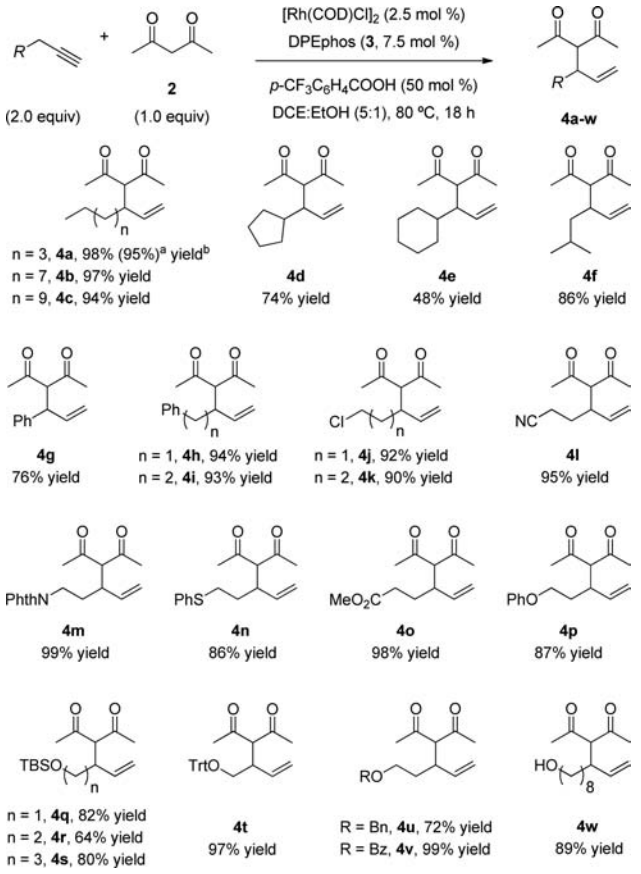
derivatives revealed that p-$CF_3C_6H_4CO_2H$ was most effective, leading to 93% yield of **4** (entry 3). Also the solvent plays an important role in this reaction. An optimized solvent mixture of DCE and ethanol (5:1) allowed to reduce the amount of p-$CF_3C_6H_4CO_2H$ to 50 mol %, still providing the highest yield (entry 4). In all cases the branched allylic addition product was the only regioisomer that could be observed.

With these optimized conditions in hand we next explored the scope of alkynes. A large number of commercially available or easily accessible terminal alkynes were suitable substrates for the reaction and afforded exclusively branched products in good to excellent yields (Scheme 2). Additionally, linear alkyl-, aliphatic

Scheme 2. Scope of Alkynes with Acetylacetone (2)

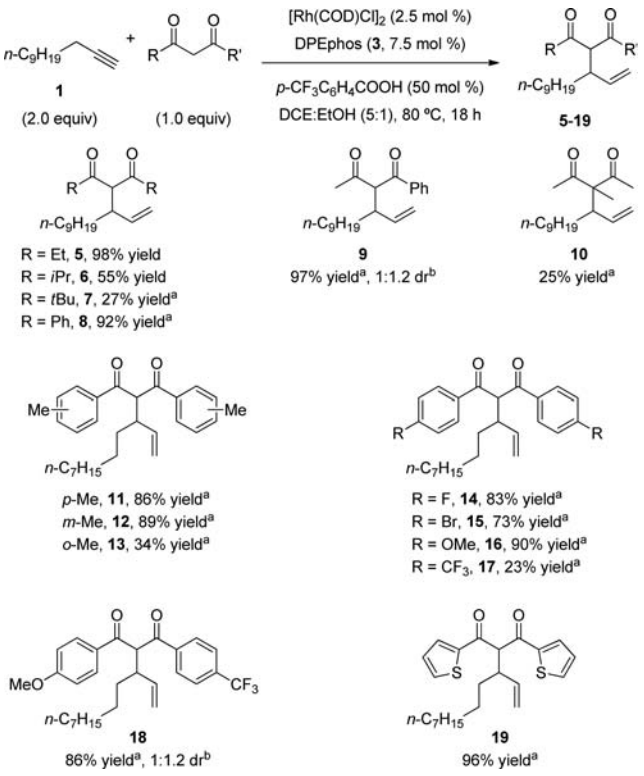


[a]This reaction was additionally performed in a 5 mmol scale and gave **4a** in 95% isolated yield. [b]All yields are isolated yields.

cyclic-, phenyl-, and linear ω-substituted alkynes were applicable. To our delight even prehalogenated alkynes were tolerated well (**4j**, **4k**), and additionally, several other functional groups such as a cyano substituent (**4l**), a phthalimidoyl function (**4m**), and a thioether function(**4n**) were compatible. Also substrates with protecting groups for hydroxy functions, including silyl ether (**4q**–**4s**), trityl ether (**4t**), benzyl ether (**4u**), and benzoate functions (**4v**) behaved well. Even the presence of a hydroxy group was well tolerated (**4w**).

Next, the reaction could be applied to a variety of 1,3-diketones (Scheme 3). The reaction of heptane-3,5-dione with 1-dodecyne (**1**) led to the branched product **5** with an excellent yield of 98% (Scheme 3), albeit yields dropped for sterically more congested derivatives. The addition of the symmetric bisbenzoyl

Scheme 3. Scope of 1,3-Dicarbonyl Compounds with 1-Dodecyne (1)



[a]Reaction was carried out over 66 h. [b]The diastereomeric ratio (dr) was determined by ^{1}H NMR analysis.

methane led to **8** in 92% yield. Also, with benzoyl acetone, high yields of **9** (97%, 1:1.2 dr) were obtained.

Varying the pattern of functional groups on the aryl moiety of bisbenzoyl methane was possible and furnished the desired addition products in mostly good yields. Furthermore, the heterocyclic bisthiophenoyl propane-1,3-dione could be applied to yield **19** in 96% yield.

The resulting α-allylated 1,3-dicarbonyl compounds are useful starting materials for heterocycle synthesis of medicinal interest.[15,16] Hence, reaction of **4a** with hydroxylamine led to the oxazole **20**. Correspondingly, reaction with hydrazine and phenylhydrazine furnished the pyrazoles **21** and **22**, respectively, in good to excellent yields (Scheme 4). Pyrazoles are suitable substrates for a further functionalization by rhodium-catalyzed N-allylation with allenes developed in our laboratories.[1j] Subjection of the α-allylated 1,3-dicarbonyl compounds to ethanolic potassium hydroxide solution initiated a deacetylation resulting in the formation of γ,δ-unsaturated ketones in quantitative yield (Scheme 4). This facile access to γ,δ-unsaturated methyl ketones represents a synthetic alternative to an enolate allylation reaction or a Claisen/Carroll-type rearrangement.[17]

Furthermore, treatment of either chlorine or silylether functionalized substrates **4j** and **4r** under basic or acidic conditions, respectively, led to the formation of the dihydropyran system **24** in good yields (Scheme 4).[18]

In order to attain first insights into the reaction mechanism, the following control experiments were performed. Subjecting the allylic benzoic ester **25** to the reaction conditions furnished **4a**, the product of an allylic substitution reaction. This indicates that **25** might be an intermediate during the course of this

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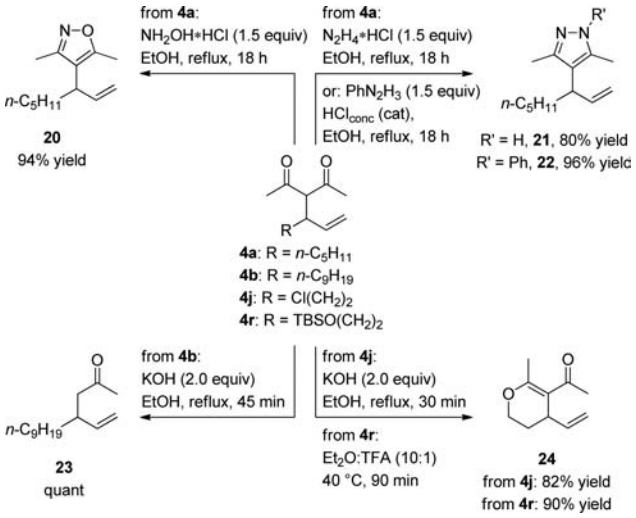
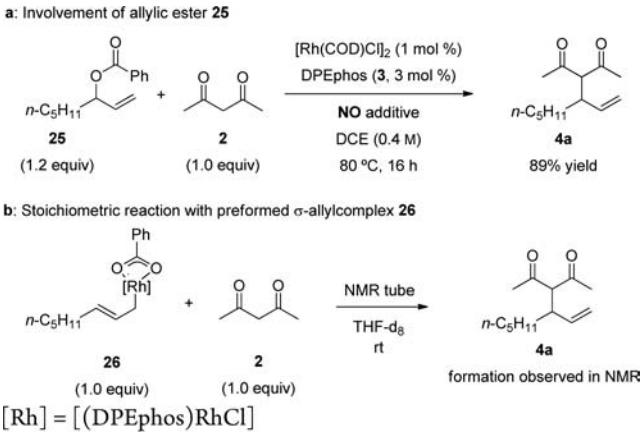
Scheme 4. Applications in the Synthesis of Trisubstituted Oxazoles, Tri- or Tetra-Substituted Pyrazoles, Deacetylation, and Cyclization



reaction (Scheme 5). However, from our previous mechanistic studies on the rhodium-catalyzed addition of benzoic acid to

Scheme 5. Control Experiments



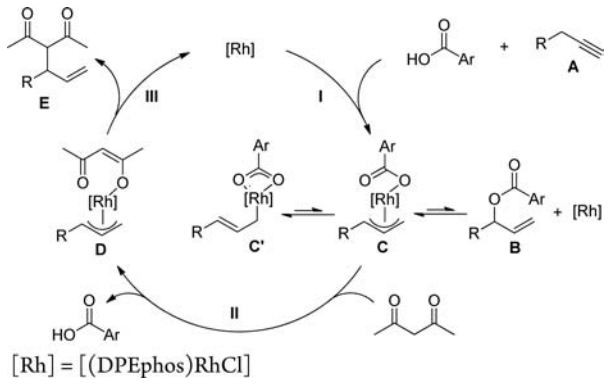
terminal alkynes furnishing branched allylic benzoates, it is known that allylic esters can undergo reaction with the rhodium catalyst to furnish σ-allyl rhodium complex **26**, which has been isolated previously representing the resting state of the catalyst.

Hence, to clarify whether the σ-allyl rhodium complex **26** is an intermediate in the reaction with acetylacetone as a nucleophile, a stoichiometric reaction with the preformed rhodium complex **26** was monitored in an NMR experiment. Indeed, formation of the allylic addition product **4a** could be observed suggesting the rhodium complex **26** to be an intermediate of the catalytic cycle. Additionally, isotope-labeling experiments with deuterated substrate showed deuterium incorporation in all positions of the alkene function of the product,[19] which is in agreement with previously made observations for the rhodium-catalyzed addition of different pronucleophiles to allenes[1a,b,j] and alkynes.[2a]

Based on these experiments and previous results, we propose the following catalytic cycle (Scheme 6).

Starting step **I** is the known formation of the σ-allyl complex **C**′, obtained by reaction of the alkyne and the aryl carboxylic acid. **C**′ is presumably in equilibrium with π-allyl complex **C** and

Scheme 6. Proposed Catalytic Cycle



the allylic ester **B**. Anion exchange of **C** with acetylacetone would provide allyl complex **D**. Reductive elimination from **D** would release the allylic addition product **E**.

To conclude, starting from simple terminal alkynes and 1,3-dicarbonyls we have developed a highly regioselective rhodium-catalyzed C−C bond forming reaction furnishing valuable branched α-allylated 1,3-dicarbonyl compounds in good to excellent yields. The utility of the obtained products was demonstrated through one step transformations to heterocyclic systems of medicinal interest. Furthermore, hydroxide mediated deacetylation provided products of a formal methylketone enolate allylation or Claisen/Carroll-type rearrangement. Further attempts regarding extensions of this method to the formation of quaternary centers, other (carbon-) nucleophiles as well as the development of an asymmetric variant are ongoing in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03391.

Experimental procedures and analytical data for synthesized alkynes, diarylpropane-1,3-diones, and α-allylated 1,3-dicarbonyl compounds, including ^{1}H NMR and ^{13}C NMR (PDF)

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Notes

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(19) For further details about deuterium labeling experiments, see Supporting Information.

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Fe-Catalyzed Olefin Hydroamination with Diazo Compounds for Hydrazone Synthesis

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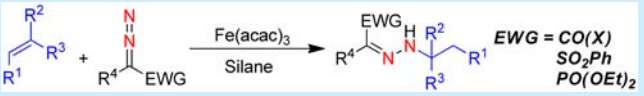
Supporting Information

ABSTRACT: A novel Fe-catalyzed olefin hydroamination with diazo compounds for accessing hydrazones has been developed. Diazo compounds are used as radical acceptors and can be trapped by the *in situ* generated alkyl radical toward C−N bond formation. The reaction conditions are mild, and the substrate scope is broad. Additionally, this hydroamination protocol is applicable for intramolecular reactions to construct diverse heterocycles.



The synthesis of nitrogen-containing molecules is important and interesting since these compounds exist widely in medicinal chemistry, fine chemicals, and materials.[1] Among numerous methods, transition-metal-catalyzed olefin hydroamination represents a rapid and distinct approach (Figure 1A).[2] Mukaiyama reported a seminal example of olefin hydroamination to access amines with the reaction of Fe-catalyzed hydrogen atom transfer (HAT), in which phenylsilane was used as the reductant and butyl nitrite was used as the amination source.[3] Carreira developed versatile Co-catalyzed olefin hydroamination using differential amination sources such as *p*-tolylsulfonylazide (*p*-TsN_3), azodicarboxylates.[4] Shigehisa also reported a Co-catalyzed hydroamination of unactivated olefins for accessing nitrogen-containing heterocyclic compounds.[5] Recently, Boger extended the Fe-catalyzed olefin hydroamination method using simple NaN_3 as amination sources.[6] Meanwhile, Shenvi developed chemoselective olefin isomerization and hydrogenation utilizing the HAT style.[7] More recently, Baran invented a practical olefin hydroamination with nitroarenes for the achievement of hindered amines.[8] On the other hand, Buchwald and coworkers reported elegant work that included Cu-catalyzed asymmetric olefin hydroamination for synthesis of enantiomeric amines.[9] Despite the advances in this field, the development of olefin hydroamination for accessing other nitrogen-containing molecules such as hydrazone remains to be explored.

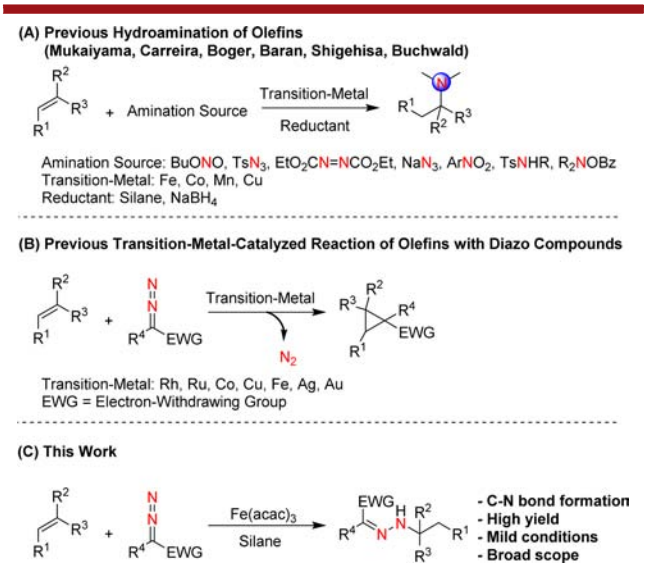


Figure 1. Olefin hydroamination of and metal-catalyzed reaction of olefins with diazo compounds.

Diazo compounds are known as versatile building blocks in organic synthesis.[10] In the presence of a transition-metal catalyst, diazo compounds mainly convert to short-lived metal-carbenes with the extrusion of nitrogen gas, and they give rise to various carbenoid reactions with a remarkable degree of chemo-, regio-, and stereoselectivity.[11] Typically, diazo compounds undergo cyclopropanation with olefins in the presence of a variety of transition-metal catalysts, including Rh, Ru, Co, Cu, Fe, Ag, Au (Figure 1B).[12] Recently, Feng and coworkers reported a $Sc(OTf)_3$-catalyzed new electrophilic addition of α-diazoesters with ketones for enantioselective C−N bond formation.[13] Meanwhile, Fox developed Rh(II)-catalyzed reactions of diazoesters with organozinc reagents to access hydrazones.[14] Heinrich also reported that aryl diazonium salts could act as amination sources with nonactivated olefins.[15] These findings revealed that diazo compounds could act as amination reagents, therefore driving the need to explore this building block for access to nitrogen-containing molecules.

In pursuit of our interest in olefin functionalization and diazo compounds transformation,[16] we proposed that diazo compounds could serve as radical acceptors.[7] Herein, we wish to report an Fe-catalyzed olefin hydroamination with diazo compounds for hydrazone synthesis (Figure 1C).

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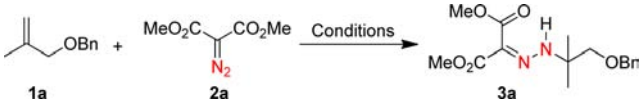
We commenced our study by investigating olefin **1a** and α-diazomalonate **2a**. When the reaction was subjected to Boger's $Fe_2(ox)_3{\cdot}6H_2O$ and $NaBH_4$ conditions in ethanol at 60 °C, the hydroamination product was not observed (Table 1, entry 1).

Table 1. Optimization of the Reaction Conditions[a,b]



entry	Fe(III) salt	reductant	solvent	t (°C)	yield (%)[b]
1	$Fe_2(OX)_3{\cdot}6H_2O$	$NaBH_4$	EtOH	60	–
2	$Fe_2(OX)_3{\cdot}6H_2O$	Et_3SiH	EtOH	60	–
3	$Fe_2(OX)_3{\cdot}6H_2O$	$PhSiH_3$	EtOH	60	–
4	$Fe(acac)_3$	Et_3SiH	EtOH	60	–
5	$Fe(acac)_3$	$PhSiH_3$	EtOH	60	88
6	$Fe(acac)_3$	$PhSiH_3$	EtOH	25	56
7	$Fe(acac)_3$	$PhSiH_3$	THF	60	62
8	$Fe(acac)_3$	$PhSiH_3$	CH_3CN	60	–

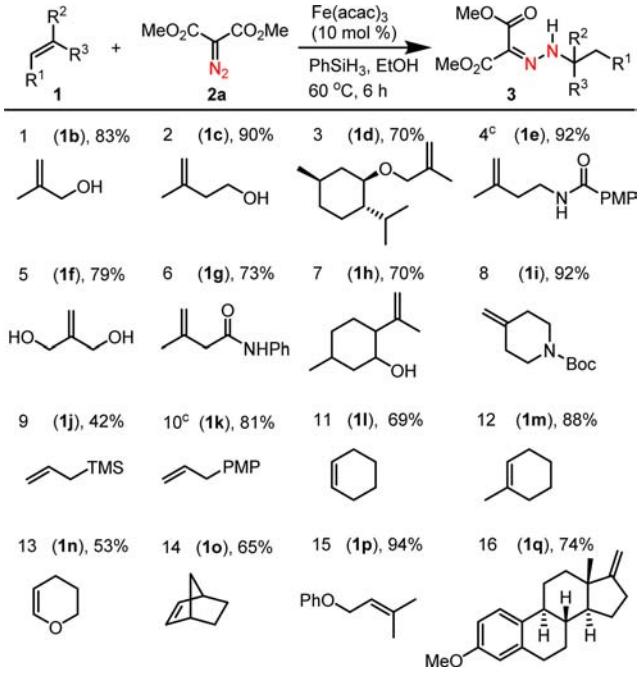
[a]Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), Fe(III) salt (10 mol %), reductant (0.4 mmol), in 2 mL of solvent under argon for 6 h. [b]Isolated yields are given.

Variation of the reductant to Et_3SiH and $PhSiH_3$ did not give any improvement (entries 2−3). The next combination of $Fe(acac)_3$ and Et_3SiH was also ineffective (entry 4). Gratifyingly, when $PhSiH_3$ was used as a reductant, a remarkable hydrazone product **3a** was observed in 88% yield (entry 5), indicating a pathway of olefin hydroamination, and the hydrogen of hydrazone has a significant chemical shift (δ = 11.61 ppm) in ^1H NMR, probably because of a hydrogen bond occurring between the carbonyl group and the hydrazone. An attempt to lower the temperature to 25 °C gave a decreased yield (entry 6). The survey of solvents showed that THF and CH_3CN were inferior, either giving a lower yield or shutting down the reactivity (entries 7−8).

With the optimized conditions in hand, we set out to explore the substrate scope of this transformation (Scheme 1). Various olefins served as viable donor substrates to achieve the formation of hydrazones. For example, 2-methylallyl alcohol (**1b**) and 3-methylhomoallyl alcohol (**1c**) were well applicable in this transformation, exhibiting good tolerance for the hydroxy group. Other disubstituted terminal olefins were also amenable to this hydroamination (entries 3−8), with valuable functional groups such as ether, amide, and the piperidine ring. When monosubstituted terminal alkenes with valuable trimethylsilyl and *para*-methoxyphenyl functional groups were subjected to this process, the reaction proceeded smoothly to enable access to secondary hydrazones in moderate to good yields (entries 9−10). Morever, cyclic olefins including cyclohexene, dihydropyran, and norbornene could also be used in this transformation. It should be noted that the C−N bond formation of dihydropyran occurred at the 2-position, probably because the formed radical intermediate was more stable. The trisubstituted olefin **1p** was also practical to generate the product in excellent yield. Notably, the sterically encumbered estrone 3-methyl ether derivative **1q** could be applicable to deliver the product in 74% yield. Therefore, this method provides a simple, rapid access to secondary and tertiary hydrazones, with readily available starting materials.

Next, a variety of diazo compounds were utilized to react with (*S*)-(−)-β-Citronellol **1r** to construct diverse hydrazones

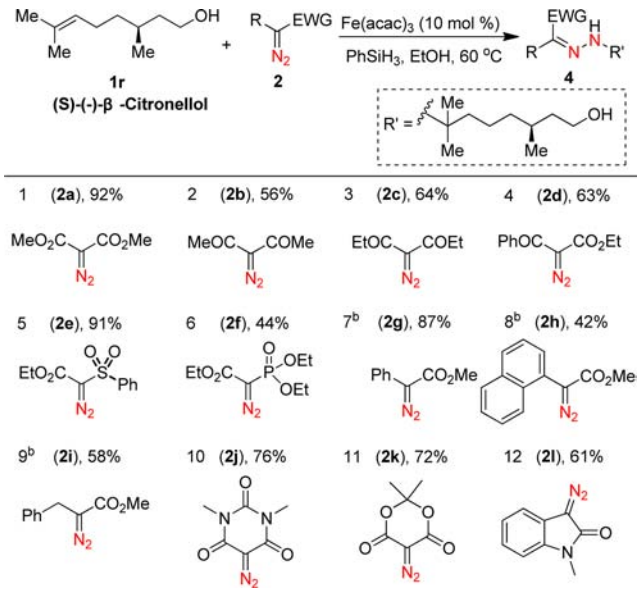
Scheme 1. Scope of the Olefin[a,b]



[a]Reaction conditions: **1** (0.4 mmol), **2a** (0.2 mmol), $Fe(acac)_3$ (10 mol %), $PhSiH_3$ (0.4 mmol), in EtOH (2 mL) at 60 °C for 8 h, argon. [b]Isolated yields are shown. [c]PMP = *para*-methoxyphenyl.

(Scheme 2). Gratifyingly, various diazo compounds, regardless of the acceptor/acceptor type or the donor/acceptor type, were

Scheme 2. Scope of the Diazo Compounds[a,b]



[a]Standard conditions; isolated yields are shown. [b]Solvent: THF (2 mL) and EtOH (0.4 mmol).

well tolerated. Those substituents, such as ester, ketone, diethyl phosphornate, sulfone, phenyl, and benzyl, were well applicable to furnish the products in moderate to good yields (Scheme 2, entries 1−9). Additionlly, the cyclic diazo compounds, with the scaffold of barbituric acid, Meldrum's acid, and oxindole, could also be utilized in this protocol to furnish the valuable

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functionalized hydrazone products in good yields, thus demonstrating the synthetic utility. Morever, the structure of **4m** which is prepared from **1f** and **2j** was confirmed by X-ray analysis,[18] wherein a OH group is disordered and distributed in three different positions (Figure 2).

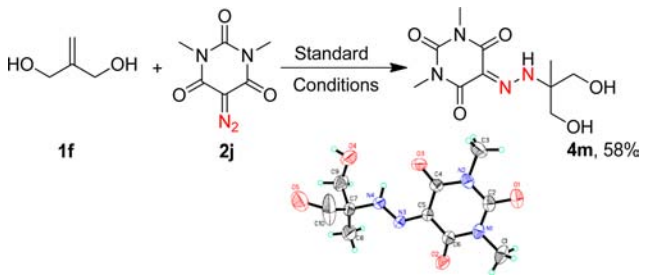
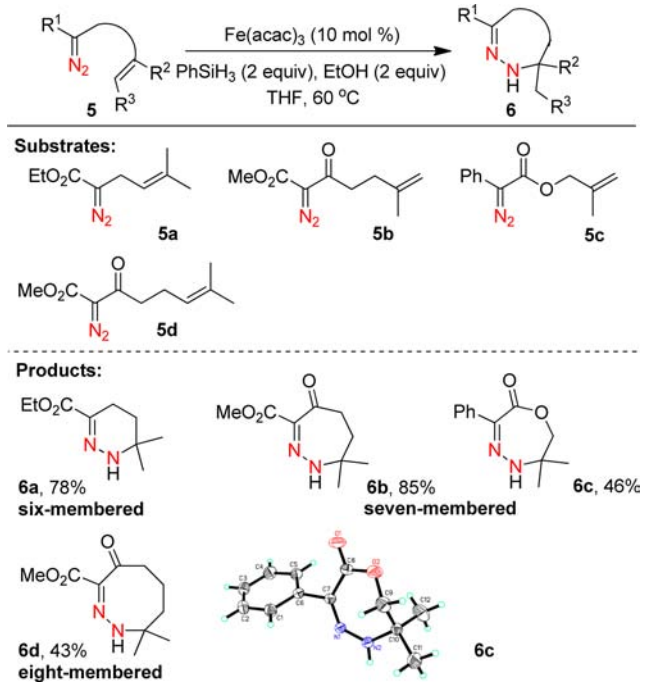


Figure 2. X-ray analysis of **4m**.

The applicability of this protocol to intramolecular reaction was also examined (Scheme 3). Various olefins could be easily

Scheme 3. Scope of the Intramolecular Hydroamination[a]



[a]Reaction conditions: **2** (0.2 mmol), $Fe(acac)_3$ (10 mol %), $PhSiH_3$ (0.4 mmol), EtOH (0.4 mmol), in THF (2 mL) at 60 °C for 8 h, argon; isolated yields are shown.

functionalized with a diazo group (**5a**−**5d**) and subjected to the hydroamination conditions using THF as solvent to furnish diverse cyclic hydrazones (**6a**−**6d**) in good yields, including six-, seven-, and eight-membered architecture. The structure of compound **6c** was confirmed by X-ray analysis.[19] Interestingly, the chemical shift of these cyclic hydrazone hydrogens was about δ = 6.0 ppm in ^{1}H NMR spectra, probably due to the hydrogen bond not occurring in these cyclic products. Thus, this method demonstrates a distinct approach to heterocycle synthesis.

Based on these results and others previously reported in the literature, a plausible mechanism is proposed in Figure 3.

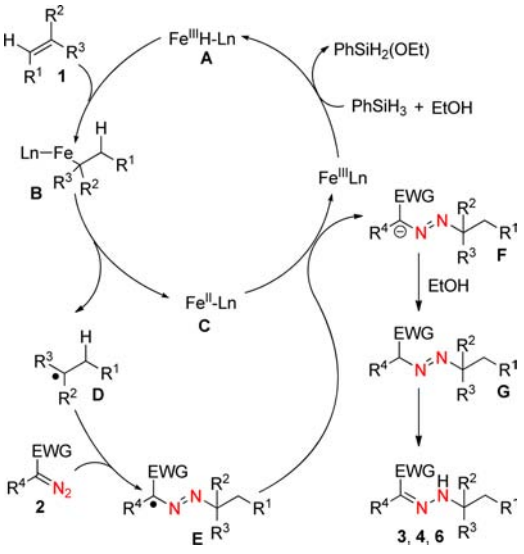


Figure 3. Proposed mechanism.

Initially, the Fe(III)-catalyst is converted to Fe hydride species **A** in the presence of phenylsilane and ethanol.[3,7,8,16a,20] Then **A** regioselectively adds olefin **1** to form **B**, placing the Fe atom on the more substituted carbon atom. The dissociation of **B** delivers Fe(II) species **C** and alkyl radical **D**, which is trapped by diazo compounds **2** to generate intermediate **E**. The single-electron transfer between **E** and **C** delivers **F**, which is protonated to **G**. Finally, the rapid isomerization of **G** furnishes the hydrazone products.

In summary, an Fe-catalyzed olefin hydroamination with diazo compounds to access secondary and tertiary hydrazones has been reported. This protocol features mild conditions and a broad scope. Additionally, various olefins were easily functionalized with the diazo group and were converted to diverse heterocycles in this protocol.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03317.

Full experimental procedures, spectral data (PDF)
Crystallographic datacompound **4m** (CIF)
Crystallographic data compound **6c** (CIF)

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Notes

The authors declare no competing financial interest.

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Stereoselective Alkylation of the Vinylketene Silyl *N,O*-Acetal and Its Application to the Synthesis of Mycocerosic Acid

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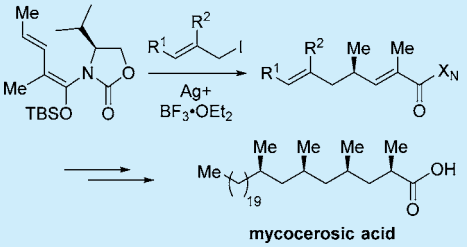
Supporting Information

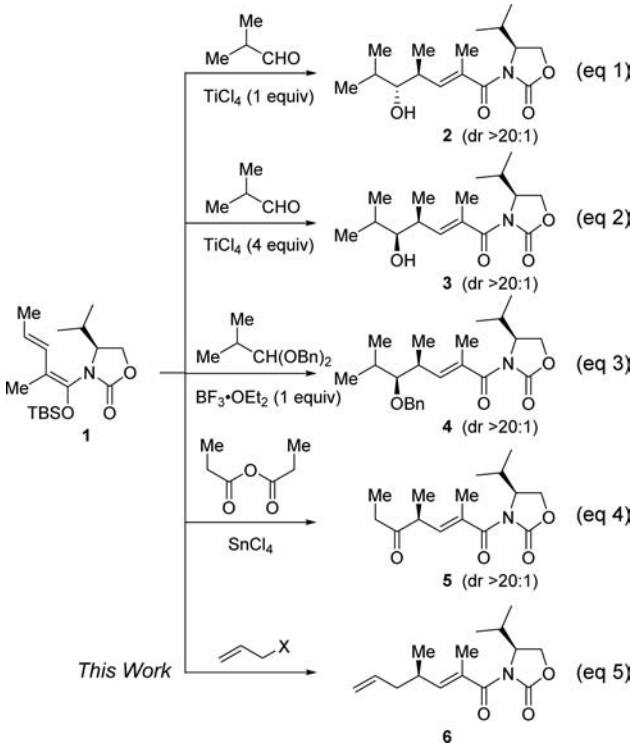
ABSTRACT: Stereoselective alkylation of the vinylketene silyl *N,O*-acetal possessing a chiral auxiliary has been achieved by using activated alkyl halides including allyl iodides, benzyl iodides, and propargyl iodide with Ag(I) ion in the presence of $BF_3{\cdot}OEt_2$. The reaction proceeded to give reduced polyketides in high stereoselectivity. The synthesis of mycocerosic acid, a component of the cell envelope of *Mycobacterium tuberculosis*, has been accomplished by this methodology. During the synthetic studies, 2-methylbenzimidazole was found to be a bulky proton source which worked in the presence of liquid ammonia.



Reduced polyketides are ubiquitous in natural products including secondary metabolites[1] and pheromones of insects.[2] Methodologies toward reduced polypropionates have been developed by several groups. Some of them are iterative routes[3] while others include organometallic reactions.[4] Recently, we reported the stereoselective and short-step synthesis of all isomers of the branched methyl groups of 2,4,6-trimethyloctanoic acid derivatives having a hydroxy group at the C5 position by using our remote asymmetric induction reaction[5] and the regio- and stereoselective reductions.[6] We applied the methodology to accomplish the first total synthesis of septoriamycin A.[6] This methodology is a powerful tool to synthesize partially reduced polyketides having a hydroxy group or a δ-lactone. However, further steps for deoxygenation are required to prepare the reduced polypropionate having no oxygen in their chains. A stereoselective alkylation of a dienolate would be a straightforward and concise method to prepare reduced polypropionates. To the best of our knowledge, there is no precedent of the asymmetric alkylation of the γ-position of a dienolate derived from α,β-unsaturated carboxylic acid.[7] Herein, we report the stereoselective alkylation of the vinylketene silyl *N,O*-acetal possessing a chiral auxiliary and its application to the synthesis of mycocerosic acid [(2*R*,4*R*,6*R*,8*R*)-2,4,6,8-tetramethyloctacosanoic acid], a component of the cell envelope of *Mycobacterium tuberculosis*.

During the course of our synthetic studies on acyclic polyketides, we have developed remote asymmetric induction reactions including the vinylogous Mukaiyama aldol reactions and the acylation reaction (Scheme 1).[5,8] These reactions showed high stereoselectivity, although the reaction position (the terminal carbon of the dienol ether) was directed far from the chiral center of the auxiliary. These reactions construct stereogenic centers and introduce the enone attaching the chiral auxiliary simultaneously, so that they realize short-step syntheses of polypropionates.[6,8c,9] Based on these results, we examined a stereoselective alkylation of silyl dienol ether **1**, which would be a straightforward method to synthesize reduced polyketides.[10]

Scheme 1. Remote Asymmetric Induction Reactions Using the *E,E*-Vinylketene Silyl *N,O*-Acetal 1



At first, we investigated various Lewis acids in the presence of allyl iodide (Table 1). Frequently used Lewis acid including

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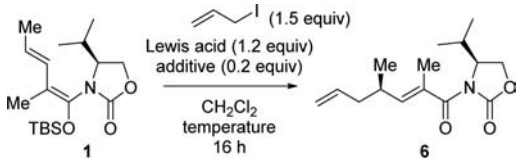
Table 1. Reaction of the *E,E*-Vinylketene Silyl *N,O*-Acetal 1 and Allyl Iodide in the Presence of Lewis Acid



entry	Lewis acid	additive	temp (°C)	yield (%)	dr[a]
1	$TiCl_4$		0	0	
2	$SnCl_4$		0	0	
3	$AlCl_3$		0	0	
4	$BF_3{\cdot}OEt_2$		rt	0	
5	$ZnBr_2$		rt	0	
6	$AgNO_3$		rt	10	10:1
7	Ag_2SO_4		rt	18	6:1
8	$AgClO_4$		0	24	18:1
9	$AgBF_4$		−20	45	10:1
10	AgOTf		−20	46	>20:1
11	AgTFA		−20	58	>20:1
12	AgTFA	$BF_3{\cdot}OEt_2$	−20	65	>20:1
13[b]	AgTFA		−20	80	>20:1
14[b]	AgTFA	$BF_3{\cdot}OEt_2$	−40	83	>20:1

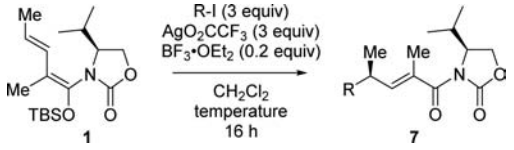
[a]The ratio was determined by 400 MHz ^{1}H NMR. [b]Allyl iodide (3 equiv), AgTFA (3 equiv), and $BF_3{\cdot}OEt_2$ (0.2 equiv) were used.

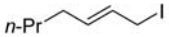
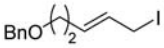
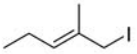
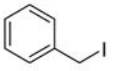
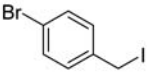
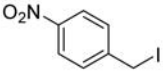
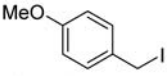
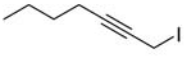
$TiCl_4$, $SnCl_4$, $AlCl_3$, $BF_3{\cdot}OEt_2$, and $ZnBr_2$ did not provide the allylated product **6** (Table 1, entries 1 to 5), while silver(I) salts[11] facilitated the reaction to give γ-adduct **6** with good to excellent stereoselectivity (entries 6−11).[12] Among silver(I) salts, silver trifluoromethanesulfonate (AgOTf) and silver trifluoroacetate (AgTFA) gave the adduct **6** in moderate yield with excellent selectivity (entries 10 and 11). No α-alkylated compound was observed. Addition of a catalytic amount of $BF_3{\cdot}OEt_2$[11a] in the presence of AgTFA gave better yield without affecting the stereoselectivity (entry 12). Increasing the amount of AgTFA and allyl iodide gave a higher yield of **6** (entry 13). After all, the reaction in the presence of $BF_3{\cdot}OEt_2$ proceeded at −40 °C to afford γ-adduct **6** in high yield with excellent regio- and stereoselectivity (entry 14). Therefore, the conditions of entry 14 were employed for the following reactions.

Next, we examined the alkylation reaction with a variety of alkyl iodides. Although *n*-Pr-I gave no adducts, activated iodides reacted with dienol ether **1** to provide γ-alkylated compounds (Table 2). Disubstituted allyl iodides gave the corresponding adducts in good yield with excellent stereoselectivity (Table 2, entries 2−4). Trisubstituted allyl iodide gave the adduct in moderate yield but stereoselectivity was high (entry 5). Benzyl iodides including benzyl iodide, *p*-bromobenzyl iodide, and *p*-nitrobenzyl iodide gave adducts in good yield with excellent selectivity (entries 6−8); however, *p*-methoxybenzyl iodide gave moderate yield with good selectivity (entry 9). In this reaction, we observed production of *p*-methoxybenzyl trifluoroacetate as a byproduct. Propargyl iodide also facilitated the reaction to give the corresponding propargyl adduct in good yield with good stereoselectivity (entry 10).

To investigate the reaction mechanism *Z*-olefin **8** was used as an electrophile in the alkylation reaction (Scheme 2). The reaction proceeded at −90 °C and provided a mixture of allylated compounds **9** and **10**. The *E*-isomer **10** was produced about the same amount as *Z*-isomer **9**. Additionally, ethyl iodoacetate did not afford the corresponding adduct (not shown in Scheme 2).

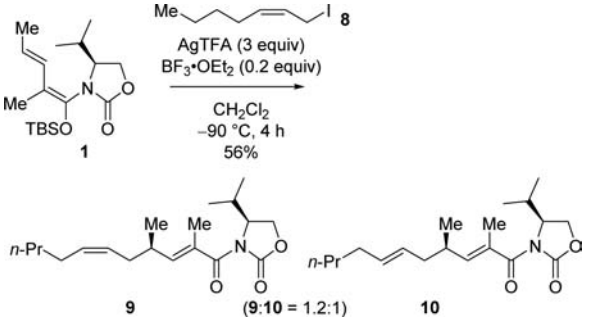
Table 2. Reaction with the *E,E*-Vinylketene Silyl *N,O*-Acetal 1 and Alkyl Halide in the Presence of AgTFA and $BF_3{\cdot}OEt_2$



entry	R-I	temperature (°C)	product	yield (%)	dr[a]
1		−78 to −40	**6**	83	>20:1
2		−78	**7a**	75	>20:1
3		−90	**7b**	77	>20:1
4		−78	**7c**	71	17:1
5		−90	**7d**	43	18:1
6[b]		−78	**7e**	76	>20:1
7		−78 to −40	**7f**	75	16:1
8		−20	**7g**	66	>20:1
9		−90	**7h**	58	9:1
10		−78	**7i**	73	13:1
11		−78 to −40	-	0	-

[a]The ratio was determined by 400 MHz ^{1}H NMR. [b]BnI (1.5 equiv) and AgTFA (1.2 equiv) were employed.

Scheme 2. Alkylation with *Z*-Allyl Iodide 8



These results suggest that the reaction involves cation intermediates.

Based on these results, we applied this alkylation reaction to natural product synthesis. Mycocerosic acid is a component of phthiocerol dimycocerosate (PDIM), a virulent factor of *Mycobacterium tuberculosis* (Figure 1).[13] Tuberculosis is a worldwide problem as a leather infection disease caused by *Mycobacterium tuberculosis*. PDIM is required for further investigation of the infection system of *M. tuberculosis*. The Minnaard group has achieved the total syntheses of mycocerosic acid and PDIM by the iterative catalytic asymmetric conjugate addition of methyl group to α,β-unsaturated thioester.[14] During the course of synthesis of polyketide compounds in our

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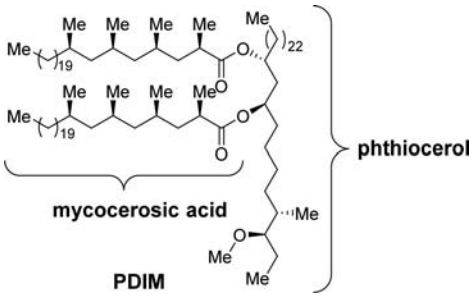
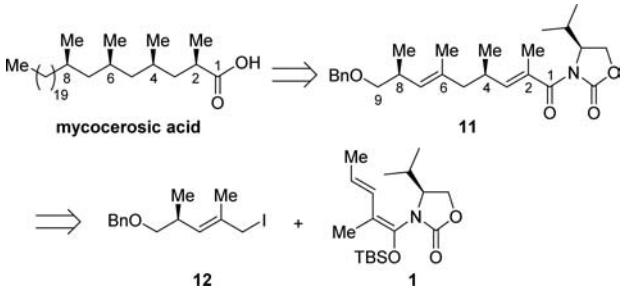


Figure 1. Structure of PDIM.

laboratory, we started the synthesis of PDIM. Herein, we report the concise synthesis of mycocerosic acid by using our stereoselective alkylation reaction. As shown in Scheme 3, we

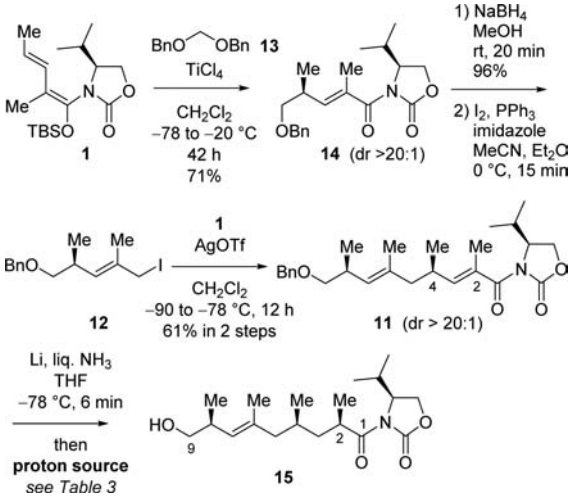
Scheme 3. Synthetic Plan toward Mycocerosic Acid



planned to synthesize mycocerosic acid by regio- and stereoselective reductions of two olefins of imide **11**, which would be synthesized by the stereoselective alkylation reaction with allyl iodide **12** and dienol ether **1**.

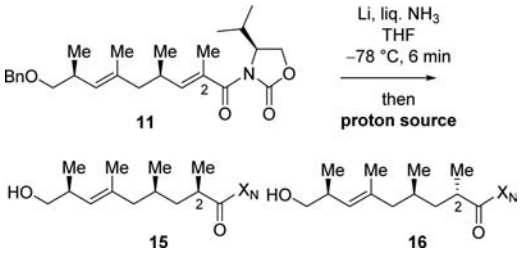
The synthesis started from the remote asymmetric induction reaction using vinylketene silyl *N*,*O*-acetal **1** and dibenzyl acetal **13** (Scheme 4). The reaction proceeded to give **14** in a

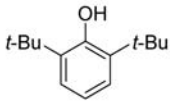
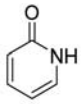
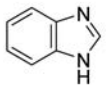
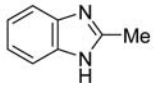
Scheme 4. Synthesis of C1−C9 Moiety of Mycocerosic Acid



stereoselective manner. Reduction of the imide to the primary alcohol, followed by Appel reaction, afforded unstable allyl iodide **12** which was immediately used in the next reaction. The reaction of **12** with vinylketene silyl *N*,*O*-acetal **1** in the presence of silver triflate gave **11** in good yield with good stereoselectivity. Subsequent Birch reduction promoted both reduction of α,β-unsaturated imide and removal of the benzyl group. In this reaction, we examined the proton source to prepare C2 position of the desired **15** (Table 3). When we added ammonium chloride

Table 3. Birch Reduction of Imide 11



entry	proton source	yield (%)	dr[a] (15:16)
1	NH_4Cl	72	2:1
2		86	2:1
3		61	4:1
4		86	12:1
5		81	>20:1

[a]The ratio was determined by 400 MHz ^{1}H NMR.

as a proton source, diastereoisomer at the C2 position (**16**) was produced as a minor product in a ratio of 2:1 (Table 3, entry 1). Although we employed 2,6-di-*tert*-butylphenol,[15] a frequently used phenol as a bulky proton source, the diastereoselectivity was not improved (entry 2). 2-Pyridone, reported by the Davies group[16] as a good proton source to react with the enolate attaching an oxazolidinone, improved the diastereoselectivity to 4:1 (entry 3). Considering the acidity of the proton source, we examined benzimidazole (pK_a 12.75[17]), which gave **15** in good yield with high stereoselectivity (entry 4). Finally, we added 2-methylbenzimidazole as a more bulky and commercially available proton source, and the desired **15** was obtained in good yield with excellent selectivity (entry 5).

After achieving the stereoselective reduction of α,β-unsaturated imide accompanied by deprotection to give primary alcohol **15**, the stereoselective reduction of the internal olefin was performed by the hydroxy group directed hydrogenation (Scheme 5). Shrock−Osborn catalyst worked very well to produce *all-syn* compound **17** in high yield with excellent stereoselectivity.[18] Oxidation of the primary alcohol was followed by Kocienski olefination to give olefin **18**, which was hydrogenated to give saturated imide **19**. Hydrolysis of the imide afforded mycocerosic acid, spectral data of which were identical to those reported previously[14a] in all respects. Therefore, mycocerosic acid has been synthesized in 10 steps from **1**.

In conclusion, we have established the remote asymmetric induction-type alkylation of vinylketene silyl *N*,*O*-acetal **1** with activated alkyl halides in the presence of silver(I) salt and boron trifluoride diethyl etherate and applied the reaction to synthesize

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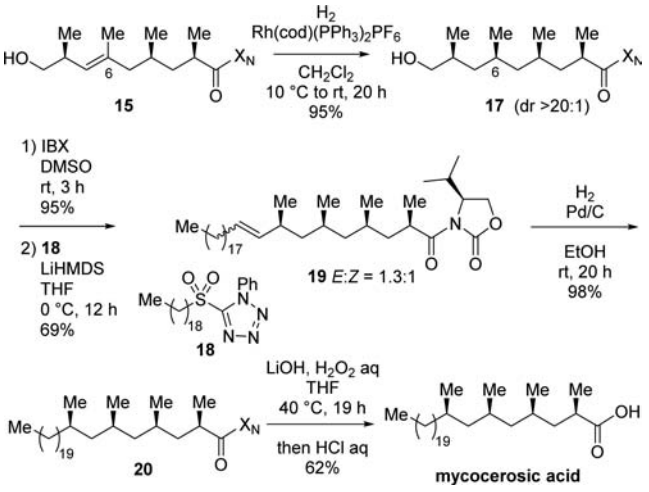
Scheme 5. Synthesis of Mycocerosic Acid



mycocerosic acid. In the Birch reduction of an unsaturated imide, 2-methylbenzimidazole was found to be an effective bulky proton source. These methods are useful to the synthesis of reduced polypropionates. Further application of these method to total synthesis of natural products is 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.5b03422.

Experimental procedure and physical property of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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Nickel-Catalyzed Borylation of Benzylic Ammonium Salts: Stereospecific Synthesis of Enantioenriched Benzylic Boronates

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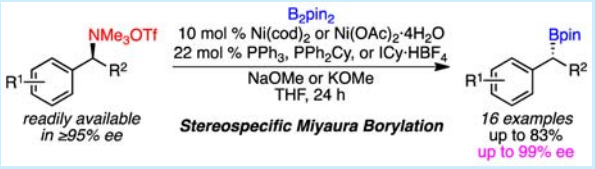
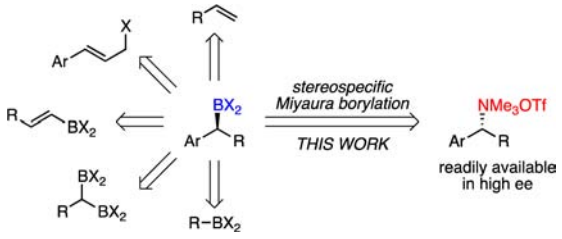
Supporting Information

ABSTRACT: We have developed a stereospecific, nickel-catalyzed cross-coupling of secondary benzylic ammonium salts and diboronate esters to deliver highly enantioenriched benzylic boronates. This reaction utilizes amine-derived electrophiles, which are readily available in high enantiopurity, and simple, inexpensive nickel catalysts. This reaction has broad scope, enabling synthesis of a variety of secondary benzylic boronates in good yields and excellent ee's.



Enantioenriched secondary benzylic boronic esters are valuable synthetic intermediates for the construction of complex molecules. Their C−B bonds can be converted with enantiomeric fidelity to C−O bonds by oxidation[1] or C−C bonds by cross-couplings[2] or Matteson-type homologations.[1b,d,3] Due to their utility, various methods have been developed to deliver these compounds in high enantiomeric enrichment (Scheme 1). From alkenes, catalytic, enantioselective hydroboration,[4] β-boration of α,β-unsaturated carbonyls,[5] diboration,[6] and 1,1-arylboration[7] methods have been developed. Borylation of allylic electrophiles also delivers enantioenriched benzylic boronates.[8] Boronate starting materials can also be utilized to prepare enantioenriched benzylic boronates. Methods utilizing boronate substrates include cross-couplings of diboranes;[9] hydrogenation, hydroboration, and conjugate additions of vinyl boronates;[10] and homologation approaches, such as Aggarwal's asymmetric deprotonation/borylation route.[11]

Scheme 1. Asymmetric Synthesis of Secondary Benzylic Boronates



Conspicuously absent from the previously reported asymmetric syntheses of secondary benzylic boronates is a Miyaura borylation of a benzylic electrophile.[12,13] This approach would offer a powerful alternative route from readily available starting materials. Notable methods for C−B cross-couplings of alkyl halides, tosylates, ammonium triflates, and ethers have been developed using copper and nickel catalysts; however, to date these methods only deliver achiral or racemic products.[14−16] Miyaura borylations of alkyl electrophiles to deliver enantioenriched products are currently limited to allylic electrophiles.[8,17]

We have reported a stereospecific, nickel-catalyzed Suzuki−Miyaura cross-coupling of benzylic ammonium triflates with arylboronic acids.[18,19] Amine-derived substrates are ideal electrophiles for stereospecific cross-couplings, because amines can be readily prepared in near-perfect enantiomeric excess via a variety of methods.[20] These amines can then be readily transformed to trimethylammonium salts via a two-step alkylation sequence, which requires only a single column chromatography purification.[21,22] In addition, amine-derived substrates offer a functional group handle orthogonal to ethers, and both amines and ammonium salts are stable to long-term storage. We envisioned that a stereospecific Miyaura borylation of these attractive amine-derived electrophiles would be possible by changing the arylboronic acid to a diborane coupling partner.[23] Herein we report an enantiospecific, nickel-catalyzed Miyaura borylation of secondary benzylic ammonium salts to deliver benzylic boronate esters in high yields and ee's. This reaction represents the first example of a cross-coupling of a benzylic electrophile to deliver a highly enantioenriched borane and is one of the first examples of a stereospecific cross-coupling of a benzylic electrophile and a heteroatomic nucleophile.[14,13] Furthermore, it offers complementary scope to existing methods for asymmetric synthesis of benzylic boronate esters, such as asymmetric hydroboration of styrenes.

We selected the borylation of ammonium triflate **1a** for our optimization. The amine precursor of **1a** is commercially available in >99% ee. We assume no loss in ee during its conversion to ammonium triflate **1a**. Using bis(pinacolato)-diboron (B_2pin_2) under conditions similar to those optimized for the arylation of secondary benzylic ammonium triflates,[18a] a low yield of boronate **2** was observed (Table 1, entry 1).

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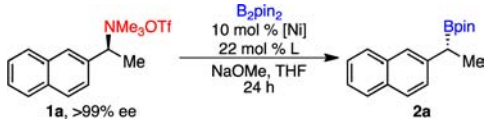
Table 1. Optimization of Borylation[a]



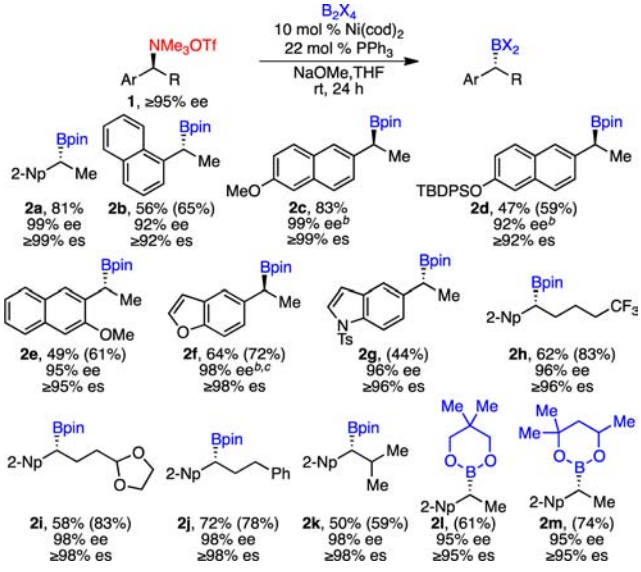
entry	[Ni]	L	temp (°C)	yield (%)[b]	ee (%)[c]
1[d]	$Ni(cod)_2$	P(*o*-Tol)$_3$	70	12	n.d.[e]
2	$Ni(cod)_2$	P(*o*-Tol)$_3$	70	78	95
3	$Ni(cod)_2$	P(*o*-Tol)$_3$	rt	84	98
4	$Ni(cod)_2$	PPh_3	rt	86	99
5	$Ni(cod)_2$	None	rt	81	97
6	$Ni(OAc)_2{\cdot}4H_2O$	PPh_3	rt	80	99
7[f]	none	PPh_3	rt	trace	n.d.[e]
8[g]	$Ni(cod)_2$	PPh_3	rt	0	n.d.[e]

[a]Conditions: ammonium triflate **1a** (>99% ee, 0.1 mmol, 1.0 equiv), B_2pin_2 (1.5 equiv), [Ni] (10 mol %), ligand (L, 22 mol %), NaOMe (1.5 equiv), THF (0.2 M), 24 h, unless otherwise noted. [b]Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as internal standard. [c]Ee's of the subsequent alcohol, formed via oxidation with H_2O_2 and NaOMe. Determined by HPLC analysis using a chiral stationary phase. [d]K_3PO_4 replaced NaOMe. [e]n.d. = not determined. [f]11 mol % PPh_3. [g]No base. 5 mol % $Ni(cod)_2$, 11 mol % PPh_3.

However, by changing the base from K_3PO_4 to NaOMe, a 78% yield and excellent stereochemical fidelity (95% ee) were achieved (entry 2).[24] By lowering the reaction temperature, protodeboration is minimized, leading to an even higher yield (entry 3). Investigation of the ligand showed that P(*o*-Tol)$_3$ can be replaced with PPh_3 (entry 4). Phosphine-less conditions are also successful, but provide **2** in a slightly lower yield and ee (entry 5). In addition, air-stable $Ni(OAc)_2{\cdot}4H_2O$ can be used, with only a slight reduction in yield for the model reaction (entry 6). However, with some other substrates, $Ni(OAc)_2{\cdot}4H_2O$ proved inferior to $Ni(cod)_2$ (not shown). Control experiments confirmed that both nickel and base are required for this reaction (entries 7 and 8). To obtain the highest levels of reactivity and enantiospecificity across a range of substrates, $Ni(cod)_2/PPh_3$ was selected as the optimal catalyst system (entry 4). Under these conditions, lower yields were obtained when iodide or methyl sulfate replaced triflate in the ammonium salt (30% and 72%, respectively, not shown). Consistent with the Suzuki arylation of benzylic ammonium triflates, this borylation proceeds with inversion of configuration.[22] These results compare favorably with asymmetric hydroboration of 2-vinylnaphthalene to deliver **2a**; via Rh- or Cu-catalyzed hydroboration, **2a** is formed in only 85−86% ee.[4b,d]

Under the optimized conditions, a variety of benzylic ammonium triflates successfully underwent borylation, delivering boronate products in good yields and excellent ee's (Scheme 2).[24] In every case, the benzylic amine precursors were prepared or purchased in high enantiopurity, highlighting an advantage of amine-derived electrophiles. Amines that were not commercially available were prepared via additions to Ellman's sulfinimines.[20b−d] The sulfinamide intermediates were isolated as single diastereomers (≥95% de), as determined by ^{1}H NMR, and we assume the subsequent ammonium triflates are prepared in ≥95% ee.[22] As shown by the comparison of yields determined by ^{1}H NMR analysis and isolated yields, the purification of some of these benzylic boronates often resulted in 10−15% loss of product due to unavoidable decomposition

Scheme 2. Scope of Ammonium Triflate[a]



[a]Conditions: ammonium triflate **1** (≥95% ee, 0.30 mmol, 1.0 equiv), B_2X_4 (1.5 equiv), $Ni(cod)_2$ (10 mol %), PPh_3 (22 mol %), NaOMe (1.5 equiv), THF (0.2 M), rt, 24 h, unless otherwise noted. Isolated yields. Yields in parentheses determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as internal standard. Ee's of the subsequent alcohol, formed via oxidation with H_2O_2 and NaOMe, determined by HPLC analysis using a chiral stationary phase. Enantiospecificity (es) = $ee_{prod}/ee_{sm} \times 100$. [b]Opposite enantiomer of **1** used. [c]50 °C.

of these sensitive compounds. Nonetheless, synthetically useful yields are obtained.

In addition to the 2-naphthyl substituent, a variety of other arenes with extended π-systems are well tolerated, including the more sterically hindered 1-naphthyl (**2b**) and both methyl and silyl ether substituted naphthyls (**2c−e**). Substrates with heteroaryl groups also undergo borylation. Benzofuran **2f** was formed in 64% yield and 98% ee. Indoles can also be utilized, providing excellent levels of stereochemical fidelity, albeit in lower yield (**2g**).

With respect to the alkyl substituent (R, Scheme 2), a wide variety of groups can be used. Linear alkyl groups are well tolerated, including those with trifluoromethyl and acetal functional groups (**2h−j**). Impressively, the borylation is also effective with branched alkyl substituents, such as a bulky *i*-Pr group (**2k**). Notably, asymmetric hydroboration cannot deliver benzylic boronates with branched substituents in this position. Dibenzylic ammonium salts (R = aryl) were unsuccessful in this borylation; no desired product was formed.

These reaction conditions are also amenable to the use of alternative diboranes. Borylation with bis(neopentylglycolato)-diboron (B_2neop_2) and bis(hexylene glycolato)diboron (B_2hex_2) delivered benzylic boronates **2l** and **2m** in good yields and excellent levels of stereochemical fidelity (Scheme 2). However, these benzylic boronates proved unstable to isolation, limiting their utility to downstream reactions that do not require purification after the Miyaura borylation.

To demonstrate the synthetic utility and robustness, we conducted the borylation of ammonium triflate **1c**, prepared in ≥95% ee, on a 1-g scale (eq 1). We employed air-stable $Ni(OAc)_2{\cdot}4H_2O/PPh_3$ as the catalyst, allowing benchtop setup. Boronate **2c** was isolated in 68% yield and near-perfect enantiopurity (99% ee). In contrast, asymmetric hydroboration

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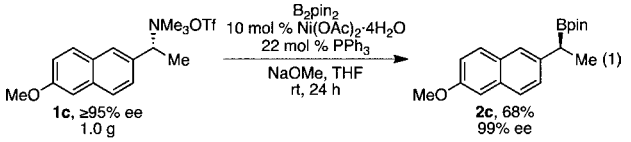
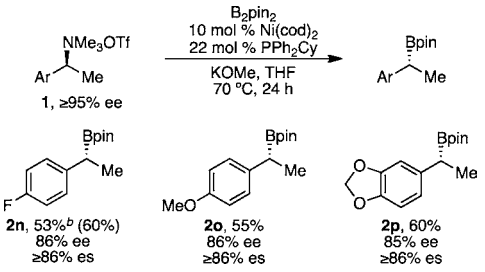


resulted in only 88% ee of **2c**.[4b] This boronate is a direct precursor to the anti-inflammatory drug (*S*)-naproxen, as shown by the Crudden group.[4b]

A current limitation of these conditions is that substrates must contain an aryl substituent with an extended π-system, such as naphthyl.[25] The borylation to form *p*-fluorophenyl-substituted **2n** under the standard $Ni(cod)_2/PPh_3$ conditions led to only 5% yield after 6 h. Hypothesizing that the lower reactivity of these substrates stems from difficulty in the oxidative addition, we investigated the use of more electron-donating ligands. By using a catalyst generated from $Ni(cod)_2$ and either 1,3-bis(cyclohexyl)imidazolium tetrafluoroborate ($ICy{\cdot}HBF_4$) or PPh_2Cy with KOMe as base at increased reaction temperature, synthetically useful yields and good ee's of benzylic boronates **2n**–**p** were achieved (Scheme 3).

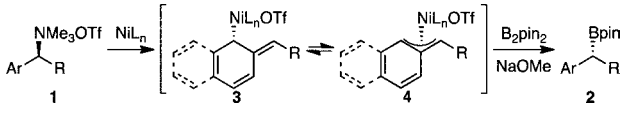
Scheme 3. Borylation of Non-naphthyl Substrates[a]



[a]Conditions: ammonium triflate **1** (≥95% ee, 0.3 mmol, 1.0 equiv), B_2pin_2 (1.5 equiv), $Ni(cod)_2$ (10 mol %), PPh_2Cy (22 mol %), KOMe (1.7 equiv), THF (1.0 M), 70 °C, 24 h, unless otherwise noted. Average isolated yields (±3%). Yields in parentheses determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as internal standard. Average ee's (±1%) of the subsequent alcohol, formed via oxidation with H_2O_2 and NaOMe, determined by HPLC analysis using a chiral stationary phase. [b]0.5 mmol scale. $ICy{\cdot}HBF_4$ (12 mol %) in place of PPh_2Cy. Result of a single experiment.

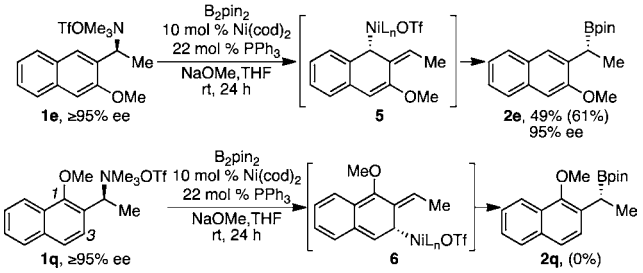
This reaction likely proceeds via an oxidative addition to generate a benzylic nickel species, which then undergoes transmetalation and reductive elimination to deliver an enantioenriched benzylic boronate product (Scheme 4). As is

Scheme 4. Proposed Mechanism



commonly observed in stereospecific cross-couplings of benzylic electrophiles, greater reactivity is observed for substrates containing aryl substituents with extended π systems.[25] This observation, along with the overall inversion of configuration, is consistent with oxidative addition occurring in an S_N2' fashion via attack of the nickel catalyst at the ortho carbon to generate nickel intermediates **3** and/or **4**, at least when the loss of aromaticity is not too costly. Further support for this hypothesis is seen by comparing the borylations of **1e** and **1q** (Scheme 5). The borylation of **1e** is effective, but borylation of **1q** resulted in no desired product. In this case, the

Scheme 5. Substituent Effects on Reactivity[a]



[a]Isolated yields. Yields in parentheses determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as internal standard. Ee's of the subsequent alcohol, formed via oxidation with H_2O_2 and NaOMe, determined by HPLC analysis using a chiral stationary phase.

methoxy group may hinder attack at C1. Attack at C3 would result in a less stable *syn*-allyl nickel intermediate **6** and a complete loss of aromaticity.[26]

In conclusion, we have developed a stereospecific, nickel-catalyzed Miyaura borylation of secondary, benzylic ammonium triflates to deliver benzylic boronates in good yields and excellent ee's. For naphthyl-substituted substrates, this reaction utilizes a simple and inexpensive $Ni(cod)_2/PPh_3$ or $Ni(OAc)_2{\cdot}H_2O/PPh_3$ catalyst. By using a more electron-rich ligand, borylation of non-naphthyl substrates has also been accomplished. This reaction represents the first example of a Miyaura borylation of a benzylic electrophile to deliver highly enantioenriched benzylic boronates, which represent a valuable class of intermediates for 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.5b03455.

Full experimental data, details on methods and starting materials, and copies of spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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The Hydroxyalkyl Moiety As a Protecting Group for the Stereospecific Alkylation of Masked Secondary Phosphine-Boranes

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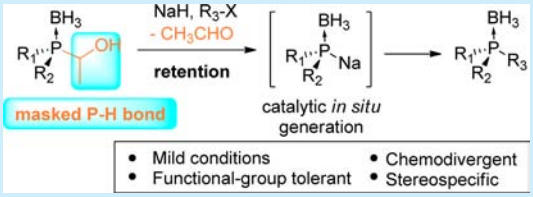
Supporting Information

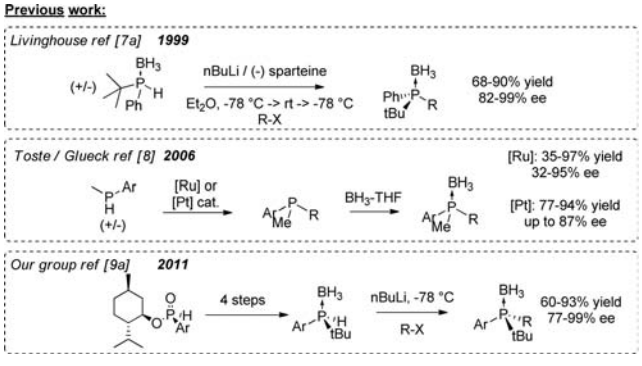
ABSTRACT: The synthesis of functionalized tertiary phosphine-boranes has been developed via a chemodivergent approach from readily accessible (hydroxymethyl) phosphine-boranes under mild conditions. O-Alkylation or decarbonylative P-alkylation product could be exclusively obtained. The P-alkylation reaction was found to proceed in moderate to very good yields and very high enantiospecificity (es >95%) using a variety of alkyl halides as electrophiles. The configurational stability of the sodium phosphido-borane intermediate was also investigated and allowed a deeper understanding of the reaction mechanism, furnishing secondary phosphine-boranes in moderate yield and enantiopurity.



In asymmetric catalysis, the use of chiral phosphines has allowed a wide array of enantioselective transformations, where the phosphine can be used either as a ligand for transition metals[1] or as an organocatalyst.[2] While most of the phosphine ligands used in asymmetric transition-metal catalysis have a chiral backbone,[3] the ones bearing the chiral center at the phosphorus atom (P-stereogenic phosphines) have been given much less attention, mostly due to their difficult asymmetric synthesis. However, in some cases, P-stereogenic phosphines feature better reactivity and/or selectivity than their chiral-backboned counterparts.[4] In this context, the synthesis of P-stereogenic phosphines remains a challenging area of research. Among the numerous methods leading to these chiral compounds, functionalization of secondary phosphines (SPs) or phosphine-boranes (SPBs) has been intensively documented.[5] More specifically, the design of P-stereogenic tertiary phosphines through alkylation of P-chiral secondary phosphines has been investigated[6] (Scheme 1). Indeed, in the late 1990s, Livinghouse described the sparteine-mediated Dynamic Thermodynamic Resolution (DTR) of *tert*-butyl (phenyl) SPB.[7a] The key point of the success of this method was the precipitation of one diastereomer of the lithiated phosphine-borane−sparteine complex at 25 °C, involving probably a crystallization-induced process.[7b] The metal-catalyzed dynamic kinetic resolution (DKR) of secondary phosphine has also been investigated by Toste and Glueck employing chiral ruthenium(II)[8a,b] or platinum(II)[8c−e] complexes as catalysts. Indeed, using methyl (aryl) phosphine, the authors described the preparation of a variety of chiral mono- and bis-phosphines, which may then be quenched by BH_3−THF[8a,b] to yield the corresponding phosphine-boranes. More recently, our group also developed the stereospecific alkylation of enantioenriched *tert*-butyl (aryl) SPB using *n*-BuLi as a base.[9a]

The reaction was found to occur with high conservation of chiral information as long as the reaction was run at −78 °C. Despite the remarkable efficiency of these methods, access to aryl(alkyl) or diaryl SPBs remains difficult, especially for enantioenriched compounds. Furthermore, although the alkylation of configurationally stable dialkylphosphido-boranes proceeds in high conservation of chiral information,[9c] the use of aryl(alkyl) or diaryl SPBs can be problematic, as partial racemization may occur following the alkylation temperature.[9a,b] The use of excess organolithium compounds as a base can also be prejudicial to the functional-group tolerance and, thus, limits the use of functionalized electrophiles (especially with carbonyl and halogen functional groups). Recently, Hayashi described the palladium-catalyzed decarbonylative arylation of (hydroxymethyl) phosphine sulfides in excellent yields[10] (Scheme 2). This retroaddition process had already been observed earlier by Imamoto under basic and thermal conditions,[11] and more recently by Kann, who noted the formation of racemic P-alkylation products.[11c] Pietrusiewicz[12a] and our group[12b] independently reported the stereo-

Scheme 1. Asymmetric Alkylation of SPs and SPBs



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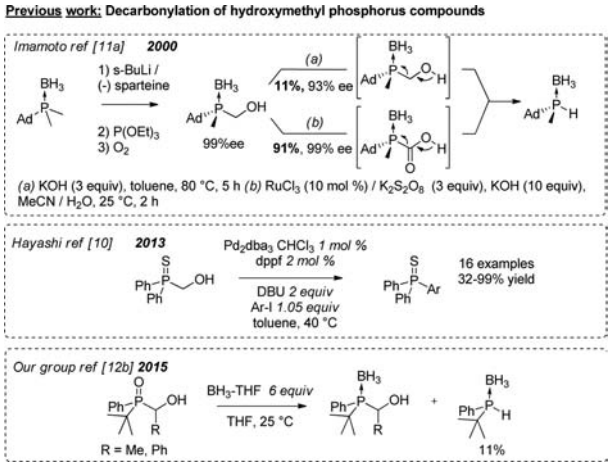
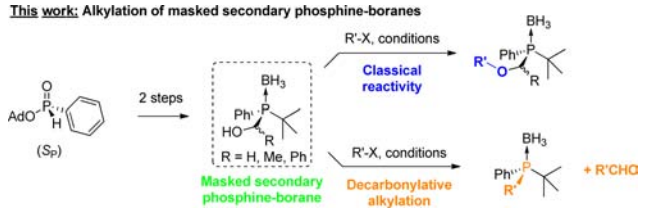
Scheme 2. Decarbonylations of (Hydroxymethyl) Phosphorus Compound



specific reduction of α-hydroxyphosphine oxides under mild conditions (Scheme 2).

When a carbon substituent was present on the α atom, we observed an erosion of the diastereoselectivity, and some SPB was isolated, along with the desired product.[13b] We also attributed this fact to the possible retroaddition of the hydroxyalkyl moiety under borane conditions. On the basis of these observations, we turned our attention to the development of a selective method for the decarbonylative alkylation of hydroxymethyl phosphine-boranes, which are readily obtained from H-adamantylphosphinates[12b,13] (Scheme 3).

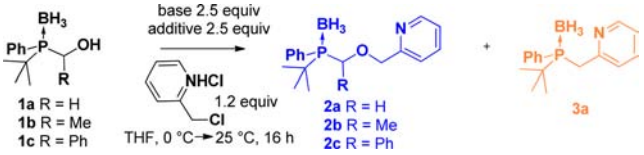
Scheme 3. Envisioned Strategy for the Alkylation of Masked SPBs



To optimize the conditions, we first screened the reaction parameters, using compound **1a** and *o*-(chloromethyl)pyridine hydrochloride as an electrophile. When the reaction was run at room temperature in THF and sodium hydride as the base, a nearly 1:1 mixture of O-alkylation (**2a**) and decarbonylative P-alkylation (**3a**) products was obtained in moderate yield (Table 1, entry 1). The formation of the latter product, resulting from the retro-addition (i.e., decarbonylation) of the α-hydroxyalkyl-phosphine-borane, was postulated to go through a sodium phosphido-borane, which would then be trapped by the electrophile *in situ*. When conducting the reaction on enantioenriched starting material, we obtained 29% of **2a** with nearly fully conserved chiral information (er = 97.5:2.5, entry 2) and 32% of **3a**, also with minor loss of enantiomeric excess (er = 95.5:4.5, entry 2). When looking at the influence of the solvent, we observed that both polar and nonpolar solvents favored the formation of **2a**, although THF gave a nearly 1:1 mixture (entries 2−4).

In the case of DMF, the enantiomeric ratio of **2a** decreased to 83:17 (entry 3), suggesting racemization of the sodium

Table 1. Optimization of the Reaction Conditions



entry	1[a]	base / additive	2/3a[b]	yield [%] (er)
1	(+/-) **1a**	NaH	1.1/1	30 (50:50)
				25 (50:50)
2	(S_P)-**1a**	NaH	1.1/1	29 (97.5:2.5)
				32 (95.5:4.5)
3[c]	(S_P)-**1a**	NaH	2.5/1	26 (83:17)
4[d]	(S_P)-**1a**	NaH	4.1/1	39 (98:2)
				9 (94:6)
5	(S_P)-**1a**	NaH / LiCl	-	-
6	(S_P)-**1a**	NaH / $MgCl_2$	-	-
7	(S_P)-**1a**	NaH / KCl	1.5/1	38 (98:2)
				28 (96:4)
8	(S_P)-**1a**	NaH / CsCl	1/1.5	28 (96.5:3.5)
				40 (97.5:2.5)
9	(S_P)-**1a**	NaH / Bu_4NCl	>1/20	48 (50:50)
10[e]	(S_P)-**1a**	NaH	>20/1	80 (97.5:2.5)
11	(S_P)-**1b**	NaH	>1/20	57 (93:7)
12	(S_P)-**1c**	NaH	>1/20	36 (93:7)
13[f]	(S_P)-**1b**	NaH	>1/20	77 (95:5)
14[f]	(R_P)-**1b**	NaH	>1/20	79 (4.5:94.5)

[a] **1a**: er = 98:2. **1b**: dr ~1/1, er = 95:5 (both diastereomers). **1c**: dr =2.6/1, er (major dia) = 98.5:1.5 and er (minor dia) = 87:13. [b] Determined by ^{31}P NMR of the crude. [c] DMF used as solvent. [d] Toluene used as solvent. [e] 2-(Bromomethyl)pyridine hydrobromide used as the electrophile. [f] 3 equiv of NaH were used.

phosphido-borane intermediate in a more dissociating solvent.[11c] Then, we turned our attention to the influence of an alkoxide counterion using THF as solvent, and we observed that the more the ion pair was separated, the more formation of **3a** was favored (entries 2, 5−9). However, in the case of the ammonium counterion, this was also accompanied by complete racemization at the phosphorus atom (entry 9). This is consistent with the formation of *tert*-butyl(phenyl)phosphido borane, the configurational stability of which would depend on the counterion.[9b,14] It is worth noting that when using strongly coordinated Mg or Li counterions (entries 5−6), the reaction did not proceed at room temperature. When changing the leaving group on the electrophile from Cl to Br, only product **2a** was obtained in 80% isolated yield and 97:3 er (entry 10). This is also in accordance with retroaddition of the hydroxymethyl group, as when using a better leaving group (X = Br), SN_2 of the alkoxide on the alkyl halide (i.e., "Williamson"-type reaction) may kinetically outcompete the retroaddition, thus allowing the selective formation of **2a**. Finally, we evaluated the influence of substitution on the α-carbon on the selectivity. When a carbon substituent was present (R= Me, Ph, entries 11−12), highly selective formation of **3** was observed. Indeed, the use of methyl substituted substrate **1b** did furnish the desired product **3** without any detectable amount of the O-alkylated product **2b**, in a moderate 57% yield and high enantiomeric ratio (er = 93:7, entry 11). The use of phenyl substituted substrate **1c** gave similar

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reactivity and selectivity for the formation of **3** (36% yield, er = 93:7, entry 12). Finally, when the amount of sodium hydride was raised to 3 equiv, the reaction of **1b** gave the desired compound **3a** in a good 77% yield and very good enantiomeric ratio (er = 95:5, entry 13). The substitution occurred stereospecifically with retention of configuration at the phosphorus atom, as the reaction of the other enantiomer gave a similar yield and afforded the other enantiomer of the product in nearly equal selectivity (entry 14). Unlike previously reported protocols,[11b] the reactions did not lead to detectable amounts of aldehyde reduction products by the sodium phosphido-borane at operating temperature (assessed by the absence of degradation products on ^{31}P NMR). With these optimized conditions in hand, we turned our attention to expanding the scope of the decarbonylative P-alkylation of **1b**, using a variety of alkyl halides (Figure 1). When a variety of benzylic halides were used (Figure 1, **3b**−**f**), electron-donating groups on the aromatic ring favored the reaction.

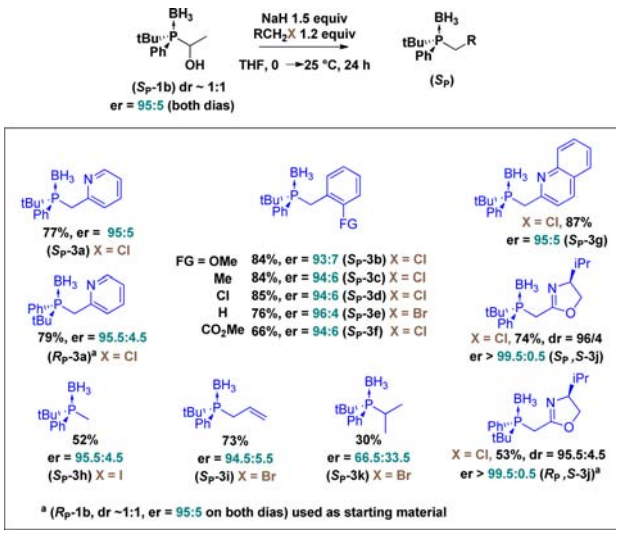
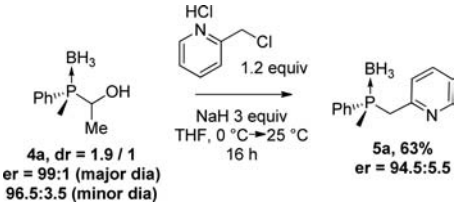


Figure 1. Scope of the P-alkylation of compound **1b** (dr ∼1/1, er = 95:5 (both diastereomers)).

The use of methyl iodide or allyl bromide also allowed the formation of compounds **3h** and **3i**, respectively, in moderate yields. In all these cases, minor to no erosion of the stereochemical information was observed (es >95%).[15] This method also allowed the use of (chloromethyl) chiral oxazoline as an electrophile, to furnish P, C stereogenic phosphine/oxazoline preligands (compounds **3j**) in moderate yields and with high diastereo- and enantioselectivity. Again, no racemization was observed on the product. Indeed, as a chiral electrophile is used in this case, the racemization can be assessed by comparing the er of the starting material with the dr of the product, given that the carbon center does not undergo racemization under these conditions. The use of less reactive secondary alkyl bromide resulted in decreased reactivity and selectivity using the optimized conditions (**3k**, 30% yield, er = 66.5:33.5). In this case, 36% of SPB (resulting from unreacted sodium phosphido-borane) was also isolated.

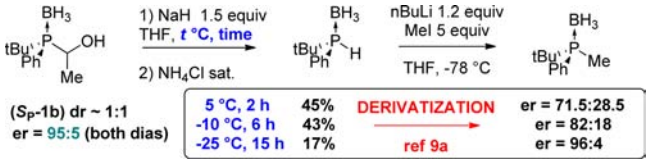
Using methyl(phenyl) masked SPB **4a**, the access to tertiary phosphine **5a** was enabled under the same conditions. In this case, the reaction was found to be slower but occurred in similar enantiospecificity, as only minor racemization occurred (Scheme 4). This remarkable result testifies to the versatility of

Scheme 4. Alkylation of Other Group Functionalized P-Stereogenic Phosphine-Borane



the method, which allows the formation of enantioenriched compounds which are challenging to access using reported methods.[8a] To gain information on the reaction mechanism, we used a proton source as the electrophile. The corresponding SPB was obtained, and its enantiomeric ratio was assessed by derivatizing to the corresponding P-Me compound[9a] (Scheme 5). When the deprotonation was run at 5 °C for 2 h, 45% of

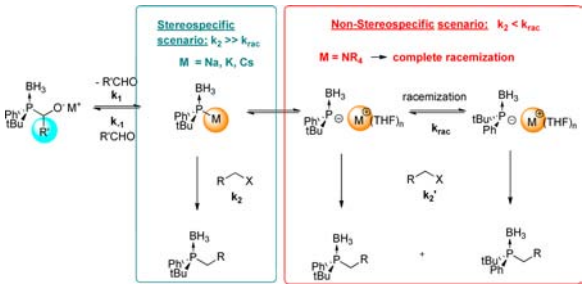
Scheme 5. Configurational Stability of Sodium Phosphido-Borane



SPB was isolated, and substantial racemization occurred. At −10 °C, the reaction outcome was similar to the case for 5 °C, although racemization was diminished. At −25 °C, the reaction provided desired SPB in low yield (17%) but without erosion of enantiomeric ratio, accounting for the higher stability of the alkoxide at low temperature.

These results suggest that the sodium secondary phosphido-borane seems to be configurationally more stable than its lithium counterpart.[9b,14] However, as detectable racemization occurs despite the temperature, this does not explain the complete stereospecificity observed during the alkylation process. To rationalize this result, we propose a mechanism where the sodium phosphido-borane would be generated in a catalytic amount through the reaction time, and in the presence of the electrophile, alkylation at the phosphorus atom would be faster than racemization of the anionic intermediate ($k_2 \gg k_{rac}$, Scheme 6). This mechanism would also explain complete racemization using the ammonium counterion, as in this case of $k_2 < k_{rac}$. In the case of a less electrophilic secondary alkyl halide, a diminished k_2 value may account for the decrease in stereoselectivity of the process ($k_2 \approx k_{rac}$).

Scheme 6. Proposed Reaction Scenario



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In conclusion, we have synthesized a variety of functionalized tertiary phosphine-boranes by a straightforward approach, with moderate to good yields and excellent enantiomeric ratios. In the present report, the configurational instability of alkyl(aryl)-phosphido-boranes has been circumvented by catalytic *in situ* generation of these reactive species under mild conditions via decarbonylation of hydroxyalkylphosphine-borane. The synthesis of these compounds has been achieved in a three-step enantiospecific sequence, from readily available, enantiopure H-adamantyl phosphinate (which are separated via semipreparative chiral HPLC).[13a]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03450.

Experimental procedures, products characterization, NMR spectra, and HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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(15) Enantiospecificity es = ee (product)/ee (starting material). The absolute stereochemistry was determined by comparing the sign of optical rotation of compound **3e** with ref 9a, confirming the retention of configuration at the phosphorus atom.

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In Situ Generated Ag^{II}-Catalyzed Selective Oxo-Esterification of Alkyne with Alcohol to α-Ketoester: Photophysical Study

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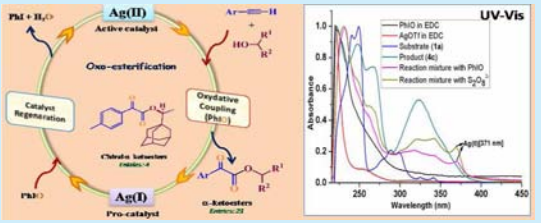
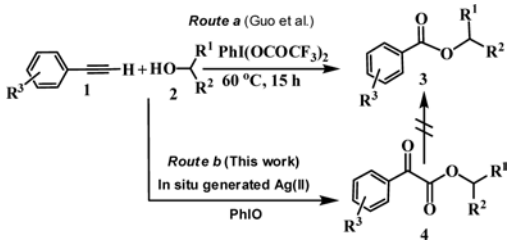
Supporting Information

ABSTRACT: An expert and easy one-step catalytic method for the multi O−C coupling of alkyne is developed for the synthesis of valuable α-ketoesters and their chiral analogues, in contrast to the generation of esters by a noncatalytic method. The in situ generated powerful Ag^{II} catalyst from AgOTf is the workhorse in the oxidative grafting of alkyne with PhIO and alcohol. The radical mechanism is confirmed in our controlled experiments and UV−vis study.



Direct introduction of two vicinal functional groups into a C−C triple bond has found immense application in recent times.[1,2] The intermolecular heterodifunctionalization is an especially attractive process to achieve valuable synthons, intermediates, pharmaceuticals, bioactive natural products, and their synthetic analogues.[1] In a continual effort to study the reaction of alkynes with λ^3-hypervalent iodines[3] under mild reaction conditions,[1b,4] we envisaged that a terminal alkyne can be directly transformed into valuable α-ketoesters (**4**, route b, Scheme 1) through simultaneous installation of two oxo groups

Scheme 1. Selective Synthesis of α-Ketoester over Ester



into both the alkyne carbons and O−C coupling to ≡C−H with alcohols. Interestingly, during preparation of our oxidative difunctionalization strategy, Guo and co-workers published a noncatalytic reaction to esters (**3**, route a, Scheme 1) through cleavage of alkynes with fluorinated λ^3-hypervalent iodine [$PhI(OCOCF_3)_2$] at 60 °C (15 h).[5] Thus, it is a great challenge for direct syntheses of α-ketoesters (**4**, route b) without generation of ester **3**. We were looking for efficient catalyst, neutral hypervalent iodine, and mild reaction conditions to avoid breakage of the labile keto-ester bond (C_2−C_1) of **4**, which may produce the byproduct **3** (route b). Ag^{II} species[6] was the catalyst of choice, and PhIO[7] was chosen as an oxygen source for keeping reaction medium neutral, rather than making harmful acidic conditions for the use of $PhI(OCOR)_2$.

α-Ketoesters and their analogues are widespread in Nature, valuable pharmaceuticals, and bioactive natural products such as cysteine and serine proteinase inhibitors α-ketoester-β-amines, thrombin inhibitor α-ketoester peptides, cancer cell growth inhibitors and insecticidal antibiotic respirantin, and anti-influenza-active angelicin.[8] α-Ketoesters bearing strongly electron-deficient carbonyl and neighboring binding-capable ester functionalities make them useful synthons for asymmetric reduction, fluorination, aminohydroxylation, and aldol reactions, tandem heterocyclization, lactonization, construction of bioactive natural products, and efficient epoxidation catalysis and have strongly chelation-guided optical properties.[9] α-Ketoesters were synthesized using Pd^{II}, Cu^{I}, Cu powder, and I_2-mediated coupling of alcohol to carbon monoxide, 1,3-diketones, 1,3-ketoaldehydes, and acetophenones, respectively.[10] α-Functionalized esters were the preferred precursor for α-ketoesters, which were achieved using Rh^{I}, $^{n}BuLi$, Bu_4NF−KF, Ru^{II}, and PDIA−H_2SO_4.[11] There are also a few other reported methods.[12] Syntheses of α-ketoesters were also reported through oxidation of trimethylsilyl-activated acetylenes using OsO_4−$^{t}BuO_2H$,[13a] Co(salen)-catalyzed reaction,[13b] and a similar two-step reaction using the strong oxidant $KMnO_4$ under basic conditions.[13c] Direct synthesis of α-ketoesters and their chiral analogues through coupling of alkyne with alcohol under low catalyst loading will be an exciting addition to the existing approaches.

We have reported several benign strategies using PhIO under neutral conditions.[7a−d] To synthesize α-ketoester **4a**, this work begins with (Table 1) treatment of a mixture of 4-biphenylacetylene (**1a**, 1 mmol), PhIO (3 mmol), and methanol (1 mmol) in 1,2-ethylene dichloride (EDC) with a suitable catalyst (1 mol %). Our early catalyst screening using several potential metal salts and complexes (only two are only shown, entries 1 and 2, Table 1) were unsuccessful. Gratifyingly, upon use of metal catalysts such as Fe^{III}, Pd^{0}, Ir^{III}, and Rh^{III} the reactions were successful (entries 3−6) in producing the desired product **4a**. However, the poor yields were a major concern of these reactions, and the yields were not improved (18−25%)

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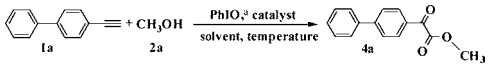
Table 1. Survey and Optimization of the Reaction



entry	catalyst[b]	solvent[c]	temp (°C)	time (h)	yield[d] (%)
1	$Ni(OAc)_2.4H_2O$	EDC	80	8	
2	$RuCl_3.xH_2O$	EDC	80	10	
3	$FeCl_3$	EDC	80	8	20
4	$Pd(PPh_3)_4$	EDC	80	8	25
5	$IrCl_3$	EDC	80	6	18
6	$RhCl_3.3H_2O$	EDC	80	4	22
7	AgOTf	EDC	rt	12	58
8	AgOTf	EDC	80	1.5	68
9	AgOTf	EDC	40	1.5	71
10	**AgOTf[e]**	**EDC**	**40**	**1.5**	**70**
11[f]	AgOTf	EDC	40	1.5	63
12[g]	AgOTf	EDC	40	8.0	
13		EDC	40	9.0	12
14	AgOTf	EDC	80	1	50
15	AgOTf	MeOH	40	1.5	65
16	AgOTf	THF	40	1.5	62
17	AgOTf	$PhCH_3$	40	1.5	45
18	$AgClO_4$	EDC	40	2	60
19	$AgNO_3$	EDC	40	3	40
20	$AgVO_3$	EDC	40	6	25
21	Ag_2O	EDC	40	6	20

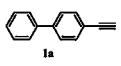
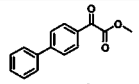
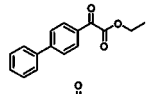
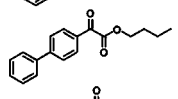
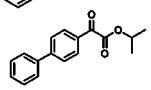
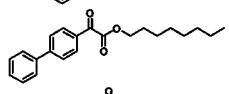
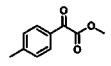
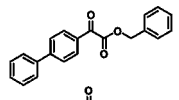
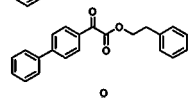
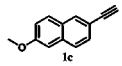
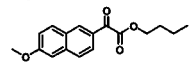
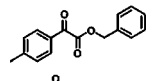
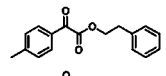
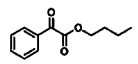
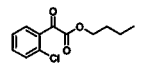
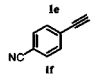
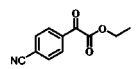
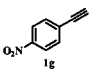
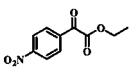
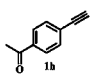
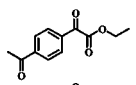
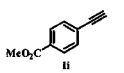
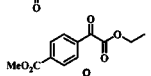
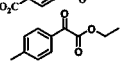
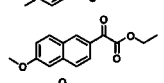
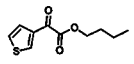
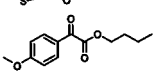
[a]PhIO (3 mmol), **1a** (1 mmol), and **2a** (1 mmol). [b]1 mol %. [c]5 mL. [d]Purified by column chromatography. [e]0.1 mol %. [f]PhIO (2.5 mmol). [g]No PhIO.

with higher catalyst loading and reaction temperature. Surprisingly, the yield of **4a** was significantly improved (58%, entry 7) upon use of AgOTf (1 mol %) at ambient temperature. Both the yield (71%) and reaction rate (1.5 h) were further improved under warming (40 °C) conditions (entries 8−11). Optimized conditions were developed using only 0.1 mol % of AgOTf catalyst to complete the reaction within 1.5 h (entry 10) in 70% yield. Our controlled experiments (entries 11−14) confirm the presence of AgOTf catalyst (0.1 mol %) and oxidant PhIO (3 mmol) were essential for the heterodifunctionalization process. EDC was found as the best solvent (entries 10 and 15−17). Other silver salts (entries 18−21) were not found to be better catalysts.

The tolerance of various functionalities was successfully examined for this new method (Scheme 2) through synthesis of a wide range of compounds bearing both unsubstituted and substituted aromatic rings (Table 2), heterocycles (**4t**), biphenyl systems (**4a−e,g,h**), and naphthalene ring (**4i**). The manipulation of substrates has been achieved using primary, secondary (**4d**), and long-chain alcohols (**4e**). Arylalkynes bearing deactivating group halogen, nitrile, nitro, ketone, and ester

Scheme 2. Synthetic Route to α-Ketoesters

Table 2. Synthesised α-Ketoesters

Entry	Alkyne (1)	Alcohol (2)	Product (4)	Time (h)	Yield (%)
1	 1a	CH_3OH		1.0	4a, 70
2	1a	C_2H_5OH		1.5	4b, 78
3	1a	$^nC_4H_9OH$		1.0	4c, 77
4	1a			1.0	4d, 80
5	1a	$^nC_8H_{17}OH$		1.5	4e, 78
6	 1b	CH_3OH		1.5	4f, 70
7	1a			2.0	4g, 66
8	1a			2.0	4h, 67
9	 1c	$^nC_4H_9OH$		3.0	4i, 55
10	1b			2.0	4j, 70
11	1b			2.0	4k, 74
12	 1d	$^nC_4H_9OH$		2.0	4l, 65
13	 1e	$^nC_4H_9OH$		3.0	4m, 65
14	 1f	C_2H_5OH		3.0	4n, 62
15	 1g	C_2H_5OH		3.0	4o, 65
16	 1h	C_2H_5OH		4.0	4p, 72
17	 1i	C_2H_5OH		3.5	4q, 71
18	1b	C_2H_5OH		2.0	4r, 68
19	1c	C_2H_5OH		3.0	4s, 54
20	 1j	$^nC_4H_9OH$		4.0	4t, 64
21	 1k	$^nC_4H_9OH$		4.0	4u, 52

(**4m−q**, entries 13−17) were tolerated, but alkene was not tolerated. The unorthodox carbonylation via an esterification strategy to functionalized α-ketoesters (**4a−u**) was rapid (1.0−4.0 h) and moderate to high yielding (52−80%). The substrate (**1**) bearing a strongly electron-rich aromatic substituent such as alkyne **1c** and **1k** (entries 9, 19, and 21) reduced the yield of **4i**, **4s**, and **4u** substantially (52−55%) because of the formation of

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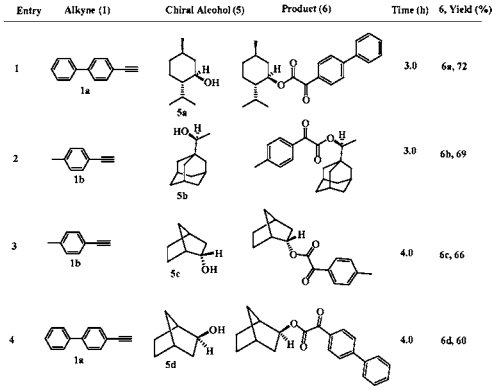
the corresponding degradation byproduct esters (**3**, Scheme 1). The structure of compound **4g** was confirmed by single-crystal X-ray diffraction data analyses (Scheme 2).[14]

To explore the scope of the benign strategy for synthesis of thermally labile chiral α-ketoesters we have carried out the reaction using secondary chiral alcohols (**5**, Table 3). Gratifyingly, chiral alcohols bearing sterically congested menthyl (**5a**, entry 1, Table 3), adamentyl (**5b**, entry 2), and norbornyl (**5c,d**, entries 3 and 4) groups smoothly underwent an oxidative difunctionalization reaction to afford optically pure new α-ketoesters (**6a−d**, Table 3). Most of the reported methods have limits for direct access to the chiral α-ketoesters.

Table 3. Scope of the Strategy for Chiral α-Ketoesters



The Ag^{II} complex is a metastable species[15] and appeared as a transient intermediate. In our control experiment, we noted that the reaction was almost arrested in the presence of radical scavenger TEMPO. This result suggested the reaction follows a radical pathway. Our UV−vis study of the dynamic reaction along with separate solutions containing EDC and AgOTf, AgOTf with PhIO, and a combination of AgOTf, PhIO, and substrate 4-phenylphenylacetylene (Figure 1) reveals the appearance of a new peak at 371 nm. The peak was intensified upon addition of $K_2S_2O_8$. Kochi and Anderson[15] achieved similar results using a solution of $AgNO_3$ and stronger electron acceptor $S_2O_8^{2-}$, which absorbed at 381 nm[15a] because of forming Ag^{II}. With these experiments we have not only confirmed that this reaction is catalyzed by in situ produced metastable Ag^{II} species from procatalyst[16] AgOTf but also discovered formation of the active oxidative radical Ag^{II} catalyst upon treatment of λ^3-hypervalent iodines. It will definitely find considerable application in frequently used Ag^{I}-hypervalent iodine mediated reactions.

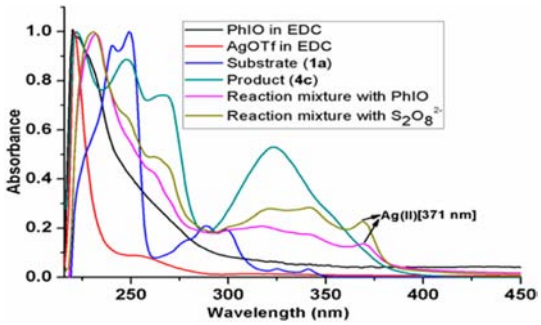
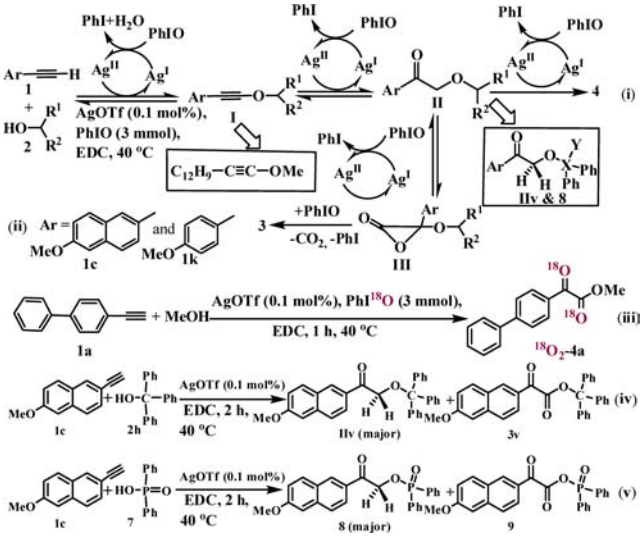


Figure 1. UV−vis study and detection of Ag^{II} species.

Based on our control experiments, UV−vis study, and literature evidence,[6,14,15] we have proposed a radical mechanism for this reaction (Scheme 3). PhIO is a well-known λ^3-hypervalent iodine reagent that follows a radical reaction pathway.[17] PhIO transforms procatalyst Ag^{I} into transient Ag^{II} species through single electron capturing, which converts **1** into the Ar−C≡C$^{\bullet}$ radical followed by O−C coupling with alcohol (**2**) to deliver an intermediate **I** (eq i). The intermediate **I** for **4a** was identified by mass spectrometry (Supporting Information), which appeared at retention time 20.20 min with desired mass 208 ($C_{12}H_9$−C≡C−OCH_3). The reaction is expected to pass through formation of **II** and transfer of "O" from PhIO leading to construction of **4**. Transfer of both "O" from PhIO was established using $PhI^{18}O$, which produced $^{18}O_2$−**4a** (eq iii) of mass 245.0948 (M + H). On the other hand, installation of two "oxo" groups and migration of Ar with release of CO_2 may produce a simple ester (eq ii), which was observed by Guo et al. (**3**, Scheme 1).[5] Upon use of strongly activated alkynes such as **1c** and **1k** (entries 9, 19, and 21, Table 2), we found corresponding esters (**3**) about 5% under the reaction conditions, which were increased by elevated temperature and longer reaction time. Herein, transformation of intermediate **II** to product **4** is expected to be a fast process because our attempts for trapping the intermediate **II** were unsuccessful (eq iv,v). Surprisingly, upon use of electronic and sterically congested triphenyl carbinol (**2h**) and diphenylphosphinic acid (**7**) the corresponding intermediates **IIv** and **8** were trapped, isolated, and characterized. This supports the proposed mechanism.

Scheme 3. Possible Reaction Pathways



In conclusion, we have demonstrated an in situ generation of robust Ag^{II} catalyst from a procatalyst Ag^{I} using PhIO under neutral reaction conditions. Our preliminary mechanistic study reveals that carbonylation via esterification of alkynes follows the radical pathway. It is an expert, selective, and simple method for direct synthesis of α-ketoesters through oxidative grafting of terminal alkynes and alcohols using very low catalyst loading. The simple and benign one-step strategy for the multi O−C coupling reaction brings another frontier into metal catalysis, which is compatible for easy access to valuable chiral α-ketoesters.

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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.5b03484.

X-ray data for **4g** (CIF)
Detailed experimental procedures, XRD, and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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