Organic LETTERS

Letter

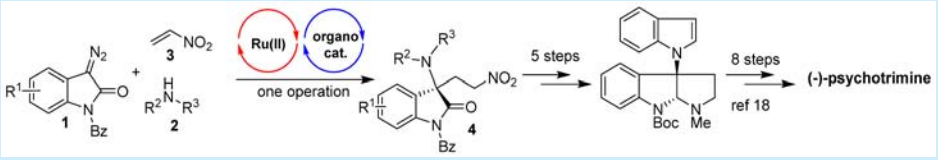
pubs.acs.org/OrgLett

Ru(II)/Organo Relay Catalytic Three-Component Reaction of 3-Diazooxindoles, Amines, and Nitroalkene: Formal Synthesis of (−)-Psychotrimine

Xiao-Lei Lian, Jing Meng, and Zhi-Yong Han*

Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei 230026, China

Supporting Information



ABSTRACT: A highly enantioselective carbenoid-associated N−H functionalization/Michael addition cascade reaction is developed by virtue of Ru(II)/chiral organo bifunctional catalyst relay catalysis. In this way, a variety of optically pure 3-amino-3-alkyloxindoles can be easily achieved. Moreover, on the basis of this metal/organo relay catalytic three-component protocol, a key intermediate for the formal synthesis of (−)-psychotrimine could be obtained in six steps with 25% overall yield.

3,3-Disubstituted oxindoles are privileged structural motifs found in a large number of natural products, drugs, and pharmaceutical agents.[1] Specifically, 3-amino-3-alkyloxindoles have received increasing attention due to their frequent occurrence in bioactive compounds and natural products (Figure 1).[2] For instance, AG-041R was found to be a potent gastrin/CCK-B receptor antagonist.[3] Juanlimycins A and B, as the latest isolated members of the family of ansamycins, which has shown a high degree of druggability, feature the structure of tethered bis-3-amino-3-alkyloxindoles.[4] Moreover, on the basis of 3-amino-3-alkyloxindoles, it is rather convenient to construct hexahydropyrrolo[2,3-*b*]indoles,[5] which are the key structural elements in a wide selection of alkaloids exemplified by psychohenin[6] and psychotrimine.[7]

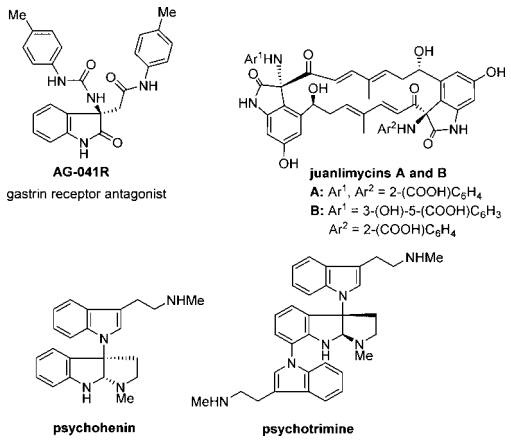


Figure 1. Representative biologically active molecules and natural products containing 3-amino-3-alkyloxindole and their derivatives.

Because of their structural importance and also driven by the fact that the absolute configuration at the C3 position of oxindoles strongly affects their biological activities, a number of methods have been developed for the asymmetric synthesis of 3-amino-3-alkyloxindoles.[8] These methodologies include addition of various nucleophiles to isatin imines,[9] addition of oxindoles to azodicarboxylate and nitrosobenzene,[10] Morita−Baylis−Hillman reactions,[11] palladium-catalyzed intramolecular arylation,[12] rhodium(II)-catalyzed oxidative intramolecular aza-spiroannulation and addition/cyclization of 3-isothiocyanato-2-oxindoles.[13] Notably, Yuan and co-workers reported a highly enantioselective organo-catalyzed asymmetric Michael addition of 3-amino-oxindoles to nitroalkenes to afford chiral oxindoles.[14] Recently, a promising strategy based on metal/organo relay or cooperative catalyzed elaboration of diazooxindoles has emerged as a potentially general approach to chiral 3,3-disubstituted oxindoles.[15] In the regard of asymmetric synthesis of 3-amino-3-alkyloxindoles, Gong and co-workers have developed a Rh(II)/chiral phosphoric acid cooperatively catalyzed three-component reaction of diazooxindoles, anilines, and ethyl glyoxylates.[15a] Despite these achievements, highly efficient synthetic methods to access optically active 3-amino-3-alkyloxindoles are still in great demand. Herein, we describe a Ru(II)/chiral bifunctional organocatalyst catalyzed multicomponent reaction of diazooxindoles, amines, and nitroalkene leading to chiral 3-amino-3-alkyloxindoles. Based on this methodology, we have successfully completed the formal synthesis of trimeric indole alkaloid (−)-psychotrimine (Figure 2).

Received: July 11, 2016
Published: August 16, 2016

DOI: 10.1021/acs.orglett.6b02019
Org. Lett. 2016, 18, 4270−4273

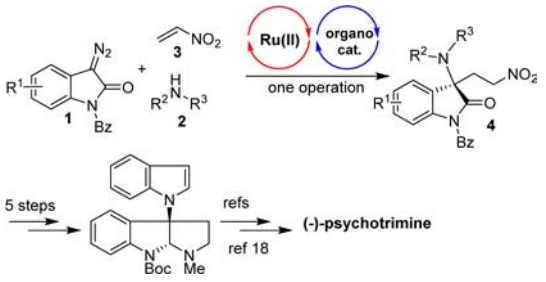
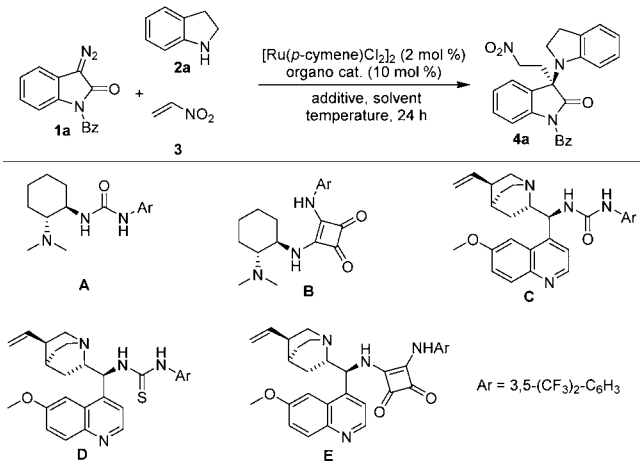


Figure 2. Metal/organo binary catalytic reaction and application to the formal synthesis of psychotrimine.

Influenced by previous work,[15a,c,e] we initiated this study from the reaction of benzoyl-protected diazooxindole **1a**, indoline **2a**, and nitroalkene **3** in the presence of 2 mol % of $[Ru(p\text{-cymene})Cl_2]_2$ and 10 mol % of bifunctional catalyst **A** in dichloromethane at room temperature (Table 1, entry 1). To our delight, 3-amino-3-alkyloxindole **4a** was obtained with 78% enantiomeric excess, albeit with only 32% yield (Table 1, entry 1). Bifunctional squaramide−tertiary amine catalyst **B** afforded the product with slightly lower enantioselectivity (entry 2). Quinine-incorporated urea **C**, which proved to be a promising catalyst for the reaction, rendered the reaction with 83% ee (entry 3). Quinine−thiourea catalyst **D** resulted in a completely unproductive reaction, probably due to the poisoning effect of thiourea to the metal catalyst (entry 4). Tuning the urea motif of **C** to squaramide afforded a slight improvement of the ee value (entry 5). Having identified **E** as the optimal organocatalyst, we investigated the effect of additives and solvents to the reaction (entries 7−11). Drying agents exhibited a positive effect on the yield of the reaction, and 4 Å MS was found to be the best additive with regard to the combination of both yield and enantioselectivity (entry 8). Changing the solvent to toluene could dramatically increase the enantioselectivity to 94% ee without diminishing the yield (entry 12). A further detailed examination of the reaction temperature identified that best results could be afforded at 35 °C (entry 15).

Table 1. Optimization of Catalysts and Reaction Conditions[a]

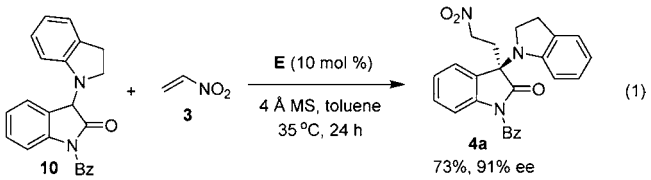


entry	organo cat.	solvent	additive	temp (°C)	yield[b] (%)	ee[c] (%)
1	A	DCM		25	32	78
2	B	DCM		25	35	61
3	C	DCM		25	28	83
4	D	DCM		25	N.R.	
5	E	DCM		25	30	84
7	E	DCM	3 Å MS	25	54	78
8	E	DCM	4 Å MS	25	57	81
9	E	DCM	5 Å MS	25	47	81
10	E	DCM	$MgSO_4$	25	47	82
11	E	DCM	Na_2SO_4	25	43	81
12	E	toluene	4 Å MS	25	57	94
13	E	toluene	4 Å MS	0	18	96
14	E	toluene	4 Å MS	40	69	91
15	E	toluene	4 Å MS	35	78	92
16	E	toluene	4 Å MS	50	73	91

[a]Unless indicated otherwise, the reaction was performed with **1a** (0.1 mmol), **2a** (0.1 mmol), **3a** (0.15 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (2 mol %), organo catalyst (10 mol %), and additive (100 mg) in 2 mL of solvent at 35 °C under N_2 atmosphere. [b]Isolated yield. [c]Determined by HPLC, and the absolute configuration was assigned by comparing the optical rotation with the literature value.

The substrate scope was then examined under the optimized reaction conditions. Various substituents at the aromatic core of diazooxindole, either electron-donating or electron-withdrawing, were well tolerated, giving rise to 3-amino-3-alkyloxindoles with fair to good yields and generally excellent enantioselectivities (Table 2, **4b−g**). A series of indoline derivatives also afforded the corresponding products with fair yields and good optical selectivities (**4h−l**). It is worth mentioning that other secondary amines (e.g., tetrahydroquinoline, methyl, and benzyl anilines) could participate in this three-component reaction smoothly as well, giving rise to **4m−o** with satisfying results.

According to previous findings,[15a,c] the one-pot reaction might principally encompass two catalytic cycles in a relay catalytic manner (Scheme 1). The reaction of **2a** with in situ generated metal carbenoid **I** produces zwitterion **II**, which undergoes a fast proton-transfer process to obtain **10**. As documented, a chiral bifunctional catalyst could promote enolization of **10**,[14,16] thereby enabling an enantioselective Michael addition to **3** to form the product **4**. Starting from the isolated compound **10**, in the presence of catalyst **E**, product **4a** could be obtained with 73% yield and 91% ee, which is very close to the result of the three-component reaction, indicating that the cascade reaction proceeds via the key intermediate **10** (eq 1).

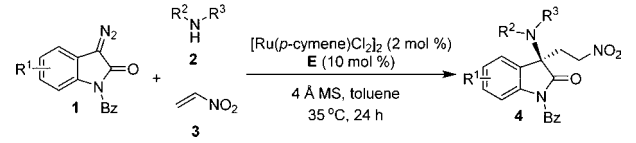


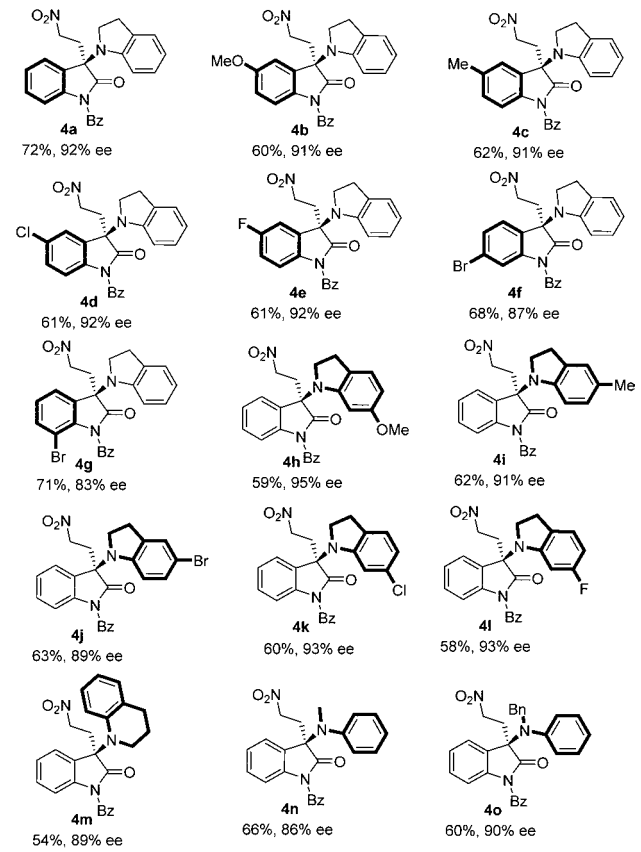
(1)

To demonstrate the synthetic potential of this asymmetric three-component reaction, a formal synthesis of (−)-psychotrimine was performed based on 3-amino-3-alkyloxindole **4a**. Psychotrimine was first isolated by the Takayama group in 2004 during their studies of indole alkaloids possessing analgesic activity.[7b] Then they and Baran group independently completed the first total synthesis of (±)-psychotrimine.[17] The first asymmetric total synthesis of (+)-psychotrimine was also reported by the Takayama group in 2010.[18] Later, Shishido and co-workers reported a formal synthesis of (+)-psychotrimine based on Takayama's intermediate (−)-**9a**, which was synthesized by a longest linear sequence of 21 steps.[19] Our synthetic pathway to psychotrimine was depicted as shown in

DOI: 10.1021/acs.orglett.6b02019
Org. Lett. 2016, 18, 4270−4273

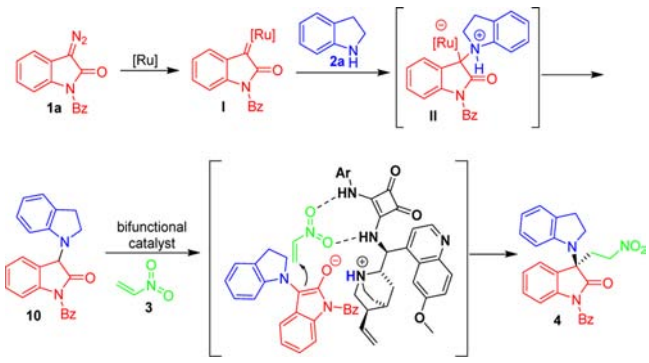
Table 2. Substrate Scope for the Three-Component Reaction[a]





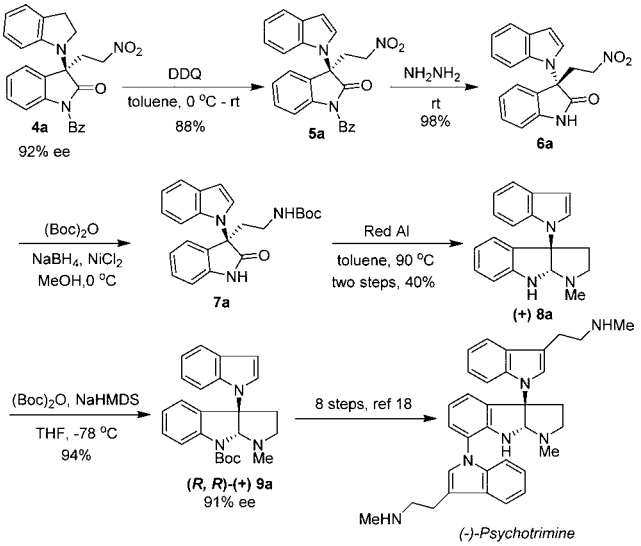
[a]Unless indicated otherwise, the reaction was performed with **1** (0.1 mmol), **2** (0.1 mmol), **3** (0.15 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (2 mol %), **E** (10 mol %), and 4 Å MS (100 mg) in 2 mL of toluene at 35 °C under N_2 atmosphere. Enantiomeric excesses were determined by HPLC.

Scheme 1. Proposed Reaction Pathway



Scheme 2. Chiral 3-amino-3-alkyloxindole **4a**, obtained through the current methodology with 78% yield and 92% ee, was first treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to oxidize the indoline unit, affording compound **5a** in 88% yield. Then the benzoyl group of **5a** was removed by

Scheme 2. Application of the Metal/Organo Relay Catalytic Three-Component Reaction to the Formal Synthesis of (−)-Psychotrimine



hydrazine hydrate to yield compound **6a**. After treatment with $NaBH_4$, $NiCl_2$, and di-*tert*-butyl dicarbonate, the nitro group in **6a** was reduced and in situ protected, giving rise to *tert*-butyl carbamate **7**. Treating **7** with Red-Al could reduce both the carbamate group and the lactam motif in **7** and trigger an instantaneous cyclization to afford hexahydropyrrolo[2,3-*b*]-indole **8a**. Boc-protection of **8a** led to compound **9a**, which was a key intermediate in the reported procedures for the total synthesis of (+)-psychotrimine.[18] By comparing the optical rotation of the **9a** ($[\alpha]_D^{20}$ = +36.7) with the literature value reported by Takayama ($[\alpha]_D^{24}$ = −48.6),[18] the absolute configuration can be assigned to be (*R*, *R*)-(+)-**9a**. Overall, based on the current methodology, (*R*,*R*)-(+)-**9a** could be obtained in six steps and 25% overall yield. Finally, with the key intermediate (+)-**9a** in hand, (−)-psychotrimine could be accessed by following the synthetic route developed by Takayama.[18]

In conclusion, we have developed a highly enantioselective carbenoid-associated N−H functionalization/Michael addition cascade reaction by virtue of Ru(II)/chiral bifunctional catalyst relay catalysis. In this way, a variety of optically pure 3-amino-3-alkyloxindoles can be easily achieved. Moreover, on the basis of this metal/organo relay catalytic three-component protocol, a key intermediate of (−)-psychotrimine was accomplished in six steps with 25% overall yield.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02019.

Experimental details and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hanzy@ustc.edu.cn.

Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.orglett.6b02019
Org. Lett. 2016, 18, 4270−4273

■ ACKNOWLEDGMENTS

We are grateful for financial support from the NSFC (21502183) and the Fundamental Research Funds for the Central Universities (WK2060190041).

■ REFERENCES

(1) (a) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381−1407. (b) Klein, J. E. M. N.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2011**, *2011*, 6821−6841. (c) Shen, K.; Liu, X.; Lin, L.; Feng, X. *Chem. Sci.* **2012**, *3*, 327−334. (d) Dalpozzo, R.; Bartoli, G.; Bencivenni, G. *Chem. Soc. Rev.* **2012**, *41*, 7247−7290. (e) Mohammadi Ziarani, G.; Moradi, R.; Lashgari, N. *Tetrahedron: Asymmetry* **2015**, *26*, 517−541. (f) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748−8758. (g) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, *2003*, 2209−2219. (h) Trost, B.; Brennan, M. *Synthesis* **2009**, *2009*, 3003−3025.

(2) Chauhan, P.; Chimni, S. S. *Tetrahedron: Asymmetry* **2013**, *24*, 343−356.

(3) (a) Kitamura, H.; Kato, A.; Esaki, T. *Eur. J. Pharmacol.* **2001**, *418*, 225−230. (b) Ochi, M.; Kawasaki, K.; Kataoka, H.; Uchio, Y.; Nishi, H. *Biochem. Biophys. Res. Commun.* **2001**, *283*, 1118−1123.

(4) Zhang, J.; Qian, Z.; Wu, X.; Ding, Y.; Li, J.; Lu, C.; Shen, Y. *Org. Lett.* **2014**, *16*, 2752−2755.

(5) (a) Crich, D.; Banerjee, A. *Acc. Chem. Res.* **2007**, *40*, 151−161. (b) Ruiz-Sanchis, P.; Savina, S. A.; Albericio, F.; Álvarez, M. *Chem. - Eur. J.* **2011**, *17*, 1388−1408.

(6) Liu, Y.; Wang, J.-S.; Wang, X.-B.; Kong, L.-Y. *J. Asian Nat. Prod. Res.* **2014**, *16*, 29−33.

(7) (a) Schallenberger, M. A.; Newhouse, T.; Baran, P. S.; Romesberg, F. E. *J. Antibiot.* **2010**, *63*, 685−687. (b) Takayama, H.; Mori, I.; Kitajima, M.; Aimi, N.; Lajis, N. H. *Org. Lett.* **2004**, *6*, 2945−2948.

(8) Badillo, J. J.; Hanhan, N. V.; Franz, A. K. *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 758−776.

(9) (a) Li, T.-Z.; Wang, X.-B.; Sha, F.; Wu, X.-Y. *J. Org. Chem.* **2014**, *79*, 4332−4339. (b) Miyabe, H.; Yamaoka, Y.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 3324−3327. (c) Lesma, G.; Landoni, N.; Pilati, T.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2009**, *74*, 4537−4541. (d) Guo, Q.-X.; Liu, Y.-W.; Li, X.-C.; Zhong, L.-Z.; Peng, Y.-G. *J. Org. Chem.* **2012**, *77*, 3589−3594. (e) He, Q.; Wu, L.; Kou, X.; Butt, N.; Yang, G.; Zhang, W. *Org. Lett.* **2016**, *18*, 288−291. (f) Yan, W.; Wang, D.; Feng, J.; Li, P.; Zhao, D.; Wang, R. *Org. Lett.* **2012**, *14*, 2512−2515. (g) Montesinos-Magraner, M.; Vila, C.; Cantón, R.; Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R. *Angew. Chem., Int. Ed.* **2015**, *54*, 6320−6324. (h) Zhao, J.; Fang, B.; Luo, W.; Hao, X.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 241−244.

(10) (a) Cheng, L.; Liu, L.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2009**, *11*, 3874−3877. (b) Mouri, S.; Chen, Z.; Mitsunuma, H.; Furutachi, M.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 1255−1257. (c) Bui, T.; Borregan, M.; Barbas, C. F. *J. Org. Chem.* **2009**, *74*, 8935−8938. (d) Qian, Z.-Q.; Zhou, F.; Du, T.-P.; Wang, B.-L.; Ding, M.; Zhao, X.-L.; Zhou, J. *Chem. Commun.* **2009**, 6753−6755. (e) Yang, Z.; Wang, Z.; Bai, S.; Shen, K.; Chen, D.; Liu, X.; Lin, L.; Feng, X. *Chem. - Eur. J.* **2010**, *16*, 6632−6637.

(11) (a) Zhang, H.; Zhang, S.-J.; Zhou, Q.-Q.; Dong, L.; Chen, Y.-C. *Beilstein J. Org. Chem.* **2012**, *8*, 1241−1245. (b) Zhao, X.; Li, T.-Z.; Qian, J.-Y.; Sha, F.; Wu, X.-Y. *Org. Biomol. Chem.* **2014**, *12*, 8072−8078. (c) Hu, F.-L.; Wei, Y.; Shi, M.; Pindi, S.; Li, G. *Org. Biomol. Chem.* **2013**, *11*, 1921−1924. (d) Yang, H.-B.; Zhao, Y.-Z.; Sang, R.; Shi, M. *J. Org. Chem.* **2014**, *79*, 3519−3528.

(12) (a) Tolstoy, P.; Lee, S. X. Y.; Sparr, C.; Ley, S. V. *Org. Lett.* **2012**, *14*, 4810−4813. (b) Jia, Y.-X.; Hillgren, J. M.; Watson, E. L.; Marsden, S. P.; Kundig, E. P. *Chem. Commun.* **2008**, 4040−4042.

(13) (a) Sato, S.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y. *Chem. Commun.* **2009**, 6264−6266. (b) Chen, W.-B.; Wu, Z.-J.; Hu, J.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2011**, *13*, 2472−2475.

(14) Cui, B.-D.; You, Y.; Zhao, J.-Q.; Zuo, J.; Wu, Z.-J.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Chem. Commun.* **2015**, *51*, 757−760.

(15) (a) Ren, L.; Lian, X.-L.; Gong, L.-Z. *Chem. - Eur. J.* **2013**, *19*, 3315−3318. (b) Chen, D.-F.; Han, Z.-Y.; Zhou, X.-L.; Gong, L.-Z. *Acc. Chem. Res.* **2014**, *47*, 2365−2377. (c) Chen, D.-F.; Zhao, F.; Hu, Y.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2014**, *53*, 10763−10767. (d) Cao, Z.-Y.; Wang, Y.-H.; Zeng, X.-P.; Zhou, J. *Tetrahedron Lett.* **2014**, *55*, 2571−2584. (e) Chen, D.-F.; Zhang, C.-l.; Hu, Y.; Han, Z.-Y.; Gong, L.-Z. *Org. Chem. Front.* **2015**, *2*, 956−960. (f) Cao, Z.-Y.; Zhao, Y.-L.; Zhou, J. *Chem. Commun.* **2016**, *52*, 2537−2540.

(16) (a) Liu, X.-L.; Wu, Z.-J.; Du, X.-L.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2011**, *76*, 4008−4017. (b) Ding, M.; Zhou, F.; Liu, Y.-L.; Wang, C.-H.; Zhao, X.-L.; Zhou, J. *Chem. Sci.* **2011**, *2*, 2035−2039.

(17) (a) Matsuda, Y.; Kitajima, M.; Takayama, H. *Org. Lett.* **2008**, *10*, 125−128. (b) Newhouse, T.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 10886−10887.

(18) Takahashi, N.; Ito, T.; Matsuda, Y.; Kogure, N.; Kitajima, M.; Takayama, H. *Chem. Commun.* **2010**, *46*, 2501−2503.

(19) Araki, T.; Ozawa, T.; Yokoe, H.; Kanematsu, M.; Yoshida, M.; Shishido, K. *Org. Lett.* **2013**, *15*, 200−203.

DOI: 10.1021/acs.orglett.6b02019
Org. Lett. 2016, 18, 4270−4273