Organic LETTERS
Cite This: Org. Lett. XXXX, XXX, XXX-XXX
Letter
pubs.acs.org/OrgLett

Catalytic Asymmetric Mukaiyama–Mannich Reaction of Cyclic *C*-Acylimines with Difluoroenoxysilanes: Access to Difluoroalkylated Indolin-3-ones

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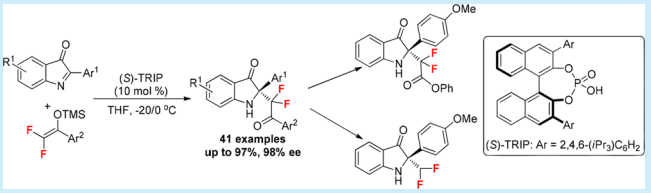
Supporting Information

ABSTRACT: A catalytic enantioselective Mukaiyama–Mannich reaction of cyclic *C*-acylimines with difluoroenoxysilanes is reported. (*S*)-TRIP enables the enantioselective synthesis of a series of novel difluoroalkylated indolin-3-ones bearing a quaternary stereocenter in up to 97% yield and 98% ee. The synthetic utility of this protocol is highlighted by efficient conversion of the products to the corresponding indolin-3-one derivatives without any erosion of the enantiopurity.



Oxindoles are prominent scaffolds in natural products with diverse biological activities.[1] Therefore, the development of convenient synthetic methods for the enantioselective assembly of oxindoles has become the subject of intensive research in the field of synthetic organic chemistry.[2] Likewise, the selective incorporation of a fluoroalkyl group into a target organic molecule often significantly changes the properties of the molecule, such as the metabolic stability, bioavailability, lipophilicity, and membrane permeability, which have extensive applications in pharmaceutical research.[3] Consequently, the synthesis of fluoroalkyl-substituted oxindoles has gained great attention.[4] Most of the recent developments in this context have focused on the trifluoromethylation of oxindoles, whereas the catalytic enantioselective difluoroalkylation of oxindoles is still less exploited (Figure 1).[5] In 2012, Zhou and co-workers

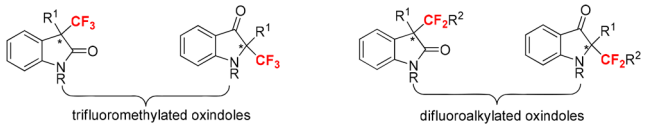
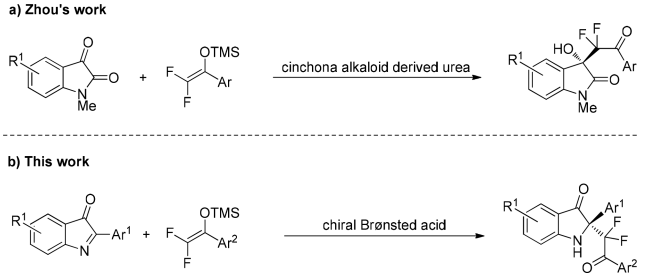


Figure 1. Structure motifs of trifluoromethylated and difluoroalkylated oxindoles.

reported the first example of highly enantioselective organocatalytic synthesis of 3-difluoroalkyl-substituted 3-hydroxyindolin-2-ones by employing a hydroquinine-derived urea catalyst (Scheme 1a).[6] However, to the best of our knowledge, no attempt has been reported for the installation of a difluoroalkyl group into the indolin-3-one framework, and the resulting difluoroalkylated products might be interesting for medicinal studies (Figure 1, highlighted in red). Encouraged by this interesting investigation, along with our interest in the Brønsted acid-catalyzed asymmetric construction of fluorinated organic compounds,[7] we envisioned that difluoroalkylated indolin-3-ones bearing a quaternary stereocenter could be constructed through the Mukaiyama–Mannich reaction of cyclic *C*-acylimines (2-substituted-3*H*-indol-3-ones) with difluoroenoxysilanes in the presence of chiral phosphoric acids (Scheme 1b). Herein, we report our preliminary results on this subject.

Scheme 1. Strategies for Enantioselective Synthesis of Difluoroalkylated Indolin-2-ones and Indolin-3-ones



2-Aryl-3*H*-indol-3-ones **1**, important cyclic ketimines activated by the coplanar carbonyl group, are useful synthetic intermediates for the synthesis of 2,2-disubstituted indolin-3-one derivatives.[8] However, 2-aryl-3*H*-indol-3-ones are not easily accessible and have to be prepared through a troublesome stepwise transformation.[9] One recent report by Sperry and coworkers has addressed one example involving one-pot multistep synthesis of indolone.[10] According to this procedure, we prepared a series of 2-aryl-3*H*-indol-3-ones on a gram-scale in moderate to good yields (Scheme 2).

With 3*H*-indol-3-ones **1** in our hands, we first examined the reaction between 2-phenyl-3*H*-indol-3-one **1a** and difluoroenoxysilane **2a** by using a series of chiral phosphoric acids **4a–k** (Table 1). We were delighted to find that the reaction

Received: October 14, 2017

DOI: 10.1021/acs.orglett.7b03213
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Scheme 2. General Procedure for the Preparation of 2-Aryl-3*H*-indol-3-ones 1

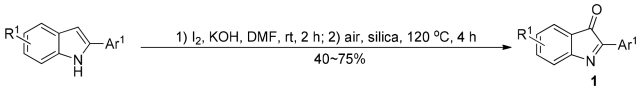
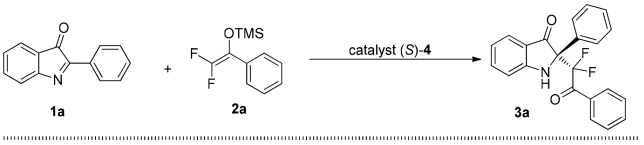
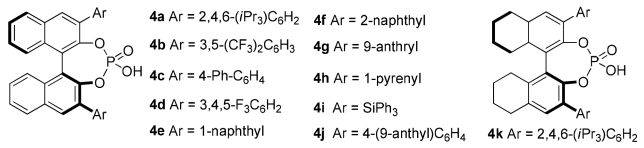


Table 1. Catalyst Screening and Condition Optimization[a]





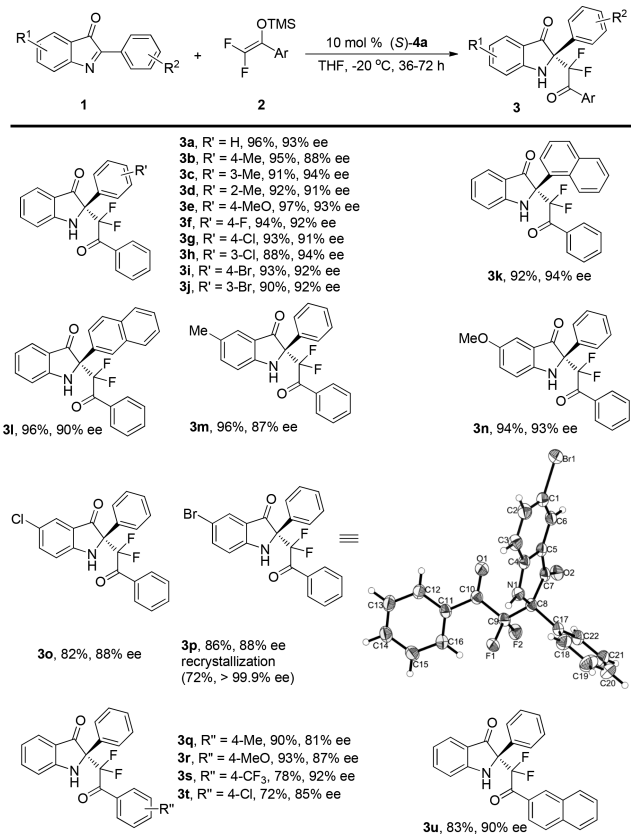
entry	catalyst	solvent/temp (°C)/time (h)	yield (%)[b]	ee (%)[c]
1	**4a**	THF/25/48	86	89
2	**4a**	THF/0/60	93	91
3	**4a**	Et_2O/0/48	80	85
4	**4a**	toluene/0/72	46	62
5	**4a**	CH_2Cl_2/0/72	32	35
6	**4a**	THF/−20/72	96	93
7	**4a**	THF/−40/144	0	
8	**4b**	THF/−20/24	89	70
9	**4c**	THF/−20/72	87	67
10	**4d**	THF /−20/24	84	54
11	**4e**	THF /−20/72	93	84
12	**4f**	THF/−20/24	81	57
13	**4g**	THF/−20/36	88	85
14	**4h**	THF/−20/24	86	84
15	**4i**	THF/−20/84	84	73
16	**4j**	THF/−20/36	79	70
17	**4k**	THF/−20/36	82	77
18[d]	**4a**	THF/−20/96	87	89

[a]General reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), and catalyst **4** (10 mol %) in solvent (1 mL) at the given temperature for the stated time. [b]Isolated yield. [c]Enantiomeric excess (ee) was determined by chiral HPLC analysis. [d]5 mol % of catalyst was used.

proceeded smoothly to afford the desired product **3a** in good yield with 89% ee in the presence of the catalyst (*S*)-TRIP **4a**[11] in THF at room temperature (entry 1). Lowering the reaction temperature to 0 °C improved the yield and enantioselectivity slightly (entry 2). Subsequently, the solvent was found to have a pronounced effect on the reactivity and selectivity (entries 3−5). Among the solvents tested, THF was found to be the best with respect to the asymmetric induction. Further improvement in enantioselectivity was achieved by decreasing reaction temperature with a prolonged reaction time (entry 6). Subsequent attempts to conduct the reaction at −40 °C failed (entry 7). Other chiral phosphoric acids **4b−k** were then tested at −20 °C (entries 8−17), and we found that phosphoric acid **4a** proved to be the best (entry 6). Reducing the catalyst loading from 10 to 5 mol % had a deleterious effect on both yield and ee (entry 18).

With the optimized reaction conditions in hand, a series of 2-aryl-substituted 3*H*-indol-3-one derivatives **1** was reacted with various difluoroenoxysilanes **2** to probe the generality of the reaction (Scheme 3). In general, 2-phenyl-3*H*-indol-3-ones **1** bearing electron-donating or electron-withdrawing groups on

Scheme 3. Scope of the Enantioselective Mukaiyama−Mannich Reaction of 2-Aryl-3*H*-indol-3-ones 1 with Difluoroenoxysilanes 2

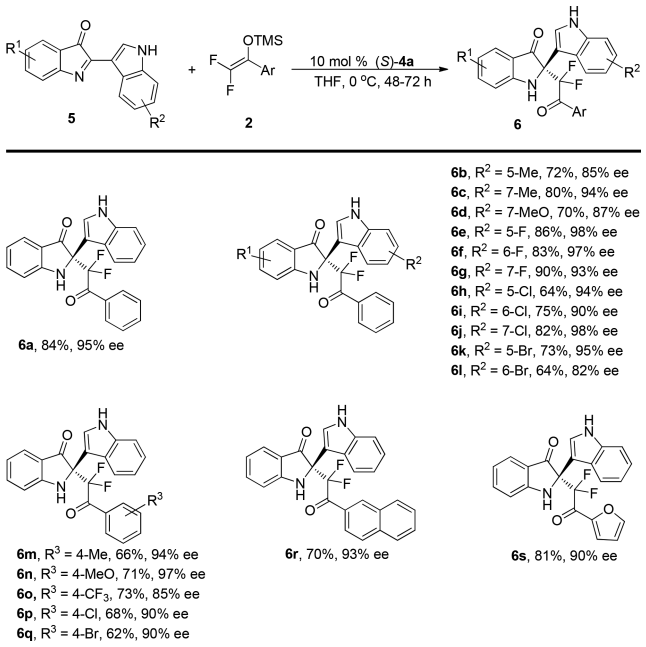


the phenyl ring could be well tolerated in the reaction with difluoroenoxysilane **2a**, affording the corresponding products **3a−j** in good yields and with high enantioselectivities. 1- and 2-Naphthyl-substituted 3*H*-indol-3-ones **1k** and **1l** also delivered the Mannich products **3k** and **3l** with high enantioselectivity, a similar results were obtained for 2-phenyl-3*H*-indol-3-ones **1** with both electron-donating and -withdrawing groups on the indolone ring (**3m−p**). X-ray crystallographic analysis of **3p** allowed the absolute configuration of the stereogenic center to be assigned as *R*. Several aryl-substituted difluoroenoxysilanes **2q−u** also gave corresponding products **3q−u** in good yields with good to high ee values. In addition, we investigated the Mannich reaction of 2-phenyl-3*H*-indol-3-one **1a** with benzyl-substituted difluoroenoxysilane. This alkyl-substituted difluoroenoxysilane substrate was found to be unsuitable for this asymmetric transformation, and no desired product was observed.

Apart from 2-aryl-3*H*-indol-3-ones, a series of indolones, 1′*H*,3*H*-[2,3′-biindol]-3-ones **5** (indoxyl red derivates, which were isolated from the glycoside indicant with a strong purple-red color),[12] were also viable substrates under the established conditions (Scheme 4). C2−C3′ bisindole-3-ones with electron-donating or withdrawing groups on the indole ring all worked well, and the reactions were all completed within 48−72 h to give the products **6a−l** in good yields with good to excellent enantioselectivities. Difluoroenoxysilanes **2** with different substituents on the phenyl ring also gave the corresponding products **6m−s** in good yields with excellent ee values. It should be noted that a higher temperature was required for the Mannich reaction, probably due to the lower reactive activities of these substrates.

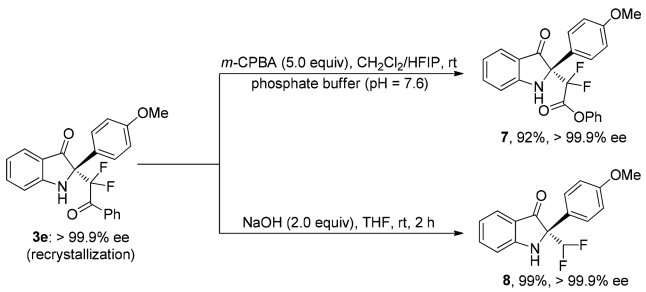
DOI: 10.1021/acs.orglett.7b03213
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Scope of the Enantioselective Mukaiyama–Mannich Reaction of 1′*H*,3*H*-[2,3′-Biindol]-3-ones 5 with Difluoroenoxysilanes 2



To demonstrate the synthetic utility of this protocol, we conducted further manipulation by using the product **3e** (Scheme 5). The Baeyer–Villiger oxidation[13] of **3e** (>99.9% ee

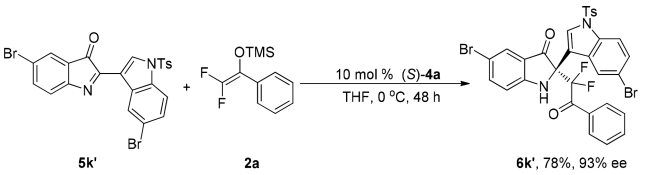
Scheme 5. Further synthetic transformations



after one recrystallization) gave corresponding ester **7** in 92% yield without any loss of ee. Of particular interest, we found that the C–C bond adjacent to the carbonyl group in these α,α-difluoroketones could be readily cleaved to afford the optically pure indolin-3-one **8** bearing CF_2H group in the presence of 2.0 equiv of NaOH at room temperature.[14] The resulting CF_2H-containing molecules are biologically interesting because of their frequent use in medicinal chemistry, owing to the fact that the CF_2H group often acts as a bioisostere for alcohols and thiols.[15]

To probe the substitution effect of the remote *N*-protecting group on the indole ring, the reaction between *N*-tosylated 1′*H*,3*H*-[2,3′-biindol]-3-one **5k′** and difluoroenoxysilane **2a** was performed to give the comparable enantioselectivity with unprotected indol-3-one **5k**, indicating that the hydrogen on the N atom of the indole moiety is not essential for the activation of the reactant by the phosphoric acid catalyst in this reaction (Scheme 6). Based on this result and the stereochemical outcome of the Mannich adduct with the *R* configuration, a potential transition state was proposed. As shown in Figure 2, the phosphoric acid could activate cyclic ketimine through the

Scheme 6. Reaction of 5,5′-Dibromo-1′-tosyl-1′*H*,3*H*-[2,3′-biindol]-3-one 5k′ with Difluoroenoxysilane 2a



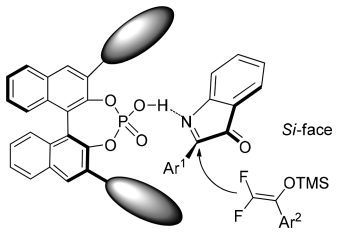


Figure 2. Proposed transition state for the reaction of difluoroenoxysilanes with 3*H*-indol-3-ones.

hydrogen bonding interaction, therefore creating a chiral environment wherein the enol silyl ethers attack the *Si* face of the C=N group preferentially. Further studies are required to fully elucidate the detailed mechanism of this Mukaiyama–Mannich reaction.

In summary, we have successfully developed a chiral phosphoric acid-catalyzed enantioselective Mukaiyama–Mannich reaction of cyclic *C*-acylimines with difluoroenoxysilanes. This method tolerates a series of 2-aryl-substituted 3*H*-indol-3-ones, affording the difluoroalkylated indolin-3-ones bearing a quaternary stereocenter in high yields (up to 97%) and enantioselectivities (up to 98% ee). Moreover, the products obtained can be readily converted into optically active esters and α-CF_2H derivatives by simple modifications. Further development and applications of this Mannich reaction, as well as the one-pot procedure for the synthesis of compounds containing CF_2H groups, is ongoing 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.7b03213.

Experimental details, spectral data of all the new compounds, and HPLC analytic results for **3a–u**, **6a–6s**, **7**, and **8** (PDF)

Accession Codes

CCDC 1575423 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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DOI: 10.1021/acs.orglett.7b03213
Org. Lett. XXXX, XXX, XXX–XXX

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (No. 21225208, 21472137, and 21532008), the National Basic Research Program of China (973 Program, 2014CB745100), and Tianjin Municipal Science & Technology Commission (14JCZDJC33400).

■ REFERENCES

(1) (a) Williams, R. M.; Glinka, T.; Kwast, E.; Coffman, H.; Stille, J. K. *J. Am. Chem. Soc.* **1990**, *112*, 808. (b) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904. (c) Wu, P.-L.; Hsu, Y.-L.; Jao, C.-W. *J. Nat. Prod.* **2006**, *69*, 1467. (d) Steven, A.; Overman, L. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 5488. (e) Liu, J.-F.; Jiang, Z.-Y.; Wang, R.-R.; Zeng, Y.-T.; Chen, J.-J.; Zhang, X.-M.; Ma, Y.-B. *Org. Lett.* **2007**, *9*, 4127. (f) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, *18*, 3003. (g) Kim, J.; Movassaghi, M. *Chem. Soc. Rev.* **2009**, *38*, 3035. (h) Tsukamoto, S.; Umaoka, H.; Yoshikawa, K.; Ikeda, T.; Hirota, H. *J. Nat. Prod.* **2010**, *73*, 1438. (i) Millemaggi, A.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2010**, *2010*, 4527. (j) Abe, T.; Kukita, A.; Akiyama, K.; Naito, T.; Uemura, D. *Chem. Lett.* **2012**, *41*, 728. (k) Kumar, C. V. S.; Puranik, V. G.; Ramana, C. V. *Chem. - Eur. J.* **2012**, *18*, 9601. (l) Gu, W.; Zhang, Y.; Hao, X.-J.; Yang, F.-M.; Sun, Q.-Y.; Morris-Natschke, S. L.; Lee, K.-H.; Wang, Y.-H.; Long, C.-L. *J. Nat. Prod.* **2014**, *77*, 2590.

(2) (a) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36. (b) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (c) Higuchi, K.; Masuda, K.; Koseki, T.; Hatori, M.; Sakamoto, M.; Kawasaki, T. *Heterocycles* **2007**, *73*, 641. (d) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381. (e) Jin, C.-Y.; Wang, Y.; Liu, Y.-Z.; Shen, C.; Xu, P.-F. *J. Org. Chem.* **2012**, *77*, 11307. (f) Guo, C.; Schedler, M.; Daniliuc, C. G.; Glorius, F. *Angew. Chem., Int. Ed.* **2014**, *53*, 10232. (g) Chen, T.-G.; Fang, P.; Hou, X.-L.; Dai, L.-X. *Synthesis* **2015**, *47*, 134. (h) Liu, R.-R.; Ye, S.-C.; Lu, C.-J.; Zhuang, G.-L.; Gao, J.-R.; Jia, Y.-X. *Angew. Chem., Int. Ed.* **2015**, *54*, 11205. (i) Chen, S.-R.; Wang, Y.-M.; Zhou, Z.-H. *J. Org. Chem.* **2016**, *81*, 11432. (j) Yarlagadda, S.; Ramesh, B.; Reddy, C. R.; Srinivas, L.; Sridhar, B.; Reddy, B. V. S. *Org. Lett.* **2017**, *19*, 170. (k) Guo, J.; Lin, Z.-H.; Chen, K.-B.; Xie, Y.; Chen, A. S.-C.; Weng, J.; Lu, G. *Org. Chem. Front.* **2017**, *4*, 1400. For recent reviews, see: (l) Dalpozzo, R.; Bartoli, G.; Bencivenni, G. *Chem. Soc. Rev.* **2012**, *41*, 7247. (m) Dalpozzo, R. *Adv. Synth. Catal.* **2017**, *359*, 1772.

(3) (a) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119. (b) Dolbier, W. R. *J. Fluorine Chem.* **2005**, *126*, 157. (c) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, U.K., 2006. (d) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (e) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (f) Purser, S.; Moore, P. R.; Swal low, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (g) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (h) Zhang, W.; Cai, C. *Chem. Commun.* **2008**, 5686. (i) Hu, J.-B.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, 7465. (j) Ma, J.-A.; Li, S. *Org. Chem. Front.* **2014**, *1*, 712. (k) Ni, C.-F.; Zhu, L.-G.; Hu, J.-B. *Huaxue Xuebao* **2015**, *73*, 90. (l) Ni, C.-F.; Hu, M.-Y.; Hu, J.-B. *Chem. Rev.* **2015**, *115*, 765. (m) Yang, X.-Y.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826.

(4) For selected examples, see: (a) Hou, Y.-K.; Higashiya, S.; Fuchigami, T. *J. Org. Chem.* **1997**, *62*, 8773. (b) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164. (c) Ishimaru, T.; Shibata, N.; Horikawa, T.; Yasuda, N.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4157. (d) Tang, X.-J.; Thomoson, C. S.; Dolbier, W. R., Jr. *Org. Lett.* **2014**, *16*, 4594. (e) Yu, J.-S.; Liao, F.-M.; Gao, W.-M.; Liao, K.; Zuo, R.-L.; Zhou, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 7381.

(5) (a) Saidalimu, I.; Fang, X.; He, X.-P.; Liang, J.; Yang, X.-Y.; Wu, F.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 5566. (b) Xu, P.; Xie, J.; Xue, Q.-C.; Pan, C.-D.; Cheng, Y.-X.; Zhu, C.-J. *Chem. - Eur. J.* **2013**, *19*, 14039. (c) Leifert, D.; Artiukhin, D. G.; Neugebauer, J.; Galstyan, A.; Strassert, C. A.; Studer, A. *Chem. Commun.* **2016**, *52*, 5997.

(6) Liu, Y.-L.; Zhou, J. *Chem. Commun.* **2012**, *48*, 1919.

(7) (a) Zhang, G.-W.; Wang, L.; Nie, J.; Ma, J.-A. *Adv. Synth. Catal.* **2008**, *350*, 1457. (b) Nie, J.; Zhang, G.-W.; Wang, L.; Fu, A.-P.; Zheng, Y.; Ma, J.-A. *Chem. Commun.* **2008**, 2356. (c) Zhang, G.-W.; Zheng, D.-H.; Nie, J.; Wang, T.; Ma, J.-A. *Org. Biomol. Chem.* **2010**, *8*, 1399. (d) Pei, Z.-K.; Zheng, Y.; Nie, J.; Ma, J.-A. *Tetrahedron Lett.* **2010**, *51*, 4658. (e) Wang, T.; Zhang, G.-W.; Teng, Y.; Nie, J.; Zheng, Y.; Ma, J.-A. *Adv. Synth. Catal.* **2010**, *352*, 2773. (f) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455. (g) Zhang, K.-F.; Nie, J.; Guo, R.; Zheng, Y.; Ma, J.-A. *Adv. Synth. Catal.* **2013**, *355*, 3497. (h) Tang, X.-D.; Li, S.; Guo, R.; Nie, J.; Ma, J.-A. *Org. Lett.* **2015**, *17*, 1389.

(8) (a) Li, L.-Q.; Han, M.-Y.; Xiao, M.-X.; Xie, Z.-X. *Synlett* **2011**, *12*, 1727. (b) Rueping, M.; Raja, S.; Nuñez, A. *Adv. Synth. Catal.* **2011**, *353*, 563. (c) Yin, Q.; You, S.-L. *Chem. Sci.* **2011**, *2*, 1344. (d) Parra, A.; Alfaro, R.; Marzo, L.; Moreno-Carrasco, A.; García Ruano, J. L.; Alemán, J. *Chem. Commun.* **2012**, *48*, 9759. (e) Rueping, M.; Rasappan, R.; Raja, S. *Helv. Chim. Acta* **2012**, *95*, 2296. (f) Rueping, M.; Raja, S. *Beilstein J. Org. Chem.* **2012**, *8*, 1819. (g) Liu, J.-X.; Zhou, Q.-Q.; Deng, J.-G.; Chen, Y.-C. *Org. Biomol. Chem.* **2013**, *11*, 8175. (h) Nakamura, S.; Matsuda, N.; Ohara, M. *Chem. - Eur. J.* **2016**, *22*, 9478.

(9) (a) Ling, K.-Q. *Synth. Commun.* **1995**, *25*, 3831. (b) Liu, Q.-L.; Chen, P.-H.; Liu, G.-S. *ACS Catal.* **2013**, *3*, 178. (c) Najahi, E.; Valentin, A.; Fabre, P.-L.; Reybier, K.; Nepveu, F. *Eur. J. Med. Chem.* **2014**, *78*, 269. (d) Yamashita, M.; Nishizono, Y.; Himekawa, S.; Iida, A. *Tetrahedron* **2016**, *72*, 4123.

(10) Lindsay, A. C.; Leung, I. K. H.; Sperry, J. *Org. Lett.* **2016**, *18*, 5404.

(11) For a review: Adair, G.; Mukherjee, S.; List, B. *Aldrich. Acta.* **2008**, *41*, 31.

(12) (a) Yin, B.; Huang, P.-P.; Lu, Y.-B.; Liu, L.-X. *RSC Adv.* **2017**, *7*, 606. (b) Song, J.-Y.; Kitamatsu, M.; Imamura, K.; Ohmori, H.; Watanabe, K.; Nakanishi, K. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 627.

(13) (a) Kobayashi, S.; Tanaka, H.; Amii, H.; Uneyama, K. *Tetrahedron* **2003**, *59*, 1547. (b) Kashikura, W.; Mori, K.; Akiyama, T. *Org. Lett.* **2011**, *13*, 1860. (c) Yu, J.-S.; Zhou, J. *Org. Chem. Front.* **2016**, *3*, 298.

(14) (a) Ge, S.-Z.; Chaładaj, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 4149. (b) Wu, Y.-B.; Lu, G.-P.; Zhou, B.-J.; Bu, M.-J.; Wan, L.; Cai, C. *Chem. Commun.* **2016**, *52*, 5965.

(15) Banik, S. M.; Medley, J. W.; Jacobsen, E. N. *Science* **2016**, *353*, 51.

DOI: 10.1021/acs.orglett.7b03213
Org. Lett. XXXX, XXX, XXX−XXX