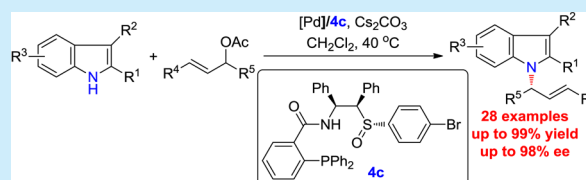


Enantioselective Direct Functionalization of Indoles by Pd/Sulfoxide-Phosphine-Catalyzed *N*-Allylic AlkylationLi-Yan Chen,^{†,§} Xiao-Ye Yu,^{†,§} Jia-Rong Chen,^{*,†} Bin Feng,[†] Hong Zhang,[†] Ying-Hua Qi,[†] and Wen-Jing Xiao^{*,†,‡}[†]Key Laboratory of Pesticide and Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, China[‡]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

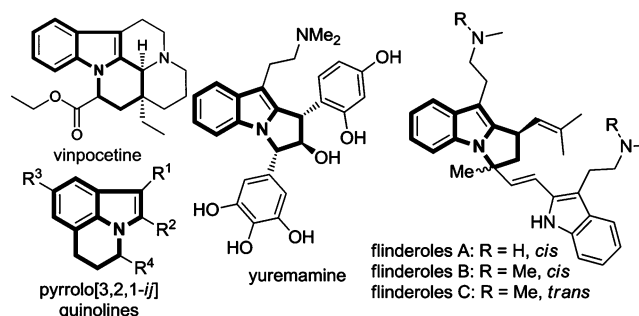
S Supporting Information

ABSTRACT: A general and efficient Pd/sulfoxide-phosphine complex-catalyzed direct asymmetric *N*-allylic alkylation of indoles has been developed to allow for the preparation of various *N*-allylated indoles in generally good yields with excellent enantioselectivities. This catalytic system could also be extended to other *N*-containing heterocycles with good results.



Chiral indole derivatives represent a ubiquitous class of privileged nitrogen-containing heterocycles with wide occurrence in numerous biologically active natural products and pharmaceuticals, and are valuable building blocks in the synthesis of indole-based polycyclic heterocycles.¹ As a result, a great deal of research has been devoted to the development of efficient strategies for catalytic asymmetric functionalization of indoles.² In this context, the majority of the known methods are typically based on the inherent nucleophilicity of the C3- or C2-position of indoles as exemplified by their enantioselective 1,2- or 1,4-additions to electron-deficient C=C and C=X (X = O or N) systems³ as well as asymmetric allylic alkylation (AAA).^{4,5} In stark contrast, the direct catalytic asymmetric functionalization at the N1-position of indoles remains largely underdeveloped. Recently, intensive exploration of the N1-reactivity of the indole core by fine-tuning its electronic properties or rational design of precursors by several research groups including ours has resulted in several efficient and highly stereoselective approaches to *N*-alkylated indole derivatives.⁶ Notably, the resulting *N*-functionalized products are also useful building blocks for the construction of various biologically active and chiral polycyclic indolyl alkaloids, such as vinpocetine, yuremamine, and flinderols (Scheme 1).

In particular, the transition-metal- or small organic molecule-catalyzed enantioselective *N*-allylic alkylation of indoles has attracted considerable attention as the resulting highly functionalized products enable further manipulations to various indole derivatives.⁷ Pioneered by Trost's work on palladium-catalyzed *N*-allylic alkylation of (bis)indole lactams and glyoxamide,^{7a} Hartwig's group in 2009 described the first example of an Ir/phosphoramidite-catalyzed highly enantioselective *N*-allylation of electron-deficient or C3-substituted indoles with achiral linear allylic carbonates as allylic precursors (Scheme 2, eq 1).^{7b,c} You and co-workers recently developed a powerful Ir-catalyzed one-pot procedure for the highly enantioselective formation of *N*-allyl indole derivatives, wherein a sequential allylic alkylation/

Scheme 1. Biologically Active *N*-Functionalized Indole Alkaloids

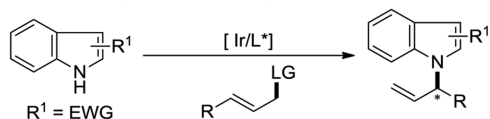
oxidation of indolines using a stoichiometric amount of DDQ as an oxidant was involved (Scheme 2, eq 2).^{7d,e} It should be noted that organocatalytic *N*-allylic alkylation of indoles developed by the group of Chen^{7f} using Morita–Baylis–Hillman carbonates as electrophiles has also provided an efficient entry to *N*-allylation of indoles with high functional group compatibility and enantioselectivities. Despite these impressive advances, it would still be beneficial to develop more efficient and general methods for direct enantioselective allylic alkylation at the N1-position of indoles that are tolerant with various substituents and use easily available starting materials. Based on our recent experience on the indole chemistry and asymmetric catalysis with chiral sulfoxide-phosphines,^{6i,8} we recently achieved a general Pd-catalyzed direct *N*-allylic alkylation of indoles with these ligands to give the corresponding valuable *N*-allylated indole derivatives in consistently high yields and enantioselectivities (Scheme 2, eq 3). Herein, we wish to communicate our preliminary results.

Received: January 9, 2015

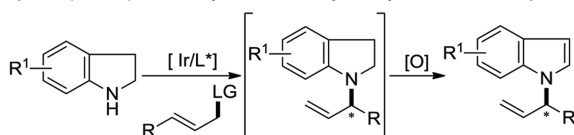
Published: March 4, 2015

Scheme 2. Transition-Metal-Catalyzed Enantioselective *N*-Allylation of Indoles

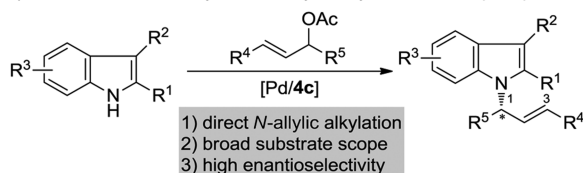
1) N1-reactivity control by tuning electronical property (Hartwig, 2009)



2) One-pot sequential asymmetric *N*-allylic alkylation/oxidation (You, 2012)

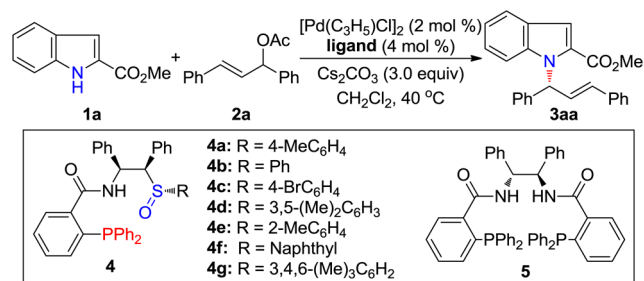


3) This work-direct *N*-allylation catalyzed by Pd/sulfoxide-phosphine



At the outset, we first examined our previously developed sulfoxide-phosphine ligands **4** in the model reaction between methylindole-2-carboxylate **1a** and racemic (*E*)-1,3-diphenylallyl acetate **2a** (Table 1). Gratifyingly, all of the palladium catalyst

Table 1. Screening of Ligands^a



entry	<i>t</i> (h)	ligand	yield ^b (%)	ee ^c (%)
1	26	4a	98	97
2	26	4b	99	97
3	7	4c	99	97
4	19	4d	96	98
5	19	4e	91	97
6	19	4f	99	97
7	26	4g	92	97
8	24	<i>ent</i> - 4a	96	−94
9 ^d	11	4c	91	96
10	24	5	— ^e	—

^aUnless noted, reactions were performed with **1a** (0.30 mmol), **2a** (0.45 mmol), [Pd(C₃H₅)Cl]₂ (2 mol %), **4** (4 mol %), Cs₂CO₃ (0.90 mmol) in CH₂Cl₂ (3.0 mL) at 40 °C for the time indicated. ^bIsolated yield. ^cDetermined by chiral HPLC analysis. ^dThe reaction was performed under air. ^eNo desired product.

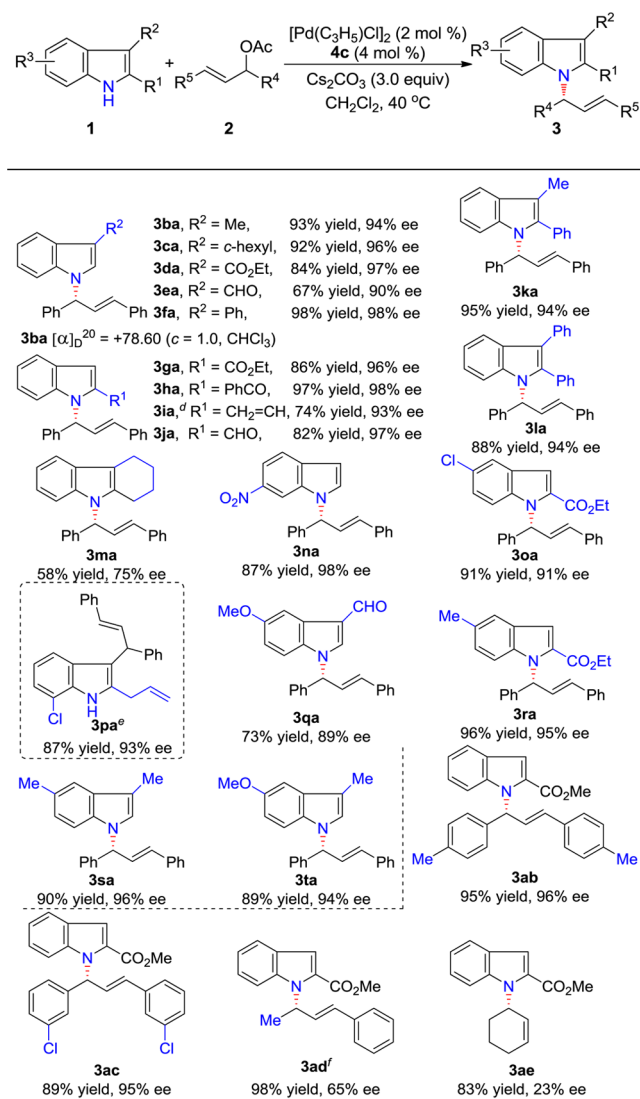
systems generated from [Pd(C₃H₅)Cl]₂ and sulfoxide-phosphine ligands **4** proved to be suitable for the reaction in the presence of Cs₂CO₃ as the base in CH₂Cl₂, affording the desired *N*-allylated indole **3aa** with 91–99% yields and 97–98% ee (Table 1, entries 1–7). In accordance with our previous observation,^{8b,c} ligand **4c** was also confirmed to be optimal in terms of reaction efficiency and stereoselectivity (Table 1, entry

3). Importantly, the use of the corresponding enantiomeric ligand *ent*-**4a** could also furnish the opposite configuration of product **3aa** in good yield with excellent ee (Table 1, entry 8). Notably, the air and moisture stable ligand **4c** also allowed the reaction to be performed under air with no deleterious effect on the results (Table 1, entry 9). In contrast, the use of Trost's ligand **5** led to no formation of the expected product under the current reaction conditions (Table 1, entry 10). Further optimization of other reaction parameters such as metal sources, temperature, and bases gave the optimal conditions: the combination of 2 mol % of [Pd(C₃H₅)Cl]₂ and 4 mol % of ligand **4c** as the catalyst, 3.0 equiv of Cs₂CO₃ as the base, and 40 °C in CH₂Cl₂ (99% yield, 97% ee) (Table 1, entry 3).⁹

First, a wide variety of indoles were subjected to the above-mentioned optimal conditions to prove the generality of this methodology (Scheme 3). In contrast to Hartwig's study,^{7b} all the indoles with various aliphatic or electron-withdrawing groups at the C3-position reacted very well to afford the corresponding alkylated indoles **3ba**–**3fa** with good yields (67–98%) and enantioselectivities (90–98% ee). Moreover, a range of synthetically useful residues R¹ connected to the C2-position of the indoles were also well accommodated, furnishing the products **3ga**–**3ja** in high yields (74–97%) and with excellent ee values (93–98% ee). Surprisingly, the reaction with 2-vinyl indole **1i** only gave rise to the *N*/*C*-dialkylated product **3ia** as a single diastereomer with 95:5 dr and 93% ee.^{7i,9} Notably, the reaction with sterically encumbered indoles **1k**–**1m** bearing substituents at both the C2- and C3-positions also proceeded smoothly to give the *N*-allylated indoles **3ka**–**3ma** with satisfactory results (58–95% yield, 75–94% ee). Also, indole **1n** with a strongly electron-withdrawing nitro group incorporated into the phenyl ring gave the products **3na** in 87% yield with 98% ee. More importantly, multisubstituted indoles **1o**–**1t** with electron-withdrawing and -donating groups at the C-2, C-3, and phenyl ring can be also well employed to yield the *N*-allylation products in 73–96% yield with 89–96% ee with the exception of **1p**, which underwent the allylic alkylation at the C3 position of indole to afford the product **3pa** in 87% yield with 93% ee.

Encouraged by these promising results, we then continued to simply evaluate the scope of allyl acetates. For example, the incorporation of the methyl group into the *para*-position of the aromatic ring of allyl acetate **2b** resulted in the product **3ab** with a 95% yield and 96% ee, while racemic (*E*)-1,3-di(*meta*-chlorophenyl) allyl acetate **2c** could also react very smoothly to give the expected product **3ac** in 89% yield with 95% ee. Interestingly, the reaction with 1-methyl-3-phenyl allyl acetate **2d** showed high regioselectivity with **3ad** being isolated in 98% yield with only 65% ee. Unfortunately, cyclic acetates such as **2e** proved to be ineffective under the current catalyst system, giving the expected product **3ae** with only 23% ee. Finally, the absolute configuration of **3ba** was determined to be *R* by comparison of its optical rotation ([α]_D²⁰ = +78.60 (c = 1.0, CHCl₃)) with that of an identical compound from You's study,^{7h} and all other *N*-allylated products were tentatively assigned by analogy.

To further extend the substrate scope of this methodology, we also briefly examined a range of other nucleophilic nitrogen-containing heterocycles such as imidazole, benzotriazole, and benzimidazole because of the established biological activities of these compounds and their derivatives (Scheme 4).¹⁰ Using **2a** as an allylic precursor, the reactions with unactivated imidazole, pyrrole, benzimidazole, and benzotriazole all proceeded smoothly to give the corresponding *N*-allylated products **6a**–**6d** with good yields and enantioselectivities (64–96% yield, 57–

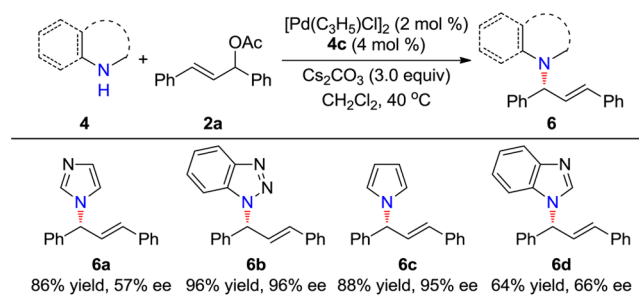
Scheme 3. Substrate Scope^{a,b,c}

^aUnless otherwise noted, reactions were carried out with 1 (0.30 mmol), 2 (0.45 mmol), [Pd(C₃H₅)Cl]₂ (2 mol %), 4c (4 mol %), Cs₂CO₃ (0.90 mmol) in CH₂Cl₂ (3.0 mL) at 40 °C. ^bIsolated yield. ^cThe ee was determined by chiral HPLC analysis. ^dThe reaction only gave rise to N/C-dialkylated product 3ia as a single diastereomer with d.r. > 95:5;^{7i,9} the absolute configuration of 3ia was not determined. ^eDetermined by H/D exchange experiment.⁹ The absolute configuration of 3pa was not determined. ^fK₂CO₃ (0.90 mmol) was used as the base at 10 °C.

96% ee). Thus, the reaction provides a complementary method for N-alkylation of those privileged heterocycles.^{6f,7c}

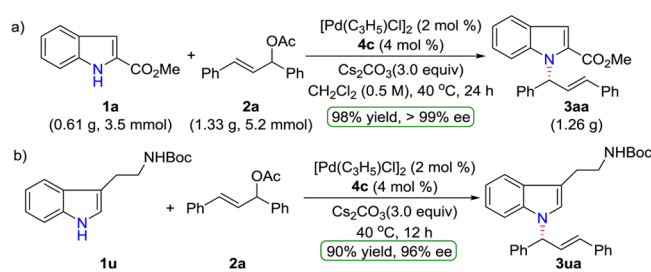
A gram-scale reaction with 1a and 2a under the standard conditions also proceeded well to afford N-allylated product 3aa with excellent results (98% yield, >99% ee), implying that this method is amenable to large-scale production (Scheme 5a). Notably, the reaction with N-Boc tryptamine 1u as a nucleophile resulted in the synthesis of 3ua with a 90% yield and 96% ee, which could be a potentially useful synthon for the construction of yurenamine analogues.^{6i,7d,11}

In conclusion, we have developed a general and efficient Pd-catalyzed direct asymmetric N-allylic alkylation of indoles and other biologically related N-heterocycles using our own sulfoxide-phosphine. The reaction gave the corresponding N-

Scheme 4. Scope of other Nucleophilic N-Heterocycles^{a,b,c}

^aUnless otherwise noted, reactions were carried out with 4 (0.30 mmol), 2a (0.45 mmol), [Pd(C₃H₅)Cl]₂ (2 mol %), 4c (4 mol %), Cs₂CO₃ (0.9 mmol) in CH₂Cl₂ (3.0 mL) at 40 °C. ^bIsolated yield. ^cThe ee was determined by chiral HPLC analysis.

Scheme 5. Proof of the Synthetic Potential of the Method



allylated products in consistently good yields and with excellent enantioselectivities. Further expansion of the substrate scope is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, HPLC, and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: chenjiarong@mail.ccnu.edu.cn.

*E-mail: wxiao@mail.ccnu.edu.cn.

Author Contributions

[§]L.-Y.C. and X.-Y.Y. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge financial support from the NNSFC (Nos. 21272087, 21472058, 21202053, and 21232003) and the National Basic Research Program of China (973 program, No. 2011CB808603) for support of this research. We also thank the anonymous referees for helpful suggestions.

■ REFERENCES

- (1) (a) Somel, M.; Yamada, F. *Nat. Prod. Rep.* **2003**, *21*, 278–311. (b) Galm, U.; Hager, M. H.; Lanen, S. G. V.; Ju, J. H.; Thorson, J. S.; Shen, B. *Chem. Rev.* **2005**, *105*, 739–758. (c) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911. (d) Hamann, M. T.; Anna, J. K. *Chem. Rev.* **2010**, *110*, 4489–4497. (e) Inman, M.; Moody, C. J. *Chem. Sci.* **2013**, *4*, 29. (f) Lancianesi, S.; Palmieri, A.; Petrini, M. *Chem.*

Rev. **2014**, *114*, 7108–7149. (g) Paris, D.; Cottin, M.; Demonchaux, P.; Augert, G.; Dupassieux, P.; Lenoir, P.; Peck, M. J.; Jasserand, D. *J. Med. Chem.* **1995**, *38*, 669–685.

(2) For selected reviews, see: (a) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem.* **2004**, *116*, 560–566; *Angew. Chem., Int. Ed.* **2004**, *43*, 550–556. (b) Umani-Ronchi, A.; Bandini, M.; Melloni, A.; Tommasi, S. *Synlett* **2005**, 1199–1222. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920. (d) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644–4680. (e) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903–2915. (f) Bandini, M.; Eichholzer, A. *Angew. Chem.* **2009**, *121*, 9786–9824; *Angew. Chem., Int. Ed.* **2009**, *48*, 9608–9644. (g) You, S.-L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190–2201. (h) Zeng, M.; You, S.-L. *Synlett* **2010**, 1289–1301. (i) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Chem. Soc. Rev.* **2010**, *39*, 4449–4465. (j) Shirai, M. *Chem. Rev.* **2012**, *112*, 3508–3549.

(3) For selected recent examples, see: (a) Rueping, M.; Nachtsheim, B. J.; Moreth, S. A.; Bolte, M. *Angew. Chem.* **2008**, *120*, 603–606; *Angew. Chem.* **2008**, *47*, 593–596. (b) Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 16464–16465. (c) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem.* **2008**, *120*, 4080–4082; *Angew. Chem., Int. Ed.* **2008**, *47*, 4016–4018. (d) Gao, J.-R.; Wu, H.; Xiang, B.; Yu, W.-B.; Han, L.; Jia, Y.-X. *J. Am. Chem. Soc.* **2013**, *135*, 2983–2986. (e) Kang, Q.; Zhao, Z.-A.; You, S.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1484–1485. (f) Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q.-L. *Angew. Chem.* **2007**, *119*, 5661–5663; *Angew. Chem., Int. Ed.* **2007**, *46*, 5565–5567. (g) Zhang, Y.; Liu, X.; Zhao, X.; Zhang, J.; Zhou, L.; Lin, L.; Feng, X.-M. *Chem. Commun.* **2013**, *49*, 11311. (h) Chiarucci, M.; Mocchi, R.; Synttrivani, L.-D.; Cera, G.; Mazzanti, A.; Bandini, M. *Angew. Chem.* **2013**, *125*, 11050–11053; *Angew. Chem., Int. Ed.* **2013**, *52*, 10850–10853.

(4) For selected reviews on asymmetric allylic alkylation, see: (a) Trost, B. M. *Chem. Rev.* **1996**, *96*, 395–422. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2943. (c) Lu, Z.; Ma, S. M. *Angew. Chem.* **2008**, *120*, 264–303; *Angew. Chem., Int. Ed.* **2008**, *47*, 258–297. (d) Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci.* **2010**, *1*, 427–440. (e) Zhuo, C.-X.; Zheng, C.; You, S.-L. *Acc. Chem. Res.* **2014**, *47*, 2558–2573.

(5) For selected examples on catalytic asymmetric alkylation at the C2- or C3-position of indoles, see: (a) Bandini, M.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **2006**, *128*, 1424–1425. (b) Cheung, H. Y.; Yu, W.-Y.; Lam, F. L.; Au-Yeung, T. T.-L.; Zhou, Z.; Chan, T. H.; Chan, A. S. C. *Org. Lett.* **2007**, *9*, 4295–4298. (c) Trost, B. M.; Quancard, J. J. *Am. Chem. Soc.* **2008**, *128*, 6314–6315. (d) Kagawa, N.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2008**, *10*, 2381–2384. (e) Liu, W.-B.; He, H.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2008**, *10*, 1815–1818. (f) Bandini, M.; Eichholzer, A. *Angew. Chem.* **2009**, *121*, 9697–9701; *Angew. Chem., Int. Ed.* **2009**, *48*, 9533–9537. (g) Wu, Q.-F.; Zheng, C.; You, S.-L. *Angew. Chem.* **2012**, *124*, 1712–1715; *Angew. Chem., Int. Ed.* **2012**, *51*, 1680–1683. (h) Xu, Q.-L.; Zhuo, C.-X.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2013**, *15*, 5909–5911. (i) Liu, Y.; Du, H.-F. *Org. Lett.* **2013**, *15*, 740–743. (j) Zhang, X.; Han, L.; You, S.-L. *Chem. Sci.* **2014**, *5*, 1059.

(6) For selected examples on catalytic asymmetric N-alkylation of indoles, see: (a) Bandini, M.; Eichholzer, A.; Tragni, M.; Umani-Ronchi, A. *Angew. Chem.* **2008**, *120*, 3282–3285; *Angew. Chem., Int. Ed.* **2008**, *47*, 3238–3241. (b) Bandini, M.; Bottoni, A.; Eichholzer, A.; Miscione, G. P.; Stenta, M. *Chem.—Eur. J.* **2010**, *16*, 12462–12473. (c) Ni, Q.-J.; Zhang, H.; Grossmann, A.; Loh, C. C.; Merckens, C.; Enders, D. *Angew. Chem.* **2013**, *125*, 13806–13811; *Angew. Chem., Int. Ed.* **2013**, *52*, 13562–13566. (d) Cai, Q.; Zheng, C.; You, S.-L. *Angew. Chem.* **2010**, *122*, 8848–8851; *Angew. Chem., Int. Ed.* **2010**, *49*, 8666–8669. (e) Hong, L.; Sun, W.; Liu, C.; Wang, L.; Wang, R. *Chem.—Eur. J.* **2010**, *16*, 440–444. (f) Trost, B. M.; Osipov, M.; Dong, G. B. *J. Am. Chem. Soc.* **2010**, *132*, 15800–15807. (g) Xie, Y.-J.; Zhao, Y.-W.; Qian, B.; Yang, L.; Xia, C.-G.; Huang, H.-M. *Angew. Chem.* **2011**, *123*, 5800–5804; *Angew. Chem., Int. Ed.* **2011**, *50*, 5682–5686. (h) Shi, Y.-C.; Wang, S.-G.; Yin, Q.; You, S.-L. *Org. Chem. Front.* **2014**, *1*, 39–43. (i) Cheng, H.-G.; Lu, L.-Q.; Wang, T.; Yang, Q.-Q.; Liu, X.-P.; Li, Y.; Deng, Q.-H.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem.* **2013**, *125*, 3332–3336; *Angew. Chem., Int. Ed.* **2013**, *52*, 3250–3254.

(7) For recent examples on enantioselective N-allylation of indoles, see: (a) Trost, B. M.; Krische, M. J.; Berl, V.; Grenzer, E. M. *Org. Lett.* **2002**, *4*, 2005–2008. (b) Stanley, L. M.; Hartwig, J. F. *Angew. Chem.* **2009**, *121*, 7981–7984; *Angew. Chem., Int. Ed.* **2009**, *48*, 7841–7844. (c) Stanley, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 8971–8983. (d) Liu, W.-B.; Zhang, X.; Dai, L.-X.; You, S.-L. *Angew. Chem.* **2012**, *124*, 5273–5277; *Angew. Chem., Int. Ed.* **2012**, *51*, 5183–5187. (e) Ye, K.-Y.; Dai, L.-X.; You, S.-L. *Chem.—Eur. J.* **2014**, *20*, 3040–3044. (f) Cui, H.-L.; Feng, X.; Peng, J.; Lei, J.; Jiang, K.; Chen, Y.-C. *Angew. Chem.* **2009**, *121*, 5847–5850; *Angew. Chem., Int. Ed.* **2009**, *48*, 5737–5740. (g) Huang, L.; Wei, Y.; Shi, M. *Org. Biomol. Chem.* **2012**, *10*, 1396. (h) Zhao, Q.; Zhuo, C.-X.; You, S.-L. *RSC Adv.* **2014**, *4*, 10875–10878. (i) Bandini, M.; Melloni, A.; Achille, U.-R. *Org. Lett.* **2004**, *6*, 3199–3202.

(8) (a) Chen, J.-R.; Li, C.-F.; An, X.-L.; Zhang, J.-J.; Zhu, X.-Y.; Xiao, W.-J. *Angew. Chem.* **2008**, *120*, 2523–2526; *Angew. Chem., Int. Ed.* **2008**, *47*, 2489–2492. (b) Cheng, H.-G.; Feng, B.; Chen, L.-Y.; Guo, W.; Yu, X.-Y.; Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Chem. Commun.* **2014**, *50*, 2873–2875. (c) Feng, B.; Cheng, H.-G.; Chen, J.-R.; Deng, Q.-H.; Lu, L.-Q.; Xiao, W.-J. *Chem. Commun.* **2014**, *50*, 9550–9553.

(9) Please see the Supporting Information for details.

(10) (a) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409–548. (b) Alamgir, M.; Black, D. S. C.; Kumar, N. *Top. Heterocycl. Chem.* **2007**, *9*, 87–118. (c) De Luca, L. *Curr. Med. Chem.* **2006**, *13*, 1–23.

(11) Dethle, D. H.; Boda, R.; Das, S. *Chem. Commun.* **2013**, *49*, 3260–3262.