

Copper-Catalyzed Highly Enantioselective Cyclopentannulation of Indoles with Donor–Acceptor Cyclopropanes

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S Supporting Information

ABSTRACT: A highly diastereo- and enantioselective BOX/Cu(II)-catalyzed C2,C3-cyclopentannulation of indoles with donor–acceptor cyclopropanes has been developed on the basis of asymmetric formal [3 + 2] cycloaddition of indoles. This reaction provides rapid and facile access to a series of enantioenriched cyclopenta-fused indoline products and can be further extended to the construction of tetracyclic pyrroloindolines. The synthetic potential of the reaction was demonstrated in a four-step synthesis of the core structure of borreverine.

C2,C3-fused indolines are widely present as core structures in a large number of natural products and biologically active

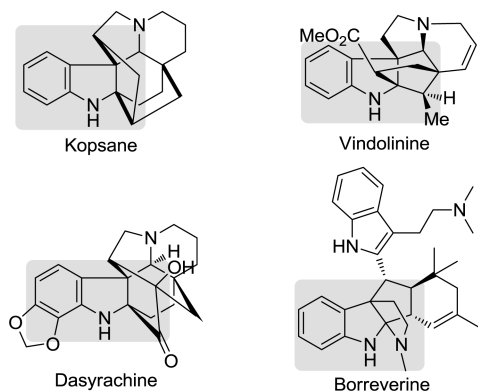
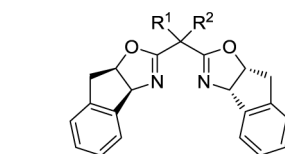


Figure 1. Cyclopenta-fused indolines in natural products.

molecules and have been the focus of extensive synthetic efforts for a long time.¹ Recently, catalytic asymmetric transformations of indoles have been emerging as a powerful enantioselective strategy for the synthesis of these products, featuring the rapid assembly of the multicyclic skeleton in a cascade fashion using readily available indole feedstocks.^{2–4} The key step in these transformations is the generation of the chiral electrophilic indoleniminium intermediate, which is susceptible to intramolecular attack by a pendant group to close the ring. The asymmetric organocatalytic Friedel–Crafts reaction is the most studied approach for generating chiral incipient indoleniminiums,³ while asymmetric metal-catalyzed

Table 1. Reaction Optimization^a



R¹ = Me, R² = H (L4a)

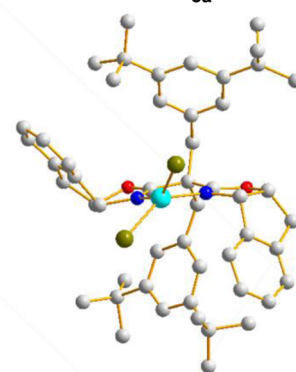
R² = Bn (L4b)

R² = (L4c)

R¹ = R² = Bn (L5a)

4-^tBuC₆H₄CH₂ (L5b)

3,5-^tBu₂C₆H₃CH₂ (L5c)



| Entry | Ligand | <i>t</i> (h) | Yield (%) ^b | dr ^c | ee (%) ^d |
|----------------|----------|--------------|------------------------|-----------------|---------------------|
| 1 | Ph-DBFOX | 24 | NR | – | – |
| 2 | Ph-PyBOX | 24 | NR | – | – |
| 3 | L4a | 24 | 86 | 7.5/1 | 55 |
| 4 | L4b | 2 | 93 | 10/1 | 80 |
| 5 | L4c | 30 | 76 | 7/1 | 68 |
| 6 | L5a | 2 | 88 | 7/1 | 63 |
| 7 | L5b | 2 | 94 | 10/1 | 86 |
| 8 | L5c | 2 | 93 | 14/1 | 88 |
| 9 ^c | L5c | 5 | 95 | 20/1 | 91 |

^a1a/2a = 1.2/1 and [2a] = 0.3 mmol in toluene (3 mL) under N₂.
^bIsolated yields. ^cDetermined by ¹H NMR analysis. ^dDetermined by chiral HPLC. ^e1a/2a = 1/1.5 and [2a] = 0.3 mmol in toluene (3 mL) at 0 °C.

reactions such as palladium-catalyzed C3 allylation of indoles,^{4a} copper-catalyzed arylation,^{4c} and gold-catalyzed alkenylation^{4f} have also proved to be effective. Recently, Barluenga and co-workers^{4b} reported the use of tungsten Fischer carbenes in the asymmetric C2–C3 annulation reaction of indoles, and Lian

Received: April 27, 2013

Published: May 7, 2013

Table 2. Reaction Scope^a

| Entry | Product | t | Yield (%) ^b | dr ^c | ee (%) ^d | Entry | Product | t | Yield (%) ^b | dr ^c | ee (%) ^d |
|-------|------------------|-----|------------------------|-----------------|---------------------|------------------|---|------|------------------------|-----------------|------------------------|
| 1 | | 5h | 95 | 20/1 | 91 | 14 | 5-OMe (3na) | 8h | 92 | >30/1 | 95 |
| 2 | 5-Me (3ba) | 5h | 95 | 19/1 | 90 | 15 | | 5h | 98 | 3.3/1 | 80 /94 ^e |
| 3 | 5-Br (3ca) | 28h | 96 | >20/1 | 90 | 16 | | 42h | 77 | >50/1 | 96 ^f |
| 4 | 5-Cl (3da) | 25h | 96 | >20/1 | 91.5 | 17 | R ³ = 4-(TBSO)-C ₆ H ₄ (3nb) | 36h | 88 | >30/1 | 94 |
| 5 | 5-OMe (3ea) | 3h | 96 | >20/1 | 93 | 18 | 2-furyl (3nc) | 8h | 94 | 12/1 | 86 |
| 6 | 4-Me (3fa) | 5h | 95 | >50/1 | 95 | 19 | 2-thienyl (3nd) | 12h | 94 | 20/1 | 92 |
| 7 | 7-Me (3ga) | 5h | 94 | >20/1 | 90 | 20 | 3,4,5-(MeO) ₃ C ₆ H ₂ (3ne) | 7d | 83 | >20/1 | 89 |
| 8 | 7-Br (3ha) | 36h | 91 | >30/1 | 94 | 21 | CH=CHPh (3nf) | 12h | 83 | 12/1 | 90 |
| 9 | 6-Me (3ia) | 5h | 95 | >20/1 | 90 | 12 ^g | R ³ = vinyl (3ag) | 72h | 45 | 3.5/1 | 84 |
| 10 | R ¹ = | 5h | 95 | 19/1 | 93 | 23 ^{hi} | Ph (3ah) | 168h | 88 | 10/1 | 89 |
| 11 | | 36h | 85 | >20/1 | 86 | 24 ^{hj} | 4-I-C ₆ H ₄ (3ai) | 106h | 90 | 9/1 | 86 |
| 12 | X = H (3la) | 30h | 90 | >20/1 | 95 | | | | | | |
| 13 | 5-Me (3ma) | 24h | 97 | >20/1 | 93 | | | | | | |

^a1 (0.2 mmol), 2 (0.3 mmol), Cu(OTf)₂ (0.02 mmol), and L5c (0.022 mmol) in toluene (3 mL). ^bIsolated yields. ^cDetermined by ¹H NMR analysis. ^dDetermined by HPLC using a chiral stationary phase. ^eWith 2.0 equiv of 2a at -30 °C. ^fWith 3.5 equiv of 2a at -30 °C. ^gWith 3.0 equiv of 2g at 40 °C. ^hKinetic resolution at 40 °C with 2.0 equiv of cyclopropane. ⁱ49% conversion; recovered (S)-2h: 90% ee, S = 94. ^j51% conversion; recovered (S)-2i: 89% ee, S = 38.

and Davies^{4c} established a rhodium-catalyzed version with vinyl diazoacetates. The two works represent the few enantioselective examples of the synthesis of cyclopenta-fused indoline, which is a common structure in many natural products^{1,7} such as kopsane, vindolinine, and dasyrachine (Figure 1). Within this scenario, here we report a new entry to this arsenal, a highly diastereo- and enantioselective Lewis acid-catalyzed formal [3 + 2] cycloaddition^{5,6} of indoles with donor-acceptor (D-A) cyclopropanes. In particular, pyrroloindoles can also participate in this annulation reaction, providing the core structure in borreverines.⁷

We initiated our study with the ligand screening, using indole 1a and cyclopropane 2a as the model substrates and Cu(OTf)₂ as the copper source. The tridentate bis(oxazoline) (BOX) ligands Ph-DBFOX and Ph-PyBOX, which have shown good selectivity in cycloadditions of cyclopropanes with nitrones and

aldehydes or imines,^{6a,c,d} did not show any activity in the current reaction (Table 1, entries 1 and 2). Indane-BOX ligand L4a gave the desired cyclopentannulation product 3a in 86% yield with a promising 55% ee (entry 3). To our delight, modification of the bridging carbon by the introduction of a benzyl group (L4b) not only increased the catalytic activity but also significantly improved the enantioselectivity to 80% ee (entry 4). However, the coordinating oxazoline side-arm group⁸ in L4c retarded the reaction rate and decreased the enantioselectivity by 12%, perhaps because of the weakened Lewis acidity due to the ligation of the additional oxazoline to copper (entry 5). Further elaboration of the ligand was thus focused on using benzyl side-arm groups. Unfortunately, both steric and electronic alterations of the benzene ring failed to provide an obvious improvement in the enantioselectivity.⁹ Recently, we found that a type of cagelike BOX ligand

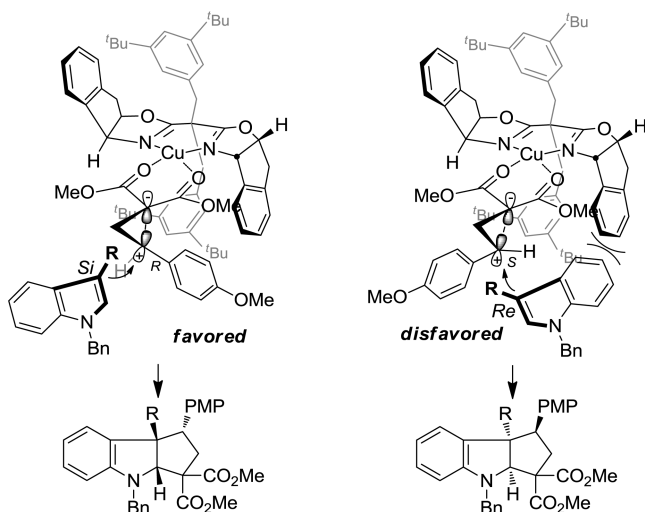
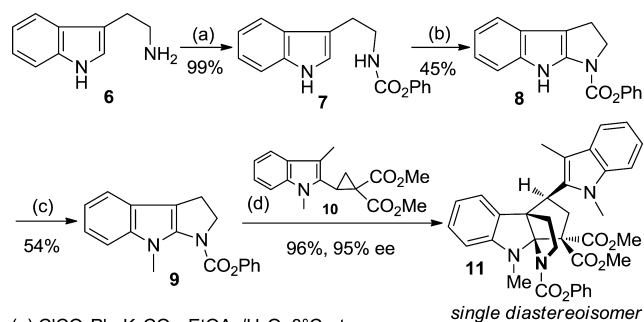


Figure 2. Proposed working model for the stereoselection.

Scheme 1. Synthesis of the Core of Borreverine



(a) ClCO_2Ph , K_2CO_3 , $\text{EtOAc}/\text{H}_2\text{O}$, 0°C -r.t.
 (b) $t\text{-BuOCl}$, Et_3N , DCM , N_2 , 0°C -r.t. (c) NaH , MeI , DMF , 0°C -r.t.
 (d) $\text{Cu}(\text{OTf})_2/\text{L5c}$ (10 mol%), toluene, -40°C

containing two aryl side-arm groups (**L5a**, **L5b**) can significantly improve the enantioselectivity in the cyclopropanation reaction of alkenes compared with ligands having only one aryl side-arm group or without this side-arm modification.¹⁰ Though initial replacement of **L4b** with **L5a** led to a significant drop in selectivity (entry 6), introduction of a *tert*-butyl group at the para position or the two meta positions of the pendant phenyl group improved both the diastereo- and enantioselectivity (entries 7 and 8), and the new ligand **L5c** was identified as the best (the crystal structure of **L5c**/ CuBr_2 is shown in Table 1).⁹ Varying the substrate ratio and lowering the temperature to 0°C further improved the stereoselectivity to a decent level (20/1 dr and 91% ee; entry 9).

Under the optimized conditions, the reaction scope was examined (Table 2). The reaction worked well with a range of indoles. Compared with 5-methyl-substituted indole **1b**, the reactions of 5-bromo- and 5-chloro-substituted indoles **1c** and **1d** were slower, but the electronic effect on the enantioselectivity was negligible (entries 2 and 5 vs 3 and 4). 4-Methyl-substituted indoles were converted with slightly higher diastereo- and enantioselectivity (>50/1 dr and 95% ee; entry 6) than 5-, 6-, or 7-substituted ones (entries 2, 7, and 9). It is noteworthy that indole C3 substituents other than methyl^{4b,c} are also compatible with the current reaction (entries 10–14), allowing additional functionalities such as hydroxy, amino, and allyl groups to be introduced into the final products. In the case of **1k**, the pendant carbamate group may also act as a competing nucleophile to give pyrroloindoline as a side

product, but this was not observed by ^1H NMR analysis of the crude product (entry 11). Remarkably, the reaction of penta-fused indole **1o** also proceeded smoothly under these conditions, delivering [3,3,3,0]-tetracyclic indoline **3oa** containing two quaternary bridging carbons in high yield with good stereoselectivities (entry 15). Also, the reaction of 2,3-dimethylindole **1p** also proceeded well at -30°C (96% ee; entry 16). It is worth mentioning that indoles without a C3 substituent normally gave only the product of Friedel–Crafts alkylation at C3 with high ee rather than the [3 + 2] annulation product.¹¹ On the other hand, cyclopropanes with heteroaryl (2-furyl, 2-thienyl) or alkenyl substituents participated in the annulation reaction with high enantioselectivity (entries 18, 19, and 21). To our delight, vinylcyclopropane **3g** also reacted well with good enantioselectivity, affording a vinyl group for further modifications (entry 22), while alkylcyclopropanes ($\text{R}^3 = \text{H}$, Me) were inert under the current reaction conditions and formed no product even after 2 days at 50°C . In general, except for **1o** and **2g**, all of the reactions proceeded with excellent diastereocontrol (from 12/1 to >50/1 dr). The absolute configuration of **3ha** was assigned by X-ray crystallography,⁹ and the configurations of the other products were assigned by analogy. For less reactive cyclopropanes, the present reactions could proceed with a concurrent kinetic resolution of the cyclopropanes, though the reactions were normally slower. At ca. 50% conversion, both the [3 + 2] annulation products and the recovered (*S*)-cyclopropanes **2h** and **2i** were obtained in high yields with high enantioselectivities (entries 23 and 24).

On the basis of the crystal structure of the **L5c**/ CuBr_2 complex, the square-planar geometry of **Box**/ Cu^{2+} /dicarbonyl complexes,¹² and the stepwise annulation mechanism,⁵ a working model (Figure 2) was tentatively proposed to explain the enantioselection in the present reaction. In view of the steric demand in the nucleophilic attack of C3-substituted indoles at an sp^3 carbon and the donor-group stabilization effect, the cyclopropane C2 carbon must have a significant carbenium ion character.^{6a,13} The approach of the *Si* face of the indole to the transient (*R*)-cyclopropane (left) should be more favored, experiencing less steric interaction with the ligand indanyl substituent. The preference for the (*R*)-cyclopropane is in line with the kinetic resolution results (Table 2, entries 23 and 24), in which (*S*)-cyclopropanes were recovered.

Inspired by the beneficial electronic effect of the electron-donating groups and the good enantioselectivity in the reaction of penta-fused indole **1o**, a synthetic route for the synthesis of the tetracyclic core of borreverine^{7e} based on the cyclopentannulation of pyrroloindole **9** was designed (Scheme 1). Gratifyingly, the [3 + 2] annulation of **9** with **10** could even be carried out at -40°C , and only a single diastereoisomer was observed with high enantioselectivity (95% ee). The four-step synthesis starting from tryptamine **6** gave the desired product **11** in 23% overall yield. The success with pyrroloindole-type substrates provides a novel and rapid access to tetracyclic pyrroloindoline structures.

In summary, a highly diastereo- and enantioselective cyclopentannulation reaction of indoles with cyclopropanes has been successfully developed. The reaction performed well with a series of indoles and D–A cyclopropanes under mild conditions, giving penta-fused indoline products with excellent diastereoselectivities (up to >50/1 dr) and enantioselectivities (up to 96% ee). The application of this reaction to pyrroloindoles established an unprecedented approach to

tetracyclic pyrroloindoline compounds. The synthetic potential of the current reaction was demonstrated in a four-step synthesis of the core structure of borreverine.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterizations and analytical data of ee values of products, and a zip file containing CIFs for **11**, **3ha**, **3oa**, and **LSc/CuBr₂**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Author Contributions

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support from the National Natural Science Foundation of China (20932008 and 21121062), the Major State Basic Research Development Program (2009CB825300), the NSFC/RGC Joint Research Scheme (21061160493 to Y.T. and N_CUHK470/10 to Z.X.), and the Chinese Academy of Sciences. Dedicated to Professor Guoqiang Lin on the occasion of his 70th birthday.

■ REFERENCES

(1) (a) Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*, 2nd ed.; Wiley: New York, 2002. (b) Fattorusso, E.; Tagliatalata Scafati, O. *Modern Alkaloids*; Wiley-VCH: Weinheim, Germany, 2008.

(2) For a recent highlight and review, see: (a) Loh, C. C. J.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 46. (b) Zhuo, C.-X.; Zhang, W.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 12662.

(3) For selected organocatalytic examples, see: (a) Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482. (b) Jones, S. B.; Simmons, B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 13606. (c) Zheng, C.; Lu, Y.; Zhang, J.; Chen, X.; Chai, Z.; Ma, W.; Zhao, G. *Chem.—Eur. J.* **2010**, *16*, 5853. (d) Cai, Q.; Zheng, C.; Zhang, J.-W.; You, S.-L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8665. (e) Xiao, Y.-C.; Wang, C.; Yao, Y.; Sun, J.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10661. (f) Lozano, O.; Blessley, G.; Martinez del Campo, T.; Thompson, A. L.; Giuffredi, G. T.; Bettati, M.; Walker, M.; Borman, R.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2011**, *50*, 8105. (g) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183. (h) Cai, Q.; You, S.-L. *Org. Lett.* **2012**, *14*, 3040. (i) Cai, Q.; Liu, C.; Liang, X.-W.; You, S.-L. *Org. Lett.* **2012**, *14*, 4588.

(4) For metal-catalyzed asymmetric reactions, see: (a) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314. (b) Barluenga, J.; Tudela, E.; Ballesteros, A.; Tomás, M. *J. Am. Chem. Soc.* **2009**, *131*, 2096. (c) Lian, Y.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 440. (d) Repka, L. M.; Ni, J.; Reisman, S. E. *J. Am. Chem. Soc.* **2010**, *132*, 14418. (e) Zhu, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 10815. (f) Cera, G.; Chiarucci, M.; Mazzanti, A.; Mancinelli, M.; Bandini, M. *Org. Lett.* **2012**, *14*, 1350.

(5) For selected annulations of indoles with cyclopropanes, see: (a) Harrington, P.; Kerr, M. A. *Tetrahedron Lett.* **1997**, *38*, 5949. (b) Kerr, M. A.; Keddy, R. G. *Tetrahedron Lett.* **1999**, *40*, 5671. (c) England, D. B.; Kuss, T. D. O.; Keddy, R. G.; Kerr, M. A. *J. Org. Chem.* **2001**, *66*, 4704. For recent examples, see: (d) Bajtos, B.; Yu, M.; Zhao, H.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2007**, *129*, 9631.

(e) Abd Rabo Moustafa, M. M.; Pagenkopf, B. L. *Org. Lett.* **2010**, *12*, 3168.

(6) For leading references on catalytic asymmetric annulations of D–A cyclopropanes, see: (a) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 5764. (b) Kang, Y.-B.; Sun, X.-L.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3918. (c) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 3122. (d) Parsons, A. T.; Smith, A. G.; Neel, A. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2010**, *132*, 9688. (e) Trost, B. M.; Morris, P. *J. Angew. Chem., Int. Ed.* **2011**, *50*, 6167. (f) Zhou, Y.-Y.; Li, J.; Ling, L.; Liao, S.-H.; Sun, X.-L.; Li, Y.-X.; Wang, L.-J.; Tang, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 1452.

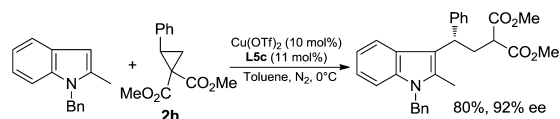
(7) (a) Review: Gataullin, R. R. *Russ. J. Org. Chem.* **2009**, *45*, 321. (b) Magnus, P.; Gallagher, T.; Brown, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 2105. (c) Ahond, A.; Janot, M.-M.; Langlois, N.; Lukacs, G.; Potier, P.; Rasoanaivo, P.; Sangaré, M.; Neuss, N.; Plat, M.; Men, J. L.; Hagaman, E. W.; Wenkert, E. *J. Am. Chem. Soc.* **1974**, *96*, 633. (d) Kam, T.-S.; Subramaniam, G.; Chen, W. *Phytochemistry* **1999**, *51*, 159. (e) Tillequin, F.; Koch, M.; Pousset, J.-L.; Cavé, A. *J. Chem. Soc., Chem. Commun.* **1978**, 826.

(8) For reviews of the sidearm strategy, see: (a) Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2005**, *34*, 664. (b) Hargaden, G. C.; Guiry, P. J. *Chem. Rev.* **2009**, *109*, 2505. For selected examples, see: (c) Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030. (d) Rasappan, R.; Hager, M.; Gissible, A.; Reiser, O. *Org. Lett.* **2006**, *8*, 6099. (e) Seitz, M.; Capacchione, C.; Bellemin-Laponnaz, S.; Wadeh, H.; Ward, B. D.; Gade, L. H. *Dalton Trans.* **2006**, 193. (f) Gade, L. H.; Bellemin-Laponnaz, S. *Chem.—Eur. J.* **2008**, *14*, 4142. (g) Schätz, A.; Rasappan, R.; Hager, M.; Gissibl, A.; Reiser, O. *Chem.—Eur. J.* **2008**, *14*, 7259. (h) Rendina, V. L.; Moebius, D. C.; Kingsbury, J. S. *Org. Lett.* **2011**, *13*, 2004. (i) Castillo, M. R.; Castillón, S.; Claver, C.; Fraile, J. M.; Gual, A.; Martín, M.; Mayoral, J. A.; Sola, E. *Tetrahedron* **2011**, *67*, 5402. (j) Rendina, V. L.; Kaplan, H. Z.; Kingsbury, J. S. *Synthesis* **2012**, *44*, 686. (k) Zhou, Y.-Y.; Wang, L.-J.; Li, J.; Sun, X.-L.; Tang, Y. *J. Am. Chem. Soc.* **2012**, *134*, 9066.

(9) For details, see the Supporting Information.

(10) Deng, C.; Wang, L.-J.; Zhu, J.; Tang, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 11620.

(11) In the reactions of *N*-benzyl-2-methylindole, only Friedel–Crafts alkylation products were isolated, and with 2.0 equiv of cyclopropane **2h**, good enantioselectivity (92% ee) was also achieved.



(12) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561.

(13) (a) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642. (b) Campbell, M. J.; Johnson, J. S.; Parsons, A. T.; Pohlhaus, P. D.; Sanders, S. D. *J. Org. Chem.* **2010**, *75*, 6317.