

RESEARCH ARTICLE

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N-alkylation of indole *via* ring-closing metathesis/isomerization/Mannich cascade under ruthenium/chiral phosphoric acid sequential catalysis†

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A sequential catalysis by combining the **Zhan-1B** catalyst with chiral phosphoric acid has been utilized for *N*-alkylation of indole through a ring-closing metathesis/double bond isomerization/Mannich reaction cascade. Enantioenriched γ -lactams were synthesized in up to 92% yield and 95% ee.

Introduction

Cascade reactions have broad applications in organic synthesis,¹ often reduce time, labor and waste, and enable the construction of complex targets from simple starting materials. It has been proved to be a very efficient strategy to synthesize the indole alkaloids through cascade reactions involving the alkylation of indole.² Recently, the combination of transition-metal catalyst and chiral phosphoric acid (CPA) has become a subject of intense research for developing new transformations beyond the utilization of the single catalytic system.^{3,4} Inspired by the pioneering work of Xiao and co-workers on the Ru-catalyzed tandem cross-metathesis/intramolecular Friedel–Crafts alkylation of indoles,⁵ we recently introduced a sequential catalysis involving a Ru-complex and chiral phosphoric acid.⁶ Several transformations on the asymmetric alkylation of indole have been realized. However, in general, the asymmetric *N*-alkylation of indole has been much less explored than the asymmetric Friedel–Crafts alkylation reaction of indole at the C3 position.^{7,8}

To be noted, an elegant chiral phosphoric acid catalyzed isomerization of α,β -unsaturated lactam to *N*-acyl iminium in an enantioselective *N*-H functionalization of indoles was reported by Huang and co-workers (Scheme 1, top).⁹ As part of our research program towards the efficient asymmetric transformation of indoles,¹⁰ we envisaged that a sequential catalysis combining a Ru-catalyst and chiral phosphoric acid might be able to realize the *N*-alkylation of indole in a more efficient fashion by employing readily available starting materials (Scheme 1, bottom).

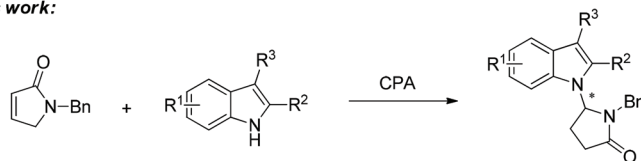
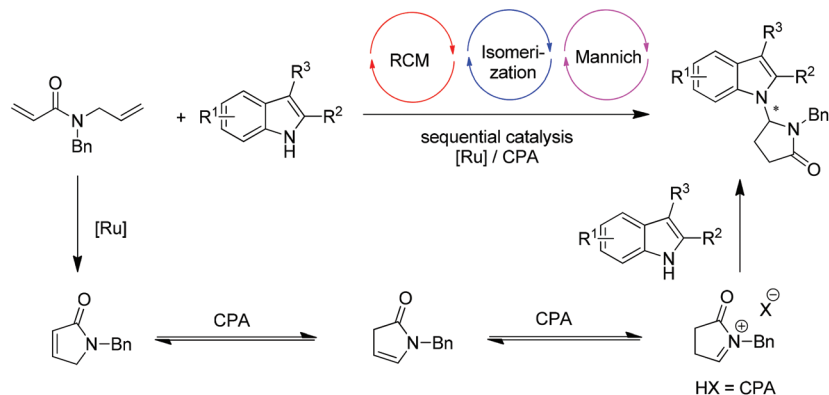
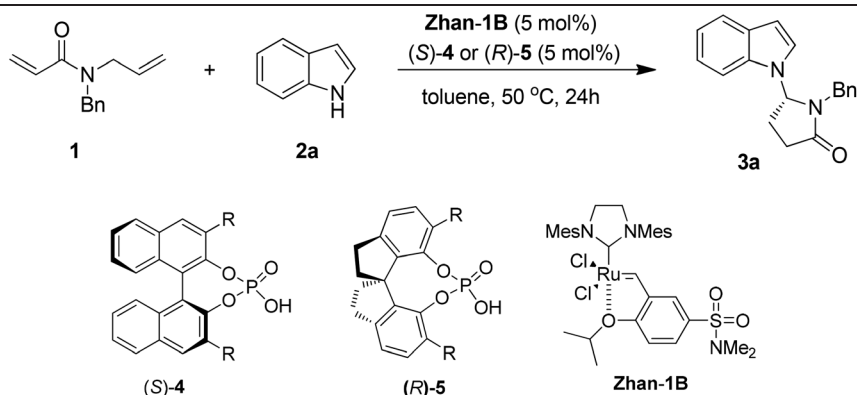
To test our hypothesis, *N*-allyl-*N*-benzylacrylamide **1** was treated with 1.2 equivalents of indole (**2a**) in the presence of 5 mol% chiral phosphoric acid **4a** and 5 mol% **Zhan-1B** in toluene. After stirring at room temperature for 3 days, the reaction gave the desired product **3a** in 23% yield and 78% ee (entry 1, Table 1). Prolonging the reaction time to 7 days, the yield of **3a** was improved to 52% without decreasing the enantioselectivity (78% ee) (entry 2, Table 1). When the reaction temperature was increased to 50 °C, starting material **1** disappeared after 24 h and the product was obtained in 67% yield and 78% ee (entry 3, Table 1). Under these reaction conditions, more chiral phosphoric acids were tested.

First, a series of (*S*)-BINOL-derived chiral phosphoric acids was tested (entries 1–10, Table 1). The 4-(*tert*-butyl)-2,6-diisopropylphenyl substituted phosphoric acid afforded an improved enantioselectivity (81% ee, entry 10, Table 1). The sterically congested phosphoric acid catalysts might be crucial for the enantioselective control. Then the (*R*)-SPINOL-derived phosphoric acids (entries 11–13, Table 1) were screened. To our great delight, the reaction with catalyst **5c** bearing 2,4,6-triisopropylphenyl groups led to the best combination of yield and enantioselectivity (76% yield, 92% ee, entry 13, Table 1).

Examination of the reaction temperatures revealed that the enantioselectivity was not influenced at lower temperature (entries 1 and 2, Table 2) but decreased at higher temperatures (entries 1, 3 and 4, Table 2). The yields decreased at 30 °C and 110 °C comparing to those at 50 °C and 80 °C. Investigation of the ruthenium catalysts disclosed that both the Grubbs II and Hoveyda–Grubbs II catalysts gave excellent enantioselectivity. The Hoveyda–Grubbs II catalyst could give a comparable yield (entry 6, Table 2) but the reaction with Grubbs II catalyst resulted in a lower yield (entry 5, Table 2). The reactions in benzene and *o*-xylene (entries 7 and 8, Table 2) afforded comparable enantioselectivity but decreased yields, while the reaction in DCE led to the drop of both yield and enantioselectivity (entry 9, Table 2). The optimized reaction conditions obtained

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Huang's work:*This work:***Scheme 1** Ring-closing metathesis/isomerization/Mannich reaction sequence.**Table 1** Screening of chiral phosphoric acids

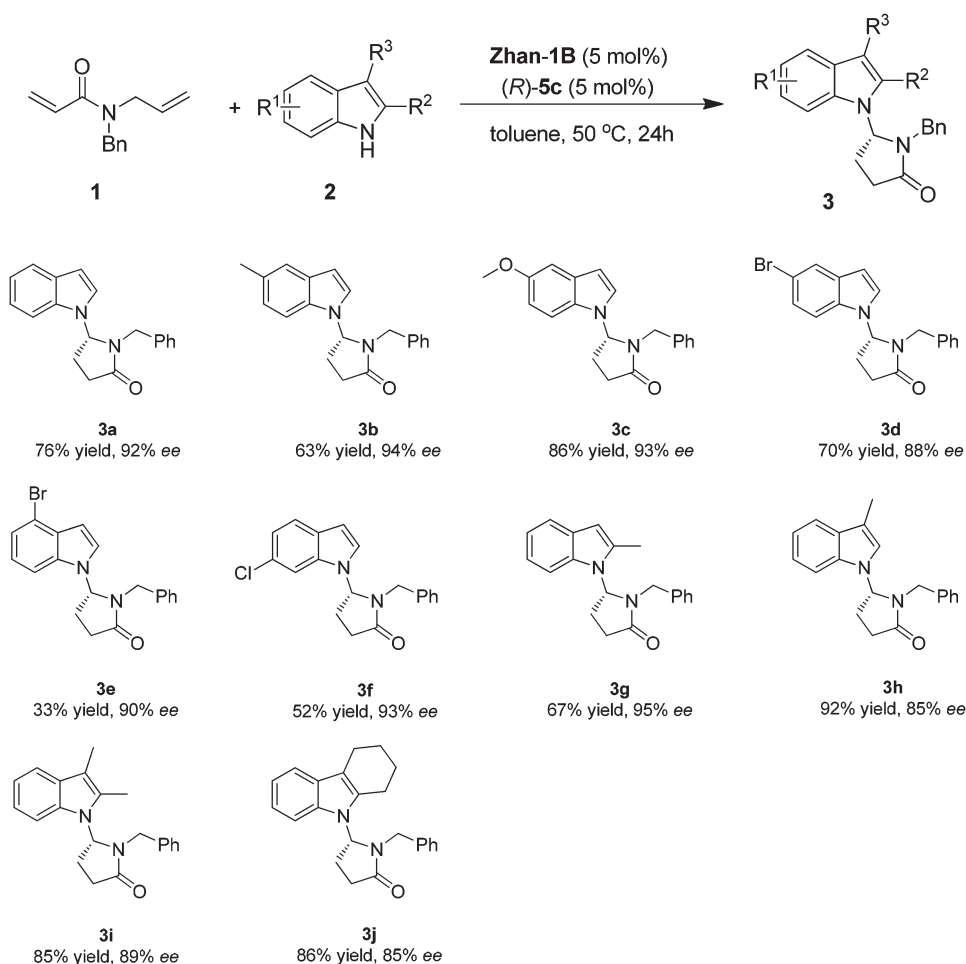
Entry ^a	Catalyst	R	Yield ^b (%)	ee ^c (%)
1 ^d	4a	2,4,6-(ⁱ Pr) ₃ -C ₆ H ₂	23	78
2 ^e	4a	2,4,6-(ⁱ Pr) ₃ -C ₆ H ₂	52	78
3	4a	2,4,6-(ⁱ Pr) ₃ -C ₆ H ₂	67	78
4	4b	Ph	7	25
5	4c	3,5-(CF ₃) ₂ -C ₆ H ₃	23	–5
6	4d	2-Naphthyl	16	21
7	4e	1-Naphthyl	8	36
8	4f	SiPh ₃	41	12
9	4g	9-Anthryl	53	50
10	4h	2,6-(ⁱ Pr) ₂ -4- ^t Bu-C ₆ H ₂	51	81
11	5a	4-Cl-C ₆ H ₄	21	29
12	5b	3,5-(CF ₃) ₂ -C ₆ H ₃	12	33
13	5c	2,4,6-(ⁱ Pr) ₃ -C ₆ H ₂	76	92

^a Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol), **Zhan-1B** (5 mol%), **4** or **5** (5 mol%) in 1.5 mL toluene. ^b Isolated yield. ^c Determined by HPLC analysis. ^d Room temperature for 3 d. ^e Room temperature for 7 d.

Table 2 Screening of temperature, solvents and Ru catalysts

Entry ^a	[Ru] catalyst	Solvent	T (%)	Yield ^b (%)	ee ^c (%)
1	Zhan-1B	Toluene	50	76	92
2	Zhan-1B	Toluene	30	17	92
3	Zhan-1B	Toluene	80	72	85
4	Zhan-1B	Toluene	110	29	34
5	Grubbs II	Toluene	50	19	92
6	Hoveyda–Grubbs II	Toluene	50	73	92
7	Zhan-1B	Benzene	50	34	90
8	Zhan-1B	<i>o</i> -Xylene	50	71	91
9	Zhan-1B	DCE	50	31	83

^a Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol), [Ru] (5 mol%), (*R*)-**5c** (5 mol%) in 1.5 mL toluene. ^b Isolated yield. ^c Determined by HPLC analysis.



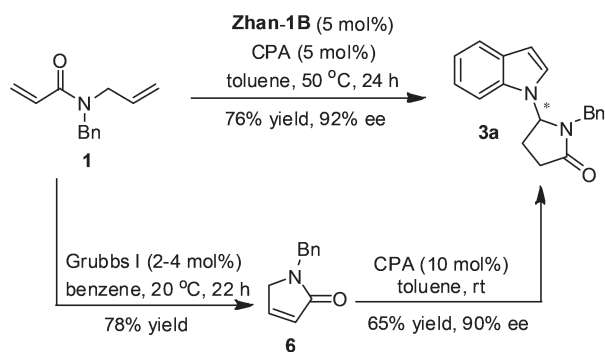
Scheme 2 Substrate scope for cascade RCM/isomerization/Mannich reaction. Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), Zhan-1B (5 mol%), (*R*)-**5c** (5 mol%) in 1.5 mL toluene.

were as following: 5 mol% **Zhan-1B**, 5 mol% (*R*)-**5c**, 1.2 equivalents of indole in toluene at 50 °C (entry 1, Table 2).

Under the optimized reaction conditions, various indole derivatives were examined to test the generality of the cascade reaction. The results are summarized in Scheme 2. The absolute configuration of product was assigned as *R* by comparing the sign of the optical rotation with the known compounds reported in the literature.⁹ In general, all the tested substrates varying substituents on the indole such as 5-Me, 5-OMe, 5-Br, 4-Br, and 6-Cl were tolerated with excellent enantioselectivity (88–94% ee, **3b–3f**). The yields are in general moderate to good (52–86% yields) except for 4-Br substituted indole (33% yield). In addition, indole substrates bearing a substituent at the C-3 or C-2 position such as 2-Me, 3-Me, 2,3-(Me)₂, and 2,3-(C₄H₈) could be well tolerated (67–92% yield, 85–95% ee, **3g–3j**).

The cascade reaction enabled by the sequential catalysis not only reduced the synthetic steps but also offered a more efficient synthesis overall. For example, with **1** and indole as the substrates, the yield and enantioselectivity of the product obtained from this cascade with those derived from the two step reactions in the literature were compared (Scheme 3). The first RCM step afforded compound **6** in 78% yield in the presence of 5 mol% Grubbs I catalyst in benzene¹¹ and the second asymmetric double bond isomerization and Mannich reactions gave product **3a** in 65% yield and 90% ee according to the literature.⁹ Therefore, the combined yield of the two steps was 51% yield, which is lower than the cascade reaction (76% yield). To be noted, the enantioselectivity of the current study in general is higher comparing with those reported by Huang because two different chiral phosphoric acids were utilized, respectively.

In conclusion, we have developed an efficient *N*-alkylation of indole through a RCM/isomerization/Mannich reaction cascade. In the presence of a ruthenium complex and chiral phosphoric acid, 5-(1*H*-indol-1-yl)pyrrolidin-2-one derivatives were synthesized in good yields and excellent enantioselectivity. The sequential catalysis allowing three distinctive steps to be performed in a cascade displayed superior efficiency over the stepwise reactions. Further exploration of efficient reactions based on the Ru complex/chiral phosphoric acid sequential catalysis is undergoing in our lab.



Scheme 3 Comparison between cascade reaction and stepwise reaction.

Acknowledgements

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References

- For selected reviews, see: (a) L. F. Tietze and U. Beifuss, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 131; (b) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (c) S. E. Denmark and A. Thorarensen, *Chem. Rev.*, 1996, **96**, 137; (d) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem., Int. Ed.*, 2006, **45**, 7134; (e) A. M. Walji and D. W. C. MacMillan, *Synlett*, 2007, 1477; (f) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, 2010, **2**, 167; (g) H. Pellissier, *Adv. Synth. Catal.*, 2012, **354**, 237; (h) H. Pellissier, *Chem. Rev.*, 2013, **113**, 442.
- For selected organocatalytic reactions, see: (a) J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao and D. W. C. MacMillan, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5482; (b) D. Enders, A. A. Narine, F. Toulgoat and T. Bisschops, *Angew. Chem., Int. Ed.*, 2008, **47**, 5661; (c) C. Gioia, A. Hauville, L. Bernardi, F. Fini and A. Ricci, *Angew. Chem., Int. Ed.*, 2008, **47**, 9236; (d) C. Zheng, Y. Lu, J. Zhang, X. Chen, Z. Chai, W. Ma and G. Zhao, *Chem.-Eur. J.*, 2010, **16**, 5853; (e) D. Enders, C. Wang, M. Mukanova and A. Greb, *Chem. Commun.*, 2010, **46**, 2447; (f) B. Tan, G. Hernández-Torres and C. F. Barbas III, *J. Am. Chem. Soc.*, 2011, **133**, 12354; (g) Y.-J. Cao, H.-G. Cheng, L.-Q. Lu, J.-J. Zhang, Y. Cheng, J.-R. Chen and W.-J. Xiao, *Adv. Synth. Catal.*, 2011, **353**, 617; (h) X. Wu, X. Dai, H. Fang, L. Nie, J. Chen, W. Cao and G. Zhao, *Chem.-Eur. J.*, 2011, **17**, 10510; (i) S. B. Jones, B. Simmons, A. Mastracchio and D. W. C. MacMillan, *Nature*, 2011, **475**, 183; (j) Z. Zhang and J. C. Antilla, *Angew. Chem., Int. Ed.*, 2012, **51**, 11778; (k) Z. Chen, B. Wang, Z. Wang, G. Zhu and J. Sun, *Angew. Chem., Int. Ed.*, 2013, **52**, 2027; For selected metal-catalyzed reactions, see: (l) B. M. Trost and J. Quancard, *J. Am. Chem. Soc.*, 2006, **128**, 6314; (m) T. Arai and N. Yokoyama, *Angew. Chem., Int. Ed.*, 2008, **47**, 4989; (n) J. Barluenga, E. Tudela, A. Ballesteros and M. Tomás, *J. Am. Chem. Soc.*, 2009, **131**, 2096; (o) Y. Lian and H. M. L. Davies, *J. Am. Chem. Soc.*, 2010, **132**, 440; (p) L. M. Repka, J. Ni and S. E. Reisman, *J. Am. Chem. Soc.*, 2010, **132**, 14418; (q) Y. Duan, M.-W. Chen, Z.-S. Ye, D.-S. Wang, Q.-A. Chen and Y.-G. Zhou, *Chem.-Eur. J.*, 2011, **17**, 7193; (r) G. Cera, M. Chiarucci, A. Mazzanti, M. Mancinelli and M. Bandini, *Org. Lett.*, 2012, **14**, 1350; (s) M. E. Kieffer, L. M. Repka and S. E. Reisman, *J. Am. Chem. Soc.*, 2012, **134**, 5131; (t) H. Xiong, H. Xu, S. Liao, Z. Xie and Y. Tang, *J. Am. Chem. Soc.*, 2013, **135**, 7851; (u) H.-G. Cheng, L.-Q. Lu, T. Wang, Q.-Q. Yang, X.-P. Liu, Y. Li, Q.-H. Deng, J.-R. Chen and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2013, **52**, 3250.

- 3 For reviews: (a) Z. Shao and H. Zhang, *Chem. Soc. Rev.*, 2009, **38**, 2745; (b) M. Rueping, R. M. Koenigs and I. Atodiresei, *Chem.-Eur. J.*, 2010, **16**, 9350; (c) J. Zhou, *Chem.-Asian J.*, 2010, **5**, 422; (d) C. Zhong and X. Shi, *Eur. J. Org. Chem.*, 2010, 2999; (e) Z. Du and Z. Shao, *Chem. Soc. Rev.*, 2013, **42**, 1337; (f) X. Wu, M. Li and L. Gong, *Acta Chim. Sin.*, 2013, **71**, 1091; (g) F. Lv, S. Liu and W. Hu, *Asian J. Org. Chem.*, 2013, **2**, 824.
- 4 For selected recent examples: (a) M. Rueping, A. P. Antonchick and C. Brinkmann, *Angew. Chem., Int. Ed.*, 2007, **46**, 6903; (b) S. Mukherjee and B. List, *J. Am. Chem. Soc.*, 2007, **129**, 11336; (c) K. Sorimachi and M. Terada, *J. Am. Chem. Soc.*, 2008, **130**, 14452; (d) W. Hu, X. Xu, J. Zhou, W.-J. Liu, H. Huang, J. Hu, L. Yang and L.-Z. Gong, *J. Am. Chem. Soc.*, 2008, **130**, 7782; (e) Z.-Y. Han, H. Xiao, X.-H. Chen and L.-Z. Gong, *J. Am. Chem. Soc.*, 2009, **131**, 9182; (f) M. E. Muratore, C. A. Holloway, A. W. Pilling, R. I. Storer, G. Trevitt and D. J. Dixon, *J. Am. Chem. Soc.*, 2009, **131**, 10796; (g) M. Terada and Y. Toda, *J. Am. Chem. Soc.*, 2009, **131**, 6354; (h) X.-Y. Liu and C.-M. Che, *Org. Lett.*, 2009, **11**, 4204; (i) C. A. Holloway, M. E. Muratore, R. I. Storer and D. J. Dixon, *Org. Lett.*, 2010, **12**, 4720; (j) J. Jiang, H.-D. Xu, J.-B. Xi, B.-Y. Ren, F.-P. Lv, X. Guo, L.-Q. Jiang, Z.-Y. Zhang and W.-H. Hu, *J. Am. Chem. Soc.*, 2011, **133**, 8428; (k) Q.-A. Chen, D.-S. Wang, Y.-G. Zhou, Y. Duan, H.-J. Fan, Y. Yang and Z. Zhang, *J. Am. Chem. Soc.*, 2011, **133**, 6126; (l) Q.-A. Chen, M.-W. Chen, C.-B. Yu, L. Shi, D.-S. Wang, Y. Yang and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2011, **133**, 16432; (m) Z.-Y. Han, D.-F. Chen, Y.-Y. Wang, R. Guo, P.-S. Wang, C. Wang and L.-Z. Gong, *J. Am. Chem. Soc.*, 2012, **134**, 6532; (n) X.-F. Tu and L.-Z. Gong, *Angew. Chem., Int. Ed.*, 2012, **51**, 11346; (o) M. Terada and Y. Toda, *Angew. Chem., Int. Ed.*, 2012, **51**, 2093; (p) H. Qiu, M. Li, L.-Q. Jiang, F.-P. Lv, L. Zan, C.-W. Zhai, M. P. Doyle and W.-H. Hu, *Nat. Chem.*, 2012, **4**, 733; (q) Q.-A. Chen, K. Gao, Y. Duan, Z.-S. Ye, L. Shi, Y. Yang and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2012, **134**, 2442; (r) H. Wu, Y.-P. He and L.-Z. Gong, *Org. Lett.*, 2013, **15**, 460.
- 5 (a) J.-R. Chen, C.-F. Li, X.-L. An, J.-J. Zhang, X.-Y. Zhu and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2008, **47**, 2489; (b) X.-L. An, J.-R. Chen, C.-F. Li, F.-G. Zhang, Y.-Q. Zou, Y.-C. Guo and W.-J. Xiao, *Chem.-Asian J.*, 2010, **5**, 2258; Also see: (c) E. Ascic, J. F. Jensen and T. E. Nielsen, *Angew. Chem., Int. Ed.*, 2011, **50**, 5188; (d) E. Ascic, S. T. Le Quement, M. Ishoey, M. Daugaard and T. E. Nielsen, *ACS Comb. Sci.*, 2012, **14**, 253; (e) M. T. Petersen and T. E. Nielsen, *Org. Lett.*, 2013, **15**, 1986.
- 6 (a) Q. Cai, Z.-A. Zhao and S.-L. You, *Angew. Chem., Int. Ed.*, 2009, **48**, 7428; (b) Q. Cai, C. Zheng and S.-L. You, *Angew. Chem., Int. Ed.*, 2010, **49**, 8666; (c) Q. Cai, X.-W. Liang, S.-G. Wang, J.-W. Zhang, X. Zhang and S.-L. You, *Org. Lett.*, 2012, **14**, 5022; (d) Q. Cai, X.-W. Liang, S.-G. Wang and S.-L. You, *Org. Biomol. Chem.*, 2013, **11**, 1602; (e) J.-W. Zhang, Q. Cai, Q. Gu, X.-X. Shi and S.-L. You, *Chem. Commun.*, 2013, **49**, 7750; Also see a recent example from Yu's group: (f) H. Liu, C. Zeng, J. Guo, M. Zhang and S. Yu, *RSC Adv.*, 2013, **3**, 1666.
- 7 For selected asymmetric *N*-alkylation of indole: (a) B. M. Trost, M. J. Krische, V. Berl and E. M. Grenzer, *Org. Lett.*, 2002, **4**, 2005; (b) M. Bandini, A. Eichholzer, M. Tragni and A. Umani-Ronchi, *Angew. Chem., Int. Ed.*, 2008, **47**, 3238; (c) H.-L. Cui, X. Feng, J. Peng, J. Lei, K. Jiang and Y.-C. Chen, *Angew. Chem., Int. Ed.*, 2009, **48**, 5737; (d) L. M. Stanley and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2009, **48**, 7841; (e) D. Enders, C. Wang and G. Raabe, *Synthesis*, 2009, 4119; (f) L. Hong, W. Sun, C. Liu, L. Wang and R. Wang, *Chem.-Eur. J.*, 2010, **16**, 440; (g) D. Enders, A. Greb, K. Deckers, P. Selig and C. Merckens, *Chem.-Eur. J.*, 2012, **18**, 10226; (h) W.-B. Liu, X. Zhang, L.-X. Dai and S.-L. You, *Angew. Chem., Int. Ed.*, 2012, **51**, 5183; (i) D. Enders, C. Joie and K. Deckers, *Chem.-Eur. J.*, 2013, **19**, 10818.
- 8 For reviews on asymmetric Friedel-Crafts reaction, see: (a) M. Bandini, A. Melloni and A. Umani-Ronchi, *Angew. Chem., Int. Ed.*, 2004, **43**, 550; (b) T. B. Poulsen and K. A. Jørgensen, *Chem. Rev.*, 2008, **108**, 2903; (c) S.-L. You, Q. Cai and M. Zeng, *Chem. Soc. Rev.*, 2009, **38**, 2190; (d) M. Bandini and A. Eichholzer, *Angew. Chem., Int. Ed.*, 2009, **48**, 9608; (e) V. Terrasson, R. M. Figueiredo and J. M. Campagne, *Eur. J. Org. Chem.*, 2010, 2635; (f) M. Zeng and S.-L. You, *Synlett*, 2010, **9**, 1289.
- 9 Y. Xie, Y. Zhao, B. Qian, L. Yang, C. Xia and H. Huang, *Angew. Chem., Int. Ed.*, 2011, **50**, 5682.
- 10 For selected examples: (a) Q. Kang, Z.-A. Zhao and S.-L. You, *J. Am. Chem. Soc.*, 2007, **129**, 1484; (b) Q.-F. Wu, H. He, W.-B. Liu and S.-L. You, *J. Am. Chem. Soc.*, 2010, **132**, 11418; (c) Q. Yin and S.-L. You, *Chem. Sci.*, 2011, **2**, 1344; (d) Q. Cai, C. Zheng, J.-W. Zhang and S.-L. You, *Angew. Chem., Int. Ed.*, 2011, **50**, 8665; (e) Q.-F. Wu, C. Zheng and S.-L. You, *Angew. Chem., Int. Ed.*, 2012, **51**, 1680; (f) Q. Cai and S.-L. You, *Org. Lett.*, 2012, **14**, 3040; (g) Q. Cai, C. Liu, X.-W. Liang and S.-L. You, *Org. Lett.*, 2012, **14**, 4588; (h) M. Zeng, W. Zhang and S.-L. You, *Chin. J. Chem.*, 2012, **30**, 2615; (i) Q.-L. Xu, L.-X. Dai and S.-L. You, *Chem. Sci.*, 2013, **4**, 97; (j) Q. Yin, S.-G. Wang and S.-L. You, *Org. Lett.*, 2013, **15**, 2688; (k) Q. Yin and S.-L. You, *Org. Lett.*, 2013, **15**, 4266; (l) C.-X. Zhuo, Q.-F. Wu, Q. Zhao, Q.-L. Xu and S.-L. You, *J. Am. Chem. Soc.*, 2013, **135**, 8169.
- 11 G. C. Fu, S. T. Nguyen and R. H. Grubbs, *J. Am. Chem. Soc.*, 1993, **115**, 9856.