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Ruthenium-Catalyzed Enantioselective Hydrogenation of 1,8-Naphthyridine Derivatives

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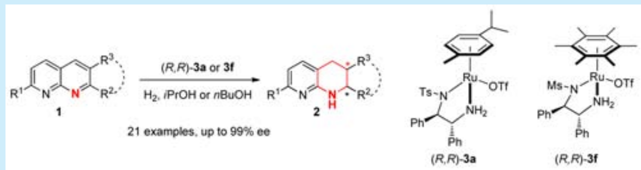
Supporting Information

ABSTRACT: The first asymmetric hydrogenation of 2,7-disubstituted 1,8-naphthyridines catalyzed by chiral cationic ruthenium diamine complexes has been developed. A wide range of 1,8-naphthyridine derivatives were effectively hydrogenated to give 1,2,3,4-tetrahydro-1,8-naphthyridines with up to 99% ee and full conversions. The method provides a practical and facile approach to the preparation of valuable chiral heterocyclic building blocks and useful motifs for a new kind of P,N-ligand.



The 1,2,3,4-tetrahydro-1,8-naphthyridine ring systems are attractive structural motifs because of their wide distribution in bioactive molecules and pharmaceuticals, as represented by a potent antagonist of the $\alpha_v\beta_3$ receptor,[1] CETP (cholesterol ester transfer protein) inhibitor,[2] and EP_1 (prostaglandin E_1 receptor 1) antagonist[3] (Figure 1). To date, many methods have been developed for the preparation of 1,2,3,4-tetrahydro-1,8-naphthyridines such as hydroboration of naphthyridine,[4a] intramolecular Chichibabin cyclization,[1c,d,4b] tin-free radical cyclization,[4c] *ortho*-alkylation of Boc-protected aminopyridines,[4d] regioselective hydrogenation,[1a,b,3,4e,f] and transfer hydrogenation of naphthyridines.[4g] However, the asymmetric synthesis of 1,2,3,4-tetrahydro-1,8-naphthyridine derivatives is rare.[1c,d]

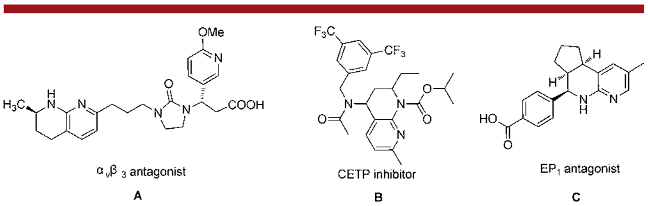
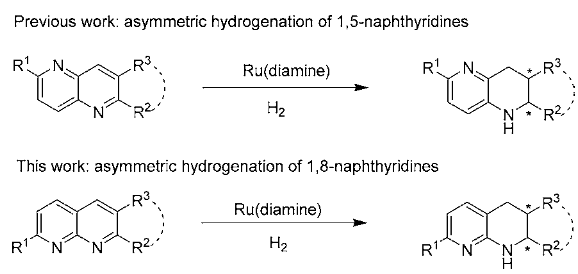


Figure 1. Representative biologically active compounds.

In the past decade, asymmetric hydrogenation of heteroaromatic compounds has become one of the most straightforward ways toward the synthesis of optically active compounds with chiral heterocyclic skeleton.[5−8] In this context, we found that the phosphine-free, cationic ruthenium complexes of chiral monotosylated diamine are highly effective catalysts for asymmetric hydrogenation of quinolines,[6b,c] quinoxalines,[7e] and 1,10-phenanthrolines[8a] with unprecedentedly high reactivities and excellent enantioselectivities. Very recently, we applied the cationic ruthenium complexes to the hydrogenation of 1,5-naphthyridine derivatives with excellent regio- and enantioselectivity (Scheme 1).[8c] Encouraged by these results, we hope to expand the substrate scope from 1,5-naphthyridines to 1,8-naphthyridines, which are usually regarded as difficult substrates due to their strong coordinating abilities. To date, only a few examples were reported, and most of them included heterogeneous regioselective hydrogenation.[1a,b,3,4e,f] Most recently, Zhang and co-workers reported a novel straightforward synthesis of 1,2,3,4-tetrahydronaphthyridines via a ruthenium-catalyzed selective transfer hydrogenation of a pyridyl ring with alcohols.[4g] However, only racemic products were obtained. Herein, we report the first highly efficient asymmetric hydrogenation of a range of 1,8-naphthyridine derivatives with good to excellent enantioselectivities and full conversions.

Scheme 1. Asymmetric Hydrogenation of Naphthyridine Derivatives



In the initial experiment, 1,8-naphthyridine was chosen to be hydrogenated with (*R*,*R*)-**3a** in *i*PrOH under 50 atm of H_2. However, 1,2,3,4-tetrahydro-1,8-naphthyridine was not detected (Table 1, entry 1). In contrast, 1,5-naphthyridine

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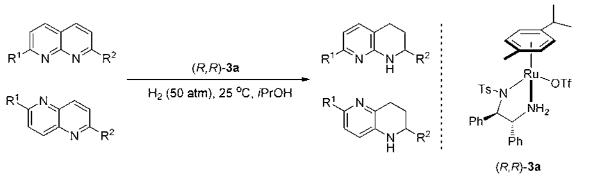
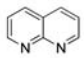
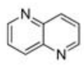
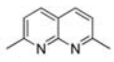
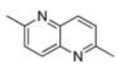
Table 1. Comparison of Hydrogenation Activity between 1,8-Naphthyridines and 1,5-Naphthyridines[a]



entry	substrate	S/C	time (h)	yield[b]	ee[c]
1[d]		50	3	0	/
2		50	3	92%	/
3		100	24	64%	94%
4[e]		100	3	86%	92%

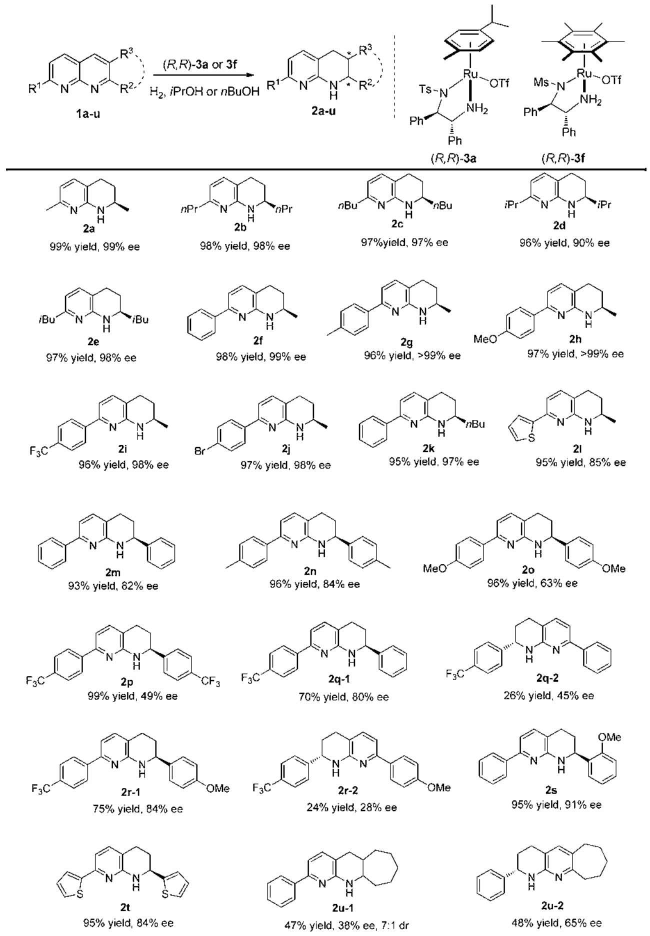
[a]Reaction conditions: substrate (0.1 mmol), *i*PrOH (1 mL), (*R*,*R*)-**3a**, H_2 (50 atm), stirred at 25 °C. S/C = substrate/catalyst. [b]Determined by ^{1}H NMR. [c]The ee values were determined by a chiral OD-H column. [d]About 7% byproduct was observed, and substrate can be recovered. [e]Data were reported in ref 8c.

could be hydrogenated smoothly in 92% yield under the same conditions (entry 2). The result indicated that the ruthenium catalyst was deactivated by the 1,8-naphthyridine substrate. We envisioned that the introduction of a substituent at the *ortho* position of both pyridyl rings could reduce their coordinating ability.[9] To our delight, 2,7-dimethyl-1,8-naphthyridine could be hydrogenated by using 1.0 mol % catalyst, giving the desired chiral product in 64% yield with 94% ee. Slightly higher enantioselectivity was achieved although a much lower yield was observed as compared with 2,6-dimethyl-1,5-naphthyridine (entry 3 vs 4). These results illustrated that 1,8-naphthyridines were much more difficult substrates for hydrogenation than 1,5-naphthyridines.

Encouraged by these promising results, the influences of solvent, catalyst, temperature, and hydrogen pressure were studied by using 2,7-dimethyl-1,8-naphthyridine **1a** as the model substrate and (*R*,*R*)-**3a** as the catalyst (see the Supporting Information (SI)). After a number of solvents were screened, isopropanol was found to be optimal in terms of reactivity and enantioselectivity (Table S1, SI). Then, the influence of different catalysts was investigated by using isopropanol as the solvent (Table S2, SI). Further improvement of enantioselectivity was achieved by using the ruthenium catalyst bearing a hexamethylbenzene ligand (*R*,*R*)-**3f** (99% ee). In addition, the enantioselectivity of the reaction was found to be insensitive to hydrogen pressure and temperature (Table S3, SI).

With the optimized reaction conditions in hand, we turned our attention to investigate the scope of the disubstituted 1,8-naphthyridine derivatives, and the results were summarized in Scheme 2. Generally, 2,7-dialkyl-substituted 1,8-naphthyridines were hydrogenated smoothly in the presence of 2.0 mol % (*R*,*R*)-**3f** with excellent enantioselectivities (97–99% ee) regardless of the length of the side chain (**1a**–**c**, **1e** in Scheme 2). Substrate bearing steric alkyl substituent **1d** gave obviously low enantioselectivity. Moreover, for the unsymmetrical substrates bearing one alkyl substituent at the 2-position and

Scheme 2. Asymmetric Hydrogenation of 2,7-Disubstituted and 2,3,7-Trisubstituted 1,8-Naphthyridines[a]



[a]Reaction conditions: substrates **1a**–**l** (0.2 mmol), *i*PrOH (1 mL), 2.0 mol % of (*R*,*R*)-**3f**, H_2 (50 atm), stirred at 25 °C for 12 h; substrates **1m**–**u** (0.2 mmol), *n*BuOH (1 mL), 5.0 mol % of (*R*,*R*)-**3a**, 50 atm of H_2, stirred at 25 °C for 24 h. Yields of isolated product were given. The ee values were determined by chiral HPLC analysis. The absolute configuration of **2i** was determined to be *R* and **2m** was determined to be *S* based on single-crystal X-ray analysis (Schemes S1, S3, SI). The configurations of the other products were proposed by analogy.

one aryl substituent at the 7-position (**1f**–**l**), excellent enantioselectivities were also obtained. Interestingly, only the pyridyl ring bearing an alkyl group was hydrogenated. Notably, the electronic properties of the substituents at the *para* position of the phenyl ring had no apparent effect on enantioselectivity (**1f**–**j**). Substrate **1l** bearing a 2-thienyl substituent gave obviously low enantioselectivity.

The hydrogenation of 2,7-diaryl-substituted 1,8-naphthyridines were also examined. From the screening of a variety of solvents (Table S4, SI) and catalysts (Table S5, SI) using **1m** as the model substrate, the optimal reaction conditions were determined to be 5.0 mol % (*R*,*R*)-**3a** in *n*BuOH. Subsequently, a variety of 2,7-diaryl-substituted 1,8-naphthyridines (**1m**–**t**) were evaluated. As shown in Scheme 2, all 2,7-diarylsubstituted substrates were hydrogenated with full conversions and moderate to good enantioselectivities. Notably, substrates bearing strong electron-donation group **1o** and strong electron-withdrawing group **1p** at the *para* positions of both phenyl rings gave much lower enantioselectivities. In the cases of unsymmetrical 2,7-diarylsubstituted substrates (**1q**–**r**), the

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pyridyl ring bearing an electron-rich substituent was preferred to be hydrogenated. Interestingly, substrate **1s** bearing a methoxy group at the *ortho* position of one phenyl ring gave excellent regioselectivity and high enantioselectivity (91% ee). 2,7-Dithienyl-substituted substrate **1t** was hydrogenated with 84% ee. In addition, 2,3,7-trisubstituted 1,8-naphthyridine **1u** could be hydrogenated smoothly with moderate enantioselectivity but much lower regioselectivity.

The absolute configuration of **2i** was determined to be *R* based on single-crystal X-ray analysis (Scheme S1, SI). Similarly, the configuration of **2m** was assigned as *S* by single-crystal X-ray analysis of the corresponding *N*-tosylated derivative compound **5** (Scheme S3, SI). The configurations of the other chiral products were assigned by analogy.

Based on these results and our previous study on the asymmetric hydrogenation of quinoline,[6c] we proposed a cyclic 10-membered transition structure with the participation of the TfO anion for the asymmetric hydrogenation of 1,8-naphthyridines. For both types of substrates bearing an alkyl or aryl group at the 2-position, the enantioselectivity originates from the CH−π interaction between the η^6-arene ligand in the ruthenium complex and the fused pyridine ring (TS1 and TS2 in Figure 2). Notably, in the case of 2,7-diaryl-substituted 1,8-naphthyridines, the transition structure is different from that of 2,6-diaryl-substituted 1,5-naphthyridines, which uses the substituted phenyl ring instead of the fused pyridine ring to form the CH−π interaction.[8c] This difference might explain the lower regioselectivities than those in the asymmetric hydrogenation of unsymmetric diaryl substituted 1,5-naphthyridines.

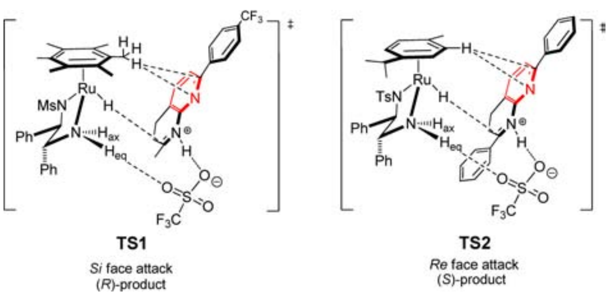
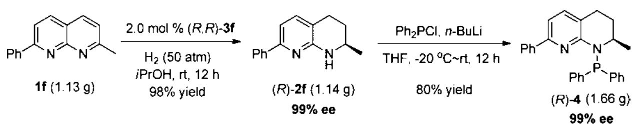


Figure 2. Proposed transition states involving (*R,R*)-**3a** and (*R,R*)-**3f** as the catalysts.

Finally, we applied this new protocol to the synthesis of a new kind of chiral naphthyridine-derived P−N ligand (*R*)-**4** (Scheme 3). The asymmetric hydrogenation of **1f** was carried out on a gram scale (1.13 g) to give the optically pure (*R*)-**2f** in 98% yield with 99% ee, subsequent treatment with Ph_2PCl in the presence of *n*-BuLi provided the new chiral P−N ligand (*R*)-**4** in high yield (80%).

Scheme 3. Synthesis of a Chiral Naphthyridine-Derived P−N Ligand



In conclusion, we have developed the first asymmetric hydrogenation of 2,7-disubstituted 1,8-naphthyridines by using phosphine-free chiral cationic ruthenium diamine catalysts with good to excellent enantioselectivities. This new protocol provides an easy way for the construction of optically pure 1,2,3,4-tetrahydro-1,8-naphthyridine ring systems which are key substructures in bioactive molecules and pharmaceuticals. In addition, these chiral compounds are of great interest in the development of a new kind of modular P−N ligand. Further studies on the synthesis and application of these new P−N ligands are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01186.

X-ray data for compound **2i** (CIF)
X-ray data for compound **5** (CIF)
Experimental procedures, the synthesis method of the starting materials, and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Duggan, M. E.; Duong, L. T.; Fisher, J. E.; Hamill, T. G.; Hoffman, W. F.; Huff, J. R.; Ihle, N. C.; Leu, C.-T.; Nagy, R. M.; Perkins, J. J.; Rodan, S. B.; Wesolowski, G.; Whitman, D. B.; Zartman, A. E.; Rodan, G. A.; Hartman, G. D. *J. Med. Chem.* **2000**, *43*, 3736. (b) Hutchinson, J. H.; Halczenko, W.; Brashear, K. M.; Breslin, M. J.; Coleman, P. J.; Duong, L. T.; Fernandez-Metzler, C.; Gentile, M. A.; Fisher, J. E.; Hartman, G. D.; Huff, J. R.; Kimmel, D. B.; Leu, C.-T.; Meissner, R. S.; Merkle, K.; Nagy, R.; Pennypacker, B.; Perkins, J. J.; Prueksaritanont, T.; Rodan, G. A.; Varga, S. L.; Wesolowski, G. A.; Zartman, A. E.; Rodan, S. B.; Duggan, M. E. *J. Med. Chem.* **2003**, *46*, 4790. (c) Hartner, F. W.; Hsiao, Y.; Eng, K. K.; Rivera, N. R.; Palucki, M.; Tan, L.; Yasuda, N.; Hughes, D. L.; Weissman, S.; Zewge, D.; King, T.; Tschaen, D.; Volante, R. P. *J. Org. Chem.* **2004**, *69*, 8723. (d) Breslin, M. J.; Duggan, M. E.; Halczenko, W.; Hartman, G. D.; Duong, L. T.; Fernandez-Metzler, C.; Gentile, M. A.; Kimmel, D. B.; Leu, C.-T.; Merkle, K.; Prueksaritanont, T.; Rodan, G. A.; Rodan, S. B.; Hutchinson, J. H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4515. (e) Madaan, A.; Verma, R.; Kumar, V.; Singh, A. T.; Jain, S. K.; Jaggi, M. *Arch. Pharm.* **2015**, *348*, 837.

(2) Fernandez, M.-C.; Escribano, A.; Mateo, A. I.; Parthasarathy, S.; de la Nava, E. M. M.; Wang, X.; Cockerham, S. L.; Beyer, T. P.; Schmidt, R. J.; Cao, G.; Zhang, Y.; Jones, T. M.; Borel, A.; Sweetana, S. A.; Cannady, E. A.; Stephenson, G.; Frank, S.; Mantlo, N. B. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3056.

(3) Nuria, A.; Carles, F. J.; Emma, T.; Elena, C. G.; Jordi, S. S. I. N. PCT Int. 149997, 2013.

(4) (a) Keller, P. C.; Marks, R. L.; Rund, J. V. *Polyhedron* **1983**, *2*, 595. (b) Palucki, M.; Hughes, D. L.; Yasuda, N.; Yang, C.; Reider, P. J. *Tetrahedron Lett.* **2001**, *42*, 6811. (c) Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2004**, *6*, 3671. (d) Davies, A. J.; Brands, K. M. J.; Cowden, C. J.; Dolling, U.-H.; Lieberman, D. R. *Tetrahedron Lett.* **2004**, *45*, 1721. (e) Nam, T.; Rector, C. L.; Kim, H.; Sonnen, A. F.-P.; Meyer, R.; Nau, W. M.; Atkinson, J.; Rintoul, J.; Pratt, D. A.; Porter, N.

DOI: 10.1021/acs.orglett.6b01186
Org. Lett. 2016, 18, 2730−2733

A. *J. Am. Chem. Soc.* **2007**, *129*, 10211. (f) Yasuda, N.; Hsiao, Y.; Jensen, M. S.; Rivera, N. R.; Yang, C.; Wells, K. W.; Yau, J.; Palucki, M.; Tan, L.; Dormer, P. G.; Volante, R. P.; Hughes, D. L.; Reider, P. J. *J. Org. Chem.* **2004**, *69*, 1959. (g) Xiong, B.; Li, Y.; Lv, W.; Tan, Z.; Jiang, H.; Zhang, M. *Org. Lett.* **2015**, *17*, 4054.

(5) For recent reviews on asymmetric hydrogenation of heteroaromatic compounds: (a) Glorius, F. *Org. Biomol. Chem.* **2005**, *3*, 4171. (b) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357. (c) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. *Chem. Rev.* **2012**, *112*, 2557. (d) He, Y.-M.; Song, F.-T.; Fan, Q.-H. *Top. Curr. Chem.* **2014**, *343*, 145. (e) Xie, J.; Zhou, Q. *Huaxue Xuebao* **2012**, *70*, 1427.

(6) For selected recent examples of asymmetric hydrogenation of quinolines: (a) Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*, 10536. (b) Zhou, H.; Li, Z.; Wang, Z.; Wang, T.; Xu, L.; He, Y.-M.; Fan, Q.-H.; Pan, J.; Gu, L.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 8464. (c) Wang, T.; Zhuo, L.-G.; Li, Z.; Chen, F.; Ding, Z.; He, Y.; Fan, Q.-H.; Xiang, J.; Yu, Z.-X.; Chan, A. S. C. *J. Am. Chem. Soc.* **2011**, *133*, 9878. (d) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683. (e) Wang, C.; Li, C.; Wu, X.; Pettman, A.; Xiao, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6524. (f) Zhang, Z.; Du, H. *Org. Lett.* **2015**, *17*, 6266. (g) Zhang, Z.; Du, H. *Org. Lett.* **2015**, *17*, 2816.

(7) For selected recent examples of asymmetric hydrogenation of other *N*-containing heteroaromatic compounds: (a) Tang, W.; Xu, L.; Fan, Q.-H.; Wang, J.; Fan, B.; Zhou, Z.; Lam, K.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 9135. (b) Urban, S.; Ortega, N.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 3803. (c) Chen, Q.-A.; Wang, D.-S.; Zhou, Y.-G.; Duan, Y.; Fan, H.-J.; Yang, Y.; Zhang, Z. *J. Am. Chem. Soc.* **2011**, *133*, 6126. (d) Zhang, Z.; Du, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 623. (e) Qin, J.; Chen, F.; Ding, Z.; He, Y.-M.; Xu, L.; Fan, Q.-H. *Org. Lett.* **2011**, *13*, 6568. (f) Lu, S.-M.; Wang, Y.-Q.; Han, X.-W.; Zhou, Y.-G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2260. (g) Shi, L.; Ye, Z.-S.; Cao, L.-L.; Guo, R.-N.; Hu, Y.; Zhou, Y.-G. *Angew. Chem., Int. Ed.* **2012**, *51*, 8286. (h) Iimuro, A.; Yamaji, K.; Kandula, S.; Nagano, T.; Kita, Y.; Mashima, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 2046. (i) Ye, Z.-S.; Guo, R.-N.; Cai, X.-F.; Chen, M.-W.; Shi, L.; Zhou, Y.-G. *Angew. Chem., Int. Ed.* **2013**, *52*, 3685. (j) Kuwano, R.; Sato, K.; Kurokawa, T.; Karube, D.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7614. (k) Wang, D.-S.; Chen, Q.-A.; Li, W.; Yu, C.-B.; Zhou, Y.-G.; Zhang, X. *J. Am. Chem. Soc.* **2010**, *132*, 8909. (l) Duan, Y.; Li, L.; Chen, M.-W.; Yu, C.-B.; Fan, H.-J.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2014**, *136*, 7688. (m) Xiao, Y.-C.; Wang, C.; Yao, Y.; Sun, J.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10661. (n) Kuwano, R.; Kashiwabara, M.; Ohsumi, M.; Kusano, H. *J. Am. Chem. Soc.* **2008**, *130*, 808. (o) Wang, D.-S.; Ye, Z.-S.; Chen, Q.-A.; Zhou, Y.-G.; Yu, C.-B.; Fan, H.-J.; Duan, Y. *J. Am. Chem. Soc.* **2011**, *133*, 8866. (p) Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 8966. (q) Ye, Z.-S.; Chen, M.-W.; Chen, Q.-A.; Shi, L.; Duan, Y.; Zhou, Y.-G. *Angew. Chem., Int. Ed.* **2012**, *51*, 10181. (r) Chang, M.; Huang, Y.; Liu, S.; Chen, Y.; Krska, S. W.; Davies, I. W.; Zhang, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 12761. (s) Ortega, N.; Tang, D.-T. D.; Urban, S.; Zhao, D.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 9500. (t) Qin, J.; Chen, F.; He, Y.-M.; Fan, Q.-H. *Org. Chem. Front.* **2014**, *1*, 952. (u) Kuwano, R.; Hashiguchi, Y.; Ikeda, R.; Ishizuka, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 2393.

(8) For asymmetric hydrogenation of heteroaromatic compounds bearing two heterocycles: (a) Wang, T.; Chen, F.; Qin, J.; He, Y.-M.; Fan, Q.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 7172. (b) Huang, W.-X.; Yu, C.-B.; Shi, L.; Zhou, Y.-G. *Org. Lett.* **2014**, *16*, 3324. (c) Zhang, J.; Chen, F.; He, Y.-M.; Fan, Q.-H. *Angew. Chem., Int. Ed.* **2015**, *54*, 4622.

(9) (a) Pai, C.-C.; Lin, C.-W.; Lin, C.-C.; Chen, C.-C.; Chan, A. S. C. *J. Am. Chem. Soc.* **2000**, *122*, 11513. (b) Guo, C.; Sun, D.-W.; Yang, S.; Mao, S.-J.; Xu, X.-H.; Zhu, S.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2015**, *137*, 90.

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Org. Lett. 2016, 18, 2730−2733