

Asymmetric Ruthenium-Catalyzed Hydrogenation of 2,6-Disubstituted 1,5-Naphthyridines: Access to Chiral 1,5-Diaza-*cis*-Decalins**

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Abstract: The first asymmetric hydrogenation (AH) of 2,6-disubstituted and 2,3,6-trisubstituted 1,5-naphthyridines, catalyzed by chiral cationic ruthenium diamine complexes, has been developed. A wide range of 1,5-naphthyridine derivatives were efficiently hydrogenated to give 1,2,3,4-tetrahydro-1,5-naphthyridines with up to 99% ee and full conversions. This facile and green protocol is applicable to the scaled-up synthesis of optically pure 1,5-diaza-*cis*-decalins, which have been used as rigid chelating diamine ligands for asymmetric synthesis.

The 1,2,3,4-tetrahydronaphthyridine ring system is an important structural unit in many biologically active compounds.^[1] Their optically pure derivatives (such as those outlined in Figure 1) have shown great potential for pharmaceutical development.^[1b] In addition, 1,5-diaza-*cis*-decalins, which can be obtained from the chiral 1,2,3,4-tetrahydronaphthyridines, are unique diamines widely used as rigid chelating ligands in asymmetric synthesis.^[2,4b] Consequently, the synthesis of these optically pure heterocycles is of great importance. However, there are only a few reports describing the asymmetric synthesis of substituted 1,2,3,4-tetrahydro-1,5-naphthyridines,^[3] and the practical synthesis of chiral 1,5-diaza-*cis*-decalin derivatives is still a challenge.^[4]

During the past decade, asymmetric hydrogenation (AH) of heteroaromatic compounds has proven to be a powerful method for the synthesis of optically active compounds with chiral heterocyclic skeletons.^[5] A number of heteroaromatic substrates

have been successfully hydrogenated with excellent enantioselectivities.^[6–15] However, despite the progress made in this field, to our knowledge, there are few successful examples reported on the AH of polycyclic heteroarenes (containing more than one heterocycle) because of the strong coordinating ability of the multiheteroatom-containing substrates and/or products.^[16]

Most recently, we found that the cationic ruthenium complexes of chiral monotosylated diamines are very efficient

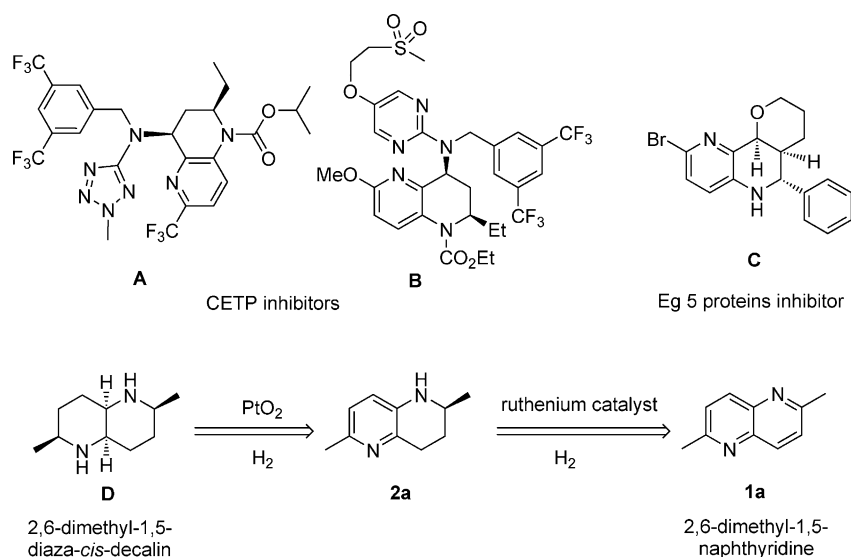


Figure 1. Representative biologically active compounds and the retrosynthetic analysis.

catalysts for AH of quinolines^[6c,d] and quinoxalines^[8b] with excellent reactivity and enantioselectivity. Particularly, this catalytic system has been demonstrated to be highly enantioselective for the AH of challenging polycyclic 1,10-phenanthrolines.^[16a] Encouraged by these results and given our continuing interest in the application of this phosphine-free catalytic system^[17] to the hydrogenation of more challenging substrates, we envisioned that it could be applied to the yet unsolved AH of 2,6-disubstituted 1,5-naphthyridine derivatives^[18,19] to give the corresponding 1,2,3,4-tetrahydronaphthyridines, and consequently provide easy access to chiral 1,5-diaza-*cis*-decalins (e.g., **D**; Figure 1). Herein, we report the first highly efficient AH of 2,6-disubstituted 1,5-naphthyridine derivatives with excellent enantioselectivity.

In our initial study, the AH of 2,6-dimethyl-1,5-naphthyridine (**1a**) with the catalyst (*R,R*)-**3a** (see Table 1) was chosen as the model reaction for the optimization of the reaction conditions. As seen from Table S1 (see the Supporting

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Information), ethanol was found to be optimal in terms of both reactivity and enantioselectivity. Upon the screening of a variety of catalysts, the catalyst bearing the hexamethylbenzene ligand (*R,R*)-**3b** was found to give the highest enantioselectivity (99% *ee*; see Table S2 in the Supporting Information). In addition, the enantioselectivity of the reaction was insensitive to hydrogen pressure and temperature (see Table S3 in the Supporting Information). Notably, when the catalyst loading of (*R,R*)-**3b** was decreased to 0.2 mol%, identical enantioselectivity was still observed.

Under the optimized reaction conditions, a variety of 2,6-dialkyl-substituted 1,5-naphthyridines (**1a–f**) were smoothly hydrogenated in the presence of 0.2 mol% (*R,R*)-**3b**, thus affording the corresponding chiral tetrahydronaphthyridines with excellent enantioselectivities (89–99% *ee*; Table 1). Substrates bearing long or branched alkyl substituents like isobutyl and *n*-hexyl gave slightly lower enantioselectivities (**1d** and **1e**). The unsymmetrical 2,6-dialkyl-substituted 1,5-naphthyridine substrate **1f** was hydrogenated with high enantioselectivity, albeit with low regioselectivity. Moreover, substrates bearing one phenyl substituent at the 2-position (**1g–j**) could also be reduced with excellent enantioselectivities (98–99% *ee*). 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 at the 2-position had no apparent effect on enantioselectivity (**1g–j**).

The hydrogenation of 2,6-diaryl-substituted 1,5-naphthyridines were also examined. To our delight, hydrogenation of **1k**, performed in a mixture of isopropanol (IPA) and toluene, with 2.0 mol% (*R,R*)-**3a** as the optimal catalyst, gave good enantioselectivity (see Table S4 in the Supporting Information). Under the optimized reaction conditions, all 2,6-diaryl-substituted 1,5-naphthyridines (**1k–o**; Table 1) were hydrogenated with full conversions and very good enantioselectivities (80–85% *ee*). After a single recrystallization from petroleum ether and CH₂Cl₂, **2l** with 98% *ee* could be obtained. It was found that the electronic properties of the substituents at the phenyl ring could influence the regioselectivity of the reaction. For the unsymmetrical 2,6-diaryl-substituted substrates (**1m–o**), the pyridyl rings bearing more electron-rich substituents are more easily reduced.

Encouraged by the above exciting results, AH of the more challenging 2,3,6-trisubstituted 1,5-naphthyridines (**1p–r**; Table 1) were further investigated with the catalyst (*R,R*)-**3c** (1.0 mol%). Notably, all the three substrates were hydrogenated smoothly to give reduced products in full conversions but with quite different regioselectivity. For the cyclic substrates **1p** and **1q**, excellent diastereoselectivities were obtained, and the enantioselectivities increased from 12 to 85% *ee* when the cycle becomes larger. Unexpectedly, for the acyclic substrate **2r**, a clear selectivity for the hydrogenation of the pyridyl ring bearing a phenyl group was observed, and moderate enantioselectivity was obtained.

The absolute configuration of **2a** was determined to be *R* based on single-crystal X-ray analysis of *N*-tosyl-2,6-dimethyl-tetrahydro-naphthyridine (**2s**; see Scheme S1 in the Supporting Information).^[20] Similarly, the configuration of **2l** (see Scheme S2 in the Supporting Information) was

Table 1: AH of 2,6-disubstituted and 2,3,6-trisubstituted 1,5-naphthyridines.^[a]

[a] Reaction conditions: substrate (0.6 mmol) in 1.0 mL of EtOH, (*R,R*)-**3b** (0.2 mol%), 50 atm of H₂, stirred at 20 °C for 10 h. Yields of isolated products are given (for **1n** and **1o**, yields are determined by ¹H NMR spectroscopy). Enantiomeric excesses were determined by HPLC analysis using a chiral column. [b] Used **1k–o** (0.2 mmol) in 1.0 mL of IPA/toluene (1/1, v/v), and (*R,R*)-**3a** (2.0 mol%). [c] The absolute configurations were assigned by analogy to **2a** and **2l**, respectively (see Schemes S1 and S2),^[20] which were characterized by single-crystal X-ray analysis. [d] After recrystallization from petroleum ether/CH₂Cl₂ (1:1, v/v). [e] Data in brackets are yields of the other regioselective product in which the pyridyl rings bearing electron-withdrawing substituents were hydrogenated. [f] Used **1p–r** (0.2 mmol) in 1.0 mL of methanol, (*R,R*)-**3c** (1.0 mol%).

assigned as *R* by single-crystal X-ray analysis.^[20] The configurations of the other chiral products are assigned by analogy.

Based on these results and to further understand the origin of stereoselectivity, we propose the cyclic 10-membered transition states for the AH of 2,6-disubstituted 1,5-naphthyridines (Figure 2). In the case of substrates bearing at least one alkyl group at the 2-position, the transition state is similar to the one we proposed previously for the AH of quinoline.^[6d] Notably, for 2,6-diaryl-substituted 1,5-naphthyridines, the

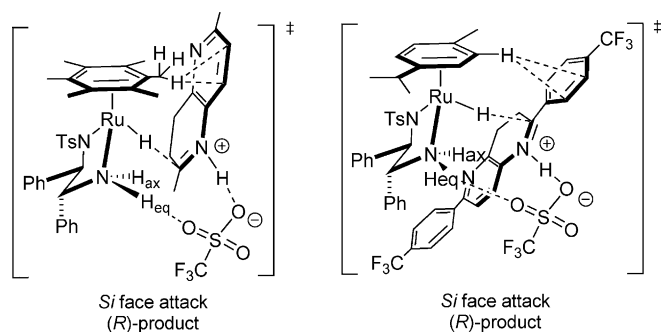
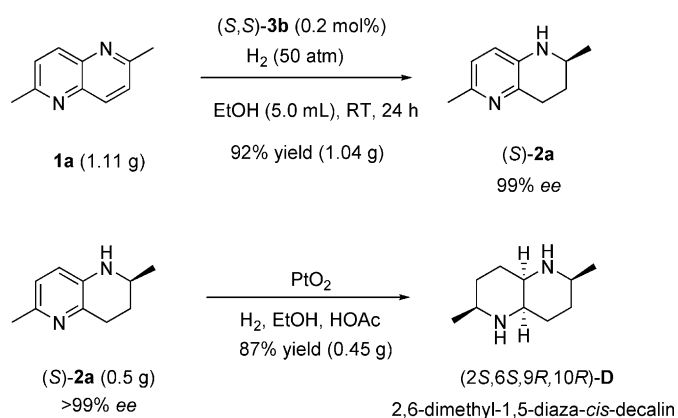


Figure 2. Proposed transition states involving (*R,R*)-**3a** and (*R,R*)-**3b** as the catalysts.

enantioselectivity originates from the CH- π attraction between the η^6 -arene ligand in the ruthenium complex and the substituted phenyl ring, instead of the fused pyridine ring. The hydride is transferred from the ruthenium center to the *Si* face of the C=N moiety to give the *R*-configured product. This transfer is also consistent with the experiment result of high regioselectivities in the AH of substrates bearing electronically unsymmetrical 2,6-diaryl substituents **1m–o** (Table 1). In these cases, the CH- π interaction with the π -electron-rich aromatic ring is greater than that of the π -electron-deficient one, thus possibly leading to good regioselectivities.^[21]

Finally, we explored the further hydrogenation of the remaining pyridine ring to attain the corresponding 2,6-disubstituted 1,5-diaza-*cis*-decalins using an achiral heterogeneous catalyst (Scheme 1). Firstly, the AH of **1a** with (*S,S*)-**3b**



Scheme 1. Synthesis of chiral 2,6-dimethyl-1,5-diaza-*cis*-decalin.

was carried out on a gram scale (1.11 g) to give (*S*)-**2a** in 92% yield with 99% *ee*. After a single recrystallization from petroleum ether and ethyl acetate, **2a** in 90% yield with greater than 99% *ee* could be obtained. Subsequently, the optically pure (*S*)-**2a** (0.5 g) was smoothly reduced using PtO₂ as a catalyst to provide the desired (2*S*,6*S*,9*R*,10*R*)-2,6-dimethyl-1,5-diaza-*cis*-decalin in 87% yield as the sole product without other diastereomers (see the Supporting Information). In view of the unfavorable steric hindrance between the surface of the PtO₂ catalyst and the methyl group in the 2-position, the opposite face of molecule is more inclined to approach the heterogeneous catalyst surface.^[15]

In conclusion, we have developed the first highly enantioselective hydrogenation of 2,6-disubstituted and 2,3,6-trisubstituted 1,5-naphthyridines using chiral cationic ruthenium diamine catalysts with good to excellent enantioselectivities. Moreover, this new method provides a practical and facile approach to the synthesis of optically pure 1,2,3,4-tetrahydronaphthyridines and 1,5-diaza-*cis*-decalin derivatives. Further studies on a detailed mechanism and application of the unique chiral cyclic diamines in asymmetric synthesis are in progress.

Keywords: asymmetric catalysis · enantioselectivity · heterocycles · hydrogenation · ruthenium

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- [1] a) M.-C. Fernandez, A. Escibano, A. I. Mateo, S. Parthasarathy, E. M. Martin de La Nava, X. Wang, S. L. Cockerham, T. P. Beyer, R. J. Schmidt, G. Cao, Y. Zhang, T. M. Jones, A. Borel, S. A. Sweetana, E. A. Cannady, G. Stephenson, S. Frank, N. B. Mantlo, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3056; b) N. B. Mantlo, A. Escibano, *J. Med. Chem.* **2014**, *57*, 1; c) K. Schiemann, S. Anzali, H. Drosdat, U. Emde, D. Finsinger, J. Gleitz, B. Hock, H. Reubold, F. Zenke, WO 2005063735, **2005**.
- [2] For selected examples of 1,5-diaza-*cis*-decalin used as chiral diamine ligands, see: a) X. Li, L. B. Schenkel, M. C. Kozlowski, *Org. Lett.* **2000**, *2*, 875; b) X. Li, J. Yang, M. C. Kozlowski, *Org. Lett.* **2001**, *3*, 1137; c) X. Xie, P.-W. Phuan, M. C. Kozlowski, *Angew. Chem. Int. Ed.* **2003**, *42*, 2168; *Angew. Chem.* **2003**, *115*, 2218; d) C. A. Mulrooney, X. Li, E. S. DiVirgilio, M. C. Kozlowski, *J. Am. Chem. Soc.* **2003**, *125*, 6856; e) X. Li, J. B. Hewgley, C. A. Mulrooney, J. Yang, M. C. Kozlowski, *J. Org. Chem.* **2003**, *68*, 5500; f) E. S. DiVirgilio, E. C. Dugan, C. A. Mulrooney, M. C. Kozlowski, *Org. Lett.* **2007**, *9*, 385; g) J. B. Hewgley, S. S. Stahl, M. C. Kozlowski, *J. Am. Chem. Soc.* **2008**, *130*, 12232.
- [3] For selected examples of asymmetric synthesis of substituted 1,2,3,4-tetrahydro-1,5-naphthyridine derivatives, see: a) F. Palacios, C. Alonso, A. Arrieta, F. P. Cossío, J. M. Ezpeleta, M. Fuertes, G. Rubiales, *Eur. J. Org. Chem.* **2010**, 2091; b) F. Palacios, C. Alonso, M. Fuertes, J. M. Ezpeleta, G. Rubiales, *Eur. J. Org. Chem.* **2011**, 4318.
- [4] For selected examples of asymmetric synthesis of 1,5-diaza-*cis*-decalin derivatives, see: a) M. C. Kozlowski, Z. Xu, A. G. Santos, *Tetrahedron* **2001**, *57*, 4537; b) Z. Xu, M. C. Kozlowski, *J. Org. Chem.* **2002**, *67*, 3072; c) X. Li, Z. Xu, E. F. DiMauro, M. C. Kozlowski, *Tetrahedron Lett.* **2002**, *43*, 3747.
- [5] For recent reviews on AH of heteroaromatic compounds, see: a) F. Glorius, *Org. Biomol. Chem.* **2005**, *3*, 4171; b) Y.-G. Zhou, *Acc. Chem. Res.* **2007**, *40*, 1357; c) D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557; d) Y.-M. He, F.-T. Song, Q.-H. Fan, *Top. Curr. Chem.* **2014**, *343*, 145.
- [6] For selected examples of asymmetric reduction of quinolines, see: a) W.-B. Wang, S.-M. Lu, P.-Y. Yang, X.-W. Han, Y.-G. Zhou, *J. Am. Chem. Soc.* **2003**, *125*, 10536; b) Z.-J. Wang, G.-J. Deng, Y. Li, Y.-M. He, W.-J. Tang, Q.-H. Fan, *Org. Lett.* **2007**, *9*, 1243; c) H. Zhou, Z. Li, Z. Wang, T. Wang, L. Xu, Y. He, Q.-H. Fan, J. Pan, L. Gu, A. S. C. Chan, *Angew. Chem. Int. Ed.* **2008**, *47*, 8464; *Angew. Chem.* **2008**, *120*, 8592; d) T. Wang, L.-G. Zhuo, Z. Li, F. Chen, Z. Ding, Y. He, Q.-H. Fan, J. Xiang, Z.-X. Yu, A. S. C. Chan, *J. Am. Chem. Soc.* **2011**, *133*, 9878; e) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem. Int. Ed.* **2006**, *45*, 3683; *Angew. Chem.* **2006**, *118*, 3765; f) C. Wang, C. Li, X. Wu, A. Pettman, J. Xiao, *Angew. Chem. Int. Ed.* **2009**, *48*, 6524; *Angew. Chem.* **2009**, *121*, 6646.

- [7] For selected examples of asymmetric reduction of isoquinolines, see: a) S.-M. Lu, Y.-Q. Wang, X.-W. Han, Y.-G. Zhou, *Angew. Chem. Int. Ed.* **2006**, *45*, 2260; *Angew. Chem.* **2006**, *118*, 2318; b) L. Shi, Z.-S. Ye, L.-L. Cao, R.-N. Guo, Y. Hu, Y.-G. Zhou, *Angew. Chem. Int. Ed.* **2012**, *51*, 8286; *Angew. Chem.* **2012**, *124*, 8411; c) Z.-S. Ye, R.-N. Guo, X.-F. Cai, M.-W. Chen, L. Shi, Y.-G. Zhou, *Angew. Chem. Int. Ed.* **2013**, *52*, 3685; *Angew. Chem.* **2013**, *125*, 3773; d) A. Iimuro, K. Yamaji, S. Kandula, T. Nagano, Y. Kita, K. Mashima, *Angew. Chem. Int. Ed.* **2013**, *52*, 2046; *Angew. Chem.* **2013**, *125*, 2100.
- [8] For selected recent examples of asymmetric reduction of quinoxalines, see: a) W. Tang, L. Xu, Q.-H. Fan, J. Wang, B. Fan, Z. Zhou, K.-H. Lam, A. S. C. Chan, *Angew. Chem. Int. Ed.* **2009**, *48*, 9135; *Angew. Chem.* **2009**, *121*, 9299; b) J. Qin, F. Chen, Z. Ding, Y.-M. He, L. Xu, Q.-H. Fan, *Org. Lett.* **2011**, *13*, 6568; c) S. Urban, N. Ortega, F. Glorius, *Angew. Chem. Int. Ed.* **2011**, *50*, 3803; *Angew. Chem.* **2011**, *123*, 3887; d) Q.-A. Chen, D.-S. Wang, Y.-G. Zhou, Y. Duan, H.-J. Fan, Y. Yang, Z. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 6126; e) Q.-A. Chen, K. Gao, Y. Duan, Z.-S. Ye, L. Shi, Y. Yang, Y.-G. Zhou, *J. Am. Chem. Soc.* **2012**, *134*, 2442.
- [9] For selected examples of asymmetric reduction of indoles, see: a) R. Kuwano, K. Sato, T. Kurokawa, D. Karube, Y. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 7614; b) A. Baeza, A. Pfaltz, *Chem. Eur. J.* **2010**, *16*, 2036; c) D.-S. Wang, Q.-A. Chen, W. Li, C.-B. Yu, Y.-G. Zhou, X. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 8909; d) Y.-C. Xiao, C. Wang, Y. Yao, J. Sun, Y.-C. Chen, *Angew. Chem. Int. Ed.* **2011**, *50*, 10661; *Angew. Chem.* **2011**, *123*, 10849; e) Y. Duan, L. Li, M.-W. Chen, C.-B. Yu, H.-J. Fan, Y.-G. Zhou, *J. Am. Chem. Soc.* **2014**, *136*, 7688.
- [10] For selected recent examples of asymmetric reduction of pyridines, see: a) F. Glorius, N. Spielkamp, S. Holle, R. Goddard, C. W. Lehmann, *Angew. Chem. Int. Ed.* **2004**, *43*, 2850; *Angew. Chem.* **2004**, *116*, 2910; b) C. Y. Legault, A. B. Charette, *J. Am. Chem. Soc.* **2005**, *127*, 8966; c) Z.-S. Ye, M.-W. Chen, Q.-A. Chen, L. Shi, Y. Duan, Y.-G. Zhou, *Angew. Chem. Int. Ed.* **2012**, *51*, 10181; *Angew. Chem.* **2012**, *124*, 10328; d) M. Rueping, A. P. Antonchick, *Angew. Chem. Int. Ed.* **2007**, *46*, 4562; *Angew. Chem.* **2007**, *119*, 4646; e) Y. Liu, H. Du, *J. Am. Chem. Soc.* **2013**, *135*, 12968; f) M. Chang, Y. Huang, S. Liu, Y. Chen, S. W. Krska, I. W. Davies, X. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 12761; *Angew. Chem.* **2014**, *126*, 12975.
- [11] For selected examples of asymmetric reduction of (benzo)furan, see: a) S. Kaiser, S. P. Smidt, A. Pfaltz, *Angew. Chem. Int. Ed.* **2006**, *45*, 5194; *Angew. Chem.* **2006**, *118*, 5318; b) N. Ortega, S. Urban, B. Beiring, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 1710; *Angew. Chem.* **2012**, *124*, 1742; c) J. Wysocki, N. Ortega, F. Glorius, *Angew. Chem. Int. Ed.* **2014**, *53*, 8751; *Angew. Chem.* **2014**, *126*, 8896.
- [12] For selected examples of asymmetric reduction of pyrroles, see: a) R. Kuwano, M. Kashiwabara, M. Ohsumi, H. Kusano, *J. Am. Chem. Soc.* **2008**, *130*, 808; b) D.-S. Wang, Z.-S. Ye, Q.-A. Chen, Y.-G. Zhou, C.-B. Yu, H.-J. Fan, Y. Duan, *J. Am. Chem. Soc.* **2011**, *133*, 8866.
- [13] R. Kuwano, N. Kameyama, R. Ikeda, *J. Am. Chem. Soc.* **2011**, *133*, 7312.
- [14] S. Urban, B. Beiring, N. Ortega, D. Paul, F. Glorius, *J. Am. Chem. Soc.* **2012**, *134*, 15241.
- [15] N. Ortega, D.-T. D. Tang, S. Urban, D. Zhao, F. Glorius, *Angew. Chem. Int. Ed.* **2013**, *52*, 9500; *Angew. Chem.* **2013**, *125*, 9678.
- [16] a) T. Wang, F. Chen, J. Qin, Y.-M. He, Q.-H. Fan, *Angew. Chem. Int. Ed.* **2013**, *52*, 7172; *Angew. Chem.* **2013**, *125*, 7313; b) W.-X. Huang, C.-B. Yu, L. Shi, Y.-G. Zhou, *Org. Lett.* **2014**, *16*, 3324.
- [17] a) T. Ohkuma, N. Utsumi, K. Tsutsumi, K. Murata, C. Sandoval, R. Noyori, *J. Am. Chem. Soc.* **2006**, *128*, 8724; b) C. Li, J. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 13208; c) Y.-M. He, Q.-H. Fan, *Org. Biomol. Chem.* **2010**, *8*, 2497.
- [18] To the best of our knowledge, only one example of homogeneous hydrogenation of 2,6-dimethyl-1,5-naphthyridine (only one substrate) catalyzed by iridium-complexes has been reported. See: K.-I. Fujita, Y. Tanaka, M. Kobayashi, R. Yamaguchi, *J. Am. Chem. Soc.* **2014**, *136*, 4829.
- [19] For examples of heterogeneous hydrogenation of 1,5-naphthyridine and its derivatives, see: X. Xie, D. A. Freed, M. C. Kozlowski, *Tetrahedron Lett.* **2001**, *42*, 6451; and refs. [2a] and [4c].
- [20] CCDC 1031420 (**2s**) and 1031763 (**21**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [21] M. Yamakawa, I. Yamada, R. Noyori, *Angew. Chem. Int. Ed.* **2001**, *40*, 2818; *Angew. Chem.* **2001**, *113*, 2900.

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