Synthetic Methods

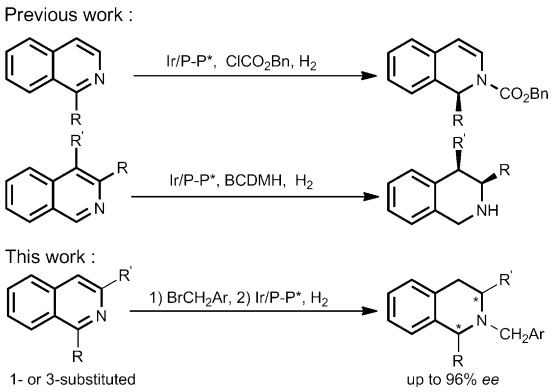
DOI: 10.1002/anie.201208300

Enantioselective Iridium-Catalyzed Hydrogenation of 1- and 3-Substituted Isoquinolinium Salts**

*Zhi-Shi Ye, Ran-Ning Guo, Xian-Feng Cai, Mu-Wang Chen, Lei Shi, and Yong-Gui Zhou**

Chiral 1,2,3,4-tetrahydroisoquinolines are ubiquitous structural motifs in many natural alkaloids and biologically active compounds.[1] Among the various catalytic methods developed for the construction of chiral tetrahydroisoquinolines during the past decades,[2] asymmetric hydrogenation of isoquinolines unquestionably serves as one of the most straightforward and powerful methods. So far, significant progress on the asymmetric hydrogenation of aromatic compounds has been implemented successfully[3] for substrates such as quinolines,[4] quinoxalines,[5] indoles,[6] pyrroles,[7] pyridines,[8] furans,[9] imidazoles,[10] thiophenes[11] and aromatic carbocyclic rings.[12] However, the development of the enantioselective hydrogenation of isoquinolines has met with limited success, probably owing to lower reactivity and strong coordination to the catalyst. In 2006, our group reported the first iridium-catalyzed asymmetric hydrogenation of isoquinolines, which were activated by chloroformates, with moderate enantioselectivity and yield.[13] Very recently, an enantioselective hydrogenation of 3,4-disubstituted isoquinolines employing catalyst activation was successfully described,[14] nevertheless, this strategy is not suitable for 1-substituted isoquinolines. Moreover, there is no report on the asymmetric hydrogenation of 3-substituted isoquinolines heretofore. Therefore, the development of a general and efficient strategy for asymmetric hydrogenation of 1- and 3-substituted isoquinolines is still a very valuable and challenging area of chemical research.

Recently, our group successfully documented the iridium-catalyzed asymmetric hydrogenation of simple pyridinium salts, which were formed by using benzyl bromide and possess higher reactivity than the corresponding pyridines.[15] As part of our ongoing efforts to promote the development of asymmetric hydrogenation of heteroaromatic compounds,[3a,b] and considering the similar structure of pyridine to isoquinoline, we envisioned that activating isoquinoline as the N-benzyl isoquinolinium salt would effectively improve the reactivity to facilitate hydrogenation (Scheme 1). Herein, we report the iridium-catalyzed asymmetric hydrogenation of 1- and 3-substituted isoquinolinium salts with up to 96% *ee*, as well as the application of the method to the synthesis of the chiral drug (+)-solifenacin.



Scheme 1. General strategy for asymmetric hydrogenation of 1- and 3-substituted isoquinolines. BCDMH = 1-bromo-3-chloro-5,5-dimethylhydantoin.

To begin the study, *N*-benzyl-1-phenyl isoquinolinium bromide (**1**; Ar = Ph) was chosen as a model substrate for the iridium-catalyzed asymmetric hydrogenation (Table 1). The reaction occurred smoothly in CH_2Cl_2 to give the desired product with moderate enantioselectivity and yield (entry 1). Further assessment of solvent revealed that the transformation was very sensitive to the reaction medium. The protic polar solvents displayed lower reactivity and enantioselectivity (entries 4 and 5). Gratifyingly, the mixed solvent system of THF/CH_2Cl_2 (1:1) gave the best result in terms of enantioselectivity and yield (entry 7). Subsequently, exploration of various commercially available bisphosphine ligands showed that (R_{ax},*S*,*S*)-C3*-TunePhos was the best ligand with respect to the yield and enantioselectivity (entry 13), whereas (*R*)-Binap gave lower enantioselectivity despite with high reactivity. Replacement of the bromide counterion by the trifluoromethanesulfonate anion resulted in no reactivity. In particular, when the CO_2iPr group was introduced at the 2-position of the benzyl group [**1**; Ar = 2-(iPrCO$_2$)C$_6$H$_4$], the enantioselectivity was increased slightly, possibly because of its steric bulk and/or interaction with the iridium atom (entry 13 versus 16).

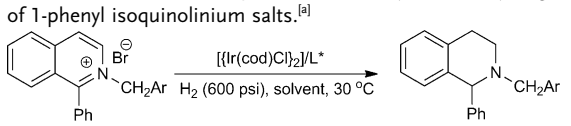
With the optimized reaction conditions in hand, we turned our attention to investigate the scope of 1-substituted isoquinolinium salts, and the results are summarized in Table 2. It is noteworthy that various 1-substituted isoquinolinium salts proved to be good substrates under the standard reaction conditions. The transformation proceeded with excellent enantioselectivity and yield regardless of the

[*] Z.-S. Ye, R.-N. Guo, X.-F. Cai, M.-W. Chen, L. Shi, Prof. Y.-G. Zhou
State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences
457 Zhongshan Road, Dalian 116023 (China)
E-mail: ygzhou@dicp.ac.cn
Homepage: http://www.lac.dicp.ac.cn/

[**] Financial support from the National Natural Science Foundation of China (21202162 and 21125208) and the National Basic Research Program of China (2010CB833300) is acknowledged.

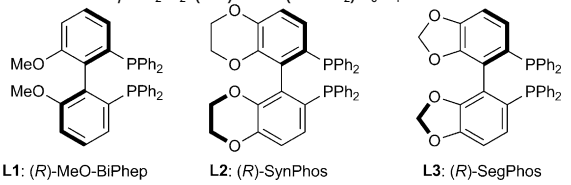
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201208300.

Table 1: Evaluation of reaction parameters for asymmetric hydrogenation of 1-phenyl isoquinolinium salts.[a]



1 2

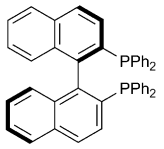
Entry	Solvent	Ar	Ligand	Yield [%][b]	*ee* [%][c]
1	CH_2Cl_2	Ph	**L1**	83	84
2	THF	Ph	**L1**	99	83
3	PhMe	Ph	**L1**	39	80
4	MeOH	Ph	**L1**	7	8
5	EtOH	Ph	**L1**	11	65
6	THF/CH_2Cl_2 (2:1)	Ph	**L1**	96	83
7	THF/CH_2Cl_2 (1:1)	Ph	**L1**	99	86
8	THF/CH_2Cl_2 (1:2)	Ph	**L1**	97	81
9	THF/CH_2Cl_2 (1:1)	Ph	**L2**	92	87
10	THF/CH_2Cl_2 (1:1)	Ph	**L3**	97	90
11	THF/CH_2Cl_2 (1:1)	Ph	**L4**	95	55
12	THF/CH_2Cl_2 (1:1)	Ph	**L5**	96	92
13	THF/CH_2Cl_2 (1:1)	Ph	**L6**	99	93
14[d]	THF/CH_2Cl_2 (1:1)	Ph	**L6**	< 5	–
15[e]	THF/CH_2Cl_2 (1:1)	Ph	**L6**	< 5	–
16	THF/CH_2Cl_2 (1:1)	2-(*i*PrCO$_2$)C$_6$H$_4$	**L6**	99	96



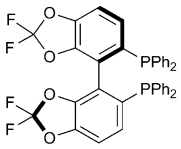
L1: (*R*)-MeO-BiPhep

L2: (*R*)-SynPhos

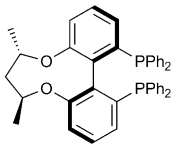
L3: (*R*)-SegPhos



L4: (*R*)-Binap



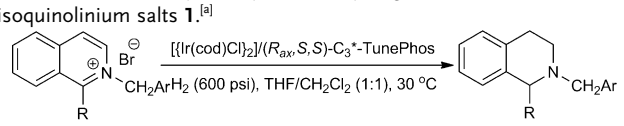
L5: (*R*)-DifluorPhos



L6: (R_{ax},*S*,*S*)-C$_3$*-TunePhos

[a] **1** (0.25 mmol), [{Ir(cod)Cl}$_2$] (1 mol%), **L** (2.2 mol%), H_2 (600 psi), solvent (3 mL), 20 h, 30°C. [b] Yield of isolated product. [c] Determined by HPLC. [d] 10 mol% I_2 was added. [e] Br counterion was replaced by OTf anion. cod = cyclo-1,5-octadiene, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

Table 2: Iridium-catalyzed asymmetric hydrogenation of 1-substituted isoquinolinium salts **1**.[a]



1 2

Entry	R	Ar	Yield [%][b]	*ee* [%][c]
1	Ph	Ar[1]	99 (**2a**)	93 (*R*)
2	4-MeOC$_6$H$_4$	Ph	99 (**2b**)	94 (–)
3	4-CF$_3$C$_6$H$_4$	Ph	97 (**2c**)	92 (–)
4	Me	Ph	99 (**2d**)	70 (+)
5[d]	*i*Pr	Ph	99 (**2e**)	74 (+)
6	Ph	2-(*i*PrCO$_2$)C$_6$H$_4$	99 (**2f**)	96 (–)
7	4-MeC$_6$H$_4$	2-(*i*PrCO$_2$)C$_6$H$_4$	99 (**2g**)	95 (–)
8	3-MeC$_6$H$_4$	2-(*i*PrCO$_2$)C$_6$H$_4$	97 (**2h**)	95 (–)
9	4-MeOC$_6$H$_4$	2-(*i*PrCO$_2$)C$_6$H$_4$	99 (**2i**)	94 (–)
10	3-MeOC$_6$H$_4$	2-(*i*PrCO$_2$)C$_6$H$_4$	99 (**2j**)	94 (–)
11	4-ClC$_6$H$_4$	2-(*i*PrCO$_2$)C$_6$H$_4$	99 (**2k**)	94 (–)
12	4-CF$_3$C$_6$H$_4$	2-(*i*PrCO$_2$)C$_6$H$_4$	96 (**2l**)	93 (–)
13	4-FC$_6$H$_4$	2-(*i*PrCO$_2$)C$_6$H$_4$	99 (**2m**)	94 (–)
14	3,5-F$_2$C$_6$H$_3$	2-(*i*PrCO$_2$)C$_6$H$_4$	99 (**2n**)	90 (–)

[a] **1** (0.25 mmol), [{Ir(cod)Cl}$_2$] (1 mol%), (R_{ax},*S*,*S*)-C3*-TunePhos (2.2 mol%), H_2 (600 psi), THF/CH_2Cl_2 (1:1, 3 mL), 20 h, 30°C. [b] Yield of isolated product. [c] Determined by HPLC. [d] [{Ir(cod)Cl}$_2$] (2 mol%), (R_{ax},*S*,*S*)-C3*-TunePhos (4.4 mol%).

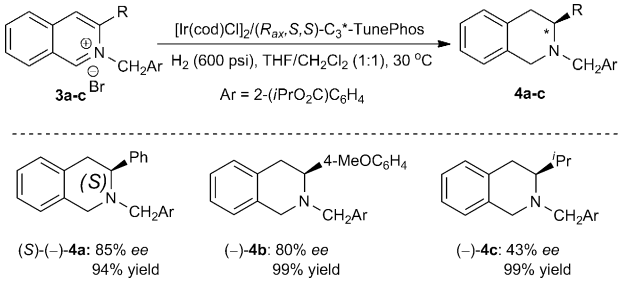


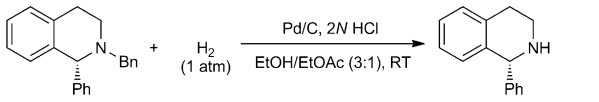
Figure 1. Iridium-catalyzed asymmetric hydrogenation of 3-substituted isoquinolinium salts **3**.

electronic properties of the substituent at C1 of the aromatic ring (entries 2, 3, 9, and 12). Although the 1-alkylisoquinolinium salts performed very well in the transformation to give **2d** and **2e**, respectively, moderate enantioselectivities were obtained (entries 4 and 5).

Subsequently, 3-substituted isoquinolinium salts were also evaluated to demonstrate the generality of our methodology (Figure 1). As expected, the hydrogenation proceeded smoothly with the present catalytic system. Notably, the 3-arylisoquinolinium salts **3a** and **3b** furnished the desired products in good enantioselectivities. However, the 3-alkylisoquinolinium salt **3c** only gave a moderate 43% *ee* with full conversion.

The absolute configuration of the hydrogenation product, *N*-benzyl-1-phenyl 1,2,3,4-tetrahydroisoquinoline (**2a**; which can be increased to 99% *ee* by a simple recrystallization with *n*-hexane), was determined to be *R* by comparison of the sign of the optical rotation of the deprotected product **5a** with data reported literature (Scheme 2).[16,17]

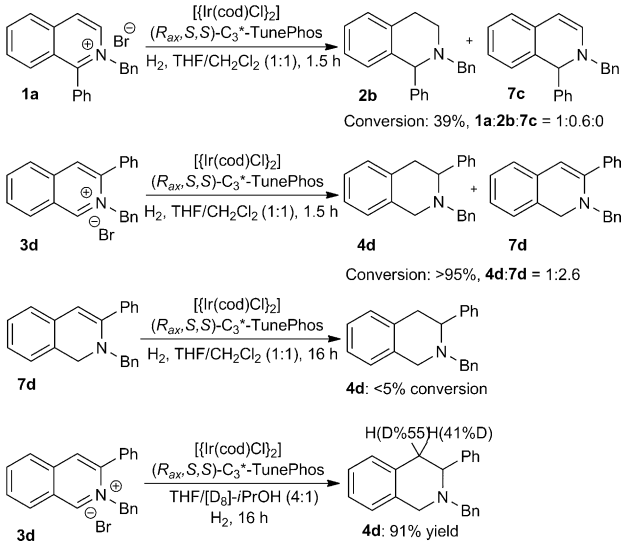
To gain insight into the reaction mechanism, a series of control experiments were conducted (Scheme 3). On the basis of our previous reports[13,14a] and research from other groups on the 1,2-addition of *N*-alkyl or *N*-acyl isoquinolinium salts,[2h–k] we speculated that the hydrogenation may start with a 1,2-hydride addition.[18] Unfortunately, we were unable to detect the corresponding intermediate in the hydrogenation of 1-substituted isoquinolinium salts. Nevertheless, when the



(*R*)-**2a**: >99% *ee*

(*R*)-(–)-**5a**
>99% *ee*, 98% yield
$[\alpha]^{29}_D$ = -12.6
(Lit.16b: $[\alpha]^{25}_D$ = -10.9 for *R*)

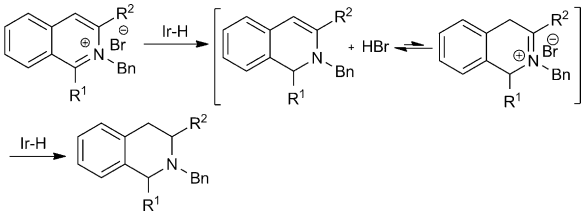
Scheme 2. The determination of the absolute configuration of **2a**.



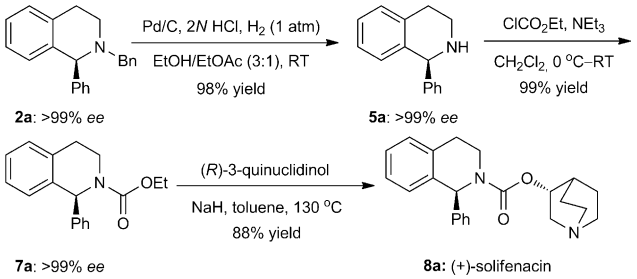
Scheme 3. Mechanistic investigation of the iridium-catalyzed asymmetric hydrogenation of 1- and 3-substituted isoquinolinium salts.

hydrogenation of the 3-substituted isoquinolinium salt **3d** was stopped after 1.5 hours, and the reaction mixture was analyzed by ^{1}H NMR spectroscopy, the reaction mixture was found to contain the intermediate **7d**, a product of the 1,2-hydrogenation. Additionally, hydrogenation of the enamine intermediate **7d**, the most probable intermediate in the second reduction, failed to proceed in the absence of HBr. Almost one deuterium atom was incorporated into the C4-position when **3d** was hydrogenated in THF/[D_8]-*i*PrOH (4:1) as the solvent, thus suggesting that the hydrogenation of the enamine intermediate **7d** was conducted via an iminium intermediate and the tautomerization process of enamine to iminium salt is slower than the hydrogenation of iminium salt.[19,20]

Based on the above experimental results, a possible mechanism is proposed to account for the asymmetric hydrogenation of isoquinolinium salts (Scheme 4). The reaction is initiated by 1,2-hydride addition to give the partially hydrogenated intermediate, 1,2-dihydroisoquinoline, with subsequent isomerization of 1,2-dihydroisoquinoline to the iminium salt in the presence of in situ generated HBr. The salt then undergoes rapid hydrogenation to deliver the desired product. In addition, an alternative mechanism that involves initial direct 1,4-reduction of isoquinolinium salt cannot currently be ruled out.[21]



Scheme 4. Proposed hydrogenation mechanism.



Scheme 5. Synthesis of the chiral drug (+)-solifenacin.

Finally, to demonstrate the utility of this method, we focused on the synthesis of the urinary antispasmodic drug (+)-solifenacin (Scheme 5).[22] Synthesis of this chiral drug requires an optical resolution of the racemic 1-phenyl tetrahydroisoquinoline using tartaric acid in industry.[23] Hydrogenolysis of the hydrogenation product **2a** afforded the product **5a** in the presence of a Pd/C catalyst without loss of enantioselectivity. Subsequent acylation and transesterification with (*R*)-3-quinuclidinol furnished the (+)-solifenacin in 85% overall yield.

In summary, an iridium-catalyzed asymmetric hydrogenation of 1- and 3-substituted isoquinolinium salts was successfully developed with up to 96% *ee*. Preliminary mechanistic studies indicate that the reaction involves a 1,2-hydride addition, isomerization between enamine and iminium intermediate, and hydrogenation of the iminium. Moreover, this methodology was also employed as the key step for the synthesis of urinary antispasmodic drug (+)-solifenacin. Further studies on the extension of the strategy to other heteroaromatic compounds are ongoing in our laboratory.

Experimental Section

Typical procedure for asymmetric hydrogenation of isoquinolinium salts: In a nitrogen-filled glove box, a mixture of [{Ir(cod)Cl}$_2$] (1.7 mg, 0.0025 mmol) and (R_{ax},*S*,*S*)-C3*-TunePhos (3.4 mg, 0.0055 mmol) in THF/CH_2Cl_2 (1:1, 1.0 mL) was stirred at room temperature for 20–30 min. The mixture was then transferred by a syringe to a stainless steel autoclave, in which substrate **1** or **3** (0.25 mmol) was placed beforehand. The hydrogenation was performed at 30 °C under H_2 (600 psi) for 20–24 h. After carefully releasing the hydrogen, saturated $NaHCO_3$ was added and the mixture was stirred for 15–30 min. The organic layer was separated and extracted with CH_2Cl_2 twice, and the combined organic extracts were dried over Na_2SO_4 and concentrated. Purification was performed by a silica gel column [eluent: *n*-hexane/ethyl acetate (10:1)] to give the desired product. The enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase.

Received: October 16, 2012
Revised: January 18, 2013
Published online: February 19, 2013

Keywords: heterocycles · hydrogenation · iridium · reaction mechanisms · synthetic methods

[1] a) J. D. Phillipson, M. F. Roberts, M. H. Zenk, *The Chemistry and Biology of Isoquinoline Alkaloids*, Springer, Berlin, **1985**;

b) R. Paul, J. A. Coppola, E. Cohen, *J. Med. Chem.* **1972**, *15*, 720; c) N. M. Gray, B. K. Cheng, S. J. Mick, C. M. Lair, P. C. Contreras, *J. Med. Chem.* **1989**, *32*, 1242; d) K. W. Bentley, *Nat. Prod. Rep.* **2006**, *23*, 444; For review, see: e) J. D. Scott, R. M. Williams, *Chem. Rev.* **2002**, *102*, 1669; f) P. M. Dewick, *Medicinal Natural Products*, Wiley, Chichester, **2002**, p. 315.

[2] a) M. Chrzanowska, M. D. Rozwadowska, *Chem. Rev.* **2004**, *104*, 3341; b) K. Ito, S. Akashi, B. Saito, T. Katsuki, *Synlett* **2003**, 1809; c) C. Shi, I. Ojima, *Tetrahedron* **2007**, *63*, 8563; d) S.-I. Murahashi, Y. Imada, T. Kawakami, K. Harada, Y. Yonemushi, N. Tomita, *J. Am. Chem. Soc.* **2002**, *124*, 2888; e) T. Itoh, M. Miyazaki, H. Fukuoka, K. Nagata, A. Ohsawa, *Org. Lett.* **2006**, *8*, 1295; f) Z. Li, P. D. MacLeod, C.-J. Li, *Tetrahedron: Asymmetry* **2006**, *17*, 590; g) G. Zhang, Y. Ma, S. Wang, Y. Zhang, R. Wang, *J. Am. Chem. Soc.* **2012**, *134*, 12334; h) A. M. Taylor, S. L. Schreiber, *Org. Lett.* **2006**, *8*, 143; i) K. Funabashi, H. Ratni, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 10784; j) M. S. Taylor, N. Tokunaga, E. N. Jacobsen, *Angew. Chem.* **2005**, *117*, 6858; *Angew. Chem. Int. Ed.* **2005**, *44*, 6700; k) K. Frisch, A. Langda, S. Saaby, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 6212; *Angew. Chem. Int. Ed.* **2005**, *44*, 6058; For recent asymmetric hydrogenation of 3,4-dihydroisoquinolines, see: l) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, *111*, 1713; m) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029; n) M. Chang, W. Li, X. Zhang, *Angew. Chem.* **2011**, *123*, 10867; *Angew. Chem. Int. Ed.* **2011**, *50*, 10679; o) F. Berhal, Z. Wu, Z. Zhang, T. Ayad, V. Ratovelomanana-Vidal, *Org. Lett.* **2012**, *14*, 3308; p) J.-H. Xie, P.-C. Yan, Q.-Q. Zhang, K.-X. Yuan, Q.-L. Zhou, *ACS Catal.* **2012**, *2*, 561; q) M. Ružič, A. Pečavar, D. Prudič, D. Kralj, C. Scriban, A. Zanotti-Gerosa, *Org. Process Res. Dev.* **2012**, *16*, 1293; r) C. Li, J. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 13208; s) C. A. Willoughby, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 8952; t) N. Mršić, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *J. Am. Chem. Soc.* **2009**, *131*, 8358; u) M. Kitamura, Y. Hsiao, M. Ohta, M. Tsukamoto, T. Ohta, H. Takaya, R. Noyori, *J. Org. Chem.* **1994**, *59*, 297.

[3] For reviews on hydrogenation of aromatic compounds, see: a) Y.-G. Zhou, *Acc. Chem. Res.* **2007**, *40*, 1357; b) D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557; c) F. Glorius, *Org. Biomol. Chem.* **2005**, *3*, 4171; d) R. Kuwano, *Heterocycles* **2008**, *76*, 909; e) N. Fleury-Brégeot, V. de La Fuente, S. Castillón, C. Claver, *ChemCatChem* **2010**, *2*, 1346; f) S.-M. Lu, X.-W. Han, Y.-G. Zhou, *Chin. J. Org. Chem.* **2005**, *25*, 634.

[4] For representative reports on asymmetric hydrogenation 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) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 3765; *Angew. Chem. Int. Ed.* **2006**, *45*, 3683; c) Q.-S. Guo, D.-M. Du, J. Xu, *Angew. Chem.* **2008**, *120*, 771; *Angew. Chem. Int. Ed.* **2008**, *47*, 759; d) 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.* **2008**, *120*, 8592; *Angew. Chem. Int. Ed.* **2008**, *47*, 8464; e) C. Wang, C. Li, X. Wu, A. Pettman, J. Xiao, *Angew. Chem.* **2009**, *121*, 6646; *Angew. Chem. Int. Ed.* **2009**, *48*, 6524; f) 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; g) Q.-A. Chen, K. Gao, Y. Duan, Z.-S. Ye, L. Shi, Y. Yang, Y.-G. Zhou, *J. Am. Chem. Soc.* **2012**, *134*, 2442.

[5] For representative reports on asymmetric hydrogenation of quinoxalines, see: a) C. Bianchini, P. Barbaro, G. Scapacci, E. Farnetti, M. Graziani, *Organometallics* **1998**, *17*, 3308; b) W. Tang, L. Xu, Q.-H. Fan, J. Wang, B. Fan, Z. Zhou, K.-H. Lam, A. S. C. Chan, *Angew. Chem.* **2009**, *121*, 9299; *Angew. Chem. Int. Ed.* **2009**, *48*, 9135; c) 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; d) M. Rueping, F. Tato, F. R. Schoepke, *Chem. Eur. J.* **2010**, *16*, 2688.

[6] For representative reports on asymmetric hydrogenation of indoles, see: a) R. Kuwano, K. Sato, T. Kurokawa, D. Karube, Y. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 7614; b) D.-S. Wang, Q.-A. Chen, W. Li, C.-B. Yu, Y.-G. Zhou, X. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 8909.

[7] For reports on asymmetric hydrogenation 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.

[8] For representative reports on asymmetric hydrogenation of pyridines, see: a) C. Y. Legault, A. B. Charette, *J. Am. Chem. Soc.* **2005**, *127*, 8966; b) M. Rueping, A. P. Antonchick, *Angew. Chem.* **2007**, *119*, 4646; *Angew. Chem. Int. Ed.* **2007**, *46*, 4562; c) X.-B. Wang, W. Zeng, Y.-G. Zhou, *Tetrahedron Lett.* **2008**, *49*, 4922; d) F. Glorius, N. Spielkamp, S. Holle, R. Goddard, C. W. Lehmann, *Angew. Chem.* **2004**, *116*, 2910; *Angew. Chem. Int. Ed.* **2004**, *43*, 2850; e) M. Studer, C. Wedemeyer-Exl, F. Spindler, H.-U. Blaser, *Monatsh. Chem.* **2000**, *131*, 1335; f) W.-J. Tang, J. Tan, L.-J. Xu, K.-H. Lam, Q.-H. Fan, A. S. C. Chan, *Adv. Synth. Catal.* **2010**, *352*, 1055.

[9] For reports on asymmetric hydrogenation of furans, see: a) S. Kaiser, S. P. Smidt, A. Pfaltz, *Angew. Chem.* **2006**, *118*, 5318; *Angew. Chem. Int. Ed.* **2006**, *45*, 5194; b) N. Ortega, S. Urban, B. Beiring, F. Glorius, *Angew. Chem.* **2012**, *124*, 1742; *Angew. Chem. Int. Ed.* **2012**, *51*, 1710.

[10] For a report on asymmetric hydrogenation of imidazoles and oxazoles, see: R. Kuwano, N. Kameyama, R. Ikeda, *J. Am. Chem. Soc.* **2011**, *133*, 7312.

[11] For a report on asymmetric hydrogenation of thiophenes, see: S. Urban, B. Beiring, N. Ortega, D. Paul, F. Glorius, *J. Am. Chem. Soc.* **2012**, *134*, 15241.

[12] For reports on asymmetric hydrogenation of carbocyclic ring of aromatic compounds, see: a) S. Urban, N. Ortega, F. Glorius, *Angew. Chem.* **2011**, *123*, 3887; *Angew. Chem. Int. Ed.* **2011**, *50*, 3803; b) R. Kuwano, R. Morioka, M. Kashiwabara, N. Kameyama, *Angew. Chem.* **2012**, *124*, 4212; *Angew. Chem. Int. Ed.* **2012**, *51*, 4136.

[13] S.-M. Lu, Y.-Q. Wang, X.-W. Han, Y.-G. Zhou, *Angew. Chem.* **2006**, *118*, 2318; *Angew. Chem. Int. Ed.* **2006**, *45*, 2260.

[14] a) L. Shi, Z.-S. Ye, L.-L. Cao, R.-N. Guo, Y. Hu, Y.-G. Zhou, *Angew. Chem.* **2012**, *124*, 8411; *Angew. Chem. Int. Ed.* **2012**, *51*, 8286; Homogeneous racemic hydrogenation of isoquinolines, see: b) J. Deng, J. Zhu, J. Wu, J. Liao, *Synlett* **2006**, 2059; c) J. Wu, C. Wang, W. Tang, A. Pettman, J. Xiao, *Chem. Eur. J.* **2012**, *18*, 9525.

[15] Z.-S. Ye, M.-W. Chen, Q.-A. Chen, L. Shi, Y. Duan, Y.-G. Zhou, *Angew. Chem.* **2012**, *124*, 10328; *Angew. Chem. Int. Ed.* **2012**, *51*, 10181.

[16] a) M. Binanzer, S.-Y. Hsieh, J. W. Bode, *J. Am. Chem. Soc.* **2011**, *133*, 19698; b) R. Pedrosa, C. Andrés, J. M. Iglesias, *J. Org. Chem.* **2001**, *66*, 243; c) M. Ludwig, H. Beer, H. Lotter, K. T. Wanner, *Tetrahedron: Asymmetry* **1997**, *8*, 2693; d) B. Wünsch, S. Nerdinger, *Eur. J. Org. Chem.* **1998**, 711.

[17] See the Supporting Information for the details of the determination of the absolute configuration of the hydrogenation product **4a**.

[18] The 3,4-hydride addition could be excluded as the first reduction. See the Supporting Information for the details.

[19] Compared with C=C bonds, iridium complexes were shown to prefer the hydrogenation of C=N bonds. See Ref. [2l] and a) J. H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Soc. Rev.* **2012**, *41*, 4126; b) A. J. Minnaard, B. L. Feringa, L. Lefort, J. G. de Vries, *Acc. Chem. Res.* **2007**, *40*, 1267; c) G.-H. Hou, J.-H. Xie, L.-X. Wang, Q.-L. Zhou, *J. Am. Chem. Soc.* **2006**, *128*, 11774.

[20] C.-B. Yu, K. Gao, D.-S. Wang, L. Shi, Y.-G. Zhou, *Chem. Commun.* **2011**, *47*, 5052.
[21] Initial 1,4-reduction of isoquinolinium salts affords a partially hydrogenated intermediate, 1,4-dihydroisoquinolinium, which then undergoes rapid isomerization to deliver the 1,2-dihydroisoquinoline intermediate.
[22] a) R. Naito, Y. Yonetoku, Y. Okamoto, A. Toyoshimata, K. Ikeda, M. J. Takeuchi, *J. Med. Chem.* **2005**, *48*, 6597; b) S. Wang, M. B. Onaran, C. T. Seto, *Org. Lett.* **2010**, *12*, 2690; c) W. Leithe, *Monatsh. Chem.* **1929**, *53*, 956.
[23] a) N. Mealy, J. Castaner, *Drugs Future* **1999**, *24*, 871; b) M. Takeuchi, R. Naito, M. Hayakawa, Y. Okamoto, Y. Yonetoku, Y. Isomura, EP0801067A1, **1997**; c) V. T. Mathad, J. D. Lilakar, G. Gilla, S. Kikkuru, R. R. Chinta, S. Dudipala, WO/2008/011462A2, **2008**.

