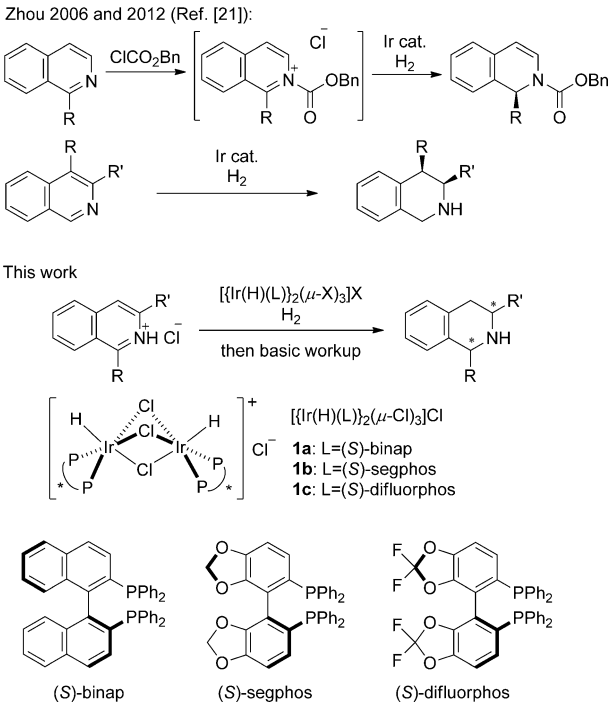
Asymmetric Synthesis

DOI: 10.1002/anie.201207748

Asymmetric Hydrogenation of Isoquinolinium Salts Catalyzed by Chiral Iridium Complexes: Direct Synthesis for Optically Active 1,2,3,4-Tetrahydroisoquinolines**

*Atsuhiro Iimuro, Kenta Yamaji, Sathaiah Kandula, Takuto Nagano, Yusuke Kita, and Kazushi Mashima**

1,2,3,4-Tetrahydroisoquinolines (THIQs), a class of highly important molecular skeletons abundant in natural alkaloids and biologically active compounds, are often used as key intermediates for the synthesis of pharmaceutical drugs and drug candidates.[1] To date, synthetic efforts have focused on introducing chirality at the C1 position with configurational integrity by employing the following synthetic methodologies:[2] 1) the formation of the six-membered ring through a Bischler–Napieralski cyclization/reduction[3] or a Pictet–Spengler reaction,[4] 2) the C_1–C_α connectivity approach by attaching nucleophilic or electrophilic carbon units to the C1 position of tetrahydroisoquinoline derivatives,[5] and 3) the asymmetric hydrogenation of alkylidene-1,2,3,4-tetrahydroisoquinoline derivatives.[6] However, these methods have some limitations, such as a limited substrate scope and the need for stoichiometric amounts of a chiral auxiliary. In contrast to 1-substituted THIQs, the synthesis of 3-substituted THIQs has rarely been achieved,[7] although their unique structural and diverse biologic properties have been noted.[8] Accordingly, the development of more general and straightforward synthetic methods toward 1- and 3-substituted THIQs is in high demand. Although asymmetric hydrogenation of substituted isoquinolines is considered the most attractive and straightforward synthetic protocol, isoquinoline is regarded as the most challenging substrate in asymmetric hydrogenation. An efficient catalytic system has not even been found for the reduction of isoquinolines in a nonenantioselective manner.[9] Nonetheless, the recent development of an asymmetric hydrogenation of aromatic and heteroaromatic compounds was remarkable,[10–20] and Zhou and co-workers reported the catalytic asymmetric hydrogenation of isoquinolines, although the substrate scope is limited and an activating reagent is sometimes required (Scheme 1).[21]



Scheme 1. Asymmetric hydrogenation of isoquinoline derivatives.

As part of our continuing interest in the asymmetric hydrogenation of N-heteroaromatic compounds using halogen-bridged dinuclear iridium(III) complexes,[22] we previously reported the additive effect of aryl amine derivatives in the asymmetric hydrogenation of quinoxalines,[22d] where the addition of more-basic aliphatic amines retarded the reaction, presumably because of their tight coordination to the iridium center. These findings strongly suggested that the difficulties of catalytic hydrogenation of isoquinolines upon catalysis by iridium complexes might be due to the strong basicity of the corresponding THIQs. This hypothesis prompted us to study the asymmetric hydrogenation of isoquinolinium chlorides to give the corresponding tetrahydroisoquinolinium chlorides, thus avoiding the deactivation of the iridium catalyst and providing a direct transformation of isoquinolines to THIQs in an enantioselective manner by a simple basic workup (Scheme 1).

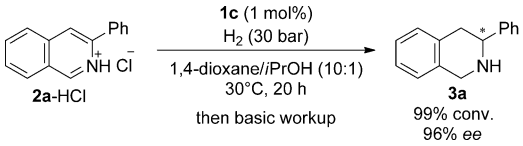
We first examined the asymmetric hydrogenation of the 3-phenylisoquinolinium salt **2a**-HCl with H_2 (30 bar) and the catalyst [{Ir(H)[(*S*)-binap]}$_2$(μ-Cl)$_3$]Cl (**1a**) in methanol at

[*] A. Iimuro, K. Yamaji, Dr. S. Kandula, T. Nagano, Dr. Y. Kita, Prof. Dr. K. Mashima
Department of Chemistry, Graduate School of Engineering Science, Osaka University, CREST
Toyonaka, Osaka 560-8531 (Japan)
E-mail: mashima@chem.es.osaka-u.ac.jp

[**] This work was financially supported by the Core Research for Evolutional Science and Technology (CREST), the program of the Japan Science and Technology Agency (JST), and a Grant-in-Aid for Scientific Research on Innovative Areas, "Molecular Activation Directed toward Straightforward Synthesis", from the Ministry of Education, Culture, Sports, Science and Technology (MEXT).

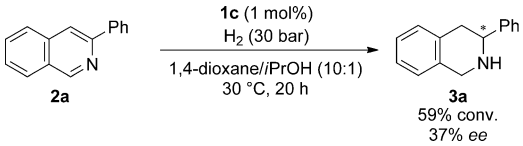
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201207748.

30 °C for 20 hours. As expected, the intended reaction afforded 3-phenyl-1,2,3,4-tetrahydroisoquinoline (**3a**) with 99 % conversion and 57 % *ee* after a basic workup. Encouraged by the successful hydrogenation of the isoquinolinium salt, we screened the reaction conditions[23] and finally selected [{Ir(H)[(*S*)-difluorphos]}$_2$(μ-Cl)$_3$]Cl (**1c**) as catalyst and a 10:1 mixture of 1,4-dioxane/isopropanol as solvent based on the catalytic activity and enantioselectivity. The reaction under these optimized conditions produced **3a** in 96 % *ee* with 99 % conversion [Eq. (1)]. In sharp contrast,



(1)

however, asymmetric hydrogenation of 3-phenylisoquinoline (**2a**) under the optimized reaction conditions resulted in low conversion and low enantiomeric excess [Eq. (2)], thus

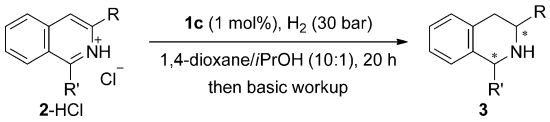


(2)

demonstrating the clear advantages of using the salt. Another advantage of employing the salt is the easy synthesis of unprotected THIQs, whereas the activation approach[21] with an acylating agent requires a deprotection step to obtain secondary amines.

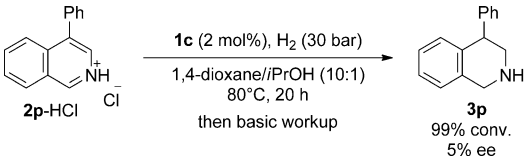
A series of 3-substituted isoquinolinium salts was subjected to asymmetric hydrogenation under the optimized reaction conditions (Table 1). 3-Aryl-substituted isoquinolinium salts were readily hydrogenated with high enantioselectivity, regardless of the electronic effect of substituents on the aryl group (entries 1–3). However, hydrogenation of **2d**-HCl and **2e**-HCl, the aryl groups of which bear *ortho* substituents, led to lower enantioselectivity, presumably because of the steric hindrance of the substituent in *ortho* position (entries 4 and 5). Benzyl- and cyclohexyl-substituted substrates could also be hydrogenated with this catalytic system (entries 6 and 7), affording the corresponding products with high to excellent enantioselectivity. The present catalytic system could also be used for the reduction of 1-substituted isoquinolinium salts with high efficiency, although a much higher temperature (80 °C) was required. Aryl-substituted substrates gave the corresponding products **3h**, **3i**, and **3j** in 96, 98, and 99 % *ee*, respectively (entries 8–10). It is noteworthy that a bromo substituent on the aryl group was tolerated, and the resulting aryl halide product (entry 10) could be a useful substrate for cross-coupling reactions. Substrates with benzyl (entry 12), cyclohexyl (entry 13), and isopropyl (entry 14) substituents were also hydrogenated, however, only moderate enantiomeric excesses were achieved (**3l**: 85 % *ee*, **3m**: 79 % *ee*, **3n**: 91 % *ee*, respectively). 1,3-Disubstituted substrates are also possible substrates for this catalytic reaction. As expected, the asymmetric hydrogenation of 1,3-diphenyl-substituted substrate **2o**-HCl furnished THIQ **3o** with 98 % conversion and high selectivity (98 % *ee*, d.r. > 99 %, entry 15). In sharp contrast to the 1- and 3-substituted isoquinolinium salts, asymmetric hydrogenation of the 4-phenylisoquinolinium salt **2p**-HCl at 80 °C provided the corresponding THIQ **3p** in almost racemic form (5 % *ee*), thus suggesting that the hydrogenation proceeded through a mechanism that involves racemization at the C4 position [Eq. (3)].

Table 1: Asymmetric hydrogenation of 1- and 3-substituted isoquinolinium salts.[a]



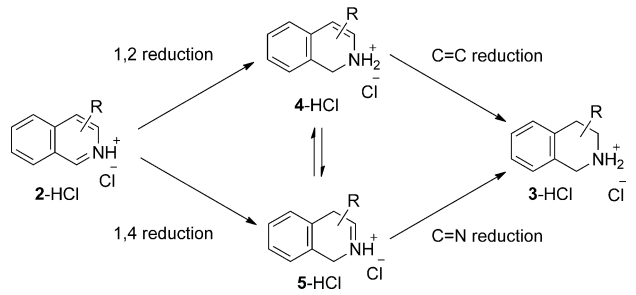
Entry	**2**-HCl	R/R′	*T* [°C]	**3**	Conv. [%][b]	*ee* [%][c]
1	**2a**-HCl	Ph/H	30	**3a**	99	96 (+)
2	**2b**-HCl	4-OMe-C$_6$H$_4$/H	30	**3b**	99	95 (+)
3	**2c**-HCl	4-CF$_3$-C$_6$H$_4$/H	30	**3c**	99	96 (+)
4	**2d**-HCl	2-Me-C$_6$H$_4$/H	30	**3d**	94	79 (+)
5	**2e**-HCl	2-OMe-C$_6$H$_4$/H	30	**3e**	93	81 (+)
6	**2f**-HCl	Bn/H	30	**3f**	87	97 (+)
7	**2g**-HCl	Cy/H	30	**3g**	98	91 (+)
8[d]	**2h**-HCl	H/Ph	80	**3h**	99	96 (*S*)
9[d]	**2i**-HCl	H/4-CF$_3$-C$_6$H$_4$	80	**3i**	99	98 (+)
10[d]	**2j**-HCl	H/4-OMe-C$_6$H$_4$	80	**3j**	99	99 (S)
11[d]	**2k**-HCl	H/2-Br-C$_6$H$_4$	80	**3k**	75	96 (*R*)
12[e]	**2l**-HCl	H/Bn	50	**3l**	63	85 (*S*)
13[d]	**2m**-HCl	H/Cy	80	**3m**	99	79 (−)
14[d]	**2n**-HCl	H/*i*Pr	80	**3n**	98	91 (S)
15[f]	**2o**-HCl	Ph/Ph	80	**3o**	98	98 (*S,S*)

[a] Reaction conditions: A mixture of isoquinoline (0.24 mmol), **1c** (2.4 μmol), and solvent (3 mL) under H_2 atmosphere (30 bar) was heated at 30 °C for 20 h. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC analysis. [d] 4.8 μmol of **1c** was used. [e] 4.8 μmol of [{Ir(H)[(*S*)-DM-segphos]}$_2$(μ-Cl)$_3$]Cl (**1d**) was used as the catalyst. DM-segphos = 5,5′-bis[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole. [f] *cis*:*trans* > 99:1



(3)

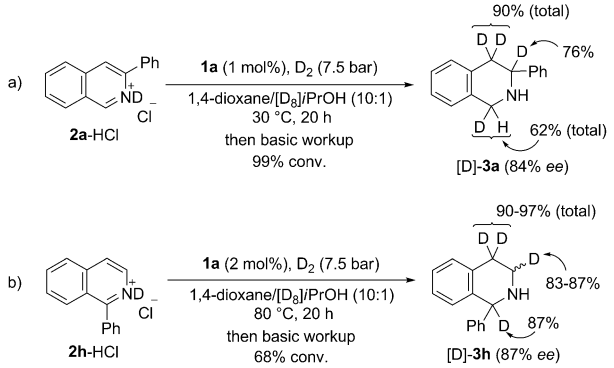
Scheme 2 shows a plausible mechanism for the hydrogenation of isoquinolinium salts **2**-HCl. For the first reduction step, three pathways are possible: 1,2 reduction, 1,4 reduction, and 3,4 reduction. Among these possibilities, 3,4 reduction can be excluded because of the general tendency of iridium complexes to disfavor the hydrogenation of C=C bonds compared with C=N bonds.[24] The 1,2 and 1,4 reductions afforded dihydroisoquinolinium salts **4**-HCl and **5**-HCl, respectively, which were in equilibrium through a predictable enamine–imine tautomerization. Subsequently, **4**-HCl and **5**-HCl were hydrogenated to the desired product, **3**-HCl. The second reduction of **4**-HCl was a C=C reduction of the enamine moiety, while the second reduction of **5**-HCl was a C=N reduction of the imine moiety. Because asymmetric hydrogenation of unprotected enamines was presumed to



Scheme 2. Possible pathways to THIQs from isoquinolinium salts.

proceed via the imine tautomer rather than directly through hydrogenation of the enamine,[24] the C=N reduction of iminium salt **5**-HCl is assumed to be the major second reduction pathway.

To elucidate the mechanism, we performed deuterium labeling experiments using D_2 under the same hydrogenation conditions as described above (Scheme 3). The asymmetric



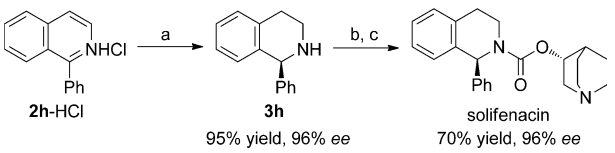
Scheme 3. Deuterium labeling experiments.

hydrogenation of **2a**-HCl and **2h**-HCl by D_2 (10 bar) followed by a basic workup gave [D]-**3a** (85% *ee*) and [D]-**3h** (72% *ee*), respectively. Based on the deuterium content at the C1 position (62%) of [D]-**3a** (the original hydrogen atom at this position was partially replaced with a deuterium atom), we concluded that the first step was reversible. This partial incorporation of deuterium at the C1 position demonstrated that the reoxidation of dihydroisoquinoline was slower than its generation. On the other hand, the deuterium distribution of [D]-**3a** and [D]-**3h** at the C4 position was determined to be 90% and 90–97%, respectively, thus indicating that the original hydrogen atom at the C4 position of isoquinoline substrates was replaced with deuterium (Scheme 3a and b) mainly as a result of the tautomerization between the partly-reduced enaminium (**4**-HCl) and iminium (**5**-HCl) intermediates. The high deuterium content at the C4 position suggested that the tautomerization between **4**-HCl and **5**-HCl was rapid, which explained the low enantioselectivity observed in the hydrogenation of the 4-phenylisoquinolinium salt **2p**-HCl [Eq. (3)]. Similar tautomerization between imine and enamine was reported for asymmetric hydrogenation of 2,3-disubstituted indoles and 3,4-disubstituted isoquinolines.[17d,21b] To gain further insight into the reaction mechanism, we conducted experiments monitored by NMR spectroscopy and obtained two important pieces of information: a) asymmetric hydrogenation of the 3-substituted substrate **2a**-HCl under atmospheric pressure of H_2 afforded **5a**-HCl, which gradually converted to the final product **3a**-HCl, and b) under the same conditions, 1- and 4-substituted substrates could not be reduced efficiently. Thus, 1,4 reduction rather than 1,2 reduction seemed more likely, because the substituent of the C1 or C4 position clearly retarded the reaction, and the substituent at the C3 position did not affect the reaction.[23]

Based on these control experiments, we concluded that the present hydrogenation involved a 1,4 reduction and subsequent C=N reduction, though a 1,2 reduction could not be excluded as the first reduction, as reported by Zhou and co-workers (Scheme 1).[21] Although the effects of the salt were not clear, we speculate that the salt enhanced the substrate reactivity by decreasing the aromaticity, and inhibited the coordination of the amine product to a metal center by forming the salt of the amine product. We previously reported similar effects for the asymmetric hydrogenation of quinolinium salts,[22a] in which enantioselectivity was improved by the use of quinolinium salts. Other groups also reported the asymmetric hydrogenation of heteroaromatic compounds using Brønsted acids.[26]

To demonstrate the advantage of our synthetic protocol, we applied this asymmetric hydrogenation as a key step in the synthesis of the prescription drug solifenacin (Scheme 3), which has antispasmodic effects and is used for the treatment of an overactive bladder with or without urge incontinence.[27] The scaled-up catalytic hydrogenation of **2h**-HCl followed by a basic workup gave the same results as the original reaction on smaller scale (95% yield, 96% *ee*; Table 1, entry 7). An alkoxycarbonyl group was attached to the nitrogen atom without loss of enantiomeric purity, thus achieving the asymmetric synthesis of solifenacin (Scheme 4).

In summary, we developed the synthesis of chiral THIQs by direct asymmetric hydrogenation of isoquinoline derivatives. The salts of 1- and 3-substituted and 1,3-disubstituted isoquinolines were hydrogenated by using [{Ir(H)[(*S*)-difluorphos]}$_2$(μ-Cl)$_3$]Cl (**1c**) to afford the corresponding THIQs in high enantiomeric excess. One of the advantages of this catalytic system compared with traditional methods is the easy access to chiral 3-substituted THIQs. Current efforts are directed toward mechanistic studies of the hydrogenation of isoquinolinium salts as well as the investigation of further applications of this catalytic system to the asymmetric hydrogenation of other N-heteroaromatic compounds.



Scheme 4. Synthetic application of Ir-catalyzed hydrogenation. Reagents and conditions: a) **1c** (1 mol%), 1,4-dioxane/*i*PrOH (10:1), 80°C, H_2 (30 bar), 24 h, then basic workup; b) $ClCO_2C_6H_4$-4-NO_2, K_2CO_3, CH_2Cl_2, RT; c) (*R*)-quinuclidine-3-ol, NaH, toluene, reflux.

Experimental Section

The dinuclear iridium complex (2.4 μmol, 1.0 mol%) and the isoquinolinium salt (0.24 mmol, 1 equiv) were added to a glass tube in the reactor, and the tube was charged with argon gas. A 10:1 mixture of 1,4-dioxane/dry *i*PrOH (3 mL) was added to the glass tube in the reactor through the inlet, the glass tube was charged with H_2, and the pressure was increased to required value. The reaction mixture was stirred for 20 hours. After the release of H_2 from the tube, the solvent was removed in vacuo (rotary evaporator). The residual liquid was poured into a saturated solution of $NaHCO_3$ in water, and extracted with ethyl acetate. The separated organic layer was washed with brine and dried over Na_2SO_4. The conversions were determined by ^1H NMR analysis of the products after the basic workup. The enantiomeric excesses were determined by HPLC analysis.

Received: September 26, 2012
Revised: November 12, 2012
Published online: January 9, 2013

Keywords: asymmetric synthesis · hydrogenation · iridium · isoquinolines · tetrahydroisoquinolines

[1] a) J. D. Scott, R. M. Williams, *Chem. Rev.* **2002**, *102*, 1669; b) K. W. Bentley, *Nat. Prod. Rep.* **2006**, *23*, 444; c) K. Bhadra, G. S. Kumar, *Med. Res. Rev.* **2011**, *31*, 821.

[2] a) M. D. Rozwadowska, *Heterocycles* **1994**, *39*, 903; b) M. Chrzanowska, M. D. Rozwadowska, *Chem. Rev.* **2004**, *104*, 3341; c) T. S. Kaufman, *Tetrahedron: Asymmetry* **2004**, *15*, 1203; d) T. S. Kaufman, *Synthesis* **2005**, 339.

[3] For recent examples of the reduction step, see: a) M. Chang, W. Li, X. Zhang, *Angew. Chem.* **2011**, *123*, 10867; *Angew. Chem. Int. Ed.* **2011**, *50*, 10679; b) M. Ružič, A. Pečavar, D. Prudič, D. Kralj, C. Scriban, A. Zanotti-Gerosa, *Org. Process Res. Dev.* **2012**, *16*, 1293.

[4] J. Stöckigt, A. P. Antonchick, F. Wu, H. Waldmann, *Angew. Chem.* **2011**, *123*, 8692; *Angew. Chem. Int. Ed.* **2011**, *50*, 8538.

[5] a) A. I. Meyers, D. A. Dickman, M. Boes, *Tetrahedron* **1987**, *43*, 5108; b) M. Ahamed, M. H. Todd, *Eur. J. Org. Chem.* **2010**, *31*, 5935; c) S. Wang, M. B. Onaran, C. T. Seto, *Org. Lett.* **2010**, *12*, 2690.

[6] For selected examples of the hydrogenation of alkylidene–THIQs, see: a) M. Kitamura, Y. Hsiao, M. Ohta, M. Tsukamoto, T. Ohta, H. Takaya, R. Noyori, *J. Org. Chem.* **1994**, *59*, 297; b) M. Tsukamoto, M. Yoshimura, K. Tsuda, M. Kitamura, *Tetrahedron* **2006**, *62*, 5448; c) P.-C. Yan, J.-H. Xie, G.-H. Hou, L.-X. Wang, Q.-L. Zhou, *Adv. Synth. Catal.* **2009**, *351*, 3243.

[7] a) I. Tellitu, D. Badía, E. Domínguez, F. J. García, *Tetrahedron: Asymmetry* **1994**, *5*, 1567; b) L. Carrillo, D. Badía, E. Domínguez, F. Ortega, I. Tellitu, *Tetrahedron: Asymmetry* **1998**, *9*, 151; c) F. A. Davis, Y. W. Andemichael, *J. Org. Chem.* **1999**, *64*, 8627; d) J. L. Vicario, D. Badía, E. Domínguez, L. Carrillo, *J. Org. Chem.* **1999**, *64*, 4610; e) R. Pedrosa, C. Andrés, J. M. Iglesias, M. A. Obeso, *Tetrahedron* **2001**, *57*, 4005; f) J. L. Vicario, D. Badía, L. Carrillo, E. Anakabe, *Tetrahedron: Asymmetry* **2003**, *14*, 347; g) T. Kawabata, S. Majumdar, K. Tsubaki, D. Monguchi, *Org. Biomol. Chem.* **2005**, *3*, 1609; h) T. Kawabata, S. Matsuda, S. Kawakami, D. Monguchi, K. Moriyama, *J. Am. Chem. Soc.* **2006**, *128*, 15394; i) J. M. Concellón, P. Tuya, V. del Solar, S. García-Granda, M. R. Díaz, *Org. Lett.* **2009**, *11*, 3750.

[8] a) "The Napthylisoquinoline Alkaloids": G. Bringmann, F. Pokorny in *The Alkaloids*, *Vol. 46* (Ed.: G. A. Cordell), Academic Press, New York, **1995**, p. 127; b) "Transformation Reactions of Protoberberine Alkaloids": M. Hanaoka in *The Alkaloids*, *Vol. 33* (Ed.: A. Brossi), Academic Press, New York, **1988**, p. 141; c) "Amaryllidaceae Alkaloids with Antitumor Activity": R. Plot in *Organic Synthesis: Theory and Applications*, *Vol. 3* (Ed.: T. Hudlicky), JAI, Greenwich, **1996**, p. 109.

[9] a) Y. Watanabe, T. Ohta, Y. Tsuji, T. Hiyoshi, Y. Tsuji, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2440; b) S.-i. Murahashi, Y. Imada, Y. Hirai, *Tetrahedron Lett.* **1987**, *28*, 77; c) S.-i. Murahashi, Y. Imada, Y. Hirai, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2968; d) K. Fujita, C. Kitatsuji, S. Furukawa, R. Yamaguchi, *Tetrahedron Lett.* **2004**, *45*, 3215; e) P. Frediani, L. Rosi, L. Cetarini, M. Frediani, *Inorg. Chim. Acta* **2006**, *359*, 2650.

[10] For reviews, 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.

[11] For pioneering works, see: a) S. Murata, T. Sugimoto, S. Matsuura, *Heterocycles* **1987**, *26*, 763; b) C. Bianchini, P. Barbaro, G. Scapacci, E. Farnetti, M. Graziani, *Organometallics* **1998**, *17*, 3308; c) C. Bianchini, P. Barbaro, G. Scapacci, *J. Organomet. Chem.* **2001**, *621*, 26.

[12] For selected examples of the hydrogenation of quinolines, see: a) N. Mršić, L. Lefort, B. Laurent, A. F. Jeroen, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *Adv. Synth. Catal.* **2008**, *350*, 1081; b) S.-M. Lu, C. Bolm, *Adv. Synth. Catal.* **2008**, *350*, 1101; 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.* **2008**, *120*, 8592; *Angew. Chem. Int. Ed.* **2008**, *47*, 8464; d) D. W. Wang, X.-B. Wang, D.-S. Wang, S.-M. Lu, Y.-G. Zhou, Y.-X. Li, *J. Org. Chem.* **2009**, *74*, 2780; e) F.-R. Gou, W. Li, X. Zhang, Y.-M. Liang, *Adv. Synth. Catal.* **2010**, *352*, 2441; f) M. Rubio, A. Pizzano, *Molecules* **2010**, *15*, 7732; g) J. L. Núñez-Rico, H.-F. Fernández-Pérez, J. Benet-Buchholz, A. Vidal-Ferran, *Organometallics* **2010**, *29*, 6627; h) M. Rueping, R. M. Koenigs, *Chem. Commun.* **2011**, *47*, 304; i) T. Wang, L.-G. Zhou, 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; j) G. E. Dobereiner, A. Nova, N. D. Schley, N. Hazari, S. J. Miller, O. Eisenstein, R. H. Crabtree, *J. Am. Chem. Soc.* **2011**, *133*, 7547; k) Q.-A. Chen, K. Gao, Y. Duan, Z.-S. Ye, Y. Yang, Y.-G. Zhou, *J. Am. Chem. Soc.* **2012**, *134*, 2442.

[13] For selected examples of the hydrogenation of quinoxalines, see: a) N. Mršić, T. Jerphagnon, A. Minnaard, B. L. Feringa, J. de Varies, *Adv. Synth. Catal.* **2009**, *351*, 2549; 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) J. Qin, F. Chen, Z. Ding, Y.-M. He, L. Xu, Q.-H. Fan, *Org. Lett.* **2011**, *13*, 6568; e) S. Urban, N. Ortega, F. Glorius, *Angew. Chem.* **2011**, *123*, 3887; *Angew. Chem. Int. Ed.* **2011**, *50*, 3803.

[14] For recent examples of the hydrogenation of pyridine derivatives, see: a) X. B. Wang, W. Zeng, Y.-G. Zhou, *Tetrahedron Lett.* **2008**, *49*, 4922; b) W. Tang, Y. Sun, X. Lijin, T. Wang, F. Qinghua, K.-H. Lam, A. S. C. Chan, *Org. Biomol. Chem.* **2010**, *8*, 3464; c) W.-J. Tang, J. Tan, L.-J. Xu, K.-H. Lam, Q.-H. Fan, A. S. C. Chan, *Adv. Synth. Catal.* **2010**, *352*, 1055; d) 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.

[15] For recent examples of the hydrogenation of pyrroles, see: a) R. Kuwano, *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.

[16] For recent examples of the hydrogenation of imidazoles and oxazoles, see: R. Kuwano, N. Kameyama, R. Ikeda, *J. Am. Chem. Soc.* **2011**, *133*, 7312.

[17] For recent examples of the hydrogenation of indoles, see: a) A. M. Maj, I. Suisse, C. Méliet, F. Agbossou-Niedercorn, *Tetrahedron: Asymmetry* **2010**, *21*, 2010; b) N. Mršíc, T. Jerphagnon, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *Tetrahedron: Asymmetry* **2010**, *21*, 7; c) A. Baeza, A. Pfaltz, *Chem. Eur. J.*

2010, *16*, 2036; d) D.-S. Wang, Q.-A. Chen, C.-B. Yu, Y.-G. Zhou, X. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 8909; e) D.-S. Wang, J. Tang, Y.-G. Zhou, M.-W. Chen, C.-B. Yu, Y. Duan, G.-F. Jiang, *Chem. Sci.* **2011**, *2*, 803; f) Y. Duan, M. W. Chen, Z.-S. Ye, D.-S. Wang, Q.-A. Chen, Y.-G. Zhou, *Chem. Eur. J.* **2011**, *17*, 7193; g) Y. Duan, M.-W. Chen, Q.-A. Chen, C.-B. Yu, Y.-G. Zhou, *Org. Biomol. Chem.* **2012**, *10*, 1235.

[18] For recent examples of the hydrogenation of furans and benzofurans, see: a) M. Sebek, J. Holz, A. Börner, K. Jähnisch, *Synlett* **2009**, 461; b) N. Ortega, S. Urban, B. Beiring, F. Glorius, *Angew. Chem.* **2012**, *124*, 1742; *Angew. Chem. Int. Ed.* **2012**, *51*, 1710.

[19] For recent examples of the hydrogenation of thiophenes: S. Urban, B. Beiring, N. Ortega, D. Paul, F. Glorius, *J. Am. Chem. Soc.* **2012**, *134*, 15241.

[20] For recent examples of the hydrogenation of naphthalenes: R. Kuwano, R. Morioka, M. Kashiwabara, N. Kameyama, *Angew. Chem.* **2012**, *124*, 4212; *Angew. Chem. Int. Ed.* **2012**, *51*, 4136.

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

[22] a) H. Tadaoka, D. Cartigny, T. Nagano, T. Gosavi, T. Ayad, J.-P. Genêt, T. Ohshima, V. Ratovelomanana-Vidal, K. Mashima, *Chem. Eur. J.* **2009**, *15*, 9990; b) D. Cartigny, T. Nagano, T. Ayad, J.-P. Genêt, T. Ohshima, K. Mashima, V. Ratovelomanana-Vidal, *Adv. Synth. Catal.* **2010**, *352*, 1886; c) D. Cartigny, F. Berhal, T. Nagano, P. Phansavath, T. Ayad, J.-P. Genêt, T. Ohshima, K. Mashima, V. Ratovelomanana-Vidal, *J. Org. Chem.* **2012**, *77*, 4544; d) T. Nagano, A. Iimuro, R. Schwenk, T. Ohshima, Y. Kita, A. Togni, K. Mashima, *Chem. Eur. J.* **2012**, *18*, 11578.

[23] See the Supporting Information for details.

[24] a) A. J. Minnaard, B. L. Feringa, L. Lefort, J. G. de Vries, *Acc. Chem. Res.* **2007**, *40*, 1267; b) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, *111*, 1713; c) J. H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Soc. Rev.* **2012**, *41*, 4126.

[25] a) Y. Hsiao, N. R. Rivera, T. Rosner, M. Kubryk, E. Njolito, F. Wang, Y. Sun, J. D. Armstrong III, E. J. J. Grabowski, R. D. Tillyer, F. Splindler, C. Malan, *J. Am. Chem. Soc.* **2004**, *126*, 9918; b) K. B. Hansen, Y. Hsiao, F. Xu, R. A. Clausen, M. Kubryk, S. Krska, R. B. Simmons, J. Balsells, N. Ikemoto, Y. Sun, F. Splindler, C. Malan, E. J. J. Grabowski, J. D. Armstrong III, *J. Am. Chem. Soc.* **2009**, *131*, 8798.

[26] For a review, see: Z. Yu, W. Jin, Q. Jiang, *Angew. Chem.* **2012**, *124*, 6164; *Angew. Chem. Int. Ed.* **2012**, *51*, 6060.

[27] P. Abrams, K.-E. Andersson, *BJU Int.* **2007**, *100*, 987.

