Asymmetric Catalysis

DOI: 10.1002/anie.201410607

# Catalytic Asymmetric Hydrogenation of Pyrimidines**

*Ryoichi Kuwano,* Yuta Hashiguchi, Ryuhei Ikeda, and Kentaro Ishizuka*

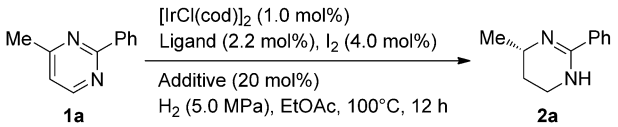
***Abstract:*** *The asymmetric hydrogenation of pyrimidines proceeded with high enantioselectivity (up to 99% ee) using an iridium catalyst composed of [IrCl(cod)]$_2$, a ferrocene-containing chiral diphosphine ligand (Josiphos), iodine, and Yb(OTf)$_3$ (cod = 1,5-cyclooctadiene). The chiral catalyst converted various 4-substituted pyrimidines into chiral 1,4,5,6-tetrahydropyrimidines in high yield. The lanthanide triflate is crucial for achieving the high enantioselectivity as well as for activating the heteroarene substrate.*

The catalytic asymmetric hydrogenation of azaarenes is a useful method to prepare optically active nitrogen-containing heterocycle constituents, which are present in numerous alkaloids. In the last decade, a variety of azaarenes have been reduced with high enantioselectivities by using various asymmetric catalysts,[1] including using organocatalysts.[2] Iridium is frequently used for the highly enantioselective hydrogenation of 6-membered azaarene rings.[3–6] However, the highly enantioselective reduction of some nitrogen-containing heteroarenes still remains difficult.

The asymmetric hydrogenation of pyrimidines has been an unexplored issue in organic synthesis. The reaction will be an attractive method for the synthesis of 6-membered cyclic amidines, which often occur in natural products and potent pharmaceutical compounds.[7] However, the generation of the amidine functionality may cause a problem in the development of the asymmetric reduction of pyrimidines because the product binds strongly to the metal atom in the catalyst as a result of its strong Lewis basicity. Herein, we report the highly enantioselective hydrogenation of pyrimidines. To achieve a high yield of the amidine product as well as high enantioselectivity, a chiral iridium complex was used as the catalyst in combination with a lanthanide triflate.

Previously, we reported a highly enantioselective hydrogenation of *N*-Boc-imidazoles (Boc = *tert*-butoxycarbonyl).[8,9] The hydrogenation yielded the chiral imidazoline products with up to 99% *ee* using the chiral [Ru($\eta^3$-methallyl)$_2$(cod)]–PhTRAP catalyst (cod = 1,5-cyclooctadiene; PhTRAP = 2,2′-bis[1-(diphenylphosphino)ethyl]-1,1′-biferrocene). Structural analogy between imidazoles and pyrimidines inspired us to attempt the hydrogenation of 4-methyl-2-phenylpyrimidine (**1a**) with the PhTRAP–ruthenium catalyst. No hydrogenation of the pyrimidine, however, was detected and the substrate **1a** remained intact after the reaction mixture was stirred at 80°C for 4 hours under a hydrogen atmosphere (5.0 MPa). Thus, our attention turned to the use of an iridium catalyst, which is commonly used for the hydrogenation of 6-membered arenes containing one or two nitrogen atoms. First, the hydrogenation of **1a** was attempted using a [IrCl(cod)]$_2$–**L1**–I$_2$ catalytic system, where **L1** is (*R*)-BINAP (Table 1, entry 1; BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl). Using the iridium catalyst, it was possible to produce the desired 1,4,5,6-hydrogenated product **2a** at 100°C, but in low yield and with low stereoselectivity. To enhance the reactivity of **1a**, the asymmetric reduction was carried out in the presence of Brønsted acids, which have been often used for activating nitrogen-

***Table 1:*** Optimization of reaction conditions for the catalytic asymmetric hydrogenation of **1a**.[a]




| Entry | Ligand | Additive | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|
| 1 | **L1** | None | 11 | 24 (+) |
| 2 | **L1** | TsOH·H$_2$O | 25 | 18 (+) |
| 3 | **L1** | Cu(OTf)$_2$ | 27 | 10 (+) |
| 4 | **L1** | Dy(OTf)$_3$ | 43 | 11 (+) |
| 5 | **L2** | Dy(OTf)$_3$ | 56 | 72 (−) |
| 6 | **L3** | Dy(OTf)$_3$ | 63 | 40 (−) |
| 7 | **L4** | Dy(OTf)$_3$ | 64 | 45 (−) |
| 8 | **L5** | Dy(OTf)$_3$ | 68 | 6 (+) |
| 9 | **L6** | Dy(OTf)$_3$ | 55 | 65 (−) |
| 10 | **L7** | Dy(OTf)$_3$ | 51 | 72 (−) |
| 11 | **L8** | Dy(OTf)$_3$ | 61 | 33 (−) |
| 12 | **L2** | Yb(OTf)$_3$ | 53 | 78 (−) |
| 13[d] | **L2** | Yb(OTf)$_3$ | 49 | 89 (−) |
| 14[d,e] | **L2** | Yb(OTf)$_3$ | >99[f] | 87 (−) |
| 15[d,e,g] | **L2** | Yb(OTf)$_3$ | 94[f] | 88 (−) |

[a] Unless otherwise noted, reactions were conducted on a 0.2 mmol scale in EtOAc (1.0 mL) under H$_2$ (5.0 MPa) at 100°C for 12 h. The ratio of **1a**:[IrCl(cod)]$_2$:ligand:I$_2$:additive was 100:1.0:2.2:4.0:20. [b] Determined by $^1$H NMR spectroscopic analysis. [c] Determined by chiral HPLC analysis after treating **2a** with (Boc)$_2$O. Signs of optical rotations are given in parentheses. [d] At 50°C. [e] For 72 h. The ratio of **1a**/Yb(OTf)$_3$ was 100:50. [f] Yield of isolated product. [g] On a 1.0 mmol scale. OTf = trifluoromethanesulfonate.

[*] Prof. R. Kuwano, Y. Hashiguchi, R. Ikeda, Dr. K. Ishizuka
Department of Chemistry, Graduate School of Sciences, and International Research Center for Molecular Systems (IRCMS)
Kyushu University, 6-10-1 Hakozaki, Higashi-ku
Fukuoka 812-8581 (Japan)
E-mail: rkuwano@chem.kyushu-univ.jp
Prof. R. Kuwano
JST ACT-C, 6-10-1 Hakozaki, Higashi-ku, Fukuoka 812-8581 (Japan)
Dr. K. Ishizuka
Education Center for Global Leaders in Molecular Systems for Devices, Kyushu University
774 Motooka, Nishi-ku, Fukuoka, 819-0395 (Japan)

[**] This work was partly supported by ACT-C (JST). We thank the Cooperative Research Program of the "Network Joint Research Center for Material and Devices" for HRMS measurement.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201410607.

containing substrates in catalytic asymmetric hydrogenation reactions.[10–12] The use of *p*-toluenesulfonic acid resulted in a slight increase in the yield of **2a** (entry 2). Next, we turned our attention to use of Lewis acids. After screening various metal salts, lanthanide triflates were found to remarkably improve the hydrogenation of **1a** (entry 4). However, the enantiomeric excess of **2a** still remained low.

A broad range of chiral phosphine ligands were evaluated for the iridium-catalyzed hydrogenation of **1a** in the presence of $Dy(OTf)_3$ (Figure 1).[13] The enantioselectivity was remarkably enhanced by using Josiphos ligand **L2** (Table 1, entry 5).[14] The catalytic activity of the Josiphos–iridium complex was little affected by the substituents $R^1$ and $R^2$ on its phosphorus atoms (entries 5–11). In contrast, changing the substituents has an impact on the enantioselectivity of the reaction. The selectivity significantly decreased when either the *tert*-butyl or the phenyl group on **L2** was replaced by a cyclohexyl group (entries 6 and 7, using ligands **L3** and **L4**, respectively). Furthermore, use of Josiphos **L5** bearing two diarylphosphino groups resulted in the formation of an almost racemic product (entry 8). Installing electron-deficient aryl groups as the $R^2$ substituent caused a slight decrease in enantioselectivity (entry 9). The stereoselectivity of methoxy-substituted Josiphos **L7** was comparable to **L2** (entry 10). The chiral induction of the iridium catalyst is controlled not only by the combination of $R^1$ and $R^2$ substituents but also by their relative positions. Significantly lower enantioselectivity was observed in the reaction using ligand **L8**, which has *tert*-butyl and phenyl groups as substituents $R^2$ and $R^1$, respectively (entry 11). Furthermore, a series of lanthanide triflates were evaluated for the iridium-catalyzed hydrogenation of **1a** with ligand **L2**.[13] Relatively high enantioselectivities were observed in the reactions using $Yb(OTf)_3$ (entry 12) as well as $Pr(OTf)_3$, $Sm(OTf)_3$, $Gd(OTf)_3$, and $Tb(OTf)_3$ (see Table S2 in the Supporting Information). The stereoselectivity was improved without significant loss of the yield by conducting the reaction at 50 °C (entry 13).[15,16] Furthermore, the complete conversion of **1a** into **2a** was accomplished by using 0.5 equivalents of $Yb(OTf)_3$ per 1 equivalent of **1a** (entry 14). The desired product **2a** was quantitatively obtained with 87 % *ee*.

As shown in Table 2, the optimized reaction conditions allow a variety of 2,4-disubstituted pyrimidines **1** to be converted into cyclic amidines **2** with high enantiomeric excesses and in high yields. The enantioselectivity of the hydrogenation was scarcely affected by the *para* substituents on the 2-aryl groups in **1b** and **1c** (entries 1 and 2). Installing a substituent at the *ortho* position led to improvements in the stereoselectivity (entries 3–6). In particular, 2-(*o*-tolyl)pyrimidine derivative **1f** gave the desired product **2f** with 95 % *ee*. The pyrimidines bearing a substituent other than methyl group as the $R^2$ group also undergo hydrogenation with high stereoselectivity. 4-Ethylpyrimidine **1h** was quantitatively transformed into **2h** with 96 % *ee* (entry 7). The hydrogenation of **1i**, which has a secondary alkyl group, proceeded with high stereoselectivity (entry 8). The substrate was completely consumed within 48 hours, but the reaction mixture at 96 hours contained 4-cyclohexyl-1,6-dihydropyrimidine **3i** in 25 % yield. Pyrimidine **1j** also underwent the hydrogenation at its N1–C6 bond, but the C4–C5 double bond of **3j** remained intact (entry 9). The aryl groups on the C4 atom of **1k**–**1n** (i.e. the $R^2$ substituents) are favorable for achieving high stereoselectivity (entries 10–13). It is noteworthy that the amidines **2l**–**2n** were obtained with 98–99 % *ee*. The acetoxy group of **1o** was compatible with the reaction, leading to the formation of product **2o** with 88 % *ee* (entry 14). Chiral amidines **2p** and **2q**, each with an electron-withdrawing group at the stereogenic center, were also obtained in high yields from the asymmetric hydrogenation (entries 15 and 16). However, the enantiomeric excesses of **2p** and **2q** were very low. The **L2**–iridium catalyst also showed high enantioselectivity for the hydrogenation of pyrimidines bearing $R^1$ substituents other than aryl groups (entries 17 and 18). Cyclic guanidine **2s** was produced with 91 % *ee* in

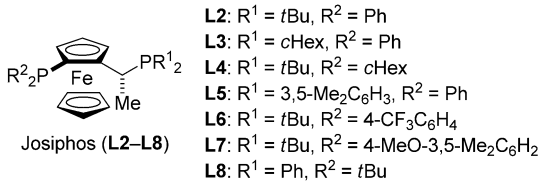
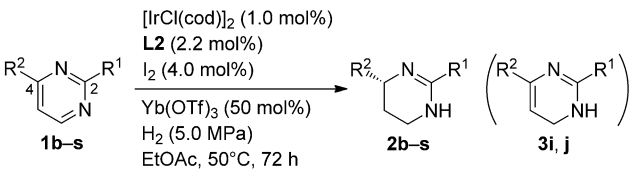



***Figure 1.*** Structures of Josiphos ligands employed in this study. *c*Hex = cyclohexyl.

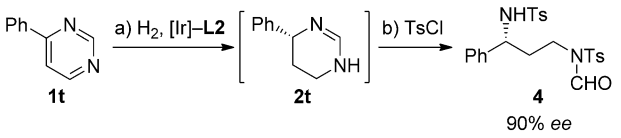
***Table 2:*** Catalytic asymmetric hydrogenation of 2,4-disubstituted pyrimidines **1**.[a]




| Entry | $R^1$ | $R^2$ | **1** | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1[d] | 4-$CF_3C_6H_4$ | Me | **1b** | 87 | 86 |
| 2[d] | 4-$MeOC_6H_4$ | Me | **1c** | 93 | 86 |
| 3 | 2-$FC_6H_4$ | Me | **1d** | 92 | 92 |
| 4 | 2-$ClC_6H_4$ | Me | **1e** | 92 | 94 |
| 5 | 2-$MeC_6H_4$ | Me | **1f** | 98 | 95 |
| 6 | 2-$MeOC_6H_4$ | Me | **1g** | 99 | 87 |
| 7 | 2-$MeC_6H_4$ | Et | **1h** | > 99 | 96 |
| 8[d] | 2-$MeC_6H_4$ | *c*Hex | **1i** | 68[e] | 97 |
| 9 | 2-$MeC_6H_4$ | *t*Bu | **1j** | 0[f] | – |
| 10[d] | Ph | Ph | **1k** | 92 | 97[g] |
| 11[d] | 2-$MeC_6H_4$ | Ph | **1l** | 94 | 99 |
| 12[d] | 2-$MeC_6H_4$ | 4-$CF_3C_6H_4$ | **1m** | 98 | 98 |
| 13[d] | 2-$MeC_6H_4$ | 4-$MeOC_6H_4$ | **1n** | 98 | 99 |
| 14 | Ph | $CH_2OAc$ | **1o** | 80 | 88 |
| 15 | 2-$MeC_6H_4$ | $CF_3$ | **1p** | 94 | 9 |
| 16 | 2-$MeC_6H_4$ | $CO_2Et$ | **1q** | 80 | 22 |
| 17[d] | Me | Ph | **1r** | 92 | 92 |
| 18[d,h] | $NMe_2$ | Ph | **1s** | 87 | 91 |

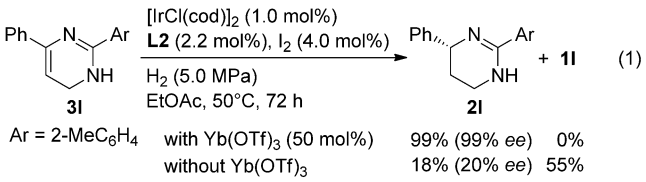
[a] Unless otherwise noted, reactions were conducted on a 0.2 mmol scale in EtOAc (1.0 mL) under $H_2$ (5.0 MPa) at 50 °C for 72 h. The ratio of **1**:$[IrCl(cod)]_2$:**L2**:$I_2$:$Yb(OTf)_3$ was 100:1.0:2.2:4.0:50. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis after treating **2** with $(Boc)_2O$. [d] For 96 h. [e] **3i** was formed in 25 % yield (calculated by $^1H$ NMR spectroscopy). [f] **3j** was formed in 99 % yield (calculated by $^1H$ NMR spectroscopy). [g] The absolute configuration of **2k** is *R*. [h] At 100 °C.

high yield by the hydrogenation of **1s**, although the reaction required a higher reaction temperature (100 °C). Pyrimidine **1t** bearing no substituent at the C2 position (i.e. $R^1 = H$) was also hydrogenated to form **2t** with a high enantiomeric excess (Scheme 1). The chiral product was obtained as protected 1,3-diamine **4** after treatment with TsCl (*p*-toluenesulfonyl chloride) and alkali, because **2t** could not be purified by chromatography.

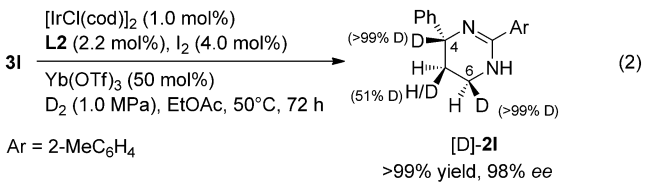



***Scheme 1.*** Catalytic asymmetric hydrogenation of 4-phenylpyrimidine (**1t**). Reagents and conditions: a) $H_2$ (5.0 MPa), $[IrCl(cod)]_2$ (1.0 mol%), **L2** (2.2 mol%), $I_2$ (4.0 mol%), $Yb(OTf)_3$ (0.5 equiv), EtOAc, 50 °C, 72 h; b) TsCl (2.2 equiv), $Et_3N$ (2.2 equiv), $CH_2Cl_2$, followed by treatment with saturated aqueous $Na_2CO_3$. Cumulative yield of **4**: 83% from **1t**.

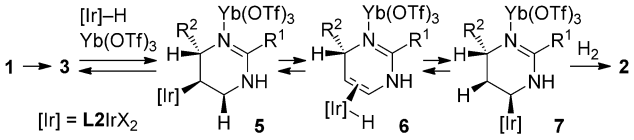
The formation of **3** in entries 8 and 9 of Table 2 implies that the iridium-catalyzed hydrogenation of **1** proceeds through stepwise additions of two $H_2$ molecules to the N1–C6 and C4–C5 bonds. To confirm this speculation, the hydrogenation of **3l** was carried out with the $[IrCl(cod)]_2$–**L2**–$I_2$–$Yb(OTf)_3$ catalytic system [Eq. (1)]. The dihydropyrimidine was converted into **2l** with 99% *ee* in high yield as expected. The Lewis acid is required for the reduction of **3** as well as for the dearomatization of the pyrimidine, because **2l** was obtained with only 20% *ee* in low yield without using $Yb(OTf)_3$. Furthermore, the reaction was accompanied by the formation of **1l** (see entry 11 in Table 2 for the structure). The dehydrogenation indicates that **1l** and **3l** are in equilibrium in the presence of the iridium catalyst. However, the undesirable reverse reaction might be restricted by using the lanthanide triflate in the reaction.[13]




To investigate the pathway from intermediate **3** to product **2**, the deuteration of **3l** was undertaken [Eq. (2)]. In the product [D]-**2l**, the deuterium atom was incorporated in more than 99% on the C4 center. Hydrogen/deuterium scrambling took place at the pro-*R* position on the C5 atom. To our surprise, the pro-*S* hydrogen on the C6 atom in **3l** was

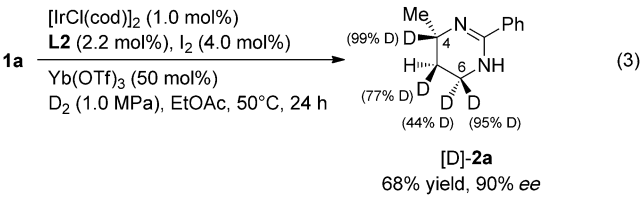



completely replaced by deuterium. It has been established that the hydrogenation reaction using the $[IrCl(cod)]_2$–bisphosphine–$I_2$ catalytic system proceeds through a hydridoiridium(III) species.[3b,11d,17] Consequently, the observed deuterium distribution suggests that the hydrogenation of **1** proceeds through the following pathway (Scheme 2). The pyrimidine **1** is activated by coordination




***Scheme 2.*** Proposed pathway for the hydrogenation of **1** to form **2**. X = I or Cl.

to $Yb(OTf)_3$.[17a] The N1–C6 bond of **1** is reduced with $H_2$ to give the dihydropyrimidine **3**. The C4–C5 double bond of **3** is inserted into the Ir–H bond to form intermediate **5**. The transformation of **5** into **2** would proceed through the migration of the iridium atom from C5 to C6, because deuterium should be incorporated in 100% at the pro-*R* position on C5 if the hydrogenation proceeded without the migration. In the deuteration of **3l**, the hydride on iridium in intermediate **6** might be replaced by deuterium through a molecular $D_2$ complex.[18] Consequently, the hydrogen/deuterium exchange would cause the 51% deuterium incorporation at the C5 atom in [D]-**2l**. The Ir–C6 bond in **7** would be protonated through σ-bond metathesis with $H_2$ or a sequence composed of oxidative addition followed by reductive elimination. Furthermore, the deuteration of **1a** was conducted using the **L2**–iridium catalyst [Eq. (3)]. The deuteration was also accompanied by hydrogen/deuterium




scrambling at the C5 position and complete incorporation of deuterium at the C6 position.

In conclusion, we have successfully developed a chiral catalyst for the asymmetric hydrogenation of 4-substituted pyrimidines **1**. A broad range of pyrimidines were converted into the corresponding 1,4,5,6-tetrahydropyrimidines **2** with high enantiomeric excesses using an $[IrCl(cod)]_2$–Josiphos–$I_2$ catalytic system. Furthermore, the addition of $Yb(OTf)_3$ brought about a remarkable improvement of the stereoselectivity as well as an enhanced yield of **2**. The lanthanide triflate facilitates the hydrogenation of 1,6-dihydropyrimidine intermediate **3** as well as the initial reduction of the N1–C6 double bond in pyrimidine **1**.

Received: October 31, 2014
Revised: December 6, 2014
Published online: January 7, 2015

**Keywords:** asymmetric catalysis · heterocycles · hydrogenation · iridium · lanthanides

[1] For reviews on asymmetric hydrogenation of azaarenes, see: a) F. Glorius, *Org. Biomol. Chem.* **2005**, *3*, 4171 – 4175; b) Y.-G. Zhou, *Acc. Chem. Res.* **2007**, *40*, 1357 – 1366; c) R. Kuwano, *Heterocycles* **2008**, *76*, 909 – 922; d) D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557 – 2590; e) D. Zhao, F. Glorius, *Angew. Chem. Int. Ed.* **2013**, *52*, 9616 – 9618; *Angew. Chem.* **2013**, *125*, 9794 – 9796; f) K. Mashima, T. Nagano, A. Iimuro, K. Yamaji, Y. Kita, *Heterocycles* **2014**, *88*, 103 – 127.

[2] For selected examples, see: a) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem. Int. Ed.* **2006**, *45*, 3683 – 3686; *Angew. Chem.* **2006**, *118*, 3765 – 3768; b) M. Rueping, A. P. Antonchick, *Angew. Chem. Int. Ed.* **2007**, *46*, 4562 – 4565; *Angew. Chem.* **2007**, *119*, 4646 – 4649; 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 – 6129.

[3] For selected examples of the hydrogenations of quinolines with a chiral iridium catalyst, see: a) W.-B. Wang, S.-M. Lu, P.-Y. Yang, X.-W. Han, Y.-G. Zhou, *J. Am. Chem. Soc.* **2003**, *125*, 10536 – 10537; b) D.-W. Wang, X.-B. Wang, D.-S. Wang, S.-M. Lu, Y.-G. Zhou, Y.-X. Li, *J. Org. Chem.* **2009**, *74*, 2780 – 2787; c) W. Tang, Y. Sun, X. Lijin, T. Wang, F. Qinghua, K. H. Lam, A. S. C. Chan, *Org. Biomol. Chem.* **2010**, *8*, 3464 – 3471.

[4] For the hydrogenations of isoquinolines with chiral iridium catalyst, see: L. Shi, Z.-S. Ye, L.-L. Cao, R.-N. Guo, Y. Hu, Y.-G. Zhou, *Angew. Chem. Int. Ed.* **2012**, *51*, 8286 – 8289; *Angew. Chem.* **2012**, *124*, 8411 – 8414.

[5] For the hydrogenation of pyridines with a chiral iridium catalyst, see: X.-B. Wang, W. Zeng, Y.-G. Zhou, *Tetrahedron Lett.* **2008**, *49*, 4922 – 4924.

[6] For selected examples of the hydrogenation of quinoxalines with a chiral iridium catalyst, see: a) C. Bianchini, P. Barbaro, G. Scapacci, E. Farnetti, M. Graziani, *Organometallics* **1998**, *17*, 3308 – 3310; b) 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 – 9138; *Angew. Chem.* **2009**, *121*, 9299 – 9302; c) D. Cartigny, T. Nagano, T. Ayad, J.-P. Genêt, T. Ohshima, K. Mashima, V. Ratovelomanana-Vidal, *Adv. Synth. Catal.* **2010**, *352*, 1886 – 1891; d) T. Nagano, A. Iimuro, R. Schwenk, T. Ohshima, Y. Kita, A. Togni, K. Mashima, *Chem. Eur. J.* **2012**, *18*, 11578 – 11592.

[7] a) J. Kobayashi, F. Kanda, M. Ishibashi, H. Shigemori, *J. Org. Chem.* **1991**, *56*, 4574 – 4576; b) I. Ohtani, R. E. Moore, M. T. C. Runnegar, *J. Am. Chem. Soc.* **1992**, *114*, 7941 – 7942; c) L. A. McDonald, L. R. Barbieri, G. T. Carter, E. Lenoy, J. Lotvin, P. J. Petersen, M. M. Siegel, G. Singh, R. T. Williamson, *J. Am. Chem. Soc.* **2002**, *124*, 10260 – 10261; d) F. Reyes, R. Fernández, A. Rodríguez, A. Francesch, S. Taboada, C. Ávila, C. Cuevas, *Tetrahedron* **2008**, *64*, 5119 – 5123; e) J. M. Pastor, M. Salvador, M. Argandoña, V. Bernal, M. Reina-Bueno, L. N. Csonka, J. L. Iborra, C. Vargas, J. J. Nieto, M. Cánovas, *Biotechnol. Adv.* **2010**, *28*, 782 – 801.

[8] R. Kuwano, N. Kameyama, R. Ikeda, *J. Am. Chem. Soc.* **2011**, *133*, 7312 – 7315.

[9] For selected reports by us on the catalytic asymmetric hydrogenations of arenes, see: a) R. Kuwano, K. Sato, T. Kurokawa, D. Karube, Y. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 7614 – 7615; b) R. Kuwano, M. Kashiwabara, *Org. Lett.* **2006**, *8*, 2653 – 2655; c) R. Kuwano, M. Kashiwabara, M. Ohsumi, H. Kusano, *J. Am. Chem. Soc.* **2008**, *130*, 808 – 809; d) R. Kuwano, R. Morioka, M. Kashiwabara, N. Kameyama, *Angew. Chem. Int. Ed.* **2012**, *51*, 4136 – 4139; *Angew. Chem.* **2012**, *124*, 4212 – 4215.

[10] For a review on the activation of nitrogen-containing substrates with Brønsted acids for catalytic asymmetric hydrogenations, see: Z. Yu, W. Jin, Q. Jiang, *Angew. Chem. Int. Ed.* **2012**, *51*, 6060 – 6072; *Angew. Chem.* **2012**, *124*, 6164 – 6177.

[11] For the asymmetric hydrogenation of azaarenes activated by a Brønsted acid, see: a) Z.-W. Li, T.-L. Wang, Y.-M. He, Z.-J. Wang, Q.-H. Fan, J. Pan, L.-J. Xu, *Org. Lett.* **2008**, *10*, 5265 – 5268; b) 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 – 9994; c) D.-S. Wang, Y.-G. Zhou, *Tetrahedron Lett.* **2010**, *51*, 3014 – 3017; d) A. Iimuro, K. Yamaji, S. Kandula, T. Nagano, Y. Kita, K. Mashima, *Angew. Chem. Int. Ed.* **2013**, *52*, 2046 – 2050; *Angew. Chem.* **2013**, *125*, 2100 – 2104; e) R. N. Guo, X. F. Cai, L. Shi, Z. S. Ye, M. W. Chen, Y. G. Zhou, *Chem. Commun.* **2013**, *49*, 8537 – 8539; f) Y. Kita, A. Iimuro, S. Hida, K. Mashima, *Chem. Lett.* **2014**, *43*, 284 – 286; g) D.-S. Wang, Q.-A. Chen, W. Li, C.-B. Yu, Y.-G. Zhou, X. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 8909 – 8911; h) 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 – 8869; i) Y. Duan, L. Li, M.-W. Chen, C.-B. Yu, H.-J. Fan, Y.-G. Zhou, *J. Am. Chem. Soc.* **2014**, *136*, 7688 – 7700.

[12] For selected examples of the asymmetric hydrogenation of azaarenes activated by quarternarization of their nitrogen atom, see: a) C. Y. Legault, A. B. Charette, *J. Am. Chem. Soc.* **2005**, *127*, 8966 – 8967; b) S. M. Lu, Y. Q. Wang, X. W. Han, Y. G. Zhou, *Angew. Chem. Int. Ed.* **2006**, *45*, 2260 – 2263; *Angew. Chem.* **2006**, *118*, 2318 – 2321; c) Z.-S. Ye, M.-W. Chen, Q.-A. Chen, L. Shi, Y. Duan, Y.-G. Zhou, *Angew. Chem. Int. Ed.* **2012**, *51*, 10181 – 10184; *Angew. Chem.* **2012**, *124*, 10328 – 10331; d) Z.-S. Ye, R.-N. Guo, X.-F. Cai, M.-W. Chen, L. Shi, Y.-G. Zhou, *Angew. Chem. Int. Ed.* **2013**, *52*, 3685 – 3689; *Angew. Chem.* **2013**, *125*, 3773 – 3777; e) M. Chang, Y. Huang, S. Liu, Y. Chen, S. W. Krska, I. W. Davies, X. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 12761 – 12764; *Angew. Chem.* **2014**, *126*, 12975 – 12978.

[13] See the Supporting Information.

[14] A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, *J. Am. Chem. Soc.* **1994**, *116*, 4062 – 4066.

[15] The $^1$H NMR spectra of mixtures of **2a** and $Yb(OTf)_3$ suggest that the amidine interacts with the Lewis acid in a solution to form a Yb-**2a** complex. The ligand exchange of **2a** on the Yb center is fast on the NMR timescale. See the Supporting Information.

[16] One reviewer pointed out that the pyrimidine substrate may be activated with triflic acid, which is eliminated from $Yb(OTf)_3$. However, the activation with the Brønsted acid is ruled out in this asymmetric hydrogenation. A mixture of some unidentified compounds and remaining **1a** (ca. 60%) was obtained when stoichiometric triflic acid was used as the additive in place of the lanthanide triflate under the optimized conditions (at 12 h). The strong acid might cause the ring cleavage of **1a** or **3a**.

[17] a) 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 – 7562; b) R. Dorta, D. Broggini, R. Stoop, H. Ruegger, F. Spindler, A. Togni, *Chem. Eur. J.* **2004**, *10*, 267 – 278; c) D. Xiao, X. Zhang, *Angew. Chem. Int. Ed.* **2001**, *40*, 3425 – 3428; *Angew. Chem.* **2001**, *113*, 3533 – 3536.

[18] R. H. Crabtree, M. Lavin, L. Bonneviot, *J. Am. Chem. Soc.* **1986**, *108*, 4032 – 4037.