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Asymmetric Hydrogenation of 3-Substituted Pyridinium Salts

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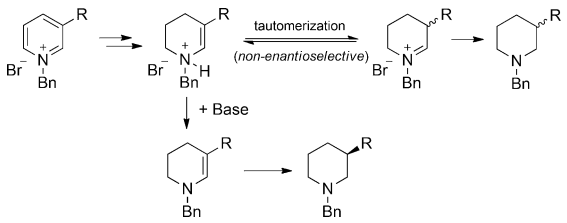
Abstract: The use of an equivalent amount of an organic base leads to high enantiomeric excess in the asymmetric hydrogenation of N-benzylated 3-substituted pyridinium salts into the corresponding piperidines. Indeed, in the presence of Et_3N, a Rh-JosiPhos catalyst reduced a range of pyridinium salts with *ee* values up to 90%. The role of the base was elucidated with a mechanistic study involving the isolation of the various reaction intermediates and isotopic labeling experiments. Additionally, this study provided some evidence for an enantiodetermining step involving a dihydropyridine intermediate.

The asymmetric hydrogenation (AH) of double bonds is one of the most efficient methods to prepare enantiopure organic compounds.[1] Although AH has been applied to a wide range of substrates, the development of catalysts for the AH of substituted N-heteroaromatic substrates is still in its early stages.[2] Such substrates are particularly challenging due to their high resonance stabilization energy and strong ability to deactivate the catalyst by irreversible coordination. Among the N-heteroaromatic substrates, substituted pyridines are of special interest, since the products of their hydrogenation, that is, chiral piperidines, are subunits of many biologically active compounds. Moreover, hundreds of pyridines are commercially available and countless methods exist for their preparation. During the last ten years, several successful methods have been disclosed for the homogeneous AH of 2-substituted pyridines,[3] and more recently of di- and trisubstituted pyridines.[4] In most of these contributions, a quaternization of the pyridine nitrogen atom is used to lower the resonance energy of the ring and prevent substrate coordination to the catalyst.[5] Unfortunately, the translation of these methods to 3-substituted pyridines is not straightforward. All reports dealing with this class of substrates are restricted to nicotinic acid or its esters,[6] and the obtained enantiomeric excesses were overall low. Only indirect protocols relying on the use of a chiral auxiliary[6d] or a two-step hydrogenation procedure[6e] allowed to obtain high *ee* values.

Although there is no general agreement on the mechanism of the AH of N-heteroarenes,[7,8] the current data led us to speculate that the poor enantiomeric excesses obtained with 3-substituted pyridines in comparison to their 2-substituted analogues were due to a non-enantioselective enaminium–iminium isomerization of a partially hydrogenated intermediate (Scheme 1).[9] Based on this hypothesis, we surmised that the addition of a base in the AH of N-benzylated pyridines[5] could retard the tautomerization by scavenging HBr produced during the reaction. As a consequence, the formation and subsequent hydrogenation of a racemic iminium salt would be prevented (Scheme 1).



Scheme 1. Proposed mechanism for the hydrogenation of 3-substituted pyridinium salts and possible effect of the addition of base.

For our initial trials, we selected Rh-JosiPhos as AH catalyst. Rh has indeed been extensively used for the AH of enamines and enamides.[10] Equally, the chiral bis-phosphine, JosiPhos J002-2 was shown to be an efficient ligand[11] for the AH of related substrates, that is, 2,4-disubstituted pyrimidines[12] and 3,4-disubstituted pyridinium salts.[13] Diisopropylamine (DIPEA) was chosen as the base to prevent the iminium formation. Indeed, its steric bulkiness was expected to decrease its propensity to coordinate to the rhodium center. A mixture of THF/MeOH was selected as solvent to solubilize both the catalyst and the pyridinium salt. Our first hydrogenation was carried out with *N*-benzyl-3-phenylpyridinium bromide (**1a**) as a substrate at 50 °C under 50 bar of H_2 with and without DIPEA (Scheme 2). In both cases, *N*-benzylpiperidine **2a** was obtained in low yield (13 and 16%, respectively) together with some *N*-

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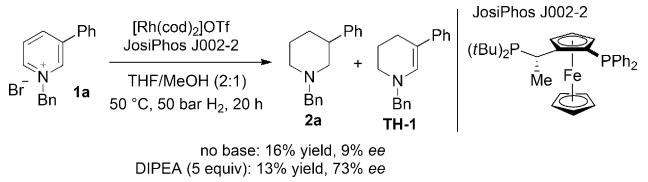
benzyl tetrahydropyridine **TH-1**. In the absence of base, the piperidine was obtained with only 9% *ee*. In sharp contrast, when DIPEA (5 equivalents relative to the substrate) was added to the reaction, the enantiomeric excess rose to 73%, which was, to our knowledge, the highest enantiomeric excess ever obtained in the direct AH of a 3-substituted pyridine.



Scheme 2. First hydrogenation attempts of *N*-benzyl-3-phenylpyridinium bromide **1a**, with and without base.

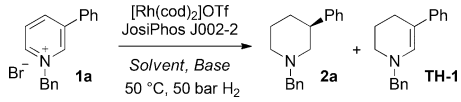
Encouraged by this result, we initiated a solvent and base screening (Table 1) in order to increase both yield and *ee* of **2a** and to minimize the amount of side product **TH-1**. When pure MeOH was used as solvent, a high yield but a low *ee* was obtained (Table 1, entry 2). In pure THF, the reaction gave the opposite enantiomer with very low yield (entry 3). THF/alcohol mixtures turned out to be optimal, as they allowed to obtain good yields and high *ee* values. Among the mixtures tested, 2:1 THF/trifluoroethanol (TFE) gave the best result (entry 6) and thus was selected for further experiments.

In the absence of base or in the presence of weak bases ($pK_{BH^+} < 8$, entries 9–11), a lesser amount of **TH-1** was detected, but the obtained *ee* values were very low. On the contrary, the use of stronger amines gave the best *ee* values, together with a significant amount of **TH-1** (entries 12–13). Among them, Et_3N was found to be the best performing (entry 13). When the reaction time was reduced from 20 to 16 h, a slightly higher *ee* was obtained at the expense of the yield (entry 13 vs. 15), suggesting an erosion of *ee* with time. Varying the amount of base had little effect as long as at least one equivalent of base relative to the substrate was used (entries 16–18). Unfortunately, further catalyst screening involving 8 metal precursors (including an iridium source) and 25 chiral ligands failed to give better results (see the Supporting Information).

Under the optimized conditions, a substrate screening (Table 2) was performed both in the presence and in the absence of Et_3N. The best results were obtained with N-benzylated pyridines bearing an aromatic substituent. For these substrates, the *ee* values of the corresponding *N*-benzylpiperidines ranged from 75 to 90% in the presence of Et_3N, as compared with the 14–40% *ee* obtained without base (Table 2, entries 1–6). The presence of the base was also beneficial with alkyl-substituted pyridines, but overall the *ee* values were lower with this class of substrates (entries 7 and 11).

Finally, lower conversions were obtained for substrates possessing electron-withdrawing groups (entries 3, 8 and 10). Since the catalyst was optimized with 3-phenylpyridine as model substrate, it is not surprising that the best results were obtained with aryl substituents. However, a positive effect of the base was observed for all substrates, suggesting a similar hydrogenation pathway for all substrates.

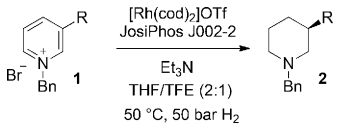
Table 1. Selected results on the optimization of the reaction conditions.[a]



#	Solvent	Base (pK_{BH^+} in H_2O)	**2a** [%][b]	*ee* [%][b]	TH-1 [%][b]
1	THF/MeOH (2:1)	DIPEA (11.07)	13	73	34
2	MeOH	DIPEA	81	13	9
3	THF	DIPEA	5	−59[c]	41
4	THF/EtOH (2:1)	DIPEA	10	63	50
5	THF/*i*PrOH (2:1)	DIPEA	6	34	48
6	THF/TFE (2:1)	DIPEA	27	83	17
7	THF/TFE (1:1)	DIPEA	40	68	2
8	THF/TFE (1:2)	DIPEA	40	52	2
9	THF/TFE (2:1)	–	5	23	0
10	THF/TFE (2:1)	2,6-lutidine (6.65)	98	31	0
11	THF/TFE (2:1)	*N*-Me-morpholine (7.38)	40	74	6
12	THF/TFE (2:1)	DMAP (9.2)	23	84	13
13	THF/TFE (2:1)	Et_3N (10.75)	57	85	20
14	THF/TFE (2:1)	Cs_2CO_3 (10.32)	40	48	32
15	THF/TFE (2:1)	Et_3N	50[d]	90	26
16	THF/TFE (2:1)	Et_3N [0.5 equiv]	40	76	9
17	THF/TFE (2:1)	Et_3N [1 equiv]	54	85	16
18	THF/TFE (2:1)	Et_3N [10 equiv]	58	78	16

[a] Reaction conditions: **1a** (0.025 mmol), $[Rh(cod)_2]OTf$ (2 mol%), JosiPhos J002-2 (2.2 mol%), base (5 equiv relative to the substrate unless otherwise indicated), solvent (1.5 mL), 50 °C, 50 bar H_2, 20 h. [b] Determined by GC analysis with CP-Chirasil-Dex CB column and dodecane as internal standard. [c] *R* configuration was obtained in this case. [d] Reaction time: 16 h.

Table 2. Substrate scope under the optimized conditions, with and without base.[a]



#	R=	With Et_3N **2** [%][b]	With Et_3N *ee* [%][b]	Without Et_3N **2** [%][b]	Without Et_3N *ee* [%][b]
1	Ph (**1a**)	50	90 (*S*)	5	23 (*S*)
2	Ph (**1a**)[c]	57 (52)[d]	84 (*S*)		
3	4-$CF_3C_6H_4$ (**1b**)	20	83 (−)	12	14 (−)
4	2-MeC_6H_4 (**1c**)	50	75 (−)	7	30 (−)
5	4-$MeOC_6H_4$ (**1d**)	52	90 (−)	8	40 (−)
6	2-naphthyl (**1e**)	42	86 (−)	21	20 (−)
7	Me (**1f**)	36	57 (*R*)	<1	n.d.
8	CO_2Et (**1g**)	2	33	3	−17[e]
9	NHBoc (**1h**)	24	55 (*R*)	25	27 (*R*)
10	CF_3 (**1i**)	2	41	2	11
11	*n*Bu (**1j**)	43	32 (−)	<1	n.d.

[a] Reaction conditions: **1** (0.025 mmol), $[Rh(cod)_2]OTf$ (2 mol%), JosiPhos J002-2 (2.2 mol%), Et_3N (5 equiv), THF/TFE (2:1, 1.5 mL), 50 °C, 50 bar H_2, 16 h. [b] Determined by GC or HPLC analysis with dodecane as internal standard. Absolute configuration assigned by comparison of the optical rotation with literature data (see the Supporting Information). [c] Reaction performed on 500 mg scale (1.53 mmol) for 20 h. [d] Isolated yield. [e] The opposite enantiomer was obtained.

To gain some insight into the mechanism, the reaction was monitored over time by GC and NMR spectroscopy (Figure 1). The starting material **1a** was consumed relatively quickly (over 90% conversion within the first 4 h), with concomitant formation of piperidine **2a** and of several partially hydrogenated intermediates that were identified as N-benzylated tetrahydropyridines.[14] Tetrahydropyridine **TH-1**, the main side product at the end of the reaction, was formed at a fast rate during the first two hours and then its amount very slowly decreased. This compound was isolated and fully characterized (see the Supporting Information). A small amount of tetrahydropyridine **TH-2**[15] (<3% yield) was also produced, and remained constant during the course of the reaction.

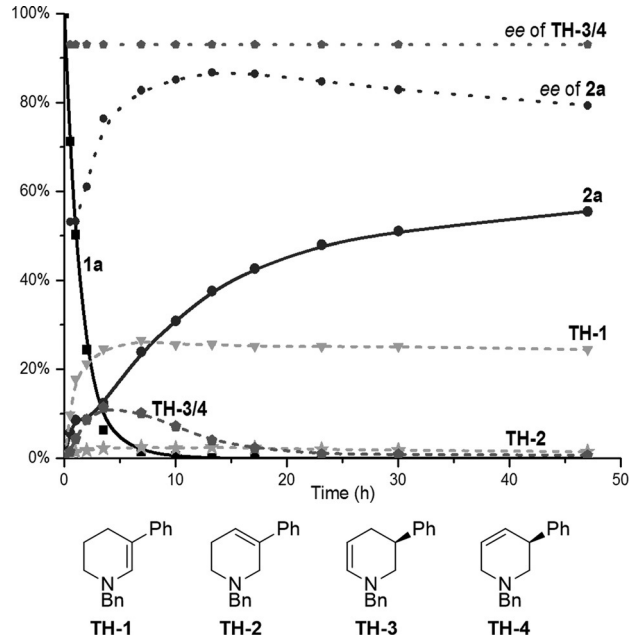
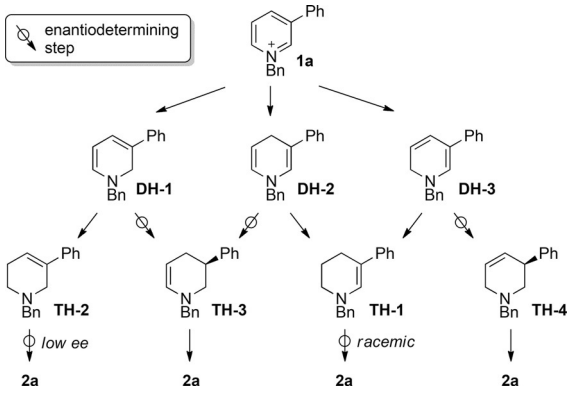


Figure 1. Evolution of the yield and *ee* of different reaction species over time. Reaction conditions: **1a** (1.53 mmol), $[Rh(cod)_2]OTf$ (2 mol%), JosiPhos J002-2 (2.2 mol%), Et_3N (5 equiv), THF/TFE (2:1, 27 mL), 50 °C, 50 bar H_2. Consumption of **1a** determined by NMR spectroscopy with dimethyl terephthalate as internal standard. Yield and *ee* of **2a** and the different tetrahydropyridines monitored by GC analysis with CP-Chirasil-Dex CB column with dodecane as internal standard.

A third compound, also identified by GC-MS (*m/z* 249) as an *N*-benzyl tetrahydropyridine, was formed in appreciable amounts at the beginning of the reaction and then was slowly consumed. Although it was not possible to isolate or synthesize it by alternative methods, this compound showed two peaks when injected in a chiral GC column, suggesting that it contains a stereocenter and therefore may be either tetrahydropyridine **TH-3** or **TH-4**. Remarkably, its *ee* was very high (93%) and remained constant during the entire course of the reaction. *N*-Benzylpiperidine **2a** was slowly formed with an enantiomeric excess that increased sharply during the first 10 h of the reaction and then slowly decreased over the next 10 h. Furthermore, the monitoring the reaction by NMR spectroscopy revealed that one equivalent of triethylammonium bromide formed at the same rate as that of the pyridinium salt consumption (see the Supporting Information). This finding confirms the role of the added base as a scavenger of HBr.

The tetrahydropyridines **TH-1** and **TH-2** were submitted to hydrogenation under optimized conditions. After 20 h of reaction, only 7% of **TH-1** was hydrogenated to give the racemic piperidine product. Similarly, the hydrogenation of **TH-2** occurred with 7% conversion to **2a** (with 15% *ee*) and 13% isomerization to **TH-1**.[16] These results strongly indicate that **TH-1** and **TH-2** are not involved in the enantioselective formation of **2a**. Since they are the only prochiral tetrahydropyridines, the enantioselective step must occur through the hydrogenation of a dihydropyridine leading to an unidentified tetrahydropyridine derivative (**TH-3** or **TH-4**), the *ee* of which was measured and found to be high (Figure 1).

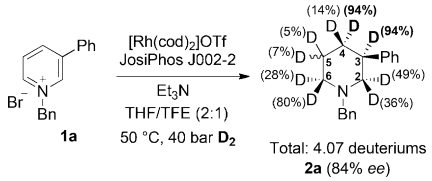
The possible pathways for the hydrogenation of the pyridinium salt **1a** are shown in Scheme 3. The first hydride addition can occur at the 2-, the 4- or the 6-position leading to three different dihydropyridines (**DH-1**, **DH-2** and **DH-3**, respectively) that are not observed experimentally due to their instability or high reactivity. Their enantioselective reduction into **TH-3** or **TH-4** involves either the reduction of the conjugated enamine double bond (**DH-3**→**TH-4** or **DH-2**→**TH-3**) or the reduction of the C3-C4 double bond (**DH-1**→**TH-3**).



Scheme 3. Possible pathways and intermediates for the AH of **1a** to **2a**.

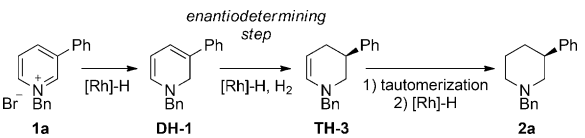
To identify the main pathway, an isotopic labeling experiment was carried out by conducting the AH of **1a** with D_2 instead of H_2 (Scheme 4). As expected from all the possible intermediates involved in this reaction, the deuteration pattern of **2a** was complex but provided some useful information. One of the most important observations is the *syn* incorporation of two deuterium atoms in C3 and C4. According to the postulated pathways (Scheme 3), this can be due to the hydrogenation of either **TH-2**→**2a**, or **DH-1**→**TH-3**. Since the hydrogenation of isolated **TH-2** was shown to occur with very poor stereocontrol (see above), it is reasonable to assume that the conversion **DH-1**→**TH-3** is the one leading to high enantiomeric excess (93% *ee*) and to assign the unidentified tetrahydropyridine as **TH-3**. A second observation is that the total amount of deuterium incorporated accounts for four deuterium atoms. Therefore, one proton from the solvent is incorporated, probably in

the least deuterated carbon C5 through an enamine–iminium tautomerization of **TH-3**. Finally, it should be noted that, while the deuterium incorporation at the two diastereotopic positions of C2 is quite similar (36 vs. 49%), the extent of deuteration of the pro-*S* hydrogen at C6 is remarkably higher than that of the pro-*R* hydrogen (80 vs. 28%). A possible interpretation of this finding is that the hydride attack at C2 occurs before the formation of the stereocenter at C3 (and thus is only influenced by the chiral catalyst), whereas the hydride attack at C6 occurs after the stereocenter formation, so that a remarkable substrate control also operates.[17] The analysis of the deuterium distribution in the isolated intermediates **TH-1** and **TH-2** (see the Supporting information) suggests that these compounds are formed by hydrogenation of **DH-3** and **DH-1**, respectively (Scheme 3).



Scheme 4. Isotopic labeling experiment for the AH of *N*-benzyl-3-phenylpyridinium bromide **1a**.

On the basis of these experimental data, a pathway for the highly enantioselective formation of piperidine **2a** can be proposed (Scheme 5). Initially, a 1,2-hydride addition at the C2 position takes place. The formed dihydropyridine **DH-1** is then enantioselectively hydrogenated to **TH-3** by reduction of the C3=C4 double bond. Finally, **TH-3** slowly tautomerizes to the iminium form and a final 1,2-hydride addition at the C6 position affords the enantioenriched piperidine **2a**. At the same time, at least one other pathway operates, involving the prochiral enamine **TH-1** (which is observed as a side-product) as a key intermediate. As the hydrogenation of **TH-1** occurs with no enantioselectivity, the reaction path(s) involving this intermediate lead to erosion of the final observed *ee*. A plausible role of the added base is to scavenge HBr generated by the first hydride addition, thus slowing down the tautomerization of **TH-1** to the corresponding iminium form and its non-enantioselective hydrogenation to **2a**. The other enamine **TH-3** is more readily hydrogenated than **TH-1** because it is more prone to tautomerization due to the absence of an adjacent aromatic group leading to stabilization through conjugation. Overall, the high enantiomeric excess of **2a** is in part due to the inhibition of the hydrogenation of **TH-1**.[18]



Scheme 5. Proposed mechanism for the AH of *N*-benzyl-3-phenylpyridinium bromide **1a** to the piperidine **2a**.

In conclusion, we have successfully developed the first highly enantioselective hydrogenation of 3-substituted pyridines using a Rh-JosiPhos system. The use of a simple base, like Et_3N, remarkably improved the yields and *ee* values obtained in the AH of such substrates. Furthermore, our mechanistic studies shed some light on the complex reaction network involved in the AH of pyridines. All experimental data point towards an enantioselective step taking place during the hydrogenation of one of the dihydropyridine intermediates. The beneficial role of the base was also identified as preventing the erosion of *ee* of the piperidine by retarding the non-enantioselective hydrogenation of one of the prochiral enamines. We hope that our results will contribute to the rational design of more efficient catalysts towards an efficient production of 3-substituted chiral piperidines.

Experimental Section

Inside a glovebox, $[Rh(cod)_2]OTf$ (0.23 mg, 2 mol%) and JosiPhos J002-2 (0.30 mg, 2.2 mol%) were stirred for 1 h at 40 °C in 0.5 mL of THF. The catalyst solution was then transferred into a vial containing a mixture of **1** (0.025 mmol), Et_3N (17.4 μL, 0.125 mmol) and dodecane (10 mg) in 0.5 mL of THF and 0.5 mL of TFE. The vial was capped and placed into a Premex A96 hydrogenation reactor. After being flushed five times with N_2 and five times with H_2, the vial was pressurized to 50 bar of H_2 and stirred at 50 °C for 16 h. The yield and *ee* of the reaction were determined by GC or HPLC using dodecane as internal standard. Alternatively, the reaction crude could be concentrated and purified by flash column chromatography with hexane/AcOEt.

Acknowledgements

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Keywords: asymmetric catalysis · homogeneous catalysis · hydrogenation · pyridines · reaction mechanisms

[1] a) *The Handbook of Homogeneous Hydrogenation* (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, **2007**; b) D. J. Ager, A. H. M. de Vries, J. G. de Vries, *Chem. Soc. Rev.* **2012**, *41*, 3340 – 3380.

[2] For reviews on the asymmetric hydrogenation N-heteroaromatic compounds see: a) D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557 – 2590; b) Y.-G. Zhou, *Acc. Chem. Res.* **2007**, *40*, 1357 – 1366; c) F. Glorius, *Org. Biomol. Chem.* **2005**, *3*, 4171 – 4175; d) Y.-M. He, F.-T. Song, Q.-H. Fan, *Stereoselective Formation of Amines* (Eds.: W. Li, X. Zhang), Springer, Heidelberg, **2014**, pp. 145 – 190.

[3] a) C. Y. Legault, A. B. Charette, *J. Am. Chem. Soc.* **2005**, *127*, 8966 – 8967; b) X.-B. Wang, W. Zeng, Y.-G. Zhou, *Tetrahedron Lett.* **2008**, *49*, 4922 – 4924; c) A. Cadu, P. K. Upadhyay, P. G. Andersson, *Asian J. Org. Chem.* **2013**, *2*, 1061 – 1065; d) 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; 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.

[4] a) Y. Kita, A. Iimuro, S. Hida, K. Mashima, *Chem. Lett.* **2014**, *43*, 284 – 286; b) M.-W. Chen, Z.-S. Ye, Z.-P. Chen, B. Wu, Y.-G. Zhou, *Org. Chem. Front.* **2015**, *2*, 586 – 589.

[5] For a review on different substrate activation methods for the catalytic asymmetric hydrogenation of N-heteroarenes, see: B. Balakrishna, J. L. Núñez-Rico, A. Vidal-Ferran, *Eur. J. Org. Chem.* **2015**, 5293 – 5303.

[6] a) H.-U. Blaser, H. Hönig, M. Studer, C. Wedemeyer-Exl, *J. Mol. Catal. A* **1999**, *139*, 253 – 257; b) M. Studer, C. Wedemeyer-Exl, F. Spindler, H.-U. Blaser, *Monatsh. Chem.* **2000**, *131*, 1335 – 1343; c) S. A. Raynor, J. M. Thomas, R. Raja, B. F. Johnson, R. G. Bell, M. D. Mantle, *Chem. Commun.* **2000**, 1925 – 1926; d) L. Hegedűs, V. Háda, A. Tungler, T. Máthé, L. Szepesy, *Appl. Catal. A* **2000**, *201*, 107 – 114; e) A. Lei, M. Chen, M. He, X. Zhang, *Eur. J. Org. Chem.* **2006**, 4343 – 4347.

[7] Mechanistic investigations on the metal-catalyzed homogeneous asymmetric hydrogenation of quinolines and isoquinolines: a) 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; b) M. Rueping, T. Theissmann, *Chem. Sci.* **2010**, *1*, 473 – 476; c) 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; 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 – 9891; e) G. Erős, K. Nagy, H. Mehdi, I. Pápai, P. Nagy, P. Király, G. Tárkányi, T. Soós, *Chem. Eur. J.* **2012**, *18*, 574 – 585; f) X.-F. Cai, R.-N. Guo, M.-W. Chen, L. Shi, Y.-G. Zhou, *Chem. Eur. J.* **2014**, *20*, 7245 – 7248; g) 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; h) 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; i) 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; j) Y. Kita, K. Yamaji, K. Higashida, K. Sathaiah, A. Iimuro, K. Mashima, *Chem. Eur. J.* **2015**, *21*, 1915 – 1927.

[8] For a mechanistic study on the non-enantioselective transfer hydrogenation of pyridines see: J. Wu, W. Tang, A. Pettman, J. Xiao, *Adv. Synth. Catal.* **2013**, *355*, 35 – 40.

[9] As pointed out by one of the reviewer, high enantioselectivities can be obtained with 2,3-disubstituted N-heterocycles even if a non-enantioselective enamine-imine tautomerization takes place. This involves a dynamic kinetic resolution process. See for example: a) Y. Duan, L. Li, M.-W. Chen, C.-B. Yu, H.-J. Fan, Y.-G. Zhou, *J. Am. Chem. Soc.* **2014**, *136*, 7688 – 7700; b) 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; and ref. [7g].

[10] a) Y. Liu, K. Ding, *J. Am. Chem. Soc.* **2005**, *127*, 10488 – 10489; b) A. Ohashi, S. Kikuchi, M. Yasutake, T. Imamoto, *Eur. J. Org. Chem.* **2002**, 2535 – 2546; c) S. Enthaler, G. Erre, K. Junge, J. Holz, A. Börner, E. Alberico, I. Nieddu, S. Gladiali, M. Beller, *Org. Process Res. Dev.* **2007**, *11*, 568 – 577; d) H. Bernsmann, M. van den Berg, R. Hoen, A. J. Minnaard, G. Mehler, M. T. Reetz, J. G. de Vries, B. L. Feringa, *J. Org. Chem.* **2005**, *70*, 943 – 951; e) D. Peña, A. J. Minnaard, J. G. de Vries, B. L. Feringa, *J. Am. Chem. Soc.* **2002**, *124*, 14552 – 14553; f) V. I. Tararov, R. Kadyrov, T. H. Riermeier, J. Holz, A. Börner, *Tetrahedron Lett.* **2000**, *41*, 2351 – 2355; g) Y. J. Zhang, J. H. Park, S. Lee, *Tetrahedron: Asymmetry* **2004**, *15*, 2209 – 2212; h) L. A. Oro, D. Carmona, *The Handbook of Homogeneous Hydrogenation, Part I* (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, **2007**, pp. 3 – 30.

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

[12] R. Kuwano, Y. Hashiguchi, R. Ikeda, K. Ishizuka, *Angew. Chem. Int. Ed.* **2015**, *54*, 2393 – 2396; *Angew. Chem.* **2015**, *127*, 2423 – 2426.

[13] S. G. Ruggeri, J. M. Hawkins, T. M. Makowskim, J. L. Rutherford, F. J. Urban (Pfizer Prod Inc. Groton, CT (US)), WO 2007/012953A2, **2007**.

[14] The observed products do not account for the complete disappearance of the starting material due to the partial decomposition of the unstable enamine intermediates during sampling and subsequent analysis (see the Supporting information where we report the relatively fast decomposition of the enamines even after isolation).

[15] A reference sample of this compound was separately synthesized and characterized.

[16] Rh-diphosphine complexes are known to catalyze allylamine-enamine isomerizations: S. Otsuka, K. Tani, T. Yamagata, S. Akutagawa, H. Kumobayashi, M. Yagi (Takasago Perfumery Co., Ltd., Tokyo (Japan)), EP 0068506A1, **1983**.

[17] The preferential deuteration of the pro-S hydrogen can be explained by the Fürst-Plattner effect (A. Fürst, P. A. Plattner, *Helv. Chim. Acta* **1949**, *32*, 275 – 283), where the hydride attack on the iminium intermediate arising from the tautomerization of **TH-3** takes places from the side of the phenyl substituent (see the Supporting Information for further details).

[18] The low *ee* for **2a** at the beginning of the reaction is consistent with the initial fast formation of **TH-1** whose non-enantioselective conversion into **2a** can compete at this stage with the enantioselective pathways due to the large excess of **TH-1** relative to **TH-3**. As the reaction proceeds, the concentration of **TH-3** increases and the enantioselective pathway overrules the pathway via **TH-1** leading to the observed increase of *ee*. A similar profile for the *ee* is obtained from a kinetic model based on our proposed reaction mechanism (see the Supporting Information).

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