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Asymmetric Hydrogenation of Pyridines: Enantioselective Synthesis of Nipecotic Acid Derivatives

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An asymmetric hydrogenation process of 3-substituted pyridine derivatives has been developed with the use of a Rh-TangPhos complex as the catalyst. The whole process consists of an efficient partial hydrogenation of nicotinate and a subsequent highly enantioselective, Rh-catalyzed, homogeneous hydrogenation. A series of chiral nipecotic acid derivatives have been synthesized.

An increase in the demand for the production of enantiomerically pure pharmaceuticals, agrochemicals, flavors, and other fine chemicals has advanced the field of asymmetric catalytic technologies.[1] As one of the most efficient methods for the preparation of chiral compounds, asymmetric hydrogenation has been intensively studied. Tremendous success has been achieved in the reductions of the C=C, C=O, and C=N functionalities.[2–4] However, asymmetric hydrogenation of an aromatic ring, one of the most readily available unsaturated compounds, has received little attention and is generally regarded as the greatest challenge in the asymmetric hydrogenation field.[5–8] Some positive results have been reported recently concerning the asymmetric hydrogenation of polycyclic heteroaromatic compounds,[9,10] such as 2-substituted quinolines[11–13] and indoles.[14–18] Some promising results have been reported in the preparation of optically active 2-piperazine derivatives by the reduction of tetrahydropyrazines derived from pyrazines.[19–21] However, the asymmetric reduction of monocyclic pyridine derivatives has yet to have success. A homogeneous Rh-catalyst system has been used in the asymmetric hydrogenation of monosubstituted pyridines and furans, but only 24–27% *ee* values were obtained.[22,23] Very recently, Glorius et al. reported an example of an efficient asymmetric hydrogenation of pyridine through the introduction of a chiral auxiliary,[24] and Charette et al. communicated their results regarding the asymmetric hydrogenation of *N*-iminopyridinium ylides.[25]

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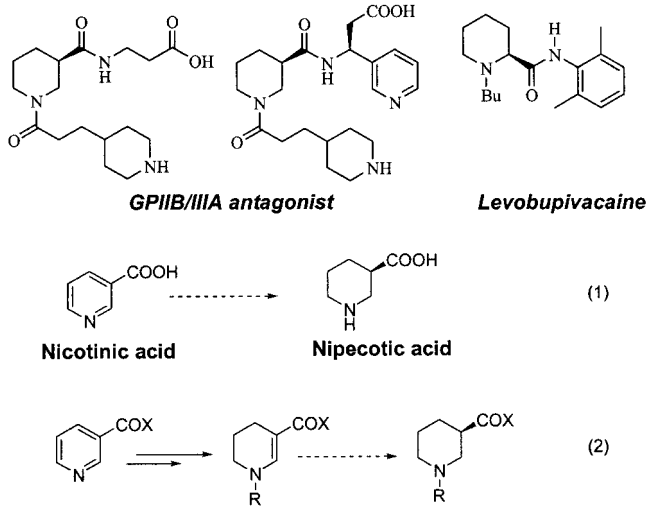
As readily available heteroaromatic compounds, pyridine and its derivatives are very attractive materials for the synthesis of *N*-containing building blocks in pharmaceuticals and in agrochemicals (Scheme 1). The development of an efficient method for the production of enantiomerically pure piperidine derivatives can be of significant value. For example, enantiomerically pure nipecotic acid ($ 113.70/g, Aldrich) is 2000 times more expensive than its pyridine analog, nicotinic acid. Although the direct asymmetric hydrogenation of nicotinic acid to form enantiomerically enriched nipecotic acid [Scheme 1, Equation (1)] would have practical industrial applications, no such process has been successfully developed so far. Herein we report our preliminary results on the asymmetric hydrogenation of substituted pyridines. We describe a two-step method as an alternative solution for the preparation of nipecotic acid derivatives. First, partial hydrogenation of nicotinate provides the tetrahydro-intermediates under heterogeneous catalytic conditions; second, the homogeneous chiral catalysts are used to reduce the remaining double bond in high enantioselectivity [Scheme 1, Equation (2)]. In fact, a similar approach has been reported, and chiral modifiers were involved in the heterogeneous catalytic system. However, the enantioselectivities (<24% *ee*) were low.[26,27]

Partial hydrogenation of ethyl nicotinate under heterogeneous catalytic conditions was previously reported.[28–30] We carried out the reaction on different scales with EtOH as the solvent, and 10% Pd/C as the catalyst. The H_2 pressure, which ranged from 30–300 psi, did not seem to be critical for this transformation. The reaction can be easily scaled-up to a practical industrial process while the work-up procedure is also very convenient. The possible impurities of the reaction are the unreacted starting materials and over-reduced ethyl nipecotinate, which can be simply removed by the passage of the product through a short acidic silica gel column. The partial hydrogenation product is vinylogous amide **2**, which is stabilized by the conjugation of

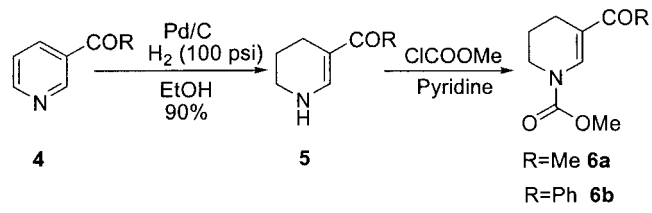


Scheme 1.

the lone pair of electrons on the nitrogen atom with the C=C bond and the carbonyl group. This conjugation may be the reason why hydrogenation can be stopped at this stage under the above conditions.

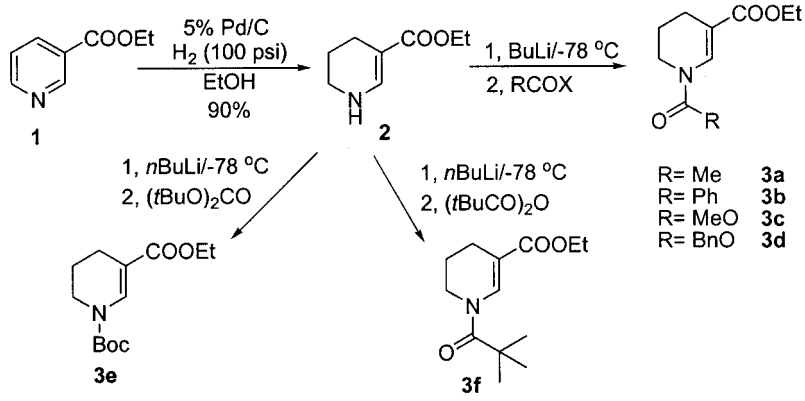
Acylation of intermediate **2** to generate compounds with various protecting groups on nitrogen was performed (Scheme 2). Vinylogous amide **2** was deprotonated with *n*BuLi (1.6 M in hexane) at –78 °C, and then quenched by the addition of electrophilic reagents, such as acyl chloride or -anhydride. Acetic, benzoic and trimethylacetic amides **3a**, **3b**, and **3f** were obtained in high yields. The same synthetic method can also be applied to prepare methoxy carbamate **3c**, benzyloxy carbamate (Cbz) **3d**, and *tert*-butyloxy carbamate (Boc) **3e**.

The partial hydrogenation strategy could also be applied to 3-acetylpyridine and 3-benzoylpyridine. Unsaturated ketones **6a** and **6b** were obtained in high yields from the corresponding vinylogous amides **5**; this reaction was carried out in pyridine at 100 °C (Scheme 3).



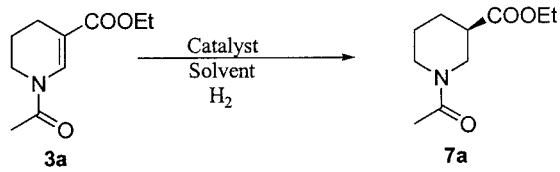
Scheme 3. Synthesis of *N*-acetyl vinylogous amides **6**.

The search for catalysts and reaction conditions are important tasks in asymmetric hydrogenation. Our lab has recently discovered some efficient hydrogenation catalysts, Ru-TunePhos, Rh-Binapine, and Rh-TangPhos, for the reduction of olefins and ketones.[31–36] As a result, these catalytic systems were used for the hydrogenation of substrates **2**, **3**, **5**, and **6**. Although low reactivities were generally found for the hydrogenation of **2** and **5**, the hydrogenation of substrate **3a** proceeded smoothly with some chiral Rh catalysts. Rh complexes with electron-donating ligands showed promise in the resolution of this problem. The Rh-binapine system provided hydrogenation product **7a** in 55.5% *ee*, albeit in low conversion (Table 1, Entry 3). When the Rh-TangPhos catalyst was used, much better results were observed. For example, when the hydrogenation was performed in THF under 30 psi of hydrogen pressure for twenty-four hours, the hydrogenation product was obtained in 88.5% *ee* and in 74% conversion (Table 1, Entry 4). Further results showed that the enantioselectivity was very sensitive to the solvent. When methanol and toluene were chosen as the solvent, no conversion was observed (Table 1, Entries 5 and 8). Methylene chloride and THF were found to be appropriate solvents for the hydrogenation reaction. The enantioselectivity slightly decreased when ethyl acetate and ethanol were used as solvents. In addition, the *ee* value seemed to be insensitive to the hydrogen pressure and the temperature. When the reaction was carried out with a hydrogen pressure of 1500 psi, 84.7% *ee* and 100% conversion were realized. Chiral Ru catalysts with BINAP or (*R*)-C_4-TunePhos ligands were also employed in this hydrogenation



Scheme 2. Syntheses of *N*-acyl and *N*-arbamate vinylogous amides **3a–f**.

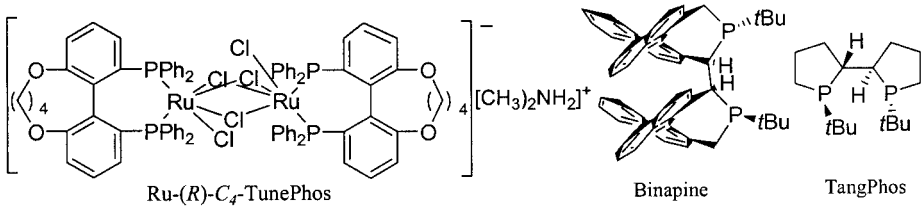
Table 1. Optimized reaction conditions for the asymmetric hydrogenation of *N*-acetyl vinylogous amide **3a**.



3a **7a**

entry	catalyst	solv.	temp	H_2(psi)	*ee* (%)[a]	conv. (%)
1	[Ru-(*R*)-C_4-Tunephos]	THF	25	30	NA	0
2	[Ru-(*R*)-C_4-Tunephos]	EtOH	80	1500	50	1.2
3	[Rh(NBD)(Binapine)]SbF_6	THF	25	30	55.5	2.5
4	[Rh(NBD)(Tangphos)]SbF_6	THF	25	30	88.5	74
5	[Rh(NBD)(Tangphos)]SbF_6	MeOH	25	1500	NA	0
6	[Rh(NBD)(Tangphos)]SbF_6	EtOH	80	1500	70	54
7	[Rh(NBD)(Tangphos)]SbF_6	EtOAc	25	1500	77.7	100
8	[Rh(NBD)(Tangphos)]SbF_6	Toluene	25	1500	NA	0
9	[Rh(NBD)(Tangphos)]SbF_6	CH_2Cl_2	25	1500	85.7	100
10	[Rh(NBD)(Tangphos)]SbF_6	THF	25	1500	84.7	100

[a] The *R* configuration was assigned by comparing with (*S*)-nipecotic acid ethyl ester. Enantiomeric excesses (*ee*) were determined by chiral HPLC. See Experimental Section for details.

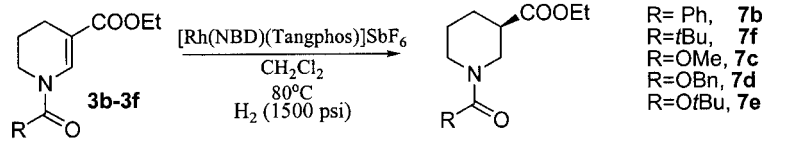


reaction and low reactivities were observed under various conditions (Table 1, Entries 1 and 2).

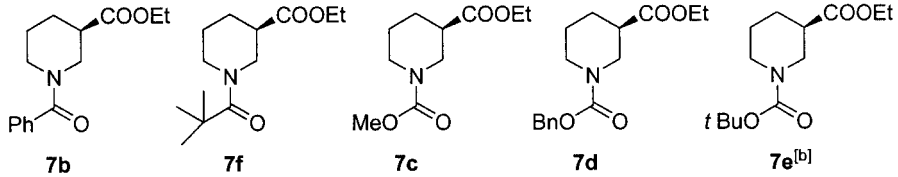
Substrates with different *N*-protecting groups were also subjected to the hydrogenation reaction and different enantioselectivities were observed as shown in Table 2. When carbamates were employed as the protecting groups, enantioselectivities were high, especially with the Boc protecting group. When the acetoxy protecting group was introduced, the increased steric hindrance of the alkyl groups led to decreased *ee* values.

Substrates **6** were also subjected to hydrogenation with the Rh-TangPhos catalyst. Excellent chemoselectivities and good enantioselectivities were observed. The carbon–carbon double bond (100% chemoselectivity) was selectively

Table 2. Asymmetric hydrogenation of *N*-acyl vinylogous amides **3b**–**3f**.[a]



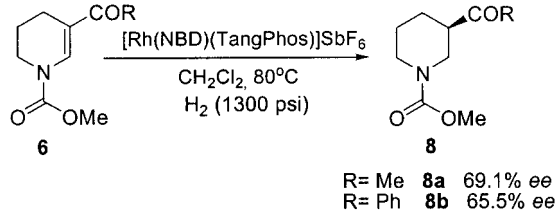
3b-3f



7b	**7f**	**7c**	**7d**	**7e**[b]
65.5 % *ee*	47.7 % *ee*	91% *ee*	90 % *ee*	> 99 % *ee*

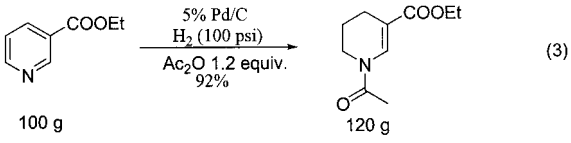
[a] The (*R*) configuration was assigned by comparison with (*S*)-nipecotic acid ethyl ester. Enantiomeric excesses (*ee*) were determined by chiral HPLC. See Experimental Section for details. [b] The conversion of **3e** to **7e** is 29% and determined by NMR spectroscopy.

reduced while the carbonyl group remained intact. Hydrogenation products **8a** and **8b** were obtained in 69.1% *ee* and 65.5% *ee*, respectively (Scheme 4). The obtained hydrogenated products are functionalized piperidines, which are important building blocks for organic synthesis.



Scheme 4. Asymmetric hydrogenation of *N*-methoxyl carbamate vinylogous amides **6**.

Partial hydrogenation of ethyl nicotinate in the presence of 1.2 equiv. of Ac_2O with THF as the solvent was investigated, and we are pleased to find that the reaction produced **3a** in high yield and excellent selectivity. Further experimentation revealed that this reaction could be carried out without the use of any solvent in a 100 g-scale of the nicotinate ester [Equation (3)]. The product after filtration (removal of the Pd/C catalyst) and washing (removal of AcOH and Ac_2O) could be directly employed in the asymmetric hydrogenation step.



Attempts at the partial hydrogenation of 2-substituted pyridines with Pd/C catalysts were not successful. Under similar reaction conditions used for the hydrogenation of nicotinate, the reactivity of the 2-substituted pyridines was found to be much lower, and the only hydrogenated product obtained was a fully reduced, racemic 2-substituted piperidine. Partial hydrogenation of 2,3-disubstituted pyridine was successful, and afforded a tetrasubstituted olefin compound. However, asymmetric hydrogenation of the resulting vinylogous amide was difficult and no reactivity was observed under the various hydrogenation conditions described.

In conclusion, we have developed an efficient method for the preparation of chiral nipecotic acid derivatives by a hydrogenation reaction. The process, which combines the efficient partial hydrogenation of nicotinate with a highly enantioselective, homogeneous hydrogenation, constitutes an effective example of a highly enantioselective hydrogenation of substituted pyridines. Further investigation of the substrate scope and the development of more efficient catalysts are underway and progress will be reported in due course.

Experimental Section

General Procedure for the Asymmetric Hydrogenation of Pyridine Derivatives: To a solution of the vinylogous amide substrate (0.2 mmol) in dichloromethane (3.0 mL) in a glove box was added [Rh{(*S*,*S*,*R*,*R*)-TangPhos}NBD][SbF_6] (0.004 mmol). The hydrogenation was performed at 80 °C under 1500 psi of hydrogen pressure for 72 h. After the hydrogen was released, the reaction mixture was passed through a short silica gel column to remove the catalyst. The (*R*) configuration was assigned by comparison with (*S*)-nipecotic acid ethyl ester. Enantiomeric excesses were determined by HPLC with Chiralcel AD and OJ-H columns (1 mL/min, hexane/*i*PrOH = 95:5).

Supporting Information (see footnote on the first page of this article): General procedures for the preparation of *N*-carbamate and *N*-acyl vinylogous amides as well as their asymmetric hydrogenation reactions. Characterization information of represented compounds.

Acknowledgments

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[1] H. U. Blaser, F. Spindler, M. Studer, *Appl. Catal. A* **2001**, *221*, 119–143.
[2] W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029–3070.
[3] R. Noyori, *Angew. Chem. Int. Ed.* **2002**, *41*, 2008–2022.
[4] W. S. Knowles, *Angew. Chem. Int. Ed.* **2002**, *41*, 1998–2007.
[5] C. Exl, E. Ferstl, H. Hoenig, R. Rogi-Kohlenprath, *Chirality* **1995**, *7*, 211–218.
[6] K. Nasar, F. Fache, M. Lemaire, J. C. Beziat, M. Besson, P. Gallezot, *J. Mol. Catal.* **1994**, *87*, 107–115.
[7] R. M. Laine, G. Hum, B. J. Wood, M. Dawson, *Stud. Surf. Sci. Catal.* **1981**, *7*, 1478–1479.
[8] S. Murata, T. Sugimoto, S. Matsuura, *Heterocycles* **1987**, *26*, 763–766.
[9] S.-M. Lu, X.-W. Han, Y.-G. Zhou, *Youji Huaxue* **2005**, *25*, 634–640.
[10] M. Petersen, M. Sauter, *Chimia* **1999**, *53*, 608–612.
[11] S.-M. Lu, Y.-Q. Wang, X.-W. Han, Y.-G. Zhou, *Angew. Chem. Int. Ed.* **2006**, *45*, 2260–2263.
[12] S.-M. Lu, X.-W. Han, Y.-G. Zhou, *Adv. Synth. Catal.* **2004**, *346*, 909–912.
[13] L. Xu, K. H. Lam, J. Ji, J. Wu, Q.-H. Fan, W.-H. Lo, A. S. C. Chan, *Chem. Commun.* **2005**, 1390–1392.
[14] W.-B. Wang, S.-M. Lu, P.-Y. Yang, X.-W. Han, Y.-G. Zhou, *J. Am. Chem. Soc.* **2003**, *125*, 10536–10537.
[15] R. Kuwano, K. Sato, T. Kurokawa, D. Karube, Y. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 7614–7615.
[16] C. Bianchini, P. Barbaro, G. Scapacci, E. Farnetti, M. Graziani, *Organometallics* **1998**, *17*, 3308–3310.
[17] H. Brunner, S. Rosenboem, *Monatsh. Chem.* **2000**, *131*, 1371–1382.
[18] R. Kuwano, K. Kaneda, T. Ito, K. Sato, T. Kurokawa, Y. Ito, *Org. Lett.* **2004**, *6*, 2213–2215.
[19] R. N. Landau, U. Singh, F. Gortsema, Y. Sun, S. C. Gomolka, T. Lam, M. Futran, D. G. Blackmond, *J. Catal.* **1995**, *157*, 201–208.
[20] R. Fuchs, J.-P. Roduit, **1996**, Eur. Pat. Appl. EP 744401.
[21] K. Rossen, S. A. Weissman, J. Sager, R. A. Reamer, D. Askin, R. P. Volante, P. J. Reider, *Tetrahedron Lett.* **1995**, *36*, 6419–6422.
[22] H. Steiner, P. Giannousis, A. Pische-Jacques, H. U. Blaser, *Top. Catal.* **2000**, *13*, 191–194.

[23] M. Studer, C. Wedemeyer-Exl, F. Spindler, H.-U. Blaser, *Monatsh. Chem.* **2000**, *131*, 1335–1343.
[24] F. Glorius, N. Spielkamp, S. Holle, R. Goddard, C. W. Lehmann, *Angew. Chem. Int. Ed.* **2004**, *43*, 2850–2852.
[25] C. Y. Legault, A. B. Charette, *J. Am. Chem. Soc.* **2005**, *127*, 8966–8967.
[26] S. A. Raynor, J. M. Thomas, R. Raja, B. F. G. Johnson, R. G. Bell, M. D. Mantle, *Chem. Commun.* **2000**, 1925–1926.
[27] H. U. Blaser, H. Honig, M. Studer, C. Wedemeyer-Exl, *J. Mol. Catal. A* **1999**, *139*, 253–257.
[28] E. Wenkert, K. G. Dave, F. Haglid, *J. Am. Chem. Soc.* **1965**, *87*, 5461–5467.
[29] P. M. Quan, L. D. Quin, *J. Org. Chem.* **1966**, *31*, 2487–2490.
[30] E. Wenkert, K. G. Dave, F. Haglid, R. G. Lewis, T. Oishi, R. V. Stevens, M. Terashima, *J. Org. Chem.* **1968**, *33*, 747–753.
[31] A. Lei, S. Wu, M. He, X. Zhang, *J. Am. Chem. Soc.* **2004**, *126*, 1626–1627.
[32] W. Tang, D. Liu, X. Zhang, *Org. Lett.* **2003**, *5*, 205–207.
[33] W. Tang, S. Wu, X. Zhang, *J. Am. Chem. Soc.* **2003**, *125*, 9570–9571.
[34] W. Tang, W. Wang, Y. Chi, X. Zhang, *Angew. Chem. Int. Ed.* **2003**, *42*, 3509–3511.
[35] W. Tang, X. Zhang, *Angew. Chem. Int. Ed.* **2002**, *41*, 1612–1614.
[36] W. Tang, X. Zhang, *Org. Lett.* **2002**, *4*, 4159–4161.

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