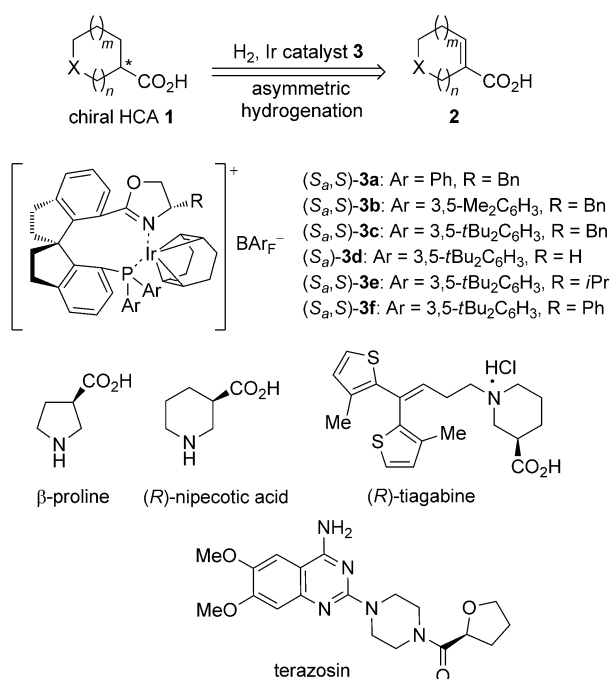


Iridium-Catalyzed Enantioselective Hydrogenation of Unsaturated Heterocyclic Acids**

Song Song, Shou-Fei Zhu, Liu-Yang Pu, and Qi-Lin Zhou*

Chiral heterocycles are ubiquitous structures in natural products and bioactive compounds.^[1] Chiral heterocyclic acid (HCA) moieties (**1**) are of special importance because they are present in various pharmaceuticals (Scheme 1).^[2] For example, the N-heterocyclic carboxylic acid (*R*)-tiagabine is an γ -aminobutyric acid reuptake inhibitor marketed for the treatment of epilepsy.^[2a] Two typical heterocyclic acids, β -proline and (*R*)-nipecotic acid, are key structural elements in synthetic peptides.^[2b-c] O-Heterocyclic carboxylic acids are key intermediates in the synthesis of many chiral drugs, such as terazosin^[2d] and nebiivolol.^[2e]



Scheme 1. Asymmetric hydrogenation of unsaturated heterocyclic acids using chiral iridium catalysts. BAR_F^- = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

The transition-metal-catalyzed enantioselective hydrogenation of unsaturated heterocyclic carboxylic acids is a direct approach to chiral heterocyclic acids. Although progress on the asymmetric hydrogenation of acyclic unsaturated carboxylic acids has been remarkable,^[3] satisfactory methods for the asymmetric hydrogenation of cyclic unsaturated carboxylic acids are lacking. Hydrogenation of unsaturated N-heterocyclic carboxylic acids over heterogeneous palladium catalysts modified with cinchona alkaloids gives *ee* values of up to 60%,^[4] and hydrogenation of unsaturated O-heterocycle-3-carboxylic acids (**2**: X = O, *n* = 1) with homogeneous ruthenium catalysts bearing chiral phosphorus ligands^[5] and heterogeneous palladium catalysts modified with cinchona alkaloids have been reported to give moderate to good enantioselectivities.^[6] However, asymmetric hydrogenation of unsaturated O-heterocycle-2-carboxylic acids (**2**, *n* = 0) has never been achieved. The development of efficient chiral catalysts for the enantioselective hydrogenation of various unsaturated heterocyclic acids is highly desirable.^[7] Herein, we report the highly enantioselective hydrogenation of unsaturated N-heterocyclic acids and O-heterocyclic acids catalyzed by chiral spirophosphine oxazoline iridium complexes (**3**). This reaction provided an efficient method for the preparation of optically active HCAs with up to 99% *ee* (Scheme 1).

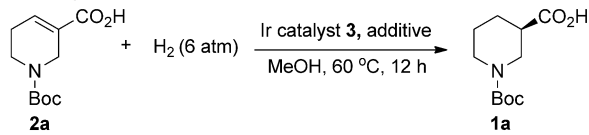
We chose *N*-Boc-1,2,5,6-tetrahydropyridine-3-carboxylic acid (**2a**) as a substrate to evaluate the activity of the catalysts **3**. The hydrogenation reactions were performed in the presence of 1 mol % of **3** under 6 atm of H₂ at 60 °C with 0.5 equivalents of Cs₂CO₃ as an additive.^[8] The catalyst (*S_aS_s*)-**3a**, which has phenyl groups on the phosphorus atom and a benzyl group on the oxazoline ring, afforded **1a** in 100% conversion with 65% *ee* (Table 1, entry 1). The substituents on the P-phenyl rings of the ligand strongly affected the enantioselectivity of the reaction. The catalyst (*S_aS_s*)-**3c**, which bears bulky 3,5-di-*tert*-butylphenyl groups on the phosphorus atom, increased the enantioselectivity to 96% *ee* (entry 3). When (*S_aS_s*)-**3c**, a diastereoisomer of (*S_aS_s*)-**3c**, was used as the catalyst both the conversion and the enantioselectivity decreased (entry 4), thus indicating that the configurations of (*S_aS_s*)-**3c** are well matched for high enantioselectivity. We also studied the effect of the substituent on the oxazoline ring of the catalyst. The catalyst (*S_a*)-**3d**, which has an unsubstituted oxazoline ring, gave the highest enantioselectivity (entry 5), and the catalyst loading could be reduced to 0.5 mol % without diminishing the conversion or enantioselectivity (entry 8). The use of 0.5 equivalents of NEt₃, 0.5 equivalents of Na₂CO₃, or 0.1 equivalents of Cs₂CO₃ as an additive lowered both the conversion and the enantioselectivity (entries 9–11). In the absence of a basic additive,

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Table 1: Optimization of the reaction conditions.^[a]



Entry	Catalyst	Additive	Conv. [%] ^[b]	ee [%] ^[c]
1	(S _a ,S)- 3a	0.5 equiv Cs ₂ CO ₃	100	65
2	(S _a ,S)- 3b	0.5 equiv Cs ₂ CO ₃	100	82
3	(S _a ,S)- 3c	0.5 equiv Cs ₂ CO ₃	100	96
4	(S _a ,R)- 3c	0.5 equiv Cs ₂ CO ₃	64	91
5	(S _a)- 3d	0.5 equiv Cs ₂ CO ₃	100	97
6	(S _a ,S)- 3e	0.5 equiv Cs ₂ CO ₃	100	93
7	(S _a ,S)- 3f	0.5 equiv Cs ₂ CO ₃	100	91
8 ^[d]	(S _a)- 3d	0.5 equiv Cs ₂ CO ₃	100	97
9 ^[d]	(S _a)- 3d	0.5 equiv NEt ₃	88	93
10 ^[d]	(S _a)- 3d	0.5 equiv Na ₂ CO ₃	100	93
11 ^[d]	(S _a)- 3d	0.1 equiv Cs ₂ CO ₃	77	90
12 ^[d]	(S _a)- 3d	none	< 5	–
13 ^[d,e]	(S _a)- 3d	0.5 equiv Cs ₂ CO ₃	51	55
14 ^[d,f]	(S _a)- 3d	0.5 equiv Cs ₂ CO ₃	78	96

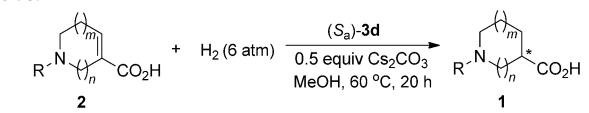
[a] Reaction conditions: 0.5 mmol **2a**, [substrate]=0.25 mol L⁻¹, 60 °C, substrate/catalyst=100:1, H₂ (6 atm). [b] Determined by ¹H NMR spectroscopy. [c] Determined by SFC analysis, using a chiral column, of the corresponding anilide. [d] Substrate/catalyst=200:1. [e] Under 50 atm H₂. [f] Under 1 atm H₂. Boc = *tert*-butoxycarbonyl.

the conversion was less than 5 %. Increasing the H₂ pressure to 50 atm substantially decreased both the conversion and the enantioselectivity (entry 13), and the reaction under 1 atm of H₂ pressure also gave low conversion (entry 14).

We then investigated the substrate scope of the reaction under the optimal reaction conditions by hydrogenating a variety of unsaturated N-heterocyclic acids. The hydrogenation of the five-membered-ring substrate **2b** catalyzed by (S_a)-**3d** (2 mol %), produced *N*-Boc β-proline (**1b**) in 94 % yield with 90 % ee (Table 2, entry 2). A seven-membered-ring unsaturated N-heterocyclic acid (**2c**) could be hydrogenated to the *N*-Boc-protected β-amino acid **1c** in 97 % yield with 95 % ee (entry 3). With (S_a)-**3d**, the substrate **2d** was hydrogenated to the cyclic γ-amino acid **1d** in 95 % yield with 97 % ee (entry 4). To our delight, the hydrogenation of **2e**, which has a tertiary amine group, proceeded smoothly without an additive when we used 1 mol % (S_a,S)-**3c**, thus producing the desired amino acid **1e** in 98 % yield with 99 % ee (entry 5).

Encouraged by the successful hydrogenation of unsaturated N-heterocyclic substrates, we investigated the use of the iridium catalysts **3** for the asymmetric hydrogenation of unsaturated O-heterocycle-2-carboxylic acids, a reaction that had not previously been achieved. With the catalyst (S_a,S)-**3c**, the hydrogenation of the unsaturated O-heterocycle-2-carboxylic acids **2f–k** proceeded smoothly in MeOH under 6 atm of H₂ at 60 °C, thus affording the corresponding saturated acids **1f–k** in high yields (96–99 %) and excellent enantioselectivities (Table 3, entries 1–6). The chiral acid **1k**, a key intermediate in the synthesis of nebulivolol,^[2e,7j] was easily prepared in 99 % yield with 93 % ee by the asymmetric hydrogenation of **2k** with 0.2 mol % of (S_a,S)-**3c**. The iridium complexes **3** were also suitable catalysts for the hydrogenation of the unsaturated O-heterocyclic acids **2l–o** to the

Table 2: Asymmetric hydrogenation of unsaturated N-heterocyclic acids.^[a]

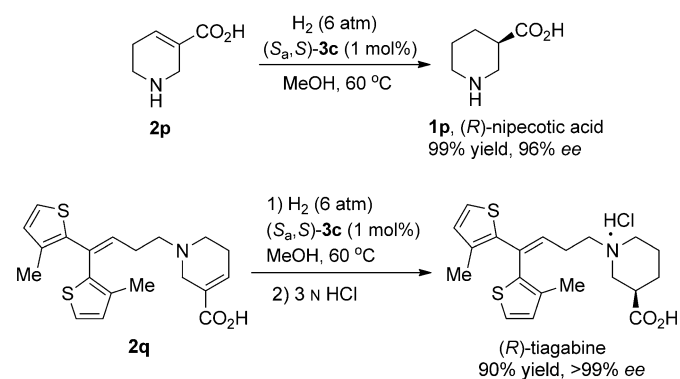


Entry	Substrate	S/C ^[b]	Product	Yield [%]	ee [%] ^[c]
1	2a	200	1a	94	97 (R)
2	2b	50	1b	94	90 (R)
3	2c	200	1c	97	95
4	2d	500	1d	95	97
5 ^[d]	2e	100	1e	98	99

[a] The reaction conditions were the same as those in Table 1, entry 8. Full conversions were obtained in all cases. [b] Substrate to catalyst ratio. [c] Determined by HPLC or SFC analysis, using chiral columns, of the corresponding anilide (see the Supporting Information). [d] Used (S_a,S)-**3c** as catalyst, without additive.

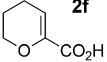
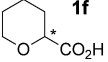
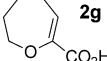
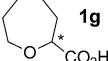
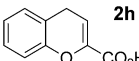
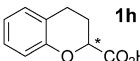
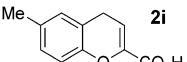
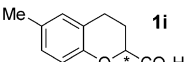
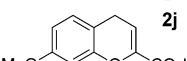
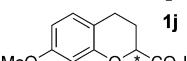
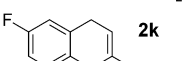
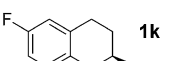
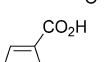
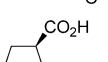
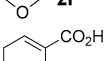
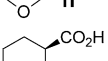
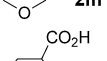
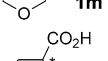
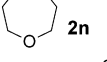
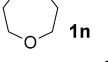
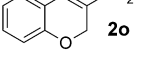
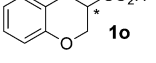
corresponding chiral HCAs in high yields (94–97 %) and high enantioselectivities (88–97 % ee, entries 7–11). The catalyst loading could be reduced to 0.1 mol % without compromising either the yield or the enantioselectivity in the hydrogenation of **2n** (entry 10).

To demonstrate the potential utility of this catalytic asymmetric reaction, we synthesized (*R*)-nipecotic acid (**1p**) and (*R*)-tiagabine (**1q**; Scheme 2). (*R*)-Nipecotic acid, a potent γ-aminobutyric acid reuptake inhibitor,^[9] is a simple cyclic γ-amino acid, but it is difficult to synthesize. The only catalytic asymmetric preparation of chiral **1p** required more than 10 steps.^[10] In addition to being available



Scheme 2. The syntheses of (*R*)-nipecotic acid and (*R*)-tiagabine.

Table 3: Asymmetric hydrogenation of unsaturated O-heterocyclic acids.^[a]

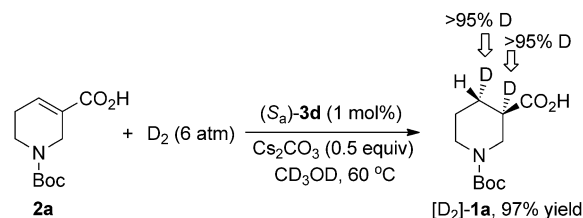
Entry	Substrate	S/C	Product	Yield [%]	ee [%] ^[b]
1		100		96	97
2		100		97	98
3		200		97	92
4		200		98	93
5		200		98	93
6		500		99	93 (S)
7 ^[c]		50		94	88 (R)
8 ^[c]		100		95	97 (R)
9 ^[c]		100		95	97
10 ^[c]		1000		94	97
11 ^[d]		50		97	89

[a] Reaction condition: 0.5 mmol scale, [substrate] = 0.25 mol L⁻¹, (*S_a*,*S*)-**3c** as catalyst, 0.5 equiv Cs₂CO₃ as additive, H₂ (6 atm), 60 °C, 20 h. [b] Determined by HPLC or SFC using chiral columns (see the Supporting Information). [c] Used (*S_a*,*S*)-**3d** as catalyst. [d] Used (*S_a*,*S*)-**3f** as catalyst.

from the hydrogenation product **1a**, (*R*)-nipecotic acid also can be synthesized by direct hydrogenation of the corresponding unsaturated N-heterocyclic acid guvacine (**2p**). Using the catalyst (*S_a*,*S*)-**3c**, we hydrogenated **2p** under neutral conditions to obtain (*R*)-nipecotic acid in 99% yield with 96% *ee*. (*R*)-Tiagabine (**1q**) was synthesized in 90% yield with 99% *ee* by (*S_a*,*S*)-**3c**-catalyzed hydrogenation of the unsaturated N-heterocyclic acid **2q** and subsequent treatment with 3*N* hydrochloric acid. The carbon–carbon double bond conjugated to the carboxy group was hydrogenated smoothly, whereas the double bond conjugated to the thiophene groups remained unchanged. This excellent chemoselectivity further demonstrates the merit of these chiral spiro iridium catalysts.

In a previous study, we demonstrated that the carboxy group is indispensable in the hydrogenation of acyclic unsaturated carboxylic acids catalyzed by chiral iridium complexes of spirophosphino oxazoline ligands.^[11] The mechanism of that reaction differs from the mechanism of iridium-

catalyzed asymmetric hydrogenation of unfunctionalized olefins.^[12] In this study, we found that when the methyl ester of **2a** was subjected to the standard hydrogenation conditions, no reaction occurred. To probe the possibility of migration of the double bond during the hydrogenation, we carried out an isotopic labeling experiment (Scheme 3). Hydrogenation of



Scheme 3. Isotopic labeling experiment.

2a with D₂ (6 atm) in CD₃OD gave **1a** with deuterium atoms attached to the carbon atoms where the double bond was originally located, thus indicating that the double bond did not migrate during the hydrogenation reaction.

In conclusion, we have realized the highly enantioselective hydrogenation of unsaturated heterocyclic acids catalyzed by chiral spirophosphine oxazoline iridium complexes. The reaction provides a direct catalytic approach to the synthesis of chiral heterocyclic acids. The concise syntheses of (*R*)-nipecotic acid and (*R*)-tiagabine demonstrates that this catalytic asymmetric reaction has the potential for wide application in organic synthesis.

Experimental Section

General hydrogenation procedure: A hydrogenation tube was charged with a stir bar, unsaturated heterocyclic acid **2** (0.5 mmol), catalyst (*S_a*,*S*)-**3**, and Cs₂CO₃ (41 mg, 0.25 mmol) in an argon-filled glove box. MeOH (2 mL) was injected into the hydrogenation tube with a syringe. The tube was placed in an autoclave and purged five times with hydrogen gas. The autoclave was charged with H₂ gas to 6 atm, and the reaction mixture was stirred at 60 °C for 12 h before the release of the H₂ pressure. The reaction solution was acidified with 3*N* HCl (pH 1) and extracted with Et₂O (3 × 10 mL). The combined extracts were washed with a saturated solution of NaCl (15 mL), dried over MgSO₄, and evaporated in vacuo. The crude product was purified by flash chromatography on a silica gel column to give a pure chiral acid. The chiral acid (0.5 mmol) reacted with aniline (50 μL, 0.55 mmol) in the presence of DMAP (4 mg, 0.032 mmol) and DCC (110 mg, 0.55 mmol) in THF (2 mL) for 2 h. The reaction mixture was filtered through celite. The filtrate was diluted with Et₂O (10 mL), washed with 3*N* HCl (10 mL), and saturated NaHCO₃ (10 mL), dried with MgSO₄, and concentrated in vacuo. After flash chromatography on a silica gel column, the resulting amide was analyzed by supercritical fluid chromatography (SFC) or HPLC to determine the *ee* value.

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- [1] a) *Heterocyclic Chemistry* (Eds.: J. A. Joule, K. Mills), Wiley-Blackwell, Oxford, **2010**; b) *Bioactive Heterocyclic Compound Classes*, (Eds.: C. Lamberth, J. Dinges), Wiley-VCH, Weinheim, **2012**.
- [2] a) P. Bose, P. Kumar, S. Mittal, Y. Kumar, WO Patent 013550, **2006**; b) M. Vendrell, A. Molero, S. González, K. Pérez-Capote, C. Lluís, P. J. McCormick, R. Franco, A. Cortés, V. Casadó, F. Albericio, M. Royo, *J. Med. Chem.* **2011**, *54*, 1080–1090; c) T. Huhtiniemi, H. S. Salo, T. Suuronen, A. Poso, A. Salminen, J. Leppänen, E. Jarho, M. Lahtela-Kakkonen, *J. Med. Chem.* **2011**, *54*, 6456–6458; d) J. J. Kyncl, B. W. Horrom, WO patent 9200073, **1992**; e) R. M. Xhonneux, G. R. E. Van Lommen, EP 0334429, **1989**.
- [3] For reviews, see: a) S. Khumsubdee, K. Burgess, *ACS Catal.* **2013**, *3*, 237–249; b) A. J. Minnaard, B. L. Feringa, L. Lefort, J. G. de Vries, *Acc. Chem. Res.* **2007**, *40*, 1267–1277; c) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029–3069; d) J.-H. Xie, Q.-L. Zhou, *Acta Chim. Sin.* **2012**, *70*, 1427–1438.
- [4] G. Szöllösi, K. Szöri, M. Bartók, *J. Catal.* **2008**, *256*, 349–352.
- [5] a) Y. T. Chen, T. Vojkovsky, X. Fang, J. R. Pocas, W. Grant, A. M. W. Handy, T. Schroter, P. LoGrasso, T. D. Bannister, Y. Feng, *MedChemComm* **2011**, *2*, 73–75; b) N. B. Johnson, I. C. Lennon, P. H. Moran, J. A. Ramsden, *Acc. Chem. Res.* **2007**, *40*, 1291–1299.
- [6] K. Szöri, G. Szöllösi, M. Bartók, *New J. Chem.* **2008**, *32*, 1354–1358.
- [7] For the preparations of chiral HCAs by using chiral starting materials or chiral auxiliary, see: a) S. P. Runyon, L. E. Brieady, S. W. Mascarella, J. B. Thomas, H. A. Navarro, J. L. Howard, G. T. Pollard, F. I. Carroll, *J. Med. Chem.* **2010**, *53*, 5290–5301; b) F. Gessier, L. Schaeffer, T. Kimmerlin, O. Flögel, D. Seebach, *Helv. Chim. Acta* **2005**, *88*, 2235–2250. By resolution, see: c) J. Mendiola, S. García-Cerrada, Ó. de Frutos, M. L. de La Puente, R. L. Gu, V. V. Khau, *Org. Process Res. Dev.* **2009**, *13*, 292–296; d) P. A. Gugger, D. C. R. Hockless, N. L. Kilah, R. C. Mayadunne, S. B. Wild, *Tetrahedron: Asymmetry* **2008**, *19*, 1810–1812. By asymmetric hydrogenation of heteroaromatic rings, see: e) D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557–2590. By other catalytic asymmetric reactions, see: f) S.-F. Zhu, X.-G. Song, Y. Li, Y. Cai, Q.-L. Zhou, *J. Am. Chem. Soc.* **2010**, *132*, 16374–16376; g) C. Nadeau, S. Aly, K. Belyk, *J. Am. Chem. Soc.* **2011**, *133*, 2878–2880; h) S. H. Chikkali, R. Bellini, B. de Bruin, J. I. van der Vlugt, J. N. H. Reek, *J. Am. Chem. Soc.* **2012**, *134*, 6607–6616; i) X.-G. Song, S.-F. Zhu, X.-L. Xie, Q.-L. Zhou, *Angew. Chem.* **2013**, *125*, 2615–2618; *Angew. Chem. Int. Ed.* **2013**, *52*, 2555–2558.
- [8] Addition of base additives changes the acid substrate to carboxylic anion which coordinates to catalyst easily. See: S. Li, S.-F. Zhu, J.-H. Xie, S. Song, C.-M. Zhang, Q.-L. Zhou, *J. Am. Chem. Soc.* **2010**, *132*, 1172–1179.
- [9] a) K.-I. Takahashi, S. Miyoshi, A. Kaneko, D. R. Copenhagen, *Jpn. J. Physiol.* **1995**, *45*, 457–473; b) H. Wang, A. A. Hussain, P. J. Wedlund, *Pharm. Res.* **2005**, *22*, 556–562.
- [10] S. Schleich, G. Helmchen, *Eur. J. Org. Chem.* **1999**, 2515–2521.
- [11] See ref. [8] and S. Song, S.-F. Zhu, Y.-B. Yu, Q.-L. Zhou, *Angew. Chem.* **2013**, *125*, 1596–1599; *Angew. Chem. Int. Ed.* **2013**, *52*, 1556–1559.
- [12] a) R. H. Crabtree, P. C. Demou, D. Eden, J. M. Mihelic, C. A. Parnell, J. M. Quirk, G. E. Morris, *J. Am. Chem. Soc.* **1982**, *104*, 6994–7001; b) A. Lightfoot, P. Schnider, A. Pfaltz, *Angew. Chem.* **1998**, *110*, 3047–3050; *Angew. Chem. Int. Ed.* **1998**, *37*, 2897–2899; c) P. Brandt, C. Hedberg, P. G. Andersson, *Chem. Eur. J.* **2003**, *9*, 339–347; d) Y. Fan, X. Cui, K. Burgess, M. B. Hall, *J. Am. Chem. Soc.* **2004**, *126*, 16688–16689.