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Asymmetric Synthesis of Tetrahydro-β-carbolines *via* Chiral Phosphoric Acid Catalyzed Transfer Hydrogenation Reaction

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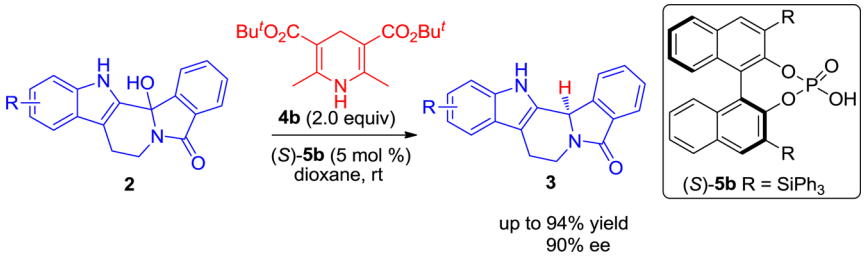
ABSTRACT



Chiral phosphoric acid catalyzed enantioselective transfer hydrogenation of hydroxylactams has been realized to provide enantioenriched tetrahydro-β-carbolines in dioxane at room temperature (up to 94% yield, 90% ee).

Chiral tetrahydro-β-carbolines are of particular importance, as they are key structural units in naturally occurring alkaloids that exhibit interestingly biological activities (Figure 1).[1,2] Therefore, the development of an efficient enantioselective synthesis of these polycycles is very essential. To date, the Pictet–Spengler reaction[3] has proven to be the most straightforward route for the construction of a tetrahydro-β-carboline framework. However, the number of successful catalytic enantioselective Pictet–Spengler reactions remains limited. Alternatively, asymmetric reduction of fused imine or iminium ions represents a practical route to synthesize enantiopure indole alkaloids.[4] In general, precious metals such as ruthenium, rhodium, and iridium are essential for these transformations. In addition, synthesis of the iminium ions usually requires a multistep

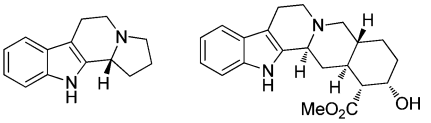


Figure 1. Selected tetrahydro-β-carboline natural products.

(1) For reviews, see: (a) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2004**, *21*, 278. (b) Kawasaki, T.; Higuchi, K. *Nat. Prod. Rep.* **2005**, *22*, 761. (c) O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, *23*, 532.

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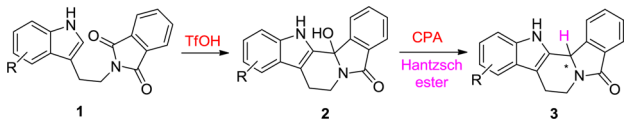
procedure. On the other hand, organocatalytic transfer hydrogenation with organic hydride donors[5] has emerged as a powerful method for the construction of diverse cyclic and acyclic amines as well as heterocycles, serving as an important supplement to the transition-metal catalyzed asymmetric hydrogenation.

Catalytic asymmetric reactions involving *N*-acyliminium ions represent a useful tactic for the construction of chiral amines in organic synthesis. Compared to ketimines and *N*-heterocycles, however, *N*-acyliminium ions have been less explored in asymmetric hydrogenation reactions. Recently, chiral phosphoric acid catalyzed enantioselective intermolecular Friedel–Crafts alkylations of indoles with *N*-acyliminium ions formed *in situ* from hydroxylactams have been reported by Rueping,[6] Zhou,[7] Lete,[8] Masson,[9] etc. In 2012, Zhou[10] et al. reported an enantioselective transfer hydrogenation reaction of 3-hydroxyisoindolin-1-ones with a Hantzsch ester catalyzed by chiral phosphoric acid. We envisaged that hydroxylactams **2**, prepared easily from tryptamine derivatives **1**,[11] could be suitable substrates in the Brønsted acid catalyzed transfer hydrogenation reaction. The corresponding *N*-acyliminium ions will be formed when the hydroxylactams are treated with Brønsted acid. Then the transfer hydrogenation of these key intermediates in the presence of a chiral Brønsted acid would afford optically active tetrahydro-β-carbolines (Scheme 1). Herein, we report such an efficient synthesis of enantioenriched tetrahydro-β-carbolines *via* chiral phosphoric acid catalyzed asymmetric transfer hydrogenation with the Hantzsch ester as the organic hydride source.[12]

Scheme 1. Proposed Hydrogenation of Hydroxylactams **2**



We began our exploration by testing substrate **2a** with Hantzsch ester **4a** as the hydride source. Several (*S*)-BINOL-derived phosphoric acids were tested in CH_2Cl_2, and the results are summarized in Table 1. In all cases, full conversions were obtained; the enantiocontrol, however, varied dramatically (entries 1–6, Table 1). The $SiPh_3$ substituted phosphoric acid (*S*)-**5b** afforded the best results (88% yield, 52% ee, entry 2, Table 1). Further screening of the catalysts showed VAPOL-derived phosphoric acid **6** and SPINOL-derived phosphoric acid **7**[13] were not efficient catalysts in terms of enantiocontrol (entries 7–8, Table 1). With (*S*)-**5b** as the catalyst, we further optimized the reaction conditions by examining the solvents, and it was found that solvents affected the reactivity and enantioselectivity significantly (entries 9–15, Table 1). Dioxane turned out to be the best choice with improved enantioselectivity (75% ee, entry 12, Table 1).

Further screening of hydride donors revealed that the utilization of Hantzsch ester **4b** could further improve the enantioselectivity (80% ee, entry 1, Table 2). Attempts using molecular sieves or $MgSO_4$ did not benefit the reaction outcome (entries 2–5, Table 2). Finally, the reaction with 5 mol % (*S*)-**5b** and Hantzsch ester **4b** as the hydride source in dioxane at room temperature led to the best combination of isolated yield and enantioselectivity (91% yield, 80% ee, entry 1, Table 2).

Under the above optimized reaction conditions, various substituted hydroxylactams **2** were examined to probe the generality of the reaction. The results are shown in Table 3.

(4) For selected examples, see: (a) Morimoto, T.; Suzuki, N.; Achiwa, K. *Heterocycle* **2004**, *63*, 2097. (b) Szawkało, J.; Czarnocki, S. J.; Zawadzka, A.; Wojtasiewicz, K.; Leniewski, A.; Maurin, J. K.; Czarnocki, Z.; Drabowicz, J. *Tetrahedron: Asymmetry* **2007**, *18*, 406. (c) Bondzić, B. P.; Eilbracht, P. *Org. Lett.* **2008**, *10*, 3433. (d) Li, C.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 13208. (e) Espinoza-Moraga, M.; Caceres, A. G.; Santos, L. S. *Tetrahedron Lett.* **2009**, *50*, 7059. (f) Evanno, L.; Ormala, J.; Pihko, P. M. *Chem.—Eur. J.* **2009**, *15*, 12963.

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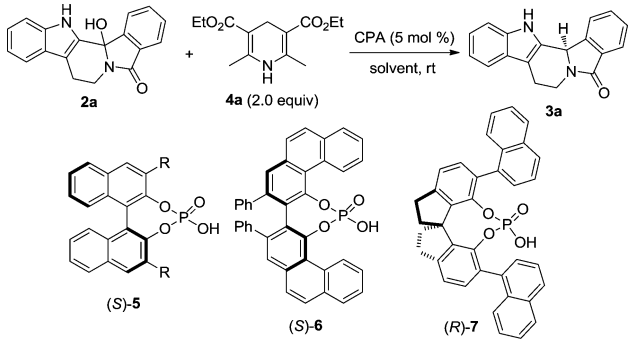
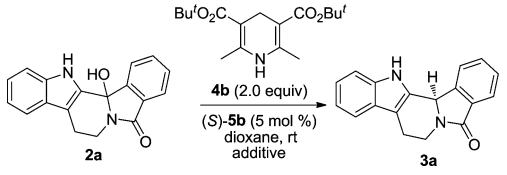
Table 1. Evaluation of Catalysts and Solvents



entry[a]	CPA	R	solvent	time (h)	yield (%)[b]	ee (%)[c]
1	**5a**	2,4,6-(^{i}Pr)$_3$-C_6H_2	CH_2Cl_2	4	87	29
2	**5b**	$SiPh_3$	CH_2Cl_2	3.5	88	52
3	**5c**	1-naphthyl	CH_2Cl_2	6	78	27
4	**5d**	3,5-$(CF_3)_2$-C_6H_3	CH_2Cl_2	5	78	8
5	**5e**	2-naphthyl	CH_2Cl_2	10	95	44
6	**5f**	biphenyl	CH_2Cl_2	6	94	49
7	**6**	–	CH_2Cl_2	5	91	18
8	**7**	–	CH_2Cl_2	12	77	−30
9	**5b**	$SiPh_3$	toluene	2.5	84	41
10	**5b**	$SiPh_3$	THF	6	91	63
11	**5b**	$SiPh_3$	$CHCl_3$	8	89	22
12	**5b**	$SiPh_3$	dioxane	24	84	75
13	**5b**	$SiPh_3$	Et_2O	48	–	–
14	**5b**	$SiPh_3$	^{t}BuOMe	48	60	6
15	**5b**	$SiPh_3$	EtOAc	24	85	55

[a] Reactions were performed with **2a** (0.1 mmol), **4a** (0.2 mmol), and 5 mol % CPA. [b] Isolated yield. [c] Determined by HPLC analysis.

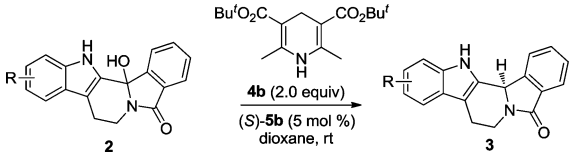
Table 2. Screening of Hydride Donor and Additives

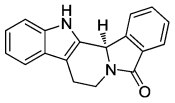
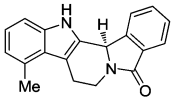
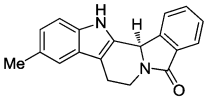
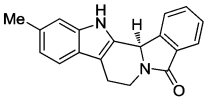
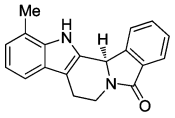
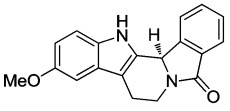
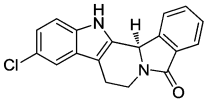
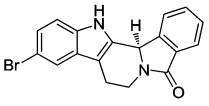
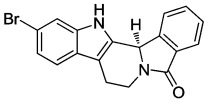
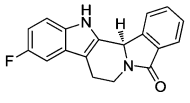


entry[a]	additive	time (h)	yield (%)[b]	*ee* (%)[c]
1	–	24	91	80
2	3 Å MS	72	35	75
3	4 Å MS	72	40	79
4	5 Å MS	72	85	73
5	$MgSO_4$	24	90	77

[a] Reactions were performed with **2a** (0.1 mmol), **4b** (0.2 mmol), additive (50 mg), and 5 mol % (*S*)-**5b**. [b] Isolated yield. [c] Determined by HPLC analysis.

Table 3. Substrate Scope

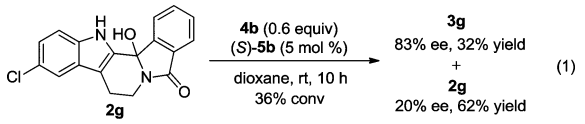


entry[a]	product	3, yield (%)[b]	ee (%)[c]
1		**3a**, 91	80
2		**3b**, 84	85
3		**3c**, 93	79
4		**3d**, 68	83
5		**3e**, 93	83
6		**3f**, 85	77
7		**3g**, 91	84
8		**3h**, 94	82
9		**3i**, 92	90
10		**3j**, 90	83

[a] Reactions were performed with **2** (0.1 mmol), **4b** (0.2 mmol), and 5 mol % (*S*)-**5b**. [b] Isolated yield. [c] Determined by HPLC analysis.

Substituted hydroxylactams **2b**–**f** containing an electron-rich group (4-Me, 5-Me, 6-Me, 7-Me, 5-MeO) at different positions of the indole ring could be well tolerated, affording their corresponding tetrahydro-β-carbolines in 68–93% yields with good enantioselectivity ranging from 77% to 85% ee (entries 2–6, Table 3). In addition, substrates **2g**–**j** bearing an electron-poor group on the indole moiety (5-Cl, 5-Br, 6-Br, 5-F) were also suitable substrates, and the reduced products were obtained in excellent yields

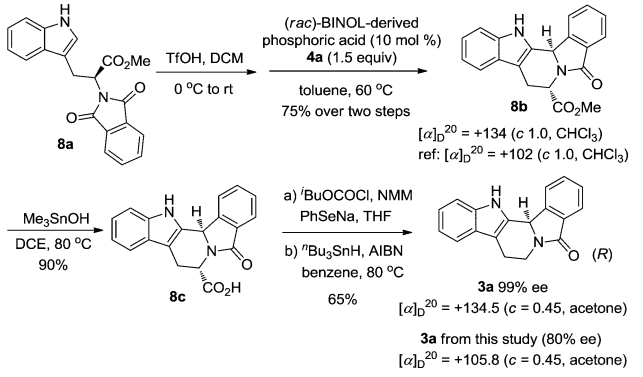
and good enantioselectivity (90−94% yield, 82−90% ee, entries 7−10, Table 3).



(1)

To gain insight into the origin of the enantioselectivity, the reaction of the racemic substrate **2g** with 0.6 equiv of Hantzsch ester **4b** was carried out in the presence of 5 mol % of (*S*)-**5b** (eq 1). Interestingly, substrate **2g** (20% ee) could be recovered, indicating that a moderate kinetic resolution of hydroxylactam exists during the asymmetric transfer hydrogenation reaction.

Scheme 2. Determination of the Absolute Configuration of **3a**



The absolute configuration of product **3a** was established by comparison of its optical rotation with that derived from a known compound, as shown in Scheme 2.[14] Compound **8b** was synthesized *via* TfOH catalyzed cyclization of (*S*)-**8a** and subsequent reduction by the Hantzsch ester. Then hydrolysis of the ester group in **8b** followed by radical decarboxylation yielded compound **3a** with 99% ee. By comparing the sign of the optical rotation, the absolute configuration of product **3a** obtained from the current study was assigned as (*R*). This was also confirmed by an X-ray crystallographic analysis of enantiopure **3a** (Figure 2).

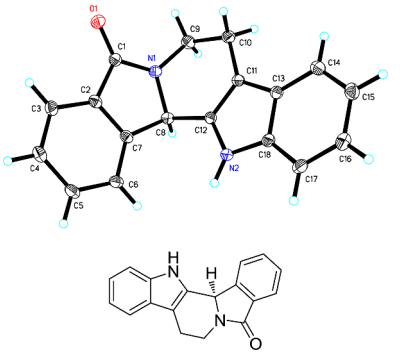


Figure 2. X-ray structure of enantiopure (*R*)-**3a**.

In summary, we have developed an efficient synthesis of enantioenriched tetrahydro-β-carbolines *via* chiral phosphoric acid catalyzed enantioselective transfer hydrogenation of hydroxylactams with up to 94% yield and 90% ee. This methodology features the ready availability of the starting materials, high yields, and mild reaction conditions. Further improvement of the enantioselectivity and application of the method into natural product synthesis are currently ongoing in our group.

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Supporting Information Available. Detailed experimental procedures and spectroscopic data for all new compounds and X-ray crystal data of **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.