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Ruthenium-Catalyzed Enantioselective Hydrogenation of Aryl-Pyridyl Ketones

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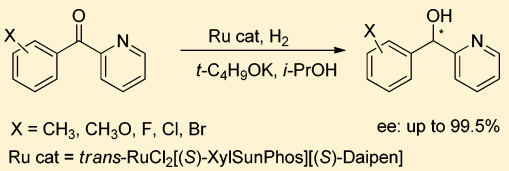
Supporting Information

ABSTRACT: Various substituted aryl-pyridyl ketones were hydrogenated in the presence of Ru-XylSunPhos-Daipen bifunctional catalytic system with enantiomeric excesses up to 99.5%. Upon introduction of a readily removable *ortho*-bromo atom to the phenyl ring, enantiomerically enriched 4-chlorophenylpyridylmethanol was obtained by hydrogenation method with 97.3% ee, which provided an important chiral intermediate for some histamine H_1 antagonists.



INTRODUCTION

Preparation of enantiomerically pure secondary alcohols is an important subject in organic synthesis, which continues to attract extensive interest. Secondary alcohols bearing heterocycles are key intermediates for many pharmaceuticals, agrochemicals, and biologically relevant compounds.[1] For example, carbinoxamine and bepotastine besilate (Figure 1) are two

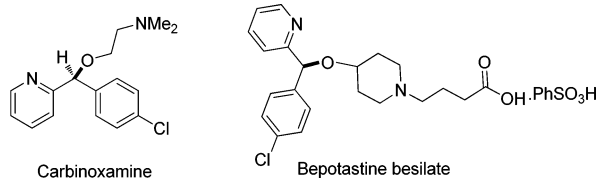


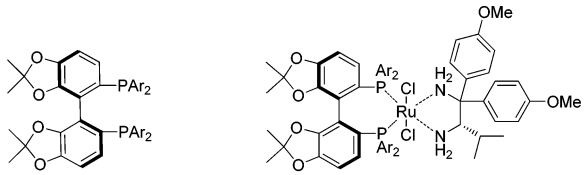
Figure 1. Structures of carbinoxamine and bepotastine besilate.

histamine H_1 antagonists.[2] They both contain an (*S*)-4-chlorophenylpyridylmethanol moiety, which has been previously produced by either resolution of the racemates or oxazaborolidine-catalyzed reduction of ketones.[3] However, both synthetic routes suffered from either low enantioselectivity or poor efficiency. Accordingly, the search for effective, highly enantioselective, and atom-economic processes to obtain such chiral moieties is of great significance.

Asymmetric hydrogenation of prochiral ketones is one of the most efficient methods for producing enantiomerically pure secondary alcohols.[4] In the 1990s, a major breakthrough was made by Noyori and co-workers with bifunctional catalyst $RuCl_2$(diphosphine)(diamine).[5] Such catalysts showed high efficiency in asymmetric hydrogenation of nonfunctionalized α,β-unsaturated ketones[5a,b] and also some heteroaromatic ketones.[6] After that, Burk et al. reported that the ruthenium complexes based upon the novel PhanePhos ligands also performed well in the highly enantioselective hydrogenation of ketones.[7] Many other ligands have also emerged and performed well in asymmetric hydrogenation of prochiral ketones.[8] As far as asymmetric hydrogenation of benzopyridine derivatives is concerned, only limited success has been achieved for such approach using Binap-type derivatives with enantiomeric excess values ranging from 3 to 80% ee and only two examples over 90% ee.[6b,9] Therefore, asymmetric hydrogenation of aryl-pyridyl ketones is still a challenging work.

Our group has designed some atropisomeric C_2-symmetric biaryl biphosphines-SunPhos ligands with complementary steric and electronic properties (Scheme 1), which were found to be

Scheme 1. SunPhos and SunPhos/Daipen-Ru(II) Catalysts



(*S*)-**1a**, Ar=C_6H_5, (*S*)-SunPhos
(*R*)-**1b**, Ar=4-$CH_3C_6H_4$, (*R*)-Tol-SunPhos
(*S*)-**1c**, Ar=3,5-$(CH_3)_2C_6H_3$, (*S*)-Xyl-SunPhos

(*S,S*)-**2a**, Ar=C_6H_5
(*R,R*)-**2b**, Ar=4-$CH_3C_6H_4$
(*S,S*)-**2c**, Ar=3,5-$(CH_3)_2C_6H_3$

very effective in asymmetric hydrogenation of α- and β-ketoesters,[10] β-ketosulfones,[10h] and several other polyfunctionalized ketones.[10i] We report herein a new application of SunPhos derivatives as ligands for the asymmetric hydrogenation of aryl-pyridyl ketones using a diphosphine−ruthenium−diamine system.

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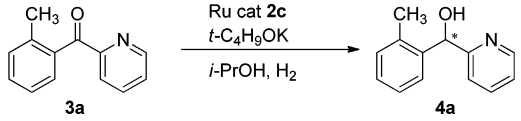
RESULTS AND DISCUSSION

The $RuCl_2$(diphosphine)(diamine) complexes were prepared according to Noyori's protocol.[5a] The catalysts **2** (Scheme 1) were prepared by reacting ligands **1** with $[RuCl_2(benzene)]_2$ in DMF at 100 °C, followed by the treatment of the resulting reddish brown solution with 1.1 equiv of Daipen at room temperature. The complexes were used as the precatalyst directly in the hydrogenation reactions without any further purification.

We initiated our study by screening catalysts in the hydrogenation of *o*-tolyl-2-pyridylmethanone **3a**. The hydrogenation of **3a** was carried out with an S/C = 200 under 8 atm of hydrogen pressure at 25 °C in *i*-PrOH containing (*S*,*S*)-**2** and *t*-C_4H_9OK. Best results were obtained in terms of enantioselectivities using Xyl-SunPhos (**1c**) compared to the parent ligands SunPhos (**1a**) or Tol-SunPhos (**1b**). Because the selectivity relies on the synergistic effects of the chiral diphosphine and diamine ligands,[5a,c,8b] the diphosphine and diamine ancillaries must be properly matched. In this context, the 3,5-dimethyl substituents on the phenyl rings of the ligand Xyl-SunPhos (**1c**) were essential for the high enantioselectivities.[11] For example, the precatalysts (*S*,*S*)-**2a** and (*R*,*R*)-**2b** without *meta*-3,5-dialkyl substituents provided the corresponding alcohols in only 60.1 and 51.3% ee under otherwise identical conditions.

Optimization of solvents, hydrogen pressure, and reaction temperatures are summarized in Table 1. Enantioselectivities in

Table 1. Optimization of Solvent, Pressure, and Temperature[a]



3a 4a

entry	solvent	*P* (atm)	*T* (°C)	ee (%)[b]
1	MeOH	8	25	96.3
2	EtOH	8	25	98.6
3	*i*-PrOH	8	25	98.9
4	*i*-PrOH	8	40	98.1
5	*i*-PrOH	8	55	93.6
6	*i*-PrOH	30	25	98.9
7	*i*-PrOH	50	25	98.8

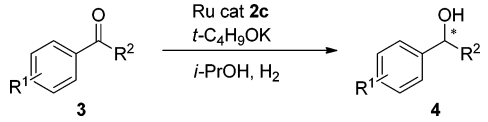
[a]Unless otherwise stated, reactions were conducted using 1 mmol of the substrate **3a** in *i*-PrOH (0.5 M) containing the precatalyst **2c** and *t*-C_4H_9OK. Substrate/catalyst/base = 200:1:10. Conversion: 100%, quantitative yield. [b]Determined by HPLC.

MeOH or EtOH were very high (entries 1 and 2, up to 98.6% ee), and *i*-PrOH was the solvent of choice for this transformation (entry 3, 98.9% ee). The results depicted in Table 1 showed that the stereochemical outcome of the hydrogenation was strongly dependent on the temperature (entries 4 and 5, 98.1 vs 93.6% ee at 40 and 50 °C).[12] Unexpectedly, the enantioselectivity was hardly affected by the hydrogen pressure in our optimization.

On the basis of these results, the optimized reaction conditions were therefore set as the following: *i*-PrOH as the solvent, (*S*,*S*)-**2c** as the catalyst, and *t*-C_4H_9OK as the base, 8 atm of H_2 at 25 °C for 16 h.

Under these reaction conditions, a variety of aryl-pyridyl ketones were hydrogenated, and the results are depicted in Table 2. A range of *ortho*-substituted substrates gave excellent enantiomeric excesses up to 99.6% (Table 2, entries 1−7). For

Table 2. Asymmetric Hydrogenation of Aryl-Pyridyl Ketones[a]



3 4

entry	3	R^1	R^2	ee (%)[b]
1	**3a**	*o*-Me	2-py	98.9
2[c]	**3a**	*o*-Me	2-py	98.8
3	**3b**	*o*-OMe	2-py	99.6
4	**3c**	*o*-F	2-py	98.9
5	**3d**	*o*-Cl	2-py	99.5
6	**3e**	*o*-Br	2-py	99.3
7	**3f**	*o*-Br-*p*-Cl	2-py	99.5[d]
8	**3g**	*m*-Me	2-py	30.4
9	**3h**	*p*-Me	2-py	26.7
10	**3i**	*p*-OMe	2-py	61.5
11	**3j**	*p*-CF_3	2-py	55.8
12	**3k**	*o*-Me	3-py	81.5
13	**3l**	*o*-Me	4-py	90.0
14	**3m**	*o*-Me	2-pyrazine	84.4

[a]Unless otherwise stated, reactions were conducted at 8 atm of H_2 for 16 h at 25 °C using 1 mmol of the substrate **3** in *i*-PrOH (0.5 M) containing the precatalyst **2c** and *t*-C_4H_9OK. Substrate/catalyst/base = 200:1:10. Conversion: 100%, quantitative yield. [b]Determined by HPLC on a ChiralPak AD-H column. [c]Reaction using 9.8 g of **3a** at 20 atm of H_2 for 48 h at 25 °C. Substrate/catalyst/base = 10000:1:50. [d]Determined by HPLC on ChiralPak OD-H column.

example, the hydrogenation of *o*-tolyl-2-pyridylmethanone **3a** in the presence of (*S*,*S*)-**2c** (substrate/catalyst/base = 200:1:10, 8 atm of H_2, 25 °C, 16 h) afforded (*R*)-**4a**[13] in 98.9% ee (Table 2, entry 1). Furthermore, the reaction proceeded smoothly on multigram scale with excellent enantiofacial discrimination up to 98.8% ee and complete conversion under 20 atm of hydrogen pressure and 25 °C using a low catalyst loading of 0.01 mol % of (*S*,*S*)-**2c** (entry 2, Table 2). Since high enantioselectivity for the hydrogenation of unsymmetrical diaryl ketones relies on the presence of an *ortho* substituent in one of the aromatic rings,[6a] we reasoned that the same steric effect may be applied to the pyridinyl ketones to override the electronic effect. Likely, the aryl-pyridyl **3d** with an electron-attracting chloro substituent, sterically similar but electronically different from methyl, gave the alcohol (*R*)-**4d**[14] in 99.5% ee. Similarly, the hydrogenation of *o*-methoxy, *o*-fluoro, and *o*-bromo aryl-pyridyl ketones **3b**, **3c**, and **3e** also displayed a high degree of enantioselectivities (entries 3, 4, and 6, respectively, 99.6, 98.9, and 99.3% ee). This indicated that the *ortho* steric effect plays a crucial role in the reduction. The sense of asymmetric induction in the reactions of these heteroatom-substituted ketones was identical to that observed with the methyl derivative, *o*-tolyl-2-pyridylmethanone **3a**, indicating that the possible interaction of the *ortho* heteroatom (F, Cl, Br) to the Ru catalyst was not the origin of enantioselection.[15] Simple *meta*- and *para*-substituted substrates led to moderate enantioselectivities (entries 8 and 9). In the presence of (*S*,*S*)-**2c**, reaction of ketone **3i** with an electron-donating methoxy group at the 4′ position afforded **4i** in 61.5% ee, while substitution of an electron-attracting trifluoromethyl group (**3j**) slightly reduced the enantioselectivity and afforded **4j** in 55.8% ee. The *meta*-methyl derivative afforded alcohol **4g** in only 30.4% ee. Electronic influences of the *para* substituents were presumed to affect the extent of the coplanarity of the benzene rings with

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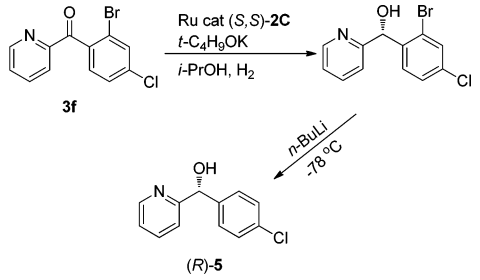
C═O function in the transition state,[16] thereby generating an asymmetric bias. Enantioselective hydrogenation of *o*-tolyl-3-pyridylmethanone (**3k**), *o*-tolyl-4-pyridylmethanone (**3l**), and *o*-tolyl-2-pyrazylmethanone (**3m**) afforded the corresponding alcohols, **4k**, **4l**, and **4m**, in 81.5, 90.0, and 84.4% ee, respectively.

Finally, a synthesis of the key intermediate of carbinoxamine and bepotastine besilate[3b,17] was performed. The hydrogenation product of *o*-bromo-*p*-chlorobenzoyl 2-pyridine (**3f**) can be converted to a key intermediate for carbinoxamine or bepotastine besilate (Scheme 2). Thus the hydrogenation of a

Scheme 2. Asymmetric Synthesis of (*R*)-4-Chlorophenylpyridylmethanol



Intermediate for Carbinoxamine and Bepotastine besilate

0.5 M solution of **3f** in *i*-PrOH containing the Ru-Xyl-SunPhos/Daipen complex (*S*,*S*)-**2c** and *t*-C_4H_9OK (substrate/catalyst/base = 200:1:10, 8 atm of H_2, 25 °C, 16 h) afforded quantitatively **4f** in 99.5% ee. Lithiation of the bromoalcohol with 2.2 equiv of *n*-BuLi in THF at −78 °C for 1.5 h followed by hydrolysis gave (*R*)-**5** in 85% yield with 97.3% ee ($[\alpha]^{23}_D$ −148 (*c* 0.4, $CHCl_3$)).[14] The chiral alcohol can readily be converted to carbinoxamine or bepotastine besilate.[3b,17]

CONCLUSION

In summary, we have developed a catalyst generated from Ru-Xyl-SunPhos and Daipen, which proved to be effective toward the enantioselective hydrogenation of a variety of aryl-pyridyl ketones, especially *ortho*-substituted aryl-pyridyl ketones with high enantiomeric excess. This atom-economical protocol offers several advantages, including operational simplicity, mild reaction conditions, high chemical yields, and enantioselectivities up to 99.5%. Studies of the catalyst in enantioselective hydrogenation of other types of substrates are in progress.

EXPERIMENTAL SECTION

General. Commercially available reagents were used throughout without further purification other than those detailed below. The solvents used in catalyst preparation and hydrogenation reactions were pretreated by the following procedures: DMF and *i*-PrOH were distilled over calcium hydride. MeOH and EtOH were distilled over magnesium under nitrogen. All reactions were carried out under an atmosphere of nitrogen using standard Schlenk techniques or in a nitrogen-filled glovebox, unless otherwise noted. ^{1}HNMR spectra were recorded at 400 MHz, with TMS as internal standard. ^{13}C NMR spectra were obtained at 101 MHz and referenced to the central peak of 77.1 ppm for $CDCl_3$. Coupling constants (*J*) are reported in hertz and refer to apparent peak multiplications. Mass spectroscopy data were collected on an HRMS-EI instrument. Flash column chromatography was performed on silica gel (300−400 mesh).

Typical Procedure for the Preparation 3a−e, 3g−m.[18] A solution of the appropriate bromophenyl derivative (20.0 mmol, 1.00 equiv) in 35.0 mL of THF was treated with magnesium (20.4 mmol, 1.02 equiv). After the formation of the Grignard reagent, the solution was added to a solution of the appropriate carbonitrile (15.3 mmol, 0.77 equiv) in THF (15.0 mL) at 0 °C. When TLC showed no more starting material, the reaction was quenched by addition of a solution of saturated NH_4Cl. The organic layer was separated and extracted twice with CH_2Cl_2. After evaporation, the organic layer was redissolved in Et_2O (80.0 mL) and 6 M HCl (10.0 mL) was added. After 30 min, the organic layer was separated, and the aqueous layer was basified with saturated $NaHCO_3$ and then extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography with petroleum ether and ethyl acetate.

***o*-Tolyl-2-pyridylmethanone**[19] **(3a):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.10−8.06 (m, 1H), 7.88 (td, *J* = 7.7, 1.7 Hz, 1H), 7.47−7.38 (m, 3H), 7.29−7.23 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.5, 155.2, 149.4, 137.9, 137.5, 137.7, 131.4, 131.5, 130.9, 126.7, 125.1, 124.2, 20.6.

2-*o*-Methoxybenzoylpyridine[20] **(3b):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73−8.67 (m, 1H), 8.01 (ddd, *J* = 7.8, 1.9, 1.0 Hz, 1H), 7.92−7.85 (m, 1H), 7.61 (ddd, *J* = 6.7, 2.7, 1.5 Hz, 2H), 7.50−7.44 (m, 1H), 7.38 (dd, *J* = 6.0, 3.8 Hz, 1H), 7.16−7.09 (m, 1H), 3.85 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7, 159.1, 155.4, 148.8, 137.9, 137.1, 129.4, 126.4, 124.0, 124.0, 119.6, 115.0, 55.4.

2-*o*-Fluorobenzoylpyridine[21] **(3c):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.16−8.10 (m, 1H), 7.91 (td, *J* = 7.7, 1.7 Hz, 1H), 7.54−7.35 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.4, 149.2, 137.0, 133.8, 133.9, 131.3, 127.0, 124.5, 123.5, 116.5, 116.1.

2-*o*-Chlorobenzoylpyridine[22] **(3d):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.16−8.10 (m, 1H), 7.91 (td, *J* = 7.7, 1.7 Hz, 1H), 7.54−7.35 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4, 153.6, 149.3, 138.5, 137.1, 132.0, 131.9, 130.4, 127.1, 126.7, 123.8.

2-*o*-Brombenzoylpyridine[21] **(3e):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.16−8.11 (m, 1H), 7.89 (td, *J* = 7.7, 1.7 Hz, 1H), 7.63−7.58 (m, 1H), 7.49−7.39 (m, 3H), 7.34 (ddd, *J* = 7.9, 7.2, 2.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.8, 153.3, 149.4, 140.3, 137.1, 133.0, 131.6, 129.8, 127.1, 127.0, 124.0, 120.9.

***m*-Tolyl-pyridylmethanone**[19] **(3g):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 3.7 Hz, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.90−7.78 (m, 3H), 7.50−7.30 (m, 3H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.3, 155.8, 148.5, 138.1, 137.8, 136.4, 133.4, 131.3, 128.3, 128.2, 126.7, 124.4, 21.8.

***p*-Tolyl-2-pyridylmethanone**[19] **(3h):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.01−7.92 (m, 3H), 7.86−7.76 (m, 1H), 7.41 (d, *J* = 4.8 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.3, 155.2, 148.3, 143.6, 136.8, 133.5, 131.3, 128.7, 125.9, 124.3, 21.6.

2-*p*-Methoxybenzoylpyridine[19] **(3i):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71−8.63 (m, 1H), 8.12−8.08 (m, 2H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.90 −7.83 (m, 1H), 7.47−7.42 (m, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.3, 163.6, 155.8, 148.4, 137.0, 133.5, 129.0, 125.9, 124.5, 113.6, 55.5.

2-*p*-Trifuoromethylbenzoylpyridine[23] **(3j):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75−8.69 (m, 1H), 8.22−8.10 (m, 3H), 7.94 (td, *J* = 7.7, 1.7 Hz, 1H), 7.77−7.71 (m, 2H), 7.53 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.0, 154.4, 148.9, 139.6, 137.5, 134.7, 134.0, 131.5, 127.0, 125.5, 125.0.

***o*-Tolyl-3-pyridylmethanone**[19] **(3k):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (dd, *J* = 2.2, 0.8 Hz, 1H), 8.79 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.17−8.10 (m, 1H), 7.43 (ddd, *J* = 4.9, 4.5, 1.1 Hz, 2H), 7.32 (ddd, *J* = 19.5, 10.6, 4.8 Hz, 4H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.0, 153.7, 151.4, 137.9, 137.1, 132.9, 131.5, 131.2, 129.1, 125.5, 124.4, 123.6, 20.3.

***o*-Tolyl-4-pyridylmethanone**[21] **(3l):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (dd, *J* = 4.5, 1.4 Hz, 2H), 7.58 (dd, *J* = 4.5, 1.5 Hz, 2H), 7.48−7.42 (m, 1H), 7.36−7.23 (m, 3H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.3, 150.7, 144.3, 138.1, 136.5, 131.7, 131.8, 129.6, 125.5, 123.0, 20.5.

***o*-Tolyl-2-pyrazylmethanone**[24] **(3m):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (d, *J* = 1.4 Hz, 1H), 8.74 (d, *J* = 2.5 Hz, 1H), 8.64

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(dd, J = 2.4, 1.5 Hz, 1H), 7.46−7.40 (m, 2H), 7.29 (dd, J = 15.3, 7.8 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.7, 149.8, 147.3, 145.8, 143.8, 138.4, 136.4, 131.7, 131.6, 130.5, 125.9, 20.7.

Typical Procedure for the Preparation 2-(2-Bromo-4-chlorobenzoyl)pyridine (3f).[25] In a 250 mL round-bottomed flask, 2-bromo-4-chlorobenzoyl chloride (5.0 g, 19.7 mmol) and 18.0 mL of THF were placed. Next, a solution of 2-pyridylzinc bromide (5.3 g, 23.6 mmol) in THF (15.0 mmol) was added into the reaction flask via a syringe. The resulting mixture was stirred at 0 °C for 4 h and quenched with saturated NH_4Cl solution, then extracted with ether (13.0 mL × 3). The combined organic layers were washed with saturated $NaHCO_3$ solution and brine and then dried with anhydrous Na_2SO_4. The crude product was purified by column chromatography (PE/EA = 5:1) to give **3f** as yellow oil: 4.8 g (82.2%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68−8.65 (m, 1H), 8.16 (td, J = 7.9, 1.0 Hz, 1H), 7.91 (td, J = 7.7, 1.7 Hz, 1H), 7.65 (t, J = 1.1 Hz, 1H), 7.49 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 7.41 (d, J = 1.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.7, 153.1, 149.2, 138.6, 137.1, 136.8, 132.8, 130.8, 127.4, 127.4, 123.9, 120.8.

Typical Procedure for the Asymmetric Hydrogenation. To a 20 mL Schlenk tube were added $[RuCl_2(benzene)]_2$ (5.0 mg, 0.01 mmol) and (*S*)-Xyl-SunPhos (17.2 mg, 0.02 mmol). The tube was vacuumed and purged with nitrogen three times before addition of freshly distilled and freeze-and-thaw degassed DMF (1.5 mL). The resulting mixture was heated at 100 °C for 10 min to form a reddish brown solution. After the solution was cooed to room temperature, (*S*)-Daipen (6.9 mg, 0.02 mmol) was added and the mixture was stirred for 3 h at 25 °C; the solvent was then removed under reduced pressure (1 Torr) to give the catalyst as a brownish yellow solid. The catalyst was dissolved in degassed *i*-PrOH (8.0 mL), and then the solution was equally divided into four vials which contained 1 mmol of substrate, and the base (t-C_4H_9OK) was added. Then the vials were transferred into an autoclave. The autoclave was purged five times with H_2, and the required pressure of H_2 was set. The autoclave was stirred under specified reaction conditions. After being cooled to ambient temperature and careful release of the hydrogen, the autoclave was opened and the solvent was evaporated. The enantiomeric excess was determined by HPLC after passing the residue through a short pad of silica gel column with petroleum ether and ethyl acetate.

***o*-Tolyl-2-pyridylmethanol**[6b] **(4a):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 4.9 Hz, 1H), 7.60 (td, J = 7.7, 1.7 Hz, 1H), 7.25−7.15 (m, 5H), 7.03 (d, J = 7.9 Hz, 1H), 5.97 (s, 1H), 5.18 (s, 1H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1, 147.9, 140.8, 136.9, 136.4, 131.0, 128.5, 127.9, 126.3, 122.5, 121.5, 72.3, 19.0; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH: 96/4, 0.7 mL min^{-1}, 220 nm) t_1 = 22.6 min, t_2 = 29.8 min.

***o*-(2-Methoxyphenyl)-2-pyridinemethanol**[20] **(4b):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (dd, J = 4.6, 1.1 Hz, 1H), 7.57 (dd, J = 7.6, 1.7 Hz, 1H), 7.33−7.27 (m, 2H), 7.23 (dd, J = 8.0, 1.7 Hz, 1H), 7.16−7.12 (m, 1H), 6.97−6.87 (m, 2H), 6.22 (s, 1H), 5.30 (s, 1H), 3.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6, 156.6, 147.7, 136.7, 131.9, 128.7, 127.8, 122.2, 121.5, 120.9, 110.7, 69.9, 55.5; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH: 92/8, 0.8 mL min^{-1}, 220 nm) t_1 = 17.7 min, t_2 = 21.9 min.

***o*-(2-Fulorophenyl)-2-pyridinemethanol**[26] **(4c):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57−8.49 (m, 1H), 7.63 (td, J = 7.7, 1.7 Hz, 1H), 7.41 (td, J = 7.5, 1.7 Hz, 1H), 7.25−7.16 (m, 3H), 7.13−7.01 (m, 2H), 6.13 (s, 1H), 5.51 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9, 137.6, 129.9, 129.1, 128.6, 128.2, 124.5, 122.7, 121.2, 115.6, 115.4, 68.3; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH: 96/4, 0.7 mL min^{-1}, 220 nm) t_1 = 22.9 min, t_2 = 28.5 min.

***o*-(2-Chlorophenyl)-2-pyridinemethanol**[27] **(4d):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62−8.49 (m, 1H), 7.61 (td, J = 7.8, 1.7 Hz, 1H), 7.46−7.35 (m, 2H), 7.28−7.07 (m, 4H), 6.28 (d, J = 3.8 Hz, 1H), 5.64 (d, J = 3.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 147.9, 140.7, 137.4, 132.8, 129.6, 128.9, 128.8, 127.3, 122.8, 121.4, 70.9; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH: 96/4, 0.7 mL min^{-1}, 220 nm) t_1 = 23.7 min, t_2 = 27.9 min.

***o*-(2-Bromophenyl)-2-pyridinemethanol**[28] **(4e):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57−8.49 (m, 1H), 7.63 (td, J = 7.7, 1.7 Hz, 1H), 7.41 (td, J = 7.5, 1.7 Hz, 1H), 7.25−7.16 (m, 3H), 7.13−7.01 (m, 2H), 6.13 (s, 1H), 5.51 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 148.1, 142.1, 137.6, 133.0, 129.8, 129.9, 128.3, 123.3, 122.9, 121.6, 73.2; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH: 96/4, 0.7 mL min^{-1}, 220 nm) t_1 = 25.6 min, t_2 = 28.6 min.

***o*-(2-Bromo-4-chlorophenyl)-2-pyridinemethanol (4f).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60−8.55 (m, 1H), 7.64 (td, J = 7.7, 1.7 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.27−7.26 (m, 1H), 7.25−7.22 (m, 2H), 6.19 (s, 1H), 5.52 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 148.3, 141.3, 137.6, 134.3, 132.4, 130.1, 128.3, 123.3, 123.3, 121.4, 72.7; HPLC (Chiralcel OD-H column, hexane/*i*-PrOH: 96/4, 0.8 mL min^{-1}, 220 nm) t_1 = 14.4 min, t_2 = 22.8 min; HRMS calcd for $C_{12}H_9BrClNO$ $(M + H)^+$ 297.9630, found 297.9631.

***m*-Tolyl-2-pyridylmethanol**[29] **(4g):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59−8.54 (m, 1H), 7.62 (td, J = 7.7, 1.7 Hz, 1H), 7.25−7.14 (m, 5H), 7.09 (d, J = 7.6 Hz, 1H), 5.72 (s, 1H), 5.27 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2, 147.1, 143.7, 138.4, 136.9, 128.7, 128.8, 127.8, 124.3, 122.5, 121.9, 75.9, 21.8; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH: 92/8, 0.7 mL min^{-1}, 220 nm) t_1 = 16.3 min, t_2 = 24.7 min.

***p*-Tolyl-2-pyridylmethanol**[29] **(4h):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57−8.54 (m, 1H), 7.61 (d, J = 1.8 Hz, 1H), 7.28−7.24 (m, 2H), 7.21−7.08 (m, 5H), 5.73 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4, 147.9, 140.4, 137.6, 136.9, 129.3, 127.1, 122.4, 121.4, 77.4, 77.1, 76.8, 74.9, 21.2; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH: 92/8, 0.7 mL min^{-1}, 220 nm) t_1 = 19.3 min, t_2 = 23.4 min.

***o*-(4-Methoxyphenyl)-2-pyridinemethanol**[6b] **(4i):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 4.6 Hz, 1H), 7.65−7.57 (m, 1H), 7.30−7.24 (m, 2H), 7.16 (ddd, J = 8.4, 7.4, 2.7 Hz, 2H), 6.89−6.83 (m, 2H), 5.71 (d, J = 3.1 Hz, 1H), 5.22 (d, J = 3.8 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2, 159.3, 147.8, 136.9, 135.6, 128.5, 122.4, 121.4, 114.0, 74.6, 55.4; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH: 92/8, 0.8 mL min^{-1}, 220 nm) t_1 = 25.4 min, t_2 = 30.8 min.

***o*-(4-Trifuoromethylphenyl)-2-pyridinemethanol**[23] **(4j):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 4.8 Hz, 1H), 7.68−7.48 (m, 5H), 7.25−7.11 (m, 2H), 5.80 (s, 1H), 5.43 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 148.2, 147.3, 137.3, 130.0, 127.4, 125.6, 125.2, 123.0, 121.4, 74.6; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH: 95/5, 0.8 mL min^{-1}, 220 nm) t_1 = 16.3 min, t_2 = 23.9 min.

***o*-Tolyl-3-pyridylmethanol**[9] **(4k):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 1.9 Hz, 1H), 8.31 (dd, J = 4.8, 1.4 Hz, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.49−7.45 (m, 1H), 7.23−7.16 (m, 3H), 7.15−7.11 (m, 1H), 5.96 (s, 1H), 4.50 (s, 1H), 2.20 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4, 148.0, 141.0, 139.6, 135.5, 135.7, 130.7, 127.8, 126.8, 126.6, 123.5, 70.5, 19.4; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH: 92/8, 0.7 mL min^{-1}, 220 nm) t_1 = 21.7 min, t_2 = 27.3 min.

***o*-Tolyl-4-pyridylmethanol**[30] **(4l):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (dd, J = 4.6, 1.6 Hz, 2H), 7.30 (d, J = 2.8 Hz, 1H), 7.25 (ddd, J = 4.5, 1.3, 0.7 Hz, 2H), 7.22−7.12 (m, 3H), 5.97 (s, 1H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.7, 149.6, 140.6, 135.5, 131.1, 128.3, 127.7, 126.3, 121.9, 72.2, 19.6; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH: 96/4, 0.7 mL min^{-1}, 220 nm) t_1 = 55.7 min, t_2 = 60.1 min.

***o*-Tolyl-4-pyrazylmethanol**[31] **(4m):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 14.9 Hz, 1H), 8.58−8.44 (m, 2H), 7.44−7.32 (m, 2H), 7.21 (d, J = 5.7 Hz, 2H), 6.08 (s, 1H), 2.39 (d, J = 9.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4, 148.0, 141.0, 139.2, 135.0, 130.8, 127.8, 126.6, 126.4, 123.6, 70.8, 19.5; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH: 92/8, 0.7 mL min^{-1}, 220 nm) t_1 = 21.4 min, t_2 = 22.2 min.

***o*-(4-Chlorophenyl)-2-pyridinemethanol**[32] **(5):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (dd, J = 6.2, 2.4 Hz, 1H), 7.62 (td, J = 7.7, 3.8 Hz, 1H), 7.33−7.27 (m, 4H), 7.22−7.17 (m, 1H), 7.15−7.11 (m, 1H), 5.72 (s, 1H), 5.38 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6, 148.0, 141.8, 137.1, 133.8, 128.8, 128.5, 122.7, 121.3, 74.4; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH: 95/5, 0.8 mL min^{-1}, 220 nm) t_1 = 20.0 min, t_2 = 26.6 min.

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■ ASSOCIATED CONTENT

Supporting Information

The NMR and/or HPLC data of compounds **3**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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