JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

Chiral Phosphoric Acid-Catalyzed Enantioselective Reductive Amination of 2-Pyridyl Ketones: Construction of Structurally Chiral Pyridine-Based Ligands

Abulikemu Abudu Rexit,*[,†] Shiwei Luo,*[,‡] and Maihemuti Mailikezati[§]

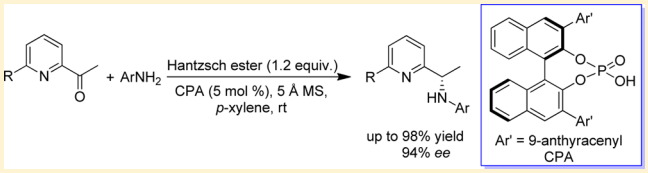
[†]Department of Chemistry, Xinjiang Normal University, Urumqi 830054, China

[‡]Department of Chemistry, University of Science and Technology of China, Hefei 230026, China

[§]School of Chemistry and Chemical Engineering, Xinjiang University, Urumqi 830046, China

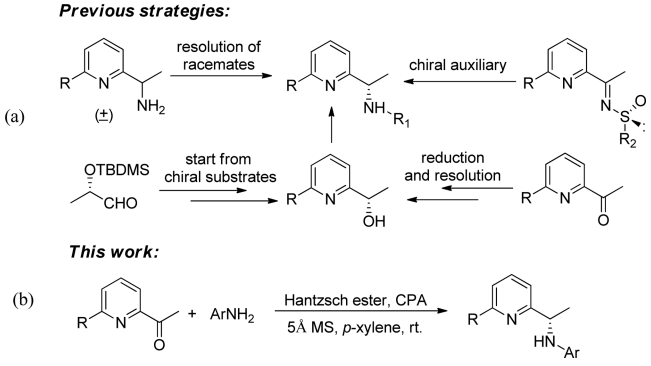
Supporting Information

ABSTRACT: A chiral phosphoric acid-catalyzed one-pot enantioselective reductive amination of 2-pyridyl ketones was realized to provide chiral pyridine-based ligands in excellent yields with high enantioselectivities (up to 98% yield, 94% ee). Computational studies on the key intermediate imine and transition state of the hydride transfer process revealed that the nitrogen atom of the pyridyl ring might be an important factor to significantly promote both the reaction activity and enantioselectivity.



Pyridine is one of the most fundamental structure moieties in organic chemistry. In this family, optically active 1-substituted-1-(pyridyl)methylamines have attracted considerable interest in both academic research and commercial production due to their extensive existence in natural products.[1−3] More importantly, structurally diverse 1-substituted-1-(pyridyl)methylamines have been primarily chosen as the chiral ligands widely in transition-metal catalysis[4] due to their active roles in raising the efficiency of metal and providing satisfactory chiral environments, thus leading to a great demand for the development of efficient and facile methods to access optically active 1-substituted-1-(pyridyl)methylamines. Conventional procedures applied to the synthesis of these chiral pyridine derivatives include resolution of their racemic mixtures,[5] chiral auxiliary assisted synthesis,[6] and some other methods that start from enantiopure substrates[7] such as chiral imines[8] or chiral alcohol[9] (Scheme 1a). For the direct construction of optically active 1-substituted-1-(pyridyl)-methylamines, the enantioselective reductive amination of 2-pyridyl ketones with primary amines undoubtedly stands out to be one of the most convenient methods. Despite the success in metal-catalyzed asymmetric hydrogenation of imines,[1,10] the strategy of organocatalytic transfer hydrogenation had been proven a powerful process since the pioneering works reported by Rueping[11] and List[12] wherein the hydrogenation of bench stable imines and quinolines was catalyzed by chiral phosphoric acids using Hantzsch esters as the organic hydride source.[13] In 2006, MacMillan and co-workers[14] reported a chiral phosphoric acid-catalyzed enantioselective reductive amination of aryl and alkyl ketones, whereas 2-pyridyl ketones were not examined. The metal/organo-catalyzed enantioselective reductive amination seems possible to offer a promising prospect for the preparation of optically active 1-substituted-1-(pyridyl)-methylamines, although formidable problems still remain: first, the desired 1-substituted-1-(pyridyl)methylamines are likely to coordinate with metal and thereby deactivate the catalysts if the reductive amination was performed with metal catalysts; second, the basic pyridine moiety might have compatibility issues with phosphoric acid catalyst. Herein, we report an efficient reductive amination of 2-pyridyl ketones catalyzed by chiral phosphoric acids for the construction of optically active 1-substituted-1-(pyridyl)methylamines with structural diversity (Scheme 1b).

Scheme 1. Strategies for the Preparation of Optically Active 1-Substituted-1-(pyridyl)methylamines

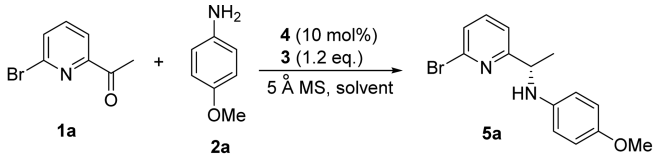


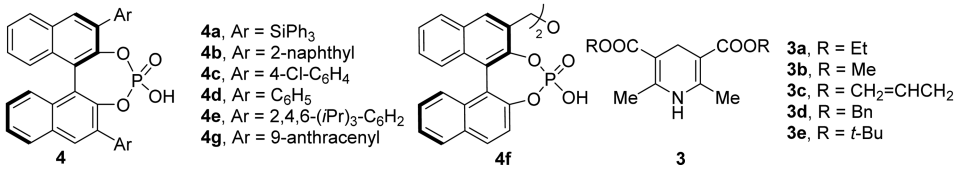
The initial investigation was carried out with bromo-substituted 2-pyridyl ketone **1a** and 4-methoxyaniline (**2a**) using Hantzsch ester **3a** (HEH) as the reducing reagent to evaluate different chiral phosphoric acid catalysts **4a−g** (Table

Received: July 25, 2016
Published: October 19, 2016

DOI: 10.1021/acs.joc.6b01772
J. Org. Chem. 2016, 81, 11384−11388

Table 1. Optimization of Catalysts and Reaction Conditions[a]





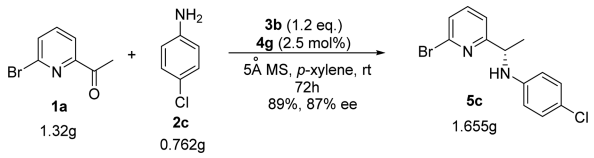
	4	3	solvent	T (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**4a**	**3a**	toluene	40	30	80	2
2	**4b**	**3a**	toluene	40	30	90	31
3	**4c**	**3a**	toluene	40	30	85	0
4	**4d**	**3a**	toluene	40	30	82	25
5	**4e**	**3a**	toluene	40	30	85	22
6	**4f**	**3a**	toluene	40	36	30	20
7	**4g**	**3a**	toluene	40	30	85	82
8	**4g**	**3b**	toluene	40	32	85	87
9	**4g**	**3c**	toluene	40	50	68	81
10	**4g**	**3d**	toluene	40	50	50	75
11	**4g**	**3e**	toluene	40	50	70	66
12	**4g**	**3b**	toluene	25	48	87	87
13	**4g**	**3b**	CH_2Cl_2	25	48	80	68
14	**4g**	**3b**	Et_2O	25	46	51	84
15	**4g**	**3b**	*p*-xylene	25	40	91	89
16[d]	**4g**	**3b**	*p*-xylene	25	46	92	91
17[e]	**4g**	**3b**	*p*-xylene	25	58	89	87
18[f]	**4g**	**3b**	*p*-xylene	25	72	85	81

[a]The reactions of **1a** (0.10 mmol), **2a** (0.11 mmol), and **3** (0.12 mmol) were carried out in toluene (2 mL) at the indicated temperature in the presence of catalyst **4** (10 mol %) with 5 Å MS (100 mg). [b]Isolated yield. [c]Determined by HPLC. [d]Catalyst **4g** (5 mol %). [e]Catalyst **4g** (2.5 mol %). [f]Catalyst **4g** (1 mol %).

1, entries 1−7). The reactions were performed in toluene at 40 °C with 5 Å MS as the water scavenger. Chiral phosphoric acid **4g** with 9-anthracenyl substituents proved to be the best catalyst for this transformation, giving the desired product **5a** in 85% yield and with 82% ee (entry 7). The variation of ester moieties on Hantzsch esters (**3b**−**e**) was also examined in this transformation (entries 8−11). It turned out that methyl Hantzsch ester **3b** could give the product with the best results in terms of both yield and enantioselectivity (entry 8). The reaction temperature was decreased to the room temperature, and a better result was obtained (entry 12). Various reaction solvents were then evaluated (entries 13−15). It is noteworthy that when the catalyst loading was reduced to 5 mol %, yield and enantioselectivity increased (entry 16). Finally, with the lower catalyst loadings (2.5 and 1 mol %) at the same temperature, lower yield and ee were observed (entries 17−18).

With the optimal reaction conditions in hand, we next examined the substrate scope for the reaction (Table 2). The reaction of bromo-substituted 2-pyridyl ketone **1a** with various anilines was examined first. To our delight, both electron-rich and electron-deficient anilines were well-tolerated in this transformation, giving the corresponding chiral amines in excellent yields and with enantioselectivities ranging from 89 to 94% ee (entries **5b**−**g**). Naphthalen-2-amine also worked well under the standard reaction conditions, leading to the product in 98% yield with 90% ee. The absolute configuration of **5c** was determined by X-ray crystallographic analysis (see the Supporting Information for details). The following examination of the generality for 2-pyridyl ketones was conducted using 3-methoxyaniline as the amine component. The alteration of substituents on 2-pyridyl ketones showed considerable impact on the stereochemical outcomes (**5h**−**j**). The removal of bromo on 2-pyridyl ketone resulted in slight drop of enantioselectivity (**5h**). Notably, the substrate with an extra ketone functional group was well-tolerated and still provided satisfactory results (**5j**, 85% yield and 81% ee).

To our delight, we found that this reaction could be successfully performed on the gram scale with 2.5 mol % catalyst loading to give the product in 89% yield and with 87% ee, implying the practicability of the reaction (eq 1).

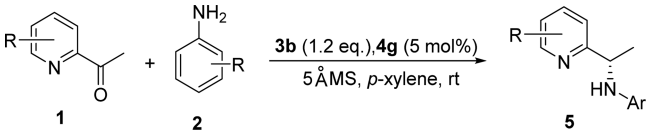


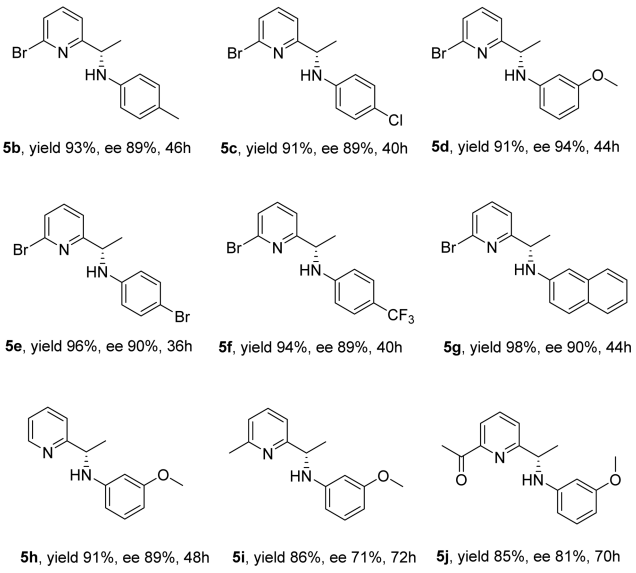
(1)

To understand the stereoselectivity of this enantioselective reductive amination, theoretical calculation with the B3LYP/6-31G(d) method was performed.[15] The special selectivity of the reductive amination process was estimated, and the located transition state structures are shown in Figure 1. Both the

DOI: 10.1021/acs.joc.6b01772
J. Org. Chem. 2016, 81, 11384−11388

Table 2. Scope of the Substrates[a]





[a]The reactions of **1** (0.10 mmol), **2** (0.11 mmol), and **3b** (0.12 mmol) were carried out in *p*-xylene (2 mL) at 25 °C in the presence of catalyst **4g** (5 mol %) with 5 Å MS (100 mg).

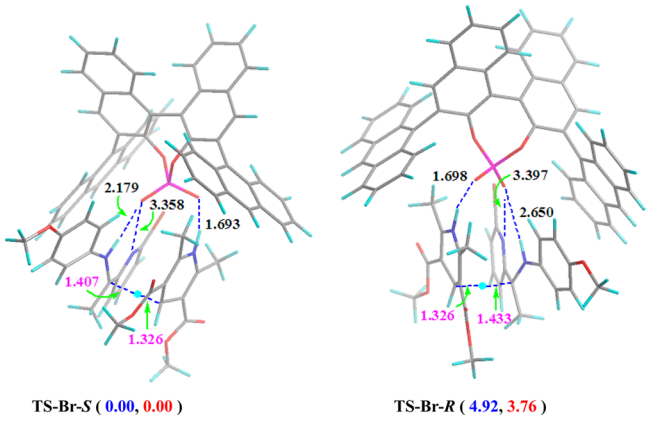


Figure 1. Located transition state structures with distance in angstroms and relative energies in kcal/mol (blue for enthalpy and red for Gibbs free energy). The atoms in the located structures were labeled as blue for nitrogen, red for oxygen, pink for phosphorus, cyan for hydrogen, and gray for carbon.

ketamine moiety in **2a** and Hantzsch ester **3b** could interact with catalyst **4g** by a hydrogen bonding interaction to form a reactant precursor of the active complex (for details, refer to the Supporting Information). The located transition states, as shown in **TS-Br-*S*** and **TS-Br-*R***, suggested the hydrogen transfer process with particular selectivity. Calculated results indicated that the Hantzsch ester approached the protonated imine from its *Re*-facial to undergo hydride transfer and, as shown in **TS-Br-*S***, was more favorable than that from its *Si*-facial, as in **TS-Br-*R***. The located transition state **TS-Br-*S*** was predicted to be more stable than **TS-Br-*R*** by ∼4 kcal/mol to afford the main product experimentally observed. This theoretical calculation agreed very well with the experimental observations and implied that the chiral phosphoric acid provides an acidic and proper chiral environment to promote the hydride transfer from the Hantzsch ester to the protonated imine with high reactivity and particular selectivity.

In light of the theoretical studies, we proposed a detailed mechanism of the transfer hydrogenation process. As shown in Figure 2, the chiral phosphoric acid might interact with both

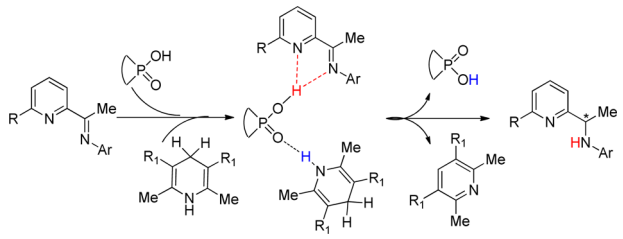


Figure 2. Proposed reaction mechanism.

intermediate imine and HEH by a hydrogen bonding interaction to increase the reactivity of both substrates to promote the transfer hydrogenation significantly and to simultaneously control the selectivity, leading to the enatioselective reductive amination. The nitrogen atom of the pyridyl ring is involved in the formation of hydrogen bonds and might act as an important factor to promote the reaction and control selectivity.

In summary, we developed an efficient chiral Brønsted acid-catalyzed enantioselective reductive amination of 2-pyridyl ketones. Various optically active 1-substituted-1-(pyridyl)-methyl amines were prepared in excellent yields and enantioselectivities. Theoretical studies on the key intermediate imine and transition states indicated the chiral phosphoric acid catalyzed the reductive amination process by a hydrogen bonding interaction with both intermediate imine and HEH. The chiral phosphoric acid provides both an acidic and proper chiral environment to promote the hydride transfer from the Hantzsch ester to the protonated imine with high reactivity and particular selectivity. This newly developed synthetic method was successfully applied in the synthesis of some chiral pyridine-based ligands.

■ EXPERIMENTAL SECTION

All starting materials, reagents, and solvents were purchased from commercial suppliers and used as supplied unless otherwise stated. Toluene and THF were dried over Na and distilled prior to use.

MeCN and CH_2Cl_2 were dried over CaH_2 and distilled prior to use. Reactions requiring anhydrous conditions were performed in oven-dried glassware under a positive pressure of nitrogen. All of the reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel (60-F254). The NMR spectra were recorded on a 400 MHz spectrometer. HRMS spectra were recorded on a TOF-Q mass spectrometer. Infrared spectra were recorded on a FT-IR spectrometer. HPLC analysis was performed. All chiral columns were purchased from Daicel Chemical Industries, Ltd.

General Procedure for the Chiral Phosphoric Acid Catalyzed Enantioselective Reductive Amination. The reaction of amine (**2**, 1.1 equiv), Hantzsch ester (**3**, 1.2 equiv), and catalyst (**4**, 5 mol %) was performed using 5 Å molecular sieves (100 mg) and py-ketone (**1**, 1.0 equiv) in *p*-xylene (2 mL). The reaction mixture was carried out at room temperature as noted and monitored by TLC. Upon completion or between 36−72 h, the crude product was directly purified by silica

DOI: 10.1021/acs.joc.6b01772
J. Org. Chem. 2016, 81, 11384−11388

gel column chromatography (silica gel, 1% of triethylamine in petroleum ether/EtOAc = 20/1) to yield the title compounds.

(S)-N-(1-(6-Bromopyridin-2-yl)ethyl)-4-methoxyaniline **5a**. Colorless oil (28.0 mg, 92% yield, 91% ee) following silica gel chromatography (silica gel, 1% of triethylamine in petroleum ether/EtOAc = 20/1). ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ (ppm) 7.44 (t, 1H, J = 8.0 Hz), 7.29−7.32 (m, 2H), 6.67−6.73 (m, 2H), 6.47−6.51 (m, 2H), 4.50 (dd, 1H, J = 13.6, J = 6.8 Hz), 4.02 (s, 1H), 3.70 (s, 3H), 1.52 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ (ppm) 165.3, 151.2, 140.7, 139. 9, 138.1, 125.2, 117.9, 113.8, 113.8, 54.7, 54.3, 22.2; IR (film) 3392, 2968, 2930, 2831, 1580, 1554, 1513, 1430, 1405, 1235, 1162, 1037, 823, 796 cm^{-1}; ESI HRMS exact mass calcd. for $[C_{14}H_{15}BrN_2O]^+$ requires m/z 306.0368, found m/z 306.0365. $[\alpha]_D^{25}$ = +47.4 (c = 0.24, $CHCl_3$). Enantiomeric excess: 91%, determined by HPLC (Chiracel-AD, hexane/isopropanol = 97/3, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 15.20 min (minor), t_R = 18.46 min (major). The absolute configuration was tentatively assigned by analogy.

(S)-N-(1-(6-Bromopyridin-2-yl)ethyl)-4-methylaniline **5b**. Colorless oil (27.2 mg, 93% yield, 90% ee) following silica gel chromatography (silica gel, 1% of triethylamine in petroleum ether/EtOAc = 20/1). ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ (ppm) 7.44 (t, 1H, J = 7.6 Hz), 7.30−7.33 (m, 2H), 6.91−6.93 (m, 2H), 6.43−6.47 (m, 2H), 4.53 (dd, 1H, J = 11.2 Hz, J = 5.2 Hz), 4.13 (s, 1H), 2.19 (s, 3H), 1.53 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ (ppm) 166.3, 144.4, 141.7, 139.2, 129.7, 126.9, 126.2, 118.9, 113.6, 113.8, 54.8, 23.2, 20.3; IR (film) 3407, 2969, 2924, 2866, 1580, 1555, 1519, 1430, 1405, 1318, 1162, 1121, 808, 795 cm^{-1}; ESI HRMS exact mass calcd. for $[C_{14}H_{15}BrN_2]^+$ requires m/z 290.0419, found m/z 290.0420. $[\alpha]_D^{25}$ = +66.7 (c = 0.25, $CHCl_3$). Enantiomeric excess: 90%, determined by HPLC (Chiracel-AD, hexane/isopropanol = 97/3, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 8.63 min (minor), t_R = 11.37 min (major). The absolute configuration was tentatively assigned by analogy.

(S)-N-(1-(6-Bromopyridin-2-yl)ethyl)-4-chloroaniline **5c**. Solid, mp: 121.0−121.2 °C (28.4 mg, 91% yield, 90% ee) following silica gel chromatography (silica gel, 1% of triethylamine in petroleum ether/EtOAc = 20/1). ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ (ppm) 7.39 (tt, 1H, J = 15.2 Hz, J = 7.6 Hz), 7.28 (d, 1H, J = 8.0 Hz), 7.12 (d, 1H, J = 8.0 Hz), 6.96−7.00 (m, 2H), 6.37−6.39 (m, 2H), 4.43−4.48 (dd, 1H, J = 13.6 Hz, J = 6.8 Hz), 4.36 (s, 1H), 1.46 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ (ppm) 166.3, 145.1, 141.8, 139.2, 129.0, 126.5, 122.4, 118.9, 114.6, 54.6, 23.0; IR (film) 3396, 3350, 3316, 2969, 2926, 1599, 1554, 1504, 1491, 1321, 1165, 1123, 816, 791 cm^{-1}; ESI HRMS exact mass calcd. for $[C_{13}H_{12}BrClN_2]^+$ requires m/z 309.9872, found m/z 311.9839 (isotopomer containing Br m/z 81). $[\alpha]_D^{25}$ = +67.5 (c = 0.23, $CHCl_3$). Enantiomeric excess: 90% determined, by HPLC (Chiracel-AD, hexane/isopropanol = 97/3, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 10.24 min (minor), t_R = 11.84 min (major). The absolute configuration was tentatively assigned by analogy.

(S)-N-(1-(6-Bromopyridin-2-yl)ethyl)-3-methoxyaniline **5d**. Colorless oil (27.8 mg, 91% yield, 94% ee) following silica gel chromatography (silica gel, 1% of triethylamine in petroleum ether/EtOAc = 20/1). ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ (ppm) 7.46 (t, 1H, J = 7.8 Hz), 7.30−7.34 (m, 2H), 7.02 (t, 1H, J = 8.0 Hz), 6.24−6.26 (m, 1H), 6.15−6.17 (m, 1H), 6.09 (t, 1H, J = 2.4 Hz), 4.54−4.59 (dd, 1H, J = 13.2 Hz, J = 6.6 Hz), 4.29 (s, 1H), 3.72(s, 3H), 1.54 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ (ppm) 165.8, 160.7, 148.1, 141.7, 139.1, 129.9, 126.3, 118.9, 106.5, 103.0, 99.5, 55.1, 54.5, 23.1; IR (film) 3403, 2967, 2931, 2834, 1615, 1582, 1554, 1495, 1430, 1211, 1161, 796, 758 cm^{-1}; ESI HRMS exact mass calcd. for $[C_{14}H_{15}BrN_2O]^+$ requires m/z 306.0368, found m/z 306.0371. $[\alpha]_D^{25}$ = +33.2 (c = 0.21, $CHCl_3$). Enantiomeric excess: 94%, determined by HPLC (Chiracel-AD, hexane/isopropanol = 97/3, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 15.31 min (minor), t_R = 19.39 min (major). The absolute configuration was tentatively assigned by analogy.

(S)-4-Bromo-N-(1-(6-bromopyridin-2-yl)ethyl)aniline **5e**. Solid, mp: 108.0−108.3 °C (34.3 mg, 96% yield, 90% ee) following silica gel chromatography (silica gel, 1% of triethylamine in petroleum ether/EtOAc = 20/1). ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ (ppm) 7.46 (t, 1H, J = 7.6 Hz), 7.34 (d, 1H, J = 8.8 Hz), 7.26 (d, 1H, J = 7.6 Hz), 7.17−7.21 (m, 2H), 6.39−6.43 (m, 2H), 4.49−4.56 (m, 1H), 4.34 (d, 1H, J = 5.8 Hz), 1.53 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ (ppm) 165.3, 145.7, 141.9, 139.2, 131.9, 126.5, 118.9, 115.1, 109.4, 54.5, 23.1; IR (film) 3390, 2978, 2924, 1591, 1551, 1500, 1445, 1396, 1166, 1072, 813, 788 cm^{-1}; ESI HRMS exact mass calcd. for $[C_{13}H_{12}Br\ {}_2N_2]^+$ requires m/z 353.9367, found m/z 355.9337 (one isotopomer containing 79 Br and one isotopomer containing Br m/z 81). $[\alpha]_D^{25}$ = +53 (c = 0.39, $CHCl_3$). Enantiomeric excess: 90%, determined by HPLC (Chiracel-AD, hexane/isopropanol = 97/3, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 11.27 min (minor), t_R = 13.29 min (major). The absolute configuration was tentatively assigned by analogy.

(S)-N-(1-(6-Bromopyridin-2-yl)ethyl)-4-(trifluoromethyl)aniline **5f**. Colorless oil (34.4 mg, 94% yield, 89% ee) following silica gel chromatography (silica gel, 1% of triethylamine in petroleum ether/EtOAc = 20/1). ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ (ppm) 7.41 (t, 1H, J = 7.6 Hz), 7.26−7.29 (m, 3H), 7.20 (d, 1H, J = 8.0 Hz), 6.48 (d, 2H, J = 8.8 Hz), 4.52−4.57 (dd, 1H, J = 13.2 Hz, J = 6.4 Hz), 1.49 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ (ppm) 164.7, 149.0, 141.9, 139.3, 126.6, 126.6 (q, J = 3.8 Hz), 124.8 (q, J = 268.9 Hz), 119.2 (q, J = 32.4 Hz), 118.8, 112.6, 54.1, 22.9; IR (film) 3326, 2974, 2928, 2854, 1620, 1581, 1557, 1432, 1337, 1162, 1097, 1063, 818, 793 cm^{-1}; ESI HRMS exact mass calcd. for $[C_{14}H_{12}BrF\ {}_3N_2]^+$ requires m/z 344.0136, found m/z 344.0135. $[\alpha]_D^{25}$ = +56 (c = 0.47, $CHCl_3$). Enantiomeric excess: 89%, determined by HPLC (Chiracel-AD, hexane/isopropanol = 97/3, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 9.09 min (minor), t_R = 9.99 min (major). The absolute configuration was tentatively assigned by analogy.

(S)-N-(1-(6-Bromopyridin-2-yl)ethyl)naphthalen-2-amine **5g**. Solid, mp: 181.0−181.5 °C (32.0 mg, 98% yield, 90% ee) following silica gel chromatography (silica gel, 1% of triethylamine in petroleum ether/EtOAc = 20/1). ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ (ppm) 7.62 (t, 2H, J = 8.8 Hz), 7.50 (d, 1H, J = 8.2 Hz), 7.43 (t, 1H, J = 7.6 Hz), 7.29−7.33 (m, 3H), 7.15−7.19 (m, 1H), 6.96 (dd, 1H, J = 8.8 Hz, J = 2.4 Hz), 6.64 (d, 1H, J = 2.2 Hz), 4.69−4.74 (dd, 1H, J = 13.6 Hz, J = 6.8 Hz), 4.48 (s, 1H), 1.60 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ (ppm) 165.6, 144.3, 141.8, 139.2, 134.9, 129.0, 127.6, 126.4, 126.3, 126.0, 122.2, 118.9, 188.0, 105.8, 54.5, 23.1; IR (film) 3411, 3050, 2972, 2929, 1629, 1555, 1521, 1405, 1227, 1164, 1126, 831, 745 cm^{-1}; ESI HRMS exact mass calcd. for $[C_{17}H_{15}BrN\ {}_2]^+$ requires m/z 326.0419, found m/z 326.0415. $[\alpha]_D^{25}$ = +3.4 (c = 0.46, $CHCl_3$). Enantiomeric excess: 90%, determined by HPLC (Chiracel-AD, hexane/isopropanol = 97/3, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 17.20 min (minor), t_R = 31.02 min (major). The absolute configuration was tentatively assigned by analogy.

(S)-3-Methoxy-N-(1-(pyridin-2-yl)ethyl)aniline **5h**. Colorless oil (22.3 mg, 91% yield, 89% ee) following silica gel chromatography (silica gel, 1% of triethylamine in petroleum ether/EtOAc = 20/1). ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ (ppm) 7.59−7.633 (m, 1H), 7.33−7.35 (m, 1H), 7.12−7.16 (m, 1H), 7.02 (t, 1H, J = 8.0 Hz), 6.18−6.25 (m, 2H), 6.12 (t, 1H, J = 2.4 Hz), 4.59−4.64 (tt, 1H, J = 13.2 Hz, J = 6.8 Hz), 4.49 (s, 1H), 3.70 (s, 3H), 1.54 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ (ppm) 163.8, 160.7, 149.3, 148.5, 136.8, 129.9, 121.9, 120.3, 106.5, 102.7, 99.4, 54.9, 54.7, 23.1; IR (film) 3400, 2957, 29260, 2855, 1725, 1614, 1590, 1494, 1464, 1433, 1208, 1161, 1051, 829, 748, 688 cm^{-1}; ESI HRMS exact mass calcd. for $[C_{14}H_{16}N_2O]^+$ requires m/z 228.1263, found m/z 228.1264. $[\alpha]_D^{25}$ = +12.1 (c = 0.13, $CHCl_3$). Enantiomeric excess: 89%, determined by HPLC (Chiracel-AD, hexane/isopropanol = 94/6, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 13.96 min (minor), t_R = 16.10 min (major). The absolute configuration was tentatively assigned by analogy.

(S)-3-Methoxy-N-(1-(6-methylpyridin-2-yl)ethyl)aniline **5i**. Colorless oil (22.2 mg, 86% yield, 71% ee) following silica gel chromatography (silica gel, 1% of triethylamine in petroleum ether/EtOAc = 20/1). ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ (ppm) 7.48 (t, 1H, J = 7.6 Hz), 7.13 (d, 1H, J = 8.0 Hz), 6.98−7.03 (m, 2H), 6.17−

DOI: 10.1021/acs.joc.6b01772
J. Org. Chem. 2016, 81, 11384−11388

6.23 (m, 2H), 6.12 (t, 1H, J = 2.0 Hz), 4.54−4.59 (m, 2H), 3.70 (s, 3H), 2.56 (s, 3H), 1.52 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ (ppm) 163.1, 160.6, 157.8, 148.5, 137.1, 129.8, 121.5, 117.0, 106.4, 102.5, 99.3, 54.9, 54.6, 24.4, 23.3; IR (film) 3404, 2959, 2926, 2855, 1728, 1592, 1496, 1458, 1210, 1159, 1048, 750, 688 cm^{-1}; ESI HRMS exact mass calcd. for $[C_{15}H_{18}N_2O]^+$ requires m/z 242.1419, found m/z 242.1421. $[\alpha]_D^{25}$ = +25.3 (c = 0.21, CHCl3). Enantiomeric excess: 71%, determined by HPLC (Chiracel-AD, hexane/isopropanol = 97/3, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 10.70 min (minor), t_R = 11.79 min (major). The absolute configuration was tentatively assigned by analogy.

(S)-1-(6-(1-((3-Methoxyphenyl)amino)ethyl)pyridin-2-yl)-ethanone ***5j***. Colorless oil (27.6 mg, 85% yield, 81% ee) following silica gel chromatography (silica gel, 1% of triethylamine in petroleum ether/EtOAc = 20/1). ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ (ppm) 7.87−7.89 (m, 1H), 7.74 (t, 1H, J = 7.8 Hz), 7.49−7.52 (m, 1H), 7.03 (t, 1H, J = 8.0 Hz), 6.19−6.27 (m, 2H), 6.14 (t, 1H, J = 2.4 Hz), 4.67−4.69 (m, 1H), 4.48 (s, 1H), 3.72 (s, 3H), 2.76 (s, 3H), 1.58 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ (ppm) 200.3, 163.3, 160.8, 153.1, 148.4, 137.6, 129.9, 123.8, 119.8, 106.7, 102.7, 99.7, 54.5, 54.0, 25.7, 23.0; IR (film) 3399, 2963, 2929, 2856, 1695, 1615, 1592, 1495, 1456, 1357, 1286, 1213, 1161, 1051, 816, 748, 688 cm^{-1}; ESI HRMS exact mass calcd. for $[C_{16}H_{18}N_2O_2]^+$ requires m/z 270.1368, found m/z 270.1364. $[\alpha]_D^{25}$ = +30.5 (c = 0.22, $CHCl_3$). Enantiomeric excess: 81%, determined by HPLC (Chiracel-AD, hexane/isopropanol = 97/3, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 15.49 min (major), t_R = 18.44 min (minor). The absolute configuration was tentatively assigned by analogy.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01772.

Crystallographic information (CIF)

CIF/PLATON report of crystallographic information (PDF)

^{1}H NMR and ^{13}C NMR spectra, HPLC chromatograms, X-ray data, atom coordinates, and absolute energies of theoretical calculated structures (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: aarexit@xjnu.edu.cn.

*E-mail: luosw@ustc.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Prof. Liu-Zhu Gong for support. We are grateful for financial support from National Natural Science Foundation of China (Grants 21662035, 21472180, and 21062021).

■ REFERENCES

(1) For reviews, see: (a) Chelucci, G. *Tetrahedron: Asymmetry* **2005**, *16*, 2353−2383. (b) Nugent, T. C.; El-Shazly, M. *Adv. Synth. Catal.* **2010**, *352*, 753−819.

(2) Smith, H. E.; Schaad, L. J.; Banks, R.; Wiant, C. J. B.; Jordan, C. F. *J. Am. Chem. Soc.* **1973**, *95*, 811−818.

(3) (a) Shin, C.; Okabe, A.; Ito, A.; Yonezawa, Y. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1583. (b) Okabe, A.; Ito, A.; Okumura, K.; Shin, C. *Chem. Lett.* **2001**, *30*, 380.

(4) (a) Baratta, W.; Benedetti, F.; Del Zotto, A.; Fanfoni, L.; Felluga, F.; Magnolia, S.; Putignano, E.; Rigo, P. *Organometallics* **2010**, *29*, 3563−3570. (b) Lyubov, D. M.; Fukin, G. K.; Cherkasov, A. V.; Shavyrin, A. S.; Trifonov, A. A.; Luconi, L.; Bianchini, C.; Meli, A.; Giambastiani, G. *Organometallics* **2009**, *28*, 1227−1232. (c) Gnanaprakasam, B.; Milstein, D. *J. Am. Chem. Soc.* **2011**, *133*, 1682−1685. (d) Felluga, F.; Baratta, B.; Fanfoni, F.; Pitacco, G.; Rigo, P.; Benedetti, F. *J. Org. Chem.* **2009**, *74*, 3547−3550. (e) Baratta, W.; Chelucci, G.; Magnolia, S.; Siega, K.; Rigo, P. *Chem. - Eur. J.* **2009**, *15*, 726−732.

(5) (a) Chiu, Y.-H.; dos Santos, O.; Canary, J. W. *Tetrahedron* **1999**, *55*, 12069−12078. (b) Skupinska, K. A.; McEachern, E. J.; Baird, I. R.; Skerlj, R. T.; Bridger, G. J. *J. Org. Chem.* **2003**, *68*, 3546−3551.

(6) (a) Chelucci, G.; Baldino, S.; Chessa, S.; Pinna, G. A.; Soccolini, F. *Tetrahedron: Asymmetry* **2006**, *17*, 3163−3169. (b) Chelucci, G.; Baldino, S.; Solinas, R.; Baratta, W. *Tetrahedron Lett.* **2005**, *46*, 5555−5558. (c) Kuduk, S. D.; DiPardo, R. M.; Chang, R. K.; Ng, C.; Bock, M. G. *Tetrahedron Lett.* **2004**, *45*, 6641−6643. (d) Cimarelli, C.; Palmieri, G. *Tetrahedron: Asymmetry* **2000**, *11*, 2555−2563. (e) Miao, C. K.; Sorcek, R.; Jones, P. J. *Tetrahedron Lett.* **1993**, *34*, 2259−2262. (f) Mehmandoust, M.; Marazano, C.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1185−1187. (g) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600−3740. (h) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **2002**, *67*, 7819−7832. (i) Chelucci, G.; Baldino, S.; Chessa, S. *Tetrahedron* **2006**, *62*, 619−626.

(7) (a) Chelucci, G. *Tetrahedron: Asymmetry* **1995**, *6*, 811−826. (b) Chelucci, G.; Cabras, M. A.; Saba, A. *Tetrahedron: Asymmetry* **1994**, *5*, 1973−1978. (c) Uenishi, J.; Hiraoka, T.; Yuyama, K.; Yonemitsu, O. *Heterocycles* **2000**, *52*, 719.

(8) (a) Alvaro, G.; Boga, C.; Savoia, D.; Umani, R. A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 875−882. (b) Alvaro, G.; Savoia, D. *Tetrahedron: Asymmetry* **1996**, *7*, 2083−2092. (c) Alvaro, G.; Pacioni, P.; Savoia, D. *Chem. - Eur. J.* **1997**, *3*, 726. (d) Alvaro, G.; Martelli, G.; Savoia, D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 775−784.

(9) (a) Aiquiao, M.; Xun, X.; Lanjun, W.; Yaozhong, J. *Synth. Commun.* **1991**, *21*, 2207. (b) Baratta, W.; Benedetti, F.; Del Zotto, A. *Organometallics* **2010**, *29*, 3563−3570. (c) Uenishi, J.; Hamada, M.; Aburatani, S.; Matsui, K.; Yonemitsu, O.; Tsukube, H. *J. Org. Chem.* **2004**, *69*, 6781−6789.

(10) (a) Xie, J. H.; Zhu, S. F.; Zhou, Q. L. *Chem. Soc. Rev.* **2012**, *41*, 4126. (b) Zheng; Chao; You, S. L. *Chem. Soc. Rev.* **2012**, *41*, 2498. (c) Han, Z. Y.; Xiao, H.; Chen, X. H.; Gong, L. Z. *J. Am. Chem. Soc.* **2009**, *131*, 9182−9183.

(11) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781−3783.

(12) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424−7427.

(13) For reviews on BINOL-phosphoric acids, see: (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (b) Terada, M. *Chem. Commun.* **2008**, 4097. (c) Adair, G.; Mukherjee, S.; List, B. *Aldrichimica Acta* **2008**, *41*, 31. (d) Terada, M. *Synthesis* **2010**, *2010*, 1929. (e) Terada, M. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 101. (f) Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res.* **2011**, *44*, 1156−1171. (g) Henseler, A.; Kato, M.; Mori, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 8180−8183.

(14) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, W. C. D. *J. Am. Chem. Soc.* **2006**, *128*, 84−86.

(15) Frisch, M. J., et al. Gaussian 03, revision D.01; Gaussian, Inc.: Wallingford, CT, 2004 (for complete ref 15, see the Supporting Information).

DOI: 10.1021/acs.joc.6b01772
J. Org. Chem. 2016, 81, 11384−11388