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Asymmetric Addition of Pyridyl Aluminum Reagents to Aldehydes Catalyzed by a Titanium(IV) Catalytic System of (*R*)-H_8-BINOLate

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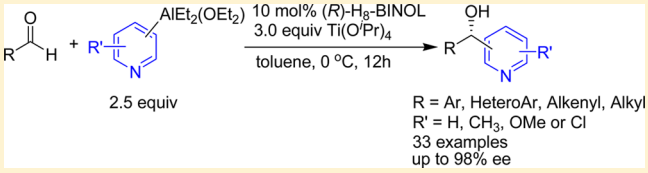
Supporting Information

ABSTRACT: The asymmetric addition of pyridyl aluminum reagents to aldehydes has been successfully developed by employing a titanium(IV) catalytic system of (*R*)-H_8-BINOLate, which affords a series of valuable optically active diarylmethanols containing various pyridyl groups in high yields with excellent enantioselectivities of up to 98% ee.



INTRODUCTION

The catalytic asymmetric synthesis of chiral aryl alcohols has attracted extensive attention in the past decade because they are very important precursors to many biologically active compounds.[1] The enantioselective addition of carbon-based nucleophiles to organic carbonyl compounds provides a straightforward strategy for the construction of optically active alcohols.[2] Arylboronic acids,[3] arylzinc,[4] arylaluminum,[5] and aryltitanium reagents[6] have demonstrated to be the excellent nucleophiles for the asymmetric addition to carbonyl compounds. Additionally, aryl Grignard reagents[7] and arylithiums[8] after mixing with $Ti(O^iPr)_4$ have been used as aryl sources for the asymmetric addition to organic carbonyl compounds, providing an alternative method for synthesizing diarylmethanols in high enantioselectivity.

Chiral diaryl alcohols bearing heteroaryls such as furyl, thienyl, pyridyl, or indolyl groups are well-known for their biological activity as well as being key substructures in bioactive compounds and pharmaceuticals.[9] Their syntheses via addition of aryl nucleophiles to heteroaryl-substituted carbonyl compounds or reduction of diaryl ketones bearing heteroaryl groups have been sporadically reported in a few papers. The catalytic enantioselective addition of heteroaryl nucleophiles to organic carbonyl compounds provided a systematical approach to synthesize chiral heteroaryl alcohols. Recently, the optically active thienyl alcohols have been realized through the asymmetric additions of thienylboronic acid[10] or thienylaluminum reagents[11] to organic carbonyl compounds in good yields and high enantioselectivities. The optically active furyl alcohols were also reported through the asymmetric addition of furylaluminum reagent[12] or furyltitanium reagent[13] to ketones in the presence of 10 mol % (*S*)-BINOL. More recently, heteroaryl zinc[14] and titanium reagents[15] bearing thienyl, benzothienyl, furyl, and indolyl groups were also applied to asymmetric addition of aldehydes affording aryl heteroaryl or diheteroaryl methanol derivatives in high enantioselectivity. However, the more attractive asymmetric addition of pyridyl nucleophiles to organic carbonyl compounds has not been reported up to now. Herein, we report the catalytic asymmetric addition of pyridyl aluminum reagents to aldehydes catalyzed by a titanium(IV) catalyst of (*R*)-H_8-BINOLate to provide a systematical synthesis of the chiral diarylmethanols bearing various pyridyl groups.

RESULTS AND DISCUSSION

The pyridyl aluminum reagents were prepared through the reaction of $AlEt_2Cl$ with the corresponding pyridyl lithium in situ produced from the halogen−lithium exchange of pyridyl bromide with ^{n}BuLi using procedures similar to those previously reported.[16] The resulting solution was filtered, followed by an evaporation of the solvent under reduced pressure to afford the corresponding pyridyl aluminum reagent (pyridyl)$AlEt_2(OEt_2)$ in a quantative yield which was directly used in the next asymmetric addition reactions. Asymmetric addition reactions of (3-pyridyl)$AlEt_2(OEt_2)$ to 4-methylbenzaldehyde (**1b**) were first screened using (*S*)-BINOL as chiral ligand, and the results are summarized in Table 1. Different from addition reactions of $AlPhEt_2(THF)$ to aldehydes,[5c] the addition of (3-pyridyl)$AlEt_2(OEt_2)$ afforded the pyridyl addition product **7a** exclusively, indicating that the addition of pyridyl aluminum to aldehyde was superior in our current reaction system. The optimal reaction conditions of 3.0 equiv of $Ti(O^iPr)_4$ and 2.5 equiv of (3-pyridyl)$AlEt_2(OEt_2)$ in the presence of 10 mol % (*S*)-BINOL in toluene at 0 °C were found to afford the corresponding product **3ba** in 88% yield with 81% ee (entry 2). Next, the different chiral ligands were tested for asymmetric addition reactions (entries 8−11). Results showed that the modified (*S*)-BINOL derivatives afforded the addition product in low enantioselectivity, and (*R*)-H_8-BINOL was the most efficient to afford **3ba** in 91% yield with excellent enantioselectivity of 90% ee (entry 11), which was consistent with the previously reported result of asymmetric addition of aldehydes probably due to the smaller

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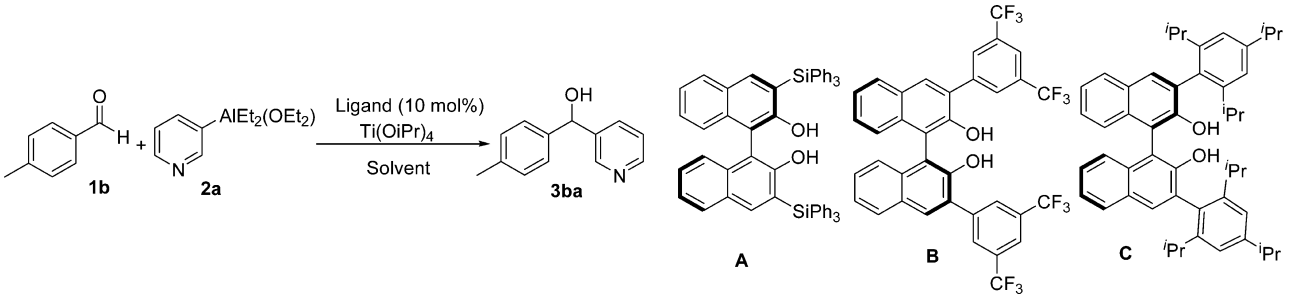
Table 1. Optimization of Enantioselective 3-Pyridyl Addition to 4-Methylbenzaldehyde[a]



entry	ligand	$Ti(O^iPr)_4$ (equiv)[b]	**2a** (equiv)[b]	solvent	temp (°C)	yield (%)	ee (%)[c]
1	(*S*)-BINOL	2.5	2.5	toluene	0	82	70
2	(*S*)-BINOL	3.0	2.5	toluene	0	88	81
3	(*S*)-BINOL	3.5	2.5	toluene	0	92	79
4	(*S*)-BINOL	3.0	2.0	toluene	0	65	73
5	(*S*)-BINOL	3.0	2.5	THF	0	86	75
6	(*S*)-BINOL	3.0	2.5	Et_2O	0	89	66
7	(*S*)-BINOL	3.0	2.5	CH_2Cl_2	0	85	64
8	**A**	3.0	2.5	toluene	0	81	7 (−)
9	**B**	3.0	2.5	toluene	0	86	10
10	**C**	3.0	2.5	toluene	0	83	rac
11	(*R*)-H_8-BINOL	3.0	2.5	toluene	0	91	90 (−)
12	(*R*)-H_8-BINOL	3.0	2.0	toluene	0	83	88 (−)
13	(*R*)-H_8-BINOL	3.0	1.5	toluene	0	75	87 (−)
14	(*R*)-H_8-BINOL	3.5	2.5	toluene	0	88	83 (−)
15	(*R*)-H_8-BINOL	2.5	2.5	toluene	0	85	90 (−)
16	(*R*)-H_8-BINOL	3.0	2.5	THF	0	88	87 (−)
17	(*R*)-H_8-BINOL	3.0	2.5	*n*-hexane	0	31	65 (−)
18	(*R*)-H_8-BINOL	3.0	2.5	Et_2O	0	85	88 (−)
19	(*R*)-H_8-BINOL	3.0	2.5	CH_2Cl_2	0	82	90 (−)
20	(*R*)-H_8-BINOL	3.0	2.5	toluene	rt	95	65 (−)
21	(*R*)-H_8-BINOL	3.0	2.5	toluene	−10	65	88 (−)

[a]4-Methylbenzaldehyde (1.00 mmol), solvent (5.0 mL), time: 12 h. [b]Equivalents of $Ti(O^iPr)_4$ and **2a** are relative to 4-methylbenzaldehyde. [c]Enantioselectivities were determined by HPLC.

dihedral angle of H_8-BINOL compared with BINOL.[17] Further optimization of the asymmetric addition of (3-pyridyl)-$AlEt_2(OEt_2)$ to 4-methylbenzaldehyde employing (*R*)-H_8-BINOL as chiral ligand (entries 11−21) showed that this reaction employing 3.0 equiv of $Ti(O^iPr)_4$ and 2.5 equiv of (3-pyridyl)$AlEt_2(OEt_2)$ in toluene was still the best (entry 11). Lowering the temperature to −10 °C did not improve the enantioselectivity of the asymmetric addition product **3ba** (entry 21).

With the optimized conditions established, the asymmetric additions of 3-pyridyl aluminums to various aromatic, heteroaromatic, α,β-unsaturated, and aliphatic aldehydes were examined, and the results are presented in Table 2. It was found that the substituent's position on the aromatic aldehydes had an effect on the enantioselectivity of 3-pyridyl addition products (entries 1−16). For aromatic aldehydes with either an electron-withdrawing or an electron-donating substituent at the para- or meta-position, 3-pyridyl additions afforded the corresponding alcohols in high yields with excellent enantioselectivities of 90% ee or greater, except for substrates 3-chlorobenzaldehyde, 4-trifluoromethylbenzaldehyde, and 4-fluorobenzaldehyde, which afforded the corresponding products **3ia** (85% ee, entry 9), **3oa** (82% ee, entry 15), and **3pa** (70% ee, entry 16), respectively. However, for aromatic aldehydes with either an electron-withdrawing or an electron-donating substituent at the ortho-position, 3-pyridyl additions afforded the corresponding products in low enantioselectivities (entries 6, 10, and 12), except for 2-methylbenzaldehyde (90% ee, entry 3). Especially, for 2-nitrobenzaldehyde, the product **3na** was obtained in low enantioselectivity of 33% ee (entry 12). For the ortho-substituted aromatic aldehydes, low enantioselectivities were obtained, probably because of the chelation effect from the ortho substitutent: coordination to the metal center resulted in small differentiation between re-face and si-face thus reducing the enantioselectivity. The effect of chelate coordination was also found for heteroaromatic aldehydes such as thiophene-2-carbaldehyde and furan-2-carbaldehyde: the diheteroaryl methanols **3qa** and **3ra** were obtained in good yields with moderate enantioselectivities (entries 17 and 18). For the α,β-unsaturated aldehydes, asymmetric addition afforded the corresponding 3-pyridyl methanols **3sa−ua** in moderate to good enantioselectivities of 66−81% ee (entries 19−22). The aliphatic aldehydes including linear, branched, and cyclic aldehydes were also examined, and the reactions afforded the corresponding products **3va−ya** in high yields but with low to moderate enantioselectivities of 48−75% ee (entries 19−22). To determine the absolute configuration of the 3-pyridyl addition products, the 3-pyridyl methanol **3ka** containing a heavy bromine atom was characterized by an X-ray diffraction study, and the crystal data confirmed an *S*-configuration for **3ka** (see Supporting Information for details).

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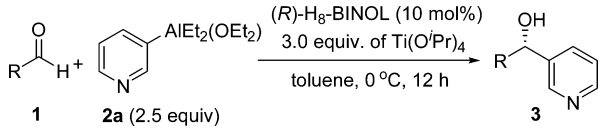
Table 2. Enantioselective Addition of 3-Pyridyl Aluminum Reagent to Aldehydes Catalyzed by the Titanium Catalyst of (*R*)-H$_8$-BINOLate[a]



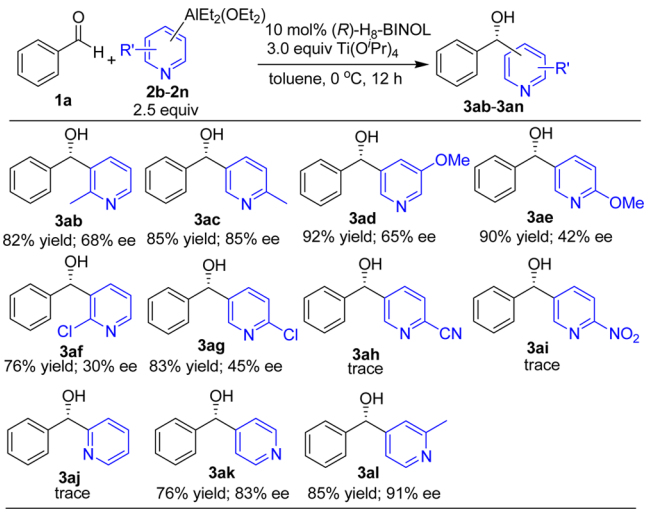
entry	RCHO	product	yield (%)	ee (%)[b]
1	C_6H_5CHO (**1a**)	**3aa**	93	89
2	4-$CH_3C_6H_4CHO$ (**1b**)	**3ba**	91	90
3	2-$CH_3C_6H_4CHO$ (**1c**)	**3ca**	86	90
4	4-^{t}BuC_6H_4CHO (**1d**)	**3da**	86	97
5	4-(MeO)C_6H_4CHO (**1e**)	**3ea**	93	90
6	2-(MeO)C_6H_4CHO (**1f**)	**3fa**	83	57
7	3,4,5-$(MeO)_3C_6H_2CHO$ (**1g**)	**3ga**	95	96
8	4-ClC_6H_4CHO (**1h**)	**3ha**	92	90
9	3-ClC_6H_4CHO (**1i**)	**3ia**	95	85
10	2-ClC_6H_4CHO (**1j**)	**3ja**	93	66
11	4-BrC_6H_4CHO (**1k**)	**3ka**	93	93 (*S*)[c]
12	2-BrC_6H_4CHO (**1l**)	**3la**	88	66
13	4-$(O_2N)C_6H_4CHO$ (**1m**)	**3ma**	90	98
14	2-$(O_2N)C_6H_4CHO$ (**1n**)	**3na**	82	33
15	4-$(F_3C)C_6H_4CHO$ (**1o**)	**3oa**	88	82
16	4-FC_6H_4CHO (**1p**)	**3pa**	93	70
17	2-thienylaldehyde (**1q**)	**3qa**	86	62
18	2-furylaldehyde (**1r**)	**3ra**	92	59
19	(*E*)-PhCH=CHCHO (**1s**)	**3sa**	93	66
20	(*E*)-2-(MeO)PhCH=CHCHO (**1t**)	**3ta**	88	67
21	$(CH_3)_2C$=CHCHO (**1u**)	**3ua**	87	81
22	^{n}PrCHO (**1v**)	**3va**	85	48
23	^{t}BuCHO (**1w**)	**3wa**	95	49
24	^{i}PrCHO (**1x**)	**3xa**	92	75
25[d]	CyCHO (**1y**)	**3ya**	93	64

[a](*R*)-H$_8$-BINOL (0.10 mmol), Ti(O^{i}Pr)$_4$ (3.00 mmol), **2a** (2.50 mmol), aldehyde (1.00 mmol), toluene (5.0 mL). [b]Enantioselectivities were determined by HPLC. [c]Absolute configuration was determined by an X-ray diffraction, and other absolute configurations were assigned on the analogy of **3ka**. [d]Cy: cyclohexyl group.

To expand the substrate scope of this protocol, various substituted pyridyl aluminum reagents were applied to the asymmetric addition of benzaldehyde (Table 3). For substituted 3-pyridyl aluminum reagents with an electron-donating group, the reactions provided the corresponding 3-pyridyl methanols **3ab**−**ae** in good yields with moderate to good enantioselectivities of 42−85% ee. Reactions of benzaldehyde with substituted 3-pyridyl aluminum reagents bearing a weak electron-withdrawing group (Cl) afforded the corresponding products **3af** and **3ag** in moderated yields with the low enantioselectivities. However, for 2-pyridyl or 3-pyridyl aluminum reagents bearing a strong electron-withdrawing group such as cyano and nitro groups, the reaction efficiency was poor probably due to the weak nucleophilicity. The catalytic system could also be suitable for 4-pyridyl aluminums to afford the corresponding products **3ak** and **3al** in moderate yields with high enantioselectivities of 83% and 91% ee, respectively.

To obtain mechanistic insight, (3-pyridyl)AlEt$_2$(OEt$_2$) additions to **1a** in the presence of 20, 40, 60, 80, or 100% ee of (*R*)-H$_8$-BINOL were examined, which afforded **3aa** in 24.4, 40.9, 41.1, 59.9, and 88.6% ee, respectively. A nonlinear effect of ee of **3aa** vs ee of (*R*)-H$_8$-BINOL (Figure 1) that was different from the asymmetric aryl addition system catalyzed by a titanium(IV) catalytic system of (*R*)-H$_8$-BINOLate,[6b] indicating that the more complex dimeric or polymeric titanium complex was probably playing a role in the asymmetric addition of pyridyl nucleophiles to aldehydes, rather than the dinuclear titanium complex [(*R*)-H$_8$-BINOLate)Ti(O^{i}Pr)$_2$]Ti(O^{i}Pr)$_4$, involves only one H$_8$-BINOL.[5a,18] Results showed that it was necessary to further explore the asymmetric addition of heteroaryl nucleophiles to organic carbonyl compounds.

Table 3. Enantioselective Addition of Various Pyridyl Aluminum Reagents to Benzaldehyde[a,b]



[a](*R*)-H$_8$-BINOL (0.10 mmol), Ti(O^{i}Pr)$_4$ (3.00 mmol), pyridyl aluminum (2.50 mmol), aldehyde (1.00 mmol), toluene (5.0 mL). [b]Enantioselectivities were determined by HPLC.

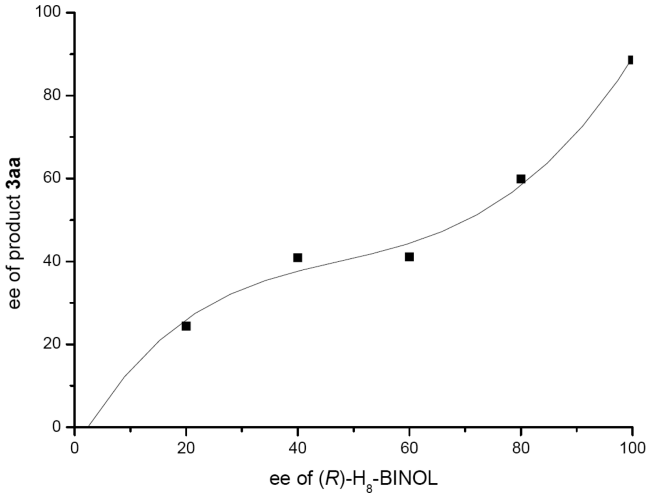


Figure 1. Nonlinear plot of ee of **3aa** vs ee of (*R*)-H$_8$-BINOL.

CONCLUSION

In summary, the catalytic enantioselective heteroarylation of pyridyl aluminum nucleophiles with aldehydes has been successfully developed, employing the simple titanium catalyst (*R*)-H$_8$-BINOLate to afford a series of chiral arylmethanols containing various pyridyl groups in high yields with excellent

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enantioselectivities. The asymmetric addition of 3-pyridyl aluminum reagent to aromatic aldehydes afforded the corresponding diarylmethanols containing a 3-pyridyl group in high yields with excellent enantioselectivities of up to 98% ee. The catalytic system could also be applied to substituted 3-pyridyl or 4-pyridyl aluminums bearing an electron-donating group to afford the corresponding diarylmethanols containing substituted 3-pyridyl or 4-pyridyl groups in good yields with high enantioselectivities of up to 91% ee. Results represent the first asymmetric addition of pyridyl nucleophiles to organic carbonyl compounds. Further investigations of heteroaryl aluminum reagents in asymmetric catalysis are currently underway.

EXPERIMENTAL SECTION

General Methods. All syntheses and manipulations of air- and moisture-sensitive materials were performed under a dry argon atmosphere using standard Schlenk techniques or in a glovebox. Solvents were refluxed and distilled over sodium/benzophenone under argon prior to use. (Pyridyl)$AlEt_2(OEt_2)$ was prepared according to previously reported procedures.[16] The *racemic* alcohols bearing pyridyl groups were prepared by procedures similar to that for the preparation of the chiral alcohols employing BINOL instead of (*R*)-H_8-BINOL. ^1H and ^{13}C NMR spectra in $CDCl_3$ were recorded at 300 MHz/75 MHz (^1H NMR/^{13}C NMR) or 500 MHz/125 MHz (^1H NMR/^{13}C NMR) with chemical shifts given in ppm from internal TMS. High resolution mass spectral (HRMS) data were obtained with an ionization mode of ESI and a TOF analyzer. Enantiomeric excesses were determined by chiral HPLC with different chiral columns (AD-H column, OD-H column, AS-H column, and OJ-H column) with *n*-hexane and ^{i}PrOH as solvents.

General Procedure for the Asymmetric Addition of Pyridyl Aluminum to Aldehydes. Under a dry nitrogen atmosphere, (*R*)-H_8-BINOL (0.0286 g, 0.10 mmol) and $Ti(O^iPr)_4$ (0.88 mL, 3.00 mmol) were mixed in toluene (5 mL) at room temperature. After stirring for 30 min, (pyridyl)$AlEt_2(OEt_2)$ (2.50 mmol) was added to the resulting solution at 0 °C. The mixture was stirred for another 10 min, and an aldehyde (1.00 mmol) was added to the resulting solution at 0 °C. The mixture was allowed to react for 12 h at this temperature and then quenched with H_2O. The aqueous phase was extracted with ethyl acetate (3 × 10 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (silica gel), eluting with petroleum ether and ethyl acetate to give the product **3**. Enantiomeric excesses of products were determined by HPLC using suitable chiral columns from Daicel.

*Phenyl(pyridin-3-yl)methanol (**3aa**).*[19] White solid. Yield (172 mg, 93%); ee = 89%; $[\alpha]^{25}_D$ = −3.64 (*c* 0.86, CH_2Cl_2). The ee was determined by HPLC (Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.8 mL/min, λ = 254 nm). t_R(major) = 16.61 min; t_R(minor) = 19.98 min. ^1H NMR (300 MHz, $CDCl_3$) δ = 8.40 (s, 1 H), 8.26−8.24 (m, 1H), 7.68−7.66 (m, 1H), 7.32−7.25 (m, 4H), 7.19−7.15 (m, 1H), 5.78 (s, 1H), 4.84 (s, br, 1H) ppm. $^{13}C\{^1H\}$ NMR (75.0 MHz, $CDCl_3$): δ = 147.9, 147.7, 143.3, 139.9, 134.5, 128.6, 127.7, 126.5, 123.5, 73.6 ppm.

*Pyridin-3-yl(p-tolyl)methanol (**3ba**).*[20] White solid. Yield (181 mg, 91%); ee = 90%; $[\alpha]^{25}_D$ = +13.33 (*c* 0.69, CH_2Cl_2). The ee was determined by HPLC (Chiralpak OJ-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.8 mL/min, λ = 254 nm). t_R(minor) = 16.50 min; t_R(major) = 17.47 min. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.57−8.54 (s, 1H), 8.46−8.40 (m, 1H), 7.71−7.68 (s, 1H), 7.27−7.21 (m, 3H), 7.17−7.14 (m, 2H), 5.83 (d, *J* = 2.4 Hz, 1H), 2.34 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125.0 MHz, $CDCl_3$): δ = 148.2, 147.9, 140.3, 139.8, 137.6, 134.2, 129.3, 126.5, 123.4, 73.7, 20.9 ppm.

*Pyridin-3-yl(o-tolyl)methanol (**3ca**).* White solid. Mp 94−95 °C. Yield (171 mg, 86%). ee = 90%; $[\alpha]^{25}_D$ = +24.46 (*c* 0.13, CH_2Cl_2). The ee was determined by HPLC (Chiralpak OJ-H column, *n*-hexane/*i*-PrOH = 95:5, flow rate = 0.8 mL/min, λ = 254 nm). t_R(minor) = 24.21 min; t_R(major) = 25.42 min. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.58 (s, 1H), 8.51−8.48 (m, 1H), 7.65−7.62 (s, 1H), 7.27−7.15 (m, 4H), 6.06 (s, 1H), 2.50 (s, 1H), 5.81 (s, 1 H), 2.27 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (75.0 MHz, $CDCl_3$): δ = 148.4, 148.1, 140.8, 138.8, 135.1, 134.9, 130.7, 127.8, 126.4, 126.3, 123.4, 70.8, 19.3 ppm. HRMS (ESI) calcd for $C_{13}H_{14}ON$ $(M + H)^+$ 200.1070, found 200.1064.

*(4-tert-Butylphenyl)(pyridin-3-yl)methanol (**3da**).* White solid. Mp 121−122 °C. Yield (207 mg, 86%). ee = 97%; $[\alpha]^{25}_D$ = −22.35 (*c* 0.51, CH_2Cl_2). The ee was determined by HPLC (Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.8 mL/min, λ = 254 nm). t_R(major) = 9.21 min; t_R(minor) = 10.95 min. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.57 (s, 1H), 8.43−8.41 (m, 1H), 7.74−7.71 (m, 1H), 7.39−7.36 (m, 2H), 7.29−7.32 (m, 2H), 5.84 (s, 1H), 3.20 (s, 1H), 1.30 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (125.0 MHz, $CDCl_3$): δ = 150.9, 148.3, 148.1, 140.2, 139.6, 134.2, 126.3, 125.6, 123.4, 73.8, 34.5, 31.3 ppm. HRMS (ESI) calcd for $C_{16}H_{20}ON$ $(M + H)^+$ 242.1539, found 242.1533.

*(4-Methoxyphenyl)(pyridin-3-yl)methanol (**3ea**).*[20] White solid. Yield (200 mg, 93%). ee = 90%; $[\alpha]^{25}_D$ = +10.25 (*c* 1.30, CH_2Cl_2). The ee was determined by HPLC (Chiralpak OJ-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.8 mL/min, λ = 254 nm). t_R(major) = 37.20 min; t_R(minor) = 45.12 min. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.59 (s, 1 H), 8.48−8.46 (m, 1H), 7.72−7.68 (m, 1H),7.30−7.23 (m, 3H), 6.91−6.87 (m, 1H), 5.84 (s, 1H), 3.80 (s, 3H), 2.66 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (125.0 MHz, $CDCl_3$): δ = 159.2, 148.2, 147.9, 140.0, 135.5, 134.2, 127.9, 123.3, 114.3, 73.5, 55.3 ppm.

*(2-Methoxyphenyl)(pyridin-3-yl)methanol (**3fa**).*[20] White solid. Yield (178 mg, 83%). ee = 57%; $[\alpha]^{25}_D$ = −7.31 (*c* 1.08, CH_2Cl_2). The ee was determined by HPLC (Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.8 mL/min, λ = 254 nm). t_R(major) = 21.45 min; t_R(minor) = 24.78 min. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.56 (s, 1H), 8.41−8.39 (m, 1H), 7.72−7.69 (m, 1H), 7.29−7.19 (m, 3H), 6.99−6.94 (m, 1H), 6.89−6.86 (m, 1H), 6.06 (s, 1H), 4.04−3.94 (m, 1H), 3.78 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (75.0 MHz, $CDCl_3$): δ = 156.3, 148.3, 148.1, 139.0, 134.2, 131.1, 129.0, 127.3, 123.2, 120.9, 110.6, 69.9, 55.3 ppm.

*Pyridin-3-yl(3,4,5-trimethoxyphenyl)methanol (**3ga**).* Colorless oil. Yield (262 mg, 95%). ee = 96%; $[\alpha]^{25}_D$ = −1.29 (*c* 0.44, CH_2Cl_2). The ee was determined by HPLC (Chiralpak OJ-H column, *n*-hexane/*i*-PrOH = 80:20, flow rate = 0.8 mL/min, λ = 254 nm). t_R(major) = 15.04 min; t_R(minor) = 25.30 min. $[\alpha]^{25}_D$ = −1.29 (*c* 0.44, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.53−8.52 (m, 1H), 8.40−8.37 (m, 1H), 7.72−7.69 (m, 1H), 7.27−7.23 (m, 1H), 6.58 (s, 2H), 5.77 (s, 1H), 3.82 (s, 3H), 3.81 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (75.0 MHz, $CDCl_3$): δ = 153.3, 148.4, 147.9, 139.5, 1389, 137.2, 134.3, 123.5, 103.3, 73.8, 60.8, 56.0 ppm. HRMS (ESI) calcd for $C_{15}H_{18}O_4N$ $(M + H)^+$ 276.1230, found 276.1223.

*(4-Chlorophenyl)(pyridin-3-yl)methanol (**3ha**).* White solid. Mp 112−114 °C. Yield (202 mg, 92%). ee = 90%; $[\alpha]^{25}_D$ = −25.49 (*c* 1.02, CH_2Cl_2). The ee was determined by HPLC (Chiralpak OJ-H column, *n*-hexane/*i*-PrOH = 95:5, flow rate = 0.8 mL/min, λ = 254 nm). t_R(major) = 36.85 min; t_R(minor) = 43.61 min. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.37 (s, 1H), 8.28−8.27 (d, *J* = 3.0 Hz, 1H), 7.67−7.63 (m, 1H), 7.31−7.18 (m, 4H), 5.76 (s, 1H), 5.36 (s, br, 1H) ppm. $^{13}C\{^1H\}$ NMR (125.0 MHz, $CDCl_3$): δ = 148.1, 147.6, 141.8, 139.6, 134.6, 133.5, 128.7, 127.8, 123.6, 72.9 ppm. HRMS (ESI) calcd for $C_{12}H_{11}ONCl$ $(M + H)^+$ 220.0524, found 220.0519.

*(3-Chlorophenyl)(pyridin-3-yl)methanol (**3ia**).* White solid. Mp 114−115 °C. Yield (208 mg, 95%). ee = 85%; $[\alpha]^{25}_D$ = −25.43 (*c* 0.70, CH_2Cl_2). The ee was determined by HPLC (Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 95:5, flow rate = 0.8 mL/min, λ = 254 nm). t_R(major) = 15.71 min; t_R(minor) = 20.61 min. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.31 (s, 1H), 8.23−8.21 (m, 1H), 7.67−7.65 (m, 1H), 7.34 (s, 1H), 7.23−7.17 (m, 4H), 6.21 (s, br, 1H), 5.73 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (125.0 MHz, $CDCl_3$): δ = 147.9, 147.4, 145.4, 139.7, 134.7, 134.4, 129.8, 127.7, 126.5, 124.6, 123.7, 72.8 ppm. HRMS (ESI) calcd for $C_{12}H_{11}ONCl$ $(M + H)^+$ 220.0524, found 220.0519.

*(2-Chlorophenyl)(pyridin-3-yl)methanol (**3ja**).* White solid. Mp 134−135 °C. Yield (204 mg, 93%). ee = 66%; $[\alpha]^{25}_D$ = +3.84 (*c* 1.46, CH_2Cl_2). The ee was determined by HPLC (Chiralpak AS-H column,

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n-hexane/*i*-PrOH = 90:10, flow rate = 0.8 mL/min, λ = 254 nm). t_R(major) = 14.98 min; t_R(minor) = 17.91 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.46 (s, 1H), 8.32−8.29 (m, 1H), 7.69−7.64 (m, 1H), 7.33−7.18 (m, 4H), 6.20 (s, 1H), 5.10 (s, br, 1H) ppm. ^{13}C{^{1}H} NMR (125.0 MHz, $CDCl_3$): δ = 148.4, 148.2, 140.5, 138.5, 134.9, 132.2, 129.5, 129.0, 127.8, 127.3, 123.5, 70.1 ppm. HRMS (ESI) calcd for $C_{12}H_{11}ONCl$ $(M + H)^+$ 220.0524, found 220.0519.

(4-Bromophenyl)(pyridin-3-yl)methanol (**3ka**). White solid. Mp 123−124 °C. Yield (245 mg, 93%). ee = 93%; $[\alpha]^{25}_D$ = −9.39 (*c* 0.99, CH_2Cl_2). The ee was determined by HPLC (Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.8 mL/min, λ = 254 nm). t_R(major) = 28.19 min; t_R(minor) = 31.85 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.38 (s, 1H), 8.31−8.29 (m, 1H), 7.67−7.63 (m, 1H), 7.47−7.43 (m, 2H), 7.27−7.19 (m, 3H), 5.76 (s, 1H), 5.02 (s, 1H) ppm. ^{13}C{^{1}H} NMR (75.0 MHz, $CDCl_3$): δ = 148.1, 147.6, 142.3, 139.6, 134.6, 131.7, 128.2, 123.6, 121.6, 73.0 ppm. HRMS (ESI) calcd for $C_{12}H_{11}ONBr$ $(M + H)^+$ 264.0019, found 264.0013.

(2-Bromophenyl)(pyridin-3-yl)methanol (**3la**). White solid. Mp 131−132 °C. Yield (232 mg, 88%). ee = 66%; $[\alpha]^{25}_D$ = +10.50 (*c* 1.20, CH_2Cl_2). The ee was determined by HPLC (Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.8 mL/min, λ = 254 nm). t_R(major) = 13.20 min; t_R(minor) = 16.46 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.54 (s, 1H), 8.38−8.36 (m, 1H), 7.70−7.62 (m, 2H), 7.54−7.51 (m, 1H), 7.39−7.33 (m, 1H), 7.26−7.14 (m, 2H), 6.19 (s, 1H), 4.40 (s, 1H) ppm. ^{13}C{^{1}H} NMR (75.0 MHz, $CDCl_3$): δ = 148.7, 148.5, 142.0, 138.2, 134.8, 132.9, 129.4, 128.3, 127.9, 123.4, 122.5, 72.5 ppm. HRMS (ESI) calcd for $C_{12}H_{11}ONBr$ $(M + H)^+$ 264.0019, found 264.0014.

(4-Nitrophenyl)(pyridin-3-yl)methanol (**3ma**). Yellow solid. Mp 187−188 °C. Yield (207 mg, 90%). ee = 98%; $[\alpha]^{25}_D$ = −24.09 (*c* 0.66, CH_2Cl_2). The ee was determined by HPLC (Chiralpak OJ-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm). t_R(major) = 37.54 min; t_R(minor) = 59.95 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.66−8.65 (m, 1 H), 8.47−8.45 (m, 1 H), 8.23−8.20 (m, 2H), 7.78−7.69 (m, 3H), 7.38−7.33 (m, 1H), 6.46−6.45 (m, 1H), 5.98−5.96 (m, 1 H) ppm. ^{13}C{^{1}H} NMR (75.0 MHz, DMSO-d_6): δ = 152.9, 149.1, 148.5, 147.0, 140.3, 134.5, 127.75, 124.1, 71.9 ppm. HRMS (ESI) calcd for $C_{12}H_{11}O_3N_2$ $(M + H)^+$ 231.0764, found 231.0759.

(2-Nitrophenyl)(pyridin-3-yl)methanol (**3na**). Yellow oil. Yield (188 mg, 82%). ee = 33%; $[\alpha]^{25}_D$ = +9.84 (*c* 1.04, CH_2Cl_2). The ee was determined by HPLC (Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm). t_R(major) = 21.52 min; t_R(minor) = 26.93 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.39 (s, 1H), 8.30−8.28 (m, 1H), 7.94−7.87 (m, 2H), 7.68−7.63 (m, 2H), 7.48−7.42 (m, 1H), 7.23−7.18 (m, 1H), 6.44 (s, 1H), 5.29 (br, 1H) ppm. ^{13}C{^{1}H} NMR (75.0 MHz, $CDCl_3$): δ = 148.12, 148.06, 147.7, 138.3, 138.2, 135.2, 133.7, 129.0, 128.6, 124.6, 123.5, 68.7 ppm. HRMS (ESI) calcd for $C_{12}H_{11}O_3N_2$ $(M + H)^+$ 231.0764, found 231.0759.

Pyridin-3-yl(4-(trifluoromethyl)phenyl)methanol (**3oa**). White solid. Mp 106−107 °C. Yield (223 mg, 88%). ee = 82%; $[\alpha]^{25}_D$ = −7.14 (*c* 1.33, CH_2Cl_2). The ee was determined by HPLC (Chiralpak OJ-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.8 mL/min, λ = 254 nm). t_R(major) = 10.79 min; t_R(minor) = 13.32 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.45 (s, 1H), 8.36 (s, 1H), 7.66−7.47 (m, 5H), 7.26−7.23 (m, 1H), 5.88 (s, 1H), 4.78 (s, br, 1H) ppm. ^{13}C{^{1}H} NMR (125.0 MHz, $CDCl_3$): δ = 148.4, 147.7, 147.2, 139.5, 134.7, 129.9 (q, *J* = 32.5 Hz), 126.7, 125.6 (q, *J* = 2.5 Hz), 124.0 (q, *J* = 270.0 Hz), 123.7, 73.1 ppm. HRMS (ESI) calcd for $C_{13}H_{11}ONF_3$ $(M + H)^+$ 254.0787, found 254.0782.

(4-Fluorophenyl)(pyridin-3-yl)methanol (**3pa**).[20] White solid. Yield (189 mg, 93%). ee = 70%; $[\alpha]^{25}_D$ = −21.38 (*c* 1.16, CH_2Cl_2). The ee was determined by HPLC (Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.8 mL/min, λ = 254 nm). t_R(major) = 16.26 min; t_R(minor) = 18.93 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.34 (s, 1H), 8.24−8.22 (m, 1H), 7.68−7.65 (m, 1H), 7.29−7.17 (m, 3H), 7.01−6.95 (m, 2H), 5.75 (s, br, 2H) ppm. ^{13}C{^{1}H} NMR (125.0 MHz, $CDCl_3$): δ = 162.1 (d, *J* = 245.0 Hz), 147.7 (d, *J* = 42.5 Hz), 140.0, 139.2 (d, *J* = 2.5 Hz), 134.5, 128.2 (d, *J* = 8.8 Hz), 123.5, 115.5, 115.3, 72.8 ppm.

Pyridin-3-yl(thiophen-2-yl)methanol (**3qa**). White solid. Mp 79−80 °C. Yield (164 mg, 86%). ee = 62%; $[\alpha]^{25}_D$ = −58.62 (*c* 0.29, CH_2Cl_2). The ee was determined by HPLC (Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.7 mL/min, λ = 254 nm). t_R(major) = 25.72 min; t_R(minor) = 33.78 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.55 (s, 1H), 8.43−8.41 (m, 1H), 7.80−7.78 (m, 1H), 7.29−7.25 (m, 2H), 6.96−6.88 (m, 2H), 6.08 (s, 1H), 4.35 (s, br, 1H) ppm. ^{13}C{^{1}H} NMR (75.0 MHz, $CDCl_3$): δ = 148.7, 147.8, 147.4, 139.0, 134.2, 126.8, 125.7, 125.0, 123.5, 69.9 ppm. HRMS (ESI) calcd for $C_{10}H_{10}ONS$ $(M + H)^+$ 192.0478, found 192.0473.

Furan-2-yl(pyridin-3-yl)methanol (**3ra**). Colorless oil. Yield (161 mg, 92%). ee = 59%; $[\alpha]^{25}_D$ = +47.56 (*c* 0.65, CH_2Cl_2). The ee was determined by HPLC (Chiralpak OJ-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.8 mL/min, λ = 254 nm). t_R(major) = 17.02 min; t_R(minor) = 19.14 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.62 (s, 1H), 8.53−8.51 (m, 1H), 7.83−7.80 (m, 1H), 7.41 (m, 1H), 7.33−7.29 (m, 1H), 6.35−6.33 (m, 1H), 6.16−6.14 (m, 1H), 5.88 (s, 1H) ppm. ^{13}C{^{1}H} NMR (125.0 MHz, $CDCl_3$): δ = 155.0, 149.22, 148.3, 142.9, 136.5, 134.4, 123.4, 110.4, 107.8, 67.9 ppm. HRMS (ESI) calcd for $C_{10}H_{10}O_2N$ $(M + H)^+$ 176.0706, found 176.0701.

(E)-3-Phenyl-1-(pyridin-3-yl)prop-2-en-1-ol (**3sa**). Colorless oil. Yield (196 mg, 93%). ee = 66%; $[\alpha]^{25}_D$ = +1.86 (*c* 0.45, CH_2Cl_2). The ee was determined by HPLC (Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.8 mL/min, λ = 254 nm). t_R(major) = 18.77 min; t_R(minor) = 24.17 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.58 (s, 1H), 8.45−8.43 (m, 1H), 7.79−7.76 (m, 1H), 7.35−7.24 (m, 6H), 6.70−6.66 (m, 1H), 6.37−6.29 (m, 1H), 5.41−5.39 (m, 1H), 3.94 (s, br, 1H) ppm. ^{13}C{^{1}H} NMR (75.0 MHz, $CDCl_3$): δ = 148.6, 147.9, 138.6, 136.1, 134.3, 131.2, 130.8, 128.6, 128.0, 126.6, 123.6, 72.7 ppm. HRMS (ESI) calcd for $C_{14}H_{14}ON$ $(M + H)^+$ 212.1070, found 212.1075.

(E)-3-(2-Methoxyphenyl)-1-(pyridin-3-yl)prop-2-en-1-ol (**3ta**). Colorless liquid. Yield (212 mg, 88%). ee = 66%; $[\alpha]^{25}_D$ = +7.89 (*c* 0.48, CH_2Cl_2). The ee was determined by HPLC (Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm). t_R(major) = 20.89 min; t_R(minor) = 30.01 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.59 (s, 1H), 8.43−8.41 (m, 1H), 7.81−7.79 (m, 1H), 7.41−7.38 (m, 1H), 7.25−7.21 (m, 2H), 7.02−6.86 (m, 3H), 6.39−6.30 (m, 1H), 5.41−5.38 (m, 1H), 4.27 (s, br, 1H), 3.81 (m, 3H) ppm. ^{13}C NMR{^{1}H} (125.0 MHz, $CDCl_3$): δ = 156.8, 148.3, 147.9, 138.9, 134.2, 131.5, 129.0, 127.1, 126.2, 125.1, 123.4, 120.5, 110.8, 73.1, 55.3 ppm. HRMS (ESI) calcd for $C_{15}H_{16}O_2N$ $(M + H)^+$ 242.1176, found 242.1177.

3-Methyl-1-(pyridin-3-yl)but-2-en-1-ol (**3ua**). Colorless liquid. Yield (142 mg, 87%). ee = 80%; $[\alpha]^{25}_D$ = +5.16 (*c* 2.19, CH_2Cl_2). The ee was determined by HPLC (Chiralpak OD-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.8 mL/min, λ = 254 nm). t_R(major) = 16.64 min; t_R(minor) = 21.81 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.39 (s, 1H), 8.28−8.26 (m, 1H), 7.68−7.65 (m, 1H), 7.18−7.09 (m, 1H), 5.41−5.38 (m, 1H), 5.29−5.27 (m, 1H), 4.48 (s, br, 1H), 1.68 (s, 3H), 1.66 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125.0 MHz, $CDCl_3$): δ = 147.7, 147.3, 140.0, 135.3, 133.8, 127.2, 123.3, 67.8, 25.7, 18.2 ppm. HRMS (ESI) calcd for $C_{10}H_{14}ON$ $(M + H)^+$ 164.1070, found 164.1075.

1-(Pyridin-3-yl)butan-1-ol (**3va**). Colorless liquid. Yield (128 mg, 85%). ee = 48%; $[\alpha]^{25}_D$ = −4.60 (*c* 0.41, CH_2Cl_2). The ee was determined by HPLC (Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.5 mL/min, λ = 254 nm). t_R(major) = 14.50 min; t_R(minor) = 17.06 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.53−8.49 (m, 2H), 7.73−7.70 (m, 1H), 7.31−7.26 (m, 1H), 4.74 (t, *J* = 6.5 Hz, 1H), 2.21 (s, br, 1H), 1.80−1.68 (m, 2H), 1.36−1.26 (m, 2H), 0.97−0.87 (m, 3H) ppm. ^{13}C{^{1}H} NMR (125.0 MHz, $CDCl_3$): δ = 148.7, 147.8, 140.2, 133.6, 123.5, 72.0, 41.2, 18.8, 13.9 ppm. HRMS (ESI) calcd for $C_9H_{14}ON$ $(M + H)^+$ 152.1070, found 152.1065.

2,2-Dimethyl-1-(pyridin-3-yl)propan-1-ol (**3wa**). White solid. Mp 91−92 °C. Yield (157 mg, 95%). ee = 49%; $[\alpha]^{25}_D$ = −21.84 (*c* 1.90, CH_2Cl_2). The ee was determined by HPLC (Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.8 mL/min, λ = 254 nm).

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t_R(major) = 8.31 min; t_R(minor) = 9.65 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.38−8.36 (m, 2H), 7.69−7.66 (m, 1H), 7.25−7.20 (m, 1H), 4.39 (s, 1H), 3.64 (s, br, 1H), 0.91 (s, 9 H) ppm. ^{13}C{^{1}H} NMR(75.0 MHz, $CDCl_3$): δ = 148.8, 148.1, 137.9, 135.3, 122.7, 79.7, 35.7, 25.7 ppm. HRMS (ESI) calcd for $C_{10}H_{16}ON$ (M + H)$^+$ 166.1226, found 166.1221.

*2-Methyl-1-(pyridin-3-yl)propan-1-ol (**3xa**).* Colorless liquid. Yield (139 mg, 92%). ee = 75%; $[\alpha]^{25}_D$ = −2.10 (*c* 0.39, CH_2Cl_2). The ee was determined by HPLC (Chiralpak OJ-H column, *n*-hexane/*i*-PrOH = 95:5, flow rate = 0.8 mL/min, λ = 254 nm). t_R(major) = 10.49 min; t_R(minor) = 13.28 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.28 (s, 2H), 7.69−7.67 (m, 1H), 7.29−7.24 (m, 1H), 4.41−4.38 (m, 1H), 1.97−1.92 (m, 1H), 0.98−0.96 (m, 3H), 0.81−0.79 (m, 3H) ppm. ^{13}C{^{1}H} NMR (125.0 MHz, $CDCl_3$): δ = 148.0, 139.4, 134.4, 123.2, 35.2, 18.6, 17.9 ppm. HRMS (ESI) calcd for $C_9H_{14}ON$ (M + H)$^+$ 152.1070, found 152.1065.

*Cyclohexyl(pyridin-3-yl)methanol (**3ya**).* White solid. Mp 70−72 °C. Yield (179 mg, 93%). ee = 64%; $[\alpha]^{25}_D$ = −9.72 (*c* 0.71, CH_2Cl_2). The ee was determined by HPLC (Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.8 mL/min, λ = 254 nm). t_R(major) = 9.81 min; t_R(minor) = 11.47 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.38−8.37 (m, 2H), 7.67−7.65 (m, 1H), 7.27−7.22 (m, 1H), 4.39 (d, *J* = 5.0 Hz, 1H), 3.77 (s, br, 1H), 1.62−0.91 (m, 11H) ppm. ^{13}C{^{1}H} NMR (125.0 MHz, $CDCl_3$): δ = 148.1, 139.3, 134. 5, 123.2, 76.5, 44.9, 29.0, 28.5, 26.3, 25.93, 25.86 ppm. HRMS (ESI) calcd for $C_{12}H_{18}ON$ (M + H)$^+$ 192.1383, found 192.1378.

*(2-Methylpyridin-3-yl)(phenyl)methanol (**3ab**).* Colorless liquid. Yield (163 mg, 82%). ee = 68%; $[\alpha]^{25}_D$ = +3.81 (*c* 0.65, CH_2Cl_2). The ee was determined by HPLC (Chiralpak OJ-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm). t_R(major) = 16.16 min; t_R(minor) = 23.70 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24−8.22 (m, 1H), 7.89−7.86 (m, 1H), 7.29−7.24 (m, 5H), 7.16−7.11 (m, 1H), 5.92 (s, 1H), 4.04 (s, br, 1H), 2.36 (s, 3H) ppm. ^{13}C{^{1}H} NMR (75.0 MHz, $CDCl_3$): δ = 155.5, 147.4, 142.2, 137.3, 134.3, 128.6, 127.9, 127.1, 121.4, 72.4, 22.1 ppm. HRMS (ESI) calcd for $C_{13}H_{14}ON$ (M + H)$^+$ 200.1070, found 200.1072.

*(6-Methylpyridin-3-yl)(phenyl)methanol (**3ac**).* Colorless liquid. Yield (169 mg, 85%). ee = 85%; $[\alpha]^{25}_D$ = +6.26 (*c* 1.82, CH_2Cl_2). The ee was determined by HPLC (Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.8 mL/min, λ = 254 nm). t_R(major) = 13.93 min; t_R(minor) = 23.09 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.42−8.41 (m, 1H), 7.58−7.54 (m, 1H), 7.35−7.27 (m, 5H), 7.10−7.08 (m, 1H), 5.82 (s, 1H), 2.93 (s, br, 1H), 2.50 (s, 3H) ppm. ^{13}C{^{1}H} NMR (75.0 MHz, $CDCl_3$): δ = 157.0, 147.1, 143.5, 137.0, 134.9, 128.5, 127.5, 126.4, 123.1, 73.5, 23.6 ppm. HRMS (ESI) calcd for $C_{13}H_{14}ON$ (M + H)$^+$ 200.1070, found 200.1077.

*(5-Methoxypyridin-3-yl)(phenyl)methanol (**3ad**).* White solid. Mp 73−74 °C.Yield (198 mg, 92%). ee = 65%; $[\alpha]^{25}_D$ = +5.63 (*c* 0.96, CH_2Cl_2). The ee was determined by HPLC (Chiralpak OJ-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.8 mL/min, λ = 254 nm). t_R(major) = 24.59 min; t_R(minor) = 30.56 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.04−7.92 (m, 2H), 7.31−7.22 (m, 6H), 5.79−5.75 (m, 1H), 3.75−3.72 (m, 3H) ppm. ^{13}C{^{1}H} NMR (75.0 MHz, $CDCl_3$): δ = 155.7, 143.3, 140.8, 140.0, 135.9, 128.6, 127.8, 126.5, 118.7, 73.4, 54.5 ppm. HRMS (ESI) calcd for $C_{13}H_{14}O_2N$ (M + H)$^+$ 216.1019, found 216.1025.

*(6-Methoxypyridin-3-yl)(phenyl)methanol (**3ae**).* Colorless liquid. Yield (193 mg, 90%). ee = 42%; $[\alpha]^{25}_D$ = +0.86 (*c* 2.32, CH_2Cl_2). The ee was determined by HPLC (Chiralpak OD-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.8 mL/min, λ = 254 nm). t_R(major) = 15.30 min; t_R(minor) = 16.41 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (s, 1H), 7.54−7.51 (m, 1H), 7.34−7.25 (m, 5H), 6.70−6.65 (m, 1H), 5.78−5.76 (m, 1H), 3.92−3.90(m, 3H), 2.56 (s, br, 1H) ppm. ^{13}C{^{1}H} NMR(75.0 MHz, $CDCl_3$): δ = 163.7, 145.1, 143.2, 137.4, 132.2, 128.6, 127.7, 126.3, 110.9, 73.7, 53.5 ppm. HRMS (ESI) calcd for $C_{13}H_{14}O_2N$ (M + H)$^+$ 216.1019, found 216.1023.

*(2-Chloropyridin-3-yl)(phenyl)methanol (**3af**).* Colorless liquid. Yield (167 mg, 76%). ee = 30%; $[\alpha]^{25}_D$ = −1.53 (*c* 0.45, CH_2Cl_2). The ee was determined by HPLC (Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.8 mL/min, λ = 254 nm). t_R(major) = 19.59 min; t_R(minor) = 22.71 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.18 (s, 1H), 8.02−8.00 (m, 1H), 7.34−7.27 (m, 6H), 6.10 (s, 1H), 3.47 (s, 1H) ppm. ^{13}C{^{1}H} NMR (125.0 MHz, $CDCl_3$): δ = 149.3, 148.2, 141.4, 138.0, 136.9, 128.6, 128.1, 126.9, 122.8, 72.0 ppm. HRMS (ESI) calcd for $C_{12}H_{11}ClON$ (M + H)$^+$ 220.0524, found 220.0525.

*(6-Chloropyridin-3-yl)(phenyl)methanol (**3ag**).* Colorless liquid. Yield (182 mg, 83%). ee = 45%; $[\alpha]^{25}_D$ = +2.20 (*c* 0.54, CH_2Cl_2). The ee was determined by HPLC (Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.8 mL/min, λ = 254 nm). t_R(major) = 15.05 min; t_R(minor) = 18.75 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.28−8.26 (m, 1H), 7.64−7.61 (m, 1H), 7.33−7.22 (m, 6H), 5.80 (s, 1H), 3.50 (s, 1H) ppm. ^{13}C NMR(75.0 MHz, $CDCl_3$): δ = 150.1, 147.8, 142.6, 138.4, 137.2, 128.8, 128.1, 126.4, 124.0, 73.3 ppm. HRMS (ESI) calcd for $C_{12}H_{11}ClON$ (M + H)$^+$ 220.0524, found 220.0526.

*Phenyl(pyridin-4-yl)methanol (**3ak**).* White solid. Mp 135.5−140.2 °C. Yield (135 mg, 73%). ee = 83%; $[\alpha]^{25}_D$ = +36.25 (*c* 0.16, CH_2Cl_2). The ee was determined by HPLC (Chiralpak OD column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.5 mL/min, λ = 254 nm). t_R(major) = 34.88 min; t_R(minor) = 36.57 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.46−8.44 (m, 2H), 7.36−7.27 (m, 7H), 5.79 (s, 1H) ppm. ^{13}C{^{1}H} NMR(125.0 MHz, $CDCl_3$): δ = 152.8, 149.5, 142.7, 128.8, 128.3, 126.8, 121.3, 74.9. ppm. HRMS (ESI) calcd for $C_{12}H_{11}ON$ (M + H)$^+$ 186.0913, found 186.0915.

*(2-Methylpyridin-4-yl)(phenyl)methanol (**3al**).* White solid. Mp 83−84 °C. Yield (175 mg, 88%). ee = 91%; $[\alpha]^{25}_D$ = +10.19 (*c* 0.52, CH_2Cl_2). The ee was determined by HPLC (Chiralpak OD-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.5 mL/min, λ = 254 nm). t_R(major) = 18.02 min; t_R(minor) = 23.16 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.18−8.16 (m, 1H), 7.32−7.23 (m, 5H), 7.18 (s, 1H), 7.08−7.07 (m, 1H), 5.71 (s, 1H), 4.71 (s, br, 1H), 2.43 (s, 3H) ppm. ^{13}C{^{1}H} NMR(75.0 MHz, $CDCl_3$): δ = 158.1, 153.5, 148.5, 143.1, 128.6, 127.9, 126.7, 120.8, 118.6, 74.7, 24.0 ppm. HRMS (ESI) calcd for $C_{13}H_{14}ON$ (M + H)$^+$ 200.1070, found 200.1071.

X-ray Crystallography. The X-ray diffractions of suitable crystals of compounds (*S*)-**3ka** were performed on a Burker SMART CCD area detector diffractometer using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å); temperature 273(2) K; φ and ω scan technique; SADABS effects and empirical absorption were applied in the data corrections. All structures were solved by direct methods (SHELXTL-97), completed by subsequent difference Fourier syntheses, and refined by full-matrix least-squares calculations based on F^2 (SHELXTL-97).[21] All hydrogen atoms were refined using a riding model. Crystal data for (*S*)-**3ka**: $C_{12}H_{10}BrNO$, *M* = 264.12, Orthorhombic, space group $P2_12_12_1$, *T* = 293(2) K, *a* = 5.8390(11) Å, *b* = 7.5480(14) Å, *c* = 24.921(5) Å, *V* = 1098.3(4) Å^3, *Z* = 4, absorption coefficient = 3.713 mm^{-1}, total reflections collected 9269, unique 2514 (R_{int} = 0.0401), goodness of fit indicator = 1.032, R_1 = 0.0404, wR_2 = 0.0990. Absolute structure parameter = 0.033(16).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01410.

Copies of HPLC analytic data and ^{1}H and ^{13}C NMR spectra of compounds **3** (PDF)

CIF file of (*S*)-**3ka** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Barouh, V.; Dall, H.; Patel, D.; Hite, G. *J. Med. Chem.* **1971**, *14*, 834−836. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (c) Ramón, D. J.; Yus, M. *Curr. Org. Chem.* **2004**, *8*, 149−183. (d) Bolshan, Y.; Chen, C.; Chilenski, J. R.; Gosselin, F.; Mathre, D. J.; O'Shea, P. D.; Roy, A.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 111−114. (e) Magnus, N. A.; Anzeveno, P. B.; Coffey, D. S.; Hay, D. A.; Laurila, M. E.; Schkeryantz, J. M.; Shaw, B. W.; Staszak, M. A. *Org. Process Res. Dev.* **2007**, *11*, 560−567.

(2) For reviews, see: (a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757. (b) Walsh, P. J. *Acc. Chem. Res.* **2003**, *36*, 739. (c) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 284−287. (d) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, *35*, 454. (e) Hatano, M.; Ishihara, K. *Chem. Rec.* **2008**, *8*, 143. (f) Hatano, M.; Ishihara, K. *Synthesis* **2008**, *2008*, 1647. (g) Paixão, M. W.; Braga, A. L.; Lüdtke, D. S. *J. Braz. Chem. Soc.* **2008**, *19*, 813.

(3) (a) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850−14851. (b) Rudolph, J.; Schmidt, F.; Bolm, C. *Adv. Synth. Catal.* **2004**, *346*, 867. (c) Özçubukçu, S.; Schmidt, F.; Bolm, C. *Org. Lett.* **2005**, *7*, 1407. (d) Dahmen, S.; Lormann, M. *Org. Lett.* **2005**, *7*, 4597. (e) Ji, J.-X.; Wu, J.; Au-Yeung, T. T.-L.; Yip, C.-W.; Haynes, R. K.; Chan, A. S. C. *J. Org. Chem.* **2005**, *70*, 1093. (f) Liu, X.; Wu, X.; Chai, Z.; Wu, Y.; Zhao, G.; Zhu, S. *J. Org. Chem.* **2005**, *70*, 7432. (g) Wu, X.; Liu, X.; Zhao, G. *Tetrahedron: Asymmetry* **2005**, *16*, 2299. (h) Braga, A. L.; Lüedtke, D. S.; Vargas, F.; Paixão, M. W. *Chem. Commun.* **2005**, 2512. (i) Lu, G.; Kwong, F. Y.; Ruan, J.-W.; Li, Y.-M.; Chan, A. S. C. *Chem.—Eur. J.* **2006**, *12*, 4115. (j) Hatano, M.; Gouzu, R.; Mizuno, T.; Abe, H.; Yamada, T.; Ishihara, K. *Catal. Sci. Technol.* **2011**, *1*, 1149.

(4) (a) Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444−445. (b) Bolm, C.; Muñiz, K. *Chem. Commun.* **1999**, 1295−1296. (c) Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 7940−7956. (d) Huang, W.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 4222−4223. (e) Bolm, C.; Hermanns, N. J.; Hildebrand, P.; Muñiz, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3465−3467. (f) Bolm, C.; Kesselgruber, M.; Hermanns, N.; Hildebrand, J. P.; Raabe, G. *Angew. Chem., Int. Ed.* **2001**, *40*, 1488−1490. (g) Qin, Y.-C.; Pu, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 273−277. (h) Sedelmeier, J.; Bolm, C. *J. Org. Chem.* **2007**, *72*, 8859−8862. (i) Shannon, J.; Bernier, D.; Rawson, D.; Woodward, S. *Chem. Commun.* **2007**, 3945−3947. (j) Glynn, D.; Shannon, J.; Woodward, S. *Chem. - Eur. J.* **2010**, *16*, 1053.

(5) (a) Wu, K.-H.; Gau, H.-M. *J. Am. Chem. Soc.* **2006**, *128*, 14808. (b) Wu, K.-H.; Chen, C.-A.; Gau, H.-M. *Angew.Chem., Int. Ed.* **2007**, *46*, 5373−5376. (c) Zhou, S.; Wu, K.-H.; Chen, C.-A.; Gau, H.-M. *J. Org. Chem.* **2009**, *74*, 3500. (d) Zhou, S.; Chuang, D.-W.; Chang, S.-J.; Gau, H.-M. *Tetrahedron: Asymmetry* **2009**, *20*, 1407−1412.

(6) (a) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 7473. (b) Wu, K.-H.; Zhou, S.; Chen, C.-A.; Yang, M.-C.; Chiang, R.-T.; Chen, C.-R.; Gau, H.-M. *Chem. Commun.* **2011**, *47*, 11668−11670. (c) Wu, K.-H.; Kuo, Y.-Y.; Chen, C.-A.; Huang, Y.-L.; Gau, H.-M. *Adv. Synth. Catal.* **2013**, *355*, 1001−1008. (d) Chang, S.-J.; Zhou, S.; Gau, H.-M. *RSC Adv.* **2015**, *5*, 9368.

(7) (a) Muramatsu, Y.; Harada, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 1088. (b) Muramatsu, Y.; Harada, T. *Chem.—Eur. J.* **2008**, *14*, 10560.

(8) Nakagawa, Y.; Muramatsu, Y.; Harada, T. *Eur. J. Org. Chem.* **2010**, *2010*, 6535.

(9) Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*, 2nd ed.; John Wiley: New York, 2002.

(10) (a) Schmidt, F.; Rudolph, J.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 703−708. (b) Liu, X.; Qiu, L.; Hong, L.; Yan, W.; Wang, R. *Tetrahedron: Asymmetry* **2009**, *20*, 616−620.

(11) Biradar, D. B.; Zhou, S.; Gau, H.-M. *Org. Lett.* **2009**, *11*, 3386.

(12) Wu, K.-H.; Chuang, D.-W.; Chen, C.-A.; Gau, H.-M. *Chem. Commun.* **2008**, 2343.

(13) Zhou, S. L.; Chen, C.-R.; Gau, H.-M. *Org. Lett.* **2010**, *12*, 48−51.

(14) Salvi, L.; Kim, J. G.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 12483−12493.

(15) Uenishi, A.; Nakagawa, Y.; Osumi, H.; Harada, T. *Chem.— Eur. J.* **2013**, *19*, 4896−4905.

(16) (a) Chen, X.; Zhou, S.; Li, Y.; Xie, T.; Zhou, S. *J. Org. Chem.* **2014**, *79*, 230−239. (b) Zhou, S.; Yang, Z.; Chen, X.; Li, Y.; Zhang, L.; Fang, H.; Wang, W.; Zhu, X.; Wang, S. *J. Org. Chem.* **2015**, *80*, 6323−6328.

(17) (a) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857−898. (b) DeBerardinis, A. M.; Turlington, M.; Ko, J.; Sole, L.; Pu, L. *J. Org. Chem.* **2010**, *75*, 2836−50. (c) Abreu, A. R.; Lourenço, M.; Peral, D.; Rosado, M. T. S.; Eusébio, M. E. S.; Palacios, Ò.; Bayón, J. C.; Pereira, M. M. *J. Mol. Catal. A: Chem.* **2010**, *325*, 91−97.

(18) Waltz, K. M.; Carroll, P. J.; Walsh, P. J. *Organometallics* **2004**, *23*, 127−134.

(19) Doudouh, A.; Woltermann, C.; Gros, P. C. *J. Org. Chem.* **2007**, *72*, 4978−4980.

(20) Ágai, B.; Nádor, A.; Proszenyák, A.; Tárkányi, G.; Faigl, F. *Tetrahedron* **2003**, *59*, 7897−7900.

(21) Sheldrick, G. M. *SHELXTL*, Version 5.10; Bruker Analytical X-ray Systems, Inc., Madison, WI, 1997.

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