Synthesis of Chiral Pyridyl Alcohols Using a Two-Step Catalytic Approach

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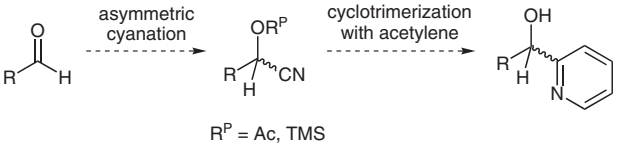
Abstract: Chiral pyridyl alcohols have been prepared by developing a two-step approach that uses the asymmetric cyanation of aldehydes to give cyanohydrins and subsequent [2+2+2]-cyclotrimerization reaction with acetylene.

Key words: asymmetric synthesis, cyclotrimerization, cyanohydrin, pyridine, aldehyde

Over the few last decades, the principle of constructing benzene and, more recently, pyridine ring systems by cyclotrimerization reactions of acetylenes and nitriles catalyzed by transition-metal complexes has found a great deal of attention.[1] While the synthesis of achiral pyridines has already been thoroughly explored,[1a,b,d] the selective synthesis of chiral derivatives by this methodology was, until recently, still in its infancy. However, several examples have been reported in the literature of the cyclotrimerization of alkynes with chiral nitriles,[2] which also describe problems with the sometimes drastic conditions that could negatively influence the stereochemical outcome. Aiming for more convenient conditions, we have recently developed in our laboratory an efficient method not only for the synthesis of biaryls possessing axial chirality,[3] but also for the synthesis of pyridine derivatives by light-promoted cobalt(I)-catalyzed cyclotrimerization of two molecules of an acetylene with one molecule of a nitrile.[4] The mild conditions under which the reaction can, in general, be successfully performed has already proved to be very promising for the synthesis of chiral pyridines when the stereogenic center was attached to the nitrile.[4a] The products in these reactions contained the preserved stereochemical information without loss.

We are looking to apply our methodology in the synthesis of interesting classes of chiral compounds and came across the cyanohydrins, a well-known class of chiral building blocks.[5] These nitriles are easy accessible in enantiomerically pure form by a number of methods, but have not previously been used as nitrile components in cyclotrimerization reactions. Applying the chiral nitriles together with acetylenes in cyclotrimerizations would, therefore, yield pyridyl alcohols.[6a–e] Chiral pyridyl alcohols have seen a number of applications as privileged catalysts and ligands for enantioselective synthesis and catalysis. Examples amenable to catalysis with pyridyl alcohols include the epoxidation of allylic alcohols,[6f] the conjugate addition of dialkylzinc reagents to α,β-unsaturated ketones,[6g–i] and the nucleophilic addition of dialkylzinc reagents to aldehydes.[6j–n] Recently, phosphorus ligands derived from pyridyl alcohols were successfully applied to iridium-catalyzed asymmetric hydrogenation.[6o] Many enantiomerically pure pyridyl alcohols are also biologically relevant compounds and key intermediates for commercial drugs [e.g. (*R*,*S*)-mefloquine or (*S*)-carbinoxamine].

We have developed a novel two-step catalytic approach to pyridyl alcohols starting from aldehydes and involving a [2+2+2]-cyclotrimerization step for the assembly of the pyridine moiety (Scheme 1).



Scheme 1 Proposed two-step synthetic route to pyridyl alcohols starting from aldehydes

We started our investigations by synthesizing two different cyanohydrin derivatives as precursor compounds for the cyclotrimerization reaction. They only differ in the protection of the free hydroxy group: the acetyl and trimethylsilyl groups were chosen as convenient protection groups. Recent progress in the transition-metal-catalyzed asymmetric synthesis of cyanohydrins has made these important chiral building blocks increasingly readily available in industry and in academia.[7] We decided to utilize chiral transition-metal–salen complexes as reliable source of asymmetric induction for the preparation of the chiral cyanohydrins. Here, binuclear titanium(IV)–salen and mononuclear vanadium(IV)–salen catalysts (such as **2** and **5**) based on the Jacobsen ligand system are worthy of particular attention. They have been introduced into practical use by Belokon and North and exhibit excellent activity and selectivity in the cyanation of aldehydes with different reagents such as trimethylsilyl cyanide,[8] potassium cyanide/acetic anhydride,[9] ethyl cyanoformate,[10] or acetyl cyanide.[11]

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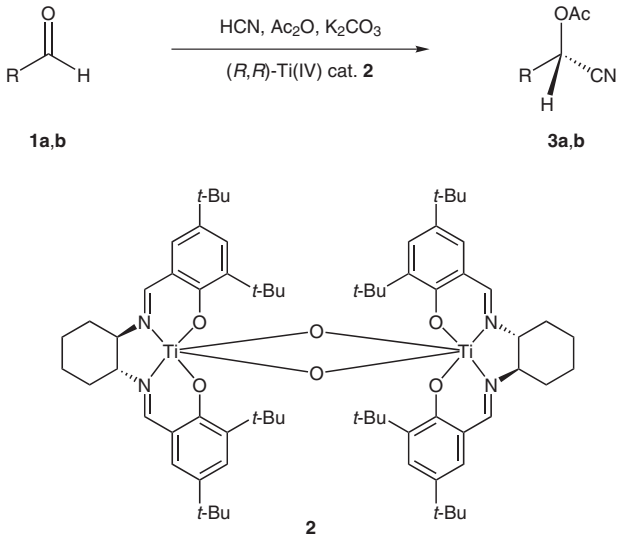
Initial experiments with benzaldehyde using a chiral titanium(IV)–salen complex and hydrogen cyanide for the synthesis of the unprotected cyanohydrins gave good yields (90–93%), but fairly low enantioselectivities (49–68% ee) even at low temperatures (up to –40 °C). We envisioned that the most effective method to fix this problem and prevent side reactions and racemization that lower the enantiomeric excess of the desired cyanohydrins could be an in situ derivatization procedure. Therefore, we screened reaction conditions that, in addition to the hydrogen cyanide, also contained acetic anhydride and potassium carbonate as in situ acylation reagents (Table 1, entries 1–3). While the yields of **3a** were very good (>93%) with benzaldehyde under all conditions tested, the highest enantioselectivity was obtained at a reaction temperature of –40 °C. Comparable reaction conditions were then applied to 4-methoxybenzaldehyde (**3b**, Table 1, entries 4 and 5). While the yields of **3b** were, in both cases, very good to excellent, the reaction at room temperature again proceeded only with mediocre enantioselectivity. The same reaction at –40 °C needed a significantly longer reaction time but the enantioselectivity found was comparable to the same experiment with benzaldehyde (Table 1, entry 3). However, this procedure afforded feasible *O*-acylated cyanohydrin substrates **3a** and **3b** for the subsequent investigation of the cyclotrimerization with acetylene in the presence of (η^5-cyclopentadienyl)(η^4-cycloocta-1,4-diene)cobalt [CoCp(cod)].

Trimethylsilyl cyanide is the reagent of choice for the synthesis of the trimethylsilyl-protected cyanohydrins **6**. Its use as a reliable source for cyanide in transition-metal-catalyzed asymmetric addition reactions has already been reported in the literature.[7,8] The resulting cyanohydrins are quite stable compounds and the subsequent deprotection step after the cyclotrimerization can be performed in situ under very mild and racemization-free conditions, so that no extra workup of the intermediate silyl ether would be required. The preparation of the starting material uses the addition reaction of trimethylsilyl cyanide to the aldehyde catalyzed by a well-defined vanadium(IV)–salen complex **5** under remarkably convenient reaction conditions (CH_2Cl_2, r.t., in air). The reaction proceeds smoothly in the presence of only 0.1–0.2 mol% of the catalysts (*R*,*R*)-**5** and (*S*,*S*)-**5** (Table 2).

Here, the catalyst (*R*,*R*)-**5** gave the *S*-enantiomers, whereas (*S*,*S*)-**5** yielded the opposite (*R*)-cyanohydrins. Distillation of the crude reaction mixtures gave the silylated cyanohydrins **6** in high yields (78–94%) and very good enantiomeric excesses in the range of 81–93% ee (Table 2). Another advantage is the easy accessibility of both the *S*- and *R*-enantiomers of the cyanohydrins.

After efficiently furnishing the required cyanohydrin substrates **3** and **6** by catalytic asymmetric cyanation with titanium and vanadium complexes, we were focussed on the cyclotrimerization reaction in the next step. The thermally initiated variant of this reaction has been carried out by employing acetylene pressures above 10 bar, reaction

Table 1 Synthesis of Acylated Cyanohydrins by Catalytic Asymmetric Cyanation[a]



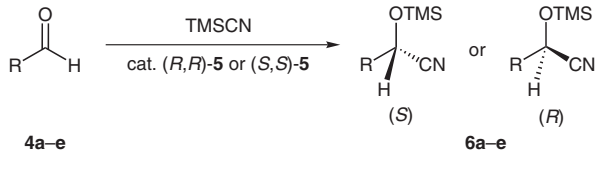
Entry	Product	R	Temp. (°C)	Time (h)	Yield (%)	ee[b] (%)
1	**3a**	Ph	25	24	93	53 (*S*)
2	**3a**	Ph	–20	4	99	81 (*S*)
3	**3a**	Ph	–40	18	98	88 (*S*)
4	**3b**	4-$MeOC_6H_4$	25	144	98	56 (*S*)
5	**3b**	4-$MeOC_6H_4$	–40	72	87	86 (*S*)

[a] Conditions: concentration of **1** 0.75 M with molar ratio of **1**/HCN/Ac_2O/K_2CO_3, 1:2:2:2 in the presence of 1 mol% of catalyst **2**.
[b] Determined by chiral HPLC.

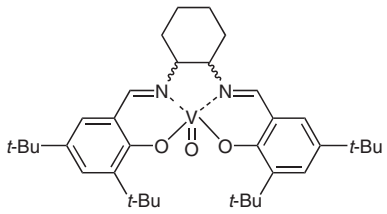
temperatures above 100 °C, longer reaction times, and high catalyst concentrations.[2] These rather drastic reaction conditions sometimes result in racemization of the starting nitrile and the enantiomeric excess strongly decreases in many cases.[2a–c] In particular, this affects substrates with acidic α-hydrogens that can easily racemize at elevated temperatures and in the presence of a base, such as the resulting pyridines. Here we use our photochemical approach, which delivers the necessary energy via irradiation at ambient temperature and atmospheric pressure, thus minimizing the problems associated with drastic reaction conditions. This is especially useful in the case of sensitive substrates such as cyanohydrins. For the model reaction we used *O*-acetyl mandelonitriles **3a**,**b** as substrates and 1–5 mol% of [CoCp(cod)] as a catalyst under visible light irradiation (350–500 nm) and atmospheric pressure of acetylene (Table 3).

The results of these experiments were disappointing, but did show that the *O*-acetyl cyanohydrins **3a**,**b** have rather low activities in the cyclotrimerization reaction with acetylene; yields did not exceed 25% under various conditions (Table 3). These low yields did not allowed the determination of the enantioselectivity of the cyclotrimerization

Table 2 Synthesis of Silylated Cyanohydrins by Catalytic Asymmetric Cyanation[a]



4a–e 6a–e

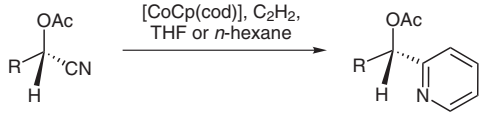


(*R*,*R*)-**5** or (*S*,*S*)-**5**

Entry	Product R		Catalyst **5** (mol%)	Yield[b] (%)	ee[c] (%)
1	Ph	(*S*)-**6a**	(*R*,*R*)-**5** (0.1)	78	91
		(*R*)-**6a**	(*S*,*S*)-**5** (0.1)		92
2	4-$MeOC_6H_4$	(*S*)-**6b**	(*R*,*R*)-**5** (0.2)	71	90
		(*R*)-**6b**	(*S*,*S*)-**5** (0.2)		91
3	3-$MeOC_6H_4$	(*S*)-**6c**	(*R*,*R*)-**5** (0.1)	92	93
		(*R*)-**6c**	(*S*,*S*)-**5** (0.1)		93
4	4-ClC_6H_4	(*S*)-**6d**	(*R*,*R*)-**5** (0.2)	91	88
		(*R*)-**6d**	(*S*,*S*)-**5** (0.2)		88
5	*t*-Bu	(*S*)-**6e**	(*R*,*R*)-**5** (0.1)	94	81
		(*R*)-**6e**	(*S*,*S*)-**5** (0.1)		82

[a] Conditions: **4**, TMSCN (mol ratio of aldehyde/TMSCN 1:1.1), (*R*,*R*)-**5** or (*S*,*S*)-**5**, +25 °C, CH_2Cl_2, stirring, 24 h.
[b] Isolated yields.
[c] Determined by chiral GC or HPLC.

Table 3 Cyclotrimerization Experiments with the Acylated Cyanohydrins **3a**,**b**



3a,**b** **7a**,**b**

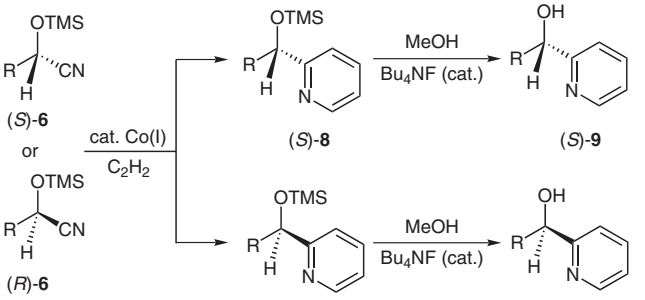
Entry	Product R		[CoCp(cod)] mol%	Solvent	Yield (%)
1	Ph	**7a**	1	THF	7
2	Ph	**7a**	5	THF	25
3	Ph	**7a**	5	*n*-hexane	12
4	4-$MeOC_6H_4$	**7b**	1	THF	4

[a] Conditions: **3**, acetylene, [CoCp(cod)], +25 °C, stirring, irradiation (λ ~420 nm), 24 h.

reactions. This failure may be for several reason, one of which could be the insufficient purity of the *O*-acetyl cyanohydrins **3** even after chromatographic purification and distillation. The cobalt-catalyzed cycloaddition reactions are occasionally affected by even small amounts of impurities or byproducts. Other reasons that can be suggested for this failure are catalyst inhibition from the acetylated pyridyl alcohol product or insufficient stability of the acetyl groups.

Even though cyanohydrin acetates are potentially desirable substrates for the cyclotrimerization process, we turned our attention to the trimethylsilyl-protected derivatives. We investigated the reactivity of *O*-trimethylsilyl cyanohydrins **6** in cyclotrimerization experiments under comparable conditions in the presence of only 0.5 mol% of [CoCp(cod)] catalyst with visible light irradiation. The obtained excellent results with **6** were incomparably better than those observed with the acetyl derivatives **3** (Table 4). In the case of 2-phenyl-2-(trimethylsiloxy)acetonitriles **6a** the pyridines **9a** were obtained with very good 85% yield via the silylated intermediates **8a**. The enantiomeric excesses of products **9a** corresponds to that of the starting cyanohydrins **6a** for both enantiomers. The deprotection step with tetrabutylammonium fluoride in methanol could reasonably be assumed to proceed quanti-

Table 4 Synthesis of the Chiral Pyridyl Alcohols **9**[a]



Entry	Substrate	Product R		Yield[b] (%)[b]	ee[c] (%)
1	(*S*)-**6a**	Ph	(*S*)-**9a**	85	91
	(*R*)-**6a**		(*R*)-**9a**		92
2	(*S*)-**6b**	4-$MeOC_6H_4$	(*S*)-**9b**	72	91
	(*R*)-**6b**		(*R*)-**9b**		91
3	(*S*)-**6c**	3-$MeOC_6H_4$	(*S*)-**9c**	84	92
	(*R*)-**6c**		(*R*)-**9c**		93
4	(*S*)-**6d**	4-ClC_6H_4	(*S*)-**9d**	81	88
	(*R*)-**6d**		(*R*)-**9d**		88
5	(*S*)-**6e**	*t*-Bu	(*S*)-**9e**	91	82
	(*R*)-**6e**		(*R*)-**9e**		82

[a] Conditions: **6**, acetylene, [CoCp(cod)] (0.5 mol%), +25 °C, THF, stirring, irradiation (λ ~420 nm), 12 h.
[b] Isolated yields.
[c] Determined by chiral GC or HPLC.
[d] Performed in *n*-hexane.

tatively. The investigation of the other chiral *O*-trimethylsilyl cyanohydrins **6b–e** as substrates for the cyclotrimerization led to identical results: the silylated pyridyl alcohols **8b–e** were obtained with high yields while retaining the starting enantiomeric excess. These compounds were deprotected without isolation to give the desired pyridyl alcohols **9b–e** in 72–91% isolated yield for the overall process (Table 4).

The enantiomeric excess could generally be increased by recrystallization, but more effective enantiomeric enrichment was achieved by precipitation of the alcohols with picric acid and recrystallization of the corresponding picrate salts from alcoholic solvents (MeOH, EtOH, *i*-PrOH) to give the highest enantiomeric purity (>99% ee). In addition a modified procedure was developed, which included the treatment of crude silylated derivatives **8** with alcoholic solutions of picric acid, and the enantiomerically pure picric salts of the free alcohols **9** usually precipitated after a period of time.

In summary, we presented a two-step catalytic approach for the synthesis of chiral pyridyl alcohols starting from aldehydes. In the first step the synthesis of cyanohydrins by cyanation of aldehydes in the presence of chiral transition-metal–salen complexes **2** or **5** was investigated using either hydrogen cyanide or trimethylsilyl cyanide as cyanide sources. In both cases the acetyl- **3a**,**b** or trimethylsilyl-protected cyanohydrins **6a–e** could be obtained in high yields and good enantiomeric excesses. The behavior of *O*-acetyl cyanohydrins **3** in the light-promoted cobalt(I)-catalyzed cyclotrimerization with acetylene has been studied, however, the results were disappointing and yields did not exceed 25%. In contrast, *O*-trimethylsilyl-protected cyanohydrins **6** have shown excellent yields in the racemization-free photochemical cyclotrimerization with acetylene to pyridines. The in situ deprotection of silylated pyridyl alcohols **8** afforded the desired pyridyl alcohols **9** in high yields, which were isolated in enantiomerically pure form by recrystallization. The developed procedures allow an easy two-step access to versatile chiral pyridyl alcohols.

NMR spectra were recorded on a Bruker ARX 400 spectrometer at 298 K. MS spectra were obtained with a Varian AMD-402 instrument at an ionization voltage of 70 eV. In general the enantiomeric excesses were analyzed by HPLC with a Liquid Chromatograph 1090 equipped with DAD (Hewlett Packard) and Chiralyser (IBZ Messtechnik GmbH) using appropriate chiral columns (for some compounds detailed conditions are listed below). Melting points were measured with a Büchi 540 melting point determination apparatus. Optical rotations were determined on a Gyromat-HP polarimeter. HCN was prepared as described previously,[6g–i] dissolved in CH_2Cl_2 to make a 3.7 M soln [HCN (1 g) in CH_2Cl_2 (10 mL)] and stored at –40 °C until needed, at which point it was warmed to 0 °C and transferred via a precooled syringe. The analytical data for compounds **3a**[12] and **3b**[13] have been reported elsewhere. In each case the analytical data for one pure enantiomer of compounds **6** and **9** are reported for better comparison.

Determination of Enantiomeric Excesses for Compounds 6 and 9

The enantiomeric excesses were analyzed by HPLC with a Liquid Chromatograph 1090 equipped with DAD (Hewlett Packard) and Chiralyser (IBZ Messtechnik GmbH), except for two cases (**6a** and **6e**), where a Agilent 6890N GLC was used. The conditions for each individual compound are as follows.

Cyanohydrins: **6a**: Lipodex E, 25 m × 0.25 mm; 80–180 °C with 2 °C/min; **6b**: Chiralcel OJ-H, *n*-hexane–EtOH (98:2); **6c**: Chiralcel OJ-H, *n*-hexane–EtOH (98:2); **6d**: Chiralpak AD-H, *n*-hexane–*i*-PrOH (95:5); **6e**: Lipodex E, 25 m × 0.25 mm; 75 °C isotherm.

Pyridyl alcohols: **9a**: Chiralcel OJ-H, *n*-hexane–EtOH (90:10); **9b**: Chiralcel OJ-H, *n*-hexane–EtOH (90:10); **9c**: Chiralpak AD-H, *n*-hexane–EtOH (95:5); **9d**: Chiralcel OJ-H, *n*-hexane–EtOH (95:5); **9e**: Chiralpak AD-H, *n*-hexane–EtOH (99:1).

2-Acetoxy-2-arylacetonitriles 3a,b; General Procedure

Anhyd CH_2Cl_2 (4 mL) was added to solid K_2CO_3 (0.42 g, 3.0 mmol) and catalyst **2** (18.5 mg, 0.015 mmol, 1 mol%) under argon, followed by aldehyde **1** (1.5 mmol) and Ac_2O (0.3 mL, 3.0 mmol). The mixture was cooled to –40 °C, and 3.7 M HCN in CH_2Cl_2 soln (0.8 mL, 3 mmol) was then added to the mixture with a precooled syringe. The mixture was stirred at –40 °C (see Table 1 for reaction times) and filtered through a column of silica gel (1.5 × 4 cm, CH_2Cl_2). For further purification the residue was chromatographed (silica gel, petroleum ether–EtOAc, 5:1).

2-[Acetoxy(aryl)methyl]pyridines 7a,b; General Procedure

A 100-mL thermostated (25 °C) reaction vessel was loaded with *O*-acetyl cyanohydrin **3** (6.4 mmol) and [CoCp(cod)] (1–5 mol%). Solvent (30 mL) was added, and the vessel was connected to an acetylene measuring and delivering device providing a constant pressure of acetylene. Alternatively, acetylene may simply be bubbled through the soln. The mixture was stirred and irradiated by 2 460-W lamps (λ ~420 nm) for 24 h. The reaction was quenched by switching off the lamps and simultaneously letting in air. The extent of the reaction, i.e. conversion of **3**, was determined by GC.

(*S*)-2-Phenyl-2-(trimethylsiloxy)acetonitrile [(*S*)-6a]; Typical Procedure[14]

Benzaldehyde (**4a**, 5.3 g, 5.08 mL, 50 mmol), vanadium(IV)–salen catalyst (*R*,*R*)-**5** [giving *S*-cyanohydrins] or (*S*,*S*)-**5** [giving *R*-cyanohydrins] (30.6 mg, 0.05 mmol) were dissolved in anhyd CH_2Cl_2 (80 mL), and TMSCN (5.49 g, 6.9 mL, 55.3 mmol) was added in one portion at 20 °C with stirring. The mixture was stirred for 24 h, the solvent was evaporated, and the residue was fractionally distilled in vacuo to give (*S*)-**6a** (8 g, 78%) as a colorless liquid; bp 72–74 °C/2.2·10^{-1} mbar; 91% ee (HPLC). The catalyst could be recovered from the residue.

$[\alpha]_D^{22}$ –26.1 (*c* 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.35 (m, 5 H), 5.46 (s, 1 H), 0.20 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.5, 129.6, 129.2, 126.6, 119.5, 63.9, 0.0.

MS (70 eV): *m*/*z* (%) = 205 [19, M$^+$], 190 (100), 135 (3), 116 (20), 105 (17), 89 (11), 84 (24), 77 (6), 45 (4).

The product should be carefully degassed (3 freeze–thaw cycles) and redistilled under argon to ensure high yields in the next step.

(*S*)-2-(4-Methoxyphenyl)-2-(trimethylsiloxy)acetonitrile [(*S*)-6b][14]

Colorless liquid.

$[\alpha]_D^{22}$ –20.8 (*c* 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.43 (m, 2 H), 6.99–6.96 (m, 2 H), 5.49 (s, 1 H), 3.86 (s, 3 H), 0.26 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6, 128.7, 128.2, 119.6, 114.5, 63.6, 55.6, 0.0.

MS (70 eV): *m*/*z* (%) = 235 [36, M^+], 220 (55), 146 (100), 135 (22), 105 (7), 84 (9), 73 (9), 45 (4).

(*S*)-2-(3-Methoxyphenyl)-2-(trimethylsiloxy)acetonitrile [(*S*)-6c][14]
Colorless liquid.

$[\alpha]_D^{22}$ –26.4 (*c* 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.14 (m, 1 H), 6.90–6.87 (m, 2 H), 6.78–6.74 (m, 1 H), 5.32 (s, 1 H), 3.67 (s, 3 H), 0.09 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 138.0, 130.3, 119.4, 118.8, 115.1, 112.1, 63.8, 55.6, 0.0.

MS (70 eV): *m*/*z* (%) = 235 [27, M^+], 220 (100), 146 (20), 135 (13), 116(5), 103 (4), 84 (14), 73 (5), 45 (3).

(*S*)-2-(4-Chlorophenyl)-2-(trimethylsiloxy)acetonitrile [(*S*)-6d][14]
Colorless liquid.

$[\alpha]_D^{22}$ –16.3 (*c* 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.29 (m, 4 H), 5.40 (s, 1 H), 0.17 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.6, 135.1, 129.4, 127.9, 119.1, 63.3, 0.0.

MS (70 eV): *m*/*z* (%) = 239 [11, M^+], 226 (38), 224 (100), 204 (14), 150 (29), 139 (12), 123 (8), 105 (8), 93 (7), 84 (30), 73 (8), 45 (6).

(*S*)-3,3-Dimethyl-2-(trimethylsiloxy)butanenitrile [(*S*)-6e][14]
Colorless liquid.

$[\alpha]_D^{22}$ –43.0 (*c* 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.78 (s, 1 H), 0.80 (s, 9 H), 0.00 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 119.8, 71.3, 36.3, 25.4, 0.0.

MS (70 eV): *m*/*z* (%) = 185 [0.1, M^+], 170 (2), 143 (47), 129 (100), 114 (5), 100 (15), 84 (11), 75 (40), 73 (31), 57 (38), 41 (12).

Phenyl(pyridin-2-yl)methanol [(*S*)-9a]; Typical Procedure[15]
A 100-mL thermostated (25 °C) reaction vessel was loaded with (*S*)-2-phenyl-2-(trimethylsiloxy)acetonitrile [(*S*)-**6a**, 1.7 g, 8.28 mmol) and [CoCp(cod)] (9.6 mg, 0.0414 mmol, 0.5 mol%). THF (10 mL) was added, and the vessel was connected to an acetylene measuring and delivering device providing a constant pressure of acetylene. Alternatively, acetylene may simply be bubbled through the soln. The mixture was stirred and irradiated by two 460-W lamps (λ ~420 nm) for 12 h. The reaction was quenched by switching off the lamps and simultaneously letting in air. The extent of the reaction, i.e. conversion of (*S*)-**8a**, was determined by GC. The mixture was evaporated, and the residue was dissolved in MeOH (50 mL), together with $Bu_4NF{\cdot}3\ H_2O$ (200 mg, 6.3 mmol). The mixture was stirred at r.t. for 24 h, the solvent was removed, and the oily residue was purified by chromatography [silica gel, hexane–EtOAc, 1:1; R_f = 0.84 (siloxy-pyridine), R_f = 0.45 (deprotected pyridine)] to give (*S*)-**9a** (1.31 g, 85%); mp 64–65 °C; 91% ee (HPLC). A single crystallization (EtOAc–hexane) gave (*S*)-**9a** (861 mg, 56%); >99% ee (HPLC).

$[\alpha]_D^{22}$ +158 (*c* 0.51, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.8 (m, 1 H), 7.87–7.83 (m, 1 H), 7.65–7.51 (m, 5 H), 7.44–7.4 (m, 2 H), 6.01 (m, 1 H), 5.63 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.4, 148.3, 143.7, 137.3, 129.0, 128.2, 127.5, 122.9, 121.8, 75.5.

MS (70 eV): *m*/*z* (%) = 185 (79, M^+), 167 (12), 108 (83), 79 (100), 52 (52).

(*S*)-4-Methoxyphenyl(pyridin-2-yl)methanol [(*S*)-9b][15]
Colorless crystals; mp 63–65 °C, >99% ee.

$[\alpha]_D^{22}$ +137.4 (*c* 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51–8.43 (d, 1 H), 7.58–7.51 (m, 1 H), 7.26–7.18 (m, 2 H), 7.14–7.04 (m, 2 H), 6.67–6.72 (m, 2 H), 5.62 (s, 1 H), 5.18 (br s, 1 H), 3.71 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2, 159.3, 147.8, 136.8, 135.5, 128.38, 122.3, 122.7, 121.3, 77.3, 55.3.

MS (70 eV): *m*/*z* (%) = 215 [100, M^+], 198 (4), 186 (9), 167 (3), 154 (4), 137 (45), 121 (30), 108 (25), 94 (10), 79 (60), 52 (7), 28 (31).

(*S*)-3-Methoxyphenyl(pyridin-2-yl)methanol [(*S*)-9c][16]
Oil; >99% ee.

$[\alpha]_D^{22}$ +141.4 (*c* 0.71, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.83–8.82 (m, 1 H), 7.91–7.87 (m, 1 H), 7.55–7.45 (m, 3 H), 7.26–7.22 (m, 2 H), 7.11–7.08 (m, 1 H), 6.01 (m, 1 H), 5.54 (br s, 1 H), 4.05 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2, 160.2, 148.2, 145.3, 137.3, 130.0, 122.9, 121.7, 119.8, 113.8, 112.8, 75.3, 55.6.

MS (70 eV): *m*/*z* (%) = 215 (100, M^+), 198 (10), 154 (12), 135 (10), 108 (66), 194 (11), 79 (66).

(*S*)-4-Chlorophenyl(pyridin-2-yl)methanol [(*S*)-9d][15]
Colorless crystals, mp 84–86 °C; >99% ee.

$[\alpha]_D^{22}$ +109 (*c* 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50–8.41 (d, 1 H), 7.61–7.48 (m, 1 H), 7.33–7.20 (m, 4 H), 7.17–7.10 (m, 1 H), 7.09–7.00 (m, 1 H), 5.65 (br s, 1 H), 5.25 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 147.9, 141.8, 137.0, 133.6, 128.8, 128.4, 122.7, 121.3, 74.2.

MS (70 eV): *m*/*z* (%) = 219 [62, M^+], 201 (4), 190 (3), 166 (5), 154 (3), 141 (12), 125 (9), 108 (66), 79 (100), 53 (32), 28 (13).

(*S*)-2,2-Dimethyl-1-(pyridin-2-yl)propan-1-ol [(*S*)-9e][17]
Oil; >99% ee.

$[\alpha]_D^{22}$ –21.4 (*c* 1.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51–8.49 (m, 1 H), 7.62–7.57 (m, 1 H), 7.20–7.13 (m, 2 H), 4.42 (br s, 1 H), 4.33 (br s, 1 H), 0.89 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.3, 135.9, 123.3, 122.7, 80.8, 36.7, 26.3.

MS (70 eV): *m*/*z* (%) = 165 (0.1, M^+), 150 (2), 132 (6), 117 (6), 108 (100), 78 (15).

Purification as the Picrate Salt; General Procedure
The picrate salt was obtained by addition of a soln of picric acid (1.5 equiv) in EtOH to an ethereal soln of the pyridyl alcohol, and the bright yellow precipitate was filtered, washed with Et_2O and crystallized from alcoholic solvents (MeOH, EtOH, *i*-PrOH). The enantiomerically pure picric salt was hydrolyzed in H_2O and the free alcohol was extracted with Et_2O (3 ×). The organic phase was dried (Na_2SO_4), filtered, and concentrated to obtain the desired pyridyl alcohols with >99% ee.

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