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A C_2-symmetric chiral bipyridyldiol–titanium complex as a catalyst for the asymmetric trimethylsilylcyanation of substituted benzaldehydes

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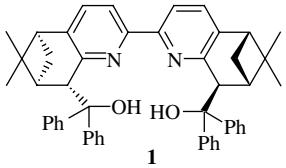
Abstract—This article describes a novel C_2-symmetric ligand that comprises a central bipyridine-pinene-derived core and two functionalized two diphenylmethanol subunits. The [8′-(hydroxy-diphenyl-methyl)-10,10,10′,10′-tetramethyl-[5,5′]bi[6-aza-tricyclo-[7.1.1.0^{2,7}]undecyl]-2(7),3,5,2′(7′),3′,5′-hexane-8-yl]-diphenyl-methanol **1** is an effective catalyst in the enantioselective addition of trimethylsilylcyanide to various aromatic aldehydes with asymmetric inductions of up to 98% ee. Importantly, the correlation between Hammett substituent constants and the enantiomeric excess, and the electron-releasing group at the *meta*- and *para*-positions of substituted benzaldehydes were demonstrated to be associated with the high enantioselectivity of the trimethylsilylcyanation reaction that involves trimethylsilylcyanide.

1. Introduction

Optically active cyanohydrins are very useful synthons for the synthesis of various valuable classes of chiral compounds, including α-hydroxy carboxylic acids,[1] α-hydroxy aldehydes,[2] α-hydroxy ketones,[3] and β-amino alcohols.[4] Numerous, efficient asymmetric biological and chemical methods have been reported for obtaining such compounds, the most important of which is the asymmetric silylcyanation of aldehydes with trimethylsilylcyanide catalyzed by a Lewis acid, including Ti(O-*i*-Pr)$_4$,[5] $TiCl_4$,[6] $AlCl_3$,[7] R_2AlCl,[8] and others,[9] in the presence of the chiral ligands, including Schiff bases, diols, diamides, phosphorus compounds, and others. Many effective chiral ligands have free hydroxyl groups or amino groups that produce the Lewis acid center of the catalyst by coordinating with the Lewis acid. This asymmetric carbon–carbon bond forming process has a wide range of synthetic applications in the pharmaceutical and agrochemical industries. Previous work[10] in this laboratory elucidated the catalytic addition of diethylzinc to various substituted benzaldehydes, providing alcohols with an (*S*)-configuration with an enantiomeric excess that typically ranged from 3% to 99% using catalytic amounts of titanium tetraisopropoxide and chiral bipyridyl-diol **1** derived from (1*R*)-(+)-α-pinene. Herein, ligand **1** was utilized as the enantioselective catalyst of the trimethylsilylcyanation reaction of the substituted benzaldehydes.



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2. Results and discussion

In the asymmetric trimethylsilylcyanation of benzaldehyde using trimethylsilylcyanide, in the presence of chiral ligand **1** and Ti(O-*i*-Pr)$_4$ in various solvents (Table 1) at room temperature, the enantiomeric excesses of acetic acid cyano-phenyl-methyl ester were acquired: in dichloromethane (34%), in acetonitrile (17%), in toluene (14%), in diethyl ether (5%), and in tetrahydrofuran (5%). Therefore, dichloromethane was chosen as the reaction solvent in the following reactions. The same reactions were performed in dichloromethane at various temperatures (Table 2), with the enantiomeric excesses of acetic acid cyano-phenyl-methyl ester obtained at 25 °C (28%), 0 °C (34%), −40 °C (43%), and −78 °C

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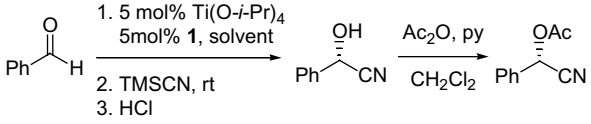
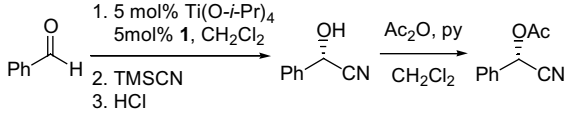
Table 1. Enantiomeric excess (%) of the trimethylsilylcyanation of benzaldehyde in the presence of Ti(IV)-**1** complex in various solvents



Entry	Solvents	Yield (%)	ee (%)
1	THF	52	5
2	Ether	60	7
3	Toluene	51	14
4	CH_3CN	66	17
5	CH_2Cl_2	70	34

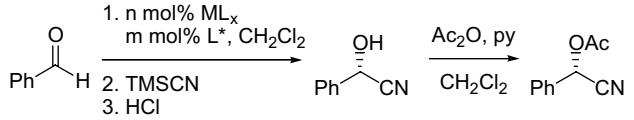
Table 2. Enantiomeric excess (%) of the trimethylsilylcyanation of benzaldehyde in the presence of Ti(IV)-**1** complex at various temperatures



Entry	Temp (°C)	Yield (%)	ee (%)
1	25	73	28
2	0	73	34
3	−40	75	43
4	−78	80	58

(58%). Accordingly, the following asymmetric reactions were conducted in dichloromethane at −78 °C. The asymmetric trimethylsilylcyanation of benzaldehyde using trimethylsilylcyanide, in the presence of various amounts of ligand **1** yielded enantiomeric excesses of acetic acid cyano-phenyl-methyl ester, as presented in Table 3. The optimal amount of catalyst was 5 mol % of ligand **1** (59% ee).

Table 3. Enantiomeric excess (%) of the trimethylsilylcyanation of benzaldehyde in the presence of various amounts of ligand **1**



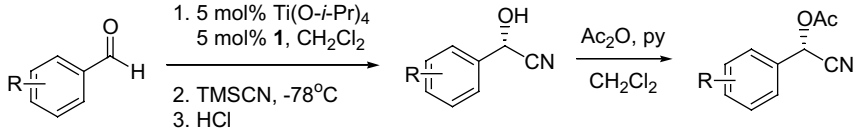
Entry	*L** (mol%)	ML_x (mol %)	Temp (°C)	Yield (%)	ee (%)
1	10	$Ti(O\text{-}i\text{-}Pr)_4$ (10)	−78	80	36
2	10	$Ti(O\text{-}i\text{-}Pr)_4$ (5)	−78	85	43
3	5	$Ti(O\text{-}i\text{-}Pr)_4$ (5)	−78	86	59
4	5	Et_2Zn (10)	rt	70	7
5	5	Et_2Zn (10)	−78	—	—
6	5	$VOSO_4$ (5)	rt	95	6

The asymmetric trimethylsilylcyanation of substituted benzaldehyde using trimethylsilylcyanide was performed in the presence of catalyst Ti(IV)-**1** complex as described below. A solution of ligand **1** and $Ti(O\text{-}i\text{-}Pr)_4$ in dichloromethane was stirred at room temperature for 1 h after which a solution of substituted benzaldehyde in dichloromethane was added. The temperature was then reduced to −78 °C, and the trimethylsilylcyanide added and stirred for 40 h. The reaction mixture was quenched by adding 1 M HCl and ethyl acetate. After purification by flash chromatography, the cyanohydrins were converted to the corresponding acetate by acetic anhydride, and the enantiomeric excesses of the product determined by HPLC. Table 4 presents the yields, ee%, and the specific rotation. The absolute configurations of all products were determined by comparing the signs of the specific rotations (α_D) as indicated in the literature.

The electronic effects in the asymmetric hydroborations,[11] epoxidations,[12] and alkylations[10] have been reported. However, the influence of purely electronic effects on the extent of asymmetric induction seem not to have been systematically investigated. In our previous study,[10] the Hammett substituent constants were strongly correlated with the enantiomeric excesses of the alkylation of *meta*-substituted benzaldehydes using diethylzinc. Importantly, the electron-releasing substituents on the *para*-position of the substituted benzaldehydes performed high enantioselectivity during alkylation using diethylzinc. In contrast, electron-withdrawing substituents on the *meta*-position of substituted benzaldehydes performed high enantioselectivity. Moreover, the weaker electron-withdrawing and electron-releasing on the *ortho*-position of substituted benzaldehydes showed higher enantioselectivity.

The asymmetric trimethylsilylcyanation of substituted benzaldehydes using trimethylsilylcyanide was performed in the presence of catalyst Ti(IV)-**1** complex. Hammett substituent constants were strongly correlated with the enantiomeric excesses produced by the trimethylsilylcyanation of *meta*- and *para*-substituted benzaldehydes using TMSCN. Importantly, the more strongly electron-releasing substituents at the *meta*- and *para*-positions exhibited higher enantiomeric excesses (*m*-Me, 69%; *m*-OMe, 57%; *p*-OMe, 71%; *p*-Me, 70%), while the more strongly electron-withdrawing substituents at the *meta*- and *para*-positions exhibited lower enantiomeric excesses (*m*-Cl, 15%; *m*-CN, 8%; *p*-Cl, 9%; *p*-CN, 2%) (Figs. 1 and 2). The moderately electron-releasing substituents at the *ortho*-position exhibited higher enantiomeric excesses (*o*-Me, 98%), while the more strongly electron-withdrawing and electron-releasing substituents at the *ortho*-position exhibited lower enantiomeric excesses (*o*-Cl, 3%; *o*-OMe, 39%) (Fig. 3). In comparison with the results of the alkylation of substituted benzaldehydes using diethylzinc, and the asymmetric trimethylsilylcyanation of substituted benzaldehydes using trimethylsilylcyanide, we found the electron-releasing substituents on the *para*-position of the substituted benzaldehydes performed high enantioselectivity. The electron-releasing substituents of benzaldehydes may enhance the π–π interaction between the phenyl group of ligand **1** and the aromatic ring of benzaldehyde. Therefore, the aromatic ring of the benzaldehydes may be tightly fixed

Table 4. The yield and enantiomeric excess (ee%) of the trimethylsilylcyanation of substituted benzaldehydes with Ti(IV)-**1** complex



Entry	R	Yield (%)[a]	ee (%)	Substituent constants[13]	Cyanohydrin $[\alpha]^{T}_{D}$ (T °C, c) CH_2Cl_2	Acetate $[\alpha]^{T}_{D}$ (T °C, c) CH_2Cl_2
1	H	86	59	σ, 0	−15.0 (23.7, 1.15)	−4.3 (24.2, 0.64)
2	*o*-OMe	45	39	σ_o, +0.12	−14.0 (19.0, 1.09)	−10.4 (24.2, 0.26)
3	*m*-OMe	53	57	σ_m, +0.12	−14.5 (24.0, 1.41)	−4.1 (24.0, 1.13)
4	*p*-OMe	83	71	σ_p, −0.27	−15.5 (24.0, 1.13)	−3.1 (24.0, 1.10)
5	*o*-Me	80	98	σ_o, +0.29	−26.7 (24.2, 1.85)	−17.0 (23.7, 1.54)
6	*m*-Me	45	69	σ_m, −0.07	−25.8 (24.2, 1.10)	−3.0 (23.6, 1.20)
7	*p*-Me	88	70	σ_p, −0.17	−26.3 (24.2, 1.41)	−3.1 (23.2, 1.60)
8	*o*-Cl	84	3	σ_o, +1.28	−1.2 (19.4, 2.06)	−0.9 (24.0, 1.93)
9	*m*-Cl	35	15	σ_m, +0.37	−16.7 (24.2, 1.51)	−0.9 (23.9, 0.40)
10	*p*-Cl	11[b]	9	σ_p, +0.23	—	−5.6 (24.0, 1.15)
11	*m*-CN	54	8[c]	σ_m, +0.56	−15.0 (22.8, 1.29)	−6.2 (16.0, 1.15)
12	*p*-CN	62	2[c]	σ_p, +0.66	−3.5 (22.6, 1.48)	−0.5 (22.0, 1.15)

[a] The yield of corresponding cyanohydrins.
[b] The yield was counted based on acetate.
[c] The enantiomeric excesses were determined by pivalate.

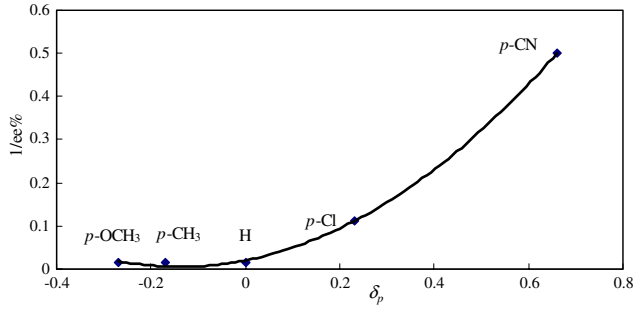


Figure 1. The correlation of substituent constants (σ_p) and the 1/ee% of the trimethylsilylcyanation of *para*-substituted benzaldehydes in the presence of Ti(IV)-**1** complex.

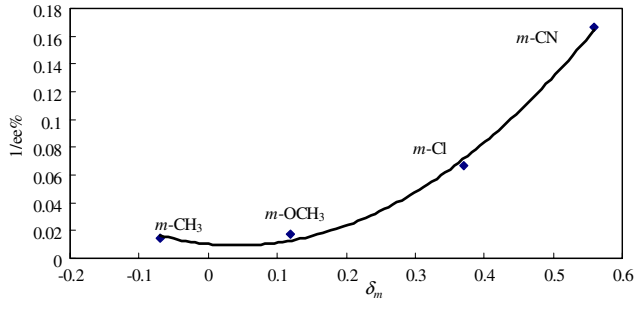


Figure 2. The correlation of substituent constants (σ_m) and the 1/ee% of the trimethylsilylcyanation of *meta*-substituted benzaldehydes in the presence of Ti(IV)-**1** complex.

and thus open the *Si*-face of the carbonyl group for alkylation and induced the higher enantioselectivity.

3. Conclusion

Herein, a chiral bipyridinyldiol **1** was prepared from highly enantiopure (>97% ee) of (1*R*)-(+)-α-pinene.[10]

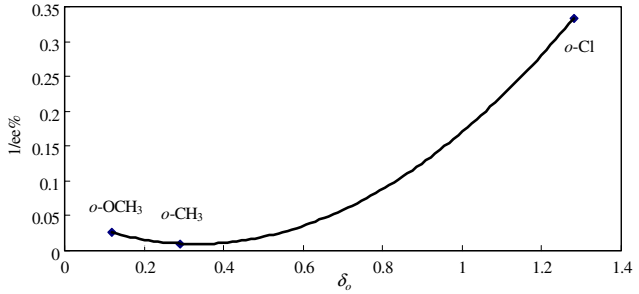


Figure 3. The correlation of substituent constants (σ_o) and the 1/ee% of the trimethylsilylcyanation of *ortho*-substituted benzaldehydes in the presence of Ti(IV)-**1** complex.

Bipyridinyldiol **1** acted as an interesting chiral catalyst of the enantioselective addition of TMSCN to various substituted benzaldehydes, yielding cyanohydrins of an (*S*)-configuration with enantiomeric excesses, generally ranging from 2% to 98%. Importantly, the electron-releasing substituents at the *meta*- and *para*-positions of the substituted benzaldehydes were highly enantioselective during cyanation using TMSCN. In contrast, electron-withdrawing substituents at the *meta*- and *para*-positions of substituted benzaldehydes were only weakly enantioselective. Other asymmetric reactions are currently being investigated to rationalize this correlation.

4. Experimental section

4.1. General

All reactions were carried out in anhydrous solvents. THF and diethyl ether were distilled from sodium-benzophenone under argon. Toluene, CH_3CN, CH_2Cl_2, and hexane were distilled from CaH_2. ^1H NMR spectra were obtained at 300 or 500 MHz (as indicated), and

^{13}C NMR spectra were obtained at 75.5 or 125.7 MHz using a Bruker NMR spectrometer. Chemical shifts (δ) are reported in ppm relative to $CDCl_3$ (7.26 and 77.0 ppm). Mass spectra (MS) were obtained using a Micromass Platform II mass spectrometer at 70 eV. High resolution mass spectra (HRMS) were obtained using a Finnigan/Thermo Quest MAT 95XL mass spectrometer. Infrared spectra were recorded using an ATI Mattson spectrometer. All asymmetric reactions were conducted in dry glassware under nitrogen using a standard glovebox. Enantiomeric excesses were determined using Lab Alliance Series III high-performance liquid chromatography (HPLC) with a Chiracel OD-H chiral column (Daicel Chemical Industries, LTD). Optical rotations were measured using a JASCO P-1010 polarimeter at the indicated temperature using a sodium lamp (D line, 589 nm). Flash column chromatography was performed using MN silica gel 60 (70–230 mesh) purchased from Macherey-Nagel. TMSCN was obtained from Sigma–Aldrich Co.

4.2. Typical procedure for the enantioselective addition of TMSCN to aldehydes catalyzed by the complex of Ti-ligand 1

The general procedure was demonstrated using benzaldehyde. To a solution of ligand **1** (10.6 mg, 14.9 μmol) in CH_2Cl_2 (0.3 mL) was added Ti(O-*i*-Pr)$_4$ (4.4 μL, 14.8 μmol) and the mixture stirred for 1 h at room temperature. The reaction mixture was cooled to −78 °C, and benzaldehyde (30 μL, 0.3 mmol) in CH_2Cl_2 (0.3 mL) and trimethylsilylcyanide (12 μL, 0.9 mmol) was added. Following stirring for 40 h at this temperature, 1 M HCl (6 mL) and ethyl acetate (12 mL) were added to the reaction solution. After further stirring for 4 h at room temperature, neutralizing the aqueous layer with 2 M NaOH, extracting with ethyl acetate, drying over anhydrous magnesium sulfate and concentrating the reaction mixture followed by column chromatography (eluent: hexane/acetone 6:1) yielded the expected (*S*)-cyanohydrin. After the specific rotation was measured, the pure cyanohydrin (0.19 mmol) was directly converted into the corresponding acetates by reaction with acetic acid anhydride (0.066 mL) and pyridine (0.03 mL) in CH_2Cl_2 (1 mL) at room temperature for 12 h. After concentration, the residue was purified by column chromatography (eluent: hexane/acetone 4:1) to yield the acetylated cyanohydrin, which was used for further analysis.

4.2.1. Hydroxy-phenyl-acetonitrile. Yield: 86%. $[\alpha]_D^{23.7} = -15.0$ (*c* 1.15, CH_2Cl_2) {lit.[14c] $[\alpha]_D^{27} = +28.9$ (*c* 1.1, $CHCl_3$) for (*R*)-enantiomer in 63% ee}. ^1H NMR (300 MHz, $CDCl_3$, δ): 7.55–7.51 (m, 2H), 7.47–7.43 (m, 3H), 5.53 (s, 1H), 3.20 (br, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 135.2, 129.9, 129.2, 126.6, 118.8, 63.6. IR (KBr, thin film): 3430, 2260, 1700, 1600 cm^{-1}. MS *m*/*z*: 134 (M^++1, 6), 133 (56), 105 (63), 73 (100). HRMS-EI (*m*/*z*): $[M]^+$ calcd for C_8H_7NO, 133.0528; found, 133.0517.

4.2.2. Acetoxy-phenyl-acetonitrile. Yield: 96%. $[\alpha]_D^{24.2} = -4.3$ (*c* 0.64, CH_2Cl_2) {lit.[14f] $[\alpha]_D^{20} = -7.2$ (*c* 2.3, $CHCl_3$)}. ^1H NMR (300 MHz, $CDCl_3$, δ): 7.51–7.46 (m, 5H), 6.41 (s, 1H), 2.17 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 170.5, 133.8, 131.3, 130.2, 128.8, 117.7, 64.2, 20.3. IR (KBr, thin film): 3037, 2944, 1753, 1216, 1023, 697 cm^{-1}. MS *m*/*z*: 176 (M^++1, 2), 167 (21), 149 (21), 147 (9), 133 (79), 91 (44), 41 (100).

4.2.3. Hydroxy-(2-methoxy-phenyl)-acetonitrile. Yield: 45%. $[\alpha]_D^{19} = -14.0$ (*c* 1.09, CH_2Cl_2) {lit.[5k] $[\alpha]_D^{25} = +19.4$ (*c* 1.0, $CHCl_3$) for (*R*)-enantiomer in 72% ee}. ^1H NMR (300 MHz, $CDCl_3$, δ): 7.44-7.38 (m, 2H), 7.05–6.97 (m, 2H), 5.55 (d, *J* = 9.0 Hz, 1H), 3.97 (s, 3H), 3.34 (d, *J* = 9.0 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 156.7, 131.1, 128.0, 123.6, 121.1, 118.8, 111.1, 60.4, 55.7. IR (KBr, thin film): 33778, 2832, 1602, 1255, 1022, 909 cm^{-1}. MS *m*/*z*: 164 (M^++1, 1), 147 (6), 133 (100), 115 (16), 91 (9).

4.2.4. Acetoxy-(2-methoxy-phenyl)-acetonitrile. Yield: 96%. $[\alpha]_D^{24.2} = -10.4$ (*c* 0.26, CH_2Cl_2) {lit.[14f] $[\alpha]_D^{20} = -19.6$ (*c* 1.6, $CHCl_3$)}. ^1H NMR (300 MHz, $CDCl_3$, δ): 7.57 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.71 (s, 1H), 2.17 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 169.1, 157.0, 131.6, 128.1, 120.6, 120.1, 116.1, 111.1, 58.2, 55.0, 18.8. IR (KBr, thin film): 2943, 1756, 1257, 1215, 1024, 757 cm^{-1}. MS *m*/*z*: 206 (M^++1, 2), 147 (44), 133 (27), 73 (100), 57 (61). HRMS-FAB (*m*/*z*): $[M+1]^+$ calcd for $C_{11}H_{11}NO_3$, 205.0746; found, 205.0739.

4.2.5. Hydroxy-(3-methoxy-phenyl)-acetonitrile. Yield: 53%. $[\alpha]_D^{24} = -14.5$ (*c* 1.41, CH_2Cl_2) {lit.[14a] $[\alpha]_D^{20} = +22.8$ (*c* 1.5, $CHCl_3$) for (*R*)-enantiomer in 58% ee}. ^1H NMR (300 MHz, $CDCl_3$, δ): 7.37 (t, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.07 (s, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 5.53 (s, 1H), 3.84 (s, 3H), 2.63 (br, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 159.9, 136.6, 130.2, 118.8, 118.7, 115.4, 111.9, 63.3, 55.4. IR (KBr, thin film): 3418, 2938, 1604, 1265, 1038, 855 cm^{-1}. MS *m*/*z*: 164 (M^++1, 1), 147 (4), 133 (100), 119 (20), 115 (38), 91 (22).

4.2.6. Acetoxy-(3-methoxy-phenyl)-acetonitrile. Yield: 97%. $[\alpha]_D^{24} = -4.1$ (*c* 1.23, CH_2Cl_2) {lit.[14f] $[\alpha]_D^{20} = -4.8$ (*c* 2.5, $CHCl_3$)}. ^1H NMR (300 MHz, $CDCl_3$, δ): 7.36 (t, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 7.04–6.97 (m, 2H), 6.38 (s, 1H), 3.84 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 170.5, 161.6, 135.1, 131.4, 120.8, 117.6, 116.7, 114.4, 64.1, 55.9, 20.3. IR (KBr, thin film): 2928, 1752, 1685, 1216, 1023, 786 cm^{-1}. MS *m*/*z*: 207 (M^++1, 4), 167 (24), 147 (31), 133 (100), 69 (68), 57 (92).

4.2.7. Hydroxy-(4-methoxy-phenyl)-acetonitrile. Yield: 83%. $[\alpha]_D^{24} = -15.5$ (*c* 1.13, CH_2Cl_2) {lit.[14a] $[\alpha]_D^{20} = +41.7$ (*c* 1.4, $CHCl_3$) for (*R*)-enantiomer in 91% ee}. ^1H NMR (300 MHz, $CDCl_3$, δ): 7.46 (d, *J* = 6.7 Hz, 2H), 6.95 (d, *J* = 6.7 Hz, 2H), 5.48 (s, 1H), 3.83 (s, 3H), 3.30 (br, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 160.6, 128.3, 127.4, 119.0, 114.5, 63.2, 55.4. IR (KBr, thin film): 3421, 2937, 2840, 1611, 1465, 1306, 1254,

1178, 834, 769 cm^{-1}. MS *m/z*: 164 (M^++1, 1), 147 (6), 133 (100), 75 (73), 57 (36).

4.2.8. Acetoxy-(4-methoxy-phenyl)-acetonitrile. Yield: 97%. $[\alpha]_D^{24} = -3.1$ (*c* 1.10, CH_2Cl_2) {lit.[14f] $[\alpha]_D^{20} = +19.0$ (*c* 1.6, $CHCl_3$)}. ^1H NMR (300 MHz, $CDCl_3$, δ): 7.45 (d, $J = 8.8$ Hz, 2H), 6.95 (d, $J = 8.8$ Hz, 2H), 6.36 (s, 1H), 3.84 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 169.1, 161.2, 129.7, 123.9, 116.4, 114.6, 62.6, 55.5, 20.5. IR (KBr, thin film): 2939, 1754, 1612, 1216, 1028, 829 cm^{-1}. MS *m/z*: 206 (M^++1, 1), 163 (3), 147 (4), 133 (100), 91 (5), 75 (69).

4.2.9. Hydroxy-*o*-tolyl-acetonitrile. Yield: 80%. $[\alpha]_D^{24.2} = -26.7$ (*c* 1.85, CH_2Cl_2) {lit.[14e] $[\alpha]_D^{26} = -26.4$ (*c* 2.0, C_6H_6) for (*R*)-enantiomer in 92% ee}. ^1H NMR (300 MHz, $CDCl_3$, δ): 7.61 (d, $J = 7.8$ Hz, 1H), 7.32 (t, $J = 7.8$ Hz, 2H), 7.26 (d, $J = 7.8$ Hz, 1H), 5.68 (d, $J = 6.2$ Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 136.2, 133.0, 131.2, 129.9, 126.9, 126.6, 118.7, 61.5, 18.7. IR (KBr, thin film): 3419, 2926, 1606, 1291, 1039, 936 cm^{-1}. MS *m/z*: 148 (M^++1, 4), 146 (19), 133 (100), 109 (14), 75 (43). HRMS-FAB (*m/z*): $[M+1]^+$ calcd for C_9H_9NO, 147.0664; found, 147.0684.

4.2.10. Acetoxy-*o*-tolyl-acetonitrile. Yield: 96%. $[\alpha]_D^{23.7} = -17.0$ (*c* 1.54, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.57–7.55 (m, 1H), 7.38–7.24 (m, 3H), 6.52 (s, 1H), 2.4 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (125.7 MHz, CD_3OD, δ): 170.4, 138.1, 132.3, 131.7, 131.4, 129.4, 127.3, 117.42, 62.6, 20.1, 18.9. IR (KBr, thin film): 2934, 1754, 1372, 1214, 1022, 961, 758 cm^{-1}. MS *m/z*: 190 (M^++1, 1), 149 (16), 133 (100), 115 (17), 75 (75). HRMS-FAB (*m/z*): $[M+1]^+$ calcd for $C_{11}H_{11}NO_2$, 189.0790; found, 189.0783.

4.2.11. Hydroxy-*m*-tolyl-acetonitrile. Yield: 45%. $[\alpha]_D^{24.2} = -25.8$ (*c* 1.10, CH_2Cl_2) {lit.[14d] $[\alpha]_D^{22} = -41.3$ (*c* 0.5, $CHCl_3$) for (*S*)-enantiomer in 92% ee}. ^1H NMR (300 MHz, $CDCl_3$, δ): 7.37–7.31 (m, 3H), 7.27–7.23 (m, 1H), 5.50 (s, 1H), 3.20–2.90 (br, 1H), 2.40 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 139.0, 135.0, 130.4, 128.9, 127.2, 123.6, 119.0, 63.3, 21.2. IR (KBr, thin film): 3419, 2924, 1610, 1250, 1039, 949 cm^{-1}. MS *m/z*: 148 (M^++1, 1), 132 (100), 131 (5), 75 (83), 57 (43).

4.2.12. Acetoxy-*m*-tolyl-acetonitrile. Yield: 97%. $[\alpha]_D^{23.6} = -3.0$ (*c* 1.20, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.34–7.26 (m, 4H), 6.37 (s, 1H), 2.40 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (125.7 MHz, CD_3OD, δ): 170.5, 140.4, 133.7, 131.9, 130.1, 129.4, 125.9, 117.7, 64.2, 21.3, 20.3. IR (KBr, thin film): 3024, 2925, 1755, 1214, 1023, 898, 699 cm^{-1}. MS *m/z*: 190 (M^++1, 2), 149 (32), 133 (33), 119 (51), 91 (47), 73 (78), 44 (100). HRMS-FAB (*m/z*): $[M+1]^+$ calcd for $C_{11}H_{11}NO_2$, 189.0790; found, 189.0765.

4.2.13. Hydroxy-*p*-tolyl-acetonitrile. Yield: 88%. $[\alpha]_D^{24.2} = -26.3$ (*c* 1.41, CH_2Cl_2) {lit.[14d] $[\alpha]_D^{22} = -48.5$ (*c* 0.5, $CHCl_3$) for (*S*)-enantiomer in 94% ee}. ^1H NMR (300 MHz, $CDCl_3$, δ): 7.41 (d, $J = 8.0$ Hz, 2H), 7.25 (d, $J = 8.0$ Hz, 2H), 5.49 (s, 1H), 2.97 (br, 1H), 2.39 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 140.0, 132.4, 129.8, 126.7, 118.8, 63.5, 21.2. IR (KBr, thin film): 3400, 2922, 1260, 1031, 1018, 818, 534 cm^{-1}. MS *m/z*: 148 (M^++1, 2), 133 (100), 131 (9), 115 (33), 75 (47), 57 (24), 45 (13). HRMS-FAB (*m/z*): $[M+1]^+$ calcd for C_9H_9NO, 147.0684; found, 147.0664.

4.2.14. Acetoxy-*o*-*p*-tolyl-acetonitrile. Yield: 97%. $[\alpha]_D^{23.2} = -3.1$ (*c* 1.60, CH_2Cl_2) {lit.[14g] $[\alpha]_D = -29.0$ (*c* 1.4, C_6H_6)}. ^1H NMR (300 MHz, $CDCl_3$, δ): 7.41 (d, $J = 8.1$ Hz, 2H), 7.26 (d, $J = 8.1$ Hz, 2H), 6.37 (s, 1H), 2.39 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (125.7 MHz, CD_3OD, δ): 170.5, 141.7, 130.9, 130.8, 128.9, 117.8, 64.1, 21.3, 20.3. IR (KBr, thin film): 2968, 1753, 1366, 1217, 1020, 814, 528 cm^{-1}. MS *m/z*: 190 (M^++1, 6), 148 (41), 133 (100), 119 (43), 91 (49), 71 (26), 55 (65). HRMS-FAB (*m/z*): $[M+1]^+$ calcd for $C_{11}H_{11}NO_2$, 189.0790; found, 189.0791.

4.2.15. (2-Chloro-phenyl)-hydroxy-acetonitrile. Yield: 84%. $[\alpha]_D^{19.4} = -1.2$ (*c* 2.06, CH_2Cl_2) [lit.[14b] $[\alpha]_D^{20} = +3.4$ (*c* 0.9, $CHCl_3$) for *S* enantiomer in 91% ee]. ^1H NMR (300 MHz, $CDCl_3$, δ): 7.74–7.71 (m, 1H), 7.48–7.37 (m, 3H), 5.88 (d, $J = 6.6$ Hz, 1H), 2.87 (d, $J = 6.6$ Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 132.6, 132.4, 130.9, 129.9, 128.2, 127.6, 118.0, 60.6. IR (KBr, thin film): 3410, 2923, 1594, 1192, 1035, 942 cm^{-1}. MS *m/z*: 168 (M^++1, 3), 141 (8), 139 (13), 133 (100), 91 (6), 77 (6), 73 (9).

4.2.16. Acetoxy-(2-chloro-phenyl)-acetonitrile. Yield: 97%. $[\alpha]_D^{24} = -0.9$ (*c* 1.93, CH_2Cl_2) {lit.[14d] $[\alpha]_D^{22} = -54.4$ (*c* 0.8, $CHCl_3$)}. ^1H NMR (300 MHz, $CDCl_3$, δ): 7.74–7.71 (m, 1H), 7.48–7.37 (m, 3H), 6.72 (s, 1H), 2.20 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 170.2, 134.3, 133.0, 131.4, 131.2, 130.5, 129.0, 116.6, 61.8, 20.0. IR (KBr, thin film): 3069, 2940, 1758, 1476, 1443, 1372, 1212, 758, 569 cm^{-1}. MS *m/z*: 210 (M^++1, 2), 167 (7), 147 (43), 133 (16), 91 (20), 73 (100), 57 (62).

4.2.17. (3-Chloro-phenyl)-hydroxy-acetonitrile. Yield: 35%. $[\alpha]_D^{24.2} = -16.7$ (*c* 1.51, CH_2Cl_2) {lit.[14d] $[\alpha]_D^{22} = -54.4$ (*c* 0.8, $CHCl_3$) for (*S*)-enantiomer in 97% ee}. ^1H NMR (300 MHz, $CDCl_3$, δ): 7.55 (s, 1H), 7.44–7.41 (m, 3H), 5.55 (d, $J = 6.7$ Hz, 1H), 2.87 (d, $J = 6.7$ Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 136.7, 135.0, 130.4, 129.9, 126.7, 124.6, 118.5, 62.5. IR (KBr, thin film): 3410, 2904, 1597, 1194, 1041, 940 cm^{-1}. MS *m/z*: 168 (M^++1, 4), 151 (6), 133 (100), 91 (26), 77 (16).

4.2.18. Acetoxy-(3-chloro-phenyl)-acetonitrile. Yield: 95%. $[\alpha]_D^{23.9} = -0.9$ (*c* 0.40, CH_2Cl_2) {lit.[14d] $[\alpha]_D^{22} = -39.4$ (*c* 0.8, $CHCl_3$)}. ^1H NMR (300 MHz, $CDCl_3$, δ): 7.52 (s, 1H), 7.40 (m, 3H), 6.38 (s, 1H), 2.19 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 170.3, 136.0, 135.9, 131.8, 128.8, 127.2, 117.2, 63.5, 20.2. IR (KBr, thin film): 3067, 2941, 1762, 1477, 1443, 1372, 1215, 788, 690 cm^{-1}. MS *m/z*: 210 (M^++1, 0.1), 167 (3), 133 (100), 91 (3), 75 (5), 57 (4).

4.2.19. Acetoxy-(4-chloro-phenyl)-acetonitrile. Yield: 28%. $[\alpha]_D^{24} = -5.6$ (*c* 1.15, CH_2Cl_2) {lit.[14h] $[\alpha]_D^{25} = -13.9$ (*c* 1.0, $CHCl_3$) for (*R*)-enantiomer in 99% ee}. ^1H NMR (300 MHz, $CDCl_3$, δ): 7.49–7.41 (m, 4H), 6.38 (s, 1H), 2.17 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 168.8, 136.6, 130.6, 130.2, 129.5, 129.3, 115.7, 62.1, 20.4. IR (KBr, thin film): 2940, 1756, 1599, 1215,

1016, 821 cm^{-1}. MS *m/z*: 210 (M^++1, 0.3), 107 (1.8), 147 (23), 133 (50), 73 (77), 44 (100). HRMS-FAB (*m/z*): $[M+1]^+$ calcd for $C_{10}H_9ClNO_2$, 209.0244; found, 210.0311.

4.2.20. 3-(Cyano-hydroxy-methyl)-benzonitrile. Yield: 54%. $[\alpha]_D^{22.8} = -15.0$ (*c* 1.29, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.87 (s, 1H), 7.81 (d, $J = 7.6$ Hz, 1H), 7.74 (d, $J = 7.6$ Hz, 1H), 7.60 (t, $J = 7.6$ Hz, 1H), 5.64 (s, 1H), 2.90 (br, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 137.0, 133.1, 131.1, 130.1, 130.0, 118.3, 118.0, 112.7, 62.1. IR (KBr, thin film): 3396, 2230, 1435, 1149, 1041, 968 cm^{-1}. MS *m/z*: 159 (M^++1, 66), 146 (100), 141 (12), 133 (69), 91 (13), 77 (23), 57 (77).

4.2.21. 2,2-Dimethylpropioxy-(3-cyano-phenyl)-acetonitrile. Yield: 91%. $[\alpha]_D^{16} = -6.2$ (*c* 1.15, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.80–7.75 (m, 3H), 7.64–7.59 (m, 2H), 6.43 (s, 1H), 1.26 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 176.1, 133.8, 133.7, 131.7, 130.9, 130.3, 117.6, 115.3, 113.7, 61.7, 38.9, 25.8. IR (KBr, thin film): 2977, 1752, 1586, 1271, 1034, 894 cm^{-1}. MS *m/z*: 243 (M^++1, 1), 133 (100), 115 (14), 75 (33), 57 (98). HRMS-FAB (*m/z*): $[M+1]^+$ calcd for $C_{14}H_{14}N_2O_2$, 242.1055; found, 243.1139.

4.2.22. 4-(Cyano-hydroxy-methyl)-benzonitrile. Yield: 62%. $[\alpha]_D^{22.6} = -3.5$ (*c* 1.48, CH_2Cl_2) {lit.[14a] $[\alpha]_D = +6.5$ (*c* 1.5, $CHCl_3$) for (*R*)-enantiomer in 20% ee}. ^1H NMR (300 MHz, $CDCl_3$, δ): 7.77 (d, $J = 7.5$ Hz, 2H), 7.69 (d, $J = 7.5$ Hz, 2H), 5.65 (d, $J = 6.1$ Hz, 1H), 2.82 (d, $J = 6.1$ Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 140.3, 133.0, 127.3, 118.2, 118.1, 113.3, 62.5. ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 140.3, 133.0, 127.1, 118.1, 118.0, 113.0, 62.3. IR (KBr, thin film): 3398, 2242, 1410, 1056, 934 cm^{-1}. MS *m/z*: 159 (M^++1, 19), 149 (33), 146 (16), 133 (91), 115 (100), 91 (8), 77 (9), 75 (96), 57 (80).

4.2.23. 2,2-Dimethylpropioxy-(4-cyano-phenyl)-acetonitrile. Yield: 94%. $[\alpha]_D^{22} = -0.5$ (*c* 1.15, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.77 (d, $J = 8.4$ Hz, 2H), 7.63 (d, $J = 8.4$ Hz, 2H), 6.45 (s, 1H), 1.26 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 176.1, 136.8, 133.0, 128.1, 117.7, 115.3, 114.4, 61.9, 38.9, 26.8. IR (KBr, thin film): 2977, 1751, 1483, 1270, 1034, 890 cm^{-1}. MS *m/z*: 243 (M^++1, 3), 133 (68), 85 (22), 57 (100), 41 (100). HRMS-FAB (*m/z*): $[M+1]^+$ calcd for $C_{14}H_{14}N_2O_2$, 242.1055; found, 243.1125.

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