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Enzymatic kinetic resolution of racemic cyanohydrins via enantioselective acylation

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ABSTRACT

Enzymatic kinetic resolution of a series of aromatic and aliphatic cyanohydrins in organic media has been investigated. The behavior of potential lipases, molecular sieves, acyl reagent, reaction temperature, and organic solvents on the kinetic resolution was studied. The influence of substrate structure, steric, and electronic nature and position of the aryl substituent on the enantioselectivity was discussed. Under the optimized reaction conditions, good enantioselectivity could be achieved for most of the investigated compounds. Specifically, substrates **1a**, **1c**, **1d**, **1f**, **1u** could be resolved with the kinetic enantiomer ratio (*E*) higher than 200.

1. Introduction

Cyanohydrins have considerable synthetic potential as chiral building blocks since they bear a hydroxyl group and a cyano group on one chiral carbon. They therefore provide a wide space for transformation into a large number of chiral molecules, especially in a wide range of pharmaceuticals and agrochemicals. Stereoselective synthesis of cyanohydrins has been extensively investigated topics and there have appeared quite a number of excellent reviews.[1] The methodology of such formation can roughly be divided into three major categories: (1) hydrocyanation of aldehydes or ketones catalyzed by chemical catalyst, (2) hydrocyanation of aldehydes or ketones catalyzed by biological catalyst, and (3) enantioselective acylation or hydrolytic deacylation of racemic cyanohydrins or racemic cyanohydrin esters catalyzed by esterase or lipase, namely, simple kinetic resolution (KR) and dynamic kinetic resolution (DKR).

In the KR, a cyanohydrin racemate is treated by an acylating reagent in the presence of a lipase or an esterase to stereoselectively obtain an acylated enantiomer and an unreacted enantiomer, or alternatively, an acylated cyanohydrin racemate is stereoselectively hydrolyzed in the presence of a lipase or an esterase to give a hydrolyzed enantiomer and an unreacted enantiomer.[2] In ideal case, both of the enantiomers can be obtained simultaneously in high enantiopurity with a yield close to 50%, which is usually not good for final product but might be good in the case where both of the resolved enantiomers are useful as starting material in synthesis.

In this article, we wish to report the results[3] obtained in our continuous effort for the preparation of enantiopure cyanohydrins.[4]

2. Results and discussion

2.1. Optimization of reaction conditions[5]

2.1.1. Variation of catalyst. A number of lipases and esterases have been reported in the literatures for the kinetic resolution of secondary alcohols. Among them we chose Apf-12, P-30, P-30(LPMO), and PS-30 due to their high efficiency and good accessibility. Screening using racemic mandelonitrile as a model compound showed that lipase PS-30 was the best one of the four, which could give a value of kinetic enantiomeric ratio (*E*) up to 102.6 at 37% conversion. Table 1 summarized the results. Lipase PS-30 was consequently used throughout this study.

2.1.2. Effect of molecular sieves. Results shown in Table 2 demonstrated that addition of 4A molecular sieves (MS) to the reaction did have a benefit effect in shortening the reaction time and enhancing the *E* values although the reaction *per se* did not yield any water.

2.1.3. Variation of acyl reagent. Vinyl acetate and isopropenyl acetate were tested as the acyl reagent and vinyl acetate gave higher *E*

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that up to 87.1 at 43% conversion after 48 h, whereas isopropenyl acetate gave an *E* value of 51.1 after 24 h (Table 3). Therefore, we used vinyl acetate as the acylating reagent in the following study.

Table 1
Variation of lipase

Entry	Lipase	Reaction time (h)	% ee_E	% ee_A	% C_{HPLC}	*E*
1	Apf-12	25	93.1	24.1	21	35.3
2	P-30	27	94.0	16.0	15	38.1
3	P-30(LPMO)	27	96.6	14.0	13	65.9
4	PS-30	27	96.6	55.7	37	102.6

Reaction conditions: 1 mmol substrate/0.05 g lipase/4 grains of 4A molecular sieves/5 ml vinyl acetate, 15 °C. ee_E and ee_A were established by CSP-HPLC. Enantioselectivity factor (*E*) is defined in Ref. 6 as $E=\ln[(1-C_{HPLC})(1-ee_A)]/\ln[(1-C_{HPLC})(1+ee_A)]$, where $C_{HPLC}=100\times ee_A/(ee_E+ee_A)$.

Table 2
Effect of molecular sieves

Entry	Lipase	MS	Reaction time (h)	% ee_E	% ee_A	% C_{HPLC}	*E*
1	P-30(LPMO)	−	47	91.9	4.8	5	24.9
2		+	27	96.6	14.0	13	65.9
3	PS-30	−	47	94.9	42.2	31	57.9
4		+	27	96.6	55.7	37	102.6

Reaction conditions: 1 mmol substrate/0.05 g lipase/5 ml vinyl acetate, 15 °C.

Table 3
Variation of acyl reagent

Entry	Acetate	Reaction time (h)	% ee_E	% ee_A	% C_{HPLC}	*E*
1	Vinyl	48	95.1	72.2	43	87.1
2	Isopropenyl	24	93.9	47.8	34	51.1

Reaction Conditions: 1 mmol substrate/0.05 g PS-30/4 grains MS/5 ml toluene, 2 equiv% acyl reagent, 15 °C.

2.1.4. Variation of temperature. As shown in Table 4 (entry 3), 15 °C appeared to be the most proper reaction temperature to give a high *E* value with a reasonable conversion in shorter reaction time. At lower temperature (0 °C), PS-30 showed low activity, which led to low *E* and conversion after a prolonged reaction time. *E* value was also low when the reaction temperature was raised to 40 °C, which might cause decomposition of the substrate and racemation of the product.

Table 4
Variation of temperature

Entry	*T*(°C)	Reaction time (h)	% ee_E	% ee_A	% C_{HPLC}	*E*
1	0	71	82.1	12.0	13	11.4
2	10	71	96.7	44.6	32	94.3
3	15	48	95.1	72.2	43	87.1
4	20	48	90.1	76.5	46	44.1
5	30	36	90.9	55.5	38	36.6
6	40	36	85.9	61.7	42	24.8

Reaction Conditions: 1 mmol substrate/0.05 g PS-30/4 grains MS/5 ml toluene, 2 equiv % vinyl acetate.

2.1.5. Variation of solvent. As shown in Table 5, both of the highest enantioselectivity (*E*=249) and good conversion (*c*=42%) were obtained with Et_2O as solvent at 15 °C in a relative short reaction time (24 h). Reaction at 10 °C also gave high enantioselectivity (*E*=247) with satisfied conversion (*c*=43%), but a longer reaction time (48 h) was needed (entry 6). When vinyl acetate was used as both of the acyl donor and solvent (entry 12), moderate enantioselectivity (*E*=103) was obtained. Decomposition of the substrates and racemation of the products might be caused by those solvents with high hydrophilic character, such as THF, acetone, or acetonitrile (entries 9–11), leading to low *E* values.

Table 5
Variation of solvent

Entry	Solvent	Reaction time (h)	% ee_E	% ee_A	% C_{HPLC}	*E*
1	*n*-hexane	24	71.9	72.6	50	13.1
2	Toluene	48	95.1	72.2	43	87.1
3	CCl_4	25	64.8	35.7	36	6.6
4	$CHCl_3$	24	64.1	26.6	29	5.9
5	$CHCl_3$	25	87.4	45.9	34	23.4
6[a]	Et_2O	48	98.2	74.5	43	247.7
7	Et_2O	24	98.3	71.1	42	249.3
8	*i*-Pr_2O	24	91.0	85.3	48	57.6
9	THF	49	59.7	19.0	24	4.8
10	Acetone	49	63.0	80.3	56	10.5
11	Acetonitrile	29	85.5	13.8	14	14.6
12	Vinyl acetate	27	96.6	55.7	37	102.6

Reaction conditions: 1 mmol substrate/0.05 g PS-30/4 grains of MS/5 ml solvent, 2 equiv % vinyl acetate at 15 °C.
[a] 10 °C.

In summary, by the above-mentioned optimization, we could establish our reaction conditions: in the presence of 4A molecular sieves, lipase PS-30 as the catalyst, diethyl ether as the solvent, vinyl acetate as the acylating reagent, 15 °C as the reaction temperature.

2.2. Kinetic resolution of cyanohydrins

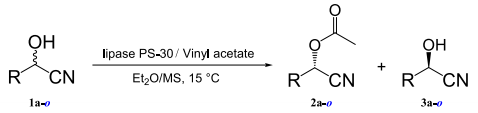
Under the above optimized reaction conditions, twenty-three racemic substrates were subjected to the kinetic resolution. Results were summarized in Table 6–8.

2.2.1. Aromatic cyanohydrins. The enantioselectivity of acylation depends on how strong the interaction between the aromatic ring of the substrate and the lipase. The interaction is a sum of electronic and steric ones in nature. Electron-donating substituent (entries 2–4) favored the interaction electronically, while such favorable effect might, to some extent, be compromised by their bulky volume. In the case of electron-withdrawing substituent (entries 5–13), the interaction was diminished both electronically and sterically. Similarly, the substrates with naphthyl group only got moderate *E* values (entry 14 and 15) since they could not fit well with the combining pocket of lipase owing to the larger space demand of the naphthyl group compared to the phenyl group.

Specifically, by comparison of the data shown in Table 6, it could be seen that mandelonitrile, the one with unsubstituted aryl group (entry 1) gave the highest *E* value. In the case of the electron-donating substitution, 4-Me group (entry 2) led to the decreasing of *E* value because its favorable electronic effect was weaker than its unfavorable steric effect. 4-MeO- (entry 3) and 4-MeS- (entry 4) substitution resulted in *E* values higher than that given by 4-Me substitution due probably to their stronger electron-donating and conjugate effects to the aromatic system. However, the larger steric hindrance of MeS- than that of MeO- made the *E* value of entry 4 lower than that of entry 3.

Meanwhile, all substrates with electron-withdrawing substituent gave low *E* values (entries 5–13). In the case of halogen substituents, with the increasing electronegativity of the substituent (Br, 2.8; Cl, 3.0; and F, 4.0),[7] the *E* values dropped down gradually (135, 123, and 94, entries 8, 11 and 7). However, when fluoro substitution was on the *meta* position of the aryl group, the inductive effect of the substituent appears to be of no much influence on the *E* value (228, entry 6). In the case of bromo substitution, when the substituents were closer to the cyanohydrin

Table 6
Enantioselective acetylation of cyanohydrins (**1a**–***o***) with vinyl acetate in diethyl ether at 15 °C catalyzed by lipase PS-30



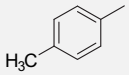
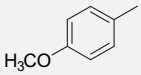
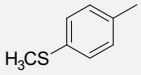
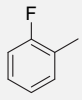
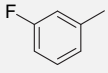
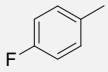
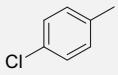
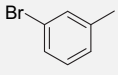
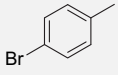
Entry	R	ee_E (**2**) (%)	ee_A (**3**) (%)	*E*	C (%)	Reaction time (h)
1	 **1a**	98.3	71.1	249	42	24
2	 **1b**	98.3	48.6	191	33	23.5
3	 **1c**	98.7	47.1	244	32	29
4	 **1d**	97.8	74.2	203	43	45.5
5	 **1e**	94.3	31.3	46	25	25
6	 **1f**	98.6	47.8	228	33	27
7	 **1g**	92.8	93. 6	94	50	50
8	 **1h**	96.3	81.3	135	46	45
9	 **1i**	37.4	8.6	2.4	19	48
10	 **1j**	92.1	57.3	43.3	38	45.5
11	 **1k**	95.5	86.3	123	47	39.5

Table 6 (*continued*)

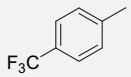
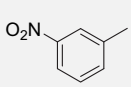
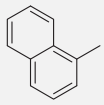
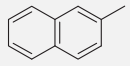
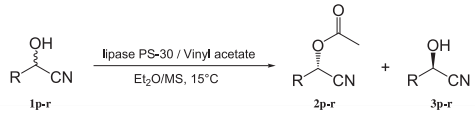
Entry	R	ee_E (**2**) (%)	ee_A (**3**) (%)	*E*	C (%)	Reaction time (h)
12	 **1*l***	89.3	17.6	21	16	46
13	 **1m**	91.4	1.5	23	2	48.5
14	 **1n**	87.2	36.5	21	30	25
15	 **1*o***	72.8	82.3	17	54	24

Table 7
Enantioselective acetylation of heteroaromatic cyanohydrins (**1p**–**r**) with vinyl acetate in diethyl ether at 15 °C catalyzed by lipase PS-30

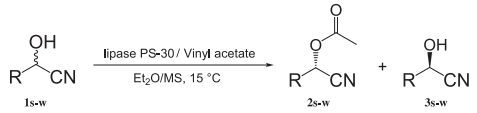


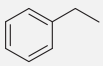
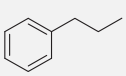
Entry	R	ee_E (**2**) (%)	ee_A (**3**) (%)	*E*	C (%)	Reaction time (h)
1	 **1p**	54.6	6.5	4	11	45
2	 **1q**	93.0	41.5	41	31	21
3	 **1r**	93.4	79.9	71.7	46	30

group (*para*- vs *meta*- vs *ortho*-), their unfavorable steric effect showed higher negative influence on the *E* values (123, 43.3, and 2.4, entry 12, 11 and 10). By comparing the results of entry 5 and entry 9, it could be seen that the –Br group on *ortho* position decreased the *E* value much effectively than the –F group because of the larger steric hindrance of –Br relative to that of –F, even though –F possesses much higher electronegativity (4.0 vs 2.0 of –Br). This meant that the steric hindrance of the substituents might affect more strongly on the *E* values of products than the inductive effect. The same conclusion could be made by comparing the results of entry 8 and entry 11.

2.2.2. Heteroaromatic cyanohydrins. The relative low *E* values given by the substrates with heterocyclic group (entry 1, 2, and 3 in Table 7)

Table 8
Enantioselective acetylation of aliphatic cyanohydrins (**1s**–**w**) with vinyl acetate in diethyl ether at 15 °C catalyzed by lipase PS-30



Entry	R	ee_E (**2**) (%)	ee_A (**3**) (%)	*E*	C (%)	Reaction time (h)
1	 **1s**	97.2	78.8	172	45	35
2	 **1t**	94.1	82.6	85	47	20
3	 **1u**	98.4	80.7	314	45	24
4	 **1v**	40.8	88.7	6	68	20
5	 **1w**	88.2	84.2	42	49	20

could be owing to the hetero atoms in the aryl ring, which might weaken the interaction between the substrates and the enzyme. The particularly low *E* value given by 2-pyridyl cyanohydrin (entry 1) reminded us the fact that 2-pyridylcarboxaldehyde gave poor outcome (40% yield, 0 ee) in the almond hydroxynitrile lyase catalyzed hydrocyanation.[4b]

2.2.3. Aliphatic cyanohydrins. Five aliphatic cyanohydrins (acyclic and cyclic) were tested as the substrates of lipase PS-30 and good results were observed. Cyclohexyl cyanohydrin (entry 1) gave good selectivity (*E*=172). Those aliphatic cyanohydrins with short carbon chain connected to a phenyl group at β or γ position (entries 2 and 3) gave high *E* values (85 and 314); comparing with the moderate *E* value (42, entry 5) of the substrate with short carbon chain connected to a methyl group at β position, it could be seen that the phenyl group on the short carbon chain might exert good influence to the combination between the substrates and the enzyme. The poor *E* value (6) in entry 4 showed the poor interaction of the substrate with long linear carbon chain and the enzyme.

2.3. Configuration assignment of the fast reacting enantiomer and the slow reacting enantiomer

According to the rule proposed by Kazlauskas[8] (Fig. 1), the –CN would act as medium-sized group located in the medium-sized pocket, thus the (*S*)-enantiomer was favorable to interact with the lipase leading to the acylated product. Therefore, the (*S*)-enantiomer was the fast reacting enantiomer, which was isolated from the reaction mixture as the acylated product, while the (*R*)-enantiomer was the slow reacting one, remaining in the reaction

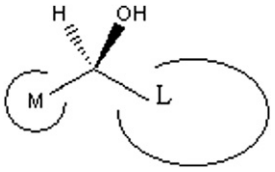


Figure 1.

system as the unacylated alcohol. Configuration of some of the acylated products and the unreacted alcohols, which were obtained after the cyanohydrins were converted into the corresponding acetate (**2a**–**2c**,[3] **2e**–**2g**,[3] **2h**,[3] **2i**–**2k**,[2a] **2l**,[9a] **2m**,[9d] **2n**,[3] **2o**,[3] **2p**,[2l] **2s**,[9b] **2t**,[3] **2u**,[3] **2v**,[2i] **2w**[9c]) were further proved by comparison of the observed optical rotations of the obtained products with those reported in the literatures. Configuration of compound **2d** was proposed to have the same assignment as the known ones based on the Kazlauskas' rule. However, in the case of furyl and thienyl compounds (**2q** and **2r**, entry 18 and 19), the slow reacting enantiomer was assigned to (*S*)-configuration by comparison of the observed optical rotation with the reported lit.[9b], while the fast reacting one to (*R*)-configuration due to the Cahn–Ingold–Prolog rule.

3. Conclusion

In this work, we have performed the kinetic resolution of a series of cyanohydrins with lipase PS-30 as the catalyst. The results showed that, in the case of aromatic cyanohydrins, where the aryl group was a phenyl group (or a phenyl group substituted by an electron-donating group) and in the case of aliphatic cyanohydrins including cyclohexyl cyanohydrin and those with a short carbon chain connected with a phenyl group, the system could give high *E* values. The influence of the inductive and the steric effects of the substituents on the phenyl group in the reaction results has also been examined. The obtained *E* values showed that a considerable number of examined cyanohydrins could be resolved to produce enantiopure forms from preparative purposes.

4. Experimental section

4.1. Method and materials

^{1}H NMR spectra were recorded on a Bruker AV-400 (400 MHz) spectrometer with Me_4Si as an internal standard. ^{19}F NMR spectra were obtained on a Bruker AM-300(282 MHz) spectrometer using $CFCl_3$ as an external standard; downfield shifts being designated as positive, all chemical shifts (δ) were expressed in ppm and coupling constants (*J*) are in Hertz. Mass spectra were recorded on a Finnigan-MAT-8430 instrument using EI ionization at 70 eV. IR spectra were recorded on a Nicolet 380 spectrometer. High-Resolution mass spectral analyses were performed on a Finnigan-MAT-8430 spectrometer. Optical rotations were measured by WZZ-2 polarimeter. Melting points were measured on a WRS-2A melting point apparatus. Enantiomeric excess values were performed by a Breeze LC system (Waters Corporation) on a Chiralcel OJ-H, OD-H or AD-H column using isopropanol–hexanes as mobile phase. All the lipases were purchased from Sigma–Aldrich™. All the solvents used in the reaction were purified by *re*-distillation. Vinyl acetate and isopropyl acetate were purified by *re*-distillation. Other reagents were used as purchased from commercial suppliers without further purification.

Racemic cyanohydrins were prepared from various aldehydes and $NaHSO_3$ and NaCN and the acylated derivatives were prepared according to known method.[5]

4.2. General kinetic resolution experiment

A 5 ml bake-dried vial charged with lipase PS-30 (0.025 g, corresponding to 0.5 mmol of the racemic cyanohydrins) and two grains of 4A molecular sieves was flushed with nitrogen for several times, the racemic cyanohydrins dissolved in dry Et_2O (1 ml) and vinyl acetate (86 mg, 1 mmol) dissolved in dry Et_2O (1.5 ml) were added. The mixture was stirred at 15 °C and analyzed by TLC [petroleum ether/ethyl acetate (20:1–3:1)] until consumption of the starting material was about 50%. The mixture was then filtered and the solid washed with dry acetone (2 ml). The solvent was evaporated in vacuo and the residue was purified on silica gel using petroleum ether/ethyl acetate as the eluent. The unreacted cyanohydrin was acylated for determination of ee value by adding 0.3 ml of an acylating solution [anhydrous pyridine (5 ml), acetic or propionic anhydride (1 mmol), and DMAP (1% wt/volume)] to 1 mg of the unreacted cyanohydrin. Enantiomeric excess was determined for the obtained acylated products on Chiralcel OJ-H, OD-H or AD-H column monitored at 220 nm or 254 nm using hexanes/*i*-propyl alcohol as the mobile phase. The absolute configuration of the resolution compounds was obtained by comparison of the observed optical rotations with the literature data.

*4.2.1. (S)-(−)-Acetoxy-phenyl-acetonitrile (**2a**)*[3]. Clear oil. $[\alpha]_D^{26}$ −5.6 (*c* 0.58, $CHCl_3$), 98.3% ee; ^{1}H NMR (400 Hz, $CDCl_3$) *δ* 7.53–7.51(m, 2H,), 7.49–7.44(m, 3H), 6.41(s, 1H), 2.17(s, 3H); Ms (EI 70 eV) *m*/*z*: 176(M+1, 31), 175(31), 159(6), 149(32), 133(73), 116(100), 115(61), 105(39), 89(26), 43(69); IR (film, cm^{-1}): 3008, 2925, 1745, 1449, 1370, 1210, 898, 755, 520; HPLC: Chiralcel OD-H, Hexane/*i*-PrOH=99:01, 1.0 ml/min, 254 nm, t_R=12.61 min, t_R=14.15 min.

*4.2.2. (S)-(−)-Acetoxy-p-tolyl-acetonitrile (**2b**)*[3]. Clear oil. $[\alpha]_D^{26}$ −14.6 (*c* 0.51, $CHCl_3$), 98.3% ee; ^{1}H NMR (400 Hz, $CDCl_3$) *δ* 7.53–7.03 (m, 4H), 6.44 (s, 1H), 3.92 (s, 3H), 2.22(s, 3H); MS (EI 70 eV) *m*/*z*: 163 (31), 145 (100), 146 (98), 135(24), 116 (15), 91 (12), 77 (15), 76(13), 43 (23); IR(film, cm^{-1}): 2969, 2917, 2849, 1738, 1652, 1540, 1455, 1365, 1216, 1123, 1032, 798, 527; Chiralcel OD-H, Hexane/*i*-PrOH=95:05, 0.4 ml/min, 220 nm, t_R=28.12 min, t_R=32.36 min.

*4.2.3. (S)-(+)-Acetoxy-(4-methoxy-phenyl)-acetonitrile (**2c**)*[3]. Clear oil. $[\alpha]_D^{26}$ +6.77 (*c* 0.69, $CHCl_3$), 98.7% ee; ^{1}H NMR (400 Hz, $CDCl_3$) *δ* 7.49–7.33 (m, 4H), 6.45 (s, 1H), 2.47 (s, 3H), 2.24 (s, 3H); MS (EI 70 eV) *m*/*z*: 205 (M^+, 1), 189(31), 147 (79), 129 (100), 119 (31), 103 (31), 91 (28), 77 (21), 65(13), 51 (11), 43 (44), 39 (9), 28 (18); IR (film, cm^{-1}): 2969, 2918, 2849, 1737, 1653, 1540, 1456, 1365, 1216, 1127, 1034, 901, 798, 527; Chiralcel OJ-H, Hexane/*i*-PrOH=95:05, 1.0 ml/min, 220 nm, t_R=20.71 min, t_R=23.04 min.

*4.2.4. (S)-(+)-Acetoxy-(4-methylsulfanyl-phenyl)-acetonitrile (**2d**).* White solid, mp 67.2–68.2 °C; $[\alpha]_D^{26.2}$ +35.0 (*c* 0.88, $CHCl_3$), (97.82% ee); ^{1}H NMR (400 Hz, $CDCl_3$) *δ* 7.36 (d, *J*=8.8 Hz, 2H), 7.22 (d, *J*=8.8 Hz, 2H), 6.29(s, 1H), 2.43(s, 3H), 2.08(s, 3H); MS (EI 70 eV) *m*/*z*: 221 (M^+,72), 222 (M+1,12), 223 (M+2, 3), 179 (39), 162 (100), 161(95), 160(38), 151(18), 146 (31), 147(24), 132(8), 43(32); HR-EI: Calcd for: $C_{11}H_{11}NO_2S$, Found: 221.0516; IR(film, cm^{-1}): 2921, 2850, 1753, 1599, 1494, 1437, 1408, 1370, 1212, 1093, 1015, 960, 904, 812, 568; HPLC: Chiralcel OJ-H, Hexane/*i*-PrOH=70:30, 0.7 ml/min, 254 nm, t_R=29.21 min, t_R=32.83 min.

*4.2.5. (S)-(−)-Acetoxy-(2-fluoro-phenyl)-acetonitrile (**2e**)*[3]. Clear oil. $[\alpha]_D^{26}$ −19.9 (*c* 0.79, $CHCl_3$), 94.3% ee; ^{1}H (400 Hz, $CDCl_3$) *δ* 7.58–7.08 (m, 4H), 6.56 (s, 1H), 2.11(s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) *δ*−116.29–−116.35(m, 1F); MS (EI 70 eV) *m*/*z*: 193 (M^+, 2), 167 (10), 166(39), 165(54), 151 (20), 134(68), 133 (28), 123(100), 107(23), 95(18), 75(160), 57(10), 43(45); IR (film, cm^{-1}): 2920, 1736, 1618, 1538, 1495, 1455, 1365, 1216, 1101, 956, 762; Chiralcel OJ-H, Hexane/*i*-PrOH=98:02, 1.0 ml/min, 254 nm, t_R=22.52 min, t_R=25.51 min.

*4.2.6. (S)-(−)-Acetoxy-(3-fluoro-phenyl)-acetonitrile (**2f**)*[3]. Clear oil. $[\alpha]_D^{26}$ −6.9 (*c* 0.49, $CHCl_3$), 98.6% ee; ^{1}H NMR (400 Hz, $CDCl_3$) *δ* 7.47–7.14 (m, 4H), 6.40 (s, 1H), 2.19 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) *δ*−110.54–−110.60 (q, *J*=7.52 Hz, 1F); MS (EI 70 eV) *m*/*z*: 193 (M^+, 14), 194 (M+1, 4), 151 (71), 134 (46), 133 (41), 123 (23), 124 (14), 107 (22), 95 (11), 75 (8), 57 (8), 43 (100); IR (film, cm^{-1}): 2929, 2851, 1755, 1617, 1596, 1490, 1453, 1372, 1270, 1212, 1143, 1026, 894, 868, 792, 690; Chiralcel OJ-H, Hexane/*i*-PrOH=95:05, 1.0 ml/min, 220 nm, t_R=29.46 min, t_R=34.85 min.

*4.2.7. (S)-(−)-Acetoxy-(4-fluoro-phenyl)-acetonitrile (**2g**)*[3]. Clear oil. $[\alpha]_D^{26}$ −3.5 (*c* 1.99, $CHCl_3$), 89.8% ee; ^{1}H NMR (400 Hz, $CDCl_3$) *δ* 7.47–7.05 (m, 4H), 6.32 (s, 1H), 2.09 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) *δ* −109.53–−109.59 (q, *J*=7.52 Hz, 1F); MS (EI 70 eV) *m*/*z*: 194 (M+1, 4), 193(M^+, 12), 151(60), 134(85), 133(100), 123(38), 107(29), 95(18), 75(12), 57(19), 43(84); IR(film, cm^{-1}): 2969, 1754, 1607, 1512, 1423, 1372, 1216, 1161, 1024, 963, 834, 789, 567; Chiralcel OJ-H, Hexane/*i*-PrOH=95:05, 0.4 mL/min, 220 nm, t_R=63.46 min, t_R=66.66 min.

*4.2.8. (S)-(+)-Acetoxy-(4-chloro-phenyl)-acetonitrile (**2h**)*[3]. Clear oil. $[\alpha]_D^{20}$ 8.26 (*c* 0.58, $CHCl_3$), 96.32% ee; ^{1}H NMR (400 Hz, $CDCl_3$) *δ* 7.49–7.41 (m, 4H), 6.38 (s, 1H), 2.17 (s, 3H); MS (EI 70 eV) *m*/*z*: 209 (M^+, 21), 210 (M^++1, 3), 211 (M^++2, 7), 167 (81), 168 (8), 169 (27), 149 (88), 150 (81), 151(36), 152 (27), 139 (28), 133 (22), 123 (22), 114 (50), 111 (16), 75 (23), 43 (100); IR(film, cm^{-1}): 2916, 2848, 1749, 1573, 1537, 1464, 1209, 1091, 1019, 803, 720; HPLC: Chiralcel OD-H, Hexane/*i*-PrOH=90:10, 0.7 ml/min, 220 nm, t_R=11.25 min, t_R=12.51 min.

*4.2.9. (S)-(−)-Acetoxy-(2-bromo-phenyl)-acetonitrile (**2i**)*[2a]. Clear oil. $[\alpha]_D^{24.2}$ −10.3(*c* 0.66, CH_2Cl_2), 37.4%ee; ^{1}H NMR (400 Hz, $CDCl_3$) *δ* 7.75–7.73 (d, *J*=7.68 Hz, 1H), 7.66–7.64 (d, *J*=8.0 Hz, 1H), 7.47–7.43 (t, *J*=7.6 Hz, 1H), 7.38–7.33 (m, 1H), 6.67 (s, 1H), 2.20(s, 3H); MS (EI 70 eV) *m*/*z*: 255 (M+1, 2), 253 (M−1, 2), 213 (16), 211 (17), 196 (19), 194 (19), 174 (60), 132 (91), 115 (28), 114 (56), 43 (100), 44 (23); IR (film, cm^{-1}): 3068, 2937, 1757, 1580, 1466, 1437, 1372, 1207, 1026, 967, 910, 757, 571; HPLC: Chiralcel OD-H, Hexane/*i*-PrOH=90:10, 0.7 ml/min, 220 nm, t_R=10.42 min, t_R=12.58 min.

*4.2.10. (S)-(−)-Acetoxy-(3-bromo-phenyl)-acetonitrile (**2j**)*[2a]. Clear oil. $[\alpha]_D^{22.6}$ −11.3 (*c* 0.5, CH_2Cl_2), 92.1% ee; ^{1}H NMR (400 Hz, $CDCl_3$) *δ* 7.67 (br s, 1H), 7.58 (d, *J*=8.0 Hz, 1H), 7.46 (d, *J*=8.0 Hz, 1H), 7.33 (t, *J*=7.8 Hz, 1H), 7.31(s, 1H), 6.37(s, 1H), 2.19 (s, 3H); MS (EI 70 eV) *m*/*z*: 255(M+1, 13), 253(M−1, 13), 213(29), 211(30), 196(14), 194(15), 132(17), 116(24), 114(48), 88(11), 50(11), 43(100); IR(film, cm^{-1}): 3072, 2937, 1758, 1580, 1474, 1425, 1374, 1207, 1029, 882, 785, 693, 600; HPLC: Chiralcel OD-H, Hexane/*i*-PrOH=95:05, 0.8 ml/min, 220 nm, t_R=12.56 min, t_R=14.09 min.

*4.2.11. (S)-(−)-Acetoxy-(4-bromo-phenyl)-acetonitrile (**2k**)*[2a]. Clear oil. $[\alpha]_D^{22.8}$ −17.3 (*c* 0.52, CH_2Cl_2), 95.5% ee; ^{1}H NMR (400 Hz, $CDCl_3$) *δ* 7.61–7.58 (d, *J*=8.52 Hz, 2H), 7.41–7.38 (d, *J*=8.48 Hz, 2H), 6.369 (s, 1H), 2.171 (s, 3H); MS (EI 70 eV) *m*/*z*: 255 (M+1, 23), 253 (M−1, 23), 213 (53), 211 (55), 196 (35), 195 (34), 194 (36), 193 (32), 132 (17), 115 (38), 114 (87), 88 (19), 75 (11), 43 (100); IR (film, cm^{-1}): 2925, 2847, 1756, 1589, 1491, 1409, 1368, 1213, 1070, 962, 815; HPLC: Chiralcel OD-H, Hexane/*i*-PrOH=90:10, 0.7 ml/min, 220 nm, t_R=13.77 min, t_R=16.46 min.

*4.2.12. (S)-(−)-Acetoxy-(4-trifluoromethyl-phenyl)-acetonitrile (**2l**)*[9a]. Clear oil. $[\alpha]_D^{20}$−4.21 (*c* 1.91, $CHCl_3$), 89.3% ee; ^{1}H NMR (400 Hz,

$CDCl_3$) δ 7.722–7.652 (dd, J=8.4, 27.6 Hz, 4H), 6.470 (s, 1H), 2.196 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.97 (s, 3F); MS (EI 70 eV) m/z: 243 (M^+, 6), 201 (83), 184 (49), 183 (46), 173 (35), 145 (12), 134 (23), 43 (100); IR (KBr, cm^{-1}): 2945, 1758, 1622, 1420, 1374, 1327, 1215, 1170, 1130, 1068, 1020, 963, 912, 828, 744, 602; HPLC: Chiralcel OD-H, Hexane/*i*-PrOH=90:10, 1.0 ml/min, 220 nm, t_R=8.06 min, t_R=9.48 min.

*4.2.13. (S)-(−)-Acetoxy-(3-nitro-phenyl)-acetonitrile (**2m**)*[9d]. $[\alpha]_D^{20}$ −5.6 (*c* 0.43, $CHCl_3$), 91.4% ee; ^{1}H NMR (400 Hz, $CDCl_3$) δ 8.405–8.330 (m, 2H), 7.890 (d, J=8.0 Hz, 1H), 7.692 (t, J=8.0 Hz, 1H), 6.508 (s, 1H), 2.227 (s, 3H); MS (EI 70 eV) m/z: 193 (9), 178 (31), 161 (31), 160 (24), 134 (34), 114 (39), 88 (9), 43 (100); IR (KBr, cm^{-1}): 2917, 2848, 1757, 1576, 1535, 1467, 1430, 1352, 1207, 1091, 1029, 807, 734, 594; HPLC: Chiralcel OJ-H, Hexane/*i*-PrOH=70:30, 1.0 ml/min, 254 nm, t_R=46.30 min, t_R=59.09 min.

*4.2.14. (S)-(−)-Acetoxy-(1-naphthyl)-acetonitrile (**2n**)*[3]. Clear oil. $[\alpha]_D^{26}$ −42.6 (*c* 0.53, $CHCl_3$), 87.2% ee; ^{1}H NMR (400 Hz, $CDCl_3$) δ 8.02 (d, J=8.4 Hz, 1H), 7.99–7.93 (m, 2H), 7.82 (d, J=7.2 Hz, 1H), 7.64–7.51 (m, 3H), 7.03 (s, 1H), 2.23 (s, 3H); MS (EI, 70 eV) m/z: 225 (M^+, 26), 183 (24), 166 (64), 165 (100), 164 (17), 155 (20), 140 (17), 139 (20), 127 (18), 43 (30); IR (film, cm^{-1}): 2926, 2854, 1742, 1441, 1369, 1211, 1091, 1022, 901, 799, 773, 520; Chiralcel OJ-H, Hexane/*i*-PrOH=95:05, 0.4 ml/min, 220 nm, t_R=84.92 min, t_R=94.06 min.

*4.2.15. (S)-(+)-Acetoxy-(2-naphthyl)-acetonitrile (**2o**)*[3]. White sold, mp 33.8–34.5 °C; $[\alpha]_D^{26}$ +18.6 (*c* 0.6, $CHCl_3$), 72.9% ee; ^{1}H NMR (400 Hz, $CDCl_3$) δ 7.95(s, 1H), 7.94–7.79 (m, 3H), 750–7.47 (m, 3H), 6.51 (s, 1H), 2.11 (s, 3H); MS (EI, 70 eV) m/z: 225 (M^+, 42), 183 (95), 166 (70), 165 (100), 164 (22), 155 (19), 140 (19), 139 (21), 127 (22), 43 (27); IR (film, cm^{-1}): 3058, 2925, 2852, 1754, 1602, 1509, 1432, 1370, 1214, 1022, 943, 894, 817, 749; Chiralcel OJ-H, Hexane/*i*-PrOH=99:01,1.0 ml/min, 220 nm, t_R=50.76 min, t_R=57.83 min.

*4.2.16. (S)-(−)-Acetoxy-(2-pyridyl)-acetonitrile (**2p**)*[2l]. Clear oil. $[\alpha]_D^{22.9}$ −10 (*c* 0.30, $CHCl_3$), 54.6% ee; ^{1}H NMR (400 Hz, $CDCl_3$) δ 8.67 (d, J=4.8 Hz, 1H), 7.85–7.80(td, J=1.6, 7.6 Hz, 1H), 7.55 (d, J=7.6 Hz, 1H), 7.40–7.37 (m, 1H), 6.50(s, 1H), 2.23 (s, 3H); MS (EI, 70 eV) m/z: 176 (M^+, 3), 134 (100), 117 (14), 106 (15), 90 (14), 79 (72), 78 (28), 51 (14), 43 (70); IR (film, cm^{-1}): 3061, 2925, 2854, 1758, 1590, 1468, 1438, 1372, 1215, 1101, 1049, 996, 967, 907, 776, 618, 571; Chiralcel AD-H, Hexane/*i*-PrOH=95:05, 1.0 ml/min, 254 nm, t_R=14.34 min, t_R=16.61 min.

*4.2.17. (R)-(+)-Acetoxy-(2-furyl)-acetonitrile (**2q**)*[9b]. Pale yellow oil. $[\alpha]_D^{24.2}$ 20.9(*c* 1.05, $CHCl_3$), 93.0% ee; ^{1}H NMR (400 Hz, $CDCl_3$) δ 7.51 (dd, J=0.68, 1.80 Hz, 1H), 7.69 (d, J=3.32 Hz, 1H), 6.48 (s, 1H), 6.45 (dd, J=1.88, 3.36 Hz, 1H), 2.17 (s, 3H); MS (EI, 70 eV) m/z: 165 (M^+, 38), 123 (57), 106 (100), 105 (36), 95 (14), 78 (18), 77 (52), 68 (5), 51 (24), 43 (77), 28 (25); IR (film, cm^{-1}): 2917, 2849, 1732, 1575, 1539, 1466, 1090, 799; HPLC: Chiralcel AD-H, Hexane/*i*-PrOH=95:05, 1.0 ml/min, 220 nm, t_R=7.37 min, t_R=8.32 min.

*4.2.18. (R)-(+)-Acetoxy-(2-thienyl)-acetonitrile (**2r**)*[9b]. Clear oil. $[\alpha]_D^{23.2}$ +11.05 (*c* 0.51, $CHCl_3$), 93.38% ee; ^{1}H NMR (400 Hz, $CDCl_3$) δ 7.46 (dd, J=1.02, 5.12 Hz, 1H), 7.36 (dd, J=0.6, 3.64 Hz, 1H), 7.05 (dd, J=3.64, 5.12 Hz, 1H), 6.64 (s, 1H), 2.17 (s, 3H); MS (EI, 70 eV) m/z: 181 (M^+, 15), 139 (16), 139 (15), 122 (100), 121 (46), 111 (64), 95 (10), 83 (8), 69 (8), 58 (11), 51 (4), 45 (15), 43 (16), 39 (18), 32 (6), 28 (20); IR(film, cm^{-1}): 3111, 2931, 2853, 1755, 1431, 1371, 1212, 1019, 941, 848, 715; HPLC: Chiralcel OJ-H, Hexane/*i*-PrOH=90:10, 1.0 ml/min, 220 nm, t_R=18.38 min, t_R=19.61 min.

*4.2.19. (S)-(−)-Acetoxy-(2-cyclohexyl)-acetonitrile (**2s**)*[9b]. Clear oil. $[\alpha]_D^{22.5}$ −54.5 (*c* 0.52, CH_2Cl_2), 97.2% ee; ^{1}H NMR (400 Hz, $CDCl_3$) δ 5.18 (d, J=6.0 Hz, 1H), 2.15(s, 3H), 1.82(m, 6H), 1.24 (m, 5H); MS (EI, 70 eV) m/z: 139 (19), 99 (100), 83 (96), 67 (10), 57 (19), 55 (87), 43 (77), 41 (35); IR (film, cm^{-1}): 2933, 2858, 1755, 1449, 1373, 1221, 1033; Chiralcel OJ-H, Hexane/*i*-PrOH=100:0, 0.7 ml/min, 220 nm, t_R=17.42 min, t_R=20.13 min.

*4.2.20. (S)-(−)-Acetoxy-3-phenyl-propanenitrile (**2t**)*[3]. Clear oil. $[\alpha]_D^{26}$ −53.2 (*c* 0.67, $CHCl_3$), 94.1% ee; ^{1}H NMR (400 Hz, $CDCl_3$) δ 7.31–7.19 (m, 5H), 5.41 (t, J=7.2 Hz, 1H), 3.11 (d, J=6.8, 2H), 2.04 (s, 3H); MS (EI, 70 eV) m/z: 189 (M^+, 1), 130 (13), 129 (97), 103 (8), 91 (100), 77 (9), 73 (17), 71 (14), 69 (13), 65 (13), 60 (14), 57 (24), 55 (20), 51 (8), 43 (69), 41 (19), 39 (8), 29 (7), 28 (6); IR(film, cm^{-1}): 2969, 2925, 1750, 1650, 1537, 1497, 1455, 1372, 1217, 1091, 1036, 752, 701; Chiralcel OJ-H, Hexane/*i*-PrOH=95:05, 0.4 ml/min, 220 nm, t_R=102.43 min, t_R=122.04 min.

*4.2.21. (S)-(−)-Acetoxv-4-phenyl-butanenitrile (**2u**)*[3]. Clear oil. $[\alpha]_D^{26}$ −27.2 (*c* 0.7, $CHCl_3$), 98.8% ee; ^{1}H NMR (400 Hz, $CDCl_3$) δ 7.26–7.14 (m, 3H), 7.11(d, J=7.6, 2H), 5.19(t, J=6.8,1H), 2.76 (t, J=7.2, 2H), 2.19–2.14(q, J=7.2, 2H), 2.05 (s, 3H); MS (EI, 70 eV) 203 (M+, 2), 143 (100), 116 (39), 105 (25), 91 (46), 77 (12), 73 (34), 71 (27), 65 (14), 60 (28), 57 (49), 55 (38), 51 (6), 43 (93), 41 (33); IR (film, cm^{-1}): 3015, 2969, 1738, 1434, 1365, 1216, 1092, 896; Chiralcel OD-H, Hexane/*i*-PrOH=95:05, 0.4 ml/min, 220 nm, t_R=44.39 min, t_R=52.58 min.

*4.2.22. (S)-(−)-2-Acetyloxy-undecanenitrile (**2v**)*[2i]. Clear oil. $[\alpha]_D^{22.6}$ −15.4 (*c* 0.51, $CHCl_3$), 40.8% ee; ^{1}H NMR (400 Hz, $CDCl_3$) δ 5.31(t, J=6.8 Hz, 1H), 2.13(s, 3H), 1.92–1.86 (m, 2H), 1.51–1.45 (m, 2H), 1.36–1.27 (m, 12H), 0.88(t, J=6.8 Hz, 3H); MS (EI, 70 eV) m/z: 226 (M^++1, 1), 183 (9), 182 (12), 154 (7), 140 (6), 136 (11), 122 (13), 109 (12), 97 (12), 95 (26), 86 (10), 83 (13), 81 (21), 57 (12), 55 (17), 43 (100), 41 (28); IR (film, cm^{-1}): 2927, 2858, 1756, 1637, 1459, 1375, 1221, 1036; Chiralcel OJ-H, Hexane/*i*-PrOH=100:0, 0.5 ml/min, 220 nm, t_R=20.08 min, t_R=21.64 min.

*4.2.23. (S)-(−)-2-Acetoxy-(4-methyl)-pentanenitrile (**2w**)*[9c]. Clear oil. $[\alpha]_D^{24.2}$ −64.18 (*c* 1.7, $CHCl_3$), 88.2% ee; ^{1}H NMR (400 Hz, $CDCl_3$) δ 5.35 (t, J=7.62, 1H), 2.14 (s, 3H), 1.88–1.76 (m, 3H), 0.98(dd, J=4.80, 6.40, 6H); MS (EI, 70 eV) m/z: 129 (M^+−CN,5), 113 (8), 112 (9), 99 (15), 95 (10), 94 (8), 80 (14), 71 (15), 57 (44), 43 (100), 41 (33); IR (film, cm^{-1}): 2963, 2876, 1756, 1468, 1373, 1221, 1131, 1063, 1029, 931; Chiralcel OJ-H, Hexane/*i*-PrOH=100:0, 0.5 ml/min, 220 nm, t_R=24.85 min, t_R=27.00 min.

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Supplementary data

Supplementary data includes synthetic procedures of the racemic substrates, **^{1}H MNR**, **^{19}F NMR** spectra, and chiral **HPLC** chromatograms. Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2009.11.074.

References and notes

1. For examples. (a) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649–3682; (b) Brussee, J.; Van der Gen, A. In *Stereoselective Biocatalysis*; Ramesh, N. P., Ed.; Marcel Dekker: New York, NY, 2000; pp 289–320; (c) Effenberg, F. In *Stereoselective Biocatalysis*; Ramesh, N. P., Ed.; Marcel Dekker: New York, NY, 2000; pp 321–342; (d) North, M. *Tetrahedron: Asymmetry* **2003**, *14*, 147–176; (e) Brunel, J.-M.; Holems, I. P. *Angew Chem., Int. Ed.* **2004**, *43*, 2752–2778; (f) Chen, F.-X.; Feng, X. *Curr. Org. Synth.* **2006**, *3*, 77–97; (g) Roberge, C.; Fleitz, F.; Pollard, D.; Devine, P. *Tetrahedron: Asymmetry* **2007**, *18*, 208–214; (h) Khan, N. H.; Kureshy, R. I.; Abdi, S. H. R.; Agrawal, S.; Jasra, R. *Coord. Chem. Rev.* **2008**, *252*, 593–623; (i) North, M.; Usanov,

D. L.; Young, C. *Chem. Rev.* **2008**, *108*, 5146–5226; (j) Holt, J.; Hanefeld, U. *Curr. Org. Synth.* **2009**, *6*, 15–37.
2. For examples, (a) van Almsick, A.; Buddrus, J.; Honicke-Schmidt, P.; Laumen, K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1989**, 1391–1393; (b) Effenberger, F.; Gutterer, B.; Ziegler, T.; Eckhardt, E.; Aichholz, R. *Liebigs Ann. Chem.* **1991**, 47–54; (c) Inagaki, M.; Hiratake, J.; Nishioka, T.; Oda, J. *J. Org. Chem.* **1992**, *57*, 5643–5649; (d) Vänttinen, e.; Kanerva, L. T. *Tetrahedron: Asymmetry* **1995**, *6*, 1779–1786; (e) Hanefeld, U.; Li, Y.; Sheldon, R. A.; Maschmeyer, T. *Synlett* **2000**, 1775–1776; (f) Veum, L.; Kuster, M.; Telalovic, S.; Hanefeld, U.; Maschmeyer, T. *Eur. J. Org. Chem.* **2002**, 1516–1522; (g) Paizs, C.; Tahtinen, P.; Lundell, K.; Poppe, L.; Irimie, F. D.; Kanerva, L. T. *Tetrahedron: Asymmetry* **2003**, *14*, 1895–1904; (h) Levy, L. M.; Gotor, V. *J. Org. Chem.* **2004**, *69*, 2601–2602; (i) Veum, L.; Hanefelt, U. *Synlett* **2005**, 2382–2384; (j) Veum, L.; Kanerva, L. T.; Halling, P. J.; Maschmeyer, T.; Hanefeld, U. *Adv. Synth. Catal.* **2005**, *347*, 1015–1021; (k) Holt, J.; Arends, I. W. C. E.; Minnaard, A. J.; Hanefeld, U. *Adv. Synth. Catal.* **2007**, *349*, 1341–1344; (l) Hamber, A.; Lundgren, S.; Wingstrand, E.; Moberg, C.; Hult, K. *Chem.—Eur. J.* **2007**, *13*, 4334–4341; (m) Shen, Z.; Zhou, W.; Liu, Y.; Ji, S.; Loh, T. *Green Chem.* **2008**, *10*, 283–286.
3. Xu, Q.; Geng, X.; Chen, P. *Tetrahedron Lett.* **2008**, *49*, 6440–6441.
4. (a) Han, S.; Chen, P.; Lin, G.; Huang, H.; Li, Z. *Tetrahedron: Asymmetry* **2001**, *12*, 843–846; (b) Chen, P.; Han, S.; Lin, G.; Huang, H.; Li, Z. *Tetrahedron: Asymmetry* **2001**, *12*, 3273–3279; (c) Chen, P.; Han, S.; Lin, G.; Li, Z. *J. Org. Chem.* **2002**, *67*, 8251–8253; (d) Lu, W.; Chen, P.; Lin, G. *Tetrahedron* **2008**, *64*, 7822–7827.
5. (a) Ghanem, A.; Schurig, V. *Chirality* **2001**, *13*, 118–123; (b) Ghanem, A.; Schurig, V. *Tetrahedron: Asymmetry* **2003**, *14*, 2547–2555.
6. (a) Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299; (b) Kagan, H. B.; Fiaud, J. C. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; John Wiley and Sons: New York, NY, 1988; Vol. 18, pp 249–330.
7. *Data Taken from Advanced Organic Chemistry*; March, J., Ed.; John Wiley & Sons: New York, NY, 1992; p 15.
8. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656–2665.
9. (a) Sakai, T.; Wang, K.; Ema, T. *Tetrahedron* **2008**, *64*, 2178–2183; (b) Schmidt, M.; Hervé, S.; Klempier, N.; Griengl, H. *Tetrahedron* **1996**, *52*, 7833–7840; (c) Ohta, H.; Hiraga, S.; Miyamoto, K.; Tsuchihashi, G. *Agric. Biol. Chem.* **1988**, *52*, 3023–3027; (d) Yoneda, R.; Santo, K.; Harusawa, S.; Kurihara, T. *Synthesis* **1986**, 1054–1055.