Anti-Selective Aldol Reaction of Benzylic Nitriles and Synthesis of γ-Amino Alcohols

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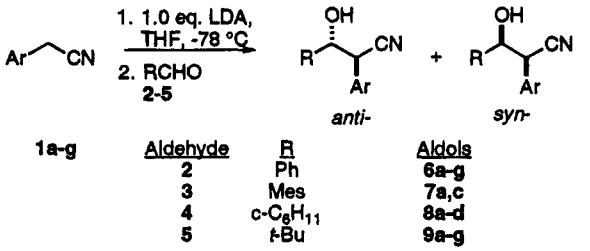
The stereochemistry of the aldol reaction of seven benzylic nitriles **1a–g** and four aldehydes **2–5** has been studied. In all cases studied the reaction is *anti*-selective. Good to excellent selectivity (10:1–>20:1) can be obtained if aldehydes with bulky secondary or tertiary substituents are used. The resulting aldols **6–9** are easily transformed to the corresponding γ-amino alcohols **12–15**, which may possess useful antidepressant activity.

The stereochemistry of addition of ketone, ester, and amide enolates to aldehydes has been extensively investigated;[1] in contrast, very little attention has been given to the stereochemistry of addition of metalated nitriles to aldehydes[2] (Scheme 1).

This lack of attention is suprising, given the fact that enantiomerically pure β-hydroxy nitriles **6–9** would be versatile synthetic intermediates.[3] Of particular interest is the potential rapid entry into γ-amino alcohols **12-15**, a functional group present in a number of widely prescribed antidepressants. However, until recently, diastereoselectivities in the nitrile aldol reaction have not been synthetically useful. In 1982, Hamana reported that di-*n*-butylboron triflate-mediated aldol reaction of phenylacetonitrile and benzaldehyde gave the two diastereomeric aldol products in a 1:1 ratio.[4] Kasatkin and co-workers reported that various titanated phenylacetonitriles underwent nonstereoselective aldol reaction with benzaldehyde.[5] In a recent chemoselectivity study, Kauffman reported obtaining unassigned mixtures of diastereomers from various metalated propiononitriles and benzaldehyde.[6] We recently disclosed that phenylacetonitrile undergoes *anti*-selective[7] aldol reaction with aldehydes.[8] We now expand our previous study by examination of other benzylic nitriles and by transforming the β-hydroxy nitrile aldol products **6–9** to the corresponding γ-amino alcohols **12–15**.

Scheme 1



In accordance with our previous study, to attain optimum diastereoselectivity, reactions were carried out in THF at 0.025 M, at −78 °C. Reaction of seven different benzylic nitriles **1a–g** with 4 aldehydes **2–5** was carried out (Table 1).

The aldols **6a–g** derived from benzaldehyde **2** are formed in low to moderate diastereoselectivity, from a low of 2.3:1 for **6g** (entry 7), to a high of 5.5:1 for **6a** (entry 1). As the steric bulk of the aldehyde is increased, selectivities enter a synthetically useful range, as we had observed in our previous study.[8] Aldol diastereoselectivity with cyclohexanecarboxaldehyde **3** is slightly higher in one case (entries 8, 9). For mesitaldehyde **4**, the aldols **8a–d** are generally formed with greater than 10:1 diastereoselectivity (entries 10–13). Finally, with the very bulky R = t-Bu substituted aldehyde **5**, the corresponding aldols **9a–g** are generally obtained with >20:1 *anti*-selectivity (entries 14–20). In most cases the minor *syn*-diastereomer can only be detected by GC or HPLC (reported ratios >20:1). Generally, for aldols **6–9,** pure *anti*-diastereomer can be obtained by means of a single recrystallization.

Assignment of each of the major β-hydroxy nitrile diastereomers as *anti* was performed in several ways (methods A–E), as outlined in Table 2.

First, the relative configuration of aldols **6a** (Table 2, entry 1) is known unambiguously from independent stereospecific synthesis.[9] Secondly, single-crystal X-ray determination of the major diastereomers of **7a**, **8d**, **9b**, and **9f** (acetate) demonstrated *anti*-relative stereochemistry (Table 2, entries 8, 20, 11, and 15). Thus *anti*-aldol stereoselectivity has been unambiguously demonstrated in at least one case for each of the four aldehydes used in this study. Consistent trends in the chemical shifts

† To whom inquiries concerning the X-ray crystal structures should be directed.

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(1) (a) Heathcock, C. H. In Comprehensive Organic Synthesis; Trost, B. M., Fleming, I., Heatchcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Volume 2, Chapter 1.6. (b) Kim, B. M.; Williams, S. F.; Masamune, S. *Ibid.* Chapter 1.7.

(2) (a) Trost has reported highly diastereoselective additions of metalated propiononitrile to various cyclic α,β-unsaturated ketones: Trost, B. M.; Florez, J.; Haller, K. J. *J. Org. Chem.* **1988**, *53*, 2394. (b) Trost has also reported axial-selective addition of metalated acetonitrile to various cyclohexanones and cyclohexenones: Trost, B. M.; Florez, J.; Jebaratnam, D. J. *J. Am. Chem. Soc.* **1987**, *109*, 613.

(3) Existing methods for the preparation of optically active β-hydroxy nitriles include (a) addition of chirally-modified (cyanomethyl)zinc bromide to aldehydes: Soai, K.; Hirose, Y.; Sakata, S. *Tetrahedron Asymm.* **1992**, *3*, 677–680. (b) Lipase-catalyzed hydrolysis of acylated β-hydroxy nitriles: Itoh, T.; Takagi, Y.; Nishiyama, S. *J. Org. Chem.* **1991**, *56*, 1521–1524. (c) Yeast reduction of 3-oxoalkyl Nitriles: Itoh, T.; Fukuda, T.; Fujisawa, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3851–3855.

(4) Hamana, H.; Sugasawa, T. *Chem. Lett.* **1982**, 1401–1404.

(5) Kasatkin, A. N.; Biktimirov, R. Kh.; Tolstikov, G. A.; Nikonenko, A. G. *J. Org. Chem. USSR* **1990**, *26*, 1037–1045. Note that according to our subsequent work, the authors' *anti*:*syn* assignments should be reversed.

(6) Kauffmann, T.; Kieper, H.; Pieper, H. *Chem. Ber.* **1992**, 899.

(7) The aldols are described as *anti*- or *syn*- according to Masamune: Masamune, S.; Ali, Sk. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557.

(8) Carlier, P. R.; Lo, K-M. *J. Org. Chem.* **1994**, *59*, 4053.

(9) Wade, P. A.; Bereznak, J. F. *J. Org. Chem.* **1987**, *52*, 2973–2977.

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Table 1

entry	Ar (nitrile)	R (aldehyde)	aldol	*anti:syn*[a]	yield[b]
1	Ph (**1a**)	Ph (**2**)	**6a**	5.5:1	70
2	2-MeO-Ph (**1b**)	Ph (**2**)	**6b**	3.2:1	84
3	4-MeO-Ph (**1c**)	Ph (**2**)	**6c**	5.3:1	84
4	4-Me-Ph (**1d**)	Ph (**2**)	**6d**	5.3:1	95
5	4-Cl-Ph (**1e**)	Ph (**2**)	**6e**	2.7:1	84
6	1-naphthyl (**1f**)	Ph (**2**)	**6f**	2.6:1	75
7	2-naphthyl (**1g**)	Ph (**2**)	**6g**	2.3:1	89
8	(**1a**)	*c*-C_6H_{11} (**3**)	**7a**	8.4:1	89
9	(**1c**)	*c*-C_6H_{11} (**3**)	**7c**	5:1	80
10	(**1a**)	Mes[c] (**4**)	**8a**	11.8:1	94
11	(**1b**)	Mes[c] (**4**)	**8b**	12.9:1	97
12	(**1c**)	Mes[c] (**4**)	**8c**	9.0:1	76
13	(**1d**)	Mes[c] (**4**)	**8d**	17.1:1	85
14	(**1a**)	*t*-Bu (**5**)	**9a**	60:1	94
15	(**1b**)	*t*-Bu (**5**)	**9b**	27:1	77
16	(**1c**)	*t*-Bu (**5**)	**9c**	22.0:1	90
17	(**1d**)	*t*-Bu (**5**)	**9d**	30:1	78
18	(**1e**)	*t*-Bu (**5**)	**9e**	16.0:1	87
19	(**1f**)	*t*-Bu (**5**)	**9f**	>20:1	82
20	(**1g**)	*t*-Bu (**5**)	**9g**	>20:1	83

[a] *anti:syn* ratio determined by ^{1}H NMR (ratios less than 20:1) or GC (ratios greater than 20:1). [b] Reported yield is weight recovery of crude aldols, corrected for remaining starting material, as determined by ^{1}H NMR. [c] Mes = mesityl (2,4,6-trimethylphenyl).

of the major and minor diastereomers within each class of aldols **6**, **7**, and **8** also suggest that *anti*-stereoselectivity is general (method C, Table 2).

Further confirmation of consistent *anti*-stereoselectivity is found in the method we previously proposed for correlating relative configuration based on vicinal coupling constants.[8] Given that β-hydroxy nitriles form only weak intramolecular hydrogen bonds,[10] it can be assumed that if the R substituent of the aldehyde is large, the most favored conformer of both *anti*- and *syn*-diastereomers should feature the R and Ar groups in an antiperiplanar (i.e. $\theta = 180°$) relationship (conformation I, Scheme 2).

In this conformation the 2,3-*anti* isomer will have a H−C−C−H dihedral angle of approximately 60°, giving rise to a small coupling constant. The 2,3-*syn* isomer would have a H−C−C−H dihedral angle of approximately 180° in this conformation, giving rise to a large coupling constant.[11] In the present study, in all aldol products derived from benzaldehyde (**6a−g**), cyclohexane carboxaldehyde (**7a,c**), and pivalaldehyde (**9a−g**) the major diastereomer possesses the smaller coupling constant,[12] consistent with the provisional assignment of *anti*-relative configuration. (Table 2, entries 1−16, correlation method D). Furthermore the trend in the magnitude of the observed coupling constants for *anti*-**6a−g**, *anti*-**7a,c**, and *anti*-**9a−g** is consistent with a first principles conformational analysis.[13] On the basis of our conformational model, the vicinal coupling constant method for assignment of relative stereochemistry can only be applied in those cases where one "small" and one "large" coupling constant is observed; however, this condition is not met for R = mesityl (aldols **8a−d**). In these cases, both *anti*- and *syn*-isomers possess unusually large coupling constants.[14] The departure of the mesitaldehyde aldols **8a−d** from the conformational preferences exhibited by aldols **6**, **7**, and **9** is not well understood.[15] Therefore the aldol stereochemistry was unambiguously confirmed in another case, by conversion of aldols **8a** to the corresponding cyclic carbamates **16a** (*vide infra*).

We have previously established that under our reaction conditions the selectivity is kinetically controlled.[8] We can therefore rationalize the observed *anti*-selectivity if we assume that reaction proceeds via a cyclic, flat six-membered transition state, as shown in Scheme 3:

It is evident that eclipsing interactions would be minimized in transition structure **A**, which gives rise to the favored 2,3-*anti*-isomer. One would also expect that as the size of the R group increases, the preference for transition structure **A** would increase; we note in our work that as R increases in size from Ph to cyclohexyl to mesityl to *t*-Bu, the diastereoselectivity increases. Therefore the transition state model is consistent with both the relative sense and trend of diastereoselection. A similar cyclic, flat six-membered transition state has been proposed for the addition of lithiated acetonitrile to cyclohexanone.[16] Also in accordance with our model, we have recently confirmed by solution ^{6}Li, ^{15}N, and ^{13}C NMR measurements that phenylacetonitrile is lithiated at nitrogen and not at carbon.[17] In this study dimers were the only detectable species in diethyl ether/toluene and TMEDA/toluene; experiments in THF were inconclusive. However, in the absence of kinetic data it is not possible to draw any conclusions regarding the aggregation state of the reactive species. Finally, at this point it appears that the proposed transition state model can only account for the aldol stereoselectivity of benzylic nitriles. Our preliminary investigation of simple alkyl nitriles has revealed that they do not react with general *anti*-selectivity.[18]

We envisioned that the utility of diastereomerically pure β-hydroxy nitriles would derive in large part from their ready transformation to γ-amino alcohols. The γ-amino ether, or γ-amino alcohol functional group is

(10) (a) Allerhand, A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1963**, *85*, 866. (b) In a solution IR study of one pair of diastereomeric β-hydroxy nitriles, Canceil and Jacques have shown that the intramolecular H-bonding is weak in the *anti*-diastereomer, and nonexistent in the *syn*-diastereomer: Canceill, J.; Jacques, J. *Bull. Soc. Chim. Fr.* **1970**, *6*, 2180.

(11) Subsequent to our first study (ref 8) we learned that Canceill and Jacques had previously proposed a correlation method based on vicinal coupling constants (ref 10b). However, confirmation of the proposed NMR assignments by chemical correlation was carried out in only one case.

(12) Or in the case of aldols **7a−g**, the only visible aldol product possesses a very small coupling constant.

(13) The observed vicinal coupling constant is a weighted average of those of the contributing conformers I−III. Therefore the smallest coupling constant would be expected for those *anti*-aldols featuring the largest Ar and R groups. In such a case only conformer I is significantly populated, and the contributions of conformers II and III to the observed coupling constant can be ignored. This is seen for the *anti*-pivalaldehyde aldols **9a−g** where $J = 0-1.8$ Hz (entries 10−16). In contrast, when the R group is somewhat smaller (aldols **6a−g**, **7a,c**), conformers II and III are also populated and the average coupling constant of the *anti*-diastereomer therefore increases as a result (entries 1−9).

(14) Examples of *anti*- and *syn*-diastereomers possessing nearly identical, large coupling constants are known in the literature: (a) 2-methyl-3-(dimethylamino)phenylpropionic acid ethyl ester ($J = 11$ Hz for both *anti*- and *syn*-): Friebolin, H. Basic One- and Two-Dimensional NMR Spectroscopy, 2nd ed.; Becconsall, J., Ed.; VCH Publishers: New York, 1993; p 89. (b) *erythro*- and *threo*-2,3-dibromo-3-(*p*-methoxyphenyl)propionic acid (J = 11.6 and 9.9 Hz, respectively): Newsoroff, G. P.; Sternhell, S. *Tetrahedron Lett.* **1964**, 3499.

(15) To account for the observed coupling constants, it must therefore be assumed that in solution the mesitaldehyde *anti*-aldols prefer conformer II, and that the corresponding *syn*-aldols in contrast prefer conformer I. Consistent with this prediction, X-ray crystallographic analysis demonstrates that *anti*-**8d** adopts conformation II in the solid state.

(16) Wu, Y-D.; Houk, K. N.; Florez, J.; Trost, B. M. *J. Org. Chem.* **1991**, *56*, 3656.

(17) Carlier, P. R.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 11602.

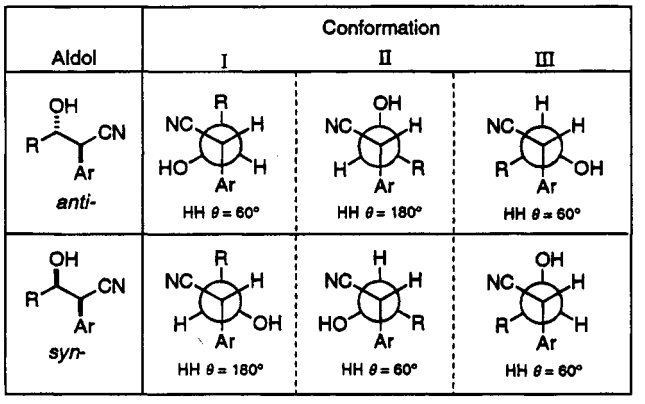
(18) A change in aggregation state of the reactive species may account for this change in diastereoselectivity (Carlier, P. R.; Lo, K.-M. Unpublished results.)

Table 2

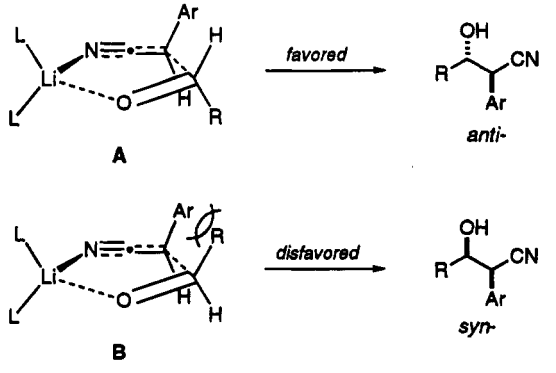
entry	aldol	Ar	R	vicinal coupling constant[a] *J* (major)	*J* (minor)	α-CN proton δ (major)	δ (minor)	correl method[b]
1	**6a**	Ph	Ph	5.8	6.8	4.06	4.14	A
2	**6b**	2-MeO-Ph	Ph	3.9	6.4	4.519	4.669	C, D
3	**6c**	4-MeO-Ph	Ph	5.9	6.4	3.991	4.07	C, D
4	**6d**	4-Me-Ph	Ph	5.9	6.8	4.033	4.085	C, D
5	**6e**	4-Cl-Ph	Ph	5.9	6.1	4.023	4.127	C, D
6	**6f**	1-naph	Ph	4.4	6.4	4.859	5.046	C, D
7	**6g**	2-naph	Ph	5.4	6.8	4.19	4.26	C, D
8	**7a**	Ph	c-C_6H_{11}	3.9	7.3	4.071	3.874	B
9	**7c**	4-MeO-Ph	c-C_6H_{11}	4.4	6.4	4.012	3.82	C, D
10	**9a**	Ph	t-Bu	1.8	na	4.054	na	D
11	**9b**	2-MeO-Ph	t-Bu	<1	na	4.52	na	B
12	**9c**	4-MeO-Ph	t-Bu	2	na	3.998	na	D
13	**9d**	4-Me-Ph	t-Bu	2	na	4.002	na	D
14	**9e**	4-Cl-Ph	t-Bu	1.5	na	3.984	na	D
15	**9f**	1-naph	t-Bu	<1	na	4.904	na	B
16	**9g**	2-naph	t-Bu	1.5	7.8	4.164	3.925	D
17	**8a**	Ph	Mes	9.8	9.3	4.408	4.334	C, E
18	**8b**	2-MeO-Ph	Mes	9.3	9.8	4.868	4.724	C
19	**8c**	4-MeO-Ph	Mes	9.8	9.8	4.359	4.277	C
20	**8d**	4-Me-Ph	Mes	10.3	9.3	4.366	4.293	B

[a] All NMR data measured at room temperature in $CDCl_3$. [b] Correlation methods: A, independent stereospecific synthesis; B, single crystal X-ray determination; C, chemical shift analogy; D, vicinal coupling constant method; E, NMR analysis of cyclic carbamate derivatives **16a**.

Scheme 2



Scheme 3



present in a number of important antidepressants, such as the selective 5-HT reuptake inhibitor Fluoxetine (**10a**),[19] related drugs Tomoxetene (**10b**) and Nisoxetine (**10c**),[20] and the recently approved Venlafaxine (**11**)[21] (Scheme 4).

Scheme 4

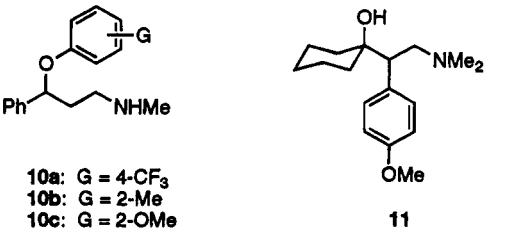
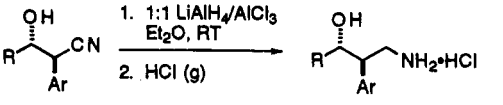


Table 3



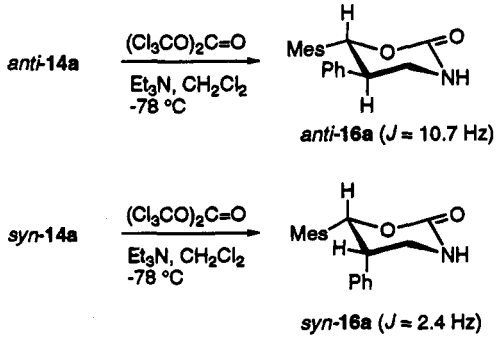
entry	γ-amino alcohol	Ar	R	% yield
1	*anti*-**12a**	Ph	Ph	69
2	*anti*-**13c**	4-MeO-Ph	*c*-C_6H_{11}	75
3	*syn*-**13c**	4-MeO-Ph	*c*-C_6H_{11}	59
4	*anti*-**14a**	Ph	Mes	86
5	*syn*-**14a**	Ph	Mes	58
6	*anti*-**15a**	Ph	tBu	75
7	*anti*-**15g**	2-naphthyl	t-Bu	63

β-Hydroxy nitriles are known to be sensitive to base, and under protic, basic conditions at room temperature they rapidly undergo retro-aldol and/or elimination.[22] We therefore explored the use of "electrophilic" reducing agents, and a number were found to be satisfactory.[23] However the best reagent in terms of yield and ease of workup proved to be $LiAlH_4/AlCl_3$ in diethyl ether[24] (Table 3).

Yields of the hydrochloride salts **12**–**15** are generally 60–85%, and no epimerization is observed. γ-Aminoalcohols **12-15** can also be transformed to the corresponding

(19) Robertson, D. W.; Krushinski, J. H.; Fuller, R. W.; Leander, J, D. *J. Med. Chem.* **1988**, *31*, 1412.
(20) (a) *Drugs Future* **1986**, *11*, 134. (b) Koenig, T. M.; Mitchell, D. *Tetrahedron Lett.* **1994**, *35*, 1339.
(21) Marketed under the name "Effexor": Yardley, J. P.; Husbands, G. E. M.; Butch, J.; Bicksler, J.; Moyer, J. A.; Muth, E. A.; Andree, T.; Fletcher, H., III; James, M. N. G.; Sielecki, A. R. *J. Med. Chem.* **1990**, *33*, 2899.
(22) We have confirmed that retro-aldol does not occur under our reaction conditions (quench performed at −78 °C, reference 8).
(23) (a)BH_3·DMS: Brown, H. C.; Choi, Y. M.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 3153. (b) $NaBH_4/AlCl_3$: Brown, H. C.; Rao, B. C. S. *J. Am. Chem. Soc.* **1956**, *78*, 2582. (c) $NaBH_4/CF_3CO_2H$: Umino, N.; Iwakuma, T.; Itoh, N. *Tetrahedron Lett.* **1976**, *33*, 2875.
(24) Nystrom, R. F. *J. Am. Chem. Soc.* **1955**, *77*, 2544.

Scheme 5



cyclic carbamates, as illustrated in the synthesis of *anti*- and *syn*-**16a** (Scheme 5).

The well-defined cyclic structure of the carbamates makes it possible to confidently predict vicinal coupling constants based on the relative stereochemistry of the starting γ-amino alcohol, providing another means of confirming the previous stereochemical assignments. *anti*-**14a** would produce carbamate *anti*-**16a**, featuring a 180° dihedral angle between the vicinal hydrogens, resulting in a large J (8–12 Hz): we observe J = 10.7 Hz. In contrast *syn*-**14a** would produce *syn*-**16a**, featuring a 60° dihedral angle between the vicinal hydrogens, resulting in a small J (1–3 Hz): we observe J = 2.4 Hz. Therefore the assignments of aldols **8a** made previously on the basis of chemical shift analogy to crystallographically characterized analog **8d** are confirmed.

In summary, we have demonstrated that benzylic nitriles undergo *anti*-selective aldol reaction. Using hindered secondary- or tertiary-alkyl substituted aldehydes, selectivities range from good to excellent (10:1 to >20:1). The β-hydroxy nitrile products are easily reduced, providing for the first time a rapid entry into a series of diastereomerically pure β-aryl γ-amino alcohols, which may find application in the synthesis of new antidepressants.

Experimental Section

All reactions were performed in oven-dried glassware under a nitrogen atmosphere. THF and Et_2O were distilled from Na/benzophenone immediately prior to use. Lithium diisopropylamide was purchased from Aldrich Co. as a 2.0 M solution in tetrahydrofuran/heptane/ethylbenzene and was titrated prior to use (2,2′-bipyridine as indicator). Nitriles **1a–g** and aldehydes **2–5** were purchased from Aldrich Chemical Co. and were distilled prior to use. Unless noted otherwise, NMR spectra were measured in $CDCl_3$ at 400 MHz (^{1}H) and at 100.75 MHz (^{13}C). Elemental analysis was performed at the Shanghai Institute of Organic Chemistry (Chinese Academy of Sciences, P.R.C.) and at Medac Ltd. (Brunel University, UK).

General Aldol Procedure. A 100 mL round bottom flask equipped with magnetic stirring bar and septum was charged with THF (40 mL) and commercial 2 M LDA solution (0.5 mL, 1 mmol), in order to achieve [LDA] = 0.025 M. After cooling to −78 °C (dry-ice/acetone), nitrile (1.0mmol) was added via syringe; after 30 min, aldehyde (1.0 mmol) was added, and after an additional 5 min the reaction was quenched by addition of saturated aqueous NH_4Cl (1.0 mL). The reaction was poured into 20 mL of 1 M HCl, the aqueous layer was extracted with Et_2O (3 × 20 mL), and the combined organic extracts were washed with saturated brine (20 mL) and dried ($MgSO_4$). Finally, concentration *in vacuo* afforded the crude aldol. Reported yields are the weight recovery of *anti*- and *syn*-aldols, corrected for residual starting material as measured by NMR. Diastereomer ratios were measured by ^{1}H NMR, HPLC, or capillary GC. In the case of solid aldols, a single recrystallization normally affords diastereomerically pure *anti*-aldol. In some cases clean separation of the *anti*- and *syn*-diastereomers can be achieved by flash chromatography ($\Delta R_f \sim 0.1$).

(2*RS*,3*SR*)-3-Hydroxy-3-phenyl-2-(2′-methoxyphenyl)-propiononitrile (*anti*-6b). An analytically pure sample was obtained by chromatography (25% ethyl acetate/hexane). ^{1}H NMR: δ 2.421 (d, J = 3.4Hz, 1H), 3.819 (s, 3H), 4.525 (d, J = 4.4Hz, 1H), 5.048 (t, J = 4.2Hz, 1H), 6.88–7.47 (m, 9H). ^{13}C NMR: δ 42.01, 55.60, 74.09, 110.84, 118.51, 121.05, 121.43, 125.88, 128.42, 129.79, 129.99, 140.16, 156.02. IR (neat): 3446 (s), 2246.0. MS (CI$^+$(NH_3)): 271 (M + NH_4). Mp: semisolid. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.87; H, 5.85; N, 5.32.

(2*RS*,3*SR*)-3-Hydroxy-3-phenyl-2-(4′-methoxyphenyl)-propiononitrile (*anti*-6c). An analytically pure sample was obtained by recrystallization (CH_2Cl_2/hexanes). ^{1}H NMR: δ 2.442 (d, J = 3.4 Hz, 1H), 3.792 (s, 3H), 4.012 (d, J = 5.9 Hz, 1H), 4.936 (dd, J = 3.9 Hz, 5.9 Hz, 1H), 6.838 (dd, J = 2.0 Hz, 6.3 Hz, 2H), 7.125 (dd, J = 2.2 Hz, 6.6 Hz, 2H), 7.24–7.35 (m, 5H). ^{13}C NMR: δ 46.56, 55.34, 76.48, 114.30, 118.95, 124.36, 126.28, 128.57, 128.73, 129.59, 139.43, 159.69. IR (KBr): 3530.0 (br), 3472.0 (br), 2248.0 (m) cm^{-1}. MS (EI$^+$): 253 (m). Mp: 101.7–102.7 °C. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.68; H, 5.90; N, 5.40.

(2*RS*,3*SR*)-3-hydroxy-3-phenyl-2-(4′-methylphenyl)propiononitrile (*anti*-6d). An analytically pure sample was obtained by recrystallization (CCl_4). ^{1}H NMR: 2.334 (s, 3H), 2.417 (d, J = 3.9 Hz, 1H), 4.029 (d, J = 5.4 Hz, 1H), 4.948 (dd, J = 3.4 Hz, 5.9 Hz, 1H), 7.10–7.36 (m, 9H). ^{13}C NMR: 21.10, 47.04, 76.41, 118.78, 126.22, 128.24, 128.55, 128.71, 129.42, 129.63, 138.44, 139.45. IR (KBr): 3518.0 (br), 2246.0 (m). MS (EI$^+$): 237 (m). Mp: 135.2–137.0 °C. Anal. Calcd for $C_{16}H_{15}NO$: C, 80.99; H, 6.37; N, 5.90. Found: C, 80.71; H, 6.40; N, 5.83.

(2*RS*,3*SR*)-3-hydroxy-3-phenyl-2-(4′-chlorophenyl)propiononitrile (*anti*-6e). An analytically pure sample enriched in the *anti*-diastereomer (*anti*:*syn* = 10:1) was isolated by chromatography (25% ethyl acetate/hexane). ^{1}H NMR: 2.645 (s, 1H), 4.115 (d, J = 5.9 Hz, 1H), 4.936 (d, J = 5.9 Hz, 1H), 7.08–7.33 (m, 9H). ^{13}C NMR: 46.56, 76.22, 118.47, 126.26, 128.64, 128.93, 129.00, 129.86, 130.92, 134.62, 139.10. IR (KBr): 3554.0 (s), 2248.0 (m). MS (CI$^+$(NH_3)): 275 (M + NH_4). Mp: 103.4–107.5 °C. Anal. Calcd for $C_{15}H_{12}NOCl$: C, 69.91; H, 4.69; N, 5.43. Found: C, 69.89; H, 4.65; N, 5.43.

(2*RS*,3*SR*)-3-Hydroxy-3-phenyl-2-(1′-naphthyl)propiononitrile (*anti*-6f). A pure sample of the *anti*-diastereomer was isolated by chromatography (25% ethyl acetate/hexane). ^{1}H NMR: 2.413 (d, J = 3.4 Hz, 1H), 4.857 (d, J = 3.9 Hz, 1H), 5.147 (t, 3.7 Hz, 1H), 7.29–7.92 (m, 12H). ^{13}C NMR: 44.37, 74.51, 118.54, 121.80, 125.40, 125.84, 126.17, 127.08, 127.45, 128.57, 128.71, 128.77, 129.46, 129.59, 130.05, 134.05, 139.87. IR (KBr): 3440.0 (s), 2246.0 (m). MS (CI$^+$(NH_3)): 291 (M + NH_4). Mp: semi-solid. ^{1}H and ^{13}C NMR spectra are provided in the supporting information as evidence of identity and purity.

(2*RS*,3*SR*)-3-Hydroxy-3-phenyl-2-(2′-naphthyl)propiononitrile (*anti*-6g). An analytically pure sample was obtained by chromatography (30% ethyl acetate/hexanes). ^{1}H NMR: 2.464 (d, J = 3.4 Hz, 1H), 4.239 (d, J = 5.4 Hz, 1H), 5.081 (dd, J = 3.4 Hz, 5.4 Hz, 1H), 7.26–7.84 (m, 12H). ^{13}C NMR: 47.57, 76.32, 118.63, 125.58, 126.22, 126.74, 127.71, 127.87, 127.98, 128.62, 128.82, 129.79, 132.97, 133.12, 129.36. IR (KBr): 3554.0 (br), 2244.0 (m). MS (EI$^+$): 273 (m). Mp: 151.8–153.1 °C. Anal. Calcd for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.12. Found: C, 83.47; H, 5.44; N, 4.94.

(2*R,3*S**)-3-Cyclohexyl-3-hydroxy-2-phenylpropiononitrile (*anti*-7a).** An analytically pure sample was obtained by recrystallization of the crude aldols (ligroin). ^{1}H NMR: 1.0–2.1 (m, 11H), 1.867 (d, J = 5.4 Hz, 1H), 3.526 (ddd, J = 3.9 Hz, 4.9 Hz, 7.3 Hz, 1H), 4.071 (d, J = 3.9 Hz, 1H), 7.34–7.43 (m, 5H). ^{13}C NMR: 25.55, 25.82, 26.13, 28.37, 29.43, 41.09, 42.30, 78.31, 118.62, 128.03, 128.42, 129.21, 133.65. IR (KBr): 3432 (br), 2256 (m). MS (CI$^+$(CH_4)): 230 (m + H).

Mp: 88.0–88.8 °C. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.57; H, 8.34; N, 6.11. Found: C, 78.58; H, 8.34; N, 6.07.

(2*RS*,3*SR*)-3-Cyclohexyl-3-hydroxy-2-phenylpropiononitrile (*syn*-7a). A sample of the *syn*-diastereomer containing less than 5% of the *anti*-isomer was prepared by flash chromatography (20% ethyl acetate in hexane). ^{1}H NMR: 1.1–1.9 (m, 11H), 1.623 (d, J = 4.9 Hz, 1H), 3.73–3.76 (m, 1H), 3.874 (d, J = 7.3 Hz, 1H), 7.34–7.43 (m, 5H). ^{13}C NMR: 25.73, 25.84, 26.12, 26.19, 30.32, 40.56, 41.53, 77.49, 119.60, 128.62, 128.69, 129.17, 133.10. IR: 3502 (br), 2246 (s). MS (CI$^+$(CH_4)): 230 (m + H). Mp: 97.8–99.8 °C. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.57; H, 8.35; N, 6.11. Found: C, 78.39; H, 8.35; N, 6.04.

(2*R,3*S**)-3-Cyclohexyl-3-hydroxy-2-(4′-methoxyphenyl)-propiononitrile (*anti*-7c).** An analytically pure sample was obtained by recrystallization (diethyl ether/petroleum ether) after separation by column chromatography (80/20 $CHCl_3$/hexane). ^{1}H-NMR: δ 1.0–1.4 (m, 5H), 1.5–1.8 (m, 5H), 1.862 (d, J = 5.4 Hz, 1H), 2.0 (m, 1H), 3.481 (m, 1H), 3.818 (s, 3H), 4.012 (d, J = 4.4 Hz, 1H), 6.924 (d, J = 8.8 Hz, 2H), 7.275 (d, J = 8.8 Hz, 2H). ^{13}C-NMR: δ 25.57, 25.86, 26.15, 28.22, 29.44, 40.91, 41.50, 55.38, 78.27, 114.59, 118.95, 125.44, 129.17, 159.60. IR (KBr): 3498 (s), 2246 (m) cm^{-1}. MS (EI$^+$): 259 (m). Mp: 112.0–113.2 °C. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.25; H, 8.15; N, 5.39.

(2*RS*,3*SR*)-3-Cyclohexyl-3-hydroxy-2-(4′-methoxyphenyl)propiononitrile (*syn*-7c). An analytically pure sample was isolated by column chromatography (80/20 $CHCl_3$/hexane). ^{1}H-NMR (($CD_3)_2CO$ + D_2O): δ 1.0–1.4 (m, 5H), 1.5–2.0 (m, 6H), 3.753 (dd, J = 4.9 Hz, 6.4 Hz, 1H), 3.811 (s, 3H), 4.089 (d, J = 6.4 Hz, 1H), 6.948 (d, J = 8.8 Hz, 1H), 7.377 (d, J = 8.8 Hz, 1H). ^{13}C-NMR: δ 25.84, 26.12, 26.19, 30.30, 40.44, 40.47, 40.65, 55.36, 77.47, 114.56, 119.84, 124.78, 129.83, 159.76. IR (KBr): 3492 (br), 2256 (w) cm^{-1}. MS (CI$^+$): 259 (m). Mp: 85.9–86.5 °C. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.81; H, 8.14; N, 5.27.

(2*RS*,3*SR*)-3-Hydroxy-2-phenyl-3-(2′,4′,6′-trimethylphenyl)propiononitrile (*anti*-8a). An analytically pure sample was obtained by recrystallization (toluene/hexanes). ^{1}H NMR: 2.125 (s, 6H), 2.208 (s, 3H), 2.551 (d, J = 3.4 Hz, 1H), 4.418 (d, J = 9.8 Hz, 1H), 5.315 (dd, J = 3.4 Hz, 9.8 Hz, 1H), 6.72–7.26 (m, 7H). ^{13}C NMR: 20.48, 20.78, 44.15, 73.45, 120.12, 128.31, 128.35, 128.57, 130.25, 131.16, 132.06, 136.78, 137.97. IR (KBr): 3448.0 (broad), 2248.0 (m). MS (CI$^+$-(NH_3)): 283 (M + NH_4). Mp: 131.5–132.4 °C. Anal. Calcd for $C_{18}H_{19}NO$: C, 81.48; H, 7.21; N, 5.28. Found: C, 81.54; H, 7.23; N, 5.27.

(2*R,3*S**)-3-Hydroxy-3-(2′,4′,6′-trimethylphenyl)-2-phenylpropiononitrile (*syn*-8a).** A pure sample of the syn diastereomer was obtained by chromatography of the mixture of *anti*- and *syn*-aldols (80/20 $CHCl_3$/hexane). ^{1}H-NMR: δ 1.896 (d, J = 3.4 Hz, 1H), 2.278 (s, 3H), 2.504 (s, 3H), 4.340 (d, J = 9.3 Hz, 1H), 5.403 (dd, J = 3.4 Hz, 9.3 Hz, 1H), 6.891 (s, 2H), 7.4–7.5 (m, 5H). ^{13}C-NMR: δ 20.87, 43.22, 73.35, 118.74, 128.58, 128.78, 129.26, 131.95, 133.69, 136.58, 138.18. MS (CI$^+$(NH_3)): 283 (M + NH_4). Mp: 130.7–132.5 °C. ^{1}H and ^{13}C NMR spectra are provided in the supporting information as evidence of identity and purity.

(2*RS*,3*SR*)3-Hydroxy-2-(2′-methoxyphenyl)--3-(2″,4″,6″-trimethylphenyl)propiononitrile (*anti*-8b). An analytically pure sample was obtained by recrystallization (toluene). ^{1}H NMR: 2.178 (s, 3H), 2.224 (s, 6H), 2.446 (d, J = 3.9 Hz, 1H), 3.486 (s, 3H), 4.871 (d, 9.3 Hz, 1H), 5.406 (dd, J = 3.7 Hz, 9.0 Hz, 1H), 6.69–7.40 (m, 6H). ^{13}C NMR: 20.45, 20.70, 38.09, 55.07, 72.31, 110.84, 120.39, 120.77, 120.90, 129.85, 129.92, 129.99, 131.64, 137.03, 137.38, 156.44. IR (KBr): 3550.0 (br), 2244.0 (m). MS (CI$^+$(NH_3)): 313 (M + NH_4). Mp: 127.7–128.9 °C. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.16; N, 4.74. Found: C, 77.44; H, 7.16; N, 4.70.

(2*RS*,3*SR*)-3-Hydroxy-2-(4′-methoxyphenyl)--3-(2″,4″,6″-trimethylphenyl)propiononitrile (*anti*-8c). Pure *anti*-**8c** was prepared by converting the mixture of aldols to the corresponding 3,5-dinitrobenzoates and recrystallization (dichloromethane/hexane) (as the 3,5-dinitrobenzoate). ^{1}H NMR: 2.218 (s, 1H), 2.3 (s, broad, 6H), 3.781 (s, 3H), 4.702 (d, J = 10.7 Hz, 1H), 6.581 (d, J=11.2 Hz, 1H), 6.77–7.03 (m, 6H), 9.21–9.26 (m, 3H). ^{13}C NMR: 20.54, 20.89, 41.31, 55.34, 75.71, 114.34, 118.67, 122.13, 122.73, 127.39, 129.52, 129.72, 133.25, 139.32, 148.83, 160.06, 161.39. IR (KBr): 2244.0 (w), 1736.0 (s). MS (CI$^+$(NH_3)): 507 (M + NH_4). Mp: 179.6–181.0 °C. Anal. Calcd for $C_{26}H_{23}N_3O_7$: C, 63.80; H, 4.73; N, 8.58. Found: C, 63.62; H, 4.64; N, 8.55.

(2*RS*,3*SR*)-3-Hydroxy-2-(4′-methylphenyl)-3-(2″, 4″, 6″-trimethylphenyl)propiononitrile (*anti*-8d). An analytically pure sample of *anti*-**8d** was obtained by chromatography of the crude aldols (30/70 hexane/dichloromethane, followed by 2:1 hexane/ethyl acetate). ^{1}H NMR: 2.135 (s, 6H), 2.213 (s, 3H), 2.279 (s, 3H), 2.533 (dd, J = 1.5 Hz, 3.4 Hz, 1H), 4.381 (d, J = 9.8 Hz, 1H), 5.291 (dd, J = 3.9 Hz, 9.8 Hz, 1H), 6.721 (s, 2H), 6.911 (d, J = 8.3 Hz, 2H), 6.998 (d, J = 8.3 Hz, 2H). ^{13}C NMR: 20.54, 20.79, 21.09, 43.78, 73.45, 120.28, 128.14, 129.00, 129.24, 130.25, 131.33, 136.79, 137.86, 138.15. IR (KBr): 3422.0 (br), 2254.0 (m). MS (CI$^+$(NH_3)): 297 (M + NH_4). Mp: 127.7–128.9 °C. The identity and purity of the sample were confirmed by a single crystal X-ray determination.

(2*RS*,3*SR*)-3-Hydroxy-4,4-dimethyl-2-phenylpentanenitrile (*anti*-9a). An analytically pure sample of *anti*-**5f** was prepared by recrystallization (toluene–hexane). ^{1}H NMR ($CDCl_3$): 1.111 (s, 9H), 1.985 (d, J = 6.4 Hz, 1H), 3.420 (dd, J = 6.4 Hz, 2.0 Hz, 1H), 4.054 (d, J = 1.5 Hz, 1H), 7.35–7.41 (m, 5H). ^{13}C NMR ($CDCl_3$): 26.17, 35.88, 39.92, 82.39, 18.89, 127.76, 128.22, 129.19, 135.81. IR (KBr): 3532, 3446 (broad), 2240 (s). MS (EI$^+$): 203 (m), 204 (m+1). Mp: 70.7–71.2 °C. Anal. Calculated for $C_{13}H_{17}NO$: C, 76.81; H, 8.42; N, 6.89. Found: C, 76.80; H, 8.43; N, 6.83.

(2*RS*,3*SR*)-3-Hydroxy-4,4-dimethyl-2-(2′-methoxyphenyl)pentanenitrile (*anti*-9b). An analytically pure sample of *anti*-**9b** was obtained by chromatography (30/70 hexane/dichloromethane followed by 2:1 hexane/ethyl acetate). ^{1}H NMR: 1.098 (s, 9H), 2.110 (d, J = 6.4 Hz, 1H), 3.369 (dd, J = 1.5 Hz, 6.4 Hz, 1H), 3.856 (3H, s), 4.520 (d, J = 1.0 Hz, 1H), 6.903 (d, J = 8.3 Hz), 7.015 (dt, J = 7.6 Hz, 1.0 Hz, 1H), 7.326 (dt, J = 7.8 Hz, 1.5 Hz, 1H), 7.552 (dd, J = 1.7 Hz, 7.6 Hz, 1H). ^{13}C NMR: 26.10, 34.29, 35.99, 55.45, 80.14, 110.70, 119.40, 121.07, 124.16, 129.37, 129.53, 155.45. IR (KBr): 3342.0 (br), 2244.0 (m). MS (CI$^+$(NH_3)): 251 (M + NH_4). Mp: 55.8–56.8 °C. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.88; H, 8.20; N, 5.96.

(2*RS*,3*SR*)-3-Hydroxy-4,4-dimethyl-2-(4′-methoxyphenyl)pentanenitrile (*anti*-9c). An analytically pure sample of *anti*-**9c** was obtained by chromatography (30/70 hexane/dichloromethane followed by 2:1 hexane/ethyl acetate). ^{1}H NMR: 1.090 (s, 9H), 2.037 (d, J = 6.3 Hz, 1H), 3.375 (dd, J = 1.5 Hz, 6.4 Hz, 1H), 3.809 (s, 3H), 3.994 (d, J = 1.5 Hz, 1H), 6.913 (dd, J = 2.2 Hz, 6.6 Hz, 2H), 7.304 (dd, J = 2.2 Hz, 6.6 Hz, 2H). ^{13}C NMR: 26.17, 35.79, 39.12, 55.38, 82.41, 114.52, 119.22, 127.74, 128.89, 159.47. IR (KBr): 3462.0 (br), 2254.0 (m). MS (CI$^+$(NH_3)): 251 (M + NH_4). Mp: 77.9–79.3 °C. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.08; H, 8.20; N, 6.00. Found: C, 71.88; H, 8.20; N, 5.94.

(2*RS*,3*SR*)-3-Hydroxy-4,4-dimethyl-2-(4′-methylphenyl)pentanenitrile (*anti*-9d). An analytically pure sample was obtained by chromatography (30/70 hexane/dichloromethane followed by 2:1 hexane/ethyl acetate). ^{1}H NMR: 1.093 (s, 9H), 2.030 (d, J = 5.9 Hz, 1H), 2.355 (s, 3H), 3.383 (dd, J = 1.5 Hz, 6.4 Hz, 1H), 4.008 (d, J = 1.5 Hz, 1H), 7.198 (d, J = 7.8 Hz, 2H), 7.273 (d, J = 7.8 Hz, 2H). ^{13}C NMR: 21.05, 26.17, 35.83, 39.54, 82.41, 119.11, 127.63, 129.81, 132.79, 138.06. IR (KBr): 3474.0 (br), 2248.0 (m). MS (CI$^+$(NH_3)): 235 (M + NH_4). Mp: 110.6–111.7 °C. Anal. Calcd for $C_{14}H_{19}$-NO: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.35; H, 8.78; N, 6.42.

(2*RS*,3*SR*)-3-Hydroxy-4,4-dimethyl-2-(4′-chlorophenyl)pentanenitrile (*anti*-9e). An analytically pure sample was obtained by chromatography of the crude aldols (30/70 hexane/dichloromethane followed by 2:1 hexane/ethyl acetate). ^{1}H NMR: 1.099 (s, 9H), 2.021 (d, J = 6.8 Hz, 1H), 3.375 (dd, J = 1.7 Hz, 6.6 Hz, 1H), 4.014 (d, J = 1.5 Hz, 1H), 7.33–7.39 (m, 4H). ^{13}C NMR: 26.10, 35.95, 39.34, 82.33, 118.54, 129.19, 129.28, 134.29, 134.40. IR (KBr): 3460.0 (br), 2252.0 (m). MS (CI$^+$(NH_3)): 237 (M + NH_4). Mp: 108.3–109.7 °C. Anal.

Calcd for $C_{13}H_{16}NOCl$: C, 65.68; H, 6.78; N, 5.89. Found: C, 65.83; H, 6.81; N, 5.81.

(2*RS*,3*SR*)-3-Hydroxy-4,4-dimethyl-2-(1′-naphthyl)pentanenitrile (*anti*-9f). An analytically pure sample was prepared by converting the crude aldols to the corresponding acetate and recrystallization from hexane (as the acetate). ^{1}H NMR: 1.175 (s, 9H), 2.036 (s, 3H), 4.951 (d, J = 2.0 Hz, 1H), 5.019 (d, J = 2.4 Hz, 1H), 7.44–7.92 (m, 7H). ^{13}C NMR: 20.50, 26.55, 34.88, 36.05, 78.84, 119.13, 121.32, 125.11, 126.15, 126.48, 127.23, 129.61, 129.66, 129.79, 134.07, 169.46. IR (KBr): 2252.0 (m), 1752.0 (s). MS (EI$^+$): 295.2 (m). Mp: 104.6–105.7 °C. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.16; N, 4.74. Found: C, 77.18; H, 7.20; N, 4.56.

(2*RS*,3*SR*)-3-Hydroxy-4,4-dimethyl-2-(2′-naphthyl)pentanenitrile (*anti*-9g). An analytically pure sample was prepared by recrystallization (toluene/hexanes). ^{1}H NMR: 1.141 (s, 9H), 2.507 (d, J = 6.3 Hz, 1H), 3.506 (dd, J = 1.2 Hz, 6.1 Hz, 1H), 4.213 (s, 1H), 7.40–7.92 (m, 7H). ^{13}C NMR: 26.23, 35.95, 40.09, 82.19, 118.95, 125.18, 126.63, 126.83, 126.96, 127.71, 127.96, 129.17, 132.83, 132.97, 133.27. IR (KBr): 3472.0 (br), 2248.0 (m). MS (EI$^+$): 253.2 (m). Mp: 90.4–91.7 °C. Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.63; H, 7.56; N, 5.48.

(2*RS*,3*SR*)-3-Hydroxy-4,4-dimethyl-2-(2′-naphthyl)pentanenitrile (*syn*-9g). The analytical sample was obtained by recrystallization of the product ($CHCl_3$/hexane) after separation by column chromatography (75/25 $CHCl_3$/hexane). ^{1}H-NMR: δ 1.072 (s, 9H), 1.670 (d, J = 4.4 Hz, 1H), 3.792 (dd, J = 4.4 Hz, 7.8 Hz, 1H), 3.925 (d, J = 7.8 Hz, 1H), 7.45–7.9 (m, 7H). ^{13}C-NMR: δ 26.39, 36.06, 39.83, 79.68, 120.74, 126.22, 126.77, 126.83, 127.76, 127.91, 128.58, 129.11, 131.13, 133.03, 133.21. IR (KBr): 3446 (s), 2248 (m) cm^{-1}. Mp: 115.0–116.0 °C. HRMS (EI$^+$): Calcd for $C_{17}H_{19}NO$: 253.1467. Found: 253.1452. ^{1}H and ^{13}C NMR spectra are provided in the supporting information as evidence of identity and purity.

General Reduction Procedure for Synthesizing γ-Aminoalcohols from β-Hydroxy Nitriles. A solution of $AlCl_3$ (143.0 mg, 1.07 mmol) was prepared in Et_2O (1 mL) and transferred via syringe into a suspension of $LiAlH_4$ (39.3 mg, 1.04 mmol) in Et_2O (1 mL) at room temperature. On standing a white solid precipitated, leaving a clear solution. The β-hydroxy nitrile (0.4 mmol) was dissolved in Et_2O (1 mL) and was added over the course of 1 min. After stirring for 5 h at room temperature the reaction was quenched by cautious addition of water (2 mL), followed by 10% H_2SO_4 (30 mL). The mixture was stirred vigorously to ensure complete dissolution of the aluminate precipitate. The aqueous phase was separated, washed with Et_2O (20 mL), and then basified with excess NaOH pellets. The aqueous layer was extracted with 3 × 20 mL of Et_2O, and the Et_2O extract was washed with saturated brine and dried (K_2CO_3). Finally, treatment with dry HCl gas and concentration *in vacuo* afforded the desired γ-hydroxy amine hydrochloride salt.

(2*RS*,3*SR*)-3-Hydroxy-2,3-diphenylpropylammonium Chloride (*anti*-12a). ^{1}H-NMR (CD_3OD): δ 3.15–3.22 (m, 1H), 3.268 (dd, J = 6.4 Hz, 12.7 Hz, 1H), 3.695 (dd, J = 7.8 Hz, 12.7 Hz, 1H), 4.902 (d, J = 9.3 Hz, 1H), 7.0–7.4 (m, 10H). ^{13}C-NMR (CD_3OD): δ 44.57, 52.71, 79.81, 127.83, 128.64, 129.02, 129.64, 129.79, 139.15, 144.09. IR (KBr): 3330 (s, br), 3200 (m), 1046 (m) cm^{-1}. MS (CI$^+$): 228 (M − Cl). Mp: 236 °C dec. Anal. Calcd for $C_{15}H_{18}ClNO$: C, 68.30; H, 6.88; N, 5.31. Found: C, 68.30; H, 6.86; N, 5.21.

(2*R,3*S**)-3-Cyclohexyl-3-hydroxy-2-(4′-methoxyphenyl)-propylammonium Chloride (*anti*-13c).** ^{1}H-NMR: δ 0.9–1.8 (m, 11H), 3.185 (dd, J = 2.9 Hz, 12.7 Hz, 1H), 3.368 (dt, J = 2.9 Hz, 9.8 Hz, 1H), 3.623 (dd, J = 10.3 Hz, 12.2 Hz, 1H), 3.789 (s, 3H), 3.958 (d, J = 10.3 Hz, 1H), 6.836 (d, J = 8.8 Hz, 2H), 7.103 (d, J = 8.8 Hz, 2H). ^{13}C-NMR: δ 24.71, 25.95, 26.32, 30.60, 40.09, 44.81, 45.99, 55.21, 80.67, 114.43, 128.84, 131.07, 158.76. IR (KBr): 3406 (m, br), 1036 (m) cm^{-1}. MS (CI$^+$): 264 (M-Cl). Mp: 207.2–208.5 °C. Anal. Calcd for $C_{16}H_{26}ClNO_2$: C, 64.09; H, 8.74; N, 4.67. Found: C, 63.88; H, 8.72; N, 4.63.

(2*RS*,3*SR*)-3-Cyclohexyl-3-hydroxy-2-(4′-methoxyphenyl)propylammonium Chloride (*syn*-13c). ^{1}H-NMR ($CDCl_3$ + d_6-DMSO + D_2O): δ 0.9–1.1 (m, 6H), 1.5–1.7 (m, 4H), 2.0 (m, 1H), 3.065 (dd, J = 5.9 Hz, 12.2 Hz, 1H), 3.177 (m, 1H), 3.384 (dd, J = 9.3 Hz, 12.2 Hz, 1H), 3.602 (dd, J = 3.4 Hz, 9.3 Hz, 1H), 3.794 (s, 3H), 6.835 (d, J = 8.8 Hz, 2H), 7.329 (d, J = 8.8 Hz, 2H). ^{13}C-NMR ($CDCl_3$ + d_6-DMSO): δ 25.66, 26.37, 28.86, 29.76, 42.85, 44.22, 55.16, 73.52, 113.83, 130.14, 130.49, 158.61. IR (KBr): 3420 (s), 1038 (s) cm^{-1}. MS (CI$^+$): 264 (M − Cl). Mp: 229.6–230.5 °C. Anal. Calcd for $C_{16}H_{26}ClNO_2$: C, 64.09; H, 8.74; N, 4.67. Found: C, 63.87; H, 8.71; N, 4.65.

(2*RS*,3*SR*)-3-Hydroxy-3-(2′,4′,6′-trimethylphenyl)-2-phenylpropylammonium Chloride (*anti*-14a). ^{1}H-NMR (CD_3OD): δ 1.7 (br, 3H), 2.128 (s, 3H), 2.65 (br, 3H), 3.323 (dd, J = 4.9 Hz, 13.2 Hz, 1H), 3.671 (td, J = 9.7 Hz, 4.9 Hz, 1H), 3.855 (dd, J = 8.8 Hz, 12.7 Hz, 1H), 5.287 (d, J = 10.3 Hz, 1H), 6.5 (br, 1H), 6.8 (br, 1H), 6.99 (m, 2H), 7.1–7.2 (m, 3H). ^{13}C-NMR (CD_3OD): δ 20.83, 21.0 (br), 44.90, 76.65, 128.60, 129.35, 129.48, 135.86, 136.0 (br), 137.84, 139.36. IR (KBr): 3330 (s, v br), 1008 (m) cm^{-1}. MS (CI$^+$): 270 (M − Cl). Mp: 230 °C dec. Anal. (as diacetate): Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.63; H, 7.78; N, 3.72.

(2*R,3*S**)-3-hydroxy-3-(2′,4′,6′-trimethylphenyl)-2-phenylpropylammonium Chloride (*syn*-14a).** ^{1}H-NMR (CD_3OD): δ 2.231 (s, 3H), 2.428 (s, 6H), 2.758 (dd, J = 3.9 Hz, 12.7 Hz, 1H), 3.224 (t, J = 12.5 Hz, 1H), 3.555 (m, 1H), 5.272 (d, J = 9.3 Hz, 1H), 6.851 (s, 2H), 7.3–7.5 (m, 5H). ^{13}C-NMR (CD_3OD): δ 20.90, 21.12, 42.70, 51.01, 73.88, 129.07, 130.23, 135.81, 138.29, 139.43. MS (CI$^+$(CH_4)): 270 (M − Cl). Mp: 210 °C dec. HRMS (CI$^+$(CH_4)): Calcd for $C_{18}H_{24}NO$: 270.1858. Found: 270.1849.

(2*RS*,3*SR*)-3-Hydroxy-4,4-dimethyl-2-phenylpentylammonium Chloride (*anti*-15a). The analytical sample was obtained by recrystallization of the crude product in methanol/diethyl ether. ^{1}H-NMR (CD_3OD): δ 0.822 (s, 9H), 3.009 (dd, J = 6.3 Hz, 12.7 Hz, 1H), 3.158 (q, J = 6.8 Hz, 1H), 3.425 (dd, J = 7.3 Hz, 12.7 Hz, 1H), 3.726 (d, J = 6.8 Hz, 1H), 7.2–7.4 (m, 5H). ^{13}C-NMR (CD_3OD): δ 27.49, 38.26, 46.22, 47.31, 84.04, 129.41, 130.07, 131.05, 143.89. IR (KBr): 3240 (s, br) cm^{-1}. MS (CI$^+$): 208 (M − Cl). Mp: 232.0–233.2 °C. Anal. Calcd for $C_{14}H_{22}ClNO$: C, 64.05; H, 9.10; N, 5.75. Found: C, 64.27; H, 9.17; N, 5.68.

(2*RS*,3*SR*)-3-Hydroxy-4,4-dimethyl-2-(2′-naphthyl)pentylammonium Chloride (*anti*-15g). ^{1}H-NMR (CD_3OD): δ 0.864 (s, 9H), 3.138 (dd, J = 6.8 Hz, 12.7 Hz, 1H), 3.338 (q, J = 6.8 Hz, 1H), 3.523 (dd, J = 7.3 Hz, 12.7 Hz, 1H), 3.840 (d, J = 6.8 Hz), 7.4–7.6 (m, 3H), 7.8–7.9 (m, 4H). ^{13}C-NMR (CD_3OD): δ 26.77, 37.64, 45.21, 46.71, 83.17, 126.96, 127.21, 127.58, 128.29, 128.77, 128.80, 130.25, 134.34, 135.19, 140.42. IR (KBr): 3242 (s, br) cm^{-1}. MS (CI$^+$): 258 (M − Cl). Mp: 247 °C dec. Anal. (as mono-3,5-dinitrobenzoate): Calcd for $C_{24}H_{25}N_3O_6$: C, 63.85; H, 5.58; N, 9.31. Found: C, 63.71; H, 5.67; N, 9.19.

General Procedure for Synthesizing Cyclic Carbamates from γ-Amino Alcohols. The synthesis of *anti*-**16a** from *anti*-**8a** is given as an example. *anti*-**8a** (355.6 mg, 1.32 mmol) and Et_3N (1.85 mL, 13.3 mmol) was dissolved in 10 mL of sieve-dried CH_2Cl_2 and cooled down to −78 °C. A CH_2Cl_2 solution of $(Cl_3CO)_2CO$ (216.5 mg, 0.73 mmol) was then added dropwise to the reaction mixture in 10 min. It was then stirred for a further 15 min at −78 °C and then allowed to warm up to room temperature.

The reaction mixture was quenched by addition of saturated NH_4Cl solution (5 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined CH_2Cl_2 extract was washed with 1 M HCl, saturated $NaHCO_3$ solution, saturated brine, dried ($MgSO_4$), and concentrated *in vacuo* to give a pale yellow solid (372.9 mg). Purification by column chromatography (90/10 EtOAc/hexane) gave *anti*-**16a** as a white solid (164.4 mg, 42% yield).

Carbamate *anti*-16a. ^{1}H-NMR (50 °C): δ 2.163 (s, br, 9H), 3.574 (td, J = 4.7 Hz, 11.2 Hz, 1H), 3.779 (dt, J = 4.4 Hz, 11.2 Hz, 1H), 3.883 (t, J = 11.2 Hz, 1H), 5.482 (s, br, 1H), 5.736 (d, J = 10.7 Hz, 1H), 6.665 (s, br, 2H), 6.97 (m, 2H), 7.16 (m, 3H). ^{13}C-NMR (50 °C): δ 20.36, 20.75, 39.44, 45.71, 79.63, 127.40, 128.26, 128.83, 129.05, 130.20, 136.35, 137.17, 137.37, 154.96. IR (KBr): 3238 (m), 1680 (s), 1134 (m), 1086 (m) cm^{-1}. MS

($CI^+(CH_4)$): 296 (M + H). Mp: 207.6–208.8 °C. Anal. (as acetate): Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.33; H, 6.96; N, 3.89.

Carbamate *syn*-16a. ^{1}H-NMR: δ 1.882 (s, br, 6H), 2.236 (s, 3H), 3.325 (m, 1H), 3.820 (dd, J = 3.9 Hz, 11.7 Hz, 1H), 4.038 (dd, J = 6.4 Hz, 11.7 Hz, 1H), 6.002 (d, J = 2.4 Hz, 1H), 6.432 (s, br, 1H), 6.715 (s, 2H), 6.91–6.93 (m, 2H), 7.15–7.30 (m, 3H). ^{13}C-NMR: δ 20.36, 20.75, 39.44, 45.71, 79.63, 127.40, 128.26, 128.83, 129.05, 130.20, 136.35, 137.17, 137.37, 154.96. MS (EI^+): 295 (m). HRMS (EI^+): Calcd for $C_{19}H_{21}NO_2$: 295.1572. Found: 295.1580. ^{1}H and ^{13}C NMR spectra are provided in the supporting information as evidence of identity and purity.

X-Ray Analysis. The crystal structures of *anti*-**7a**, *anti*-**8d**, *anti*-**9b**, and *anti*-**9f** (acetate) were determined using Mo or Cu-Kα radiation and a Siemens P4-RA four-circle diffractometer at either 198 or 295 K. The four compounds gave acceptable discrepancy indices (R-values) of $\leq$0.055, allowing all atoms, including hydrogens, to be located and unambiguously determining the relative stereochemistry of each molecule. Structure solution and refinement was carried out using the SHELTX-UNIX program package[25] on a Silicon Graphics Indy computer. Molecular thermal ellipsoid plots are included in the supporting information; cell dimensions, atom coordinates, and other crystal data have been deposited with the Cambridge Crystallographic Data Centre and can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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Supporting Information Available: Molecular thermal ellipsoid plots of *anti*-**7a**, *anti*-**8d**, *anti*-**9b**, and *anti*-**9f** (acetate); ^{1}H, ^{13}C, and COSY NMR spectra of *anti*-**6e**, *anti*-**6f**, *syn*-**8a**, *syn*-**9g**, *anti*-**15g**, *anti*-**16a**, and *syn*-**16a** (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(25) Sheldrick, G. W. SHELXTL-UNIX (1994) Siemens Analytical Instruments, Madison, WI.