Synthetic Optimization and Structural Limitations of the Nitrile Aldol Reaction

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In an effort to further optimize and to define the structural limitations of the nitrile aldol reaction, several studies were undertaken. Lithiated phenylacetonitrile **1** was demonstrated to exhibit diastereoselectivity for addition to benzaldehyde higher than that of other metalated phenylacetonitriles. With a view toward practical lab-scale synthesis of aldols derived from lithiated arylacetonitriles, the effects of reaction concentration and quenching method on isolated yields of the *anti*-aldols were readdressed. Secondary aldehydes give reasonable recrystallized yields of *anti*-aldols at reaction concentrations as high as 0.1 M; pivalaldehyde gives good results at concentrations up to 0.3 M. Thirdly, the aldol reaction of lithiated **1** with *para*-substituted benzaldehydes **6b**−**g** was then studied; increasing electron-withdrawing power of the *para* substituent was found to cause a marked decrease in diastereoselectivity. Finally, the aldol reactions of two aliphatic nitriles (isovaleronitrile **4** and *tert*-butylacetonitrile **5**) were studied. Suprisingly, aldol diastereoselectivity of aliphatic nitriles is not uniformly *anti*-selective, and selectivities overall are lower than those afforded by arylacetonitriles.

The aldol reaction of nitriles is potentially a very useful way to simultaneously construct two stereocenters and install latent amino functionality. In 1987 Trost reported that lithiated acetonitrile undergoes axial selective addition to conformationally biased cyclohexanones and cyclohexenones.[1] Addition of lithiated propionitrile to cyclohexenones occurs with even greater axial selectivity and with considerable stereoselectivity at the α-nitrile carbon.[2] On the other hand, initial reports of aldol addition of nitriles to aldehydes were characterized by little or no diastereoselectivity.[3] We recently demonstrated that lithiated arylacetonitriles undergo *anti*-selective addition to aldehydes.[4] In this report we describe efforts to further optimize diastereoselectivities and yields for the addition of arylacetonitriles to aldehydes. The effect of different metal counterions, reaction concentration, and quenching methods are discussed. The aldol reactions of substituted benzaldehydes, and two aliphatic nitriles, were also studied in order to further define the substrate domain within which useful diastereoselectivities can be obtained.

Previous optimization studies on the aldol reactions of lithiated phenylacetonitrile **1** established that diastereoselectivity is highest in THF, at or below 0.025 M, and is insensitive to the identity of amide base (LDA or LiHMDS) used for deprotonation.[4a] Under the conditions of our standard protocol (THF, 0.025 M, −78 °C, 30 min), nitrile aldol reaction diastereoselectivity was demonstrated to be kinetically controlled. Yields are generally high, and the selectivity obtained depends on the steric bulk of the aldol substituent. Tertiary aldehydes (such as pivalaldehyde **9**) typically give >20:1 *anti*:*syn* selectivity, and the minor *syn*-isomer normally cannot be detected by ^{1}H NMR. However, secondary aldehydes such as benzaldehyde **6a** often give undesirably low selectivity (2.5:1 to 6:1). In an attempt to achieve higher levels of *anti* selectivity, the use of different metal counterions was explored. The various metalated phenylacetonitriles were prepared by deprotonation with the appropriate metal amide or organometallic (method A), or by transmetalation of lithiated **1** (method B). Kauffmann has previously described transmetalation of lithiated nitriles to the corresponding Fe(II), Cr(II), Mn(II), Co(II), Ni(II), and Cu(I) derivatives.[5] Transmetalation of lithiated nitriles to the corresponding titanium,[1,5,6] zinc,[1] and aluminum[1] derivatives has also been described. In the course of our investigations more than 20 metal/oxidation state/ligand combinations were examined. The actual success or failure of the transmetalation in each case is not known, but a change in diastereoselectivity and yield was usually observed relative to lithiated **1**. However, in the end, no metal offered superior diastereoselectivity relative to lithium; representative examples are given in Table 1.

As can be seen, as the counterion changes from Li to Na or K, a significant decrease in *anti* selectivity occurs (entries 1−3, Table 1). These results match the expectation that, as M−O and M−N bonds lengthen, steric differentiation of the competing diastereomeric transition states should decrease, leading to poorer selectivity. The use of boron enolates in aldol reactions has yielded substantial improvements in selectivity relative to lithium, ostensibly as a consequence of the extremely short B−O bond length.[7] However, despite extensive variation of the boron alkyl moieties, deprotonation conditions, and workup method, poor yields resulted from use of boron in

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(1) Trost, B. M; Florez, J.; Jebaratnam, D. J. *J. Am. Chem. Soc.* **1987**, *109*, 613−615.

(2) Trost, B. M.; Florez, J.; Haller, K. J. *J. Org. Chem.* **1988**, *53*, 2396−2398.

(3) (a) Hamana, H.; Sugasawa, T. *Chem. Lett.* **1982**, 1401−1404. (b) Kasatkin, A. N.; Biktimirov, R. Kh.; Tolstikov, G. A.; Nikonenko, A. G. *J. Org. Chem. USSR* **1990**, *26*, 1037−1045.

(4) (a) Carlier, P. R.; Lo, K.-M. *J. Org. Chem.* **1994**, *59*, 4053−4055. (b) Carlier, P. R.; Lo, K.-M.; Lo, M. M.-C.; Williams, I. D. *J. Org. Chem.* **1995**, *60*, 7511−7517.

(5) Kauffmann, T.; Kieper, H.; Pieper, H. *Chem. Ber.* **1992**, *125*, 899−905.

(6) Reetz, M. T.; Steinbach, R.; Wenderoth, B.; Westermann, J. *Chem. Ind.* **1981**, 541−542.

(7) Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 239−275.

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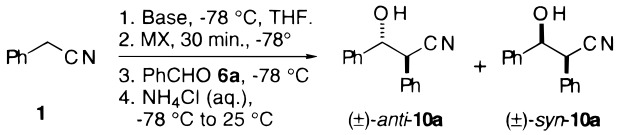
Table 1. Effect of Metal Counterion on Nitrile Aldol Reaction Diastereoselectivity



entry	metal	base	MX	anti:syn (yield)[a]
1	Li	LiHMDS		5.5:1 (86)
2	Na	NaHMDS		1.8:1 (83)
3	K	KHMDS		1.6:1 (95)
4	B	LiHMDS	$(c\text{-}C_6H_{11})_2BCl$	1.1:1 (29)[b]
5	Mg	EtMgBr		1.2:1 (63)
6	Al	LDA	$AlCl_3$	1.2:1 (48)
7	Zn	LDA	$ZnCl_2$	1.1:1 (69)
8	Ti	LDA	$(i\text{-}PrO)_3TiCl$	0.83:1 (48)
9	Zr	LDA	Cp_2ZrCl_2	1.1:1 (62)

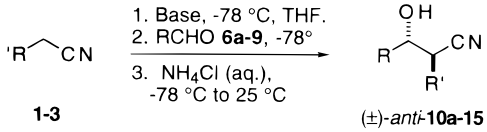
[a] Anti:syn ratios and yields determined by 400 MHz ^{1}H NMR; reported yields are weight recoveries of combined *anti* and *syn* diastereomers. [b] Reaction performed in Et_2O; workup with pH 7 buffered H_2O_2.

reactions of lithiated **1** (entry 4, Table 1). The selectivity obtained essentially matches that reported by Hamana for the same reaction mediated by di(*n*-butyl)boron triflate and $EtN(i\text{-}Pr)_2$.[3a] The use of the strongly chelating Mg, Al, and Zn counterions might be expected to improve *anti* selectivity; however in practice, the opposite result was obtained (entries 5−7, Table 1). Finally, given the high aldol selectivities exhibited by titanium and zirconium enolates,[8] the use of these metals in the nitrile aldol reaction was explored; representative examples are given in entries 8 and 9 (Table 1). Again, poorer selectivity resulted relative to lithiated **1**.[9]

Despite the low diastereoselectivities obtained in reacting lithiated arylacetonitriles with secondary aldehydes, we have found that reasonable isolated yields of the diastereomerically pure *anti*-aldols can usually be obtained, due to the high crystallinity of the major isomers. The only drawback to using our published procedure to prepare such materials on large scale is the large solvent volumes engendered by our previously recommended reaction concentration of 0.025 M. From an economic standpoint, some decrease in selectivity could be tolerated if it significantly reduced the amount of solvent required. Although we have not undertaken a detailed study of the effect of concentration on diastereoselectivity in each case, we now report that somewhat higher reaction concentrations may be used without significantly decreasing the isolated yields of *anti*-aldol obtained, particularly in the case of bulky aliphatic aldehydes (Table 2).

For example, aldol reaction of 2-naphthylacetonitrile **2** with benzaldehyde **6a** at 0.1 M gives an 63% isolated yield of the *anti*-aldol after two recrystallizations (entry 2, *anti*-**11a**). This yield is quite reasonable in view of the known *anti*:*syn* ratio of 2.3:1 at 0.025 M.[4b] Performing the reaction at 0.4 M however decreases the anti:syn selectivity to 1.2:1 and drastically lowers the recrystallized yield. Thus for reactions with secondary aldehydes we recommend concentrations of 0.1 M or less to ensure reasonable isolated yields of the desired *anti*-aldol product. On the other hand, with tertiary aldehydes such as pivalaldehyde **9**, higher reaction concentrations decrease the *anti*:*syn* selectivity only slightly, and good to excellent isolated yields of pure *anti*-aldols can be obtained at concentrations as high as 0.3 M (entries 5−6).

Table 2. Isolated Yields of *Anti* Aldols 10a−15



entry	*anti* aldol	R	R′	[nitrile] (M)	isolated yield,[a] %
1	**10a**	Ph	Ph	0.05	53
2	**11a**	Ph	2-Naphth	0.10	63
3	**12**	$c\text{-}C_6H_{11}$	4-MeOPh	0.05	68
4	**13**	Mes[b]	Ph	0.05	62
5	**14**	*t*-Bu	2-Naphth	0.32	70
6	**15**	*t*-Bu	Ph	0.26	87

[a] Isolated yield of pure *anti* aldol (anti:syn > 25:1). [b] Mes = mesityl, $2,4,6\text{-}(Me)_3C_6H_2$.

Another important factor in achieving high yields of the *anti*-aldol product is the quenching method employed. In our experience, good yields of *anti*-aldols derived from arylacetonitriles can be obtained if the protic quench (addition of saturated aqueous NH_4Cl) is carried out at −78 °C. If the reaction is allowed to warm up before the quench, aldol yield and diastereoselectivity decrease, possibly as a consequence of retro-aldol reaction. Silverman has recently reported that yields of β-hydroxy nitriles derived from acetonitrile are greatly improved if one uses a trimethylsilyl chloride trapping/*in situ* methanolysis protocol rather than a protic quench.[10] However independent reinvestigations of the Silverman quench procedure for the synthesis of aldol *anti*-**10a** indicated no improvement in yield or selectivity compared to our published procedure.[11] It is however possible that application of the Silverman protocol to the other examples in Table 2 might result in further yield improvements.

To date the diastereoselectivity of the nitrile aldol reaction has been rationalized in terms of steric effects in the competing transition structures. Clearly, electronic effects could play a major role in determining diastereoselectivity and may limit the range of useful aldehyde substrates. To determine the sensitivity of nitrile aldol diastereoselectivity to electronic factors, the reaction of lithiated **1** with various *para*-substituted benzaldehydes **6b**−**f** in THF at 0.025 M was studied (Table 3).

As can be seen in Table 3, substitution of benzaldehyde **6a** with electron-donating groups resulted in little change in the diastereoselectivity (entries 1−4). However, as the electron electron-withdrawing power of the substituent increases, selectivity decreases (entries 5−7). The effect is quite significant: reaction of *p*-nitrobenzaldehyde **6g**

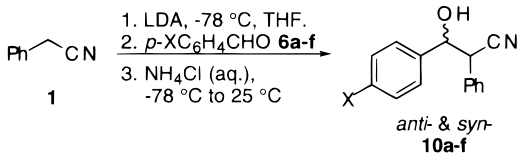
(8) Patterson, I. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 301−319.

(9) Kasatkin (ref 3b) had previously reported an threo:erythro = 54:46 ratio for addition of $(i\text{-}PrO)_3TiCl$ transmetalated lithiophenylacetonitrile to benzaldehyde in THF. Taking into consideration the fact that their assignment should be reversed (see ref 4b, footnote 5), the actual ratio they obtained corresponds to 0.85:1, essentially what we observe.

(10) Zhou, J. P. J.; Zhong, B.; Silverman, R. B. *J. Org. Chem.* **1995**, *60*, 2261−2262.

(11) Silverman et al. previously reported that application of their protocol to the reaction of phenylacetonitrile and benzaldehyde gave a single aldol product of unspecified relative configuration. However subsequent reexamination in our laboratory and in the Silverman group revealed the product to be approximately a 4:1 mixture of *anti*- and *syn*- diastereomers (private communication, R. B. Silverman to P. R. Carlier).

Table 3. Electronic Perturbation of Nitrile Aldol Reaction Diastereoselectivity



entry	aldehyde	X	anti:syn[a]	σ_p^-(X)
1	**6b**	Me_2N	5.6:1	−0.32
2	**6c**	MeO	4.7:1	−0.12
3	**6d**	Me	5.6:1	−0.14
4	**6a**	H	5.5:1	0
5	**6e**	Cl	3.4:1	0.24
6	**6f**	CF_3	1.5:1	0.62
7	**6g**	NO_2	0.9:1	1.25

[a] Anti:syn ratios determined by 400 MHz ^{1}H NMR. Yields of the combined aldols range from 73 to 98% and are given in the Experimental Section.

is completely unselective (entry 7, Table 3). Studies on the effect of benzaldehyde substituents on aldol thermochemistry[12] and diastereoselectivity[13] have been reported previously. A limited study (four substrates) of the tris(dialkylamino)sulfonium enolate of cyclohexanone demonstrated that diastereoselectivity with electron-deficient benzaldehydes was slightly higher than that with electron-rich aldehydes.[13a] Other studies on the lithium enolates of cyclohexanone[13b] and 2,6-dimethylcyclohexanone[13d] and α-halogenated Sn(II) imide enolates[13c] did not demonstate any meaningful trend. The results obtained in our study are unique in that they qualitatively match the expectation that decreasing electron density in the aldehyde would render it more reactive and consequently less selective (the so-called reactivity−selectivity principle). Why similar trends were not observed in the enolate studies described above is not clear. However to gain further insight into our results, correlation of the log(*anti*:*syn*) for reactions of lithiated **1** with **6a**−**g** versus various Hammett parameters was then performed. By far the best correlation was obtained using the σ_p^- parameter[14] ($r = 0.97$, Figure 1). The optimum correlation of log (*anti*:*syn*) with σ_p^- in our case is interesting and may be indicative of the nature of charge distribution in the transition state.[15] However at this time it is only possible to point out that synthetically useful diastereoselectivity cannot be achieved with extremely electron deficient benzaldehydes such as **6f** or **6g**.

To date our studies of the nitrile aldol reaction have been limited to arylacetonitriles. The utility of this reaction would greatly increase if aliphatic nitriles could be shown to react with reliable and high diastereoselectivity. Kauffman reported that lithiated propionitrile and the corresponding Fe(II) derivative underwent addition

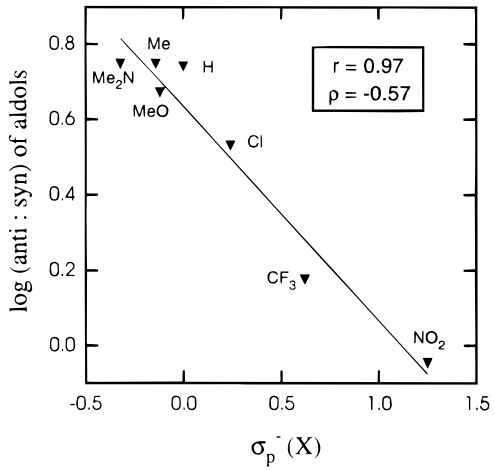


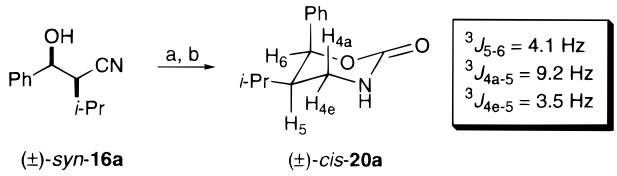
Figure 1. Plot of log(*anti*:*syn*) for aldols *anti*-**10a**−**f** versus σ_p^-(X).

Table 4. Comparison of the Aldol Diastereoselectivity of Phenylacetonitrile (1) with Isovaleronitrile (4) and *tert*-Butylacetonitrile (5)

entry	aldol	R (aldehyde)	R′ (nitrile)	anti:syn[a]
1	**10a**	Ph (**6a**)	Ph (**1**)	5.5:1
2	**15**	*t*-Bu (**9**)	Ph (**1**)	60:1
3	**16a**	Ph (**6a**)	*i*-Pr (**4**)	0.26:1
4	**17**	*t*-Bu (**9**)	*i*-Pr (**4**)	4.4:1
5	**18a**	Ph (**6a**)	*t*-Bu (**5**)	1.3:1
6	**19**	*t*-Bu (**9**)	*t*-Bu (**5**)	>20:1

[a] Anti:syn ratios determined by 300 or 400 MHz ^{1}H NMR, or capillary GC for ratios higher than 20:1. Yields of the combined aldols range from 63 to 84% and are given in the Experimental Section.

Scheme 1[a]



[a] (a) 1:1 $LiAlH_4/AlCl_3$, Et_2O; (b) $(Cl_3CO)_2CO$, Et_3N, CH_2Cl_2, −78 → 0 °C.

to benzaldehyde with little selectivity (3:1 and 2:1 respectively, unassigned).[5] To determine if increasing steric bulk in the nitrile moiety would raise selectivities to a useful level, aldol reactions of lithiated isovaleronitrile **4** and *tert*-butylacetonitrile **5** were studied in THF at 0.025 M (Table 4).

From the standpoint of aldol reaction with aldehydes, it was expected that lithiated isovaleronitrile **4** would be approximately isosteric with lithiated phenylacetonitrile **1**. However, selectivities for the reactions of **4** are markedly lower than those of **1** (cf. entries 1 and 3; entries 2 and 4, Table 4). More significantly, the reaction of **4** with **6a** is actually *syn*-selective (entry 3, Table 4). The assignment of the major diastereomer as *syn* was made on the basis of the vicinal coupling constants[4b] and was supported by transformation of the major aldol to the corresponding cyclic carbamate *cis*-**20a** (Scheme 1).

Observation that $^3J_{5-6}$ of *cis*-**20a** is 4.1 Hz confirms that the *i*-Pr and Ph substituents are *cis*; the fact that $^3J_{4a-5}$ is greater than 7 Hz indicates that the *i*-Pr substituent is equatorial, a result unexpected on the basis

(12) Arnett, E. M.; Palmer, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 7354−7360.

(13) (a) Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1983**, *105*, 1598−1608. (b) Majewski, M.; Gleave, D. M. *Tetrahedron Lett.* **1989**, *30*, 5681−5684. (c)Pridgen, L. N.; Abdel-Magid, A. F.; Lantos, I.; Shilcrat, S.; Eggleston, D. S. *J. Org. Chem.* **1993**, *58*, 5107. (d) Mateos, A. F.; Coca, G. P.; Alonso, J. J. P.; González, R. R.; Hernández, C. T. *Tetrahedron Lett.* **1995**, *36*, 961−964.

(14) Exner, O. In *Correlation Analysis of Chemical Data*; Plenum Press: New York, 1988; pp 61−62.

(15) Jacobsen *et al.* have argued that the optimum correlation of log(cis:trans) to σ (rather than σ^+) for the epoxidation of *cis*-methyl cinnamate derivatives indicates that a carbocationic intermediate is not on the reaction path (Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martinez, L. E. *Tetrahedron* **1994**, *50*, 4323−4334.)

of the relative *A* values of *i*-Pr and Ph.[16] AM1 geometry optimization calculations confirm however that the *i*-Pr-equatorial conformer is 1.3 kcal mol^{-1} more stable than the *i*-Pr-axial conformer.[17] Reactions of *tert*-butylacetonitrile **5** are of interest from the viewpoint that selectivity with benzaldehyde **6a** is remarkably low (*anti*:*syn* = 1.3:1, entry 5, Table 4). Useful stereoselectivity is achieved only when steric effects are pushed to the conceivable limit (R′ = R = *t*-Bu, entry 6, Table 4). Clearly the aldol selectivities exhibited by aliphatic nitriles **4** and **5** cannot be accounted for by the transition state model previously advanced for arylacetonitriles.[4b] It is possible that the structures of lithiated aliphatic nitriles differ considerably from their arylacetonitrile counterparts and that this difference is also reflected in the corresponding nitrile aldol transition structures. Solution structural studies on lithiated **4** and **5** may shed light on these issues.

In conclusion, we have determined that lithium offers the best diastereoselectivity in addition of metalated arylacetonitriles to aldehydes. Secondly, a reinvestigation of the effect of concentration on aldol selectivity reveals that for secondary aldehydes reasonable recrystallized yields of the *anti*-aldol products can be obtained at reaction concentrations up to 0.1 M, due to the high crystallinity of these materials. In the case of pivalaldehyde, reaction concentrations up to 0.3 M provide good to excellent isolated yields of the *anti*-aldol products. Third, aldol diastereoselectivity with *para*-substituted benzaldehydes decreases dramatically with increasing electron-withdrawing power of the substituent, to such an extent that reactions with *p*-(trifluoromethyl)benzaldehyde **6f** and *p*-nitrobenzaldehyde **6g** do not offer synthetically useful selectivity. Finally we have established that aliphatic nitriles, unlike arylacetonitriles, do not offer reliable *anti*-selectivity in reactions with aldehydes.

Experimental Section

General. All reactions were performed in oven-dried glassware under a nitrogen atmosphere. THF was distilled from Na/benzophenone immediately prior to use. Lithium diisopropylamide (2.0 M in THF) and lithium hexamethyldisilazide (1.0 M in THF) were purchased from Aldrich and titrated prior to use (2,2′-bipyridine as indicator). Sodium hexamethyldisilazide (1.0 M in THF) and potassium hexamethyldisilazide (0.5 M in toluene) were used as received from Aldrich. *tert*-Butylacetonitrile (**5**) was prepared by dehydration of the corresponding amide; all other nitriles and all aldehydes were purchased from Aldrich and distilled prior to use. Unless otherwise noted, NMR spectra were recorded in $CDCl_3$, at 400 or 300 MHz for ^{1}H, and 100.75 or 75.48 MHz for ^{13}C. Elemental analysis was performed at the Shanghai Institute of Organic Chemistry (Chinese Academy of Sciences, PRC) and at Medac Ltd. (Brunel University, UK). Aldol reactions were carried out according to the published procedure,[4b] and unless otherwise noted, all reactions were performed on a 1 mmol scale at a concentration of 0.025 M.

Representative Gram-Scale Aldol Reaction Procedure: (2*RS*,3*RS*)-3-Hydroxy-4,4-dimethyl-2-(2′-naphthyl)pentanenitrile (*anti*-15). An oven-dried 500 mL round-bottomed flask was charged with THF (100 mL) and stirring bar, capped with a septum, purged with nitrogen, and cooled to −78 °C. Phenylacetonitrile **1** (3.5 mL, 3.55 g, 30.3 mmol) and LDA (2.0 M, 18.2 mL, 36.4 mmol) were added via syringe, and the mixture was stirred for 30 min. Pivalaldehyde **9** (4.0 mL, 3.17 g, 36.8 mmol) was added via syringe; after 30 min at −78 °C, the septum was removed and saturated NH_4Cl solution (10 mL) was added all at once. The cooling bath was removed, and after 10 min 1 N HCl (100 mL) and Et_2O (100 mL) were added. Separation of layers, extraction of the aqueous phase (2 × 100 mL of Et_2O), drying of the combined organic layers ($MgSO_4$), filtration, and concentration *in vacuo* yielded the crude product, which was recrytallized from toluene (9 mL)/hexane (60 mL) to afford 5.34 g (87%) of *anti*-**15** as white crystals. The material was greater than 95% pure by ^{1}H and ^{13}C NMR (spectral and analytical data published previously[4b]).

(2*RS*,3*RS*)-3-Hydroxy-2,3-diphenylpropionitrile (*anti*-10a). Reaction of **1** and **6a** was perfomed as above on a 15 mmol scale in 300 mL of THF; recrystallization from toluene/hexane gave 1.81 g of *anti*-**10a** (53%). The material was greater than 95% pure by ^{1}H and ^{13}C NMR (spectral data published previously[18]).

(2*RS*,3*RS*)-3-Hydroxy-2-(2′-naphthyl)-3-phenylpropionitrile (*anti*-11a). Reaction of 2-naphthylacetonitrile **2** and **6a** was performed as above on a 15 mmol scale in 150 mL of THF; two successive recrystallizations from CH_2Cl_2/hexane gave 2.57 g of *anti*-**11a** (63%). The material was greater than 95% pure by ^{1}H and ^{13}C NMR (spectral and analytical data published previously[4b]).

(2*RS*,3*SR*)-3-Cyclohexyl-3-hydroxy-2-(4′-methoxyphenyl)propionitrile (*anti*-12). Reaction of *p*-methoxyphenylacetonitrile **3** and cyclohexanecarboxaldehyde **7** was performed as above on a 20 mmol scale in 400 mL of THF; two successive recrystallizations from $CHCl_3$/hexane gave 3.51 g of *anti*-**12** (68%). The material was greater than 95% pure by ^{1}H and ^{13}C NMR (spectral and analytical data published previously[4b]).

(2*RS*,3*RS*)-3-Hydroxy-2-phenyl-3-(2′,4′,6′-trimethylphenyl)propionitrile (*anti*-13). Reaction of **1** and mesityl aldehyde **8** was performed as above on a 8 mmol scale in 150 mL of THF; recrystallization from toluene/hexane gave 1.32 g of *anti*-**13** (62%). The material was greater than 95% pure by ^{1}H and ^{13}C NMR (spectral and analytical data published previously[4b]).

(2*RS*,3*RS*)-3-Hydroxy-4,4-dimethyl-2-phenylpentanenitrile (*anti*-14). Reaction of **2** and pivalaldehyde **9** was performed as above on a 30 mmol scale in 90 mL of THF; recrystallization from toluene/hexane gave 5.41 g of *anti*-**14** (70%). The material was greater than 95% pure by ^{1}H and ^{13}C NMR (spectral and analytical data published previously[4b]).

(2*RS*,3*RS*)-3-Hydroxy-2-phenyl-3-(*N*′,*N*′-dimethyl-4′-aminophenyl)propionitrile (*anti*-10b). The crude aldols were obtained in 73% yield (*anti*:*syn* = 5.6:1) from *p*-(dimethylamino)benzaldehyde **6b** and **1**. Pure *anti*-**10b** was isolated by recrystallization from dichloromethane/hexane. ^{1}H NMR: 2.307 (d, *J* = 2.9 Hz, 1H), 2.937 (s, 6H), 4.028 (d, *J* = 5.9 Hz, 1H), 4.876 (dd, *J* = 2.9 Hz, 5.9 Hz, 1H), 6.63−7.33 (m, 9H). ^{13}C NMR: 40.44, 47.27, 76.35, 112.18, 119.18, 126.99, 127.16, 128.29, 128.49, 128.77, 132.97, 150.77. IR (KBr): 3432.0 (s), 2248.0 (s). MS ($CI^+(NH_3)$): 266.7 (M + 1). Mp: 113.7−114.5 °C. Anal. Calcd for $C_{17}H_{18}N_2$: C, 76.67; H, 6.81; N, 10.52. Found: C, 76.65; H, 6.79; N, 10.50.

(2*RS*,3*RS*)-3-Hydroxy-3-(4′-methoxyphenyl)-2-phenylpropionitrile (*anti*-10c). The crude aldols were obtained in 81% yield (*anti*:*syn* = 4.7:1) from *p*-methoxybenzaldehyde **6c** and **1**. Pure *anti*-**10c** was isolated by recrystallization from toluene. ^{1}H NMR: 2.427 (d, *J* = 2.4 Hz, 1H), 3.792 (s, 3H), 4.023 (d, *J* = 5.9 Hz, 1H), 4.931 (dd, *J* = 3.4 Hz, 5.9 Hz, 1H), 6.81−6.86 (m, 2H), 7.15−7.35 (m, 7H). ^{13}C NMR: 47.38, 55−29, 76.08, 113.90, 118.87, 127.50, 128−46, 128.88, 131.49, 132.55, 159.84. IR (KBr): 3460.0 (broad), 2238.0 (m). MS ($CI^+(NH_3)$): 252.9 (M + 1). Mp: 101.1−102.9 °C. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.59; H, 5.95; N, 5.43.

(16) Eliel, E. L.; Wilen, S. H. In *Stereochemistry of Organic Molecules*; John Wiley & Sons: New York, 1994; pp 696−697.

(17) Heats of formation for the *i*-Pr-equatorial and *i*-Pr-axial conformers of *cis*-**20** were determined by means of AM1 geometry optimization calculations (Spartan 2.0 on a Silicon Graphics Personal Iris 4D/35).

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

(2*RS*,3*RS*)- and (2*RS*,3*SR*)-3-Hydroxy-3-(4′-methylphenyl)-2-phenylpropionitrile (*anti*- and *syn*-10d). The crude aldols were obtained in 77% yield (*anti*:*syn* = 5.6:1) from *p*-methylbenzaldehyde **6d** and **1**. Pure *anti*-**10d** was isolated by recrystallization from toluene. ^{1}H NMR: 2.327 (s, 3H), 2.486 (d, J = 3.4 Hz, 1H), 4.022 (d, J = 5.9 Hz, 1H), 4.922 (dd, J = 3.7 Hz, 5.7 Hz, 1H), 7.1−7.3 (m, 9H). ^{13}C NMR: 21.14, 47.29, 76.21, 118.78, 126.10, 128.42, 128.84, 129.19, 132.59, 136.45, 138.51. IR (KBr): 3418.0 (broad), 2252.0 (s). MS (EI$^+$): 237.0 (M). Mp: 110.6−111.4 °C. Anal. Calcd for $C_{16}H_{15}NO$: C, 80.99; H, 6.37; N, 5.90. Found: C, 80.96; H, 6.37; N, 5.89.

To obtain *syn*-**10d** the mother liquor was chromatographed (25% ethyl acetate in hexane). Although separation of the diastereomers was not apparent on TLC, the last fraction proved to be >95% *syn*-**10d**. ^{1}H NMR: 2.266 (d, J = 2.4 Hz, 1H), 2.348 (s, 3H), 4.123 (d, J = 6.8 Hz, 1H), 4.953 (d, J = 6.8 Hz, IH), 7.1−7.3 (m, 9H). ^{13}C NMR: 22.21, 46.63, 76.13, 118.76, 126.50, 128.60, 128.71, 128.89, 129.17, 132.11, 135.88, 138.81. IR(KBr): 3360.0 (broad,s), 2242.0 (m). MS (CI$^+$(NH$_3$)): 238.0 (M + 1). Mp: 101.0−103.0 °C. Anal. Calcd for $C_{16}H_{15}NO$: C, 80.99; H, 6.37; N, 5.90. Found: C, 80.67; H, 6.36; N, 5.89.

(2*RS*,3*RS*)-3-Hydroxy-2-phenyl-3-(4′-chlorophenyl)propionitrile (*anti*-10e). The crude aldols were obtained in 76% yield (*anti*:*syn* = 3.4:1) from *p*-chlorobenzaldehyde **6e** and **1**. TLC (25% ethyl acetate in hexane) did not exhibit visible separation of *anti*- and *syn*-**10e**, but flash chromatography and concentration of the first few aldol fractions afforded pure *anti*-**10e**. ^{1}H NMR: 2.522 (d, J = 3.4 Hz, 1H), 4.023 (d, J = 5.9 Hz, 1H), 4.974 (dd, J = 3.7 Hz, 5.6 Hz, 1H), 7.18−7.35 (m, 9H). ^{13}C NMR: 47.33, 75.69, 118.43, 127.63, 128.42, 128.73, 129.06, 132.04, 134.58, 137.75. IR (KBr): 3484.0 (s), 2244.0 (s). MS (CI$^+$(NH$_3$)): 275.1 (M + NH$_4$). Mp: 75.3−76.5 °C. Anal. Calcd for $C_{15}H_{12}NOCl$: C, 69.90; H, 4.69; N, 5.43. Found: C, 69.89; H, 4.65; N, 5.41.

(2*RS*,3*RS*)- and (2*RS*,3*SR*)-3-Hydroxy-2-phenyl-3-(4′-(trifluoromethyl)phenyl)propionitrile (*anti*- and *syn*-10f). The crude aldols were obtained in 98% yield (*anti*:*syn* = 1.5:1) from *p*-(trifluoromethyl)benzaldehyde **6f** and **1**. Flash chromatography (25% ethyl acetate/hexane) afforded separation of the aldol diastereomers.

***anti*-10f (R_f = 0.19).** ^{1}H NMR: 2.893 (s, 1H), 4.041 (d, J = 5.9 Hz, 1H), 5.033 (d, J = 4.9 Hz, 1H), 7.20−7.58 (m, 9H). ^{13}C NMR: 47.27, 75.60, 118.36, 123.91 (q, $^1J_{CF}$ = 274 Hz), 125.46 (q, $^3J_{CF}$ = 4 Hz), 126.71, 128.40, 128.86, 129.13, 130.84 (q, $^2J_{CF}$ = 31 Hz), 131.89, 143.21. IR (KBr): 3482.0 (s), 2244.0 (s), 1330.0 (s). MS (CI$^+$(NH$_3$)): 308.8 (M + NH$_4$). Mp: 94.7−96.6 °C. Anal. Calcd for $C_{16}H_{12}NOF_3$: C, 65.98; H, 4.18; N, 4.81. Found: C, 66.00; H, 4.08; N, 4.81.

***syn*-10f (R_f = 0.13).** ^{1}H NMR: 2.500 (d, J = 3.4 Hz, 1H), 4.137 (d, J = 6.8 Hz, 1H), 5.005 (dd, J =3.4 Hz, 6.4 Hz, 1H), 7.19−7.60 (m, 9H). ^{13}C NMR: 46.56, 75.51, 118−27, 123.90 (q, $^1J_{CF}$ = 272 Hz), 125.38 (q, $^3J_{CF}$ = 4 Hz), 127.10, 128.69, 128.97, 129.11, 131.27 (q, $^2J_{CF}$ = 31 Hz), 131.33, 142.57. IR (KBr): 3452.0 (s), 2242.0 (s), 1336.0 (s). MS (CI$^+$(NH$_3$)): 308.8 (M + NH$_4$). Mp: 102.0−103.4 °C. Anal. Calcd for $C_{16}H_{12}NOF_3$: C 65.98; H, 4.18; N, 4.81. Found: C, 65.69; H, 4.19; N, 4.72.

(2*RS*,3*RS*)- and (2*RS*,3*SR*)-3-Hydroxy-2-phenyl-3-(4′-nitrophenyl)propionitrile (*anti*- and *syn*-10g). The crude aldols were obtained in 88% yield (*anti*:*syn* = 0.9:1) from *p*-nitrobenzaldehyde **6g** and **1**. Flash chromatography (25% ethyl acetate/hexane) afforded separation of the aldol diastereomers.

***anti*-10g (R_f = 0.46).** ^{1}H NMR: 3.001 (s, broad, 1H), 4.081 (d, J = 5.9 Hz, 1H), 5.123 (d, J = 5.4 Hz, 1H), 7.17−7.45 (m, 7H), 8.160 (d, J = 8.8 Hz, 2H). ^{13}C NMR: 47.18, 75.27, 118.09, 123.65, 127.32, 128.40, 129−06, 129.26, 131.47, 146.25, 147−99. IR (KBr): 3464.0 (s), 2244.0 (s), 1514.0 (vs), 1350.0 (vs). MS (CI$^+$(NH$_3$)): 285.9 (M + 2NH$_3$). Mp: 143.5−144.3 °C. Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.08; H, 4.49; N, 10.45.

***syn*-10g (R_f = 0.40).** ^{1}H NMR: 2.919 (s, broad, 1H), 4.187 (d, J = 6.4 Hz, 1H), 5.140 (d, J = 6.4 Hz, 1H), 7.16−7.53 (m, 7H), 8.143 (d, J = 8.8 Hz, 2H). ^{13}C NMR: 46.47, 75.05, 118.10, 123.46, 127.71, 128.62, 129.08, 129.15, 130.89, 145.66, 148.06. IR (KBr): 3548.0 (s), 2244.0 (s), 1520.0 (vs), 1348.0 (vs). MS (CI$^+$(NH$_3$)): 285.9 (M + NH$_4$). Mp: 121.8−123.4 °C. Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.77; H, 4.40; N, 10.40.

(2*RS*,3*SR*)- and (2*RS*,3*RS*)-3-Hydroxy-3-phenyl-2-(2′-propyl)propionitrile (*syn*- and *anti*-16a). Aldol reaction of isovaleronitrile **4** and **6a** on a 20 mmol scale (crude *anti*:*syn* = 1:2.8), followed by flash chromatography (CH_2Cl_2) afforded 1.87 g of the first eluting *syn*-**16a**, 0.37 g of *anti*-**16a** (≈ 5% *syn*- impurity), and 0.53 g of a mixed fraction (*anti*:*syn* ≈ 1:1). Total isolated yield of aldols was 74%.

***syn*-16a (R_f = 0.39).** ^{1}H NMR: δ 1.062 (d, J = 6.8 Hz, 6H), 2.174 (m, 1H), 2.679 (d, J = 2.7 Hz, 1H), 2.768 (dd, J = 4.6, 8.9 Hz, 1H), 4.687 (dd, J = 2.7, 8.9 Hz, 1H), 7.35 (m, 5H). ^{13}C NMR: δ 17.71, 21.50, 26.19, 47.90, 72.08, 118.36, 126.44, 128.63, 128.75, 140.82. IR (NaCl): 3446 (s), 2244 (m) cm^{-1}. MS (CI$^+$(CH$_4$)): 190 (M + 1). Mp: liquid. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.79; H, 7.94; N, 7.33.

***anti*-16a (R_f = 0.31).** ^{1}H NMR ($CDCl_3$ + D_2O): δ 1.064 (d, J = 6.8 Hz, 3H), 1.115 (d, J = 6.8 Hz, 3H), 1.66−1.75 (m, 1H), 2.728 (dd, J = 7.3, 5.1 Hz, 1H), 4.852 (d, J = 7.3 Hz, 1H), 7.36−7.41 (m, 5H). ^{13}C NMR: δ 18.64, 21.39, 27.27, 48.51, 72.26, 119.18, 126.12, 128.62, 128.77, 140.58. IR (KBr): 3248 (s), 2256 (m) cm^{-1}. MS (CI$^+$(CH$_4$)): 190 (M + 1). Mp: 68.8−69.6 °C. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.20; H, 8.12; N, 7.40.

(2*RS*,3*RS*)-3-Hydroxy-4,4-dimethyl-2-(2′-propyl)pentanenitrile (*anti*-17). The crude aldols were obtained in 63% yield (*anti*:*syn* = 4.4:1) from **4** and pivalaldehyde **9**. An analytically pure sample of *anti*-**17** was prepared by recrystallization from hexane. ^{1}H NMR: δ 1.000 (s, 9H), 1.074 (d, J = 6.4 Hz, 3H), 1.168 (d, J = 6.8 Hz, 3H), 1.827 (d, J = 7.8 Hz, 1H), 2.008 (d, J = 6.8 Hz, 1H), 2.578 (dd, J = 1.0 Hz, 6.8 Hz, 1H), 3.351 (d, J = 7.3 Hz, 1H). ^{13}C NMR: δ 20.12, 21.01, 25.79, 30.71, 35.81, 41.28, 77.49, 119.27. IR (KBr): 3476.0 (s), 2248.0 (m). MS (CI$^+$(NH$_3$)): 187.0 (M + NH$_4$). Mp: 76.9−77.9 °C. Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.27. Found: C, 70.86; H, 11.57; N, 8.29.

(2*RS*,3*RS*)-3-Hydroxy-3-phenyl-2-*t*-butylpropionitrile (*anti*-18a). The crude aldols were obtained in 71% yield (*anti*:*syn* = 1.3:1) from *tert*-butylacetonitrile **5** and **6a**. Pure *anti*-**18a** was obtained by recrystallization from Et_2O/hexane. ^{1}H NMR: δ 1.201 (s, 9H), 2.569 (d, J = 2.1 Hz, 1H), 5.038 (d, J = 2.1 Hz), 7.31−7.44 (m, 5H). ^{13}C NMR: δ 28.32, 33.79, 53.14, 70.57, 118.30, 125.44, 128.33, 128.76, 142.51. IR (KBr): 3434 (s), 2252 (m) cm^{-1}. MS (CI$^+$(NH$_3$)): 221 (M + NH$_4$). Mp: 114.3−116.3 °C. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.84; H, 8.47; N, 7.03.

(2*RS*,3*RS*)-3-Hydroxy-4,4-dimethyl-2-*tert*-butylpentanenitrile (*anti*-19). *anti*-**19** was obtained in 84% yield from **5** and **9**. An analytically pure sample was prepared by recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$ + D_2O): 0.984 (s, 9H), 1.109 (s, 9H), 2.56 (s, 1H), 3.447 (s, 1H). ^{13}C NMR ($CDCl_3$ + D_2O): 25.62, 27.83, 33.55, 35.91, 45.34, 119.14. IR (KBr): 3492 (s), 2236 (m) cm^{-1}. MS (CI$^+$(NH$_3$)): 201 (M + NH$_4$). Mp: 129.5−129.7 °C. Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 71.85; H, 11.83; N, 7.57.

(5*RS*,6*SR*)-6-Phenyl-5-isopropyltetrahydro-1,3-oxazin-2-one (*cis*-20a). The conversion of *syn*-**16a** to the carbamate *cis*-**20a** was carried out according to our previously published two-step procedure.[4b] ^{1}H-NMR: δ 0.837 (d, J = 6.8 Hz, 1H), 1.026 (d, J = 6.8 Hz, 1H), 1.3−1.4 (m, 1H), 2.0−2.1 (m, 1H), 3.163 (dd, J = 9.8, 11.7 Hz, 1H), 3.4−3.5 (m, 1H), 5.550 (d, J = 3.9 Hz, 1H), 7.10 (br, 1H), 7.3−7.4 (m, 5H). ^{13}C NMR: δ 19.67, 21.81, 25.89, 39.75, 41.59, 80.90, 126.49, 128.15, 128.46, 137.02, 154.93. IR (KBr): 3232 (w, br), 1711 (vs) cm^{-1}. MS (CI$^+$(CH$_4$)): 220.2 (M + H). Mp: 109.7−113.8 °C. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.18; H, 7.86; N, 6.45.

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Supporting Information Available: ^{13}C and ^{1}H NMR spectra of *anti*-**16a** and *anti*-**18a** (4 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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