Enantioselective Enolate Protonation: Matching Chiral Aniline and Substrate Acidity

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Received June 2, 1999

A comparison of chiral anilines **1a**−**f** in the asymmetric protonation of enolate **15** shows that the optimum ΔpK_a value (chiral acid vs protonated enolate) for the highest enantioselectivity is ca. 3 (Table 2). An extension of this concept to amino acid enolates was possible, and **1e** was found to give the best enantioselectivity (85% ee) with the alanine-derived *N*-lithioenolate **5a** (Table 3). Changes in aniline pK_a due to variation of substituents at the aniline nitrogen were evaluated briefly, but these changes did not show consistent trends in the enantioselectivity vs pK_a.

Enolate desymmetrization by protonation with chiral acids has reached practical levels of enantioselectivity in a number of studies.[1] In the best examples, ee values in the range of 95−99% have been demonstrated, and catalytic as well as stoichiometric procedures are known at this level of enantioselectivity. Progress with the mechanistic aspects of the proton-transfer step has been slower. Enolates have several structural options in solutions that contain other species such as lithium amides, lithium halides, enolate dimers, mixed aggregates, and so on.[2] Experimental variables are also potentially complex. In our own work, the optimized procedures have typically been developed by empirical means.[1b,3] The effort required to isolate and to understand individual variables has inevitably taken much more time than the empirical optimization. On the other hand, the need to improve our understanding of the key variables is clear. Despite extraordinary levels of enantioselectivity for the best applications, the available chiral acids tend to be effective only for a narrow range of enolate substrates.

As discussed in a recent review by Fehr,[1a] highly enantioselective proton transfer between a chiral acid and a prochiral enolate is likely only if the rate of proton transfer is slow. A strongly exothermic α-carbon protonation event would probably be unselective, especially if the chiral acid is so potent that proton-transfer approaches diffusion control. On the other hand, the ideal chiral acid A*−H for a given enolate substrate E(−) must be strong enough to completely protonate the enolate and to resist the reverse reaction where the chiral carbonyl product E−H is deprotonated reversibly by the anion A*(−). This is essential if formation of racemic E−H is to be avoided.

Complete protonation of the enolate requires proton transfer on a convenient laboratory time scale and therefore involves both the kinetic and the thermodynamic acidity of the chiral acid. The latter term can be evaluated by comparing the pK_a's of the chiral acid and the protonated enolate, while the former (kinetic acidity) can be approximated by assuming that the rate of proton transfer will increase as the ΔpK_a (the value of $[pK_{aE-H}]$-$[pK_{aA^*-H}]$) increases.[4] However, there has been limited information regarding the acceptable range of ΔpK_a values (chiral acid vs protonated enolate) that allow enantioselective proton transfer. In a prior investigation from this laboratory, evidence was presented that ΔpK_a should be ca. 3, based on the behavior of two enolates that differ in the degree of anion stabilization. However, some of the earliest promising examples of enolate desymmetrization (Duhamel et al.) used chiral carboxylic acids as the proton donors, and the ΔpK_a relevant to these experiments appears to be considerably larger.[5]

We have considered the possibility that an optimum ΔpK_a range might be identified for different classes of enolate substrates in asymmetric protonation using structurally similar chiral acids based on the chiral diamine skeleton **1**. Previous studies have established that the commercially available *p*-chloro derivative **1b** functions as an excellent chiral "acid" in the enantioselective protonation of strongly basic β,γ-unsaturated amide enolates.[1b] If ΔpK_a is an important variable, then the issue can be probed by studying derivatives of **1** (Scheme 1) where the substituent X is varied systematically to change acidity. Alternatively, chiral acid pK_a can be adjusted by varying the aniline nitrogen substituent. In principle, this could be an easier approach starting from the aniline **2**, but enantiomerically pure **2** is not easy to prepare.[6] On the other hand, a dimethoxy analogue **3a** is readily available via an asymmetric hydrogenation approach and the *N*-methyl derivative **3b** is comparable to **1a** as a chiral acid in the protonation of

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(2) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539. Henderson, K. W.; Dorigo, A. E.; Liu, Q−Y.; Williard, P. G.; Schleyer, P. von R.; Bernstein, P. R. *J. Am. Chem. Soc.* **1996**, *118*, 1339.

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(4) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1.

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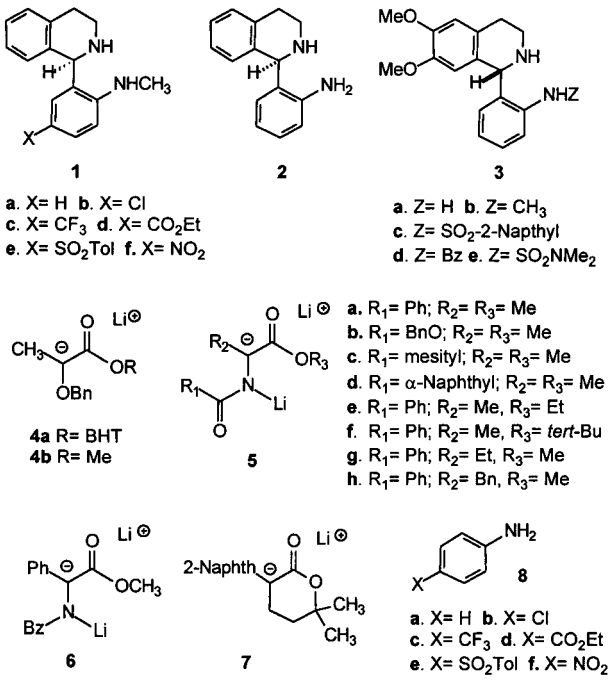
10.1021/jo990897m CCC: $18.00
Published on Web 09/23/1999

Scheme 1



amide enolates. Conversion of **3a** to **3c** has already been reported, and **3d** can be made in a similar way (Cbz protection of the secondary amine followed by *N*-benzoylation and deprotection).[6] The DMSO pK_a values for **3c** and **3d** can be estimated as ca. 12 and 19, respectively, by comparison with the parent aniline derivatives (*N*-phenylsulfonylaniline, pK_a 11.95; *N*-benzoylaniline, pK_a = 18.77) studied by Bordwell et al.[7] However, preliminary attempts to find possible applications with carboxylic acid derived enolates were not promising. Thus, the sulfonamide **3c** gave <10% ee in test reactions with ester enolates **4** or **5a**, and only marginally improved results were obtained with enolates **6** or **7** (36% ee and 28% ee, respectively). The analogous amide **3d** was ineffective in all cases (<5% ee with **4**, **6**−**7**). Only the *N*-sulfamoyl derivative **3e** gave a promising result among the anilines containing an electron-withdrawing substituent at nitrogen (58% ee with lactone enolate **7**), but similar experiments with **4a** (15% ee) and **6** (12% ee) were not encouraging. Furthermore, **3e** was difficult to make and to purify (*N*-Cbz protection of **3a** followed by treatment with Me_2NSO_2Cl/pyridine resulted in a mixture of disproportionation products; see experimental).

The asymmetric protonations with **3c** suggest a modest trend for improved enantioselectivity with the less basic enolates, as might be expected if the optimum ΔpK_a value should be relatively small. However, no trend is evident with **3e,** and the lack of any significant enantioselectivity with **3d** is problematic for an investigation of related chiral acids having varied pK_a. Other electron-withdrawing nitrogen substituents can be considered, but the preliminary results indicate that comparisons will be difficult because steric and electronic changes near the aniline nitrogen may be large enough to obscure the possible role of ΔpK_a.

An alternative approach to matching the pK_a values of chiral acid and enolate substrate was pursued, based on variations in the aniline ring substituent in **1**. The pK_a values of the series of chiral diamines **1** can be estimated from the known pK_a's of the parent anilines (Table 1) by comparison with the value determined by Bordwell and Satish for the commercially available **1b**. The measured pK_a for **1b** is 27.7 (DMSO conditions),[8a] while the parent *p*-chloroaniline **8b** has a DMSO pK_a of 29.4.[8b] The difference of 1.7 pK_a units reflects the net contribution by the *N*-methyl group and the tetrahydroisoquinoline subunit. We will assume that the same correction of 1.7 pK_a units can be applied to the other anilines **8** as an approximate way to estimate the pK_a values of the structurally related diamines **1**. Thus, diamines having a range of DMSO pK_a values from ca. 19−29 would be available for study as the aromatic substituent in **1** is modified from strong acceptors such as X = NO_2 (**1f**) to the unsubstituted aniline **1a** (X = H). Because the variable substituent X is relatively far from the aniline nitrogen, the asymmetric protonation of enolates would encounter little if any change in steric effects as the pK_a is changed. Electronic factors would also be less than in the examples **3c** or **3d** (where the nitrogen substituents were altered), although a trend toward sp^2 hybridized nitrogen might be expected in **1f** and perhaps also in **1d** due to delocalization involving the nitrogen electron pair and the para acceptor group.

Table 1. pKa(DMSO) of *p*-Substituted Anilines 8 and Chiral Acids 1

p-substituent X	aniline **8** pK_a(DMSO)[a]	chiral acid **1** pK_a(DMSO)	chiral acid **1**
H	30.7	29.0[b]	**1a**
Cl	29.4	27.7[c]	**1b**
CF_3	27.0	25.3[b]	**1c**
CO_2Et	26.5[d]	24.8[b]	**1d**
Ts	24.9[e]	23.3[b]	**1e**
NO_2	20.9	19.3[b]	**1f**

[a] pK_a(DMSO) from ref 8b unless noted otherwise. [b] Estimated as described in text. [c] Reference 1b. [d] Calculated from $\sigma^-_p = 0.74$ and $\rho = 5.67$ using the Hammett equation, $pK_{a\,p-CO_2R} - pK_{a\,p-H} = \Delta pK_a = \rho\sigma_p$ according to ref 9. [e] The pK_a value for phenylsulfonyl is listed as an estimate for toluenesulfonyl.

The synthesis of the chiral diamines (Scheme 2) began with the commercially available **1b**. Conversion to the aminal **9** was easily carried out using isobutyraldehyde in the presence of acetic acid. With the N−H bonds temporarily blocked, **9** could be transformed into the Grignard reagent **10**. Forcing conditions were necessary, but mechanically activated magnesium in refluxing THF proved sufficient for essentially complete chlorine−magnesium exchange.[10] Upon quenching the Grignard solution with aqueous ammonium chloride, **11** was recovered in high yield. Alternatively, electrophilic trapping with diethyl carbonate[11a] or *p*-toluenesulfonyl fluoride[11b] gave the ester **12** or the sulfone **13** in 71% and 85% yield, respectively. Hydrolytic cleavage of the aminals **11**, **12**, or **13** with dilute HCl gave the desired diamines **1a**, **1d**, and **1e**. The unsubstituted diamine **1a**

(7) (a) Bordwell, F. G.; Hughes, D. L. *J. Am. Chem. Soc.* **1985**, *107*, 4737. (b) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. (c) Bordwell, F. G.; Liu, W.-Z. *J. Phys. Org. Chem.* **1998**, *11*, 397.

(8) (a) The pK_a value was previously reported in ref 3. (b) Bordwell, F. G.; Algrim, D. J. *J. Am. Chem. Soc.* **1988**, *110*, 2964.

(9) Hoefnagel, A. J.; Monshouwer, J. C.; Snorn, E. C. G.; Wepster, B. M. *J. Am. Chem. Soc.* **1973**, *95*, 5350. For a review of Hammett parameters, see: Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

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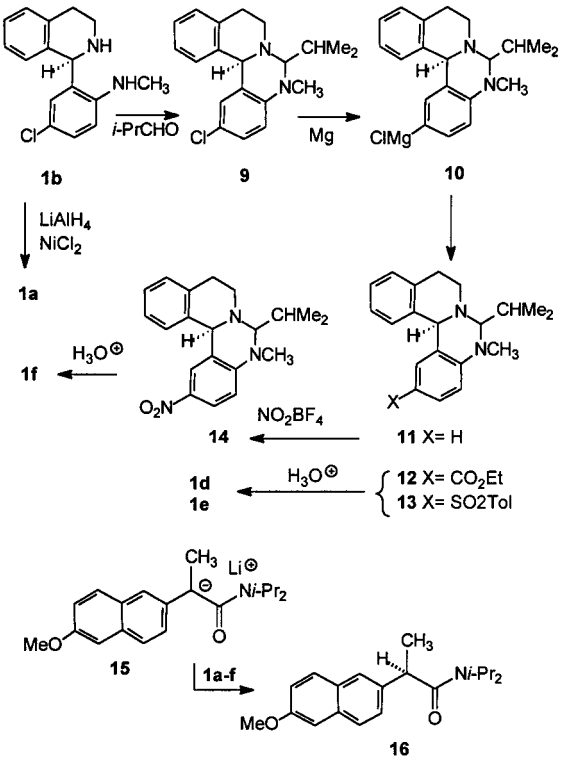
Scheme 2



was also prepared by a nickel-catalyzed dechlorination with $LiAlH_4$.

For access to the more acidic *p*-nitro analogue **1f**, the direct nitration of **1a** was briefly explored. However, this reaction proved difficult to control for the desired regioisomer. Better results were obtained by nitrating the aminal **11** with nitronium tetrafluoroborate at −40 °C. This gave the mono-nitro derivative **14**, and hydrolysis to **1f** proceeded without complications (55% overall yield). The site of nitration was confirmed by X-ray crystallography.

The trifluoromethyl diamine **1c** was prepared as previously described via a Bischler−Napieralski cyclization sequence, followed by reduction and resolution.[12] The resolution requires multiple crystallizations of the tartrate salt,[12b] so the quantity of **1c** (>99% ee) obtained by this method was sufficient only for a few test experiments involving enolate protonation.

Because the estimated pK_a values for several of the diamines **1** should be relatively high (pK_a = ca. 25 or above for **1a**−**1d**), the asymmetric protonation studies began with the strongly basic amide enolate **15**. Conversion to amide **16** was carried out by treatment with **1** at −78 °C, followed by warming to 0 °C and quenching with dilute NH_4Cl. The amide was recovered, and the enantioselectivity was established by HPLC assay using a chiral stationary phase (HPLC/CSP). As summarized in Table 2, the original lead compound **1b** was the most highly enantioselective proton donor. Lower enantioselectivity resulted for diamines **1c**−**f**, and the most acidic *p*-nitro derivative **1f** gave racemic product. This was also the fastest reaction in terms of discharge of the orange−red enolate color (seconds at − 78 °C). A smaller decrease in enantioselectivity was observed when the pK_a value of the chiral acid was increased (**1a**), and complete fading of the enolate color was slower in this experiment compared to the others.

Table 2. Asymmetric Protonation of Amide Enolate 15 with 1

chiral acid	X	pK_a(DMSO)	ee (%)
1a	H	29.0[a]	90
1b	Cl	27.7[b]	97[b]
1c	CF_3	25.3[a]	93
1d	CO_2Et	24.8[a]	40
1e	Ts	23.3[a]	37
1f	NO_2	19.3[a]	0

[a] Estimated; see Table 1 discussion. [b] Reference 1b.

The DMSO pK_a of the amide **16** is too high for accurate measurement, but a value of ca. 31 has been estimated.[13] Thus, the optimum chiral acid **1b** among the available *p*-substituted anilines **1** has a ΔpK_a value = ca. 3 compared to the protonated carbonyl product **16**. Reasonably high enantioselectivities are also obtained with **1a** and with **1c**, suggesting that ΔpK_a can be in the range of 2−5. Of course, the measured pK_a values are strictly relevant only to DMSO conditions, while the protonation experiments were conducted in THF (ion pair conditions). The ion pair pK_a's for the chiral acids and for the carbonyl product would probably be five or more pK_a units smaller in THF than in DMSO.[14] On the other hand, the ΔpK_a values should vary relatively little, assuming similar solvent effects within a family of related structures. If this is correct, then it may be possible to anticipate the best chiral acid among the derivatives of **1** for a given enolate by evaluating estimated DMSO pK_a values.

Among the enolates considered earlier, the lactone-derived **7** should have the lowest pK_a value, previously estimated as pK_a = ca. 20 in DMSO.[3] According to the pK_a's in Table 2, only the most acidic *p*-nitro aniline **1f** would have any chance for effecting the direct proton transfer to **7**. However, treatment of **7** with **1f** gave racemic lactone product. Since the estimated ΔpK_a = ca. 1, this is not a surprising result. Proton transfer should be reversible, and racemization could occur if the initial protonation event is enantioselective. More strongly basic enolates are needed to match the chiral aniline series **1** with ΔpK_a in the range of 3−5 where optimum enantioselectivity is expected.

We could find no pK_a data for enolates such as **4**, **5**, or **6**, but it is possible that **5** would be the most strongly basic among these substrates due to electron repulsion in the dianion (more accurately, the dilithiated amide). This enolate was therefore studied in asymmetric protonation experiments using several of the more readily available anilines **1**. As shown in Table 3 (entries 1−4), the optimum chiral acid proved to be the *p*-toluenesulfonyl derivative **1e** (85% ee). The less acidic analogues **1d** and **1b** gave similar, but lower, enantioselectivities, while the most acidic **1f** afforded racemic methyl *N*-benzoylalaninate. Structural modifications in the nitrogen substituent or the ester O-alkyl group in alanine-derived

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(13) The pK_a = ca. 31 for **16** is reported in ref 3 based on measurements by F. G. Bordwell and A. V. Satish.

(14) Buncel, E.; Menon, B. *J. Org. Chem.* **1979**, *44*, 317. Olmstead, W. N.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3299. Streitwieser, A., Jr. *Acc. Chem. Res.* **1984**, *17*, 353. Kaufman, M. J.; Gronert, S.; Bors, D. A.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 602. Kaufman, M. J.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 6092. Krom, J. A.; Petty, J. T.; Streitwieser, A. *J. Am. Chem. Soc.* **1993**, *115*, 8024. Fachetti, A.; Streitwieser, A. *J. Org. Chem.* **1999**, *64*, 2281.

Table 3. Asymmetric Protonation of Dilithiated Amino Acid Esters 5

entry	R_1	R_2	R_3	chiral acid	ee (%) (*S*)
1 (**5a**)	C_6H_5	CH_3	CH_3	**1b**	73
2 (**5a**)	C_6H_5	CH_3	CH_3	**1d**	71
3 (**5a**)	C_6H_5	CH_3	CH_3	**1e**	85
4 (**5a**)	C_6H_5	CH_3	CH_3	**1f**	0
5 (**5b**)	OBn	CH_3	CH_3	**1e**	50
6 (**5c**)	mesityl	CH_3	CH_3	**1e**	78
7 (**5d**)	α-naphthyl	CH_3	CH_3	**1e**	83
8 (**5e**)	C_6H_5	CH_3	Et	**1e**	81
9 (**5f**)	C_6H_5	CH_3	*t*-Bu	**1e**	47
10 (**5g**)	C_6H_5	Et	CH_3	**1e**	80
11 (**5h**)	C_6H_5	Bn	CH_3	**1e**	65

enolates resulted in lower enantioselectivity (entries 5−9). Other amino acid environments were not explored in detail, but promising enantioselectivity was observed in two cases using the optimum proton donor **1e** (entries 10, 11).

Based on the DMSO pK_a estimate for **1e** (23.3) and an optimum ΔpK_a = ca. 2−4, the pK_a for singly protonated **5** might correspond to a range of 25−27. If the lithiated amido subunit C(OLi)═N in **5** is treated as an unsaturated substituent, then the closest literature analogy having a known pK_a value could be ethyl phenylacetate ($PhCH_2CO_2Et$; DMSO pK_a = 22.6), with phenyl as the unsaturated group.[7b] Evidently, C(OLi)═N is not as effective as phenyl in stabilizing the enolate, but there is some net stabilization, given that ethyl acetate has a pK_a of ca. 30.[15]

One final series of experiments was performed using enolate **4a** as the substrate and the most important chiral acids **1b** and **1e**. Racemic products resulted in each case. Modest enantioselectivities in the range of 37−50% ee were obtained with the analogous enolate **4b** as the substrate and with **1e** as the chiral proton source, but **1b** gave 16% ee under similar conditions. These results were not deemed sufficiently promising to warrant a more detailed investigation.

Summary

The data summarized in Table 2 provide some support for the notion that asymmetric protonation of the amide enolate **15** is optimal when ΔpK_a (chiral acid vs **16**) is ca. 3. In this range of ΔpK_a, the proton transfer process is essentially complete and irreversible on the time scale of the protonation experiment, as required to minimize the formation of racemic product by enolate equilibration. The knowledge of DMSO pK_a's was helpful in the selection of chiral acids for other purposes, as in the amino acid enolate protonations summarized in Table 3, but it was by no means sufficient. Entries 1 and 2 differ less than might have been expected if ΔpK_a is the dominant factor, and other variables must play a role in the observed enantioselectivies. A similar conclusion can be made by comparing some of the enantioselectivities in Table 2. Thus, the behavior of **1d** (*p*-ethoxycarbonyl) and **1c** (*p*-trifluoromethyl) is rather different even though the difference in effective pK_a's is probably small compared to the approximation inherent in extending the numbers from DMSO to THF solution. Furthermore, the absence of any enantioselectivity in the case of **1f** in Table 2 as well as in Table 3 suggests that pK_a is not the only reason **1f** is ineffective. A hybridization change at aniline nitrogen due to delocalization with the *p*-nitro group is one possible explanation for the large difference between **1f** and the other chiral diamines.[16] A similar effect may be the reason the *p*-ethoxycarbonyl example **1d** differs so much from **1c**. The hybridization argument could also explain why **3d** is an ineffective chiral acid, but there are other variables to consider in this case. In any event, the pK_a trends in Table 2 support a qualitative correlation between enantioselectivity and the DMSO-based ΔpK_a of the proton donor and the carbonyl product, but enantioselectivity with a given enolate also depends on other factors.

The results of Table 3 describe the best asymmetric protonations for an alanine-derived substrate reported to date. However, more effort will be needed to obtain high enantioselectivity and broader substrate tolerance.[5] The latter problem remains a difficult challenge for the asymmetric protonation of enolates. Mechanistic issues also remain to be clarified. Additional experimentation will be required to probe details of the proton transfer process, and it would be premature to propose transition state models or to invoke direct proton transfer from aniline nitrogen to enolate carbon until further evidence is available.

Experimental

General. HPLC analysis was performed on a Gilson system using chiral stationary phases with detection by UV. All air- and/or moisture-sensitive reactions were run under an atmosphere of nitrogen in oven- or flame-dried glassware. Materials were purified as follows. Tetrahydrofuran and diethyl ether were freshly distilled from sodium benzophenone ketyl under N_2. Organolithium reagents were titrated using the menthol/phenanthroline procedure.

Chiral Acids. Diamine derivatives **1c**[12b] and **3a**−**3d**[6] are available in >99% ee as previously described. Diamine **1b** has also been reported,[12a] but the following procedure was used to ensure high enantiomer purity. The commercially available (−)-1-[5′-chloro-2′-(methylamino)-phenyl]-1,2,3,4-tetrahydroisoquinoline (−) tartrate (5.0 g, 14.4 mmol, Aldrich) was refluxed in 800 mL methanol for 1 h. After filtration of the hot solution, the filtrate was allowed to cool to room temperature followed by cooling to −20 °C overnight. Filtration yielded a cake of white solid. The free diamine was isolated by partitioning the tartrate salt between 40 mL ether and a solution of potassium hydroxide (2.4 g, 43.0 mmol) in 40 mL water with vigorous stirring. After dissolution was complete (2−3 h), the aqueous layer was washed with ether (40 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated to a solid 2.7 g (70%). Pure **1b** was obtained by recrystallization from ether (mp 99−99.5 °C; lit.[12a] mp 98−99 °C).

***(S)*-1-(2-*N*,*N*-Dimethylsulfamoylamino)phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3e).** Conversion of **3a** to the *N*-benzyloxycarbonyl derivative at the secondary nitrogen has been reported.[6] To a solution of the *N*-Cbz protected diamine (2.5 g) in pyridine (100 mL, distilled from CaH_2) was added *N*,*N*-dimethylsulfamoyl chloride (Acros, 6.4 mL, 59.7 mmol) and the mixture was stirred at room temperature for 48 h. Pyridine was evaporated (aspirator, below 40 °C), and the oily residue was dissolved in $CHCl_3$ (150 mL), washed with 1 N HCl (3 × 30 mL), water, and brine, and dried (Na_2SO_4). After filtration and solvent removal (aspirator), the resulting oil was purified by flash column

(15) There is disagreement on the pK_a(DMSO) of ethyl acetate (a) pK_a(DMSO) = ca. 30: Bordwell, F. G.; Branca, J. C.; Bares, J. E.; Filler, R. *J. Org. Chem.* **1988**, *53*, 780. (b) pK_a(DMSO) = 27.45: Arnett, E. M.; Harrelson, J. A., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 809.

(16) Delocalization in the *p*-nitroaniline **1f** is consistent with planarization of the *N*-methyl bond and the adjacent aromatic carbons (1.3° dihedral angle; see Supporting Information).

chromatography (column size, 150 × 50 mm) with petroleum ether−EtOAc 5:2 (fractions 1−45, 50 mL ea), and then petroleum ether−EtOAc 1:1 (fractions 46−68, 50 mL ea). Fractions 9−16 contained solid $Me_2NSO_2NMe_2$ (^{1}H NMR: single peak at 2.82 ppm in $CDCl_3$), 1.03 g. Fractions 19−36 gave a mixture of starting material and product in a ratio of 3:7 as a colorless oil that was used in the deprotection step below. Fractions 41−59 contained 1.11 g of material having no *N*-methyl signals in the ^{1}H NMR spectrum, consistent with replacement of a NMe_2 fragment by a second diamine molecule.

The crude oil from fractions 19−36 (1.03 g) was dissolved in 30 mL of glacial acetic acid and 10% Pd−C (400 mg) was added. The reaction was stirred under H_2 at room temperature. After 8 h, additional 10% Pd−C was added (200 mg) and hydrogenolysis was continued for 6 h. The reaction mixture was filtered through Celite with methanol rinsing, and the solvent was removed (aspirator, < 30 °C). The residue was dissolved in water (10 mL), and the solution was basified by slow addition of NH_4OH. The white crystalline precipitate formed was filtered, dried in vacuo (ca. 1 mmHg) over P_2O_5, and recrystallized twice from EtOAc−hexane to give 660 mg of crystalline sulfonamide **3e** containing ca. 10% of diamine **3a** (^{1}H NMR assay). Two recrystallizations yielded pure sulfonamide **3e** (560 mg, 24% overall); analytical TLC on silica gel, 1:1 hexane/EtOAc, R_f = 0.17; analytical HPLC, CHIRALCEL OD (60:40 hexane/2-propanol, 0.6 mL/min) t_R = 14.5 min (*S*) isomer); by comparison with a racemic sample, the (*R*) isomer elutes at 18.8 min. **3e**: mp 156 °C, dec, colorless needles. $[\alpha]_D$= +8.1 (*c* = 1, $CHCl_3$). Anal. Calcd: C, 58.28; H, 6.45; N, 10.73, S, 8.19. Found: C, 58.23; H, 6.40; N, 10.62; S, 8.11. IR ($CDCl_3$ film, cm^{-1}) 3325, N−H; 1330, SO_2N; NMR ($CDCl_3$, ppm) δ 7.6−6.95 (4 H, m), 6.62 (1 H, s), 6.22 (1 H, s), 5.11 (1 H, s), 3.84 (3 H, s), 3.60 (1 H, s), 3.39−3.28 (1 H, m), 3.19−3.10 (2 H, m), 2.80−2.68 (1 H, m), 2.39 (6 H, s).

(−)-1-[2′-(Methylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline (1a). To a suspension of anhydrous $NiCl_2$ (1.59 g, 12.3 mmol) and **1b** (1.16 g, 4.10 mmol) in 50 mL dry THF at −40 °C under N_2 were slowly added $LiAlH_4$ in THF (Aldrich, 1.0 M; 12.3 mL, 12.3 mmol), and the mixture was stirred for 10 min at −40 °C. The reaction mixture was warmed to RT gradually and stirred for 48 h at RT. The resulting black mixture was quenched with saturated Na_2SO_4 (50 mL), the inorganic salts were removed by filtration through a Celite pad, the filter was washed well with THF, and the THF was evaporated (aspirator) to give a yellow oil. The oil was redissolved in ether, dried (Na_2SO_4) and concentrated, and the crude yellow oil was purified by flash column chromatography (silica gel, 2 × 15 cm) (gradient elution; 30% EtOAc in hexane with 1% NEt_3 to 50% EtOAc in hexane with 1% NEt_3) to give a yellow oil containing some solid (0.70 g, 71%). The yellow oil was crystallized from hexane to give a pale-yellow powder, analytical TLC on silica gel, 30% EtOAc in hexane with 1% NEt_3, R_f = 0.21. Pure material was obtained by recrystallization from hexane, mp 77−79 °C. Molecular ion calcd for $C_{16}H_{18}N_2$: 238.14705; found *m*/*e* = 238.1470, error = 0 ppm; base peak = 132 amu; IR (neat, cm^{-1}) 3310, N−H; 1586, C=C; 200 MHz NMR (acetone-d_6, ppm) δ 7.25−6.80 (5 H, m), 6.71 (1 H, d, *J* = 7.7 Hz), 6.58 (1 H, dd, *J* = 8.0, 1.2 Hz), 6.54 (1 H, d, *J* = 7.7 Hz), 6.25 (1 H, br s), 5.03 (1 H, s), 3.3−3.13 (1 H, m), 3.06−2.82 (2 H, M), 2.8−2.6 (1 H, m), 2.63 (3 H, s). ^{13}C NMR (68 MHz, {H}, $CDCl_3$, ppm) δ 148.5, 137.4, 134.8, 130.6, 128.7, 128.5, 126.7, 126.3, 126.1, 125.6, 115.4, 110.3, 61.64, 42.5, 30.1, 29.4.

1-[5′-Chloro-2′-(methylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline Isobutylidene Aminal, 9. To a solution of **1b** (2.86 g, 10.50 mmol) in 180 mL of MeOH was added isobutyraldehyde (1.9 mL, 21 mmol, 2 equiv) and catalytic acetic acid (0.1 mL), and the mixture was stirred at room temperature for 2 h. After removal of solvent (aspirator), the residue was purified by plug filtration chromatography on EM silica gel 60, 1:4 EtOAc/hexane 1% triethylamine eluent to yield 3.6 g of crude solid. Pure material was obtained by crystallization from ether/hexane (crop 1, 1.98 g; crop 2, 0.94 g, 85%), mp 114.5−115.5 °C. Analytical TLC on EM silica gel 60, 1:9 EtOAc/hexane 1% triethylamine, R_f = 0.60. Molecular ion calcd for $C_{20}H_{23}ClN_2$: 326.15506; found *m*/*e* = 326.1541, error = 3 ppm; base peak = 283 amu; IR (KBr, cm^{-1}) 3058, =C−H; 2840−2975, C−H; 270 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 7.30−7.13 (4 H, m), 7.04 (1 H, dd, *J* = 8.8, 2.5 Hz), 6.86 (1 H, dd, *J* = 2.5, 1.2 Hz), 6.44 (1 H, d, *J* = 8.6 Hz), 5.11 (1 H, s), 3.37 (1 H, d, *J* = 9.6 Hz), 3.20−3.06 (1 H, m), 3.06 (3 H, s), 2.80−2.60 (3 H, m), 2.15−1.96 (1 H, m), 1.02 (3 H, d, *J* = 6.9 Hz), 0.97 (3 H, d, *J* = 6.6 Hz). ^{13}C NMR (68 MHz, {H}, DEPT135, $CDCl_3$, ppm) δ 141.3 s, 134.8 s, 134.6 s, 129.9 d, 129.5 d, 127.8 d, 127.4 d, 127.0 d, 125.0 d, 121.9 s, 120.0 s, 110.9 d, 87.8 d, 53.9 d, 46.1 t, 40.9 d, 33.6 q, 28.9 t, 19.9 q, 18.8 q.

1-[2′-(Methylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline Isobutylidene Aminal (11). A dry 50 mL flask with condenser, containing a 1" stir bar and magnesium turnings (600 mg, 25 mmol, Baker and Adamson) was flame dried under nitrogen flush. Mechanical activation (dry stirring) of the magnesium turnings was done for at least 5 h following the literature precedent.[10]

To another flask was added the aminal **9** (201 mg, 0.62 mmol). The solid was dissolved in 2 mL THF and transferred via cannula into the activated magnesium, followed by rinsing with THF (2 × 1 mL). Then 1,2-dibromoethane (0.1 mL, 1.1 mmol) was added, and after bubble evolution was evident, the solution was heated to reflux. After 15 h, the Grignard solution containing **10** was cooled to room temperature and 10 mL saturated NH_4Cl was added. After filtration through Celite, the layers were separated and the aqueous phase was extracted with ether (2 × 30 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and evaporated (aspirator) to afford **11,** 190 mg (100%), as an oil. Analytical TLC on EM silica gel 60, 7:3 hexane/EtOAc, R_f = 0.64. Molecular ion calcd for $C_{20}H_{24}N_2$: 292.1940; found *m*/*e* = 292.1932, error = 3 ppm; base peak = 249 amu; IR (neat, cm^{-1}) 2908, =C−H; 300 MHz NMR ($CDCl_3$, ppm) δ 7.32−7.08 (5 H, m), 6.92 (1 H, dt, *J* = 7.4, 1.2 Hz), 6.55−6.49 (2 H, m), 5.16 (1 H, s), 3.39 (1 H, d, *J* = 9.2 Hz), 3.18−3.06 (1 H, m), 3.09 (3 H, s), 2.86−2.72 (1 H, m), 2.68−2.62 (2 H, m), 2.10 (1 H, d sept, *J* = 9.2, 6.6 Hz), 1.03 (3 H, d, *J* = 6.6 Hz), 0.98 (3 H, d, *J* = 6.6 Hz).

1-[5′-Carboethoxy-2′-(methylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline Isobutylidene Aminal (12). The Grignard reagent **10** was prepared as described above from magnesium turnings (600 mg, 25 mmol) and aminal **9** (255 mg, 0.78 mmol). After 15 h, the stark black Grignard solution was transferred via cannula into diethyl carbonate[11a] (0.280 mL, 2.4 mmol), stirred for 15 h, and then quenched with saturated NH_4Cl. The organic layer was separated and washed with brine. The combined aqueous extracts were basified to pH 9 with 1 M NaOH and extracted with ether. All organic extracts were combined, dried ($MgSO_4$), filtered, and evaporated (aspirator). The residue was purified by flash chromatography on EM silica gel 60 (14 × 1 cm), 3:17 EtOAc/hexane 1% triethylamine eluent, 5 mL fractions; fractions 6−12, 251 mg of **12** (88%); analytical TLC on EM silica gel 60, 1:9 EtOAc/hexane 1% triethylamine, Rf = 0.28. Pure material was obtained by crystallization from ethanol, mp 134.8−135.0 °C. Molecular ion calcd for $C_{23}H_{28}N_2O_2$: 364.21509; found *m*/*e* = 364.2165, error = 4 ppm; base peak = 321 amu; IR (KBr, cm^{-1}) 1697, C=O; 300 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 7.80 (1 H, dd, *J* = 8.4, 2.1 Hz), 7.66 (1 H, br s), 7.37 (1 H, br d, *J* = 7.4 Hz), 7.33−7.19 (2 H, m), 7.13 (1 H, br d, *J* = 7.4 Hz), 6.51 (1 H, d, *J* = 8.6 Hz), 5.17 (1 H, s), 4.27−4.16 (2 H, m), 3.46 (1 H, d, *J* = 9.7 Hz), 3.20−3.05 (1 H, m), 3.12 (3 H, s), 2.79−2.61 (3 H, m), 2.17−2.04 (1 H, m), 1.28 (3 H, t, *J* = 7.2 Hz), 1.04 (3 H, d, *J* = 6.6 Hz), 1.00 (3 H, d, *J* = 6.6 Hz).

1-[5′-Toluenesulfonyl-2′-(methylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline Isobutylidene aminal (13). The Grignard solution containing **10** was prepared as described above from magnesium turnings (715 mg, 30 mmol) and aminal **9** (1.24 g, 3.8 mmol). After 9 h, the mixture was cooled to 0 °C and *p*-toluenesulfonyl fluoride[11b] (741 mg, 4.2 mmol, 1.1 equiv, Aldrich, purity 98%) was added as a solution in 10 mL THF. The reaction was allowed to warm to room temperature and was stirred for 13 h. After the addition of 10 mL

water, the biphasic solution was extracted with ether (4 × 40 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated (aspirator) to a foam (1.73 g). The residue was purified by flash chromatography on EM silica gel 60 (7 × 4 cm) 7:3 (100 mL) to 1:1 hexane/EtOAc eluent (10 mL fractions; fractions 2−3, 107 mg **11**, 10%; fractions 9−17, 1.43 g **13**, 85%); analytical TLC on EM silica gel 60, 7:3 hexane/EtOAc, R_f = 0.27. Molecular ion calcd for $C_{27}H_{30}N_2O_2S$: 446.20285; found *m/e* = 446.2005, error = 5 ppm; base peak = 405 amu; IR ($CHCl_3$, cm^{-1}) 1592, C=C; 300 MHz NMR ($CDCl_3$, ppm) δ 7.66 (2 H, d, J = 8.4 Hz), 7.62 (1 H, dd, J = 9.1, 2.3 Hz), 7.44 (1 H, dd, J = 2.3, 1.2 Hz), 7.34−7.16 (5 H, m), 7.12 (1 H, br d, J = 7.4 Hz), 6.51 (1 H, d, J = 8.8 Hz), 5.10 (1 H, s), 3.45 (1 H, d, J = 9.3 Hz), 3.15−3.05 (1 H, m), 3.08 (3 H, s), 2.68−2.58 (3 H, m), 2.34 (3 H, s), 2.14−1.95 (1 H, m), 1.01 (3 H, d, J = 6.8 Hz), 0.97 (3 H, d, J = 6.6 Hz).

1-[5′-Carboethoxy-2′-(methylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline (1d). A 250 mL flask was charged with **12** (1.56 g, 4.29 mmol) and 150 mL of 10% HCl and the solution was heated to 60 °C under a nitrogen stream. After 3 h, the mixture was cooled to room temperature, diluted with 60 mL of ether, neutralized with saturated sodium bicarbonate, and basified to pH 9 with 1 M NaOH. The layers were separated and the aqueous layer extracted (3 × 60 mL) with ether. The combined ethereal extracts were dried ($MgSO_4$), filtered, and evaporated (aspirator) to give **1d** (1.46 g) as a yellow oil. The residue was purified by flash chromatography on EM silica gel 60 (15 × 4 cm), 1:4 acetone/hexane 5% triethylamine eluent (15 mL fractions); fractions 10−26, 1.09 g **1d**, 82%; analytical TLC on EM silica gel 60, 1:4 EtOAc/hexane 5% triethylamine, R_f = 0.12. Molecular ion calcd for $C_{19}H_{22}N_2O_2$: 310.16815; found *m/e* = 310.1683, error = 0 ppm; IR ($CHCl_3$, cm^{-1}) 1692, C=O; 3325, N−H; 300 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 7.91 (1 H, dd, J = 8.6, 1.9 Hz), 7.75 (1 H, d, J = 1.9 Hz), 7.20−7.05 (2 H, m), 7.05−6.92 (1 H, m), 6.76 (1 H, br d, J = 8.0 Hz), 6.55 (1 H, br s), 6.52 (1 H, d, J = 8.7 Hz), 5.10 (1 H, s), 4.37−4.25 (2 H, m), 3.35−3.20 (1 H, m), 3.15−3.00 (2 H, m), 2.85−2.60 (1 H, m), 2.69 (3 H, br d, J = 3.1 Hz), 2.02 (1 H, br s), 1.36 (3 H, t, J = 7.1 Hz).

1-[5′-Toluenesulfonyl-2′-(methylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline (1e). To **13** (437 mg, 0.98 mmol) was added 50 mL of 10% HCl and the mixture was heated to 60 °C under a nitrogen stream for 3 h. After cooling to room temperature, the solution was neutralized with saturated Na_2CO_3 and taken to pH 10 with 1M NaOH. After extraction with CH_2Cl_2 (3 × 15 mL), the combined organic extracts were dried ($MgSO_4$) and evaporated (aspirator) to give a yellow oil. The residue was purified by flash chromatography on EM silica gel 60 (12 × 1.5 cm) 1:1 hexane/EtOAc eluent (10 mL fractions); fractions 8−13, 345 mg **1e**, 90%; analytical TLC on EM silica gel 60, 1:1 hexane/EtOAc, R_f = 0.32. Molecular ion calcd for $C_{23}H_{24}N_2O_2S$: 392.1559; found *m/e* = 392.1542, error = 4 ppm; IR (neat, cm^{-1}) 3323, N−H; 1146, SO_2; 300 MHz NMR ($CDCl_3$, ppm) δ 7.78−7.70 (3 H, m), 7.54 (1 H, d, J = 2.2 Hz), 7.25 (2 H, d, J = 8.1 Hz), 7.20−7.10 (2 H, m), 6.98 (1 H, td, J = 7.0, 2.6 Hz), 6.72 (1 H, br s), 6.64 (1 H, d, J = 7.7 Hz), 6.53 (1 H, d, J = 8.8 Hz), 5.07 (1 H, s), 3.28−3.18 (1 H, m), 3.12−2.96 (2 H, m), 2.85−2.71 (1 H, m), 2.68 (3 H, s), 2.38 (3 H, s), 2.04 (1 H, br s).

1-[5′-Nitro-2′-(methylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline (1f). To **1a** (987 mg, 3.38 mmol) in 30 mL of acetonitrile at −40 °C was added a solution of nitronium tetrafluoroborate (497 mg, 3.21 mmol, 0.95 equiv, Aldrich) in 35 mL of acetonitrile over 1.5 h, and the mixture was stirred at this temperature for an additional 30 min. The solution was warmed to 0 °C and quenched with saturated $NaHCO_3$ solution (50 mL). The reaction was extracted with ether (3 × 50 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated (aspirator) to give an orange−black solid. To this crude residue was added 50 mL 1.5 N HCl and 50 mL THF, and the mixture was stirred for 10 h and then was heated to 55 °C under a constant nitrogen stream for 2 h. After cooling to room temperature, the reaction was neutralized with saturated Na_2CO_3 solution and extracted with ether (4 × 50 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated (aspirator) to give an orange oil. ^{1}H NMR analysis of this material indicated a small amount of dinitration product was present, so the crude residue was purified by flash chromatography on EM silica gel 60 (5 × 3 cm, fraction 8−22) with CH_2Cl_2 eluent to give 526 mg (55%) of **1f**. Analytical TLC on EM silica gel 60, CH_2Cl_2, R_f = 0.30. Pure material was obtained by crystallization from benzene/pentane (mp 172−173.5 °C, orange cubes, 454 mg). Molecular ion calcd for $C_{16}H_{17}N_3O_2$: 283.13210; found *m/e* = 283.1315, error = 2 ppm; IR (neat, cm^{-1}) 3226, N−H; 1296, NO_2; 300 MHz NMR ($CDCl_3$, ppm) δ 8.14 (1 H, dd, J = 9.2, 2.6 Hz), 7.95 (1 H, d, J = 2.6 Hz), 7.29−7.10 (3 H, m), 7.05 (1 H, td, J = 7.1, 2.4 Hz), 6.77 (1 H, d, J = 7.7 Hz), 6.50 (1 H, d, J = 9.2 Hz), 5.14 (1 H, s), 3.33−3.24 (1 H, m), 3.15−3.05 (2 H, m), 2.85−2.78 (1 H, m), 2.79 (3 H, d, J = 5.1 Hz), 2.06 (1 H, br s).

***N*-2,4,6-Trimethylbenzoylalanine Methyl Ester (5c).** To 2,4,6-trimethylbenzoic acid (733 mg, 4.46 mmol) in 10 mL CH_2Cl_2 was added oxalyl chloride (0.40 mL, 4.46 mmol) and 1 drop DMF. After 3 h, the solvents were evaporated and 15 mL CH_2Cl_2 and racemic alanine methyl ester hydrochloride (625 mg, 4.46 mmol) were added. With a room-temperature bath for cooling, triethylamine (1.55 mL, 11.2 mmol) was added dropwise over 5 min and the solution was stirred at room temperature for 1 h. After the addition of 15 mL of 1.5 N HCl, the layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with water/saturated Na_2CO_3 (1:1, 10 mL), dried ($MgSO_4$), and evaporated (aspirator) to a golden oil. The residue was purified by flash chromatography on EM silica gel 60 (14 × 1.7 cm, 10 mL, fraction 4−8, 1.06 g, 71%), 7:3 hexane/EtOAc eluent; analytical TLC on EM silica gel 60, 7:3 hexane/EtOAc, R_f = 0.26. Pure **5c** was obtained by crystallization from ethyl acetate, mp 88.5−89.5 °C. Molecular ion calcd for $C_{14}H_{19}NO_3$: 249.13650; found *m/e* = 249.1370, error = 2 ppm; base peak = 147 amu; IR (neat, cm^{-1}) 3263, N−H; 1751, C=O; 1639, C=O; 300 MHz NMR ($CDCl_3$, ppm) δ 6.84 (2 H, s), 6.18 (1 H, d, J = 7.0 Hz), 4.83 (1 H, dq, J = 7.4, 7.4 Hz), 3.78 (3 H, s), 2.29 (6 H, s), 2.27 (3 H, s), 1.51 (3 H, d, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$, ppm) δ 173.3 s, 169.9 s, 138.6 s, 134.3 d, 128.2 s, 128.2 s, 52.5 d, 47.9 q, 21.1 q, 19.0 q, 18.5 q.

***N*-1-Naphthoyl alanine methyl ester (5d).** To 1-naphthoic acid (735 mg, 4.27 mmol) in 10 mL CH_2Cl_2 and 1 drop DMF was added oxalyl chloride (0.417 mL, 4.70 mmol). After 6 h, the solvent was evaporated and the residue was dissolved in 15 mL CH_2Cl_2. After the addition of racemic alanine methyl ester hydrochloride (596 mg, 4.27 mmol, Aldrich), triethylamine (0.892 mL, 6.4 mmol) was added dropwise while cooling with a water bath. After 1 h, 15 mL 1.5 N HCl was added and extracted with CH_2Cl_2 (2 × 30 mL). The CH_2Cl_2 layers were combined and extracted with 1:1 saturated Na_2CO_3/water (10 mL) and the aqueous layer was back extracted with 10 mL CH_2Cl_2. The combined CH_2Cl_2 layers were dried ($MgSO_4$) and evaporated to a white solid (904 mg, 82%). ^{1}H NMR analysis showed the presence of 8% of an isomeric product, probably derived from 2-naphthoic acid. The residue was purified by flash chromatography on EM silica gel 60 (20 × 3 cm, 15 mL, fractions 11−15, 545 mg, 49%), 7:3 (100 mL) to 1:1 hexane/EtOAc eluent; analytical TLC on EM silica gel 60, 7:3 hexane/EtOAc, R_f = 0.21. Pure material was obtained by crystallization from ethyl acetate/hexane, mp 130.5−131.5 °C. Molecular ion calcd for $C_{15}H_{15}NO_3$: 257.10520; found *m/e* = 257.1055, error = 1 ppm; base peak = 155 amu; IR (neat, cm^{-1}) 3280, N−H; 1743, C=O; 1643, C=O; 300 MHz NMR ($CDCl_3$, ppm) δ 8.36 (1 H, d, J = 8.6 Hz), 7.95−7.86 (2 H, m), 7.67 (1 H, dd, J = 7.0, 1.1 Hz), 7.60−7.44 (3 H, m), 6.56 (1 H, d, J = 6.3 Hz), 4.93 (1 H, dq, J = 7.4, 7.4 Hz), 3.82 (3 H, s), 1.59 (3 H, d, J = 7.4 Hz).

Deracemization of Naproxen Diisopropyl Amide (16); Representative procedure for Table 2. To racemic **16**[3] (50.0 mg, 0.16 mmol) in 2 mL of THF was added *sec*-BuLi (202 μL, 0.28 mmol, 1.38 M in cyclohexane, 1.75 equiv; Aldrich, titrated using 1,10-phenanthroline as indicator with menthol as the proton donor at −78 °C in THF), and the solution was stirred at −78 °C for 1 h. After dropwise addition of the chiral diamine **1d** (99 mg, 0.32 mmol, 2 equiv) in 1.0 mL THF over

Table 4. HPLC Assay Methods

material	chiral stationary phase	conditions, retention time (flow rate = 1 mL/min)
$BnOCH(CH_3)CO_2BHT$ (**4a**)	Chiralcel OD (Daicel)	95:5 hexane/EtOH, 12 min (minor), 17 min (major)
	(*R*,*R*)-Whelk-O 1 (Regis)	99:1 hexane/IPA, 5.0 min, 5.7 min
$BnOCH(CH_3)CO_2Et$ (**4b**)	Chiralcel OJ (Daicel)	93:7 hexane/IPA, RT 9.3 min (*S*), 10.6 min (*R*)
$BzNHCH(Ph)CO_2Me$ (**6**)	Chiralcel OD (Daicel)	9:1 hexane/IPA, 11.2 min (major), 15.1 min (minor)
2-(2-naphthyl)−6,6-dimethylvalerolactone	(*R*,*R*)-Whelk-O 1 (Regis)	EtOH, 0.5 mL/min, 16 min (major), 48 min (minor)
naproxen *N*,*N*-diisopropyl amide (**16**)	Pirkle type (*S*,*S*) β gem 1 (Regis); (*R*,*R*)-Whelk-O 1 (Regis)	9:1 hexane/IPA, 6.4 min (*S*), 9.5 min (*R*)[3]; 9:1 hexane/IPA, 15 min (*S*), 25 min (*R*)

Table 5. HPLC Methods for the α-Amino Acid Derivatives

Table 3 entry/substrate	chiral stationary phase	conditions, retention time (flow rate = 1 mL/min)
entries 1−4 (**5a**)	(*R*,*R*)-Whelk-O 1 (Regis)	17/3 hexane/IPA, 20.9 min (*R*), 25.7 min (*S*)[a]
entry 5 (**5b**)	α-Burke	19/1 hexane/IPA, 14.0 min (*R*), 14.7 min (*S*)[b]
entry 6 (**5c**)	(*R*,*R*)-Whelk-O 1	17/3 hexane/IPA, 27.6 min (*R*), 34.2 min (*S*)[c]
entry 7 (**5d**)	(*R*,*R*)-Whelk-O 1	7/3 hexane/IPA, 28.3 min (*R*), 35.6 min (*S*)[c]
entry 8 (**5e**)	α-Burke	9/1 hexane/IPA, 11.5 min (*R*), 13.0 min (*S*)[c]
entry 9 (**5f**)	α-Burke	11.5/1 hexane/IPA, 7.9 min (*R*), 8.6 min (*S*)[c]
entry 10 (**5g**)	α-Burke	9/1 hexane/IPA, 11.6 min (*R*), 12.7 min (*S*)[d]
entry 11 (**5h**)	α-Burke	39/1 hexane/IPA, 31.9 min (*R*), 34.4 min (*S*)[e]

[a] Stereochemical assignment from comparison with authentic methyl *N*-benzoyl-(*R*)-alaninate. [b] Stereochemical assignment from comparison with authentic methyl *N*-Cbz-(*S*)-alaninate. [c] Stereochemical assignment by analogy to entries 1−4 based on similar structure and chromatographic behavior. [d] Stereochemical assignment by analogy to entries 1−4 and entry 11 based on similar structure and chromatographic behavior. [e] Stereochemical assignment from authentic methyl *N*-benzoyl-(*S*)-phenylalaninate.

5 min, the solution was stirred for 30 min at −78 °C, followed by warming to 0 °C over 1 h and quenching with 1 mL saturated NH_4Cl. The reaction was partitioned between 10 mL ether and 10 mL 1.5 N HCl, and the aqueous layer was washed with 10 mL ether. The combined ether extracts were dried ($MgSO_4$) and evaporated (aspirator) to afford **16** (50 mg, 100%) in >95% purity by ^1H NMR assay. After silica plug filtration (EtOAc eluent), HPLC analysis as described in Table 4 indicated 40% ee favoring the second eluting enantiomer (*R*)-**16**. In a similar experiment, the reaction mixture was quenched with a THF/saturated NH_4Cl solution at −78 °C, but the same result was obtained. To recover the **1d**, the aqueous layer above was basified to pH 10 using a 1 M NaOH solution and extracted with ether (3 × 15 mL). The combined ether layers were dried ($MgSO_4$) and evaporated to afford 75 mg (76%) **1d**.

Deracemization of 2-(2-Naphthyl)-6,6-dimethylvalerolactone. To bromomesitylene (0.105 mM, 1.75 equiv, Aldrich) in 0.5 mL THF at −78 °C was added *t*-BuLi (0.204 mM, 3.4 equiv, 1.7 M in pentane, Aldrich), and the mixture was stirred for 30 min with formation of a white precipitate. In a separate flask, racemic 2-(2-naphthyl-6,6-dimethylvalerolactone was dissolved in 0.5 mL THF and added via cannula to the mesityllithium, followed by rinsing with an additional 0.5 mL THF, to afford the bright-yellow enolate **7**. After stirring for 1 h, a solution of sulfonamide **3e**[6] in THF (0.5 mL) was added over 5 min via syringe followed by a 0.5 mL THF rinse. The enolate color faded as **3e** was added, and a colorless mixture was obtained when addition was complete. The reaction was stirred for 30 min at −78 °C, allowed to warm to −20 °C over 45 min, and quenched with saturated NH_4Cl (1 mL). Partitioning between 5 mL 1 N HCl and 10 mL ether produced an oil, insoluble both in ether and water (HCl salt of **3e**). After separation of the ether layer, the oil and aqueous layer were washed with 10 mL ether. The combined ether extracts were dried ($MgSO_4$) and evaporated (aspirator) to afford >95% of a material contaminated with mesitylene residue. The enantiomeric excess (58% ee) was determined by HPLC (see Table 4).

Deracemization of Amino Acid Derivatives; Representative Procedure for Table 3. The procedure for the deracemization of **5a**[17a] is shown as an example. The other amino acid substrates for Table 3 including entry 5 (**5b**; *N*-Cbz methyl alaninate),[17b] entry 6 (**5c**; methyl *N*-mesitoylalaninate),[17c] entry 7 (**5d**; methyl *N*-α-naphthoylalaninate), entry 8 (**5e**; ethyl *N*-benzoylalaninate),[17d] entry 9 (**5f**; *tert*-butyl *N*-benzoylalaninate),[17e] entry 10 (**5g**; methyl α-benzamidobutyrate),[17f] and entry 11 (**5g**; methyl *N*-benzoylphenylalaninate)[17g] were deracemized by the same method; see Table 5.

To bromomesitylene (55 μL, 0.359 mmol, 2.5 equiv, Aldrich) in 0.5 mL THF at −78 °C was added *t*-BuLi (391 μL, 0.704 mmol, 4.9 mmol, 1.80 M in pentane, Aldrich), and the solution was stirred for 30 min with concomitant formation of a white precipitate. In a separate flask, **5a** (29 mg, 0.14 mmol) was dissolved in 0.5 mL THF and added via cannula to the mesityl−Li. The flask was rinsed with an additional 0.5 mL THF (added by syringe and then added via cannula to the mesityl−Li solution. After the solution was stirred for 1 h, **1e** (1.25 mL of a 0.35 M solution in THF, 0.44 mmol, 173 mg) was added over 5 min and the solution was stirred for 30 min at −78 °C, followed by warming to −20 °C over 20 min. The reaction was quenched with 1 mL saturated NH_4Cl and partitioned between 10 mL 1.5 N HCl and 10 mL ether, which produced an insoluble orange oil that crystallized on standing. After separation of the ether layer, the orange crystals (or oil) and aqueous layer were washed with 10 mL ether. The combined ether extracts were dried ($MgSO_4$) and evaporated (aspirator) to afford 29 mg of material that was greater than 90% **5a** by ^1H NMR assay and contained less than 10% residual mesitylene. HPLC analysis was conducted as shown in Table 2 to afford a 7.5:92.5 ratio of peaks for the (*R*) and (*S*) enantiomers (85% ee). To recover **1e**, the aqueous layer and the orange crystals (or oil) (dissolved in THF) were basified to pH 10 with NaOH solution and extracted with ether (2 × 20 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated (aspirator) to give 176 mg of a golden foam (**1e**, >95%).

Deracemization of Lactates; Representative Procedure. The procedure for the deracemization of ethyl *O*-benzyl lactate **4b**[18] is given as a representative example. The BHT lactate ester **4a**[19] was deracemized by a similar method, but

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with *sec*-butyllithium as the base. To hexamethyldisilazane (63.2 μL, 0.30 mmol, 2.0 equiv, Aldrich) in 0.5 mL THF at −20 °C was added dropwise *n*-BuLi (187 μL, 0.30 mmol, 2.0 equiv, Aldrich), and the solution was stirred for 20 min. After cooling this solution to −78 °C, **4b** was added (0.81 mL of a 0.19 M solution in THF, 35 mg, 0.15 mmol) and the resulting solution was warmed to −40 °C for 2 h. After cooling to −78 °C, **1e** (0.85 mL of a 0.48M solution in THF, 161 mg, 0.41 mmol) was added and the solution was stirred for 30 min at this temperature. After warming to −20 °C over 30 min, 1 mL saturated NH_4Cl was added. The resulting biphasic solution was partitioned between 10 mL ether and 10 mL 1.5 N HCl, and the aqueous layer was washed with 10 mL ether. The combined ether layers were dried ($MgSO_4$) and evaporated to give 30 mg (85%) ethyl *O*-benzyl lactate. HPLC analysis was conducted as in Table 4 to afford 45% ee favoring the second eluting enantiomer (*R*).

HPLC Methods, General. Standard procedure for the HPLC analyses included equilibrating column to constant baseline. The enantiomer separation was validated by testing the racemic mixture at the beginning of each session. Detection was by UV at 240/254 nm or 220/240 nm depending on analyte, and enantiomer ratios were obtained using both wavelengths. All flow rates are 1.0 mL/min unless otherwise stated.

Acknowledgment. This work was supported by NIH (GM 44724).

Supporting Information Available: NMR spectra of new compounds and X-ray data tables for **1f**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO990897M