Lewis Acid-Induced Internal Proton Return in Enolate Complexes with Chiral Amines

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Abstract: Treatment of a 1:1:1 mixture of enolate **5**:amine **6**:lithium amide **7** with BF_3·OEt_2 affords the naproxen amide **4a** with an enantiomer excess of 77% (>90% yield). The result is attributed to Lewis acid-induced internal proton return (ipr) in a mixed aggregate containing the enolate and the chiral amine. Use of proline-derived diamines **9** and **10** in place of **6** affords **4a** with 56−66% ee, but monoamines are relatively ineffective. Similar ipr conditions can be used to deracemize the oxazolidine **13** (50−60% ee), the lactam **14** (50% ee), and the cyclohexenyl propionamide **15** (62% ee). However, disappointing results were obtained with **6** and several esters and the lactone **18**. Lactone **18** was deracemized with the diamine **24** (70% ee) under ipr conditions, but simple acyclic esters gave marginal ee values with **24** (BF_3·OEt_2 quench). Better results were obtained with methyl *N*-benzoylalaninate **16** (73% ee). In the latter case, the dianion was generated and ipr was induced by the sequential addition of **24** and BF_3·OEt_2 as before. In the case of amide **4a**, ^1H NMR evidence shows that much of the proton transfer is complete before the addition of BF_3·OEt_2 to the solution of **24** and enolate **5**. Thus, **5** is quenched by direct proton transfer, not by ipr, when **24** is used as the chiral amine. The proton transfer pathway can be correlated qualitatively with $pK_{a\,DMSO}$ values. Thus, **24** was found to have a $pK_{a\,DMSO}$ = 27.7 while the value for **4a** is ca. 31. The relative acidity in THF is assumed to be similar, and **24** can protonate **5** directly but not the lactone enolate **19** (**18**: $pK_{a\,(DMSO)}$ = 20.1). Direct proton transfer does not occur with **6** (estimated $pK_{a\,DMSO}$ = ca. 34−35) with any of the enolates studied, and activation for ipr by BF_3·OEt_2 is necessary to activate the N−H bond. In several examples, protic acid-induced ipr was also explored. In all cases, this gave lower ee values than the BF_3·OEt_2 method.

Introduction

The structure of lithium enolates in solution is strongly dependent on the Lewis base properties of the solvent and on the presence of amines that might coordinate lithium ion.[1] Thus, enolates generated using LDA as the base can have distinctly different properties compared with those of enolates generated in the absence of amines.[1−3] One of the most striking differences is the internal proton return (ipr) phenomenon that is observed when amine-containing enolates are treated with electrophiles.[4,5] In an early paper on synthetic applications of LDA, Creger noted that attempts to label the dianion of *o*-toluic acid by D_2O quenching did not succeed even though trapping with other electrophiles gave clear evidence for carbanion formation at the benzylic position.[4] Creger correctly attributed this result to a process where the amine proton in an amine−anion complex becomes reattached to the original carbon atom faster than the carbanion can interact with the external deuterium source. A number of other electrophiles are now known to have a similar effect. Some of the more striking examples of ipr involve amine activation by alkylating agents as reported by Seebach et al.[5] The latter workers have made the connection between ipr and the structure of lithium enolate−amine complexes.[1] The amine is believed to coordinate lithium ion, and the resulting ammonium-like N−H bonds are close to the enolate carbon, perhaps within hydrogen bonding distance of the enolate π-system. The addition of an electrophile serves to increase electron demand in the complex, probably by interaction with amine nitrogen electron pairs. This increases the effective acidity of the N−H bond and results in rapid Cα protonation (internal return). This is the reason why deuteration of enolates generated by LDA often fails and why enolate functionalization reactions with electrophiles may produce recovered starting carbonyl compound even when enolate formation is complete.

Previous workers have encountered ipr in reactions of chiral amine complexes of lithium enolates. Thus, Hogeveen *et al.* found that addition of the chiral lithium amide from **1** (2 equiv) to 2,2,6-trimethylcyclohexanone followed by enolate quenching with DCl/D_2O returns the ketone with <5% deuterium incorporation and with 46% ee (ether as the solvent).[6] In another experiment, enolate generation and subsequent quenching with trimethylchlorosilane under similar conditions gave 40% of the enol silane. This evidence was used to support the argument that deprotonation with **1** is incomplete and that enantioselectivity is due to kinetic resolution of the ketone in the deprotonation step.[6,7] If the racemic ketone (ca. 40%) was formed in the enolate quenching step and the remainder of the ketone (ca. 60%) was not deprotonated, then 46% ee in the final product would correspond to a kinetic resolution of ca. 76% in the unreacted ketone during enolization. This scenario is consistent with other deprotonation experiments involving chiral lithium amide bases.[7] However, the Hogeveen experiment can also be explained by assuming that enantioselective ipr is responsible for the enantiomeric excess. Since nearly all of the enolate is quenched internally according to the labeling results, the reprotonation step occurs within the chirotopic environment of an enolate−amine complex. This situation could result in

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enantiofacial discrimination, especially if the N−H proton is within H-bonding distance of the enolate π-system.[1,8] This possibility would be difficult to rule out because electrophilic quenching experiments are unreliable indicators for the extent of enolization in a system that is capable of ipr.

We were reluctant to explore ketone enolates where changes in the substrate would require the development of a unique assay for ee in each substrate. Amide enolates were chosen for the initial study of enantioselective ipr because their structures can easily be varied starting from the same chiral carboxylic acid and because the enolates are stable over a wide range of conditions. The availability of detailed structural information for the *N,N*-dimethylpropionamide lithium enolate−*N,N,N'*-trimethylethylenediamine complex **2** (Seebach *et al.*)[8] was another advantage. According to the X-ray data, there is a ca. 2.3 Å distance between the secondary amine N−H proton and the enamine-like nitrogen of the enolate. This is a plausible distance for H bonding, and a similar geometry in solution might allow facile ipr upon activation by electrophiles as suggested by Seebach. These considerations raised the possibility of enantioselective ipr in amide−enolate complexes with chiral amines and stimulated the investigations described below. A preliminary account of our work has appeared.[9] Recently, Koga *et al.* have reported enantioselectivities in the range of 80−91% ee for several α-alkyltetralone enolates under conditions where ipr may be possible.[10] Several other techniques for achieving the deracemization of carbonyl compounds have also demonstrated promising enantioselectivity.[11,12]

Results

As already mentioned, protic acids are quite capable of inducing ipr in enolate−amine complexes. However, they may not be ideal quenching agents for enantioselective applications because their reaction with enolates produces lithium salts as products. As a consequence, the composition of lithium species undergoes drastic changes in the course of the experiment, and lithium enolate−amine complexes could be disrupted as new lithium salts or mixed aggregates are formed.[1] One alternative would be to activate the complex of a chiral secondary amine with an enolate using a neutral Lewis acid as the electrophile. This strategy would perturb the enolate−amine complex by coordination of the Lewis acid to the most available electron pair, but it would not release new lithium salts capable of producing new complexes or mixed aggregates. If the site of Lewis acid coordination is the secondary amine nitrogen, then the resulting Lewis acid−Lewis base complex would contain a relatively acidic ammonium N−H bond. Proton transfer to the enolate carbon might then occur faster than the diastereomeric complexes or their aggregates can interconvert or otherwise lose their enantiofacial bias. Even if the Lewis acid interaction occurs at an electron pair other than the one at secondary amine nitrogen, there could be a transmitted acidifying effect within the enolate−amine complex that activates the crucial N−H bond and promotes enolate protonation. If the Lewis acid does not react irreversibly with the enolate, then enantioselective ipr should be feasible. Our amide−enolate investigation began with **4a**, derived from naproxen **3a** as the parent carboxylic acid. Several chiral amines, diamines, and amino alcohols were surveyed for their ability to function as ipr agents by generating the enolate **5** with 1.2 equiv of mesityllithium[13] at −78 °C, followed by the addition of excess amine. After 30 min, excess BF_3·OEt_2 was added to force ipr, and the reaction mixture was allowed to warm to 0 °C, and then quenched by aqueous workup. The amines surveyed included **1**, *N*-isopropyl-α-methylbenzylamine, *N*-isopropyl-α-((*N,N*-diethylamino)methyl)-benzylamine, the triamine **6** (derived from proline and *N,N,N'*-trimethylethylenediamine (TriMEDA)), and an analogous triamine derived from TriMEDA and phenylalanine (not shown). Only the experiments with **6** gave indications of promising (>20%) enantiomeric excess (ee) in the preliminary survey. These early experiments were complicated by the same difficulties in defining the extent of enolate formation from **4a** that were anticipated from the Hogeveen precedent.[6] A difference in enantioselectivity between **6** and the other amines was clear, but it was difficult to connect trends in ee values with experimental variables. In one of the first experiments, (±)-**4a** was treated with excess **7** (from **6** and *n*-butyllithium) at −78 °C. Warming the mixture to room temperature produced a deep red solution containing the enolate **5**. When the solution was cooled to −78 °C and treated with BF_3·OEt_2 followed by slow warming to room temperature, the recovered **4a** was enriched in the *R* enantiomer (α_D −53°, ca. 46% ee). In similar experiments performed without warming the mixture of **4a** + **7**, the ee values were lower. Incomplete enolization was suspected as the reason, but deuterium quenching experiments gave low and variable percentages of D-incorporation regardless of the temperature used for enolization. This behavior proves that ipr is facile with enolate **5**, but it provides no clear evidence regarding the extent of enolization.

To avoid the uncertainties associated with assaying amine-containing enolate solutions, the experiments were repeated with mesityllithium (1.2 equiv) as the base. After 60 min at −78 °C, the orange-colored enolate solution was treated with ammonium chloride/D_2O to give **4a** with 80% deuterium incorporation (NMR assay). If the enolate solution at −78 °C was treated instead with 1.2 equiv of the triamine **6** followed by 1.2 equiv of BF_3·OEt_2, then **4a** was formed with 33% ee (*R*) after warming and workup. A larger excess of the base and the amine gave increased ee until a plateau was reached at ca. 2 equiv (and up to 5 equiv) of mesityllithium, triamine **6**, and BF_3·OEt_2 (70−73% ee in THF). Other solvents were investigated, but the best results were obtained in the original THF procedure (2 equiv each of base, triamine, and BF_3·OEt_2). Thus, toluene (33% ee), ether (46% ee), 2,5-dimethyltetrahydrofuran (51% ee), dimethoxyethane (36% ee), and 1:1 THF:DMPU (2% ee) all gave inferior enantioselectivity.

Eventually, it was found that enolate formation with 2 equiv of *sec*-butyllithium gave comparable results in a more conve-

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(9) Vedejs, E.; Lee, N. *J. Am. Chem. Soc.* **1991**, *113*, 5483. This paper incorrectly reports 82% ee (*R*)-**4a** from the reaction of **5** with **6** under ipr conditions using a chiral shift reagent. Line broadening in the minor enantiomer caused systematic integral errors and obscured 2.5% racemization in a reference sample of (*S*)-**4a**.

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nient procedure by comparison with the mesityllithium technique. Enolate formation was complete within 10 min at −78 °C according to quenching experiments with CF_3CO_2D at −78 °C, >95% recovery of **4a** with >95% D_1 by NMR assay. Essentially complete deprotonation under these conditions was confirmed by quenching with TMSCl, resulting in a 14:1 mixture of **8Z**:**8E**. The geometrical assignment for **8** is based on an upfield chemical shift of 0.56 ppm in the $SiMe_3$ proton signal for the *Z*- vs the *E*-isomer (**8Z**, δ −0.26 ppm; **8E**, +0.30 ppm). These chemical shifts are consistent with the expected shielding influence of the naphthalene ring in **8Z**. When the enolate **5** was preformed using 2 equiv of *sec*-butyllithium, subsequent addition of 2 equiv of triamine **6** and 2 equiv of BF_3·OEt_2 afforded the same 70–73% ee as in the best mesityllithium experiments. This stoichiometry corresponds to the presence of an equimolar ratio of enolate **5**, triamine **6**, and the *N*-lithioamine **7** as ingredients in the complex at the stage where BF_3·OEt_2 is added. The role of metal cation was probed, but no improvement in ee could be achieved. To the contrary, virtually any change had disastrous consequences for enantioselectivity. Thus, addition of anhydrous $MgBr_2$ or $ZnCl_2$ to **5** gave **4a** with 8% ee (*R*) or 6% ee (*S*), respectively, while Ti(O-*i*-Pr)$_4$ gave 34% ee (*R*). The use of the *t*-C_4H_9OK/*n*-C_4H_9Li reagent[14] followed by the usual addition of **6** and BF_3·OEt_2 gave a minimal 4% ee (*S*). Subsequent optimization experiments were therefore restricted to *sec*-butyllithium as the base.

The influence of quenching temperature was studied next. These experiments were guided by color changes that had been observed throughout the optimization effort and partly by the puzzling changes in ee values that had plagued the first experiments. The amine-free enolate **5** has a characteristic orange color in THF. The color changed rapidly to a deep wine red upon addition of the triamine **6**, presumably due to the formation of the amine–enolate complex. When this mixture was treated with BF_3·OEt_2 at −78 °C, there was little immediate change in the color, but warming the solution above −40 °C resulted in noticeable fading on a time scale of tens of minutes. At −23 °C, 5–10 min was sufficient to discharge the color completely. Based on these observations, the experiment was repeated as follows: the mixture of enolate **5**, triamine **6**, and **7** was generated in the optimal 1:1:1 ratio at −78 °C, and BF_3·OEt_2 was added. The solution was maintained at different temperatures (*T*) for sufficient time (min) to discharge enolate color and was then subjected to aqueous workup. The following ee values were obtained: T = −78 °C (120 min), 69% ee; T = −43 °C (30 min), 77% ee; T = −23 °C (10 min), 77% ee; T = 0 °C (5 min), 70% ee. The results obtained in the temperature range of −43 to −23 °C proved to be the best in terms of enantioselectivity among all of the experiments performed with amide enolates under ipr conditions. Thus, there is an optimum temperature range for enantioselective ipr, as well as an optimum ratio of enolate **5** to triamine **6** to *N*-lithioamine **7** (**5**:**6**:**7** = 1:1:1). The latter ratio suggests the involvement of a mixed aggregate species[15] in the enantioselective ipr process, while the temperature effect presumably reflects the threshold for revealing an amine electron pair to the external Lewis acid with minimal damage to the chiral aggregate. The results of the key optimization experiments presented so far are summarized in Table 1, together with additional information regarding the quenching agent, as discussed below.

No further improvements in ee could be obtained by probing other variables. However, interesting insights were obtained regarding the role of the Lewis acid (Table 1, entries 9–19). Several alternative reagents were examined under the optimized ipr conditions as replacements for BF_3·OEt_2, but none was found that approached the original in terms of ee except for BF_3·SMe_2 (53% ee). Other boron Lewis acids were much less effective: $PhBF_2$,[16] 37% ee; BCl_3, 12% ee; $PhBCl_2$,[16] 7% ee; BBu_3, <3% ee; $B(OMe)_3$, <3% ee. Although these numbers were not established with great precision (assay by optical rotation), it may be significant that all of the boron reagents that produced at least some ee gave the same preference for the *R* enantiomer. Curiously, Et_2AlCl afforded a small excess of the *S* enantiomer (15% ee), as did the bulky silicon electrophile *t*-$BuMe_2SiOSO_2CF_3$ (14% ee). Other aluminum or silicon electrophiles gave minimal ee: Me_3SiCl, 4% ee (*S*); *t*-$BuMe_2SiCl$, <3% ee; Et_3Al, <3% ee. The significance of these results is not clear because small preferences for the *S* enantiomer were also seen when the mixture of **5** + **6** was quenched with protic acids. Thus, CF_3SO_3H (addition at −109 °C to avoid an exotherm; warming to −78 °C and aqueous workup) gave 26% ee (*S*), and a similar experiment with CF_3CO_2D afforded **4a** with 6% ee (*S*) and 50% deuterium incorporation. The use of ammonium chloride at −78 °C gave essentially racemic product. Thus, aluminum or silicon Lewis acids do not give substantially different results compared to the simple protic acids, and there is no proof that these less effective Lewis acids are capable of inducing ipr by a unique mechanism. However, one conclusion is important: protic acids give much lower ee and favor the *S* enantiomer from **5** and **6**. According to the deuterium incorporation result, the protic acid experiments do involve extensive ipr. The details of the mechanism in the ipr step are obviously much different under the BF_3·OEt_2 conditions. This evidence supports the original premise of our study: Lewis acid-induced ipr is capable of higher enantioselectivity compared to protic acid-induced ipr. The aprotic conditions presumably cause less structural disruption in the enolate–amine complex during quenching. There is also the advantage that no "external" protons are available, and only the Lewis acid-activated N–H bonds of the chiral amine can participate in enolate protonation.

Several other observations were made that are relevant in the context of enolate–amine complex stability. In one control experiment, the triamine **6** was combined with BF_3·OEt_2 at −78 °C. When this solution was added to the orange-colored enolate **5** in THF, the enolate color was discharged immediately (25% ee). This experiment is in striking contrast to the optimized procedure where the order of mixing is different and where the preformed enolate–amine complex survives over 1 h with BF_3·OEt_2 present at −78 °C. In the latter case, rapid fading of the color is seen only in the vicinity of 0 °C. Another variation was examined where the enolate **5** was treated with BF_3·OEt_2 prior to the addition of **6**. This gave an intermediate ee value of 45%, a result that suggests that BF_3·OEt_2 reacts reversibly with the enolate **5**, sufficiently so to allow at least some enolate–triamine complex formation prior to proton transfer. In summary, the preformed 1:1:1 complex (mixed aggregate) of **5** with **6** and **7** is relatively stable and lacks kinetically available Lewis basic sites that can easily interact with BF_3·OEt_2 at −78 °C. The preformed enolate–BF_3 adduct is less stable and may be capable of partial reorganization to the 1:1:1 complex when **6** + **7** are added. However, the Lewis acid–Lewis base adduct of **6** + BF_3 is the most reactive and least discriminating among the potential proton donors and quenches the enolate **5** with minimal enantioselectivity.

The above results underscore the important role of lithium enolate–amine complexes in the enantioselective ipr phenom-

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Table 1. Optimization of the Enantioselective Protonation of Enolate **5a**

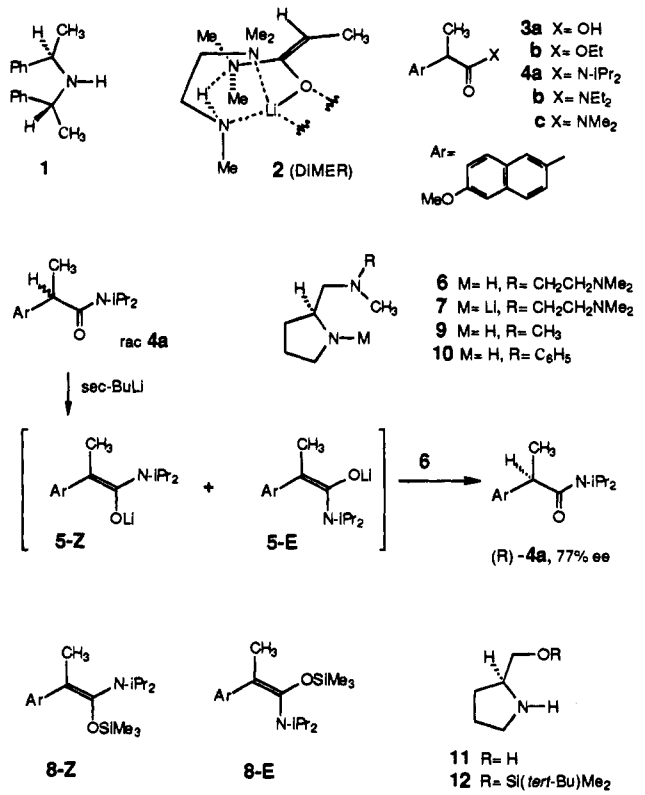
entry	base (no. of equiv)	amine (no. of equiv)	Lewis acid (no. of equiv)	temp (°C),[a] time	ee[b] (%)
1	MstlLi (1.2)	**6** (1.2)	BF_3•OEt_2 (1.2)	−78 to 0	33 (*R*)
2	MstlLi (2)	**6** (2)	BF_3•OEt_2 (2)	−78 to 0	70−73 (*R*)
3	MstlLi (5)	**6** (5)	BF_3•OEt_2 (5)	−78 to 0	70−73 (*R*)
4	*sec*-BuLi (2)	**6** (2)	BF_3•OEt_2 (2)	−78 to 0	70−73 (*R*)
5	*sec*-BuLi (2)	**6** (2)	BF_3•OEt_2 (2)	−78, 2 h	69 (*R*)
6	*sec*-BuLi (2)	**6** (2)	BF_3•OEt_2 (2)	−43, 0.5 h	77 (*R*)
7	*sec*-BuLi (2)	**6** (2)	BF_3•OEt_2 (2)	−23, 10 min	77 (*R*)
8	*sec*-BuLi (2)	**6** (2)	BF_3•OEt_2 (2)	0, 5 min	70 (*R*)
9	*sec*-BuLi (2)	**6** (2)	BF_3•OEt_2 (2)	−23	53 (*R*)
10	*sec*-BuLi (2)	**6** (2)	$PhBF_2$ (2)	−23	37 (*R*)
11	*sec*-BuLi (2)	**6** (2)	BCl_3 (2)	−23	12 (*R*)
12	*sec*-BuLi (2)	**6** (2)	$PhBCl_2$ (2)	−23	7 (*R*)
13	*sec*-BuLi (2)	**6** (2)	BBu_3 (2)	−23	<3
14	*sec*-BuLi (2)	**6** (2)	$B(OMe)_3$ (2)	−23	<3
15	*sec*-BuLi (2)	**6** (2)	$AlClEt_2$ (2)	−23	15 (*S*)
16	*sec*-BuLi (2)	**6** (2)	*t*-$BuMe_2SiOTf$ (2)	−23	14 (*S*)
17	*sec*-BuLi (2)	**6** (2)	CF_3SO_3H (2)	−109 to −78	15 (*S*)
18	*sec*-BuLi (2)	**9**	BF_3•OEt_2 (2)	−78 to −23	56 (*R*)
19	*sec*-BuLi (2)	**10**	BF_3•OEt_2 (2)	−78 to −23	66 (*R*)
20	*sec*-BuLi (2)	**11**	BF_3•OEt_2 (2)	−78 to−23	5−9 (*S*)
21	*sec*-BuLi (2)	**12**	BF_3•OEt_2 (2)	−78 to −23	32 (*R*)

[a] Temperature profile prior to aqueous quenching. [b] ee estimated by optical rotation and values over 50% were confirmed by HPLC assay on a chiral solid support.

enon. However, none of the evidence presented so far conclusively proves that the color changes observed at various temperatures are associated with proton transfer from nitrogen to carbon as proposed. To remove doubts regarding this issue, the enolate **5** was generated in deuterated THF using crystallized mesityllithium as the base to minimize interfering proton signals in the ^1H NMR spectrum. Clear evidence for enolate formation was obtained. In particular, the diastereotopic isopropyl methyl signals of **4a** (four doublets, δ 1.5−0.27 ppm) collapsed into a broad signal at δ 1.18−1.08 ppm for the *N*-isopropyl methyls (enamine-like nitrogen environment) of **5**. The α-methyl signal of **5** was partly obscured by the mesitylene methyl signals, and only a tentative assignment (δ 2.18 ppm) could be made. However, the α-CH quartet at ca. δ 4.2 ppm disappeared as expected, and substantial changes were seen in the aromatic region. When the enolate solution was treated with **6**, the signals broadened and became more complex. Chemical shift differences compared to the amine-free enolate were seen in the aromatic region, but signal integration suggested the presence of more than one complex and specific assignments could not be made. However, addition of BF_3•OEt_2 at −78 °C followed by brief warming to −23 °C resulted in a simplification of signals, the usual discharge of enolate color, and the reappearance of absorptions characteristic of **4a**. This experiment provides strong support for BF_3•OEt_2-induced ipr and for the association of the deep red color with the presence of 1:1:1 complexes of **5**, **6**, and **7**.

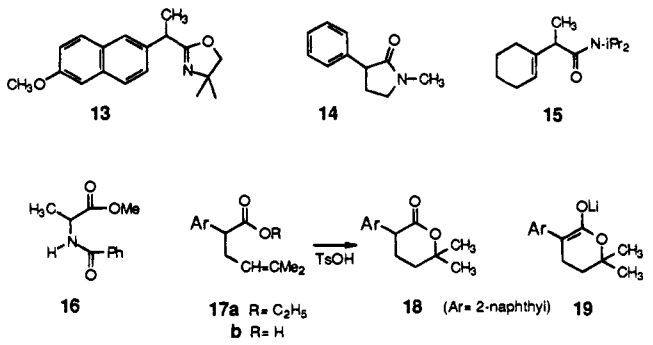
Triamine **6** was originally selected for this study on the basis of the asumption that it might function as a tridentate ligand for lithium ion. However, the 1:1:1 enolate:amine:*N*-lithioamine stoichiometry suggests at most a bidentate role for the amine. To probe this question, several other proline-derived amines **9**−**12** were investigated under the optimum conditions with the amide enolate **5**. Prolinol (**11**) was ineffective, 5−9% ee (*S*), while the corresponding silyl ether **12** produced **4a** with 32% ee of the usual *R* enantiomer. The diamines **9** and **10** gave 56% and 66% ee, respectively. These results provide some evidence for a bidentate role for the chiral amine, but a monodentate interaction is not ruled out.

The differences in ee among **6**, **9**, and **10** are not regarded as significant because experiments with **9** or **10** were not individually optimized. Differences in the ideal temperature window



and perhaps also in the optimal stoichiometry are possible. By the same logic, it is likely that a broader survey of other enolates would encounter "false negatives" because it would not be practical to perform a detailed optimization of many variables in each case. It was no surprise, therefore, to find substantial differences among the amides **4a** (77% ee), **4b** (47% ee), and **4c** (33% ee) under conditions optimized for **4a** (all *R*-selective, see Table 2). The closely related oxazolidinone **13** gave moderately encouraging values of 50−60% ee (lanthanide shift reagent assay) and so did the cyclohexenyl amide **15** (62% ee, *R*, HPLC) and the cyclic lactam **14** (50% ee; HPLC). A number of discouraging results were encountered as well. Marginal ee was obtained when the usual procedure was applied to the carboxylate dianion from **3a** (31% ee, *R*) and to some ester

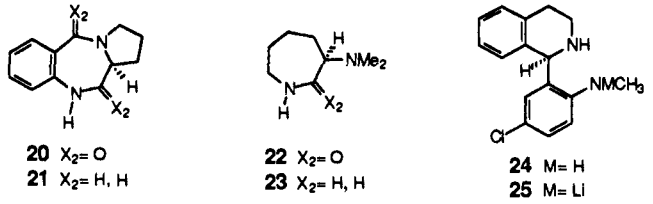
enolates: naproxen ethyl ester **3b** (33% ee, *R*), ethyl *O*-benzyl lactate (18% ee). Lactone **18** gave no ee [preparation: alkylation of ethyl α-(2-naphthyl)acetate to give **17a**; saponification and acid-catalyzed cyclization of **17b**]. Methyl *N*-benzoylalaninate (**16**) also gave a racemic product (modified procedure: 3 equiv of *sec*-butyllithium to compensate for the acidic N–H proton; 3 equiv of **6** and BF_3•OEt_2). Poor results using a standardized procedure do not necessarily prove that **6** would be ineffective under other conditions, but the marginal examples discouraged further experiments with proline derivatives. It was hoped that other chiral amine environments could be found that would be less sensitive to the choice of substrate.



The primary basis for selecting the remaining diamines discussed below was availability in one step from commercially available materials. The only other restriction imposed at the outset was the presence of a secondary nitrogen in a cyclic environment to maintain some structural analogy with **6**. Three candidates **21**, **23**, and **24** were found that satisfy these criteria. Diamines **21** and **23** were prepared by $LiAlH_4$ reduction of the corresponding lactams **20** and **22**, while **24** was obtained by base treatment of the available tartrate salt. In preliminary tests with **5** as the substrate and BF_3•OEt_2 as the Lewis acid, **21** and **23** gave <5% ee and were not explored further. However, diamine **24** was more promising and gave significant ee with several of the test substrates. Lactam **14**, one of the promising substrates with **6**, afforded only a marginal result with **24** (33% ee) under the standard BF_3•OEt_2 ipr conditions. On the other hand, similar experiments with lactone enolate **19** [generated with 2 equiv of $LiN(SiMe_3)_2$ or mesityllithium in place of *sec*-butyllithium at −78 °C; then 2 equiv of **24** followed by 2 equiv of BF_3•OEt_2 and warming to −23 °C as usual) resulted in 69–72% ee in the recovered **18**. Color changes were observed at each stage, consistent with complex formation upon addition of **24** to the enolate **19** (deepening of yellow color) and fading to colorless after ca. 3 min at −23 °C (BF_3•OEt_2 present). An NMR experiment was performed in an attempt to confirm the sequence of events (THF-d_{10}). The diastereotopic methyls of **18** (δ 1.53 and 1.46 ppm) collapsed to a singlet at δ 1.31 ppm in the enolate **19**, and other changes were seen in the aromatic region. Addition of **24** caused some broadening of signals, but no other characteristic changes were noted. In particular, the chiral amine did not split the C_6-methyl signals of **19**. The methyl groups could be nonequivalent if the chiral amine interacts selectively with one face of the enolate π-system, but no such effect was detected. Addition of BF_3•OEt_2 resulted in proton transfer as expected, and signals of **18** reappeared. Thus, **24** does not protonate **19** in the absence of the Lewis acid. However, no clear evidence for the formation of a complex from **19** + **24** was obtained from the NMR study.

When the ipr experiment was repeated with enolate **19** using only 1.1 equiv of $LiN(SiMe_3)_2$, diamine **24**, and BF_3•OEt_2, the result was unchanged (**18** with 70% ee; HPLC assay). Thus, a mixed aggregate including the *N*-lithio amine **25** is not required for the enantioselective ipr process with diamine **24**. One additional experiment was done where the enolate was generated with mesityllithium (2 equiv), followed by the addition of **24** (2 equiv) and quenching with CF_3CO_2D at −78 °C. This gave **18** with 45% ee and 20% deuterium incorporation. Since 20% of the product is formed by external proton capture, the fraction (0.8) of enolate **19** that is quenched by internal protons affords **18** with a respectable ca. 80% ee, assuming that external proton quenching is nonselective. This is the only example found among those discussed so far where significant ee was obtained in ipr induced by both the Lewis acid (BF_3•OEt_2) and the protic acid (CF_3CO_2D) activation methods.

In view of the promising results in the ipr quenching of lactone **18** by **24**, a similar experiment (2 equiv of mesityllithium as base) was performed with the ethyl ester of naproxen (**3b**). This produced racemic material (!) and so did the analogous experiment with ethyl *O*-benzyl lactate. In contrast, treatment of the dianion derived from methyl *N*-benzoylalaninate (**16**) with **24** and BF_3•OEt_2 afforded **16** with 73% ee for the *S* enantiomer. This is the best result seen in our study with any ester-derived enolate. The corresponding experiment with the dianion of **16**, 2 equiv of **24**, and protic acid (CF_3CO_2D) quenching at −78 °C gave >95% D-incorporation in **16** but only 11% ee. Thus, extensive ipr in the protic acid quench is no guarantee of significant enantioselectivity.



The results with the naproxen amide enolate **5** also appeared promising under the standard conditions (70% ee), but the characteristic orange color of **5** did not deepen to red when diamine **24** was added, in contrast to earlier experience with **6**. Instead, the solution acquired a pink hue that had not been seen in any of the other experiments with **24**. The color changes suggested that **5** may have been quenched by the relatively acidic aniline NH proton of **24** and not by the ipr pathway. This was confirmed by an NMR study. When the enolate **5** was treated with **24** (THF-d_{10} solution at −78 °C), the signals of **5** disappeared and were replaced by the characteristic absorptions of **4a**. Due to line broadening, the detection limits in this experiment were no better than 10–20%. However, most of the enolate **5** was converted into **4a** at −78 °C, prior to the addition of BF_3•OEt_2. As a result, the enantioselectivity of the ipr pathway could not be determined in this case.

Eventually, it was found that the direct proton transfer from **24** to **5** occurs efficiently if the solution is warmed to −23 °C prior to workup, a procedure that affords much improved enantioselectivities well over 90% for the amide enolates from **4a** and **15**.[17] Direct proton transfer experiments are still under investigation and will be described in due course. However, the ipr experiments are mechanistically distinct. Within the limits of ^1H NMR detection, ipr is the exclusive pathway in the BF_3•OEt_2-induced protonation of enolate **5** with the triamine **6** and in the analogous reaction of lactone enolate **19** with diamine **24**. Direct proton transfer does not occur in these examples because the amines are not acidic enough to protonate the enolates. To better understand these and related examples,

(17) Vedejs, E.; Lee, N.; Sakata, S. *J. Am. Chem. Soc.* **1994**, *116*, 2175.

Table 2. Substrate Variations in Enantioselective Enolate Protonation

entry	substrate	base (no. of equiv	amine (no. of equiv)	Lewis acid (no. of equiv)	temp[a] (°C)	ee[a] (%)
1	**4a**	*sec*-BuLi (2)	**6** (2)	BF_3•OEt_2 (2)	−78 to −23	77 (*R*)
2	**4b**	*sec*-BuLi (2)	**6** (2)	BF_3•OEt_2 (2)	−78 to −23	47 (*R*)
3	**4c**	*sec*-BuLi (2)	**6** (2)	BF_3•OEt_2 (2)	−78 to −23	33 (*R*)
4	**13**	*sec*-BuLi (2)	**6** (2)	BF_3•OEt_2 (2)	−78 to −23	50−60[b]
5	**15**	*sec*-BuLi (2)	**6** (2)	BF_3•OEt_2 (2)	−78 to −23	62
6	**3a**	*sec*-BuLi (3)	**6** (3)	BF_3•OEt_2 (3)	−78 to −23	31 (*R*)
7	**3b**	*sec*-BuLi (2)	**6** (2)	BF_3•OEt_2 (2)	−78 to −23	33 (*R*)
8	**18**	*sec*-BuLi (2)	**6** (2)	BF_3•OEt_2 (2)	−78 to −23	0
9	**16**	*sec*-BuLi (3)	**6** (3)	BF_3•OEt_2 (3)	−78 to −23	0
10	**4a**	*sec*-BuLi (2)	**21** (2)	BF_3•OEt_2 (2)	−78 to −23	<5
11	**4a**	*sec*-BuLi (2)	**23** (2)	BF_3•OEt_2 (2)	−78 to −23	<5
12	**14**	*sec*-BuLi (2)	**24** (2)	BF_3•OEt_2 (2)	−78 to −23	33
13	**18**	MstlLi (2)	**24** (2)	BF_3•OEt_2 (2)	−78 to −23	69−72
14	**18**	LiHMDS[c] (2)	**24** (2)	BF_3OEt_2 (2)	−78 to −23	70
15	**18**	LiHMDS[c] (1.1)	**24** (1.1)	BF_3•OEt_2 (1.1)	−78 to −23	70
16	**18**	MstlLi (2)	**24** (2)	CF_3CO_2D[d] (>2)	−78	45
17	**3b**	MstlLi (2)	**24** (2)	BF_3•OEt_2 (2)	−78 to −23	0
18	**16**	*sec*-BuLi (3)	**24** (3)	BF_3•OEt_2 (3)	−78 to −23	73 (*S*)
19	**16**	*sec*-BuLi (3)	**24** (3)	CF_3CO_2D[e] (>3)	−78	11 (*S*)
20	**4a**	*sec*-BuLi (2)	**24** (2)	BF_3•OEt_2 (2)	−78 to −23	70 (*R*)
21	**4a**	*sec*-BuLi (2)	**24** (2)	none	−78 to −0	>90 (*R*)

[a] The temperature profile prior to aqueous quenching is given; ee values were determined by HPLC assay on a chiral solid support except where indicated. [b] The ee value was estimated by ^1H NMR using a chiral shift reagent. [c] LiHMDS = $LiN(SiMe_3)_2$. [d] 20% deuterium incorporation. [e] >95% deuterium incorporation.

the $pK_{a\,DMSO}$ values of some of the key reactants were estimated from literature analogies,[18,19] while others were measured by Bordwell and Satish.[18d] The chiral aniline **24** has a $pK_{a\,DMSO}$ of 27.7.[18d] Since the value for 4-chloroaniline is 29.4,[18b] the greater acidity of **24** probably reflects the proximity of two amino groups. The $pK_{a\,DMSO}$ value of **4a** was too high for accurate measurement (ca. 31).[18d] The reduced acidity compared to $PhCH_2CONMe_2$ ($pK_{a\,DMSO}$ = 26.6)[18c] probably arises mostly from steric hindrance to solvation. Lactone **18** was also studied and was found to have a $pK_{a\,DMSO}$ value of 20.1.[18d]

An extrapolation of these pK_a values to the THF conditions used for the relevant ipr experiments is complicated by several factors, including differences in ion pairing[18a,19b] and the possible presence of enolate dimers, mixed aggregates, and amine complexes.[1] Nevertheless, a qualitative correlation between relative acidities in THF and DMSO can be assumed. Weak organic acids generally have similar pK_a values in non-hydroxylic solvents if there is extended delocalization in the corresponding anions. This generalization is supported by several comparisons involving imine pK_a's in THF (ion pair pK_a's) vs DMSO.[19d] There is also some reassuring data for a small number of ester and aniline examples that have been compared in DMSO and other solvents.[19b,c] On the basis of these analogies, the relative acidities of carbonyl compounds in THF can be estimated with reasonable confidence when the DMSO-based pK_a's differ by ca. 3 units or more. Thus, **24** (estimated $pK_{a\,THF}$ = 27−28) is acidic enough to protonate the amide enolate **5** (**4a**: $pK_{a\,THF}$ = ca. 31) but not the lactone enolate **19** (**18**: $pK_{a\,THF}$ = ca. 20) nor the naproxen ester **3b** ($pK_{a\,THF}$ = ca. 23−24; compare to $pK_{a\,DMSO}$ = 22.7 for $PhCH_2CO_2Et$).[18a] For the *N*-benzoyl alaninate substrate **16**, an estimate of relative acidity is more difficult. Meaningful dianionic reference compounds have not been studied, and it is not known whether the presence of a PhC(O)NLi subunit at C_α of the dianion would increase enolate stability (delocalization or chelation effects) or decrease it (electrostatic repulsion). Thus, no conclusions are possible regarding the mode of proton transfer from **24** in the case of **16**.

According to the NMR experiments, triamine **6** has a $pK_{a\,THF}$ > 31. Structurally related, but somewhat more hindered, secondary amines have been studied by Fraser *et al.* and have ion pair $pK_{a\,THF}$ values in the range of 35−39.[19e] A similar pK_a value of 37.9 is reported for the related 1,3-diamine $Me_2N(CH_2)_3NHCH(i\text{-}C_3H_7)C_4H_9$ by the same workers.[19e] A smaller value of 34−35 is assumed for **6** on the basis of the reduced steric hindrance and the possibility of improved cooperation between the nitrogens due to their greater proximity. Thus, **6** is probably not acidic enough to protonate any of the carbonyl substrates in this study and proton transfer occurs by the ipr mechanism.

Relevant pK_a information is not available for *N*-alkyl lactams related to **14**. However, the lactone **18** has a pK_a at least 3 units below that of the acyclic reference compound, ethyl α-phenylacetate, and a similar effect due to a cyclic environment with **14** would give a $pK_{a\,THF}$ of ca. 23. Direct proton transfer to this substrate is probably ruled out for **24** as well as for **6**. The lactam enolate derived from **14** is a rare example where both **6** (50% ee) and **24** (33% ee) quench the enolate with significant enantioselectivity via the ipr pathway, but neither experiment approaches the best results with acyclic amide enolates.

Conclusion

The first examples of internal proton return in enolate−amine complexes induced by a neutral Lewis acid are demonstrated. Complexes generated in solution from the chiral amines **6** or **24** and amide, ester, lactam, or lactone enolates react with BF_3•OEt_2 to give the parent carbonyl compounds (80−95% recovery) with varying levels of ee (Table 2). Among the examples shown to undergo ipr, three substrates were found

(18) (a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. (b) Aniline pK_a's: Bordwell, F. G.; Algrim, D. J. *J. Am. Chem. Soc.* **1988**, *110*, 2964. Bordwell, F. G.; Zhang, X.; Cheng, J. P. *J. Org. Chem.* **1991**, *56*, 3216. (c) $PhCH_2CO_2Et$ and $PhCH_2CONMe_2$: Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 4327. (d) The authors are indebted to F. G. Bordwell and A. V. Satish for measuring the $pK_{a\,DMSO}$ values of **4a**, **18**, and **24**.

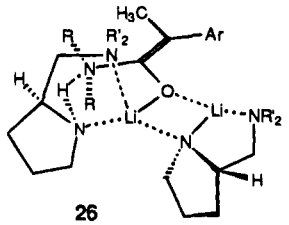
(19) (a) Streitwieser, A., Jr.; Juaristi, E.; Nebenzahl, L. L. In *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier-North Holland: Amsterdam, 1980; Part A, pp 323. (b) Arnett, E. M.; Venkatasubramaniam, K. G. *J. Org. Chem.* **1983**, *48*, 1569. (c) Valerolactone (pK_a 25.2) and ethyl acetate (pK_a 27.45 in DMSO): Arnett, E. M.; Harrolson, J. A., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 809. (d) Fraser, R. R.; Mansour, T. S.; Savard, S. *J. Org. Chem.* **1985**, *50*, 3232. (e) Fraser, R. R.; Mansour, T. S. *J. Org. Chem.* **1984**, *49*, 3442. Fraser, R. R.; Baignée, A.; Bresse, M.; Hata, K. *Tetrahedron Lett.* **1982**, *23*, 4195.

that gave promising enantioselectivity (>70% ee) in the internal proton transfer step (Table 2: **4a**, entry 1; **16**, entry 18; **18**, entries 13–16). In each of theses examples, the BF_3•OEt_2 quenching method was superior to the use of protic acids in terms of enantioselectivity. However, none of the chiral amines studied displays >70% ee with more than one enolate family under ipr conditions. Little progress was made in understanding the reasons why some enolates are quenched with >70% ee while others produce nearly racemic material under ipr conditions.

The amine-free enolate **5** was observed by ^{1}H NMR methods. Changes in the NMR spectrum of **5** were seen upon addition of triamine **6**, consistent with complex formation. Since the highest ipr enantioselectivity was obtained using a 1:1:1 stoichiometry of the amine **6**, the *N*-lithio derivative **7**, and the enolate **5**, a mixed aggregate appears to be involved in the proton transfer event. However, the ^{1}H NMR experiment did not provide clear evidence for a well-ordered mixed aggregate such as **26**, nor was it possible to show that the ratio of complexes in solution corresponds to the ca. 84:16 ratio of diastereomers that would afford **4a** with 77% ee as observed in the best enolate quenching experiment. In the analogous experiment with diamine **24**, the enolate **5** did not survive due to direct proton transfer from **24** and the amine–enolate complex could not be detected. Lactone **18** was also studied using the ^{1}H NMR method. The enolate **19** survived in the presence of **24**, but the differences in ^{1}H NMR signals between the amine-free vs the amine-containing enolate were surprisingly subtle and provided little structural information. No attempt was made to monitor **19** in the presence of triamine **6** because the corresponding ipr experiment gave racemic **18**.

A study of enantioselective quenching of chiral amine–enolate complexes has recently appeared where ipr is demonstrated by labeling methods.[10] Triamine ether **27** was used as the enolate complexing agent, and the enolate **28** was found to give the parent α-methyltetralone with up to 91% ee upon quenching with protic acids. The presence of lithium bromide was crucial for good results, and a mixed aggregate of the enolate, lithium bromide, and the triamine ether **27** was suggested as the substrate for protic acid-induced ipr. A mixed aggregate is implicated in another study where a specific combination of the amino alcohol **29**, the corresponding lithium alkoxide **30**, and the magnesium enolate **31** affords ketone **32** with >80% ee.[12b] These results are similar to ours in the **4a** + **6** + BF_3•OEt_2 ipr experiments in the sense that mixed aggregates appear to be important for high enantioselectivity. In the best enantioselective enolate protonation reported to date, Fehr *et al.* used **29** to protonate enolate **33** (99% ee!) in the absence of other additives. However, the stoichiometry ensures the presence of excess lithium alkoxide **30**, and the involvement of a mixed aggregate is possible.[12f] On the other hand, the ipr experiment with the lactone enolate **19**, diamine **24**, and BF_3•OEt_2 gives the same 70% ee result whether or not excess **25** is present. A preformed mixed aggregate is not necessary for enantioselective protonation in the latter example, and there is little indication from the ^{1}H NMR experiment for a well-defined amine–enolate complex in solution.

Enantioselectivity in the BF_3•OEt_2 experiments is strongly influenced by solvent, temperature, stoichiometry, order of mixing, the choice of Lewis acid, and the metal cation. According to preliminary indications, chiral amine reagents that quench enolates by the direct proton transfer pathway are far less sensitive to experimental variables.[12f,17] If both mechanisms (ipr and direct proton transfer) for enolate quenching require prior complex formation between the enolate and the chiral



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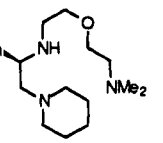

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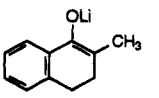

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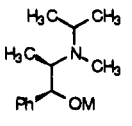
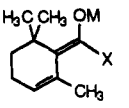
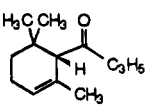


29 M= H
30 M= Li



31 M= MgCl, X= $CH_2CH{=}CH_2$
33 M= Li, X= SC_6H_5



32

amine, then this is the logical result. Direct proton transfer requires the minimum number of bond-breaking and bond-forming events, while BF_3•OEt_2-induced ipr in an enolate–amine complex appears to involve prior cleavage of at least one of the bonds between lithium and a nitrogen electron pair.

Slow proton transfer in the system, (preformed **4a** + **6**) + BF_3•OEt_2, suggests that enolate quenching occurs in a relatively stable mixed aggregate structure. When the reactants were mixed in a different order, enolate quenching was fast at −78 °C. This observation is consistent with the presence of a well-defined mixed aggregate such as **26** where internal proton transfer from the secondary amine nitrogen to carbon could occur via cleavage of the secondary nitrogen–lithium bond, followed by B- - -N coordination. However, the NMR evidence presented above suggests a more complicated situation. If structure **26** were stable on the laboratory time scale, then the two *N*-isopropyl groups (*R*) should be nonequivalent in the ^{1}H NMR spectrum and diastereotopic methyl groups would be expected in the chiral environment. Since this was not observed, the H-bonding interaction included in the speculative drawing **26** (based on the X-ray analogy of **2**)[8] may be weak or absent in solution. Cleavage of the corresponding secondary amine- - -Li bond could therefore cause major structural changes and more than one equilibrating enolate complex geometry could be intercepted by the Lewis acid. This may be the reason why experimental variables are so crucial under ipr conditions and why there is a strong substrate dependence. There appears to be much more to enantioselective enolate quenching via ipr than the recognition of an enolate subunit by the chiral amine. In an attempt to better understand this complicated problem, we are exploring structurally similar diamines that cover a range of pK_a's. Hopefully, a system can be found where both the ipr and the direct proton transfer processes can be studied side by side without changing the geometry of the enolate–amine complex. This work will be described in future publications.

Experimental Section

Mesityllithium[13] was prepared by adding *t*-BuLi (1.7 M in pentane from Aldrich) to the solution of bromomesitylene in ether or THF at −23 or −78 °C, and the concentration was determined by titration using menthol and 1,10-phenanthroline as indicators in ether at −5 °C. Diamines **9** and **10** were prepared by the method of Asami.[20] Lactam **14** was made by the method of Pinnick *et al.*,[21a] and amides **4a,b** were made according to literature procedures.[21b]

(20) Asami, M. *Chem. Lett.* **1984**, 829.
(21) (a) Pinnick, H. W.; Stevant, J. D.; Fields, S. C.; Kochhar, K. S. *J. Org. Chem.* **1987**, *52*, 2110. (b) Shanbhag, V. R.; Crider, A. M.; Gokhale, R.; Harpalani, A.; Dick, R. M. *J. Pharm. Sci.* **1992**, *81*, 149.

Preparation of Triamine 6. To (*S*)-*N*-(benzyloxycarbonyl)proline (Aldrich; 3.49 g, 14.0 mmol) in 150 mL of dry CH_2Cl_2 at 0−5 °C under N_2 was added *N,N,N'*-trimethylethylenediamine (Pfaltz & Bauer, 1.49 g, 14.0 mmol) as the neat liquid followed by NEt_3 (3.11 g, 30.8 mmol). The coupling reagent,bis(2-oxo-3-oxazolidin-1-yl)phosphinic chloride[22] (3.67 g, 15.4 mmol), was added to the mixture in one portion. The resulting mixture was stirred overnight at 0−5 °C and was washed with 200 mL of saturated $NaHCO_3$ solution. The aqueous layer was further extracted with 2 × 100 mL of CH_2Cl_2. The organic layer was combined and washed with 300 mL of water and 300 mL of saturated NaCl solution, dried ($MgSO_4$), and concentrated in vacuo to obtain a pale yellow oil.

The crude amide (14.0 mmol) and 5% Pd/C (100 mg) in 30 mL of methanol were agitated vigorously in a Parr shaker overnight under H_2 pressure (40 psi). Filtration through a Celite pad, thorough rinsing with CH_2Cl_2, and concentration of the filtrates gave a yellow oil. TLC analysis indicated complete conversion. The crude yellow oil was distilled using a short-path apparatus to give the unprotected amide as a pale yellow liquid: bp 100−105 at 30 mm; MS exact mass calcd for $C_{10}H_{21}ON_3$ 199.1685, found 199.1688, error 1.4 ppm; IR ($CHCl_3$, cm^{-1}): (N−H), 3299 1639 (C=O), 1486 (N−C); 200 MHz NMR ($CDCl_3$) δ 3.94 (1H, dd, *J* = 8, 6 Hz), 3.62 (1H, br s), 3.53 (2H, dt, *J* = 9, 7 Hz), 3.40−3.12 (1H, m), 3.17 (2H, s), 3.13 (1H, s), 2.97−2.75 (1H, m), 2.6 (2H, dt, *J* = 9, 7 Hz), 2.27 (2H, s), 2.26 (4H, s), 2.20−2.00 (1H, m), 1.95−1.45 (3H, m).

To a suspension of $LiAlH_4$ (1.50 g, 37.4 mmol) in 30 mL of dry THF at 0 °C was slowly added (cannula) a solution of the amide from above in 20 mL of THF (N_2 atrmosphere), and the reaction mixture was stirred for 1.0 h at 0 °C. Then the mixture was refluxed at 75 °C overnight, cooled to 0 °C, and quenched with a minimum amount of saturated aqueous sodium sulfate solution. The inorganic salts were filtered off and washed well with THF. The THF solution was concentrated in vacuo and the residue diluted with 20 mL of EtOAc, dried (Na_2SO_4), filtered, and evaporated in vacuo to give a yellow liquid. Distillation under reduced pressure afforded **6** as a colorless liquid (2.37 g, 91% based on the starting *N*-Cbz-proline): $[\alpha]_D20$ = +20.0° (*c* 5.2, *n*-hexanes); liquid, bp 60−62 °C at 0.05−0.06 mm, short path; MS, no peak match, parent M − C_4H_8N, 115.1239, calcd = 115.1235, error = 3.5 ppm, formula = $C_{10}H_{23}N_3$; IR (CH_2Cl_2, cm^{-1}) 3038 (N−H), 2863 (C−H), 1460 (C−N); 200 MHz NMR ($CDCl_3$) δ 3.26−3.08 (1H, m), 3.02−2.77 (2H, m), 2.62−2.24 (6H, m), 2.37 (3H, s), 2.24 (6H, s), 2.10−1.65 (3H, m), 1.43−1.23 (2H, m).

Synthesis of (*S*)-Prolinol *tert*-Butyldimethylsilyl Ether (12). A mixture of *N*-Cbz-(*S*)-prolinol (1.26 g, 5.37 mmol), *tert*-butyldimethylsilyl chloride (0.97 g, 6.45 mmol), and imidazole (0.92 g, 13.4 mmol) was stirred in 15 mL of dry DMF overnight at room temperature. The mixture was diluted with 200 mL of ether and was washed with 2 × 100 mL of 1.0 N HCl followed by brine (100 mL). The ether layer was dried ($MgSO_4$) and concentrated to afford a yellow oil. The crude oil was purified by filtration column chromatogrphy (silica gel, 2 × 20 cm) (elution, 20% EtOAc in hexane) to give an oil (1.87 g, 100%), *N*-Cbz-(*S*)-prolinol. This was dissolved in 25 mL of methanol, and 10% Pd/C (150 mg) was added. The mixture was agitated under a Paar hydrogenation conditions (45 psi of H_2 pressure). The Pd/C was filtered on a cellte pad, and the filtrate was concentrated *in vacuo* to give a yellow oil. Distillation gave **12** as a clear liquid (0.94 g, 81%): bp 150−160 °C, 0.1−0.15 mm, Kugelrohr; molecular ion calcd for $C_{11}H_{25}NOSi$ 215.17056, found *m/e* = 215.1705, error = 0 ppm; IR (neat, cm^{-1}) 3300 (N−H), 1474 (C−N); 200 MHz NMR ($CDCl_3$, ppm) δ 3.56 (1 H, dd, *J* = 10.0, 5.0 Hz), 3.49 (1H, dd, *J* = 10.0, 6.0 Hz), 3.15−2.78 (3H, m), 2.07 (1H, br s), 1.76−1.62 (3H, m), 1.42−1.30 (1H, m), 0.86 (9H, s), 0.02 (6H, s); ^{13}C NMR (68 MHz, {H}, C_6D_6, ppm) δ 66.8, 60.2, 46.8, 28.0, 26.4, 26.2, 25.7, 18.5, 2.6.

(*S*)-(+)-2,3,5,10,11,11a-Hexahydro-1*H*-pyrrolo-[2,1-*c*][1,4]-benzodiazepine (21). To a suspension of (*S*)-(+)-2,3-dihydro-1*H*-pyrro[2,1-*c*][1,4]benzodiazepine-5,11(10H,11a*H*)-dione (Aldrich, 2.03 g, 9.30 mmol) in 30 mL of dry THF at 0 °C under N_2 was slowly added $LiAlH_4$ in THF (Aldrich, 1.0 M in THF, 40 mL, 37.2 mmol) via syringe. After 20 min at 0 °C, the reaction mixture was refluxed at 80 °C overnight, cooled to 0 °C, and quenched with a minimum amount of saturated Na_2SO_4 solution. Precipitated salts were removed by filtration and washed thoroughly with THF. After solvent removal (aspirator), the yellow oil was dissolved in 20 mL of EtOAc, dried (Na_2SO_4), filtered, and evaporated. The crude yellow solid was recrystallized from toluene−hexane to give pale yellow needles (1.44 g, 85%): mp 106−107 °C molecular ion calcd for $C_{12}H_{16}N_2$ 188.13139, found *m/e* = 188.1313, error = 0 ppm, base peak = 118 amu; IR ($CHCl_3$, cm^{-1}) 3375 (N−H), 1605 (C=C), 1375 (C−N); 200 MHz NMR ($CDCl_3$, ppm) δ 7.14−7.03 (2H, m), 6.82 (1H, td, *J* = 7.4, 1.1 Hz), 6.72 (1H, d, *J* = 8.0 Hz), 3.83 (2H, d, *J* = 13.4 Hz), 3.50 (1H, d, *J* = 13.4 Hz), 3.33 (1H, dd, *J* = 12.7, 1.9 Hz), 3.15 (1H, td, *J* = 8.6, 2.9 Hz), 2.75 (1H, dd, *J* = 12.7, 9.5 Hz), 2.54−2.41 (2H, m), 1.97−1.77 (3H, m), 1.51−1.43 (1H, m); ^{13}C NMR (68 MHz, {H}, $CDCl_3$, ppm) δ 149.1, 129.8, 128.8, 126.9, 119.7, 118.3, 67.8, 58.5, 55.2, 51.8, 28.2, 21.1.

d-(+)-3-(Dimethylamino)perhydroazepine (23). To a suspension of $LiAlH_4$ (1.52 g, 39.9 mmol) in 30 mL of dry THF at 0 °C under N_2 was slowly added D-(+)-α-(dimethylamino)-ϵ-caprolactam (Fluka, 2.08 g, 13.3 mmol) in 20 mL of dry THF via cannula. The rest of the procedure was the same as for **21**, except that the residue after workup was a yellow oil. Bulb-to-bulb distillation gave a colorless liquid (1.67 g, 88%): pot temperature 150−160 °C, 0.1−0.15 mm, Kugelrohr; molecular ion calcd for $C_8H_{18}N_2$ 142.14705, found *m/e* = 142.1470, error = 0 ppm; IR (neat, cm^{-1}) 3290 (N−H), 1456 (C−N); 200 MHz NMR ($CDCl_3$, ppm) δ 3.02−2.77 (4H, m), 2.54−2.49 (1H, m), 2.27 (6H, s), 1.82−1.45 (7H, m); ^{13}C NMR (68 MHz, {H}, $CDCl_3$, ppm) δ 64.5, 49.1, 48.3, 40.0, 29.9, 26.8, 26.5, 22.3.

Diamine 24. This substance was obtained according to ref 8b by base treatment of material sold by Aldrich as (−)-1-[5-chloro-2-(methylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline (−)-tartrate (abbreviated as CAPTIQ in our laboratory). This was recrystallized from methanol, mp 199−200 °C dec; the Aldrich material melts at 196−199 °C dec, not 211−213 °C as listed. Free diamine **1** was recrystallized from ether−hexane: mp 100−101 °C, (lit.[23] mp 98−99 °C); $[\alpha]^{20}_D$ +51° (c 0.37, $CHCl_3$), lit.[23] $[\alpha]^{25}_{546}$ +48.3° (*c* 2.1, $CHCl_3$). According to ref 22, (+)-**1** should be obtained from the (+)-tartrate salt, not the (−)-tartrate as listed by Aldrich. The absolute configuration of **1** was established by X-ray crystallographic analysis (anomalous dispersion method).

***N,N*-Diisopropyl-2-(6-methoxy-2-naphthyl)propanamide (4a).** To a suspension of (+)-2-(6-methoxy-2-naphthyl)propionic acid (Aldrich, 1.26 g, 5.47 mmol) in 30 mL of dry benzene at room temperature was slowly added by syringe oxalyl chloride (Aldrich, 1.0 mL, 10.9 mmol), and the mixture was stirred overnight at room temperature. The benzene solvent was removed *in vacuo* to afford the acyl chloride as a yellow solid. The solid was dissolved in 30 mL of dry CH_2Cl_2 and cooled in an ice bath, and dry diisopropylamine (7.2 mL, 0.55 mmol) was slowly added at 0 °C. The reaction mixture was warmed to room temperature over 30 min, washed with water (100 mL), 0.5 N HCl (3 × 100 mL), and saturated $NaHCO_3$ (100 mL), dried ($MgSO_4$), and concentrated (aspirator). Filtration chromatography (silica gel, 3 × 20 cm) (elution, 20% EtOAc in hexane) gave a white solid, (+)-**4a** (1.38 g, 81%): $[\alpha]_D20$ (+)107° (*c* 2.7, EtOH). This material was found to be 95% ee by HPLC analysis on a Pirkle-type (*S,S*)-β-Gem 1 column (Regis, 25 cm × 4.6 mm i.d.) (elution, 10% ethanol in hexane at 1.5 mL/min). The 95% ee was upgraded to 99.8% ee (+)-**4a** by selectively precipitating the less soluble racemate from ether (twice) followed by recrystallization from hexane. This gave a 70% yield of 99.8% ee material: $[\alpha]_D20$ (+)112.3 (*c* 1.3, EtOH). Racemic **4a** was obtained by the deprotonation of (+)-**4a** in THF with a 5-fold excess of LDA in 1 h at −78 °C and quenching with saturated NH_4Cl: analytical tLc on silica gel (1:4 EtOAc−hexane) R_f = 0.58. Pure material was obtained by crystallization from toluene−hexane: mp 122−123 °C; molecular ion calcd for $C_{20}H_{27}NO_2$ 313.20419, found *m/e* = 313.2042, error = 0 ppm, base peak = 128 amu; IR ($CHCl_3$, cm^{-1}) 1635 (C=O), 1607 (C=C), 1441 (C−O); 200 MHz NMR ($CDCl_3$, ppm) δ 7.70 (1H, d, *J* = 8.4 Hz), 7.68 (1H, d, *J* = 9.1 Hz), 7.59 (1H, s), 7.35 (1H, dd, *J* = 8.4, 1.7 Hz), 7.13 (1H, dd, *J* = 9.1, 2.5 Hz), 7.10 (1H, s), 4.10

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(1H, sept, J = 6.7 Hz), 3.94 (1H, q, J = 6.8 Hz), 3.91 (3H, s), 3.30 (1H, sept, J = 6.7 Hz), 1.55 (3H, d, J = 6.7 Hz), 1.50 (3H, d, J = 6.8 Hz), 1.46 (3H, d, J = 6.7 Hz), 1.14 (3H, d, J = 6.7 Hz), 0.52 (3H, d, J = 6.7 Hz); ^{13}C NMR (68 MHz, {H}, $CDCl_3$, ppm) δ 172.2, 157.3, 138.0, 133.2, 129.0, 127.2, 126.0, 125.3, 118.8, 105.4, 55.1, 48.2, 45.7, 44.5, 21.1, 20.9, 20.8, 20.0, 19.6.

Preparation of *O*-Trimethylsilyl Enol Ethers 5E and 5Z. To a solution of *N,N*-diisopropyl naproxen amide **4a** (30 mg, 0.10 mmol) in 2 mL of dry THF at −78 °C under N_2 was slowly added *sec*-BuLi in cyclohexane (0.20 mmol), and the mixture was stirred for 10 min at −78 °C. Excess Me_3SiCl (0.3 mL, HCl-free) was added to the enolate solution at −78 °C by syringe, and the mixture was stirred for 30 min at −78 °C; an orange-yellow color faded to a light yellow. The reaction mixture was warmed to room temperature gradually over 30 min, and all the volatiles were removed under vacuum. The crude product was dissolved in dry $CDCl_3$ (dried over 4 Å molecular sieves and passed through an anhydrous K_2CO_3 pad) and filtered quickly through a cotton/Celite/anhydrous K_2CO_3 plug into a dry NMR tube. The NMR spectrum was recorded with a 200 MHz NMR instrument to measure the *E*/*Z* ratio.

Isolation of Mesityllithium for ^{1}H NMR Experiments. To a solution of bromomesitylene (Aldrich, 6.44 g, 32.4 mmol) in 100 mL of dry ether at −78 °C was slowly added *t*-BuLi in pentane (Aldrich, 65.0 mmol) under N_2, and the solution was stirred for 10 min at −78 °C. The reaction mixture was warmed to room temperature gradually over 30 min, and the mixture was filtered through a glass filter frit under a positive N_2 pressure. The white solid was washed with 3 × 10 mL of dry ether under N_2 and was dried under N_2 flow. The residual ether was removed from the solid under vacuum for 2 days, and the material was stored in a glovebox under N_2. The white powdery mesityllithium started to become yellow while it was being dried on the vacuum pump (3.5 g, 87%). H^1 NMR in benzene-d_6 showed that there was a trace of diethyl ether in the mesityllithium powder. Its purity was estimated to be about 80% by titrating a solution in a measured volume of THF using menthol and 1,10-phenanthroline as an indicator.

^{1}H VT NMR Experiment with 4a + Triamine 6. Into *N,N*-diisopropyl naproxen amide **4a** crystals (20 mg, 0.06 mmol) in a dry NMR tube was weighed mesityllithium (ca. 80% pure, 20 mg, 0.06 mmol) as a solid in a glovebox under N_2, and about 0.5 mL of dry THF-d_8 (distilled from Na/K and benzophenone) was vacuum-transferred into the NMR tube on a high-vacuum line at −78 °C. The reaction mixture was agitated vigorously by an NMR tube stirrer, and the resulting orange homogeneous solution was subjected to a VT ^{1}H NMR experiment with the Bruker AM 500 MHz instrument. The ^{1}H NMR spectrum of the enolate solution was recorded at −78 °C: δ 9.13 (ca. 0.05H, broad), 8.85 (ca. 0.9H, broad), 7.68 (ca. 1H, broad), 7.48 (ca. 1H, d, J = 9 Hz), 7.34 (ca. 1H, d, J = 9 Hz), 6.98 (ca. 1H, s), 6.84 (ca. 1H, d, J = 7.4 Hz), 6.8 (mesitylene), 3.35 (m overlapping trace ether residue from mesityllithium), 2.23 (s, mesitylene CH_3), 2.18 (partly obscured s), 1.18−1.08 (broad, partly overlapping trace ether residue). The chiral triamine **6** (24 mg, 0.13 mmol) was added to the enolate solution as a neat liquid via syringe. The resulting mixture was agitated vigorously for 10 min at −78 °C, and then the ^{1}H NMR spectrum was recorded for the wine-colored solution at −78 °C. The signals at δ 9.13 and 8.85 were replaced by a broad signal at δ 8.95 and a broad doublet at δ 8.82 in a ratio of 1:3, and the remainder of the aromatic signals became complex. The aliphatic region was largely obscured by the triamine signals, but the methyl absorption at 1.1801.08 was largely unchanged. To the enolate–triamine aggregate solution was added $BF_3{\cdot}Et_2$ (18 mg, 0.13 mmol) as a neat liquid at −78 °C, and the tempreature was increased to −23 °C prior to recording the ^{1}H NMR spectrum. Signals for the protonated amide **4a** were observed at −23 °C, and the enolate signals could no longer be detected.

VT H^1 NMR Monitoring of the Reaction of 4a + 24. The same procedure was used as described above for **6** with *N,N*-diisopropyl **4a** (15 mg, 0.05 mmol), mesityllithium (ca. 80% pure, 16 mg, 0.10 mmol), and 0.5 mL of dry THF-d_8. The H^1 NMR spectrum of the enolate solution was recorded at −78 °C, the chiral diamine **24** (26 mg, 0.1 mmol) in 0.5 mL of dry THF-d_8 was added to the enolate solution at −78 °C via syringe, and the H^1 NMR spectra of the enolate–amine mixture were recorded at −78 °C and room temperature, respectively. Signals for the protonated amide **2** appeared already at −78 °C (some line broadening). The spectrum became better resolved upon warming, but no further substantial changes were seen.

Synthesis of Oxazoline 13. Naproxen **3a** (Aldrich, 2.06 g, 8.76 mmol), 2-amino-2-methylpropanol (Aldrich, 0.82 g, 9.20 mmol), and a catalytic amount of *p*-toluenesulfonic acid were placed in 100 mL of dry toluene and refluxed in an oil bath for 3 days with azeotropic removal of water using a Dean–Stark trap. Toluene was evaporated in vacuo, and the residue was dissolved in CH_2Cl_2, poured into saturated $NaHCO_3$ (100 mL), extracted with 2 × 100 mL of CH_2Cl_2, dried ($MgSO_4$), and concentrated *in vacuo*. The yellow solid was purified by flash column chromatography (silica gel, 3 × 20 cm) (elution, 50% EtOAc in hexane), and the second fraction (R_f = 0.38, 50% EtOAc in hexane) gave a **13** as a white solid (1.53 g, 62%): analytical TLC on silica gel (1:1 EtOAc–hexane) R_f = 0.38. Pure material was obtained by crystallization from hexane: mp 103−105 °C; molecular ion calcd for $C_{18}H_{21}NO_2$ 283.15723, found m/e = 283.1572, error = 0 ppm, base peak = 283 amu; IR (neat, cm^{-1}) 1661 (C=N), 1607 (C=C), 1216 (C−O); 200 MHz NMR (acetone-d_6, ppm) δ 7.77 (1H, d, J = 8.9 Hz), 7.76 (1H, d, J = 8.5 Hz), 7.72 (1H, d, J = 1.9 Hz), 7.43 (1H, dd, J = 8.5, 1.9 Hz), 7.27 (1H, d, J = 2.5 Hz), 7.13 (1H, dd, J = 8.9, 2.5 Hz), 3.90 (3H, s), 3.85 (1H, d, J = 8.2 Hz), 3.81 (1H, d, J = 8.2 Hz), 3.80 (1H, q, J = 7.1 Hz), 1.52 (3H, d, J = 7.1 Hz), 1.22 (6H, s); ^{13}C NMR (68 MHz, {H}, $CDCl_3$, ppm) δ 167.4, 157.2, 136.4, 133.3, 128.9, 128.6, 126.8, 125.6, 125.3, 118.5, 105.2, 78.6, 66.5, 54.7, 39.0, 28.0, 27.8, 19.1.

***N,N*-Diisopropyl-2-(cyclohex-1-enyl)propionamide (15).** To a suspension of 2-(cyclohex-1-enyl)propionic acid[24] (1.01 g, 6.57 mmol) in 50 mL of dry benzene at room temperature under N_2 was slowly added oxalyl chloride (Aldrich, 1.2 mL, 13.1 mmol) via syringe. After the mixture was stirred overnight at room temperature, the benzene was removed under vacuum and 50 mL of dry CH_2Cl_2 was added. The mixture was cooled (ice bath), and diisopropyl amine (4.3 mL, 32.9 mmol) was added via syringe. The cooling bath was removed, and the reaction was quenched after 4 h at room temperature with 100 mL of H_2O, extracted with CH_2Cl_2 (2 × 100 mL). The CH_2Cl_2 layers were washed with saturated $NaHCO_3$ (100 mL) and brine (100 mL) and then dried ($MgSO_4$) and concentrated (aspirator) to give a pale yellow oil. Purification by filtration chromatography (silica gel, 3 × 10 cm) (elution, 10% EtOAc in hexane to 20% EtOAc in hexane) gave a white solid (1.49 g, 96%): analytical tlc on silica gel (1:5 EtOAc–hexane) R_f = 0.47. Pure material was obtained by crystallization from hexane: mp 52−53 °C; molecular ion calcd for $C_{15}H_{27}NO$ 237.20927, found m/e = 237.2093, error = 0 ppm, base peak = 128 amu; IR (neat, cm^{-1}) 1639 (C=O), 1455 (C=C); 270 MHz NMR ($CDCl_3$, ppm) δ 5.49 (1H, br s), 4.04 (1H, sept, J = 6.7 Hz), 3.32 (1H, sept, J = 6.7 Hz), 3.09 (1H, q, J = 6.8 Hz), 2.1−1.9 (4H, m), 1.7−1.5 (4H, m), 1.41 (3H, d, J = 6.7 Hz), 1.39 (3H, d, J = 6.7 Hz), 1.18 (3H, d, J = 6.8 Hz), 1.14 (3H, d, J = 6.8 Hz), 1.09 (3H, d, J = 6.6 Hz); ^{13}C NMR (68 MHz, {H}, $CDCl_3$, ppm) δ 172.0, 137.9, 122.4, 47.7, 45.8, 45.3, 25.5, 24.9, 22.6, 22.0, 20.5, 20.2, 20.1, 16.9, 16.8.

Synthesis of 3-(2-Naphthyl)-6,6-dimethyl-δ-valerolactone (18). To a solution of ethyl 2-(2-naphthyl)acetate (3.05 g, 14.3 mmol) in 100 mL of dry THF at −78 °C under N_2 was slowly added lithium hexamethyldisilazide (LiHMDS) (Aldrich, 1.0 M in THF, 15.7 mL, 15.7 mmol), and the mixture was stirred for 1 h at −78 °C. To the yellow enolate solution at −78 °C was added 4-bromo-2-methyl-2-butene (Aldrich, 2.2 mL, 17.1 mmol) as a neat liquid via syringe, and the mixture was warmed to room temperature gradually over 20 min. The mixture was quenched with saturated NH_4Cl (100 mL) and extracted with 200 mL of ether, and the ether layer was washed with brine (100 mL), dried ($MgSO_4$), and concentrated (aspirator). The crude oil was purified by flash column chromatography (silica gel, 3 × 20 cm) (gradient elution, 5% EtOAc in hexane to 10% EtOAc in hexane). The first fraction (R_f = 0.53, 10% EtOAc in hexane) gave **17a** as a yellow oil (4.08 g), and second fraction (R_f = 0.23, 10% EtOAc in hexane) was the starting ester.

The main fraction from above (3.17 g) was dissolved in a 5:1 mixture of 125 mL of MeOH and 25 mL of aqueous NaOH solution (5 g, 56.2 mmol) and stirred at room temperature overnight. Methanol was

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removed (aspirator), and the water layer was extracted with 2 × 50 mL of ether. The aqueous layer was acidified to pH ≈ 2 with H_2SO_4 and extracted with 3 × 70 mL of CH_2Cl_2. All the CH_2Cl_2 layers were combined, washed with brine (100 mL), dried ($MgSO_4$), and concentrated (aspirator) to give a white solid. The crude product was recrystallized from toluene–hexane to give a white powder (2.35 g). Pure 2-(2-naphthyl)-5-methyl-4-hexenoic acid (**17b**) was obtained by crystallization from toluene–hexane: mp 95–97 °C; molecular ion calcd for $C_{17}H_{18}O_2$ 254.13064, found *m/e* = 254.1307, error = 0 ppm; IR (neat, cm^{-1}) 3056, (O–H), 1704 (C=O), 1441 (C=C); 200 MHz NMR ($CDCl_3$, ppm) δ 7.82–7.76 (4H, m), 7.5–7.41 (3H, m), 5.06 (1H, t, *J* = 7.1 Hz), 3.72 (1H, t, *J* = 7.7 Hz), 2.93–2.79 (1H, m), 2.62–2.51 (1H, m), 1.62 (3H, s), 1.57 (3H, s).

The 2-(2-naphthyl)-5-methyl-4-hexenoic acid (**17b**) (2.20 g, 8.65 mmol) from the hydrolysis step and a catalytic amount of *p*-toluenesolufonic acid were dissolved in 300 mL of dry CH_2Cl_2 and refluxed at 60 °C overnight. The reaction mixture was cooled to room temperature and poured into dilute $NaHCO_3$ (100 mL). The CH_2Cl_2 layer was separated, washed with brine (100 mL), dried ($MgSO_4$), and concentrated (aspirator) to obtain a white solid. The crude solid was purified by flash column chromatography (silica gel, 3 × 15 cm) (gradient elution, 30% EtOAc in hexane to 50% EtOAc in hexane). The first fraction (R_f = 0.50, 50% EtOAc in hexane) gave **18** as a white solid (1.84 g, 84%), and a second fraction contained the starting acid: analytical TLC on silica gel (1:1 EtOAc–hexane) R_f = 0.50. Pure **18** was obtained by crystallization from toluene–hexane: mp 120–121 °C; molecular ion calcd for $C_{17}H_{18}O_2$ 254.13064, found *m/e* = 254.1307, error = 0 ppm, base peak = 154 amu; IR (neat, cm^{-1}) 1719 (C=O). 1372, (C=C); 200 MHz NMR ($CDCl_3$, ppm) δ 7.85–7.70 (3H, m) 7.66 (1H, br s), 7.50–7.40 (2H, m), 7.32 (1H, dd, *J* = 8.5, 1.7 Hz), 3.82 (1H, dd, *J* = 8.3, 8.1 Hz), 2.28–2.17 (2H, m), 1.94–1.8 (2H, m), 1.54 (3H, s), 1.51 (3 H, s); ^{13}C NMR (68 MHz, {H}, $CDCl_3$, ppm) δ 171.8, 137.0, 138.1, 136.6, 133.0, 132.1, 127.2, 126.6, 125.8, 125.5, 82.7, 46.9, 32.9, 29.4, 28.1, 27.9, 26.1

VT H^1 NMR Monitoring of the Reaction of 18 + 24. The same procedure was used as for **4a** + **24**, starting with **18** (15 mg, 0.06 mmol), solid mesityllithium (ca. 80% pure, 19 mg, 0.12 mmol), and 0.5 mL of dry THF-d_8. The H^1 NMR spectrum of the yellow enolate solution was recorded at −78 °C, and the chiral diamine **24** (32 mg, 0.12 mmol) in 0.5 mL of dry THF-d_8 was added at −78 °C via syringe. The H^1 NMR spectrum of amine-free **19** contained broad signals at δ 8.9, 2.5, and 1.8 ppm and a broad methyl singlet at 1.32 ppm. Upon addition of **24**, the signals became marginally broader, but there was no characteristic change and **18** could not be detected. To the enolate–amine mixture was added $BF_3{\cdot}OEt_2$ as a neat liquid by syringe at −78 °C. Signals for the protonated lactone **18** appeared already at −78 °C after the addition of $BF_3{\cdot}OEt_2$: δ 3.85 (C_α-H, dd), 1.53 (s, CH_3), and 1.44 (s, CH_3). Upon warming to 20 °C, the methyl signals shifted to 1.49 and 1.45 ppm, and the signal at 3.85 ppm became an apparent triplet, but no other substantial changes were seen.

Deracemization of 4a with *sec*-BuLi and Triamine 6. To the racemic naproxen amide **4a** (45 mg, 0.14 mmol) in 2 mL of dry THF at −78 °C was slowly added by syringe, *sec*-BuLi in cyclohexane (Aldrich, 0.28 mmol), and the solution was stirred for 10 min at −78 °C; an orange colored mixture resulted. The chiral amine **1c** (52 mg, 0.28 mmol) was added to the enolate solution by syringe as a neat liquid, and stirring was continued for 30 min at −78 °C; the orange color changed into a strong wine-red color. To the mixture was added $BF_3{\cdot}OEt_2$ (0.28 mmol) as a neat liquid, and after a few min at −78 °C, the reaction mixture was warmed to −23 °C (CCl_4–dry ice bath); a wine-red color disappeared in less than 10 min at −23 °C. The mixture was quenched with 7 mL of hexane to precipitate salts and diluted with 50 mL of CH_2Cl_2, and the organic layer was washed with saturated NH_4Cl (30 mL), dried ($MgSO_4$), and concentrated (aspirator). The crude product was purified by filtration column chromatography (silica gel, 1 × 10 cm) (elution, 20% EtOAc in hexane) to afford a white solid. The % ee was determined by HPLC analysis using a Pirkle (*S,S*)-β-Gem 1 (Regis, 25 cm × 4.6 mm i.d.).

General Procedure for BF_3–Etherate Enolate Quenching with 6 or 24 and Product Assay. To a racemic substrate (0.14–0.25 mmol, 1.0 equiv) in 2 mL of dry THF at −78 °C was slowly added alkyllithium base (2–3 equiv) by syringe, and the solution was stirred for 30 min at −78 °C. The chiral amine (2–3 equiv) was added to the enolate solution by syringe, and the solution was stirred for 30 min at −78 °C. To the mixture was added $BF_3{\cdot}OEt_2$ (the number of equivalents used was the same as for the base) as a neat liquid by syringe, and after a few minutes of stirring at −78 °C, the reaction mixture was gradually warmed to −23 °C. The reaction mixture was stirred at −23 °C until a colorless solution resulted, usually for 10–20 min. The reaction mixture was quenched with saturated NH_4Cl (10 mL) at −23 °C and was extracted with 2 × 30 mL of CH_2Cl_2 or ether. The organic layer was washed with brine (30 mL), dried ($MgSO_4$), and concentrated *in vacuo* to afford the crude product. The crude products were purified by flash column chromatography (silica gel, 1 × 10 cm), and % ee's were analyzed as described below for each substrate. The base used for enolate formation (number of equivalents), elution conditions for flash column chromatography, and the method for % ee determination are given. (1) Ethyl ester of naproxen (**3b**): enolate generation with mesityllithium (2.0 equiv); elution, 5% EtOAc in hexane; % ee estimated by ^1H NMR with Eu(hfc)$_3$ in $CDCl_3$ (α-methyl doublets resolved at δ 2.88 ppm (minor) and δ 2.78 ppm (major). (2) Ethyl *O*-benzyl lactate: mesityllithium (2.0 equiv); elution, 5% EtOAc in hexane; % ee by ^1H NMR with Eu(hfc)$_3$ in $CDCl_3$ (α-methyl doublets resolved at δ 2.29 ppm (major) and δ 2.46 ppm (minor). (3) *N,N*-Diisopropyl naproxen amide (+)-**4a**: enolate generation with *sec*-butyllithium (2 equiv); % ee determined on a (*S,S*)-β-Gem 1 column (Regis, 25 cm × 4.6 mm i.d.), elution: 10% ethanol in hexane at 1.2 mL/min, R_t = 4.6 min (*S*-isomer, minor) and 5.9 min (*R*-isomer, major). (4) *N,N*-Diethyl naproxen amide **4b**: mesityllithium (2.0 equiv); gradient elution, 20% EtOAc in hexane to 30% EtOAc in hexane; % ee was determined by ^1H NMR with Eu(hfc)$_3$ in acetone-d_6 (an aromatic doublets resolved at δ 7.31 ppm (*S*-isomer) and δ 7.31 ppm (*R* isomer)) and confirmed by HPLC on a Pirkle (*S,S*)-β-Gem 1 column (Regis, 25 cm × 4.6 mm i.d.); elution: 50% EtOH in hexane at 1.75 mL/min flow rate, R_t = 2.5 min (*S*-isomer, minor) and R_t = 4.1 min (*R*-isomer, major). (5) *N,N*-Dimethyl naproxen amide (+)-**4c**: enolate generation with *sec*-butyllithium (2 equiv); % ee determined on a (*S,S*)-β-Gem 1 column (Regis, 25 cm × 4.6 mm i.d.), elution: 50% isopropyl alcohol in hexane at 1.2 mL/min, R_t = 6.2 min (*S*-isomer, minor) and 10.1 min (*R*-isomer, major). (6) 4,4-Dimethyl-2-oxazoline of naproxen (**13**): *sec*-BuLi (2.0 equiv); gradient elution, 30% EtOAc in hexane to 50% EtOAc in hexane; % ee by ^1H NMR with Eu(hfc)$_3$ in benzene-d_6 (methoxy singlets resolved at δ 3.37 ppm (minor) and δ 3.42 ppm (major)). (7) 1-Methyl-3-phenyl-2-pyrrolidinone (**14**). A special workup was necessary to get 85% recovery; 50 mL of saturated NaCl solution was added to the reaction mixture, and the mixture was extracted with 3 × 50 mL of ether while the aqueous layer was kept saturated with NaCl. Ether layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a yellow oil. The rest of the procedure followed the standard method described above: *sec*-BuLi (2.0 equiv); elution, 80% EtOAc in hexane; % ee by ^1H NMR with Eu(hfc)$_3$ in acetone-d_6 (methyl singlets resolved at δ 3.14 ppm (major) and δ 3.18 ppm (minor)) and confirmed by HPLC on an (*R*)-α-Burke 1 column, elution: 5% EtOH in hexane at 1.2 mL/min flow rate, R_t = 14.4 min (major) and R_t = 15.7 min (minor). (8) *N,N*-Diisopropyl-2-(cyclohex-1-enyl)propionamide (**15**); HPLC on a CHIRALCEL-OD column (Regis, 25 cm × 4.6 mm i.d.), elution: 0.1% methanol–0.1% isopropyl alcohol in hexane at 0.5 mL/min flow rate, R_t = 14.1 min (minor) and 16.5 min (major). (9) *N*-Benzoyl alanine methyl ester **16**: enolate generation with mesityllithium (3.0 equiv); analysis of % ee by HPLC on an (*R*)-α-Burke 1 column (Regis), elution: 5% EtOH hexane at 2.0 mL/min flow rate, R_t = 9.6 min (*R*-isomer) and 10.7 min, (*S*-isomer). (10) 3-(2-Naphthyl)-6,6-dimethyl-δ-valerolactone (**18**): (mesityllithium (2.0 equiv) was used for enolate generation); analysis of % ee by ^1H NMR with Eu(hfc)$_3$ in $CDCl_3$ (methyl singlets resolved at δ 1.99 ppm (major) and δ 1.81 ppm (minor)) and confirmed by HPLC on an (*R*)-α-Burke 1 column (Regis, 25 cm × 10 mm i.d.), elution: 10% EtOH in hexane at 2.0 mL/min flow rate, R_t = 9.6 min (minor) and 10.6 min (major).

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