Investigating the π-Facial Discrimination Phenomenon in the Conjugate Addition of Amines to Chiral Crotonates: A Convenient Basis for the Rational Design of Chiral Auxiliaries

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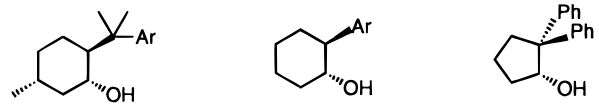
This paper is concerned with the nature of the chiral inducer in the high pressure-induced conjugate addition of amines to auxiliary-tethered crotonates. Almost complete stereocontrol was obtained in the addition of diphenylmethanamine to crotonates derived from the "arylmenthol" auxiliaries **18a**, **18c**, and **4** bearing an *o*-methoxyphenyl, *p*-phenoxyphenyl, or β-naphthyl substituent, respectively. This high efficiency has been attributed to the predominance of *stacked conformations* in such crotonates, a hypothesis supported by the ^{1}H NMR spectra, calculated energy of conformational optima of the corresponding crotonates, and X-ray crystal structure of **5a**. The arene and enoate appendages are roughly coplanar, separated by 3.4−4 Å. In contrast, only moderate selectivities could be achieved using various *trans*-2-arylcyclohexanols (**27**, **28**, **2c**, **29**) as auxiliaries. In these cases the efficiency appears to be seriously compromised by the "widening V" arrangement exhibited by the two π-systems, as shown in the X-ray crystal structures of crotonates **5h** and **5k**. The sense of stereochemical induction of this conjugate addition has been determined by condensing diphenylmethanamine with enantiopure crotonate (+)-**5a**. The adduct **9a** was converted to amino alcohol (*S*)-**11**, of known configuration. This correlation is consistent with the preferential attack of the amine to the less sterically hindered enoate π-face of (+)-**5a**, in its *s-trans* conformation. Finally, the stereochemistry of the proton transfer was determined by adding *N*,*N*-dideuteriodiphenylmethanamine to crotonate (±)-**5a**. The stereochemical outcome of this addition is consistent with the *anti*-addition of the incoming nitrogen nucleophile and the deuterium atom.

Introduction

After decades of exploratory studies, the field of asymmetric synthesis attained a high degree of sophistication when several teams succeeded in elaborating efficient and practical chiral auxiliaries. The first auxiliary that furnished important levels of asymmetric induction in a great variety of condensations was (−)-8-phenylmenthol (**1a**) (Chart 1), introduced by Corey in 1975.[1] The much higher efficiency of 8-phenylmenthol, compared to menthol itself, clearly indicates that phenyl groups (and more generally the aryl substituents) act as powerful stereodirecting steric barriers. Ten years ago, fine tuning of 8-phenylmenthyl esters led Whitesell to propose *trans*-2-phenylcyclohexanol (**2a**) as a substantially simplified substitute (bearing only two stereogenic centers) for 8-phenylmenthol (**1a**).[2] We have shown that auxiliaries **1b**,**c** and **2b**−**d**, obtained by replacing the phenyl ring in **1a** or **2a** with more bulky aromatic substituents, led to a notable enhancement of the degree of diastereodifferentiation, compared to parent compounds **1a** or **2a**, in the Michael addition of amines to chiral crotonates,[3] in the catalytical hydrogenation of chiral β-acetamidocrotonates,[4a] and in the aldol condensation of chiral silyl enol esters with aldehydes.[4b] We have also demonstrated that 2,2-diphenylcyclopentanol (**3**), although containing a *single* stereogenic center, is a powerful chiral auxiliary, as efficient as 8-phenylmenthol in the aforementioned hydrogenation reaction.[4a]

Chart 1



1a Ar = phenyl
1b Ar = *p*-phenoxyphenyl
1c Ar = β-naphthyl

2a Ar = phenyl
2b Ar = *p*-*tert*-butylphenyl
2c Ar = *p*-biphenyl
2d Ar = 9-phenanthryl

3

On the other hand, we have established that "simplified" auxiliary **4** (Chart 2, the analogous structure of 8-β-naphthylmenthol (**1c**), lacking only the methyl substituent on the cyclohexane ring) is a highly efficient chiral inducer, as potent as parent **1c**.[5] Thus, high pressure-mediated addition of diphenylmethanamine, in methanol, to the corresponding crotonate **5a** led to the expected conjugate adduct with a very high de (98%), a remarkable

[⊗] Abstract published in *Advance ACS Abstracts,* March 1, 1996.

(1) (a) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908−6909.

(2) Whitesell, J. K.; Chen, H. H.; Lawrence, R. M. *J. Org. Chem.* **1985**, *50*, 4663−4664.

(3) (a) d'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112−8114. (b) Potin, D.; Dumas, F.; Maddaluno, J. *Synth. Commun.* **1990**, *20*, 2805−2813.

(4) (a) Potin, D.; Dumas, F.; d'Angelo, J. *J. Am. Chem. Soc.* **1990**, *112*, 3483−3486. (b) Vasconcellos, M. L.; Desmaële, D.; Costa, P. R. R.; d'Angelo, J. *Tetrahedron Lett.* **1992**, *33* 4921−4922. For related "simplified" chiral auxiliaries derived from β-pinene: Vasconcellos, M. L.; d'Angelo, J; Desmaële, D.; Costa, P. R. R.; Potin, D. *Tetrahedron: Asymmetry* **1991**, *2*, 353−356.

(5) Mezrhab, B.; Dumas, F.; d'Angelo, J.; Riche, C. *J. Org. Chem.* **1994**, *59*, 500−503.

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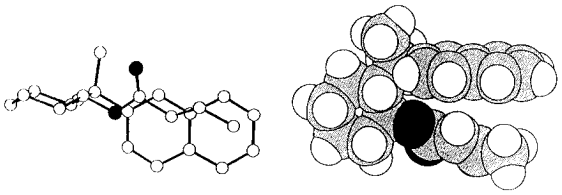
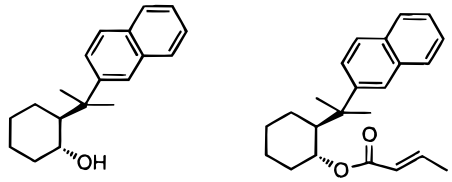


Figure 1. (Left) plot of the X-ray crystal structure of crotonate **5a**, viewing the molecule perpendicularly to the naphthalene plane (hydrogens are omitted). (Right) space-filling diagram concentrating on the π-system region.

Chart 2



(±)-4 (±)-5a

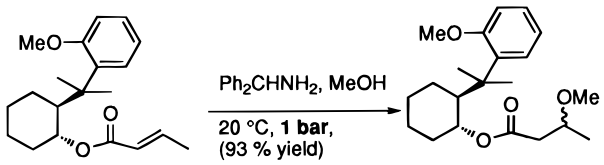
selectivity for a reaction in which the nearest stereogenic center of the inducer is located *four bonds away* from the site of C−N bond formation, in an apparently conformationally mobile substrate.[5] This high stereoselectivity has been attributed to the fact that in crotonate **5a**, the enoate side chain, and the naphthalene nucleus (which plays the role of a "stereoblocking group") have a *stacked conformation*.[6] This hypothesis was strongly supported by the X-ray crystal structure of crotonate **5a** which shows that the two π-systems are roughly coplanar, with a separation distance in the range of 3.4−4 Å (Figure 1).

The purpose of this paper is to report new chemical experiments in the addition of amines to auxiliary-tethered crotonates.[7] In order to gain a better understanding of the forces which affect the π-facial discrimination phenomenon, and consequently to improve the design of the chiral auxiliary component, the X-ray crystal structures of *trans*-2-arylcyclohexyl crotonates **5h** and **5k** have also been determined (*vide infra*). On the basis of these findings, it is highly likely that the high facial selectivity exhibited by crotonate **5a** originates from the stacked geometry of the arene and enoate moieties. In contrast, crotonates **5h** and **5k**, in which these two π-systems lie in a "widening V" arrangement (Figures 3 and 4), furnish low levels of diastereodifferentiation.

Results and Discussion

Since the present Michael reaction constitutes an enantioselective approach to β-amino esters,[8] *diphenylmethanamine* was used as an "ammonia equivalent", through the hydrogenolysis of the adducts. This amine was preferred over benzylamine since better regioselectivities (1,4- versus 1,2-addition) and diastereoselectivities were obtained. For instance, the diastereomeric excesses observed in the high pressure-promoted additions of diphenylmethanamine or benzylamine to 8-phenylmenthyl crotonate, in methanol, were 60% and 20%, respectively. *Methanol* was used as solvent, since it significantly enhanced the rate of these addition reactions, as well as the diastereoselectivities (*no* de was obtained in the absence of this alcohol). The role of the *high pressure* is crucial to the stereoselectivity: thus, addition of diphenylmethanamine to crotonate **5a**, *under atmospheric pressure* (5 days at 40 °C in MeOH), furnished the expected β-amino ester with a 50% yield, but with a very low de (10%) (when this addition was performed under 14 kbar, a 98% de was observed).[5] Incidentally, an intriguing effect of the pressure on the chemoselectivity was noted with crotonate **5b**. Thus, while the β-amino ester **9b** derived from conjugate addition of *diphenylmethanamine* was the *only* product obtained under high pressure (*vide infra*: Table 3, entry 3), surprisingly, the conjugate addition of *methanol* to furnish β-methoxy ester **6** in low de (30%) was the *only* reaction observed at atmospheric pressure (Scheme 1).

Scheme 1



(±)-5b 6

Stereochemical Sense of Induction of the Michael Addition; the Question of the Conformational Preference of the Crotonate Fragment. We have previously proposed, on the basis of the ^{1}H NMR analysis of the adduct, that the high-pressure-induced addition of diphenylmethanamine, in the presence of methanol, to *racemic* crotonate **5a** proceeded essentially (98% de) to the less sterically congested enoate π-face, in its *s-trans* conformation.[5] In order to ascertain the stereochemical sense of induction, the addition of diphenylmethanamine to enantiopure **5a**, followed by chemical correlation of the adduct with a compound of known configuration, was undertaken. Recently, Comins and Salvador claimed to have resolved auxiliary **4** by means of an enzymatic esterification procedure.[9] However, in spite of extensive experimentation, all attempts at reproducing this work were invariably unsuccessful.[10] We therefore turned to a chemical resolution, by using commercially available (+)-Naproxene [(*S*)-6-methoxy-α-methyl-2-naphthaleneacetic acid], as resolving agent. To our delight, a great solubility difference between the crystalline diastereomeric esters formed by condensing (±)-**4** with naproxen acid chloride was observed. Isomer **7** (Chart 3) was found to be the less soluble one in a methanol−hexane mixture, thereby allowing a facile and nearly quantitative resolution. Furthermore, the X-ray crystal structure determination of **7** has been made (Figure 2), establishing unambiguously the 1*S*,2*R* configuration of the alcohol component. All attempts at direct hydrolysis of **7**, under a variety of conditions (KOH, 12 h in refluxing EtOH; NaOH, 18 h in refluxing dioxane; LiOH, H_2O_2, 24 h at 20 °C), failed; this ester was cleaved by reduction with

(6) Review: Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475−497.
(7) For recent examples of conjugate addition of lithium amides to enoates, see: Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1999−2008. Enders, D.; Bettray, W.; Raabe, G.; Runsink, J. *Synthesis* **1994**, 1322−1326. Tsukada, N.; Shimada, T.; Gyoung, Y. S.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* **1995**, *60*, 143−148. Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Goodwin, C. J. *Tetrahedron: Asymmetry* **1995**, *6*, 165−176. Jenner, G. *Tetrahedron Lett.* **1995**, *36*, 233−236. Davies, S. G.; Fenwick, D. R. *J. Chem. Soc., Chem. Commun.* **1995**, 1109−1110.
(8) Reviews: Cole, D. C. *Tetrahedron* **1994**, *50*, 9517−9582. Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichim. Acta* **1994**, *27 (1)*, 3−11.
(9) Comins, D. L.; Salvador, J. M. *J. Org. Chem.* **1993**, *58*, 4656−4661.
(10) We are indebted to Dr. Robert Azerad (CNRS, Université René Descartes, Paris) for these experiments.

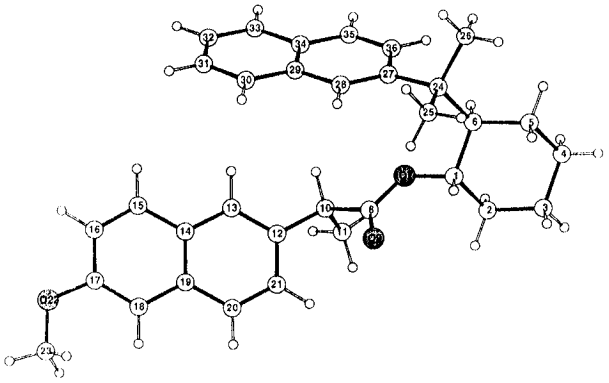


Figure 2. X-ray crystal structure of ester **7**.

Chart 3

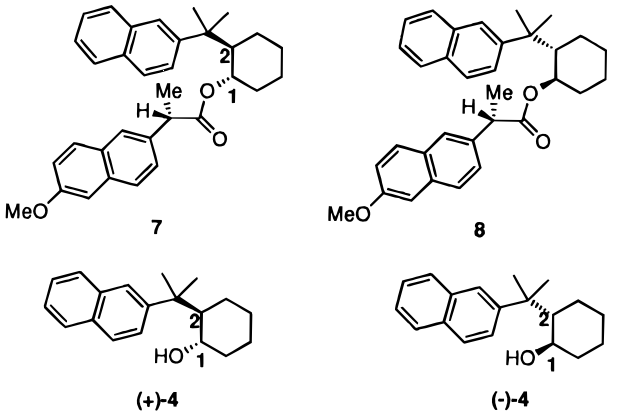
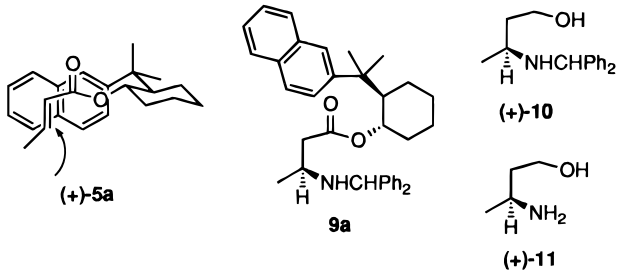


Chart 4



$LiAlH_4$, delivering quantitatively the desired enantiopure alcohol (1*S*,2*R*)-(+)-**4**. In a similar fashion, the more soluble diastereomer **8** was converted into (1*R*,2*S*)-(−)-**4**.

Diphenylmethanamine was then added to crotonate (1*S*,2*R*)-(+)-**5a**, derived from alcohol (1*S*,2*R*)-(+)-**4**. This addition (14 kbar, 12 h at 20 °C in MeOH, 67% yield) gave β-amino ester **9a** with a de of 98%. The *S* configuration at the newly created stereogenic center in **9a** was established through $LiAlH_4$ reduction to (*S*)-(+)-**10**, which upon hydrogenolysis [H_2/$Pd(OH)_2$] produced amino alcohol (*S*)-(+)-**11** of known configuration.[11] This stereochemical correlation was consistent with attack of the amine preferentially from the less sterically hindered (*Si*) enoate π-face of (+)-**5a**, *in its s-trans conformation* (arrow, Chart 4).

At this stage the crucial problem of the *s-cis*/*s-trans* stereochemistry of the crotonate **5a** arose, since X-ray analyses of this ester (Figure 1), of related crotonates **5h** and **5k** (Figures 3 and 4, *vide infra*), as well as most

(11) Kinas, R.; Pankiewicz, K.; Stec, W. J.; Farmer, P. B.; Foster, A. B.; Jarman, M. *J. Org. Chem.* **1977**, *42*, 1650−1652.

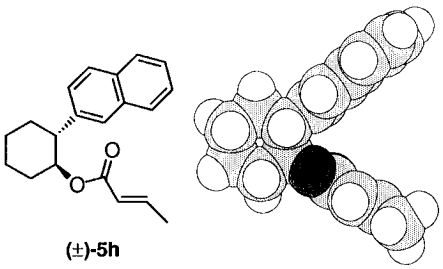


Figure 3. X-ray crystal structure of crotonate **5h**: space-filling diagram.

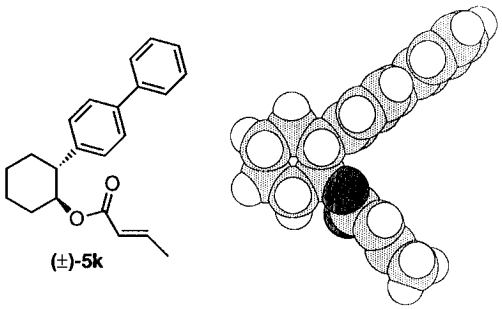
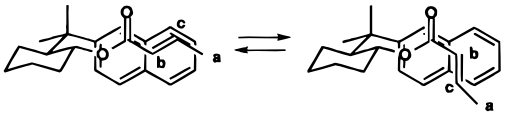


Figure 4. X-ray crystal structure of crotonate **5k**: space-filling diagram.

Table 1. Variable-Temperature 400 MHz ^{1}H NMR Study of 5a in $(CD_3)_2CO$



T, °C	δ Ha	δ Hb	δ Hc
+45	1.26	4.96	6.08
+25	1.22	4.95	6.04
−1	1.17	4.90	5.92
−31	1.05	4.87	5.73

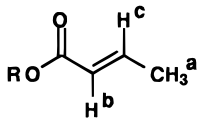
uncomplexed enoates,[12] indicate a marked *s-cis* conformational preference in the *solid state*. In view of the fact that high-pressure addition of diphenylmethanamine to **5a**, in methanol, implicates almost exclusively the *s-trans* conformer, we decided to examine the conformational preference of this crotonate in solution, *bearing in mind that, according to the Curtin−Hammett principle, the product ratio does not necessarily reflect the population of these conformers in the ground state*.[13] For this purpose, a variable-temperature ^{1}H NMR study of **5a** was first undertaken. The chemical shifts of the enoate hydrogens moved upfield upon cooling in the range of +45 °C → −31 °C, by 0.10 (α-vinylic proton), 0.35 (β-vinylic proton), and 0.20 ppm (Me protons) (Table 1). As previously pointed out by Dussault,[14] this can be interpreted in terms of a conformational equilibrium that is shifted toward the *s-trans* isomer at lower temperature; however, this experiment offers no information regarding the quantitative determination of conformers. Seeing that the presence of methanol in conversion (**5a** → **9a**) appears to be critical to gain a good diastereoselection

(12) Shida, N.; Kabuto, C.; Niwa, T.; Ebata, T.; Yamamoto, Y. *J. Org. Chem.* **1994**, *59*, 4068−4075.

(13) For the Curtin−Hammett principle, see: *Stereochemistry of Organic Compounds*; Eliel, E. L., Wilen, S. H., Eds.; John Wiley: New York, 1994; pp 647−655.

(14) Dussault, P. H.; Woller, K. R.; Hillier, M. C. *Tetrahedron* **1994**, *50*, 8929−8940.

Table 2. Solvent Effect in the ^{1}H NMR of 5a (at 25 °C)



solvent	δ Ha	δ Hb	δ Hc
$CDCl_3$	1.15	4.83	5.98
CD_3CN	1.17	4.83	5.96
CD_3OD	1.09	4.77	5.87

(thus, *no* selectivity was observed when this addition was performed under high pressure in a MeCN/Et_2O mixture), the solvent effect in the NMR study of crotonate **5a** was also investigated (Table 2). However, only a minute effect was observed by changing CD_3OD for CD_3CN, thus reflecting no significant alteration in the conformational equilibrium, *under atmospheric pressure*.

At first sight, the dramatic solvent effect on the stereoselectivity seems to be consistent with a kinetically controlled addition in methanol, while equilibration, leading to the thermodynamic product (equimolar mixture of diastereomers), possibly occurred in MeCN/Et_2O. Equilibration of β-amino esters, under thermal conditions, was actually evidenced by Hawkins.[15] However, seeing that pressurization in MeCN/Et_2O (14 kbar, 70 h at 60 °C, in the presence of a catalytical amount of Ph_2CHNH_2) of enamino ester **9a** having a 98% de, returned quantitatively the unchanged starting material, it is clear that the addition reaction of $PhCHNH_2$ to crotonate **5a** in MeCN/Et_2O is not reversible under the conditions used and that its steric course is therefore kinetically determined.

In any case, this remarkable solvent effect can be compared to theoretical calculations made by Houk on enoates.[16] Thus, when in the *ground state*, it has been established that the *s-cis* conformer of methyl acrylate is more stable than the *s-trans* isomer by 0.7 kcal mol^{-1}, while the reverse was found with the *protonated form* of this ester, the *s-trans* conformer being preferred by 3.6 kcal mol^{-1} over the *s-cis* isomer. The critical role of methanol might be therefore interpreted in terms of *hydrogen-bond formation* between this solvent and the crotonate moiety, a phenomenon favored under high pressure, because of the decrease in atomic distance and suppression of thermal motions.[17ab]

Another essential aspect of this Michael addition was the stereochemistry of the proton transfer, which was determined as follows. A solution of crotonate **5a** and Ph_2CHND_2 (prepared by stirring 1 h at 20 °C Ph_2CHNH_2 with a MeOD−D_2O mixture) in MeOD was pressurized for 12 h under 14 kbar at 20 °C to furnish deuterated adduct **12**, which was then reduced ($LiAlH_4$) to **13** (Chart 5). Careful examination of the spectral data of **13** reveals the presence of an intramolecular hydrogen bond, restricting considerably the degrees of freedom of the molecule; consequently, the ^{1}H NMR spectrum of this amino alcohol could be analyzed on the basis of a pseudo-six-membered ring, in its energetically preferred chairlike conformation (Me group adopting an "equatorial" position). Thus, after selective decoupling of the geminal methyl signal, proton Ha exhibited a residual coupling constant with the vicinal proton Hb of 9.0 Hz, unequivocally assigned to a J_{anti}, the corresponding proton in the similarly decoupled NMR spectrum of the nondeuterated parent compound **10** exhibiting by comparison two coupling constants, of 8.7 Hz (J_{anti} between Ha and Hb) and 3.8 Hz (J_{gauche} between Ha and Hc). These NMR experiments established unambiguously the relative configuration of the deuterium atom and the amine moiety in **13** (and therefore in **12**), a stereochemical outcome consistent with the *anti*-addition of the incoming nucleophile and the deuterium atom to crotonate **5a**. This stereochemical result may be interpreted as MeOD-mediated deuteron transfer, a view reinforced by the observation that methanol plays a critical role in the present Michael addition.[17b] It should be noted that the stereochemical course (*syn* or *anti*) in the conjugate addition of neutral nucleophiles to electrophilic alkenes, although not well documented, appears to be substrate dependent.[18]

Chart 5

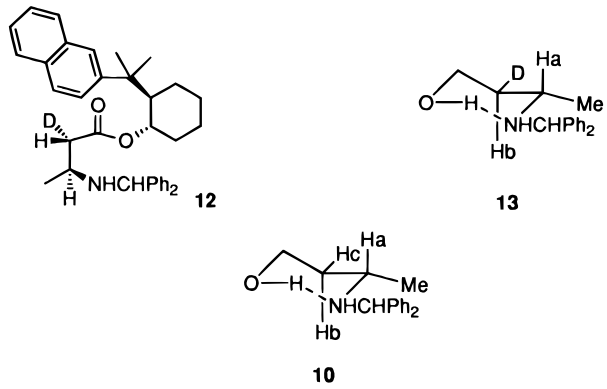


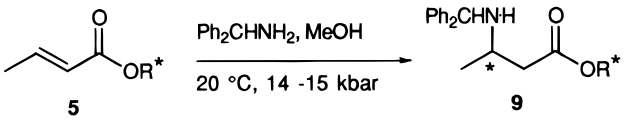
Chart 6

Modification of the Chiral Auxiliary. The influence of the nature of the chiral auxiliary component was investigated in the high-pressure addition of diphenylmethanamine to auxiliary-tethered crotonates **5** (Scheme 2). The diastereoselectivity in the resulting adducts **9** was determined by ^{1}H and ^{13}C NMR spectroscopy.

The chiral auxiliaries studied can be classified into two categories: cyclohexanols of type **4**, in which the aryl moiety is connected to the cyclohexane ring by means of a one-carbon spacer, and *trans*-2-arylcyclohexanols **2**, in which the aryl substituent is directly attached to the

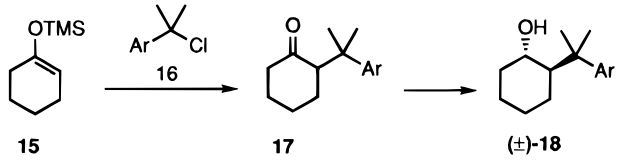
(15) Hawkins, J. M.; Fu, G. C. *J. Org. Chem.* **1986**, *51*, 2820−2822.
(16) Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14−23.
(17) (a) Thus, for example, the volume change upon hydrogen-bond formation between phenol and ethyl acetate is −4.2 mL mol^{-1}: *Organic Synthesis at High Pressure*; Matsumoto, K., Acheson, R. M., Eds.; John Wiley: New York, 1991; pp 22−24. (b) Mechanistic studies by Stirling on the addition of amines to vinyl sulfones and sulfoxides showed that these reactions were first order in MeOH, amine, and vinyl sulfone (sulfoxide) and probably involved a methanol molecule in the transition state that was H-bonded to both the amine and the vinyl sulfone (sulfoxide): Abbott, D. J.; Colonna, S.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 1* **1976**, 492−498.
(18) Thus, for example, in the condensation of thiophenol to isomeric amides **14**, in the presence of catalytic amounts of LiSPh, the *anti*-addition adduct predominates from *E*-substrate, while the *syn*-addition product predominates from the *Z*-isomer; both processes proceeded with the same degree of stereoselectivity (90% de) (Chart 6): Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T. *Tetrahedron Lett.* **1991**, *32*, 3519−3522.

Scheme 2



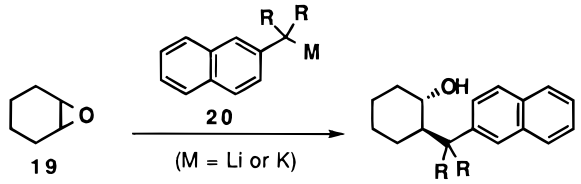
a: R*OH = 4 **g**: R*OH = 27
b: R*OH = 18a **h**: R*OH = 28
c: R*OH = 18b **i**: R*OH = 29
d: R*OH = 18c **j**: R*OH = 30
e: R*OH = 21 **k**: R*OH = 2c
f: R*OH = 26 **l**: R*OH = 3

Scheme 3



a: Ar = *o*-methoxyphenyl
b: Ar = Ph
c: Ar = *p*-phenoxyphenyl

Scheme 4



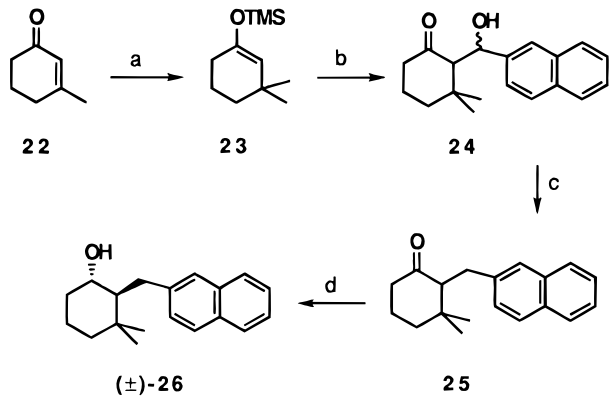
(±)-4: R = Me
(±)-21: R = H

cyclohexane. Auxiliaries of the first category were prepared as follows. Coupling of silyl enol ether **15** with tertiary chlorides **16**, in the presence of zinc chloride, led to ketones **17** with a 93−96% yield, which were then reduced (Na, *i*-PrOH) to the desired *trans* alcohols **18**, which were separated from the minor *cis* epimers by fractional crystallization (Scheme 3).[19] Because the naphthalene nucleus was partially reduced under the preceding reduction conditions, auxiliaries **4** and **21** were obtained by condensing cyclohexene oxide **19** with organometallics **20** (Scheme 4).[9] Auxiliary **26** was prepared from the following reaction sequence. Addition of Me_2-CuLi to 3-methylcyclohexenone (**22**), followed by enolate trapping with TMSCl, led to silyl enol ether **23**. The regiospecific lithio enolate, generated by MeLi cleavage of **23**, was then added to 2-naphthaldehyde, furnishing ketol **24**, albeit in a low yield (20%). Catalytic reduction (H_2, Pd/C) of **24** then afforded ketone **25** which was finally reduced ($NaBH_4$, $CeCl_3$) to an equimolar mixture of the desired *trans* alcohol **26** and its *cis* epimer, which were easily separated by flash chromatography on silica gel (Scheme 5).

The results of the addition of diphenylmethanamine to crotonates derived from the preceding "arylmenthol" auxiliaries are gathered in Table 3. To help rationalize the origin of the facial selectivity, ^{1}H NMR data and calculated energy for conformational optima (SIBFA procedure)[20] of the chiral crotonates are also presented in Table 3.

While, as expected, phenyl-substituted auxiliary **18b** furnished the same selectivity as 8-phenylmenthol (**1a**)[3a]

Scheme 5[a]

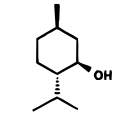
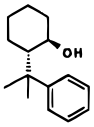
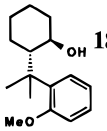
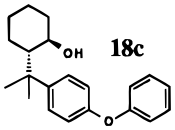
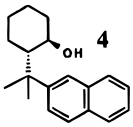
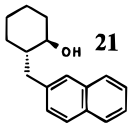
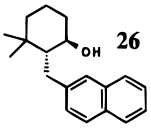


[a] Key: (a) Me_2CuLi, Et_2O, 0 °C, 40 min then TMSCl, Et_3N, HMPA, 0 °C, 15 min, 88% yield; (b) MeLi, Et_2O, 0 °C then 2-naphthaldehyde, −78 °C, 3 h, 20% yield; (c) 1.5 bar of H_2, Pd/C, AcOEt−AcOH, 4 h, 70% yield; (d) $NaBH_4$, $CeCl_3$, 30 min, 20 °C in MeOH, then separation of epimers, 90% combined yield.

(60% de, entry 2, Table 3), almost complete stereocontrol was obtained with chiral inducers **18a**, **18c**, and **4** bearing an *o*-methoxyphenyl, *p*-phenoxyphenyl, or *β*-naphthyl group, respectively (entries 3, 4, and 5). Among these auxiliaries, **18a**, which was tailored with the aid of computational modeling,[20] deserves a special comment. On the basis of semiempirical calculations, Giessner-Prettre and co-workers made the prediction that the presence of a methoxy substituent on the phenyl ring, by increasing the stabilization of the stacked geometry in the corresponding crotonate (an effect particularly marked for the *o*-methoxy derivative), would lead to a notable enhancement of efficiency of the auxiliary.[20] Thus, alcohol **18a** constitutes indisputably one of the first successful examples of *a priori* application of molecular mechanics in the *de novo* design of chiral inducers.[21] In this respect, with the exception of **18c**, a nearly perfect agreement was observed between predicted and experimental stereoselectivities, thereby providing feedback information about the reliability of the SIBFA calculation procedure used here. In other respects, this excellent accord between calculation and experiment supports the implicit hypothesis that the product ratio reflects the population of the crotonate conformers ("*stacked*", "*trans*", and "*axial*"; for a definition of these terms, see Table 3, footnote *b*) in the ground state. Furthermore, this set of results clearly indicates that the *stacked conformation* of chiral crotonates plays a crucial role in the *π*-facial discrimination,[6] a view strengthened by the ^{1}H NMR data of crotonates derived from **18b**, **18a**, **18c**, and **4**. Indeed, a significant shielding of the protons of the enoate moiety (particularly Hb and Hc) was observed (entries 2−5, Table 3), compared to the menthyl parent compound (entry 1, Table 3). Another critical aspect in the design of these inducers is the necessary presence of two methyl substituents at the "benzylic" center, as a dramatic decrease in diastereoselectivitiy was observed with auxiliary **21**, which lacked this *gem* dimethyl group (compare entries 6 and 5 of Table 3). That this drop in selectivity results from a radical conformational change was confirmed by ^{1}H NMR spectrum analysis of the crotonate derivative: *all enoate proton resonances are close to those in menthyl crotonate* (compare entries 6 and 1 of Table

(19) Whitesell, J. K.; Lawrence, R. M. *Chimia* **1986**, *40*, 318−321.
(20) Maddaluno, J. F.; Gresh, N.; Giessner-Prettre, C. *J. Org. Chem.* **1994**, *59*, 793−802.
(21) Reviews: Eksterowicz, J. E.; Houk, K. N. *Chem. Rev.* **1993**, *93*, 2439−2461. Lipkowitz, K. B.; Peterson, M. A. *Ibid.* **1993**, *93*, 2463−2486.

Table 3. Chiral Crotonates Derived from "Arylmenthol-Type" Auxiliaries: ^{1}H NMR Data, Calculated Energy for Conformational Optima, and de in the Conjugate Addition of Diphenylmethanamine

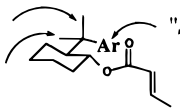
Entry	Chiral Auxiliary R*OH	^{1}H NMR of chiral crotonate **5**[a] δ Ha	δ Hb	δ Hc	Calculated energy for conformational optima of chiral crotonate **5**[b] (kcal mol^{-1})	De (%) in the addition of Ph_2CHNH_2 to chiral crotonate **5** [**5**→**9**] *predicted*[c]	*observed*	Reference
1		1.78	5.83	6.96	S 570.1 T **568.3** A 570.3	-	10	3a
2	 **18b**	1.65	5.25	6.37	S 635.3 T **635.0** A 636.8	50	60	this work
3	 **18a**	1.67	5.30	6.49	S **878.7** T 882.1 A 889.9	98	≥99	this work
4	 **18c**	1.73	5.33	6.50	S **877.3** T 878.4 A 880.0	72	97	this work
5	 **4**	1.15	4.93	6.06	S **620.2** T 623.8 A 624.9	98	98	5
6	 **21**	1.78	5.85	6.87	-	-	18	this work
7	 **26**	1.34	5.20	6.19	-	-	93	this work

a: δ ppm in $CDCl_3$.

b: after 20. By convention, the terms "*stacked*", "*trans*" and "*axial*" refer to the position of the Ar group (H in the case of menthyl derivative) in the three conformers of chiral crotonates:

"*Axial*" (A) position

"*Trans*" (T) position



"*Stacked*" (S) position

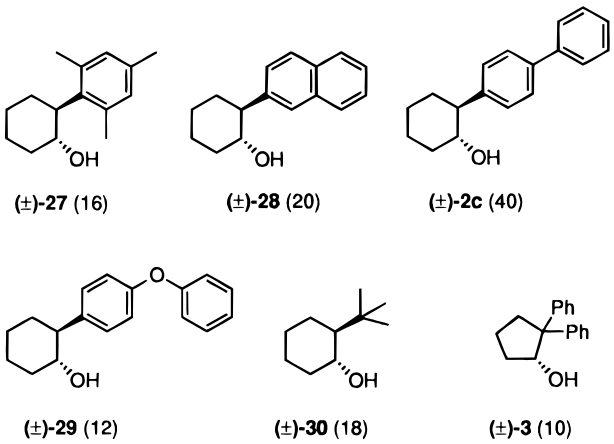
c: de evaluated on the basis of the energy for conformational optima of the crotonate, assuming that addition of the amine takes place exclusively on the less congested π-face in the stacked conformer, and almost statistically on both faces in the other conformers.

3), a view reinforced by the fact that the three conformers of *trans*-2-benzylcyclohexyl crotonate were found to be nearly isoenergetic by computational analysis.[20] In light of the preceding observation, we reasoned that the presence of an additional *gem*-dimethyl group *on the cyclohexane ring*, in the α-position to the naphthylmethyl substituent of alcohol **26**, by engendering unfavorable (Me-naphthyl) pseudo-1,3-diaxial interactions in *both "trans" and "axial"* conformers of the corresponding crotonate, can force the naphthalene nucleus to adopt the "*stacked*" orientation in order to minimize strain, hence possibly restoring the efficiency of the auxiliary. To our delight, this prediction proved correct from all points of view: an important shielding of the enoate protons of the crotonate derived from auxiliary **26** was indeed observed, while, concomitantly, excellent stereoselectivity was again obtained in the addition of Ph_2CHNH_2 to this crotonate (entry 7, Table 3).

The auxiliaries of the second category, namely *trans*-2-arylcyclohexanols **27**, **28**, **2c**, and **29**, were prepared by condensing the aryl Grignard reagents in the presence of cuprous chloride[22] or the aryl lithiocuprate complexes[23] with cyclohexene oxide. Addition of diphenylmetha-

(22) Huynh, C.; Derguini-Bouchemal, F.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, *17*, 1503−1506.

Chart 7. *trans*-2-Arylcyclohexanols and Related Auxiliaries[a]



(±)-**27** (16) (±)-**28** (20) (±)-**2c** (40)

(±)-**29** (12) (±)-**30** (18) (±)-**3** (10)

[a] The de (%) obtained in the conjugate addition of Ph_2CHNH_2 to the corresponding crotonates are in parentheses.

namine to crotonates derived from the preceding alcohols, as well as the two related auxiliaries **30**[24] and **3**,[4a] was then examined. Only disappointing stereoselectivities were obtained with these chiral inducers (Chart 7). In order to determine the cause of this modest selectivity, the X-ray crystal structures of crotonates **5h** and **5k**, derived from alcohols **28** and **2c**, respectively, were undertaken. Examination of these structures reveals that, in sharp contrast with crotonate **5a**, where the arene and enoate appendage are roughly coplanar (Figure 1, *vide supra*), the two π-systems in crotonates **5h** and **5k** lie in a "widening V" arrangement[14] (Figures 3 and 4). These crystallographic data show clearly that *both* enoate π-faces of **5h** and **5k** are now subject to nucleophilic attack; thus, these crotonates are expected to have a much lower degree of facial selectivity.

Concluding Comments

The ability of cyclohexyl-based chiral auxiliaries to control the interaction of reagents with tethered substrates has been extensively exploited for asymmetric synthesis.[25] Through this work, we have shown that an almost complete stereocontrol can be obtained in the conjugate addition of diphenylmethanamine to chiral crotonates derived from certain "arylmenthol-type" auxiliaries. This high efficiency has been attributed to the predominance, in such crotonates, of stacked conformations. We have also demonstrated that, in contrast, only moderate selectivities can be achieved with *trans*-2-arylcyclohexanols as auxiliaries. In that case the efficiency appears to be seriously compromised by the "widening V" arrangement exhibited by the arene and enoate side chain in the corresponding crotonates, hence excluding any stacking contribution to the observed selectivity. Thus, the presence of a one-carbon spacer substituted by a dimethyl group, between the aryl nucleus and the cyclohexane ring in the chiral auxiliary component, is crucial in order to gain a good facial selectivity. Finally, it must be pointed out that the proper choice of auxiliaries has been guided by the assistance of several complementary tools: chemical experiment, NMR spectroscopy, X-ray crystallography, and molecular mechanics. In this regard, the *a priori* application of the latter tool in the fascinating area of design of chiral auxiliaries looks highly promising.[21]

Experimental Section

General Methods. Melting points were recorded on a Kofler bench. Infrared (IR) spectra were obtained as neat films between NaCl plates or KBr pellets. The ^1H NMR spectra and ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise stated. Optical rotations were measured at 589 nm in a 1 dm cell at specified temperature. Mass spectra were recorded by electron impact at 70 eV. Analytical thin-layer chromatography was performed on Merk silica gel $60F_{254}$ glass precoated plates (0.25 mm layer). All liquid chromatography separations were performed using Merck silica gel 60 (230−400 mesh ASTM). Diethyl ether and tetrahydrofuran (THF) were distilled from Na−benzophenone ketyl. Methanol was dried over magnesium and distilled. Toluene, CH_2Cl_2, HMPA, and DMF were distilled from calcium hydride, under a nitrogen atmosphere. All reactions involving air- or water-sensitive compounds were routinely conducted in glassware which was flame-dried under a positive pressure of nitrogen. Organic layers were dried over anhydrous $MgSO_4$. Chemicals obtained from commercial suppliers were used without further purification, except in the case of diphenylmethanamine, which was purified by liquid chromatography prior to use. Elemental analyses were obtained from the Service de microanalyse, Centre d'Etudes Pharmaceutiques, Châtenay-Malabry, France. *High-pressure-mediated reactions* were performed in a piston-cylinder apparatus of 13 mm internal diameter for pressure up to 20 kbar. For reactions performed at temperatures higher than 20 °C, an external electric heating jacket was used. Pyrex-made cylindrical cells (1.5 mm wall-thickness, fitted with a 1 mm inner diameter capillary inlet), in which the reaction mixtures were introduced and removed by means of a syringe, were immersed in hexane, used as piezotransmitter liquid, contained in the high pressure-vessel, this being closed on the bottom side with a steel stopper. The mobile piston, equiped with Bridgman triple seals (rubber, teflon and bronze), was then inserted, and the whole assembly was placed between the pistons of the hydraulic press. The pressure was raised to an extent depending on the reaction conditions used in each case. After stabilization of the pressure, the heater was eventually swithched on, whereupon the temperature was raised to the desired value (up to 65 °C). The reaction mixture was kept under these conditions for a convenient time and then cooled to room temperature before depressurization. *X-ray crystallographic intensity data* of **7**, **5h**, and **5k** were measured using graphite-monochromated Cu Kα radiation, and the (θ−2θ) scan technique up to given θ. The structure was solved by direct methods using SHELXS86[26] and refined by full-matrix least-squares with SHELX76,[27] minimizing the function $\sum w(F_o - |F_c|)^2$. The hydrogen atoms, located in difference Fourier maps, were introduced in theoretical position (d(C−H) = 1.00 Å) and assigned an isotropic thermal factor equivalent to that of the bonded carbon atom, plus 10%. Convergence was reached at given R and R_w (with $R_w = [\sum w(F_o - |F_c|)^2/\sum wF_o^2]^{1/2}$ and $w = 1/[\sigma^2(F_o) + \text{given } F_o^2]$).[28]

Preparation of the Tertiary Chlorides 16. Tertiary Alcohols. General Procedure. To MeMgBr (3 M in diethyl ether, 52 mL, 0.15 mol) in diethyl ether (35 mL) at 0 °C was added the aromatic ketone (0.13 mol) in diethyl ether (100 mL). After the mixture was stirred for 3 h at rt, a slight excess of 1 N HCl was slowly added at 0 °C. The aqueous layer was

(23) Alexakis, A.; Jachiet, D.; Normant, J. F. *Tetrahedron* **1986**, *42*, 5607−5619.
(24) Esser, P.; Buschmann, H.; Meyer-Stork, M.; Scharf, H.-D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1190−1192.
(25) Review: Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953−964.
(26) Scheldrick, G. SHELSX86. Program for crystal structure determination: University of Göttingen: Germany, 1985.
(27) Scheldrick, G. SHELSX76. Program for crystal structure determination: University of Cambridge: United Kingdom, 1976.
(28) The authors have deposited atomic coordinates for **7**, **5h**, and **5k** with the Cambridge Crystallographic Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

separated and extracted with diethyl ether (3 × 150 mL). The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution (2 × 100 mL) and brine (2 × 50 mL), dried, concentrated, and used without any further purification.

2-(2-Methoxyphenyl)-2-hydroxypropane: 20.84 g, 96% yield; oil; IR (neat) 3458, 1584 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.69 (dd, J = 7.0, 2.0 Hz, 1H), 7.60 (dt, J = 9.0, 1.2 Hz, 1H), 7.34−7.26 (m, 2H), 4.53 (br s 1H), 4.24 (s, 3H), 1.99 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.8 (C), 135.8 (C), 128.1 (CH), 125.7 (CH), 120.9 (CH), 111.2 (CH), 72.5 (C), 55.2 (CH_3), 29.6 (2 CH_3).

2-(4-Phenoxyphenyl)-2-hydroxypropane: 28.8 g, 97% yield; white solid; mp 30−31 °C (petroleum ether); IR (neat) 3415, 1590 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.48−7.13 (m, 4H), 7.10−6.96 (m, 5H), 1.88 (br s, 1H), 1.59 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.4 (C), 155.9 (C), 144.2 (C), 129.9 (2 CH), 126.1 (2 CH), 123.3 (CH), 118.9 (2 CH), 118.6 (2 CH), 72.4 (C), 31.9 (2 CH_3).

Tertiary Chlorides 16. To 0.1 mol of tertiary alcohol in dichloromethane (20 mL) at 0 °C was slowly added 12 N hydrochloric acid (100 mL). After the mixture was stirred for 1 h at 20 °C, the organic phase was diluted with CH_2Cl_2 (200 mL), separated, concentrated under reduce pressure (0.1 Torr) at 20 °C, and used immediately without further purification.

2-(2-Methoxyphenyl)-2-chloropropane (16a): 17.8 g, 96% yield; viscous oil; IR (neat) 1600, 1582 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.66−7.51 (m, 2H), 7.30−7.22 (m, 2H), 4.22 (s, 3H), 1.93 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.0 (C), 136.0 (C), 128.2 (CH), 125.9 (CH), 121.0 (CH), 111.4 (CH), 72.6 (C), 55.3 (CH_3), 29.8 (2 CH_3).

2-(4-Phenoxyphenyl)-2-chloropropane (16c): 23.1 g, 94% yield; viscous oil; IR (neat) 1613, 1592 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.50−7.38 (m, 2H), 7.34−7.18 (m, 2H), 7.08−6.81 (m, 5H), 1.90 (s, 6H).

Preparation of Ketones 17. Compounds **17a**−**c** were prepared according to the procedure reported by Whitesell,[19] starting from the tertiary chloride (0.045 mol).

2-[1-(2-Methoxyphenyl)-1-methylethyl]cyclohexanone (17a): 7.8 g, 75% yield; viscous oil, bp 155 °C (1 Torr); IR (neat) 1709 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.25 (dd, J = 7.7, 1.7 Hz, 1H), 7.1 (dt, J = 7.7, 1.7 Hz, 1H), 6.89−6.77 (m, 2H), 3.74 (s, 3H), 3.51 (dd, J = 11.8, 4.7 Hz, 1H), 2.24−2.1 (m, 2H), 2.0−1.84 (m, 1H), 1.55−1.1 (m, 5H), 1.45 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 212.8 (C), 157.8 (C), 137.3 (C), 128.0 (CH), 127.0 (CH), 120.5 (CH), 111.8 (CH), 55.5 (CH_3), 55.2 (CH), 44.1 (CH_2), 39.8 (C), 30.4 (CH_2), 28.3 (CH_2), 26.2 (CH_2), 25.0 (CH_3), 23.9 (CH_3).

2-[1-(4-Phenoxyphenyl)-1-methylethyl]cyclohexanone (17c): 10.4 g, 75% yield; mp 90 °C (methanol); IR (neat) 1710 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.36−7.25 (m, 4H), 7.11−6.68 (m, 5H), 2.64 (dd, J = 12.1, 4.5 Hz, 1H), 2.27−2.14 (m, 2H), 2.0−1.89 (m, 1H), 1.84−1.69 (m, 2H), 1.65−1.27 (m, 3H), 1.40 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 212.1 (C), 158.6 (C), 154.9 (C), 144.7(C), 129.8 (2CH), 127.2 (2CH), 123.1 (CH), 118.9 (2CH), 118.3 (2CH), 60.6 (CH), 44.3 (CH_2), 39.0 (C), 30.4 (CH_2), 28.6 (CH_2), 26.8 (CH_3), 26.1 (CH_2), 24.3 (CH_3). Anal. Calcd for $C_{21}H_{24}O_2$: C, 81.78, H, 7.84. Found: C, 81.69, H, 7.84.

Preparation of Ketone 25. 3,3-Dimethyl-2-[1-(2-naphthyl)-1-hydroxymethyl]cyclohexanone (24). 3,3-Dimethyl-1-[(trimethylsilyl)oxy]cyclohexene (**23**)[29] (9 g, 45.3 mmol) in diethyl ether (30 mL) was added dropwise in 20 min to methyllithium (37 mL of a 1.6 M solution in diethyl ether, 59 mmol) at 0 °C. After the mixture was stirred for 2 h at 0 °C, 2-naphthaldehyde (10 g, 64 mmol) in diethyl ether (20 mL) was added in 15 min at −78 °C and allowed to stir for 3 h at this temperature. A solution of saturated aqueous NH_4Cl (50 mL) was added all at once at −78 °C, and the mixture was allowed to warm to 20 °C. The aqueous layer was separated and extracted with diethyl ether (3 × 150 mL). The combined organic phases were washed with a saturated solution of $NaHCO_3$ and brine, dried, and concentrated, and the resulting oil was purified by column chromatography (cyclohexane:ethyl acetate 20:1) to give **24** (2.3 g, 20% yield) as a white solid: mp 142 °C (diethyl ether); IR (neat) 3502, 1694 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.90−7.73 (m, 4H), 7.86−7.53 (m, 3H), 5.17 (dd, J = 9.5, 2.8 Hz, 1H), 4.72 (d, J = 9.5 Hz, 1H), 2.76 (d, J = 2.8 Hz, 1H), 2.38−2.20 (m, 2H), 2.0−1.82 (m, 2H), 1.80−1.55 (m, 2H), 1.20 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.8 (C), 142.3 (C), 133.2 (C), 132.5 (C), 127.9 (2CH), 127.5 (CH), 126.0 (CH), 125.6 (CH), 124.6 (CH), 124.3 (CH), 71.9 (CH), 65.2 (CH), 43.0 (CH_2), 40.9 (C), 40.7 (CH_2), 30.2 (CH_3), 23.2 (CH_2), 23.0 (CH_3). Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.81, H, 7.85. Found: C, 80.70, H, 7.80.

3,3-Dimethyl-2-(2-naphthylmethyl)cyclohexanone (25). A solution of aldol **24** (0.70 g, 2.5 mmol) in ethyl acetate (3 mL) and acetic acid (3 mL) was stirred in the presence of 10% Pd/C (200 mg) for 4 h under 1.5 bar of hydrogen. The catalyst was filtered off, and the product was chromatographed over silica gel (cyclohexane:ethyl acetate 20:1) to yield pure ketone **25** (0.52 g, 78% yield) as a white solid: mp 82 °C (methanol); IR (neat) 1708 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.80−7.15 (m, 3H), 7.70 (s, 1H), 7.48−7.30 (m, 3H), 3.27 (dd, J = 13.6, 9.6 Hz, 1H), 2.76 (dd, J = 13.6, 2.2 Hz, 1H), 2.60 (dd, J = 9.6, 2.2 Hz, 1H), 2.41−2.14 (m, 2H), 2.0−1.55 (m, 4H), 1.24 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 211.8 (C), 139.6 (C), 133.5 (C), 131.8 (C), 127.8 (CH), 127.7 (CH), 127.5 (CH), 127.4 (CH), 127.1 (CH), 125.8 (CH), 125.1 (CH), 63.3 (CH), 41.8 (CH_2), 40.5 (C), 40.0 (CH_2), 30.0 (CH_3), 29.7 (CH_2), 23.3 (CH_2), 21.3 (CH_3). Anal. Calcd for $C_{19}H_{22}O$: C, 85.66, H, 8.32. Found: C, 84.97, H, 8.31.

Chemical Resolution of (1*R,2*S**)-2-[1-(2-Naphthyl)-1-methylethyl]cyclohexanol (4): (2*S*,1′*R*,2′*S*)- and (2*S*,1′*S*,2′*R*)-6-Methoxy-2-methyl-2-naphthaleneacetic Acid 2′-[1-(2-Naphthyl)-1-methylethyl]cyclohexyl Esters (7) and (8).** Pyridine (3.4 mL, 42.2 mmol), followed by 4-(dimethylamino)pyridine (0.6 g, 5 mmol) and *racemic* alcohol **4**[9] (7.5 g, 27.9 mmol) dissolved in CH_2Cl_2 (30 mL), were added dropwise to naproxen acid chloride (10.5 g, 42.2 mmol) in CH_2Cl_2 (150 mL) at 0 °C. The mixture was stirred for 4 h at 20 °C, concentrated under vacuum, diluted with diethyl ether (250 mL), and washed with 1 N HCl (2 × 70 mL), a solution of saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was concentrated and chromatographed over silica gel (cyclohexane:ethyl acetate 9:1) to give 12.3 g of pure naproxen esters **7** and **8** as pale yellow crystals (92% yield). After one crystallization in MeOH/hexane (1:1), 6.0 g of **7** (44% yield) (de 87% by ^1H NMR spectroscopy) was obtained; after a second crystallization, 4.5 g of **7** (de ≥ 99%) was isolated (34% yield). The mother liquors were concentrated, and the crude was crystallized twice from hexane at 0 °C to give diastereomer **8** (4 g, 30% yield, de 95%). **(2*S*,1′*S*,2′*R*)-6-Methoxy-2-methyl-2-naphthaleneacetic acid 2′-[1-(2-naphthyl)-1-methylethyl]cyclohexyl ester (7):** white solid; mp 134 °C (MeOH:hexane 1:1); IR (neat, KBr) 1725, 1635,1610 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.82−7.63 (m, 5H), 7.55 (s, 1H), 7.5−7.38 (m, 4H), 7.24 (dd, J = 8.7, 2.0 Hz, 1H), 7.15−7.09 (m, 2H), 4.85 (dt, J = 9.9, 3.7 Hz, 1H), 3.90 (s, 3H), 3.21 (q, J = 6.8 Hz, 1H), 2.13 (dt, J = 11.5, 3.7 Hz, 1H), 2.3−1.9 (m, 1H), 1.74−0.85 (m, 7H), 1.31 (d, J = 6.8 Hz, 3H), 1.20 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.8 (C), 157.5 (C), 148.6 (C), 135.4 (C), 133.6 (C), 133.3 (C), 131.5 (C), 129.2 (CH), 128.8 (C), 128.0 (CH), 127.3 (CH), 127.2 (CH), 126.8 (CH), 126.5 (CH), 126.3 (CH), 125.7 (CH), 125.2 (CH), 125.0 (CH), 123.0 (CH), 118.7 (CH), 105.6 (CH), 75.5 (CH), 55.2 (CH_3), 50.4 (CH), 45.6 (CH), 40.3 (C), 33.3 (CH_2), 27.5 (CH_2), 27.2 (CH_3), 25.9 (CH_2), 25.6 (CH_3),24.7 (CH_2), 19.0 (CH_3). X-ray crystallographic analysis: $C_{33}H_{36}O_3$, M_w = 480.65, crystal of 0.25 × 0.50 × 0.50 mm, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 11.455(5) Å, b = 14.826(7) Å, c = 16.288(9) Å, V = 2766(2) Å^3, d_{calc} = 1.15 g cm^{-3}, $F(000)$ = 1032, l (Cu Kα) = 1.5418 Å, μ = 0.53 mm^{-1}; θ = 66°. Of the 3209 collected reflections (−7 ≤ h ≤ 13, k: 0−17, l: 0−19), 3093 were unique (R_{int} = 0.063) and 2801 were considered as observed having $I \geq 3\sigma(I)$. Cell parameters were refined from 25 well-centered reflections with 10.2 ≤ θ ≤ 18.0°. Convergence was reached at R = 0.046 and R_w = 0.052 (0.0001F_o^2). The residual electron density in the final difference map was located between −0.26 and 0.30 e

(29) Plamondon, J.; Canonne, P. *Tetrahedron Lett.* **1991**, *32*, 589−592.

Å^3. **(2*S*,1′*R*,2′*S*)-6-Methoxy-2-methyl-2-naphthaleneacetic acid, 2′-[1-(2-naphthyl)-1-methylethyl]cyclohexyl ester (8):** white solid; mp 110 °C (hexane); IR (neat, KBr) 1723, 1635, 1610 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.9−7.82 (m, 3H), 7.67 (s, 1H), 7.6−7.45 (m, 5H), 7.13−7.05 (m, 3H), 6.94 (dd, J = 8.7, 1.9 Hz, 1H), 4.82 (dt, J = 10.5, 4.3 Hz, 1H), 3.88 (s, 3H), 2.4 (q, J = 6.8 Hz, 1H), 2.13 (dt, J = 11.1, 3.7 Hz, 1H), 1.9−1.75 (m, 1H), 1.7−0.75 (m, 7H), 1.45 (s, 3H), 1.30 (s, 3H), 1.08 (d, J = 6.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.6 (C), 157.3 (C), 149.5 (C), 136.1 (C), 133.4 (C), 133.3 (C), 131.5 (C), 129.1 (CH), 128.7 (C), 127.9 (CH), 127.2 (2 CH), 126.7 (CH), 125.9 (CH), 125.7 (CH), 125.5 (CH), 125.2 (2 CH), 122.6 (CH), 118.5 (CH), 105.5 (CH), 74.4 (CH), 55.2 (CH_3), 50.3 (CH), 44.6 (CH), 39.8 (C), 32.5 (CH_2), 28.4 (CH_3), 26.8 (CH_2), 25.8 (CH_2), 24.4 (CH_2), 23.8 (CH_3), 17.7 (CH_3).

(1*R*,2*S*)-(−)- and (1*S*,2*R*)-(+)-2-[1-(2-Naphthyl)-1-methylethyl]cyclohexanols (4). Ester **7** or **8** (3.8 g, 7.9 mmol) in diethyl ether (35 mL) was added dropwise to $LiAlH_4$ (600 mg, 15.8 mmol) in diethyl ether (5 mL) at 0 °C. After the mixture was strirred for 0.5 h at 20 °C, it was hydrolyzed at 0 °C with 0.5 N NaOH (0.5 mL). The precipited solid was filtered off, the filtrate was concentrated under vacuum, and the crude product was chromatographed over silica gel (cyclohexane:ethyl acetate 1.5:1). **(1*S*,2*R*)-2-[1-(2-Naphthyl)-1-methylethyl]cyclohexanol ((+)-4):** 2.0 g, 95% yield; white solid; mp 74−75 °C (petroleum ether); $[\alpha]^{20}_D$ +25.4 (*c* 2.1, MeOH) [lit.[9] mp 71−74 °C; $[\alpha]^{23}_D$ +12.0 (*c* 2, MeOH), 99.40% ee by chiral HPLC analysis]. **(1*R*,2*S*)-2-[1-(2-Naphthyl)-1-methylethyl]-cyclohexanol ((−)-4):** 1.9 g, 93% yield; white solid; mp 73 °C (petroleum ether); $[\alpha]^{20}_D$ −21.9 (*c* 3.4, MeOH).

Preparation of the Chiral Auxiliaries. Alcohols 18a and 18c (from Ketones 17a,c). A solution of ketone (22.3 mmol) in 2-propanol (17 mL)was slowly added to molten sodium (3.8 g, 0.165 mol) in refluxing toluene (145 mL). The mixture was stirred for 21 h at 110 °C. The mixture was cooled to 20 °C and was poured into cold 6 N hydrochloric acid (30 mL). The aqueous phase was separated and extracted with toluene (3 × 100 mL). The combined organic phases were washed with a saturated solution of $NaHCO_3$ (2 × 60 mL) and brine (50 mL), dried, and concentrated under vacuum.

(1*R,2*S**)-2-[1-(2-Methoxyphenyl)-1-methylethyl]cyclohexanol (18a).** The yield was 5.2 g (95% yield) as a mixture of *trans* and *cis* alcohols (9:1 by ^{1}H NMR), from which 4.2 g of the *trans* isomer was separated by fractional crystallization from petroleum ether (76% yield) as a white solid: mp 69−70 °C; IR (neat, KBr) 3312, 1597, 1581 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.17−7.0 (m, 2H), 6.82−6.67 (m, 2H), 3.67 (s, 3H), 3.51 (dt, J = 10.0, 4.4 Hz, 1H), 2.31 (dt, J = 11.4, 3.5 Hz, 1H), 1.77−1.46 (m, 5H), 1.23 (s, 3H), 1.17 (s, 3H), 1.17−0.75 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.5 (C), 138.8 (C), 127.5 (CH), 126.2 (CH), 120.8 (CH), 112.2 (CH), 73.5 (CH), 55.1 (CH_3), 49.6 (CH), 40.2 (C), 36.5 (CH_2), 26.9 (CH_2), 26.4 (CH_2), 26.0 (CH_3), 25.1 (CH_2), 24.6 (CH_3). Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.37, H, 9.74. Found: C, 77.39, H, 9.78.

(1*R,2*S**)-2-[1-(4-Phenoxyphenyl)-1-methylethyl]cyclohexanol (18c).** The yield was 6.6 g (95% yield) as a mixture of *trans* and *cis* alcohols (24:1 by ^{1}H NMR) from which 5.2 g of the *trans* isomer was separated by fractional crystallization from methanol at 0 °C (75% yield); amorphous solid; IR (neat) 3588, 3453, 1590 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34−7.17 (m, 4H), 7.07−6.84 (m, 5H), 3.41 (dt, J = 9.7, 4.4 Hz, 1H), 1.82−1.56 (m, 5H), 1.34 (s, 3H), 1.21 (s, 3H), 1.27−0.86 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.4 (C), 155.2 (C), 146.0 (C), 129.6 (2 CH), 127.0 (2 CH), 123.0 (CH), 118.7 (2 CH), 118.6 (2 CH), 73.4 (CH), 54.5 (CH), 39.5 (C), 36.7 (CH_2), 28.7 (CH_3), 26.8 (CH_2), 26.2 (CH_2), 25.0 (CH_2), 24.5 (CH_3). Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.24, H, 8.44. Found: C, 81.60, H, 8.02.

(1*R,2*S**)-3,3-Dimethyl-2-(2-naphthylmethyl)cyclohexanol (26).** A solution of ketone **25** (0.34 g, 1.27 mmol) and cerium trichloride heptahydrate (950 mg, 2.54 mmol) in methanol (4 mL) was stirred at room temperature for 1 h. Sodium borohydride (100 mg, 2.6 mmol) was then added in small portions. The mixture was stirred for 15 min, treated with 1 N hydrochloric acid, and extracted twice with diethyl ether. The combined organic phases were washed with a saturated solution of $NaHCO_3$ and brine, dried, and concentrated under vacuum. The two diastereomeric alcohols (1:1 by ^{1}H NMR) were purified by column chromatography over silica gel (cyclohexane:ethyl acetate 20:1). *trans*-Alcohol **26**: 142 mg, 42% yield; white solid; mp 110 °C (petroleum ether); IR (CCl_4) 3616, 1633, 1597 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.85−7.7 (m, 4H), 7.50−7.36 (m, 3H), 3.67 (dt, J = 10.5, 4.3 Hz, 1H), 3.06 (dd, J = 14.3, 3.1 Hz, 1H), 2.82 (dd, J = 14.3, 6.8 Hz, 1H), 1.96 (dt, J = 10.5, 6.8 Hz, 1H), 1.63−1.06 (m, 7H), 1.07 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.7 (C), 133.7 (C), 131.9 (C), 128.0 (CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 126.7 (CH), 125.9 (CH), 125.1 (CH), 74.1 (CH), 56.1 (CH), 41.4 (CH_2), 36.3 (CH_2), 35.6 (CH_2), 35.5 (C), 31.2 (CH_3), 20.7 (CH_3), 20.5 (CH_2). Anal. Calcd for $C_{19}H_{24}O$: C, 85.02, H, 9.01. Found: C, 84.96, H, 8.98.

(1*R,2*S**)-2-(2-Naphthylmethyl)cyclohexanol (21).** *n*-Butyllithium (40 mL of a 2.5 M solution in hexanes, 0.1 mol) was added to TMEDA (15.1 mL) at 0 °C. After 15 min at this temperature, 2-methylnaphthalene (14.2 g, 0.1 mol), diluted in THF (100 mL), was added dropwise. The mixture was warmed to 20 °C and stirred for 24 h. Cyclohexene oxide (12.2 mL, 0.12 mol) was added dropwise, and the mixture was stirred for 1 day, poured into 0.1 N hydrochloric acid (100 mL) and ice (100 g), and extracted with diethyl ether (3 × 150 mL). The combined organic phases were washed with brine, dried, and concentrated. The crude alcohol was crystallized from cold pentane:diethyl ether (1:1) to give **21** (18 g, 75% yield) as a white solid; mp 82 °C (pentane:diethyl ether 1:1); IR (neat) 3397, 1634,1602 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.85−7.77 (m, 3H), 7.65 (s, 1H), 7.48−7.35 (m, 3H), 3.37 (m, 1H), 3.36 (dd, J = 13.2, 3.2 Hz, 1H), 2.54 (dd, J = 13.2, 9.0 Hz, 1H), 2.01 (dt, J = 8.2, 4.8 Hz, 1H), 1.88−1.52 (m, 5H), 1.45−0.83 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.2 (C), 133.3 (C), 131.7 (C), 127.9 (CH), 127.3 (3 CH), 127.1 (CH), 125.5 (CH), 124.8 (CH), 74.1 (CH), 46.7 (CH), 38.8 (CH_2), 35.5 (CH_2), 29.7 (CH_2), 24.1 (CH_2), 24.7 (CH_2).

Preparation of *trans*-2-Arylcyclohexanols. Alcohols **28** and **29** were prepared according to the literature,[4] starting from cyclohexene oxide (0.15 mol).

(1*R,2*S**)-2-(2-Naphthyl)cyclohexanol (28):** 89% yield; white solid; mp 90 °C (diisopropyl ether); IR (neat) 3374, 1600 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.86−7.77 (m, 3H), 7.71 (s, 1H), 7.52−7.38 (m, 3H), 3.79 (dt, J = 9.9, 4.4 Hz, 1H), 2.61 (dt, J = 9.9, 3.8 Hz, 1H), 2.17 (m, 1H), 2.02−1.32 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.7 (C), 133.5 (C), 132.4 (C), 128.2 (CH), 127.5 (2 CH), 126.5 (CH), 125.9 (CH), 125.8 (CH), 125.4 (CH), 74.0 (CH), 53.2 (CH), 34.4 (CH_2), 33.2 (CH_2), 25.9 (CH_2), 24.9 (CH_2).

(1*R,2*S**)-2-(4-Phenoxyphenyl)cyclohexanol (29):** 69% yield; amorphous solid; IR (neat) 3412, 1592 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28−6.86 (m, 9H), 3.53 (dt, J = 10.1, 4.6 Hz, 1H), 2.32 (dt, J = 12.8, 3.2 Hz, 1H), 2.04 (dt, J = 9.1, 4.6 Hz, 1H), 1.86−1.56 (m, 4H), 1.5−1.2 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.1 (C), 156.0 (C), 137.9 (C), 129.6 (2 CH), 128.9 (3 CH), 123.1 (CH), 118.9 (3 CH), 74.4 (CH), 52.4 (CH), 34.4 (CH_2), 33.4 (CH_2), 26.0 (CH_2), 25.0 (CH_2).

Preparation of Chiral Crotonates 5: General Procedure. To a stirred solution of chiral alcohol (4 mmol), crotonic acid (688 mg, 8 mmol), and DMAP (244 mg, 2 mmol) in CH_2Cl_2 (10 mL), at 0 °C, was added dropwise a solution of DCC (1.65 g, 8 mmol) in CH_2Cl_2 (2 mL). After 14 h at rt, the excess DCC was consumed with methanol (0.5 mL) and the dicyclohexylurea was filtered off and washed with hexanes. The filtrate was washed successively with 0.5 N hydrochloric acid (50 mL), a saturated aqueous solution of $NaHCO_3$ (50 mL), and brine (30 mL), dried over $MgSO_4$, and concentrated. Chromatography of the crude product (cyclohexane:ethyl acetate 20:1) afforded pure crotonates **5**.

(1*S*,2*R*)-2-[1-(2-Naphthyl)-1-methylethyl]cyclohexyl (*E*)-2-butenoate ((+)-5a): 90% yield; white solid; mp 89 °C (hexane); $[\alpha]^{20}_D$ +26.2 (*c* 7.8, EtOH); ^{1}H NMR and ^{13}C NMR spectra were found to be identical to those of *rac*-**5a**.[5]

(1*R,2*S**)-2-[1-(2-Methoxyphenyl)-1-methylethyl]cyclohexyl (*E*)-2-butenoate (5b):** 1.1 g, 87% yield; viscous oil; IR (neat) 1714, 1661, 1597 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.16−7.05 (m, 2H), 6.84−6.74 (m, 2H), 6.49 (dq, J = 15.5, 6.8 Hz, 1H), 5.28 (dq, J = 15.5, 1.6 Hz, 1H), 4.78 (dt, J = 10.4, 4.4

Hz, 1H), 3.82 (s, 3H), 2.71 (dt, J = 11.8, 3.4 Hz, 1H), 1.88 (m, 1H), 1.69−1.5 (m, 3H), 1.67 (dd, J = 6.8, 1.6 Hz, 3H), 1.33−0.81 (m, 4H), 1.28 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.8 (C), 158.1 (C), 143.3 (CH), 139.5 (C), 126.4 (CH), 126.2 (CH), 123.3 (CH), 120.6 (CH), 111.7 (CH), 74.7 (CH), 55.2 (CH_3), 46.3 (CH), 40.2 (C), 33.4 (CH_2), 27.4 (CH_3), 26.3 (CH_2), 25.5 (CH_3), 25.2 (CH_3), 24.9 (CH_2), 17.7 (CH_3).

(1*R,2*S**)-2-(1-Phenyl-1-methylethyl)cyclohexyl (*E*)-2-butenoate (5c):** 980 mg, 86% yield; viscous oil; IR (neat)-1715, 1661, 1600 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.23−7.13 (m, 4H), 7.11−7.0 (m, 1H), 6.37 (dq, J = 15.5, 6.9 Hz, 1H), 5.25 (dq, J = 15.5, 1.6 Hz, 1H), 4.73 (dt, J = 10.6, 4.4 Hz, 1H), 2.02 (dt, J = 10.6, 3.0 Hz, 1H), 1.92−1.80 (m, 1H), 1.68−1.52 (m, 3H), 1.65 (dd, J = 6.9, 1.6 Hz, 3H), 1.35−0.94 (m, 4H), 1.23 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.7 (C), 151.8 (C), 143.9 (CH), 128.1 (2 CH), 125.5 (2 CH), 124.8 (CH), 123.3 (CH), 74.5 (CH), 51.2 (CH), 40.0 (C), 33.5 (CH_2), 27.7 (CH_3), 27.2 (CH_2), 26.2 (CH_2), 25.4 (CH_3), 24.9 (CH_2), 17.9 (CH_3).

(1*R,2*S**)-2-[1-(4-Phenoxyphenyl)-1-methylethyl]cyclohexyl (*E*)-2-butenoate (5d):** 1.3 g, 87% yield; viscous oil; IR (neat) 1715, 1661, 1591 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.21−6.98 (m, 4H), 6.96−6.68 (m, 5H), 6.35 (dq, J = 15.5, 6.9 Hz, 1H), 5.25 (dq, J = 15.5, 1.5 Hz, 1H), 4.63 (dt, J = 10.2, 4.4 Hz, 1H), 1.93−1.45 (m, 5H), 1.61 (dd, J = 6.9, 1.5 Hz, 3H), 1.27−0.82 (m, 4H), 1.12 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.5 (C), 157.4 (C), 154.2 (C), 146.5 (C), 143.9 (CH), 129.5 (2 CH), 126.6 (2 CH), 123.0 (CH), 122.8 (CH), 118.5 (2 CH), 118.2 (2 CH), 74.3 (CH), 51.1 (CH), 39.5 (C), 33.3 (CH_2), 27.6 (CH_3), 27.1 (CH_2), 25.9 (CH_2), 25.5 (CH_3), 24.7 (CH_2), 17.8 (CH_3).

(1*R,2*S**)-2-(2-Naphthylmethyl)cyclohexyl (*E*)-2-butenoate (5e):** 1 g, 86% yield; viscous oil; IR (neat) 1716, 1659, 1602 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.75−7.66 (m 3H), 7.48 (s, 1H), 7.43−7.28 (m, 2H), 7.21 (dd, J = 7.9, 1.6 Hz, 1H), 6.82 (dq, J = 15.5, 6.9 Hz, 1H), 5.72 (dq, J = 15.5, 1.7 Hz, 1H), 4.61 (dt, J = 9.9, 4.3 Hz, 1H), 3.0 (dd, J = 13.4, 4.2 Hz, 1H), 2.37 (dd, J = 13.4, 9.1 Hz, 1H), 2.05−0.9 (m, 9H), 1.73 (dd, J = 6.9, 1.7 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.2 (C), 143.3 (CH), 137.1 (C), 132.6 (C), 131.1 (C), 126.9 (CH), 126.7 (CH), 126.6 (CH), 126.4 (2 CH), 124.9 (CH),124.1 (CH), 122.2 (CH), 75.7 (CH), 42.9 (CH), 38.3 (CH_2), 31.0 (CH_2), 29.3 (CH_2), 24.2 (CH_2), 23.6 (CH_2), 16.9 (CH_3).

(1*R,2*S**)-3,3-Dimethyl-2-(2-naphthylmethyl)cyclohexyl (*E*)-2-butenoate (5f):** 1.2 g, 87% yield; viscous oil; IR (neat) 1714, 1659, 1602 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.8−7.67 (m, 3H), 7.52 (s, 1H), 7.45−7.3 (m, 3H), 6.19 (dq, J = 15.5, 6.8 Hz, 1H), 5.2 (dq, J = 15.5, 1.2 Hz, 1H), 4.97 (dt, J = 10.5, 4.3 Hz, 1H), 3.06 (dd, J = 14.2, 1.8 Hz, 1H), 2.53 (dd, J = 14.2, 8.0 Hz, 1H), 2.3−1.83 (m, 2H), 1.68−1.08 (m, 5H), 1.34 (dd, J = 6.8, 1.2 Hz, 3H), 1.12 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.0(C), 143.9 (CH), 140.9 (C), 133.6 (C), 131.6 (C)127.4 (CH), 127.3 (CH), 127.2 (CH), 126.6 (CH), 125.6 (CH), 124.7 (2 CH), 122.6 (CH), 75.9 (CH), 52.2 (CH), 41.1 (CH_2), 35.6 (C), 35.5 (CH_2), 32.7 (CH_2), 31.0 (CH_3), 20.4 (CH_3), 20.2 (CH_2), 17.3 (CH_3).

(1*R,2*S**)-2-(2,4,6-Trimethylphenyl)cyclohexyl (*E*)-2-butenoate (5g):** 1.2 g, 86% yield; viscous oil; IR (neat) 1715, 1660, 1613 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.80 (s, 1H), 6.76 (s, 1H), 6.71 (dq, J = 15.6, 6.8 Hz, 1H), 5.58 (dq, J = 15.6, 1.8 Hz, 1H), 5.51 (dt, J = 10.0, 4.2 Hz, 1H), 3.23 (dt, J = 11.6, 3.9 Hz, 1H), 2.46−1.1 (m, 8H), 2.46 (s, 3H), 2.36 (s, 3H), 2.22 (s, 3H), 1.76 (dd, J = 6.8, 1.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.6 (C), 143.3 (CH), 136.9 (C), 135.7 (C), 135.2 (C), 134.8 (C), 131.0 (CH), 128.8 (CH), 122.9 (CH), 73.3 (CH), 45.3 (CH), 33.3 (CH_2), 29.0 (CH_2), 26.5 (CH_2), 24.8 (CH_2), 21.8 (CH_3), 21.5 (CH_3), 20.5 (CH_3), 17.8 (CH_3).

(1*R,2*S**)-2-(2-Naphthyl)cyclohexyl (*E*)-2-butenoate (5h):** 1.3 g, 88% yield; white solid; mp 90 °C (diethyl ether); IR (KBr) 1719, 1662, 1603 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.73−7.65 (m, 3H), 7.56 (s, 1H), 7.42−7.23 (m, 3H), 6.63 (dq, J = 15.5, 6.8 Hz, 1H), 5.47 (dq, J = 15.5, 1.6 Hz, 1H), 5.08 (dt, J = 10.3, 4.4 Hz, 1H), 2.81 (dt, J = 11.4, 3.7 Hz, 1H), 2.14 (m, 1H), 2.0−1.17 (m, 7H), 1.60 (dd, J = 6.8, 1.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.7 (C), 143.9 (CH), 140.7 (C), 133.5 (C), 132.3 (C), 127.7 (CH), 127.5 (CH), 127.4 (CH), 125.9 (CH), 125.8 (CH), 125.6 (CH), 125.1 (CH), 122.7 (CH), 75.4 (CH), 49.7 (CH), 34.1 (CH_2), 32.3 (CH_2), 25.8 (CH_2), 24.7 (CH_2), 17.6 (CH_3). X-ray crystallographic analysis: $C_{20}H_{22}O_2$, M_w = 294.39, crystal of 0.14 × 0.40 × 0.46 mm, monoclinic, space group $P2_1/c$, Z = 4, a = 12.927(9) Å, b = 5.748(6) Å, c = 22.829(15) Å, β = 101.66(5)°, V = 1661(2) Å^3, d_{calc} = 1.18 g cm^{-3}, $F(000)$ = 632, λ (Cu Kα) = 1.5418 Å, μ = 0.55 mm^{-1}; θ = 64°. Of the 2834 collected reflections ($-15 \le h \le 14$, k: 0−6, l: 0−26), 2753 were unique (R_{int} = 0.028) and 1957 were considered as observed having $I \ge 2.5\sigma(I)$. Cell parameters were refined from 25 well-centered reflections with $12.2 \le \theta \le 24.8$°. Convergence was reached at R = 0.075 and R_w = 0.112 ($0.0013F_o^2$). The residual electron density in the final difference map was located between −0.25 and 0.76 e Å^3.

(1*R,2*S**)-2-(4-Phenoxyphenyl)cyclohexyl (*E*)-2-butenoate (5i):** 1.2 g, 87% yield; viscous oil; IR (neat) 1722, 1659, 1591 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34−6.88 (m, 9H), 6.80 (dq, J = 15.3, 6.7 Hz, 1H), 5.63 (dq, J = 15.3, 1.7 Hz, 1H), 4.96 (dt, J = 10.1, 4.4 Hz, 1H), 2.68 (dt, J = 11.6, 3.5 Hz, 1H), 2.17 (m, 1H), 2.1−1.19 (m, 7H), 1.78 (dd, J = 6.7, 1.7 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.6 (C), 157.4 (C), 155.2 (C), 143.9 (CH), 138.1 (C), 129.5 (2 CH), 128.6 (2 CH), 122.8 (2 CH), 118.7 (2 CH), 118.3 (2 CH), 75.6 (CH), 48.9 (CH), 33.7 (CH_2), 32.2 (CH_2), 25.7 (CH_2), 24.6 (CH_2), 17.6 (CH_3).

(1*R,2*S**)-2-*tert*-Butylcyclohexyl (*E*)-2-butenoate (5j):** 770 mg, 86% yield; viscous oil; IR (neat) 1719, 1662 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.95 (dq, J = 15.5, 6.9 Hz, 1H), 5.82 (dq, J = 15.5, 1.6 Hz, 1H), 4.78 (dt, J = 10.1, 4.5 Hz, 1H), 1.94 (m, 1H), 1.87 (dd, J = 6.9, 1.6 Hz, 3H), 1.77−1.62 (m, 2H), 1.49−0.86 (m, 6H), 0.90 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.6 (C), 144.0 (CH), 123.6 (CH), 74.9 (CH), 50.5 (CH), 33.3 (CH_2), 32.8 (C), 29.1 (3 CH_3), 26.9 (CH_2), 25.9 (CH_2), 24.7 (CH_2), 18.0 (CH_3).

(1*R,2*S**)-2-(4-Biphenylyl)cyclohexyl (*E*)-2-butenoate (5k):** 1 g, 84% yield; white solid; mp 85 °C (methanol); IR (KBr) 1710, 1650, 1597 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.55−7.13 (m, 9H), 6.68 (dq, J = 15.5, 6.8 Hz, 1H), 5.54 (dq, J = 15.5, 1.6 Hz, 1H), 4.98 (dt, J = 10.4, 4.4 Hz, 1H), 2.68 (dt, J = 11.5, 3.6 Hz, 1H), 2.12 (m, 1H), 1.98−1.22 (m, 7H), 1.67 (dd, J = 6.8, 1.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.0 (C), 144.2 (CH), 142.6 (C), 142.0 (C), 139.2 (C), 128.9 (2 CH), 128.0 (2 CH), 127.1 (5 CH), 123.1 (CH), 75.7 (CH), 49.5 (CH), 34.3 (CH_2), 32.6 (CH_2), 26.1 (CH_2), 25.0 (CH_2), 18.0 (CH_3). X-ray crystallographic analysis: $C_{22}H_{24}O_2$, M_w = 320.43, crystal of 0.08 × 0.53 × 0.60 mm, monoclinic, space group $C2/c$, Z = 8, a = 25.262(23) Å, b = 5.694(5) Å, c = 25.405(22) Å, β = 92.14-(4)°, V = 3651(5) Å^3, d_{calc} = 1.17 g cm^{-3}, $F(000)$ = 1376, λ (Cu Kα) = 1.5418 Å, μ = 0.53 mm^{-1}; θ = 65°. Of the 3188 collected reflections ($-29 \le h \le 29$, k: 0−6, l: 0−29), 3105 were unique (R_{int} = 0.018) and 2094 were considered as observed having $I \ge 3\sigma(I)$. Cell parameters were refined from 25 well-centered reflections with $12.9 \le \theta \le 19.2$. Convergence was reached at R = 0.054 and R_w = 0.070 ($0.000\,74F_o^2$). The residual electron density in the final difference map was located between −0.18 and 0.17 e Å^3.

***rac*-2,2-Diphenylcyclopentyl (*E*)-2-butenoate (5l):** 1.1 g, 85% yield; white solid; mp 167 °C (hexane); IR (KBr) 1712, 1659 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38−7.09 (m, 10H), 6.88 (dq, J = 15.8, 6.4 Hz, 1H), 6.44 (d, J = 4.7 Hz, 1H), 5.72 (dq, J = 15.8, 1.7 Hz, 1H), 3.16 (m, 1H), 2.94−2.68 (m, 2H), 2.40−2.15 (m, 3H), 1.80 (dd, J = 7.0, 1.8 Hz, 3H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 165.7 (C), 145.6 (C), 145.0 (C), 144.1 (CH), 128.3 (2 CH), 127.9 (2 CH), 127.7 (2 CH), 126.5 (2 CH), 126.0 (CH), 125.7 (CH), 122.9 (CH), 79.2 (CH), 59.0 (C), 35.2 (CH_2), 30.5 (CH_2), 20.3 (CH_2), 17.7 (CH_3). Anal. Calcd for $C_{21}H_{22}O_2$: C, 82.31, H, 7.23. Found: C, 82.40, H, 7.32.

(1*R,2*S**,3*R**)- and (1*R**,2*S**,3*S**)-2-[1-(2-Methoxyphenyl)-1-methylethyl]cyclohexyl 3-Methoxybutyrate (6).** A solution of crotonate **5b** (250 mg, 0.8 mmol) and diphenylmethanamine (500 μL, 2.9 mmol) in methanol (150 μL) was stirred for 72 h at 20 °C. The solvent was removed under vacuum, and the residue was chromatographed, affording **6** (257 mg, 93% yield) as an oil: IR (neat) 1730, 1598, 1582 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ major diastereomer 7.17−7.09 (m, 2H), 6.88−6.80 (m, 2H), 4.77 (dt, J = 10.5, 4.7 Hz, 1H), 3.85 (s, 3H), 3.38 (m, 3H), 3.23 (s, 3H), 2.75 (dt, J = 11.7, 3.5

Hz, 1H), 2.05−1.60 (m, 6H), 1.39−1.0 (m, 4H), 1.33 (s, 3H), 1.26 (s, 3H), 1.03 (d, J = 6.4 Hz, 3H), minor diastereomer 3.50 (m, 1H), 1.06 (d, J = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ major diastereomer 170.7 (C), 158.1 (C), 139.4 (C), 126.4 (CH), 120.3 (CH), 111.6 (CH), 74.7 (CH), 73.4 (CH), 56.1 (CH_3), 55.0 (CH_3), 45.9 (CH), 41.6 (CH_2), 40.0 (C), 33.2 (CH_2), 27.0 (CH_2), 26.1 (CH_2), 25.7 (CH_3), 24.7 (CH_2), 24.5 (CH_3), 19.0 (CH_3), minor diastereomer 170.8 (C), 139.5 (C), 126.0 (CH), 74.6 (CH), 73.3 (CH), 41.2 (CH_2), 19.1 (CH_3).

Preparation of β-Amino Esters (9). General Procedure. A solution of chiral crotonate **5** (3 mmol) and diphenylmethanamine (2.4 mL, 12 mmol) in methanol (300 μL) was introduced by means of a syringe through the capillary inlet of a Pyrex cell and pressurized under 14 kbar at 20 °C for 18 h. After depressurization, the solvent was removed and the residue chromatographed over silica gel (cyclohexane:ethyl acetate 20:1) to yield pure aminobutyrate **9**.

(1*R,2*S**,3*R**)-2-[1-(2-Methoxyphenyl)-1-methylethyl]-cyclohexyl 3-(diphenylmethylamino)butyrate (9b):** 69% yield, single diastereomer by ^{1}H and ^{13}C NMR spectroscopy; viscous oil; IR (neat) 3343, 1721, 1598, 1582 cm^{-1}; ^{1}H NMR (400 MHz, CD_3COCD_3) δ 7.42 (d, J = 7.3 Hz, 4H), 7.30−7.28 (m, 4H), 7.27−7.06 (m, 4H), 6.94 (dd, J = 8.1, 1.2 Hz, 1H), 6.82 (dt, J = 7.7, 1.2 Hz, 1H), 4.94 (s, 1H), 4.73 (dt, J = 10.4, 4.4 Hz, 1H), 3.82 (s, 3H), 2.80−2.74 (m, 2H), 2.0 (dd, J = 10.3, 3.0 Hz, 1H), 1.90 (dd, J = 10.3, 3.2 Hz, 1H), 1.88−1.84 (m, 1H), 1.84−1.80 (m, 3H), 1.30−0.98 (m, 5H), 1.33 (s, 3H), 1.25 (s, 3H), 1.00 (d, J = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.8 (C), 158.4 (C), 144.6 (C), 144.2 (C), 139.7 (C), 128.3 (4 CH), 127.7 (2 CH), 127.5 (2 CH), 127.1 (2 CH), 126.7 (CH), 126.5 (CH), 120.7 (CH), 112.0 (CH), 75.1 (CH), 64.0 (CH), 55.4 (CH_3), 47.7 (CH), 46.2 (CH), 41.6 (CH_2), 40.4 (C), 33.7 (CH_2), 27.4 (CH_2), 26.4 (CH_2), 26.0 (CH_3), 26.1 (CH_2), 25.1 (CH_3), 20.6 (CH_3).

(1*R,2*S**,3*R**)- and (1*R**,2*S**,3*S**)-2-(1-Phenyl-1-methylethyl)cyclohexyl 3-(diphenylmethylamino)butyrate (9c):** 66% yield; viscous oil; IR (neat) 3312, 1721, 1600 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34−6.98 (m, 15H), 4.80 (s, 1H), 4.68 (dt, J = 10.3, 4.4 Hz, 1H), 2.72 (m, 1H), 2.0−1.50 (m, 8H), 1.32−0.9 (m, 4H), 1.22 (s, 3H), 1.12 (s, 3H), 0.93 (d, J = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, C_6D_6) δ major diastereomer 171.3 (C), 152.2 (C), 145.6 (C), 145.0 (C), 127.8 (4 CH), 127.4 (2 CH), 127.2 (2 CH), 126.8 (2 CH), 125.3 (2 CH), 124.9 (2 CH), 124.8 (CH), 74.8 (CH), 64.7 (CH), 51.4 (CH), 48.2 (CH), 42.2 (CH_2), 40.4 (C), 34.2 (CH_2), 28.2 (CH_3), 27.6 (CH_2), 26.5 (CH_2), 25.9 (CH_3), 25.2 (CH_2), 20.8 (CH_3); minor diastereomer 171.5 (C), 74.6 (CH), 48.4 (CH), 42.0 (CH_2), 28.0 (CH_3), 20.9 (CH_3).

(1*R,2*S**,3*R**)- and (1*R**,2*S**,3*S**)-2-[1-(4-Phenoxyphenyl)-1-methylethyl]cyclohexyl 3-(diphenylmethylamino)butyrate (9d):** 83% yield; viscous oil; IR (neat) 3346, 1724, 1591 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ major diastereomer 7.34−6.76 (m, 19H), 4.83 (s, 1H), 4.68 (dt, J = 10.0, 4.2 Hz, 1H), 2.78 (m, 1H), 2.04−1.74 (m, 4H), 1.70−1.48 (m, 4H), 1.26−0.88 (m, 4H), 1.21 (s, 3H), 1.12 (s, 3H), 0.98 (d, J = 6.4 Hz, 3H), minor diastereomer 4.84 (s, 1H), 0.96 (d, J = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ major diastereomer 171.2 (C), 157.4 (C), 154.4 (C), 146.5 (C), 144.3 (C), 143.7 (C), 129.6 (2 CH), 128.3 (4 CH), 127.4 (2 CH), 127.2 (2 CH), 126.8 (2 CH), 126.6 (2 CH), 122.9 (CH), 118.6 (2 CH), 118.2 (2 CH), 74.6 (CH), 63.8 (CH), 50.7 (CH), 47.3 (CH), 41.8 (C), 39.4 (CH_2), 33.3 (CH_2), 27.9 (CH_3), 27.0 (CH_2), 25.9 (CH_2), 25.3 (CH_3), 24.6 (CH_2), 20.3 (CH_3), minor diastereomer 73.8 (CH), 47.5 (CH), 41.5 (C), 26.7 (CH_2).

(1*R,2*S**,3*R**)- and (1*R**,2*S**,3*S**)-2-(2-Naphthylmethyl)cyclohexyl 3-(diphenylmethylamino)butyrate (9e):** 84% yield; viscous oil; IR (neat) 3483, 1743, 1602 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ major diastereomer 7.82−7.72 (m, 3H), 7.52 (s, 1H), 7.46−7.13 (m, 13H), 4.96 (s, 1H), 4.64 (dt, J = 10.4, 4.9 Hz, 1H), 3.06 (dt, J = 11.2, 3.82 Hz, 1H), 3.03 (dd, J = 12.8, 4.6 Hz, 1H), 2.5−2.23 (m, 3H), 2.05 (m, 1H), 1.92−1.53 (m, 7H), 1.42−0.98 (m, 2H), 1.10 (d, J = 6.3 Hz, 3H), minor diastereomer 1.13 (d, J = 6.8 Hz, 3H); ^{13}C NMR (50 MHz, CD_3COCD_3) δ major diastereomer 172.0 (C), 145.8 (C), 145.3 (C), 140.6 (C), 137.3 (C), 134.4 (C), 133.1 (CH), 129.0 (4 CH), 128.6 (CH), 128.5 (2 CH), 128.3 (4 CH), 128.2 (2 CH), 126.6 (2 CH), 125.9 (CH), 76.8 (CH), 64.6 (CH), 48.6 (CH_2), 44.5 (CH), 42.5 (CH), 42.2 (CH_2), 32.5 (CH_2), 30.6 (CH_2), 25.5 (CH_2), 20.5 (CH_3), minor diastereomer 76.7 (CH), 44.4 (CH), 42.1 (C), 20.7 (CH_3).

(1*R,2*S**,3*R**)- and (1*R**,2*S**,3*S**)-3′,3′-Dimethyl-2′-(2-naphthylmethyl)cyclohexyl 3-(diphenylmethylamino)-butyrate (9f):** 55% yield; viscous oil; IR (neat) 3343, 1726, 1602 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ major diastereomer 7.82−7.12 (m, 17H), 4.98 (dt, J = 10, 4.1 Hz, 1H), 4.64 (s, 1H), 3.04 (dd, J = 14.6, 1.8 Hz, 1H), 2.62 (dd, J = 14.6, 6.5 Hz, 1H), 2.60 (m, 1H), 2.02−0.74 (m, 10H), 1.08 (s, 3H), 0.99 (s, 3H), 0.83 (d, J = 6.4 Hz, 3H), minor diastereomer 4.73 (s, 1H), 0.76 (d, J = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ major diastereomer 171.8 (C), 144.1 (C), 143.8 (C), 140.8 (C), 133.5 (C), 131.7 (C), 128.4 (CH), 128.3 (CH), 128.2 (3 CH), 127.5 (CH), 127.4 (2 CH), 127.3 (CH), 127.2 (2 CH), 126.8 (CH),-126.7 (CH), 126.6 (CH), 125.9 (CH), 125.8 (CH), 125.0 (CH), 76.1 (CH), 63.6 (CH), 51.8 (CH), 47.1 (CH), 41.0 (2 CH_2), 35.6 (CH_2), 32.7 (CH_2), 31.0 (CH_3), 26.9 (C), 20.5 (CH_3), 20.1 (CH_2), 20.0 (CH_3), minor diastereomer 172.2 (C) 44.2 (C), 143.6 (C), 140.8 (C), 131.9 (C), 75.8 (CH), 63.7 (CH), 51.6 (CH), 47.6 (CH), 41.2 (CH), 35.4 (CH_2).

(1*R,2*S**,3*R**)- and (1*R**,2*S**,3*S**)-2-(2,4,6-Trimethylphenyl)cyclohexyl 3-(diphenylmethylamino)butyrate (9g):** 70% yield; viscous oil; IR (neat) 3340, 1721, 1612, 1601 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ major diastereomer 7.40−7.05 (m, 10H), 6.58 (s, 1H), 6.52 (s, 1H), 5.36 (dt, J = 11.5, 4.2 Hz, 1H), 4.76 (s, 1H), 3.03 (dt, J = 11.5, 3.9 Hz, 1H), 2.53 (m, 1H), 2.33−1.47 (m, 6H), 2.33 (s, 3H), 2.1 (s, 3H), 2.0 (s, 3H), 1.45−1.18 (m, 5H), 0.54 (d, J = 6.3 Hz, 3H), minor diastereomer 6.64 (s, 1H), 6.6 (s, 1H), 4.71 (s, 1H), 2.71 (m, 1H), 2.10 (s, 3H), 0.64 (d, J = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ major diastereomer 171.4 (C), 144.5 (C), 144.3 (C), 137.5 (C), 136.1 (C), 135.4 (2 C), 131.3 (CH), 129.3 (CH), 128.6 (CH), 127.6 (2 CH), 127.5 (2 CH), 127.1 (2 CH), 73.8 (CH), 64.2 (CH), 48.0 (CH), 45.3 (CH), 42.2 (CH_2), 33.4 (CH_2), 29.9 (CH_2), 26.6 (CH_2), 25.0 (CH_2), 21.7 (CH_3), 20.8 (2 CH_3), 19.8 (CH_3), minor diastereomer 171.6 (C), 64.3 (CH), 47.9 (CH), 45.5 (CH), 21.8 (CH_3), 20.0 (CH_3).

(1*R,2*S**,3*R**)- and (1*R**,2*S**,3*S**)-2-(2-Naphthyl)cyclohexyl 3-(diphenylmethylamino)butyrate (9h):** 70% yield; viscous oil; IR (neat) 3348, 1730, 1602 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ major diastereomer 7.75−7.63 (m, 3H), 7.5 (s, 1H), 7.42−7.11 (m, 13H), 5.04 (dt, J = 10.3, 4.2 Hz, 1H), 4.72 (s, 1H), 2.73 (dt, J = 11.8, 3.7 Hz, 1H), 2.67 (m, 1H), 2.2−1.23 (m, 11H), 0.46 (d, J = 6.6 Hz, 3H), minor diastereomer 5.1 (dt, J = 10.3, 4.2 Hz, 1H), 4.70 (s, 1H), 0.54 (d, J = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ major diastereomer 171.8 (C), 144.2 (C), 143.9 (C), 137.8 (C), 133.4 (C), 132.4 (C), 128.3 (4 CH), 127.8 (CH), 127.5 (2 CH), 127.4 (2 CH), 127.3 (2 CH), 126.8 (2 CH), 126.1 (CH), 125.9 (CH), 125.8 (CH), 125.2 (CH), 76.9 (CH), 63.8 (CH), 47.6 (CH), 43.6 (CH), 41.5 (CH_2), 33.8 (CH_2), 31.8 (CH_2), 30.0 (CH_2), 25.0 (CH_2), 24.5 (CH_2), 19.7 (CH_3), minor diastereomer 171.9 (C), 41.6 (CH_2).

(1*R,2*S**,3*R**)- and (1*R**,2*S**,3*S**)-2-(4-Phenoxyphenyl)-cyclohexyl 3-(diphenylmethylamino)butyrate (9i):** 73% yield; viscous oil; IR (neat) 3400, 1731, 1592 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ major diastereomer 7.35−7.19 (m, 2H), 7.17−6.68 (m, 17H), 4.87 (dt, J = 10.1, 4.5 Hz, 1H), 4.72 (s, 1H), 2.68 (m, 1H), 2.22 (dt, J = 11.5, 3.4 Hz, 1H), 2.17−1.86 (m, 3H), 1.67−0.6 (m, 8H), 0.63 (d, J = 6.2 Hz, 3H), minor diastereomer 4.70 (s, 1H), 2.78 (m, 1H), 0.66 (d, J = 5.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ major diastereomer 171.9 (C), 144.3 (C), 143.7 (C), 137.8 (C), 133.4 (C), 131.9 (C), 128.4 (4 CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 127.4 (3 CH), 127.3 (2 CH), 127.2 (2 CH), 127.1 (CH), 126.9 (CH), 126.8 (CH), 125.8 (CH), 125.1 (CH), 76.9 (CH), 64.0 (CH), 47.7 (CH), 43.5 (CH), 41.6 (CH_2), 39.2 (CH_2), 31.9 (CH_2), 25.0 (CH_2), 24.4 (CH_2), 20.4 (CH_3), minor diastereomer 171.8 (C), 127.8 (CH), 41.9 (CH_2), 30.1 (CH_2), 26.8 (CH_2).

(1*R,2*S**,3*R**)- and (1*R**,2*S**,3*S**)-2-*tert*-Butylcyclohexyl 3-(diphenylmethylamino)butyrate (9j):** 82% yield; viscous oil; IR (neat) 3342, 1726, 1600 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ major diastereomer 7.4−7.2 (m, 10H), 4.97 (s, 1H), 4.73 (dt, J = 10.2, 4.1 Hz, 1H), 3.1 (m, 1H), 2.58−2.26 (m, 2H), 2.07−1.64 (m, 5H), 1.42−0.87 (m, 5H), 1.13 (d, J = 6.4 Hz, 3H), 0.88 (s, 9H), minor diastereomer 4.72 (dt, J = 10.2, 4.1

Hz, 1H), 0.87 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ major diastereomer 171.3 (C), 144.3 (C), 143.6 (C), 128.3 (4 CH), 127.3 (2 CH), 127.2 (2 CH), 126.8 (2 CH), 75.3 (CH), 63.9 (CH), 50.2 (CH), 47.4 (C), 42.3 (CH), 33.2 (CH_2), 32.7 (CH_2), 29.0 (3 CH_3), 26.7 (CH_2), 25.8 (CH_2), 24.5 (CH_2), 20.2 (CH_3), minor diastereomer 64.0 (CH), 47.6 (CH_2), 42.1 (CH), 20.4 (CH_3).

(1*R,2*S**,3*R**)- and (1*R**,2*S**,3*S**)-2-(4-Biphenyl)cyclohexyl 3-(diphenylmethylamino)butyrate (9k):** 73% yield; viscous oil; IR (neat) 3342, 1721, 1600 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ major diastereomer 7.58−7.0 (m, 19H), 4.91 (dt, J = 10.6, 5.2 Hz, 1H), 4.76 (s, 1H), 2.84 (m, 1H), 2.58 (dt, J = 11.4, 3 Hz, 1H), 2.28−1.97 (m, 3H), 1.88−0.80 (m, 8H), 0.60 (d, J = 6.5 Hz, 3H), minor diastereomer 4.74 (s, 1H), 2.95 (m, 1H), 0.63 (d, J = 6.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ major diastereomer 171.4 (C), 144.2 (C), 144.0 (C), 142.2 (C), 141.0 (C), 139.3 (C), 128.7 (2 CH), 128.4 (5 CH), 127.9 (2 CH), 127.4 (2 CH), 127.3 (2 CH), 127.0 (6 CH), 76.1 (CH), 63.9 (CH), 49.5 (CH), 47.8 (CH), 41.6 (CH_2), 33.8 (CH_2), 32.4 (CH_2), 25.8 (CH_2), 24.8 (CH_2), 19.8 (CH_3), minor diastereomer 171.5 (C), 75.9 (CH), 64.0 (CH), 47.6 (CH), 41.1 (CH_2), 34.1 (CH_2).

(1*R,3*R**)- and (1*R**,3*S**)-2,2-Diphenylcyclopentyl 3-(diphenylmethylamino)butyrate (9l):** 72% yield; viscous oil; IR (neat) 3345, 1728, 1600 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ major diastereomer 7.37−7.05 (m, 20H), 6.07 (dd, J = 6.6, 1.9 Hz, 1H), 4.85 (s, 1H), 2.71 (m, 1H), 2.54−2.4 (m, 2H), 2.31−2.04 (m, 3H), 1.93−1.45 (m, 4H), 0.86 (d, J = 6.6 Hz, 3H), minor diastereomer 6.1 (dd, J = 6.6, 1.9 Hz, 1H), 2.83 (m, 1H), 0.87 (d, J = 6.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ major diastereomer 171.2 (C), 145.3 (C), 144.6 (C), 144.1 (C), 143.8 (C), 128.2 (6 CH), 127.8 (CH), 127.7 (4 CH), 127.3 (2 CH), 127.2 (CH), 127.1 (CH), 126.8 (CH), 126.4 (2 CH), 125.9 (CH), 125.6 (CH), 79.4 (CH), 63.9 (CH), 59.0 (CH_2), 47.4 (CH), 41.5 (C), 34.9 (CH_2), 30.6 (CH_2), 20.3 (CH_2), 20.1 (CH_3), minor diastereomer 171.4 (C), 145.2 (C), 144.7 (C), 126.3 (CH), 79.5 (CH), 41.2 (CH), 20.0 (CH_3).

Chemical Correlation of Adduct 9a to (*S*)-3-Aminobutanol ((+)-11). (1*S*,2*R*,3*S*)-2-[1-(2-Naphthyl)-1-methylethyl]cyclohexyl 3-(Diphenylmethylamino)butyrate (9a). A solution of crotonate (1*S*,2*R*)-(+)-**5a** (820 mg, 2.4 mmol) and diphenylmethanamine (1 mL, 5.7 mmol) in methanol (300 μL) was pressurized under 14 kbar at 20 °C for 18 h. After depressurization, the solvent was removed and the residue chromatographed over silica gel (cyclohexane:ethyl acetate 20:1) to give β-amino ester **9a** (826 mg, 66% yield). ^{1}H NMR and ^{13}C NMR spectra were found to be identical to those of *rac*-**9a**.[5]

(*S*)-3-(Diphenylmethylamino)butanol ((+)-10). Amino ester **9a** (0.74 g, 1.42 mmol) in diethyl ether (6 mL) was added dropwise to LAH (110 mg, 2.84 mmol) in diethyl ether (2 mL) at 0 °C. After the mixture was stirred for 0.5 h at 20 °C, it was hydrolyzed at 0 °C with 0.5 N NaOH (0.5 mL). The solid was filtered off, the filtrate was concentrated under vacuum, and the residue was chromatographed over silica gel (cyclohexane:ethyl acetate 1.5:1) to give pure amino alcohol (*S*)-(+)-**10** (308 mg, 85% yield) as a white solid: mp 64 °C (petroleum ether); $[\alpha]^{20}_D$ +42.4 (*c* 4.37, MeOH); IR (neat) 3334, 1600, 1588 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 7.4 (d, J = 7.8 Hz, 2H), 7.25 (d, J = 7.8 Hz, 2H), 7.15−6.97 (m, 6H), 4.84 (s, 1H), 3.75 (ddd, J = 11.9, 5.2, 4.2 Hz, 1H), 3.64 (ddd, J = 11.9, 7.1, 4.3 Hz, 1H), 2.61 (ddq, J = 8.7, 6.3, 3.8 Hz, 1H), 2.35 (br s, 2H), 1.35−1.24 (m, 2H), 0.77 (d, J = 6.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.9 (C), 142.6 (C), 128.6 (4 CH), 127.5 (2 CH), 127.2 (2 CH), 126.9 (2 CH), 64.1 (CH), 62.5 (CH_2), 51.3 (CH), 38.3 (CH_2), 20.2 (CH_3). Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96, H, 8.29, N, 5.48. Found: C, 79.99, H, 8.30, N, 5.44.

(*S*)-3-Aminobutanol ((+)-11). A solution of the amino alcohol **10** (260 mg, 1 mmol) in MeOH (4 mL) was stirred in the presence of 20% $Pd(OH)_2$/C (150 mg) for 5 h under 4 bar of hydrogen. The catalyst was filtered off and carefully washed with MeOH (6 × 5 mL). The filtrate was concentrated under vacuum to yield a crude product (258 mg, 99% yield) that contained only amino alcohol (*S*)-(+)-**11** and diphenylmethane (estimated respective weights by ^{1}H NMR spectroscopy: 89 mg of **11** and 169 mg of diphenylmethane): $[\alpha]^{20}_D$ +16.3 (*c* 4.5, EtOH) (lit.[11] $[\alpha]^{20}_D$ +10.5 (*c* 5.1, EtOH)]; IR (neat) 3376, 1602 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 7.3−7.02 (m, 10H), 5.0 (br s, 3H), 3.87 (s, 2H), 3.86−3.53 (m, 2H), 3.5−3.3 (m, 1H), 2.0−1.52 (m, 2H), 1.28 (d, J = 6.6 Hz, 3H).

Stereochemistry of the Proton Transfer. *N*,*N*-Dideuteriodiphenylmethanamine. A mixture of diphenylmethanamine (2 g, 10.9 mmol), CH_3OD (1 mL), and D_2O (3 mL) was vigorously stirred for 1 h at 20 °C. The deuterated amine was extracted with dry diethyl ether (3 × 10 mL), and the organic layer was dried over $MgSO_4$ and concentrated under vacuum. A ratio of *ca*. 90% of deuterium incorporation was measured by ^{1}H NMR spectroscopy: IR (neat) 2516, 2424 cm^{-1}; ^{1}H NMR (200 MHz, C_6D_6) δ 7.25 (m, 4H), 7.14−6.9 (m, 10H), 4.72 (s, 1H), 1.1 (br s, *ca*. 0.1H).

(±)-2-Deuterio-3-(diphenylmethylamino)butanol (13). A solution of *racemic* crotonate **5a** (403 mg, 1.2 mmol) and *N*,*N*-dideuteriodiphenylmethanamine (1.13 g, 6.2 mmol) in CH_3OD (300 μL) was pressurized under 14 kbar at 25 °C for 19 h. After depressurization, the solvent was removed and the crude adduct **12** was diluted in diethyl ether (4 mL) and directly added dropwise to $LiAlH_4$ (67 mg, 1.7 mmol) in diethyl ether (1 mL) at 0 °C. The mixture was strirred for 0.5 h at 20 °C and then hydrolyzed at 0 °C with 0.5 N NaOH (0.5 mL). The precipitated solid was filtered off and washed with diethyl ether, and the filtrate was concentrated under vacuum. The crude product was chromatographed over silica gel (cyclohexane:ethyl acetate, 1.5:1) to yield pure amino alcohol **13** (197 mg, 64% yield) as a white solid: mp 62 °C (petroleum ether); ^{1}H NMR (400 MHz, C_6D_6) δ 7.42 (d, J = 7.6 Hz, 2H), 7.33 (d, J = 7.6 Hz, 2H), 7.3−7.19 (m, 6H), 5.04 (s, 1H), 3.74 (dd, J = 10.8, 4.5 Hz, 1H), 3.67 (dd, J = 10.8, 8.5 Hz, 1H), 2.62 (dq, J = 9.0, 6.3 Hz, 1H), 2.6 (br s, 2H), 1.39 (m, 1H), 0.76 (d, J = 6.3 Hz, 3H); ^{13}C NMR (50 MHz, C_6D_6) δ 144.8 (C), 143.7 (C), 128.8 (4 CH), 127.9 (2 CH), 127.5 (2 CH), 127.3 (2 CH), 64.5 (CH), 61.9 (CH_2), 50.7 (CH_2), 38.7 (t, J = 18.5 Hz, CHD), 20.1 (CH_3); MS ($C_{17}DH_{20}NO$, FW 256) *m*/*z* 256 M$^+$ (13), 210 (29), 167 (100), 165 (12), 106 (18).

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Supporting Information Available: Copies of ^{1}H NMR spectra (36 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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