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Highly Enantioselective Access to α-Dibenzylamino Ketones from Chiral Nonracemic α-Bromo α′-Sulfinyl Ketones by Dynamic Kinetic Resolution: Synthesis of (2*R*,1′*S*)-2-[1-(Dibenzylamino)alkyl]oxiranes

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Dedicated to the memory of Professor Jean-Marc Kern

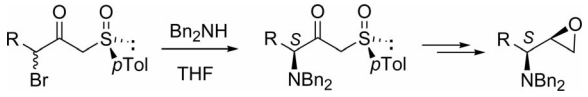
Keywords: Amino ketones / Amino alcohols / Chiral sulfoxides / Epoxidation / Kinetic resolution / Template synthesis / Chirality

A novel and efficient synthesis of enantiomerically pure α-dibenzylamino α′-sulfinyl ketones starting from a mixture of both epimers of α-bromo α′-(*R*)-sulfinyl ketone has been realized through combined in situ substitution–epimerization in a so-called Dynamic Kinetic Resolution (DKR). The scope of the reaction has been examined, and four differently substituted α-(*S*)-dibenzylamino α′-(*R*)-sulfinyl ketones were obtained in good yields with excellent diastereoselectivities. The utility of these derivatives was further illustrated with a highly stereoselective synthesis of *syn*-(2*R*,1′*S*)-2-(1-dibenzylaminoalkyl)oxiranes.

Introduction

α-Amino ketones are well-known as versatile precursors of many physiologically important compounds and useful intermediates for organic synthesis. Indeed, various synthetic approaches to the asymmetric synthesis of optically active α-amino ketones have been reported in recent years. The most common procedure for the synthesis of these valuable moieties involves the use of a natural α-amino acid as chiral pool.[1] However, with side chains not found in natural α-amino acids, this route requires additional steps, making the procedure long and inefficient. Electrophilic amination of chiral enolates is one of the most important and general strategies, and many examples of amination of lithium enolates, enamines, and enolsilanes have been documented.[2] It is only rather recently that enantioselective catalytic asymmetric variants of ketone amination using azodicarboxylates as nitrogen source have been reported.[3,4] The S_N2 halogen displacement in α-halo ketones by nitrogen nucleophiles is another alternative that requires not readily accessible enantiopure α-halo ketones.[5] This latter methodology generally involves two-step azide displacement followed by reduction of the azide group, avoiding the potentially problematic use of amines as nucleophiles that often results in racemization at the halogenated chiral centre.[6] Accordingly, flexible strategies permitting access to both (*R*) and (*S*) α-amino ketone enantiomers are of great interest in terms of developing practical processes.

This paper summarizes our studies on a new, highly stereoselective strategy that allows the recovery of enantiopure α-(*S*)-dibenzylamino ketones from chiral nonracemic α-bromo α′-(*R*)-sulfinyl ketones (Scheme 1). The reaction mechanism is discussed. Our approach involved nucleophilic displacement of the more reactive bromine epimer by dibenzylamine and epimerization of the less reactive epimer. The sulfoxide group is solely responsible for the diastereoselectivity observed and it is this process that transfers the chiral information to the substituents at the α-bromo carbon center. To the best of our knowledge, the sequence used here for the synthesis of α-amino ketones is the first example of dynamic kinetic resolution of α-halo ketones by amination so far reported.[7] Chiral sulfoxides have also not been used for this proposal.[8] An additional advantage of our strategy is the presence of the sulfoxide group in the resulting α-amino ketones, which allows further synthetic exploitation. As an application, we describe the highly diastereoselective transformation of α-(*S*)-dibenzylamino α′-



Scheme 1. Synthesis of α-(*S*)-dibenzylamino α′-(*R*)-sulfinyl ketones and their transformation into *syn*-(2*R*,1′*S*)-2-(1-dibenzylaminoalkyl)oxiranes.

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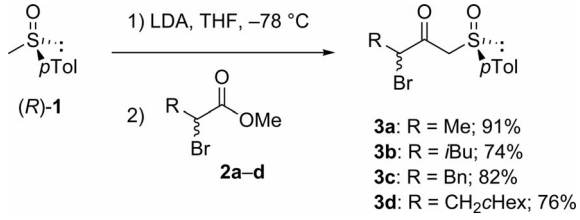
(*R*)-sulfinyl ketones into *syn*-(2*R*,1′*S*)-2-[1-(dibenzylamino)-alkyl]oxiranes, which are particularly valuable moieties in the total synthesis of biologically active compounds (Scheme 1).

Results and Discussion

The required chiral nonracemic α-bromo α′-(*R*)-sulfinyl ketones, optically pure only at the sulfur atom, were prepared by the conventional method described by Bravo.[9] Nucleophilic addition at –78 °C of the lithiated anion of (+)-(*R*)-(methyl *p*-tolyl sulfoxide) (**1**) to the (±)-(methyl 2-bromo esters) **2a**–**d**[10] was performed and it was found that the reaction occurred regioselectively on the carboxyl group of α-bromo esters (Scheme 2). Use of one equivalent excess of the nucleophile led to the corresponding α-bromo α′-sulfinyl ketone **3a**–**d**[11] by virtue of their acidity. The products were obtained in 73–91% yield after purification by column chromatography on silica gel. ^{1}H NMR spectroscopic analysis of the crude reaction mixtures showed clearly that, in each case, an approximate 1:1 mixture of diastereomers was obtained.

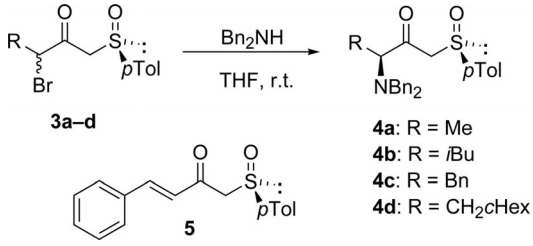


Scheme 2. Condensation of lithiated (+)-(*R*)-(methyl *p*-tolyl sulfoxide) carbanion with α-bromo esters.

Exposure of the epimeric mixture of α-bromo ketone **3a** to 2.5 equiv. of sterically hindered dibenzylamine in tetrahydrofuran (THF) was then examined at room temperature. Surprisingly, both the ^{1}H NMR and ^{13}C NMR spectra of the crude reaction mixture after 5 h showed the presence of exclusively one of the two possible diastereomeric α-dibenzylamino α′-(*R*)-sulfinyl ketones. Thus, compound **4a** was isolated as a single diastereoisomer[12] in 84% yield, after washing the solid crude material with diethyl ether (Table 1, entry 1). The influence of solvent on the stereoselectivity and reaction time was then studied. The use of acetone, acetonitrile, or methanol instead of THF did not affect the excellent diastereoselectivity of the reaction, but no improvement in reaction time was observed.[13] The use of *N*,*N*-dimethylformamide (DMF) accelerated the reaction (2.5 h) but reduced the diastereoselectivity (91:9).

The reaction with α-bromo ketones **3b**–**d** in THF was then assessed. Longer reaction times were needed for more sterically hindered side chains (Table 1, entries 2–4), but the size of the R substituent had no significant influence on the stereoselectivity. Compounds **4b**–**d** were isolated as single diastereoisomers in yields ranging from 55 to 74%, after purification by column chromatography of the corresponding crude oils, as summarized in Table 1. Partial product degradation was observed during purification, which decreased the reaction yields. In the case of substrate **3c** (Table 1, entry 3), the desired product **4c** was accompanied by the formation of α,β-unsaturated ketone **5**, which was isolated in 35% yield.

Table 1. Synthesis of enantiopure α-(*S*)-dibenzylamino α′-(*R*)-sulfinyl ketones.



Entry	Substrate	Reaction time	Yield [%]	Diastereomeric ratio[c]
1	**3a**	5 h	84[a]	>95:5
2	**3b**	12 d	68[b]	>95:5
3	**3c**	3 d	55[b][d]	>95:5
4	**3d**	10 d	74[b]	>95:5

[a] Yield after washing the crude solid with diethyl ether. [b] Yield after purification by chromatography on silica gel. [c] Determined by 300 MHz ^{1}H NMR and HPLC analyses. [d] Compound **5** was also obtained in 35% isolated yield.

At this point, the absolute configuration of the new carbon bearing the nitrogen atom was not known. The stereochemistry of the major diastereomer formed in this reaction was unambiguously established as *S* by X-ray crystallographic analysis of the α-dibenzylamino α′-(*R*)-sulfinyl ketone **4a** (Figure 1).[14]

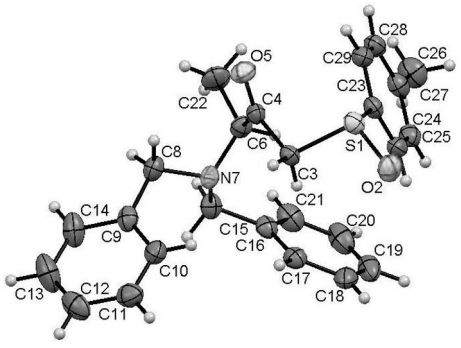
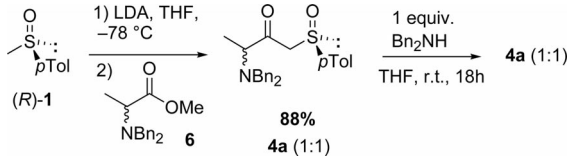


Figure 1. X-ray structure of compound **4a**.

For the possible mechanism of this transformation, we speculated that the reaction took place through a combined S_N2-displacement[15]–epimerization process that constitutes a dynamic kinetic asymmetric transformation concept, which has its origin in the 1,4-stereoinduction of the chiral sulfoxide group.[16]

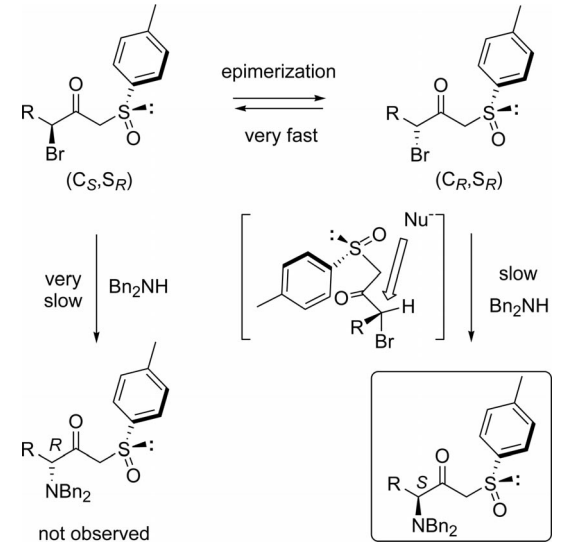
We ensured first that the enantiopure α-(*S*)-dibenzylamino α′-(*R*)-sulfinyl ketones obtained were configurationally stable and were not the result of an interconversion between the two possible diastereomeric products under the reaction conditions. To test this proposal, we synthesized a racemic mixture of both epimers of **4a** by condensing methyl (±)-2-(dibenzylamino)propionate (**6**) with the lithi-

ated anion of (*R*)-**1** according to Scheme 3. By treating **4a** with 1 equiv. of Bn_2NH in THF for 18 h, no variation in the **4a** epimer ratio was observed.



Scheme 3. Synthesis of an epimeric mixture of α-dibenzylamino α′-(*R*)-sulfinyl ketone (**4a**).

As depicted in Scheme 4, we therefore proposed that the starting material epimers (C_S,S_R) and (C_R,S_R) adopt a conformation in which the C=O and S=O bonds are aligned in opposition to minimize carbonyl–sufoxide dipole interactions,[17] and are in equilibrium under the reaction conditions. In the transition state, the C–Br bond is perpendicular to the carbonyl because this conformation permits the halogen displacement to take place much more rapidly (π* C=O).[18] The slightly less stable and faster reacting epimer (C_R,S_R) leads to displacement of the bromide ion by the bulky nucleophile dibenzylamine, which approaches from the less hindered, opposite side to the *p*-tolyl sulfoxide substituent, providing exclusively the (*S*)-dibenzylamino ketone. In addition, simultaneous in situ epimerization of the slower reacting epimer (C_S,S_R) into (C_R,S_R) allows the yield to increase to more than 50% in the transformation.



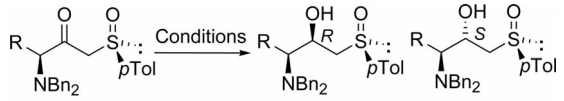
Scheme 4. Proposed mechanism for the S_N2-DKR process involving α-bromo α′-(*R*)-sulfinyl ketones and dibenzylamine.

To illustrate the utility of the α-(*S*)-dibenzylamino α′-(*R*)-sulfinyl ketone intermediates, we planned to bring about their transformation into *syn*-(2*R*,1′*S*)-2-[1-(dibenzylamino)alkyl]epoxides (DBAE), which are very useful moieties in organic synthesis[19] that have been used to prepare a large number of biologically active natural and synthetic compounds, such as hydroxyethylene dipeptide isosteres[20] and other pharmacologically important compounds.[21] Ring opening of DBAE with total regioselectivity by ketones,[22a] nitriles,[22b,22c] thiols,[22d] carboxylic acids,[22e] and organolithium compounds[22f,22g] was recently reported by Concellón and co-workers. DBAE have also been used as precursors for the synthesis of oxazolidinones,[23a] 4-(1-dibenzylaminoalkyl)-2-oxo-1,3-dioxolanes,[23b] 2,5-disubstituted-1,4-dioxanes with C_2 symmetry,[23c] and *cis*- or *trans*-3,4-disubstituted 1,2,3,4-tetrahydroisoquinolines.[23d]

Initial attention focused upon the preparation of vicinal *threo*- or *syn*-amino alcohols, which would lead to the projected DBAE by stereoselective reduction of the carbonyl of α-(*S*)-dibenzylamino α′-(*R*)-sulfinyl ketones. Various synthetic approaches to vicinal *syn*-amino alcohols have been reported in the literature.[24] Among them, it is well-documented that ketones having a dibenzylamino group α to the carbonyl can be reduced to give *syn*-rich products.[25] In our case, the stereochemical outcome of the reduction could be controlled by the dibenzylamino group but also by the chiral sulfinyl functionality.[26]

As depicted in Table 2, we initially proceeded by reacting **4a**–**d** with $NaBH_4$ in anhydrous MeOH at –15 °C (entries 1, 4, 7, and 10). In all cases the *syn* stereoisomer was the major product with the highest selectivity (>95:5) for **4d**; the diastereomerically pure material was isolated in 77% yield after column chromatography. We examined the use diisobutylaluminum hydride (DIBAL-H) at –78 °C in the presence of 1.5 equiv. of ZnI_2. An excess of DIBAL-H (2.5 equiv.) was required to achieve complete transformation of the starting materials. The reductions proceeded

Table 2. Stereoselective reduction of α-(*S*)-dibenzylamino α′-(*R*)-sulfinyl ketones to vicinal amino alcohols.



4a: R = Me
4b: R = *i*Bu
4c: R = Bn
4d: R = CH_2*c*Hex

Entry	Substrate	Conditions	Yield [%][a]	Ratio[b] *syn*-**7**/*anti*-**7**
1	**4a**	$NaBH_4$, MeOH, –15 °C	90	90:10
2	**4a**	DIBAL/ZnI_2 THF, –78 °C	86	>95:5
3	**4a**	DIBAL,THF, –78 °C	72	35:65
4	**4b**	$NaBH_4$, MeOH, –15 °C	84	90:10
5	**4b**	DIBAL/ZnI_2 THF, –78 °C	77	>95:5
6	**4b**	DIBAL,THF, –78 °C	87	30:70
7	**4c**	$NaBH_4$, MeOH, –15 °C	77	85:15
8	**4c**	DIBAL/ZnI_2 THF, –78 °C	88	>95:5
9	**4c**	DIBAL,THF, –78 °C	70	15:85
10	**4d**	$NaBH_4$, MeOH, –15 °C	77	>95:5
11	**4d**	DIBAL/ZnI_2 THF, –78 °C	86	>95:5
12	**4d**	DIBAL,THF, –78 °C	87	>5:95

[a] Yield after purification by chromatography on silica gel. [b] Determined by 300 MHz ^{1}H NMR and HPLC analyses.

with high diastereoselectivity for each substrate, and diastereomerically pure *syn*-**7a**–**d** products were obtained in high yields (Table 2entries 2, 5, 8, and 11). Alternatively, reduction of **4a**–**d** using DIBAL-H alone provided the *anti*-**7d** product with excellent yield and higher stereoselectivity (>5:95; Table 2, entry 12) and *anti*-**7a**–**c** with lower diastereoselectivity (35:65 to 15:85; Table 2, entries 3, 6, and 9).

Configurational assignment of the resulting hydroxyl carbon atoms was deduced from the ^{1}H NMR spectroscopic data for the methylene protons α to the sulfinyl group. Thus, the *syn*-**7** isomers exhibited lower J_{anti} and larger J_{gauche} values than those of their corresponding *anti*-**7** epimers. It has been established in previous studies with related systems[17b,26a,27] that these data are indicative of a (C_R,S_R) relative configuration in *syn*-**7** and a (C_S,S_R) relative configuration in *anti*-**7**. The assignment was in agreement with predictions made on the basis of the stereochimical model proposed in the literature to explain the DIBAL-H and DIBAL-H/ZnI_2 reduction of β-keto sulfoxides. The absolute configuration of **7a**–**c** was confirmed by comparison of the optical rotation of epoxides **8a**–**c** to the literature values.

The secondary amine plays a crucial role in the stereoselectivity of the reduction with the non-chelating agent $NaBH_4$, with the external hydride being delivered to the less hindered face of the carbonyl group according to the Felkin–Anh model.[25] In contrast, in the reaction with DIBAL-H/ZnI_2, the transition state involves a conformationally rigid six-membered cyclic intermediate originating from the chelation of the Lewis acid to the sulfinyl and carbonyl oxygen atoms (Figure 2, A). The approach of the electrophilic hydride is then directed by complexation with the lone electron pair of the sulfoxide or the pseudo-axial halogen.[28] Finally, in the diastereoselective reduction with DIBAL-H alone, where the opposite stereoselectivity was observed, dibenzylamine and the chiral sulfoxide operate in opposite directions, and a predominant role of the sulfinyl group in the stereoselectivity was clearly observed. The product was derived from an intramolecular hydride transfer through a six-membered cyclic transition state after formation of an O–Al bond with the basic sulfinyl oxygen (Figure 2, B). Thus, the *anti* stereoisomer was the major product obtained. However, even if the selectivity of the reduction is primarily controlled by the chiral sulfoxide group, the nitrogen atom is able to compete with the sulfinyl oxygen to chelate the metal and cause some interference, which explains why the reduction is less stereoselective and gives a mixture of epimers. These interferences became less important with increased steric hindrance on the carbon bearing the nitrogen (compare Table 2, entries 3, 6, 9, and 12).

We finally turned our attention to the preparation of three DBAE compounds **8a**–**c** that could be correlated with those derived from natural alanine, leucine, and phenylalanine and that have been described in the literature. Having amino alcohols **7a**–**c** in hand, conversion into the corresponding oxiranes **8a**–**c** was achieved by a three-step sequence involving sulfinyl reduction with *t*BuBr in refluxing chloroform,[29] followed by methylation, without further purification, of the resulting β-sulfenyl derivatives with trimethyl oxonium tetrafluoroborate in anhydrous CH_2Cl_2 and treatment of the corresponding sulfonium salts with aqueous K_2CO_3. Epoxides **8a**–**c** (Scheme 5) were obtained after purification by column chromatography in 45–67% yields from **7a**–**c**. The spectroscopic and physical data of these compounds were in accordance with the reported literature values.[30]

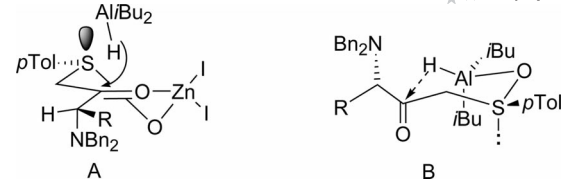
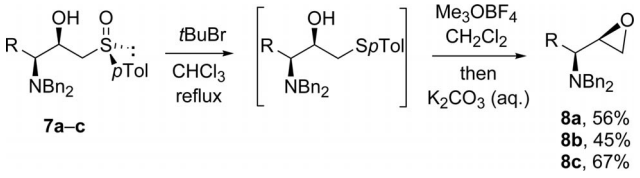


Figure 2. Proposed transition states for hydride transfer in DIBAL-H/ZnI_2 and DIBAL-H reductions.



Scheme 5. Three-step sequence leading to *syn*-(2*R*,1′*S*)-2-(1-dibenzylaminoalkyl)epoxides **8a**–**c** from the corresponding vicinal *syn*-dibenzylamino alcohols.

Conclusions

We have developed a conceptually new and synthetically efficient route to α-(*S*)-dibenzylamino α′-(*R*)-sulfinyl ketones from α-bromo α′-(*R*)-sulfinyl ketones, exploiting a combined in situ substitution–epimerization process. The absolute stereochemistry at the carbon bearing the nitrogen atom of the isomer obtained was of *S* configuration when (+)-(*R*)-(methyl *p*-tolyl sulfoxide) was used as starting material. The X-ray structure of derivative **4a** permitted unequivocal confirmation of the structural assignment. Changing the absolute configuration on the sulfoxide S_S would provide the *R* epimers using the same strategy. These derivatives were shown to be excellent precursors for the synthesis of enantiopure vicinal *syn*-amino alcohols through a highly stereoselective ketone reduction. The sulfinyl group controlled the stereochemical course of both the amination and ketone reduction steps. Finally, three useful *syn*-amino epoxides derived from alanine, leucine, and phenylalanine have been synthesized. Current investigations will expand the scope of these combined in situ substitution–epimerization processes.

Experimental Section

General Information: All reagents and solvents were purchased from commercial sources. THF was dried by distillation from sodium/benzophenone. Diisopropylamine was distilled from KOH.

Reactions were conducted in flame- or oven-dried glassware under an argon atmosphere. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in either $CDCl_3$ or [D_6]-acetone. Chemical shifts are given in ppm and are reported relative to the residual solvent peak ($CHCl_3$: δ = 7.26 and 77.16 ppm or [D_6]acetone: δ = 2.05 and 205.87 ppm). Data are reported as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants, and integration. Analytical TLC was performed on silica gel 60F_{254} plates. Column chromatography was carried out on silica gel 60 (63–200 μm). High-resolution mass spectra (HRMS) were measured using electrospray ionization (ESI) and Q-Tof detection. Melting points were measured with a Büchi apparatus and are uncorrected. Optical rotations values were measured with a Perkin–Elmer apparatus at 20 °C, 589 nm (sodium D-line), and concentrations are given in g/100 mL. HPLC analyses were performed with a Waters 2796 instrument with a variable detector [column: monolith C18; 50 × 4.6 mm; flow: 3 mL/min; eluent: H_2O (TFA 0.1%)/CH_3CN (TFA 0.1%); gradient 0–100% (4 min)].

Methyl 2-Bromo-4-methylpentanoate (2b): To a mixture of 4-methylpentanoic acid (2.5 mL, 20 mmol) and phosphorus tribromide (1.95 mL, 20.7 mmol), was slowly added bromine (2.1 mL, 41 mmol). The system was heated at 80 °C for 1.5 h and then allowed to cool to room temperature. Supplementary bromine (0.5 mL, 9.8 mmol) was then added and the mixture was heated at 80 °C overnight. The solution was cautiously treated with MeOH (8 mL) and heated to reflux for an additional 2 h before adding ice water (50 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Product **2b** was obtained as a yellowish oil (4.49 g, quantitative) and was used without further purification. R_f = 0.75 (cyclohexane/EtOAc, 9:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.28 (t, J = 7.7 Hz, 1 H, C*H*Br), 3.77 (s, 3 H, OCH_3), 1.98–1.86 (m, 2 H, CH_2CHBr), 1.83–1.68 [m, 1 H, C*H*(CH_3)$_2$], 0.95 (d, J = 6.6 Hz, 3 H, CH_3CHCH_3), 0.90 (d, J = 6.5 Hz, 3 H, CH_3CHCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8 (C=O), 53.1 (CH), 44.5 (CH_2), 43.7 (CH_3), 26.6 (CH), 22.6 (CH_3), 21.8 (CH_3) ppm. ESIMS: m/z = 209.1 [M + H]$^+$. HRMS: calcd. for $C_7H_{14}BrO_2^+$ 209.0177; found 209.0180.

Methyl 2-Bromo-3-phenylpropanoate (2c): D,L-Phenylalanine (10 g, 60.5 mmol) and sodium bromide (21.8 g, 211.9 mmol) were dissolved in H_2SO_4 (2.5 M, 80 mL). A solution of sodium nitrite (5.2 g, 75.4 mmol) in H_2O (20 mL) was then added dropwise at 0 °C and the system was stirred at 0 °C for 1 h, and at room temperature for 6 h. The phases were separated and the aqueous layer was extracted with EtOAc (3 × 75 mL). The combined organic layers were washed with brine (2 × 25 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The resulting oil was cooled to 0 °C to precipitate the unreacted phenylalanine, which was filtered off. The crude product (9.75 g, 42.6 mmol) was then cautiously treated with a solution of H_2SO_4 (95%, 1.3 mL, 23 mmol) in MeOH (80 mL). The mixture was heated at reflux for 3 h, allowed to cool to room temperature, and MeOH was then evaporated under reduced pressure. The resulting oil was dissolved in Et_2O (150 mL), washed with an aqueous solution of 5% $KHCO_3$ (3 × 50 mL), and with brine (2 × 50 mL). The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 98:2) to afford **2c** as a pure pale-yellow oil (7.22 g, 49%). R_f = 0.2 (cyclohexane/EtOAc, 95:5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.18 (m, 5 H, ArH), 4.39 (dd, J = 7.1, 8.3 Hz, 1 H, CHBr), 3.71 (s, 3 H, OCH_3), 3.45 (dd, J = 8.4, 14.1 Hz, 1 H, C$H_a$$H_b$Ph), 3.23 (dd, J = 7.1, 14.1 Hz, 1 H, CH_aH_bPh) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1 (C=O), 136.9 ($C_{arom.}$), 129.4 ($CH_{arom.}$), 128.9 ($CH_{arom.}$), 127.6 ($CH_{arom.}$), 53.1 (CH), 45.3 (CH_2), 41.3 (CH_3) ppm. ESIMS: m/z = 243.0 [M + H]$^+$. HRMS: calcd. for $C_{10}H_{12}BrO_2^+$ 243.0021; found 243.0029.

Methyl 2-Bromo-3-cyclohexylpropanoate (2d): To a mixture of 3-cyclohexylpropanoic acid (3.4 mL, 19.8 mmol) and phosphorus tribromide (1.95 mL, 20.7 mmol), was slowly added bromine (2.1 mL, 41 mmol). The system was heated at 80 °C for 1.5 h and then allowed to cool to room temperature. Supplementary bromine (0.5 mL, 9.8 mmol) was then added and heating at 80 °C was continued overnight. MeOH (8 mL) was cautiously added before heating at reflux for an additional 2 h. The reaction mixture was hydrolyzed by adding ice water (50 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. **2b** was obtained as a yellowish oil (5.9 g, quantitative) and was used without further purification. R_f = 0.7 (cyclohexane/EtOAc, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.32 (t, J = 7.7 Hz, 1 H, CHBr), 3.78 (s, 3 H, OCH_3), 1.97–1.89 (m, 2 H, CH_2CHBr), 1.72–1.64 (m, 5 H), 1.52–1.36 (m, 1 H), 1.30–1.12 (m, 3 H), 1.03–0.82 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9 (C=O), 53.1 (CH), 44.1 (CH_2), 42.4 (CH_3), 35.8 (CH), 33.3 (CH_2), 32.4 (CH_2), 26.5 (CH_2), 26.2 (CH_2), 26.1 (CH_2) ppm. ESIMS: m/z = 248.04 [M + H]$^+$. HRMS: calcd. for $C_{10}H_{18}BrO_2^+$ 249.0490; found 249.0488.

3-Bromo-1-[(*R*)-*p*-tolylsulfinyl]butan-2-one (3a): Diisopropylamine (2.9 mL, 20.6 mmol) was dissolved in THF (30 mL) and *n*-butyllithium (1.6 M in hexane, 12.9 mL, 20.6 mmol) was added dropwise at –78 °C. The system was stirred at –78 °C for 1 h before adding a solution of (*R*)-**1** (3.16 g, 20.5 mmol) in THF (20 mL). After stirring for 30 min at –78 °C, **2a** (1.1 mL, 9.85 mmol) in THF (10 mL) was added. The reaction mixture was stirred for an additional 30 min at –78 °C, and then quenched with saturated aqueous NH_4Cl (50 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 3:2) to give a 55:45 diastereomeric mixture of **3a** as a yellowish oil (2.60 g, 91%). R_f = 0.45 and 0.35 (cyclohexane/EtOAc, 1:1). ^{1}H NMR [300 MHz, [D_6]-acetone]: δ = 7.64 (d, J = 8.2 Hz, 1 H, ArH, diast. A), 7.58 (d, J = 8.2 Hz, 1 H, ArH, diast. B), 7.44–7.40 (m, 2 H, ArH, 2 diast), 4.75–7.63 (m, 1 H, CHBr, 2 diast), 4.47 (d, J = 14.2 Hz, 0.55 H, C$H_a$$H_b$SO, diast. A), 4.29–4.18 (m, 0.8 H, CH_aH_bSO, and C$H_a$$H_b$SO, diast. B), 4.05 (d, J = 14.2 Hz, 0.45 H, CH_aH_bSO, diast. A), 2.42 (s, 3 H, CH_3 *p*Tol, 2 diast), 1.67 (d, J = 6.7 Hz, 1.35 H, CH_3CH, diast. B), 1.61 (d, J = 6.7 Hz, 1.65 H, CH_3CH, diast. B) ppm. ^{13}C NMR [75 MHz, [D_6]acetone]: δ = 197.0 (C=O), 196.4 (C=O), 143.3 ($C_{arom.}$), 143.1 ($C_{arom.}$), 142.6 ($C_{arom.}$), 141.8 ($C_{arom.}$), 131.4 ($CH_{arom.}$), 131.3 ($CH_{arom.}$), 125.5 ($CH_{arom.}$), 66.8 (CH_2), 65.3 (CH_2), 50.8 (CH), 49.7 (CH), 21.9 (CH_3), 20.2 (CH_3), 19.9 (CH_3) ppm. ESIMS: m/z = 288.9 [M + H]$^+$, 576.9 [2M + H]$^+$. HRMS: calcd. for $C_{11}H_{14}BrO_2S^+$ 288.9898; found 288.9883.

3-Bromo-5-methyl-1-[(*R*)-*p*-tolylsulfinyl]hexan-2-one (3b): Prepared from **2b** (3.46 g, 16.5 mmol; reaction time: 1.5 h) as described for **3a**. Purification of the crude product by column chromatography on silica gel (cyclohexane/EtOAc, 3:2) provided a 50:50 diastereomeric mixture of **3b** as a yellowish oil (4.02 g, 74%). R_f = 0.70 (cyclohexane/EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (d, J = 8.2 Hz, 1 H, ArH, diast. A), 7.51 (d, J = 8.2 Hz, 1 H, ArH, diast. B), 7.37–7.26 (m, 2 H, ArH, 2 diast), 4.34–4.23 (m, 2

H, CHBr, 2 diast. and CH_aH_bSO, 2 diast), 3.96–3.88 (m, 1 H, CH$_a$$H_b$SO, 2 diast), 2.42 (s, 3 H, CH$_3$ *p*Tol, 2 diast), 1.78–1.57 [m, 3 H, CH_2CHBr, 2 diast. and CH(CH$_3$)$_2$, 2 diast], 0.94–0.83 [m, 6 H, CH(CH_3)$_2$, 2 diast] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.1 (C=O), 194.7 (C=O), 142.7 (C$_{arom.}$), 142.7 (C$_{arom.}$), 140.1 (C$_{arom.}$), 139.3 (C$_{arom.}$), 130.5 (CH$_{arom.}$), 130.4 (CH$_{arom.}$), 124.4 (CH$_{arom.}$), 124.3 (CH$_{arom.}$), 66.3 (CH$_2$), 64.5 (CH$_2$), 53.5 (CH), 53.4 (CH), 40.9 (CH), 40.9 (CH), 26.1 (CH$_3$), 26.0 (CH$_3$), 22.9 (CH$_3$), 21.7 (CH$_3$), 21.5 (CH$_3$), 21.5 (CH$_3$) ppm. ESIMS: *m*/*z* = 331.1 [M + H]$^+$, 661.1 [2M + H]$^+$. HRMS: calcd. for $C_{14}H_{20}BrO_2S^+$ 331.0367; found 331.0376.

3-Bromo-4-phenyl-1-[(*R*)-*p*-tolylsulfinyl]butan-2-one (3c): Prepared from **2c** (3.50 g, 14.4 mmol; reaction time: 1.5 h) as described for **3a**. Purification of the crude product by column chromatography on silica gel (cyclohexane/EtOAc, 3:2) provided a 55:45 diastereomeric mixture of **3c** as a yellowish oil (4.30 g, 82%). R_f = 0.20 (cyclohexane/EtOAc, 95:5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.01 (m, 9 H, ArH, 2 diast), 4.39–4.32 (m, 1 H, CHBr, 2 diast), 4.23 (d, *J* = 13.3 Hz, 0.55 H, CH_aH_bSO, diast. A), 4.06 (d, *J* = 13.6 Hz, 0.45 H, CH_aH_bSO, diast. B), 3.70 (m, 1 H, CH$_a$$H_b$SO, 2 diast), 3.26 (dd, *J* = 6.1, 14.7 Hz, 0.45 H, CH_aH_bPh, diast. B), 3.14 (dd, *J* = 6.4, 14.6 Hz, 0.55 H, CH_aH_bPh, diast. A), 3.00–2.88 (m, 1 H, CH$_a$$H_b$Ph, 2 diast), 2.28, 2.27 (2s, 3 H, CH$_3$ *p*Tol, 2 diast) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.6 (C=O), 194.1 (C=O), 142.7 (C$_{arom.}$), 142.5 (C$_{arom.}$), 139.9 (C$_{arom.}$), 138.9 (C$_{arom.}$), 136.8 (C$_{arom.}$), 136.7 (C$_{arom.}$), 130.5 (CH$_{arom.}$), 130.4 (CH$_{arom.}$), 129.6 (CH$_{arom.}$), 129.5 (CH$_{arom.}$), 128.8 (CH$_{arom.}$), 128.8 (CH$_{arom.}$), 127.3 (CH$_{arom.}$), 127.3 (CH$_{arom.}$), 124.3 (CH$_{arom.}$), 124.2 (CH$_{arom.}$), 66.4 (CH$_2$), 64.1 (CH$_2$), 54.4 (CH), 54.2 (CH), 38.6 (CH$_2$), 21.7 (CH$_3$) ppm. ESIMS: *m*/*z* = 365.0 [M + H]$^+$, 729.1 [2M + H]$^+$. HRMS: calcd. for $C_{17}H_{18}BrO_2S^+$ 365.0211; found 365.0209.

3-Bromo-4-cyclohexyl-1-[(*R*)-*p*-tolylsulfinyl]butan-2-one (3d): Prepared from **2d** (1.029 g, 4.09 mmol of **2d**; reaction time: 45 min) as described for **3a**. Purification of the crude product by flash chromatography on silica gel (cyclohexane/EtOAc, 85:15 to 60:40) provided a 55:45 diastereomeric mixture of **3c** as a yellowish oil (1.157 g, 76%). R_f = 0.57 and 0.53 (cyclohexane/EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58–7.32 (m, 4 H, ArH, 2 diast), 4.35–4.22 (m, 2 H, CHBr, 2 diast. and CH_aH_bSO, 2 diast), 3.93 (d, *J* = 5.1 Hz, 0.55 H, CH$_a$$H_b$SO, diast. A), 3.89 (d, *J* = 5.4 Hz, 0.45 H, CH$_a$$H_b$SO diast. B), 2.41 (s, 3 H, CH$_3$, 2 diast), 1.79–0.68 (m, 13 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.2 (C=O), 194.7 (C=O), 142.7 (C$_{arom.}$), 142.6 (C$_{arom.}$), 140.0 (C$_{arom.}$), 139.2 (C$_{arom.}$), 130.4 (CH$_{arom.}$), 130.4 (CH$_{arom.}$), 124.4 (CH$_{arom.}$), 124.3 (CH$_{arom.}$), 66.1 (CH$_2$), 64.3 (CH$_2$), 52.8 (CH), 52.8 (CH), 39.6 (CH$_2$), 35.3 (CH), 35.1 (CH), 33.5 (CH$_2$), 32.3 (CH$_2$), 32.2 (CH$_2$), 26.5 (CH$_2$), 26.5 (CH$_2$), 26.2 (CH$_2$), 26.2 (CH$_2$), 26.1 (CH$_2$), 26.0 (CH$_2$), 21.7 (CH$_3$) ppm. ESIMS: *m*/*z* = 373.1 [M + H]$^+$, 741.2 [2M + H]$^+$. HRMS: calcd. for $C_{17}H_{24}BrO_2S^+$ 371.0680; found 371.0689.

(*S*)-3-(Dibenzylamino)-1-[(*R*)-*p*-tolylsulfinyl]butan-2-one (4a): Compound **3a** (1.00 g, 5.49 mmol) was dissolved in THF (25 mL) and dibenzylamine (1.7 mL, 13.6 mmol) was added. The reaction mixture was stirred for 5 h at room temperature and treated with saturated aqueous $KHCO_3$ (50 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 75 mL). The combined organic layers were washed with an aqueous solution of 10% $KHSO_4$ (2 × 50 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The residue was washed with Et_2O (3 × 10 mL) to afford **4a** as a white solid (1.185 g, 84%). R_f = 0.60 (cyclohexane/EtOAc, 2:1); $[a]_D$ = +13.61 (*c* = 1, acetone); m.p. 89 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.12 (m, 14 H, ArH), 4.20 (d, *J* = 13.2 Hz, 1 H, CH_aH_bSO), 4.10 (d, *J* = 13.2 Hz, 1 H, CH$_a$$H_b$SO), 3.62 [d, *J* = 13.4 Hz, 2 H, N(CH_aH_bPh)$_2$], 3.33 [d, *J* = 13.4 Hz, 2 H, N(CH$_a$$H_b$Ph)$_2$], 2.83 (q, *J* = 6.6 Hz, 1 H, CHN), 2.36 (s, 3 H, CH$_3$ *p*Tol), 0.99 (d, *J* = 6.6 Hz, 3 H, CH_3CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.1 (C=O), 142.1 (C$_{arom.}$), 140.1 (C$_{arom.}$), 138.7 (C$_{arom.}$), 130.1 (CH$_{arom.}$), 127.2 (CH$_{arom.}$), 128.8 (CH$_{arom.}$), 127.8 (CH$_{arom.}$), 124.5 (CH$_{arom.}$), 66.3 (CH$_2$), 63.6 (CH), 55.0 (CH$_2$), 21.6 (CH$_3$), 6.0 (CH$_3$) ppm. ESIMS: *m*/*z* = 406.3 [M + H]$^+$. HRMS: calcd. for $C_{25}H_{28}NO_2S^+$ 406.1841; found 406.1850.

CCDC-787067 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(*S*)-3-(Dibenzylamino)-5-methyl-1-[(*R*)-*p*-tolylsulfinyl]hexan-2-one (4b): Prepared from **3b** (400 mg, 1.207 mmol; reaction time: 12 d) as described for **4a**. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 4:1) to give **4b** (368 mg, 68%) as a colorless oil. R_f = 0.45 (cyclohexane/EtOAc, 2:1); $[a]_D$ = +3.3 (*c* = 1.205, acetone). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.09 (m, 14 H, ArH), 4.20 (d, *J* = 13.1 Hz, 1 H, CH_aH_bSO), 4.11 (d, *J* = 13.1 Hz, 1 H, CH$_a$$H_b$SO), 3.61 [d, *J* = 13.4 Hz, 2 H, N(CH_aH_bPh)$_2$], 3.33 [d, *J* = 13.4 Hz, 2 H, N(CH$_a$$H_b$Ph)$_2$], 2.71 (dd, *J* = 2.4, 9.8 Hz, 1 H, CHN), 2.34 (s, 3 H, CH$_3$ *p*Tol), 1.66 (ddd, *J* = 3.6, 9.9, 13.4 Hz, 1 H, CH_aH_b-CHN), 1.17 (m, 1 H, CH$_a$$H_b$-CHN), 1.02 [m, 1 H, C$H$(CH$_3$)$_2$], 0.82 (d, *J* = 6.5 Hz, 3 H, CH_3CHCH$_3$), 0.46 (d, *J* = 6.4 Hz, 3 H, CH$_3$CHCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.9 (C=O), 142.4 (C$_{arom.}$), 139.9 (C$_{arom.}$), 138.9 (C$_{arom.}$), 130.1 (CH$_{arom.}$), 129.4 (CH$_{arom.}$), 128.7 (CH$_{arom.}$), 127.7 (CH$_{arom.}$), 124.9 (CH$_{arom.}$), 66.7 (CH$_2$), 66.0 (CH), 54.9 (CH$_2$), 30.3 (CH$_2$), 25.5 (CH), 23.8 (CH$_3$), 21.9 (CH$_3$), 21.6 (CH$_3$) ppm. ESIMS: *m*/*z* = 448.3 [M + H]$^+$. HRMS: calcd. for $C_{28}H_{34}NO_2S^+$ 448.2310; found 448.2301.

(*S*)-3-(Dibenzylamino)-4-phenyl-1-[(*R*)-*p*-tolylsulfinyl]butan-2-one (4c): Prepared from **3c** (502 mg, 1.37 mmol; reaction time: 3 d) as described for **4a**. The crude product contained a mixture of **4c** and **5**, which were separated by column chromatography on silica gel (cyclohexane/EtOAc, 4:1) to give **4c** (360 mg, 55%) as a yellowish oil. R_f = 0.5 (cyclohexane/EtOAc, 3:2); $[a]_D$ = –52.2 (*c* = 0.69, acetone). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24–6.69 (m, 19 H, ArH), 3.91 (s, 2 H, CH$_2$SO), 3.57 [d, *J* = 13.3 Hz, 2 H, N(CH_aH_bPh)$_2$], 3.28 [d, *J* = 13.4 Hz, 2 H, N(CH$_a$$H_b$Ph)$_2$], 2.87–2.63 (m, 3 H, CH$_2$Ph and CHN), 2.13 (s, 3 H, CH$_3$ *p*Tol) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.8 (C=O), 141.8 (C$_{arom.}$), 139.5 (C$_{arom.}$), 139.1 (C$_{arom.}$), 138.5 (C$_{arom.}$), 130.0 (CH$_{arom.}$), 129.7 (CH$_{arom.}$), 129.3 (CH$_{arom.}$), 128.8 (CH$_{arom.}$), 128.5 (CH$_{arom.}$), 127.8 (CH$_{arom.}$), 126.2 (CH$_{arom.}$), 124.2 (CH$_{arom.}$), 70.1 (CH), 66.7 (CH$_2$), 55.0 (CH$_2$), 28.4 (CH$_2$), 21.6 (CH$_3$) ppm. ESIMS: *m*/*z* = 482.1 [M + H]$^+$. HRMS: calcd. for $C_{31}H_{32}NO_2S^+$ 482.2154; found 482.2159.

(*R*,*E*)-4-Phenyl-1-(*p*-tolylsulfinyl)but-3-en-2-one (5): Obtained as by product with **4c** as a white solid (137 mg, 35%). R_f = 0.2 (cyclohexane/EtOAc, 3:2); $[a]_D$ = +275 (*c* = 0.8, $CHCl_3$); m.p. 85–88 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.13 (m, 10 H, ArH, PhCH=C*H*), 6.58 (d, *J* = 16.2 Hz, 1 H, PhC*H*=CH), 4.05 (d, *J* = 13.2 Hz, 1 H, CH_aH_bSO), 3.88 (d, *J* = 13.2 Hz, 1 H, CH$_a$$H_b$SO), 2.25 (s, 3 H, CH$_3$ *p*Tol) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.7 (C=O), 146.0 (C=C), 142.4 (C$_{arom.}$), 140.0 (C$_{arom.}$), 134.1 (C$_{arom.}$), 131.4 (C=C), 130.3 (CH$_{arom.}$), 129.2 (CH$_{arom.}$), 128.9 (CH$_{arom.}$), 126.0 (CH$_{arom.}$), 124.5 (CH$_{arom.}$), 67.3 (CH$_2$), 21.6 (CH$_3$) ppm. ESIMS: *m*/*z* = 285.1 [M + H]$^+$, 569.2 [2M + H]$^+$. HRMS: calcd. for $C_{17}H_{17}O_2S^+$ 285.0949; found 285.0946.

(*S*)-4-Cyclohexyl-3-(dibenzylamino)-1-[(*R*)-*p*-tolylsulfinyl]butan-2-one (4d): Prepared from **3d** (503 mg, 1.35 mmol; reaction time: 10 d) as described for **4a**. The crude product was purified by col-

umn chromatography on silica gel (cyclohexane/EtOAc, 5:1) to give **4d** (490 mg, 74%) as a white solid. R_f = 0.40 (cyclohexane/EtOAc, 2:1); $[\alpha]_D$ = –101.0 (*c* = 1.04, $CHCl_3$); $[\alpha]_D$ = –20.5 (*c* = 1.03, acetone); m.p. 82–86 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.16 (m, 12 H, ArH), 7.02 (d, *J* = 8.3 Hz, 2 H, ArH), 4.16 (d, *J* = 13.2 Hz, 1 H, CH_aH$_b$SO), 4.03 (d, *J* = 13.2 Hz, 1 H, CH$_a$$H_b$SO), 3.52 [d, *J* = 13.3 Hz, 2 H, N(CH_aH$_b$Ph)$_2$], 3.24 [d, *J* = 13.4 Hz, 2 H, N(CH$_a$$H_b$Ph)$_2$], 2.64 (dd, *J* = 2.3, 9.8 Hz, 1 H, CHN), 2.25 (s, 3 H, CH_3 *p*Tol), 1.57–0.50 (m, 13 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.1 (C=O), 142.3 ($C_{arom.}$), 139.9 ($C_{arom.}$), 138.8 ($C_{arom.}$), 130.0 ($CH_{arom.}$), 129.3 ($CH_{arom.}$), 128.6 ($CH_{arom.}$), 127.6 ($CH_{arom.}$), 124.9 ($CH_{arom.}$), 66.5 (CH), 65.3 (CH_2), 54.8 (CH_2), 34.6 (CH), 34.3 (CH_2), 32.6 (CH_2), 28.9 (CH_2), 26.5 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 21.6 (CH_3) ppm. ESIMS: *m*/*z* = 488.3 [M + H]$^+$. HRMS: calcd. for $C_{31}H_{38}NO_2S^+$ 488.2623; found 488.2631.

Methyl 2-(Dibenzylamino)propanoate (6): Compound **2a** (0.16 mL, 1.43 mmol) was dissolved in THF (10 mL) and dibenzylamine (0.7 mL, 3.53 mmol) was added. The reaction mixture was heated under microwave irradiation at 100 °C for 4 h, allowed to cool to room temperature and stirred until no starting material was detected (10 d) by HPLC analysis. A saturated aqueous solution of $KHCO_3$ (50 mL) was added, the phases were separated, and the aqueous layer was extracted with EtOAc (3× 50 mL). The combined organic layers were washed with an aqueous solution of 10% $KHSO_4$ (2× 50 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was used without further purification for the next step (155 mg, 38%). R_f = 0.7 (cyclohexane/EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.12 (m, 10 H, ArH), 3.76 [d, *J* = 14.0 Hz, 2 H, N(CH_aH$_b$Ph)$_2$], 3.66 (s, 3 H, OCH_3), 3.56 [d, *J* = 14.0 Hz, 2 H, N(CH$_a$$H_b$Ph)$_2$], 3.44 (q, *J* = 7.1 Hz, 1 H, CHN), 1.25 (d, *J* = 7.1 Hz, 3 H, CH_3CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.4 (C=O), 140.0 ($C_{arom.}$), 128.8 ($C_{arom.}$), 128.4 ($CH_{arom.}$), 127.1 ($CH_{arom.}$), 56.3 (CH), 54.6 (CH_2), 51.4 (CH_3), 15.3 (CH_3) ppm.

3-(Dibenzylamino)-1-[(*R*)-*p*-tolylsulfinyl]butan-2-one (4a *rac*): Diisopropylamine (0.16 mL, 1.148 mmol) was dissolved in THF (3 mL) and cooled to –78 °C before adding, dropwise, *n*-butyllithium (1.6 M in hexane, 0.7 mL, 1.12 mmol). The system was stirred at –78 °C for 45 min and then (*R*)-**1** (172 mg, 1.115 mmol), dissolved in THF (3 mL), was added. After 75 min at –78 °C, a solution of **6** (150 mg, 0.529 mmol) in THF (4 mL) was added. The reaction mixture was stirred for 1 h at –78 °C and quenched with saturated aqueous NH_4Cl (10 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (3× 10 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 3:2) to give a 55:45 diastereomeric mixture of **4a** as a colorless oil (188 mg, 88%). R_f = 0.40 and 0.45 (cyclohexane/EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.03 (m, 28 H, ArH), 4.14–3.74 (m, 4 H, CH_2SO, 2 diast), 3.55–3.18 [m, 9 H, N(CH_2Ph)$_2$, 2 diast. and CHN, diast. A], 2.74 (q, *J* = 6.6 Hz, 1 H, CHN, diast. B), 2.28 (s, 3 H, CH_3 *p*Tol, diast. B), 2.26 (s, 3 H, CH_3 *p*Tol, diast. A), 1.03 (d, *J* = 6.6 Hz, 3 H, CH_3CH, diast. B), 0.91 (d, *J* = 6.6 Hz, 3 H, CH_3CH, diast. A) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.5 (C=O), 203.0 (C=O), 142.1 ($C_{arom.}$), 142.0 ($C_{arom.}$), 140.5 ($C_{arom.}$), 140.0 ($C_{arom.}$), 138.6 ($C_{arom.}$), 130.1 ($CH_{arom.}$), 130.0 ($CH_{arom.}$), 129.1 ($CH_{arom.}$), 128.9 ($CH_{arom.}$), 128.7 ($CH_{arom.}$), 127.7 ($CH_{arom.}$), 127.6 ($CH_{arom.}$), 124.4 ($CH_{arom.}$), 124.4 ($CH_{arom.}$), 66.2 (CH_2), 63.8 (CH), 63.5 (CH), 54.9 (CH_2), 54.8 (CH_2), 21.6 (CH_3), 6.2 (CH_3), 6.0 (CH_3) ppm.

(2*R*,3*S*)-3-(Dibenzylamino)-1-[(*R*)-*p*-tolylsulfinyl]butan-2-ol (7a-*syn*): A solution of **4a** (102 mg, 0.25 mmol) in THF (5 mL) was added to dry ZnI_2 (123 mg, 0.385 mmol) and the system was stirred at room temperature for 30 min. DIBAL-H (1.5 M in toluene, 0.4 mL, 0.60 mmol) was added dropwise at –78 °C and the reaction mixture was stirred for 1 h. The solution was treated with MeOH (10 mL) and was allowed to reach the room temperature. The solvents were evaporated under reduced pressure and the resulting solid crude material was treated with EtOAc (25 mL) and saturated aqueous potassium sodium tartrate (25 mL). The system was then stirred overnight. The phases were separated and the aqueous layer was extracted with EtOAc (3× 25 mL). The combined organic layers were washed with brine (2× 25 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 3:2) to afford *syn*-**7a** as a colorless oil (87 mg, 86%). R_f = 0.5 (cyclohexane/EtOAc, 1:1); $[\alpha]_D$ = –9.3 (*c* = 0.53, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8.2 Hz, 2 H, ArH), 7.27–7.14 (m, 12 H, ArH), 4.37 (br. s, 1 H, OH), 3.66 [d, *J* = 13.3 Hz, 2 H, N(CH_aH$_b$Ph)$_2$], 3.44 (td, *J* = 3.0, 8.6 Hz, 1 H, C*H*OH), 3.23 [d, *J* = 13.3 Hz, 2 H, N(CH$_a$$H_b$Ph)$_2$], 2.93 (dd, *J* = 8.0, 12.9 Hz, 1 H, CH_aH$_b$SO), 2.81–2.68 (m, 2 H, CH$_a$$H_b$SO and CHN), 2.32 (s, 3 H, CH_3 *p*Tol), 0.93 (d, *J* = 6.7 Hz, 3 H, CH_3CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.6 ($C_{arom.}$), 140.8 ($C_{arom.}$), 138.6 ($C_{arom.}$), 129.9 ($CH_{arom.}$), 129.0 ($CH_{arom.}$), 128.6 ($CH_{arom.}$), 127.4 ($CH_{arom.}$), 124.5 ($CH_{arom.}$), 67.7 (CH), 62.4 (CH_2), 57.9 (CH), 53.6 (CH_2), 21.5 (CH_3), 8.3 (CH_3) ppm. ESIMS: *m*/*z* = 408.2 [M + H]$^+$, 815.5 [2M + H]$^+$. HRMS: calcd. for $C_{25}H_{30}NO_2S^+$ 408.1997; found 408.1991.

(2*R*,3*S*)-3-(Dibenzylamino)-5-methyl-1-[(*R*)-*p*-tolylsulfinyl]hexan-2-ol (*syn*-7b): Obtained from **4b** (156 mg, 0.349 mmol; reaction time: 1 h) as described for *syn*-**7a**. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 4:1) to give pure *syn*-**7b** as a white solid (120 mg, 77%). R_f = 0.25 (cyclohexane/EtOAc, 2:1); $[\alpha]_D$ = +25 (*c* = 1, acetone); m.p. 118–121 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.2 Hz, 2 H, ArH), 7.24–7.12 (m, 12 H, ArH), 4.25 (br. s, 1 H, OH), 3.77 [d, *J* = 13.3 Hz, 2 H, N(CH_aH$_b$Ph)$_2$], 3.67–3.63 (m, *J* = 7.0 Hz, 1 H, C*H*OH), 3.31 [d, *J* = 13.4 Hz, 2 H, N(CH$_a$$H_b$Ph)$_2$], 3.06 (dd, *J* = 9.2, 12.7 Hz, 1 H, CH_aH$_b$SO), 2.54 (m, 2 H, CH$_a$$H_b$SO and CHN), 2.33 (s, 3 H, CH_3 *p*Tol), 1.67–1.54 [m, 1 H, C*H*(CH_3)$_2$], 1.45–1.36 (m, 1 H, CH_aH$_b$CHN), 1.26–1.18 (m, 1 H, CH$_a$$H_b$CHN), 0.84–0.80 [m, 6 H, CH(CH_3)$_2$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.8 ($C_{arom.}$), 140.8 ($C_{arom.}$), 139.7 ($C_{arom.}$), 130.1 ($CH_{arom.}$), 129.2 ($CH_{arom.}$), 128.5 ($CH_{arom.}$), 127.3 ($CH_{arom.}$), 124.5 ($CH_{arom.}$), 68.6 (CH), 62.4 (CH_2), 60.1 (CH), 54.8 (CH_2), 34.6 (CH_2), 25.9 (CH), 23.5 (CH_3), 22.8 (CH_3), 21.6 (CH_3) ppm. ESIMS: *m*/*z* = 450.3 [M + H]$^+$. HRMS: calcd. for $C_{28}H_{36}NO_2S^+$ 450.2453; found 450.2464.

(2*R*,3*S*)-3-(Dibenzylamino)-4-phenyl-1-[(*R*)-*p*-tolylsulfinyl]butan-2-ol (*syn*-7c): Obtained from **4c** (303 mg, 0.63 mmol; reaction time: 2 h) as described for *syn*-**7a**. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 4:1) to give pure *syn*-**7c** as a colorless oil (267 mg, 88%). R_f = 0.45 (cyclohexane/EtOAc, 3:2); $[\alpha]_D$ = +37.1 (*c* = 0.97, acetone). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.07 (m, 19 H, ArH), 4.25 (br. s, 1 H, OH), 3.88 [d, *J* = 13.3 Hz, 2 H, N(CH_aH$_b$Ph)$_2$], 3.78–3.74 (m, 1 H, C*H*OH), 3.25 [d, *J* = 13.3 Hz, 2 H, N(CH$_a$$H_b$Ph)$_2$], 2.99–2.85 (m, 2 H, C$H_aH_b$SO and C$H_aH_b$Ph), 2.78–2.66 (m, 2 H, CH$_a$$H_b$SO and CHN), 2.28 (s, 3 H, CH_3 *p*Tol), 2.19 (dd, *J* = 1.6, 13.2 Hz, 1 H, CH_aH$_b$Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.8 ($C_{arom.}$), 141.1 ($C_{arom.}$), 139.8 ($C_{arom.}$), 139.6 ($C_{arom.}$), 130.2 ($CH_{arom.}$), 129.6 ($CH_{arom.}$), 129.2 ($CH_{arom.}$), 128.9 ($CH_{arom.}$), 128.6 ($CH_{arom.}$), 127.4 ($CH_{arom.}$), 126.5 ($CH_{arom.}$), 124.3 ($CH_{arom.}$), 68.4 (CH), 63.8 (CH_2), 62.3 (CH), 55.0 (CH_2), 30.9 (CH_2), 21.7 (CH_3) ppm. ESIMS: *m*/*z* =

484.3 $[M + H]^+$, 967.5 $[2M + H]^+$. HRMS: calcd. for $C_{31}H_{34}NO_2S^+$ 484.2310; found 484.2316.

(2*R*,3*S*)-4-Cyclohexyl-3-(dibenzylamino)-1-[(*R*)-*p*-tolylsulfinyl]butan-2-ol (*syn*-7d): Obtained from **4d** (400 mg, 0.82 mmol; reaction time: 1 h) as described for *syn*-**7a**. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 3:1) to give pure *syn*-**7d** as a white solid (345 mg, 86%). R_f = 0.30 (cyclohexane/EtOAc, 2:1); $[\alpha]_D$ = +13.40 (c = 0.97, $CHCl_3$); m.p. 97–99 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53 (d, J = 8.2 Hz, 2 H, ArH), 7.34–7.20 (m, 12 H, ArH), 4.30 (br. s, 1 H, OH), 3.84 [d, J = 13.3 Hz, 2 H, N(CH_aH$_b$Ph)$_2$], 3.71 (ddd, J = 2.1, 7.2, 9.2 Hz, 1 H, CHOH), 3.40 [d, J = 13.4 Hz, 2 H, N(CH$_a$$H_b$Ph)$_2$], 3.14 (dd, J = 9.3, 12.8 Hz, 1 H, CH_aH$_b$SO), 2.69–2.58 (m, 2 H, CH$_a$$H_b$SO and CHN), 2.43 (s, 3 H, CH$_3$ *p*Tol), 1.71–1.65 (m, 5 H), 1.55–1.47 (m, 1 H), 1.33–1.14 (m, 5 H), 0.94–0.81 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.9 ($C_{arom.}$), 140.9 ($C_{arom.}$), 139.8 ($C_{arom.}$), 130.2 ($CH_{arom.}$), 129.3 ($CH_{arom.}$), 128.6 ($CH_{arom.}$), 127.4 ($CH_{arom.}$), 124.5 ($CH_{arom.}$), 68.8 (CH), 62.5 (CH_2), 59.4 (CH), 54.8 (CH_2), 35.5 (CH), 34.3 (CH_2), 33.7 (CH_2), 33.2 (CH_2), 26.7 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 21.7 (CH_3) ppm. ESIMS: m/z = 490.4 $[M + H]^+$. HRMS: calcd. for $C_{31}H_{40}NO_2S^+$ 490.2780; found 490.2785.

(2*S*,3*S*)-4-Cyclohexyl-3-(dibenzylamino)-1-[(*R*)-*p*-tolylsulfinyl]butan-2-ol (*anti*-7d): To a solution of **4d** (160 mg, 0.328 mmol) in THF (10 mL) was added DIBAL-H (1.5 M in toluene, 0.55 mL, 0.825 mmol), dropwise, at –78 °C. The system was stirred at –78 °C for 75 min and treated with MeOH (15 mL). The reaction mixture was allowed to reach room temperature and the solvents were evaporated under reduced pressure. The resulting crude solid was treated with EtOAc (25 mL) and a saturated aqueous solution of potassium sodium tartrate (25 mL). The mixture was then stirred overnight. The phases were separated and the aqueous layer was extracted with EtOAc (3× 25 mL). The combined organic layers were washed with brine (2× 25 mL), dried with $MgSO_4$, and concentrated. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 3:1) to afford *anti*-**7d** as a colorless oil (140 mg, 87%). R_f = 0.30 (cyclohexane/EtOAc, 2:1); $[\alpha]_D$ = +51.61 (c = 0.62, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52 (d, J = 8.2 Hz, 2 H, ArH), 7.35 (d, J = 8.1 Hz, 2 H, ArH), 7.28–7.10 (m, 10 H, ArH), 4.50–4.46 (m, 1 H, CHOH), 4.12 (br. s, 1 H, OH), 3.61 [d, J = 13.7 Hz, 2 H, N(CH_aH$_b$Ph)$_2$], 3.43 [d, J = 13.7 Hz, 2 H, N(CH$_a$$H_b$Ph)$_2$], 2.96 (dd, J = 10.2, 13.4 Hz, 1 H, CH_aH$_b$SO), 2.67 (d, J = 13.4 Hz, 1 H, CH$_a$$H_b$SO), 2.57–2.51 (m, 1 H, CHN), 2.42 (s, 3 H, CH$_3$ *p*Tol), 1.62 (m, 6 H), 1.41 (d, J = 15.7 Hz, 1 H), 1.20 (m, 4 H), 0.94–0.82 (m, 1 H), 0.73–0.62 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.7 ($C_{arom.}$), 140.1 ($C_{arom.}$), 139.6 ($C_{arom.}$), 130.2 ($CH_{arom.}$), 129.0 ($CH_{arom.}$), 128.3 ($CH_{arom.}$), 127.1 ($CH_{arom.}$), 124.3 ($CH_{arom.}$), 66.5 (CH), 59.3 (CH_2), 58.0 (CH), 54.5 (CH_2), 34.7 (CH), 34.2 (CH_2), 34.0 (CH_2), 33.6 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 26.4 (CH_2), 21.6 (CH_3) ppm. ESIMS: m/z = 490.4 $[M + H]^+$. HRMS: calcd. for $C_{31}H_{40}NO_2S^+$ 490.2780; found 490.2778.

(2*R*,1′*S*)-2-[1-(Dibenzylamino)ethyl]oxirane (8a): A mixture of *syn*-**7a** (498 mg, 1.22 mmol) and *tert*-butyl bromide (1.2 mL, 10.34 mmol) was heated to reflux in $CHCl_3$ (15 mL) overnight. The system was then allowed to cool to room temperature and the solvents were evaporated under reduced pressure. The crude material was dissolved in CH_2Cl_2 (10 mL) before adding trimethyloxonium tetrafluoroborate (471 mg, 3.18 mmol), and the resulting solution was stirred at room temperature for 5 h. The reaction mixture was treated with saturated aqueous K_2CO_3 (10 mL) and stirred overnight. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3× 50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure by heating simultaneously at 70 °C to remove the methyl-*p*-tolyl sulfide. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 10:1) to afford **8a** as a colorless oil (183 mg, 56%). R_f = 0.45 (cyclohexane/EtOAc, 10:1); $[\alpha]_D$ = +5.7 (c = 0.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.17 (m, 10 H, ArH), 3.80 [d, J = 13.8 Hz, 2 H, N(CH_aH$_b$Ph)$_2$], 3.67 [d, J = 13.8 Hz, 2 H, N(CH$_a$$H_b$Ph)$_2$], 3.08 (ddd, J = 2.8, 4.0, 6.0 Hz, 1 H, CHO), 2.83–2.74 (m, 1 H, CHN), 2.66 (dd, J = 4.2, 4.9 Hz, 1 H, CH_aH$_b$O), 2.49 (dd, J = 2.7, 5.0 Hz, 1 H, CH$_a$$H_b$O), 1.04 (d, J = 6.9 Hz, 3 H, CH_3CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.5 ($C_{arom.}$), 128.8 ($CH_{arom.}$), 128.4 ($CH_{arom.}$), 127.0 (CH_{arom}), 54.8 (CH), 54.6 (CH_2), 54.0 (CH), 44.1 (CH_2), 11.4 (CH_3) ppm. ESIMS: m/z = 268.1 $[M + H]^+$. HRMS: calcd. for $C_{18}H_{22}NO^+$ 268.1701; found 268.1705.

(2*R*,1′*S*)-2-[1-(Dibenzylamino)-3-methylbutyl]oxirane (8b): Obtained from *syn*-**7b** (424 mg, 0.94 mmol) as described for **8a**. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 6:1) to afford **8b** as a colorless oil (131 mg, 45%). R_f = 0.65 (cyclohexane/EtOAc, 4:1); $[\alpha]_D$ = –18.6 (c = 0.59, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.10 (m, 10 H, ArH), 3.77 [d, J = 13.4 Hz, 2 H, N(CH_aH$_b$Ph)$_2$], 3.67 [d, J = 13.4 Hz, 2 H, N(CH$_a$$H_b$Ph)$_2$], 3.02 (ddd, J = 2.8, 4.0, 7.1 Hz, 1 H, CHO), 2.63–2.59 (m, 1 H, CH_aH$_b$O), 2.39–2.28 (m, 2 H, CHN and CH$_a$$H_b$O), 1.79–1.66 [m, 1 H, C$H$(CH$_3$)$_2$], 1.47 (ddd, J = 5.2, 9.1, 14.1 Hz, 1 H, CH_aH$_b$CHN), 0.98 (ddd, J = 5.3, 8.6, 13.9 Hz, 1 H, CH$_a$$H_b$CHN), 0.73 (d, J = 6.7 Hz, 3 H, CH_3CHCH$_3$), 0.46 (d, J = 6.5 Hz, 3 H, CH$_3$CHCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.5 ($C_{arom.}$), 129.2 ($CH_{arom.}$), 128.3 ($CH_{arom.}$), 126.9 ($CH_{arom.}$), 57.2 (CH), 54.5 (CH_2), 52.7 (CH), 44.1 (CH_2), 38.3 (CH_2), 24.5 (CH), 23.6 (CH_3), 22.0 (CH_3) ppm. ESIMS: m/z = 310.3 $[M + H]^+$. HRMS: calcd. for $C_{21}H_{28}NO^+$ 310.2171; found 310.2131.

(2*R*,1′*S*)-2-[1-(Dibenzylamino)-2-phenylethyl]oxirane (8c): Obtained from *syn*-**7c** (460 mg, 0.95 mmol) as described for **8a**. The crude product was purified by flash chromatography on silica gel (cyclohexane/AcOEt, 100:0 to 95:5) to afford **8c** as a colorless oil (220 mg, 67%). R_f = 0.35 (cyclohexane/Et$_2$O, 10:1); $[\alpha]_D$ = –4.9 (c = 0.61, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21–7.10 (m, 13 H, ArH), 6.96–6.93 (m, 2 H, ArH), 3.83–3.72 [m, 4 H, N(CH_2Ph)$_2$], 3.07 (ddd, J = 2.7, 4.2, 6.8 Hz, 1 H, CHO), 2.95–2.86 (m, 1 H, CH_aH$_b$Ph), 2.72–2.61 (m, 2 H, CH$_a$$H_b$Ph and CHN), 2.51 (dd, J = 4.2, 5.0 Hz, 1 H, CH_aH$_b$O), 2.12 (dd, J = 2.7, 5.1 Hz, 1 H, CH$_a$$H_b$O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.9 ($C_{arom.}$), 138.2 ($C_{arom.}$), 128.3 ($CH_{arom.}$), 127.6 ($CH_{arom.}$), 127.2 ($CH_{arom.}$), 127.1 ($CH_{arom.}$), 125.7 ($CH_{arom.}$), 125.0 ($CH_{arom.}$), 60.3 (CH), 53.3 (CH_2), 51.1 (CH), 43.4 (CH_2), 34.1 (CH_2) ppm. ESIMS: m/z = 344.2 $[M + H]^+$. HRMS: calcd. for $C_{24}H_{26}NO^+$ 344.2014; found 344.2011.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra for all compounds, chiral HPLC analysis for compounds **3a** and **4a**, crystallographic data and ORTEP for compound **4a**.

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[1] For a recent review on the synthesis and synthetic application of α-amino ketones derived from natural α-amino acids, see:

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[2] For reviews on asymmetric α-amination reactions, see: a) J.-P. Genet, C. Creck, D. Lavergne, in: *Modern Amination Methods* (Ed.: A. Ricci), Wiley-VCH, Weinheim, Germany, **2000**, chapter 3; b) C. Greck, B. Drouillat, C. Thomassing, *Eur. J. Org. Chem.* **2004**, 1377–1385; c) E. Erdik, *Tetrahedron* **2004**, *60*, 8747–8782.

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