

# Synthesis of Enantiopure $\alpha'$ -Amino $\alpha,\beta$ -Epoxy Ketones from $\alpha'$ -Amino Bromomethyl Ketones

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Preparation of enantiomerically pure  $\alpha'$ -amino  $\alpha,\beta$ -epoxy ketones **2** in an efficient synthesis starting from  $\alpha'$ -amino bromomethyl ketones **5** and the obtention of amino diepoxido **10a** as synthetic application of **2** are described. We also report the generalization of the synthesis of 1-aminoalkyl halomethyl ketones to their bromo derivatives.

## Introduction

While optically active  $\alpha$ -amino aldehydes have been widely used as chiral building blocks in organic synthesis,<sup>1</sup> the chemistry of amino ketones has not been extensively developed. A possible reason for this can be that these ketones are usually synthesized through multistep transformations of  $\alpha$ -amino acids or with moderate yields. By contrast,  $\alpha$ -amino aldehydes are readily available.<sup>1</sup> So, *N*-acyl amino acids have been converted into the corresponding ketones by reaction with organolithium reagents with moderate yields;<sup>2</sup> with other *N*-protected amino acids it is necessary to prepare carboxyl-activated derivatives in a multistep process to afford the corresponding ketones.<sup>3</sup> To synthesize  $\alpha'$ -amino  $\alpha$ -halo ketones, a more specialized method is required. Thus, the procedure most commonly used for the synthesis of  $\alpha'$ -amino  $\alpha$ -halo ketones is the treatment of the  $\alpha$ -amino acid derived mixed anhydride with diazomethane and further acidolysis with HX.<sup>4</sup> Chlorinated ketones are interesting because they serve as irreversible enzyme inhibitors<sup>5</sup> and as precursors to the hydroxyethylamine isosteres subunits present in many inhibitors of renin and HIV-protease.<sup>4g–i</sup>

Recently, we have reported an alternative method to obtain, without racemization, chiral  $\alpha'$ -amino  $\alpha$ -chloro ketones<sup>6</sup> by the direct reaction of easily available  $\alpha$ -amino esters with in situ generated chloromethyl lithium. This synthetic procedure leads to chloro ketones without the use of diazomethane. We have also described some synthetic applications of  $\alpha'$ -amino chloromethyl ketones. Thus, their reduction gives threo aminoalkyl epoxides<sup>6b</sup>

and treatment with organometallic compounds affords 3-azetidins.<sup>7</sup> Both reactions proceed with high diastereoselectivity. These results prompted us to investigate the unreported behavior of amino chloro ketones as enolates in aldol condensation reactions, which would afford chiral  $\alpha,\beta$ -epoxy ketones.

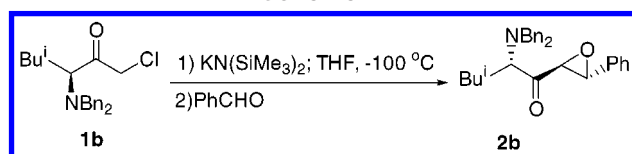
In addition,  $\alpha,\beta$ -epoxy ketones are known as versatile synthetic intermediates because of their multiple functionality. Stereoselective synthesis of  $\alpha'$ -amino  $\alpha,\beta$ -epoxy ketones would furnish a new entry into various amino polyoxygenated compounds. Moreover, tripeptide  $\alpha,\beta$ -epoxy ketones were found to be protease inhibitors and the previously reported method for their synthesis needs a multistep manipulation starting from the vinyl ketones.<sup>8</sup>

In this paper we report the preparation of enantiomerically pure  $\alpha'$ -amino  $\alpha,\beta$ -epoxy ketones **2** in an efficient synthesis starting from  $\alpha'$ -amino bromomethyl ketones **5** and the further transformation of compound

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Scheme 1



Scheme 2

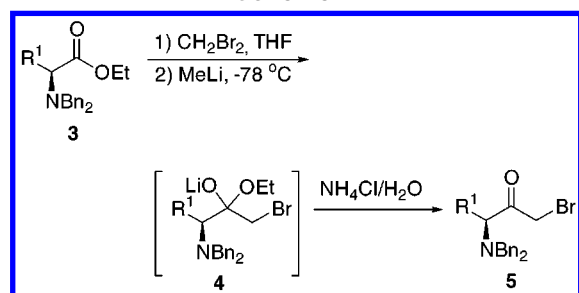


Table 1. Synthesis of Bromomethyl Ketones 5

product	R	yield (%) <sup>a</sup>
<b>5a</b>	Me	86
<b>5b</b>	<i>i</i> -Bu	83
<b>5c</b>	Bn	85

<sup>a</sup> Isolated yield based on the starting  $\alpha$ -amino ester **3**.

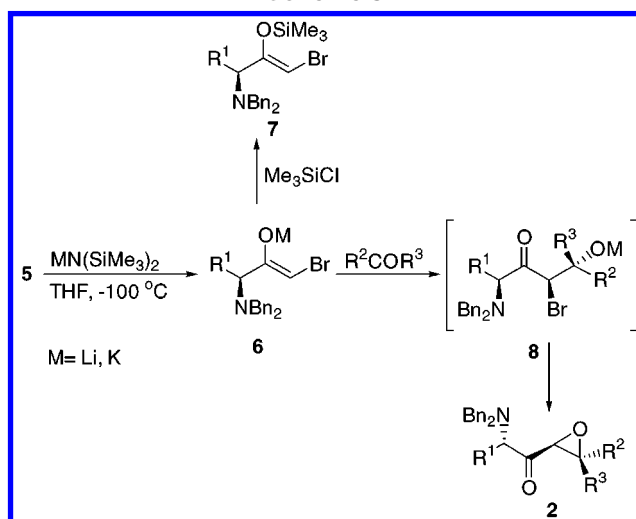
**2** into an amino diepoxide **10a** as a synthetic application. Our approach to the synthesis of enantiopure  $\alpha'$ -amino  $\alpha,\beta$ -epoxy ketones is based on the Darzens reaction which is one of the more reliable methods for the construction of  $\alpha,\beta$ -epoxy ketones.<sup>9</sup> We also describe the generalization of the synthesis of  $\alpha'$ -amino halomethyl ketones to their bromo derivatives.

## Results and Discussion

Our initial idea was to examine the suitability of  $\alpha'$ -amino chloromethyl ketones as substrates in a Darzens-type reaction with aldehydes and ketones. At first, we attempted the condensation of the  $\alpha$ -chloro ketone derived from leucine **1b** and benzaldehyde. Successive treatment of ketone **1b** with potassium hexamethyldisilazide (KHMDS) and benzaldehyde in THF at low temperature ( $-100\text{ }^{\circ}\text{C}$ ) led to the corresponding  $\alpha,\beta$ -epoxy ketone **2b** in 75% yield with moderate diastereoisomeric excess (*de* = 50%) (Scheme 1).

As bromo enolates show enhanced selectivity relative to the corresponding chloro derivatives,<sup>10</sup> we thought that the diastereoselectivity could be improved by starting from amino bromo ketones **5**. For this reason, the preparation of previously unreported chiral  $\alpha'$ -amino bromomethyl ketones **5** was carried out. Hence, treatment of ethyl *N,N*-dibenzylated  $\alpha$ -amino carboxylates **3** with in situ generated bromomethyl lithium at  $-78\text{ }^{\circ}\text{C}$  gave, after hydrolysis, the corresponding bromomethyl ketones **5** in high yields (see Scheme 2 and Table 1). Bromomethyl lithium was generated by reaction of dibromomethane with methyllithium. The isolation of the pure ketones **5** required only removal of the solvents (purity > 95%, 300 MHz  $^1\text{H}$  NMR spectroscopy). The synthesis of the bromomethyl ketones **5** proceeds via

Scheme 3

Table 2. Synthesis of  $\alpha'$ -Amino  $\alpha,\beta$ -Epoxy Ketones 2

product	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	yield (%) <sup>a</sup>	<i>de</i> <sup>b</sup>
<b>2a<sup>c</sup></b>	Me	Ph	H	85	90
<b>2b</b>	<i>i</i> -Bu	Ph	H	80	90
<b>2c</b>	Bn	Ph	H	87	>95 <sup>d</sup>
<b>2d<sup>c</sup></b>	Bn	—(CH <sub>2</sub> ) <sub>4</sub> —	H	70	>95
<b>2e</b>	Me	—(CH <sub>2</sub> ) <sub>5</sub> —	H	68	>95

<sup>a</sup> Isolated yield based on the starting ketone **5**. <sup>b</sup> Diastereoisomeric excess determined by 300 MHz  $^1\text{H}$  NMR analysis of the crude products **2**. <sup>c</sup> Lithium enolate was used. <sup>d</sup> *ee* > 99% HPLC (Chiracel OD-H; UV detector; 0.8 mL/min; 215 nm; 200:1 hexane/2-propanol; *t<sub>R</sub>* = 13.8 min).

intermediate **4**, which is stable under the reaction conditions due to the presence of the electronegative bromine and nitrogen substituents.<sup>11</sup>

Bromo enolates **6** were generated at  $-100\text{ }^{\circ}\text{C}$  in dry THF using KHMDS; enolate **6a** was isolated as the trimethylsilyl enol ether derivative **7a** by treatment with chlorotrimethylsilane. The *Z* relative configuration of **7a** was established by NOE experiments; irradiation of the vinylic proton produced a 11.5% positive NOE in the C—N methine hydrogen, and no positive NOE was observed in the methyl groups of TMS, confirming the *cis* relationship of the bromine and trimethylsilyloxy substituents<sup>12</sup> (see Scheme 3).

The reaction of potassium enolates **6** with aromatic aldehydes or cyclic ketones at  $-100\text{ }^{\circ}\text{C}$  gave, after hydrolysis, the corresponding  $\alpha,\beta$ -epoxy ketones **2** in high yields and with high diastereoselectivity (see Scheme 3 and Table 2). Using lithium enolates (from lithium hexamethyldisilazide), the corresponding  $\alpha,\beta$ -epoxy ketones **2** were isolated in similar yields after warming the reaction to  $-78\text{ }^{\circ}\text{C}$  (to see footnote in Table 2). The structures of the epoxy ketones obtained in the reactions of either potassium or lithium enolates were found to be the same. Generation of lithium enolates using LDA gave reduced yields and lower diastereoselectivities of **2**, while sodium enolates (from sodium hexamethyldisilazide) resulted in poor yields and lower diastereoselectivities of **2**.

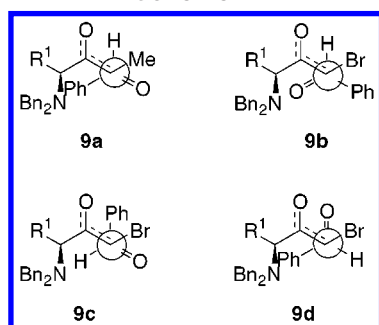
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Scheme 4



The reaction was carried out using aromatic aldehydes and cyclic ketones. With ketones, higher reaction temperatures and longer reaction times were needed to afford the Darzens condensation products, because ketones are less reactive and more sterically hindered.

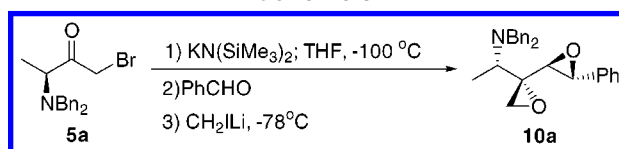
The diastereoisomeric excesses of  $\alpha,\beta$ -epoxy ketones **2** (>95%) were determined by 300 MHz  $^1\text{H}$  NMR analysis of reaction crudes showing the presence of one diastereoisomer exclusively. The degree of stereoselectivity was not affected by the size of the substituents in the bromo enolate or in the carbonyl compound employed in this study (see Table 2).

The racemization of *N*-protected carbonyl compounds derived from phenylalanine has been carefully documented.<sup>13</sup> Under the described reaction conditions, condensation of ketone **5c** derived from phenylalanine with benzaldehyde took place with no detectable racemization. The enantiomeric purity of product **2c** was determined by chiral HPLC (Chiracel OD-H) analysis, showing an enantiomeric excess (ee) >98%. A racemic mixture of **2c** was prepared, from the corresponding racemic  $\alpha$ -amino acid, to exclude the possibility of coelution of both enantiomers by HPLC.

The relative trans configuration in the oxirane ring (Scheme 3) of  $\alpha,\beta$ -epoxy ketones **2** was assigned on the basis of the value of  $^1\text{H}$  NMR coupling constants between the oxirane protons ( $J_{\text{trans}} = 1.7$  Hz; average literature values<sup>14</sup> for  $J_{\text{trans}} < 3.1$  Hz). The absolute configuration of **2c** (see Scheme 3) was established by single-crystal X-ray analysis. As depicted in Scheme 3, the absolute configuration of the newly created asymmetric centers was 1*R*,2*S*,4*S*. The configuration of the other the epoxy ketones **2** was assigned by analogy.

This stereochemistry is different from that previously reported for Liotta et al. for the aldol reactions of the sodium or lithium enolates of  $\alpha$ -(*N,N*-dibenzylamino)alkyl ethyl ketones with aldehydes, in which *E*-enolates provide adducts with syn stereochemistry of the newly generated stereocenters.<sup>15</sup> On the basis of the sodium tendency to form ionic associations with oxygen, rather than two point chelates, Liotta et al. have proposed an open transition state to explain the stereochemistry observed, in which the two oxygen atoms are oriented in opposite directions for electrostatic reasons (**9a** in Scheme 4). The only difference between enolate **6** and

Scheme 5



the enolate obtained by Liotta is the presence of a bromine atom instead of a methyl group. Taking into consideration that lithium and potassium bromo enolates **6** give the same diastereoselection and according to the results reported by Liotta, we propose open transition state **9b** (Scheme 4) to explain the stereochemistry of the epoxy ketones **2**. In this model, the aldehyde approaches from the less hindered face of the enolate, explaining the absolute configuration of a carbon atom bonded to bromine. The presence of bromine in the enolate would explain the different absolute configuration of the C–OH in our adduct compared with the C–OH of Liotta. Thus, the enolate approaches from the *si* face of the aldehyde involving an open transition state model in which the oxygen of the aldehyde and the bromine of the enolate are oriented to minimize the dipole moment.<sup>16</sup> The two remaining possibilities, **9c** or **9d**, are rejected for steric reasons (**9c**) or for electrostatic reasons (**9d**). The transition state **9b** affords the anti alcoholate **8**, which after epoxidation yields the observed (1*R*,2*S*,4*S*)  $\alpha,\beta$ -epoxy ketones **2**.

To extend the synthetic utility of  $\alpha,\beta$ -epoxy ketones **2**, **2a** was treated with iodomethyl lithium to obtain compound **10a** in high yield (75%) and with high diastereoselectivity (de = 95%). The reaction was carried out without isolating the  $\alpha,\beta$ -epoxy ketone **2a**. It is interesting to note that three new stereogenic centers have been created with high diastereoisomeric excess in a one-pot reaction starting from the  $\alpha$ -bromo ketone **5a**. Iodomethyl lithium was generated by reaction of diiodomethane and methyl lithium. The absolute configuration of **10a** (see Scheme 5) was established by single-crystal X-ray analysis. As depicted in Scheme 5, the absolute configuration of the newly created asymmetric centers was 2*S*,3*S*,4*S*,5*R*.

In conclusion, we have demonstrated the synthetic utility of the reaction of chiral  $\alpha'$ -amino bromomethyl ketones with carbonyl compounds affording enantiomerically pure  $\alpha'$ -amino  $\alpha,\beta$ -epoxy ketones with high yield and diastereoselectivity. This method is simple, the starting ketones **5** are readily available, and two new stereogenic centers are created.  $\alpha,\beta$ -Epoxy ketone **2a** was transformed into the diepoxide **10a** with high yield and diastereoselectivity.

## Experimental Section

**General.** Analytical TLC was conducted in precoated silica gel 60 F-254 on aluminum sheets; compounds were visualized with UV light or iodine.  $^1\text{H}$  NMR spectra were recorded at 300 or 200 MHz.  $^{13}\text{C}$  NMR spectra were recorded at 75 or 50 MHz.

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(16) The transition structures corresponding to the addition of bromoenolate **6** (derived from *N,N*-dimethylalanine) to the *si* and *re* faces of the benzaldehyde were located using a model of the actual compounds and located using the AM1 Hamiltonian as implemented in the program GAUSSIAN 94, Revision D. 2: M. J. Frisch et al., Gaussian, Inc., Pittsburgh, PA, 1995. According with these results, the *si* transition structure **9b** leading to the only experimentally found anti alcoholate **8** is 1.3 kcal mol<sup>-1</sup> more stable than the alternative *re* transition structure, leading to the syn isomer.



Chemical shifts are reported in ppm relative to TMS in  $\text{CDCl}_3$ . Only the molecular ions and/or base peaks in MS are given. The enantiomeric purity was determined by chiral HPLC analysis using a Chiracel OD-H ( $0.46 \times 25$  cm, Diacel) column.

Dibromomethane, methyllithium, KHMDS, LiHMDS, benzaldehyde, cyclohexanone, and cyclopentanone were purchased from Aldrich and were used without further purification. All the reactions were conducted in oven-dried glassware under dry nitrogen. All solvents were purified before use. THF was distilled from sodium benzophenone ketyl; methanol was distilled from magnesium turnings.

**General Procedure for the Synthesis of  $\alpha'$ -Amino Bromomethyl Ketones 5.** To a  $-78^\circ\text{C}$  stirred solution of the corresponding protected  $\alpha$ -amino ester **3** (10 mmol) and dibromomethane (1.25 mL; 18 mmol) in dry THF (40 mL) was added methyllithium (12 mL of 1.5 M solution in diethyl ether; 18 mmol) dropwise over 5 min. After stirring at  $-78^\circ\text{C}$  for 30 min, the mixture was treated with a saturated aqueous solution of  $\text{NH}_4\text{Cl}$  (5 mL) and extracted with diethyl ether. The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated in vacuo. The crude ketones **5** were used without further purification.

**(S)-3-(Dibenzylamino)-1-bromobutan-2-one (5a)** (86% yield):  $R_f$  0.46 (10:1 hexane–ethyl acetate);  $[\alpha]_D^{25} = -98.1^\circ$  ( $c$  0.96,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.27 (d,  $J = 6.7$  Hz, 3 H), 3.48 (d,  $J = 6.7$  Hz, 2 H), 3.66–3.78 (m, 3 H), 4.19 (d,  $J = 13.2$  Hz, 1 H), 4.27 (d,  $J = 13.2$  Hz, 1 H), 7.28–7.40 (m, 10 H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  6.6, 33.8, 54.6, 60.4, 127.4, 128.5, 128.7, 138.4, 202.8; IR (KBr)  $1734\text{ cm}^{-1}$ ; MS (EI)  $m/z$  347 ( $\text{M}^+ + 2$ ,  $<1$ ), 345 ( $\text{M}^+$ ,  $<1$ ), 224 ( $\text{M}^+ - \text{C}_2\text{H}_5\text{BrO}$ , 98), 91 (100). Anal. Calcd for  $\text{C}_{18}\text{H}_{20}\text{BrNO}$ : C, 62.44; H, 5.82; N, 4.04. Found: C, 62.35; H, 5.78; N, 4.01.

**(S)-3-(Dibenzylamino)-1-bromo-5-methylhexan-2-one (5b)** (83% yield):  $R_f$  0.24 (10:1 hexane–ethyl acetate);  $[\alpha]_D^{25} = -106.0^\circ$  ( $c$  1.17,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.84 (d,  $J = 6.0$  Hz, 3 H), 0.92 (d,  $J = 6.0$  Hz, 3 H), 1.41–1.55 (m, 2 H), 1.77–1.91 (m, 1 H), 3.41–3.61 (m, 3 H), 3.73 (d,  $J = 13.6$  Hz, 2 H), 4.07 (s, 2 H), 7.27–7.37 (m, 10 H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  21.9, 23.2, 25.2, 30.8, 33.5, 54.2, 61.7, 127.1, 128.2, 128.7, 138.6, 200.7; IR (KBr)  $1721\text{ cm}^{-1}$ ; MS (EI)  $m/z$  389 ( $\text{M}^+ + 2$ , 1), 387 ( $\text{M}^+$ , 1), 266 ( $\text{M}^+ - \text{C}_2\text{H}_5\text{BrO}$ , 90), 91 (100).

**(S)-3-(Dibenzylamino)-1-bromo-4-phenylbutan-2-one (5c)** (83% yield):  $R_f$  0.36 (10:1 hexane–ethyl acetate);  $[\alpha]_D^{25} = -105.4^\circ$  ( $c$  1.19,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.08 (dd,  $J = 3.9$ , 13.5 Hz, 1 H), 3.32 (dd,  $J = 9.6$ , 13.5 Hz, 1 H), 3.66 (d,  $J = 13.5$  Hz, 2 H), 3.84–3.97 (m, 4 H), 4.25 (d,  $J = 13.5$  Hz, 1 H), 7.25–7.46 (m, 15 H);  $^{13}\text{C}$  NMR  $\delta$  28.5, 34.2, 54.4, 66.2, 126.0, 127.3, 128.3, 128.7, 128.9, 129.3, 138.3, 138.4, 199.8; IR (KBr)  $1732\text{ cm}^{-1}$ ; MS (EI)  $m/z$  332 ( $\text{M}^+ + 2 - \text{C}_7\text{H}_7$ , 10), 330 ( $\text{M}^+ - \text{C}_7\text{H}_7$ , 10), 300 (100), 91(98). Anal. Calcd for  $\text{C}_{24}\text{H}_{24}\text{BrNO}$ : C, 68.25; H, 5.72; N, 3.31. Found: C, 68.18; H, 5.75; N, 3.27.

**General Procedure for the Synthesis of  $\alpha'$ -Amino  $\alpha,\beta$ -Epoxy Ketones 2.** To a  $-100^\circ\text{C}$  stirred solution of the corresponding  $\alpha$ -bromo ketone **4** (2 mmol) in dry THF (40 mL) was added potassium hexamethyldisilazide (2.6 mL of a 1 M solution in toluene, 2.6 mmol). After the mixture was stirred for 1 h, the aldehyde or ketone (2 mmol) was added and the reaction mixture was stirred for another 30 min at this temperature. When the carbonyl compound was a ketone, the reaction was allowed to warm to room temperature overnight. The mixture was quenched with a saturated aqueous solution of  $\text{NH}_4\text{Cl}$  (5 mL) and extracted with diethyl ether. The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated in vacuo. The amino epoxy ketones **2** were examined by  $^1\text{H}$  NMR to give the diastereomeric excess reported in Table 2. Flash column chromatography over silica gel (20:1 hexane–ethyl acetate) provided pure compounds **2**.

**(1R,2S,4S)-4-Dibenzylamino-1,2-epoxy-1-phenylpentan-3-one (2a)** (85% yield):  $R_f$  0.52 (10:1 hexane–ethyl acetate);  $[\alpha]_D^{25} = -61.8^\circ$  ( $c$  0.50,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.27 (d,  $J = 6.7$  Hz, 3H), 3.41 (d,  $J = 13.5$  Hz, 2H), 3.64 (d,  $J = 13.5$  Hz, 2H), 3.69 (q,  $J = 6.7$  Hz, 1H), 3.91 (d,  $J = 1.7$  Hz, 1H), 3.97 (d,  $J = 1.7$  Hz, 1H), 7.16–7.48 (m, 15 H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  5.7, 54.4, 59.4, 61.4, 61.6, 126.1, 127.3,

128.3, 128.6, 128.7, 129.0, 135.6, 138.4, 204.7; IR (KBr)  $1724$ ,  $3030$ ,  $3063\text{ cm}^{-1}$ ; MS (EI)  $m/z$  280 ( $\text{M}^+ - \text{C}_7\text{H}_7$ , 5), 106 (75), 91 (100); HMRS calcd for  $\text{C}_{18}\text{H}_{18}\text{NO}_2$  ( $\text{M}^+ - \text{C}_7\text{H}_7$ ) 280.1337, found 280.1339. Anal. Calcd for  $\text{C}_{25}\text{H}_{25}\text{NO}_2$ : C, 80.83; H, 6.78; N, 3.77. Found: C, 80.70; H, 6.70; N, 3.69.

**(1R,2S,4S)-4-Dibenzylamino-1,2-epoxy-6-methyl-1-phenylheptan-3-one (2b)** (80% yield):  $R_f$  0.60 (10:1 hexane–ethyl acetate);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.89 (d,  $J = 6.0$  Hz, 3H), 0.99 (d,  $J = 6.0$  Hz, 3H), 1.42–1.50 (m, 1 H), 1.55–1.60 (m, 1 H), 1.89–1.98 (m, 1 H), 3.45 (d,  $J = 13.3$  Hz, 2H), 3.58 (dd,  $J = 2.8$ , 9.7 Hz, 1H), 3.65 (d,  $J = 13.3$  Hz, 2H), 3.76 (d,  $J = 1.7$  Hz, 1H), 3.98 (d,  $J = 1.7$  Hz, 1H), 7.18–7.54 (m, 15 H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  22.0, 23.5, 25.5, 30.2, 54.2, 59.3, 62.0, 63.2, 126.0, 127.2, 128.2, 128.5, 128.8, 129.9, 135.6, 138.7, 203.2; IR (KBr)  $1724$ ,  $3030$ ,  $3063\text{ cm}^{-1}$ ; MS (EI)  $m/z$  412 ( $\text{M}^+ - 1$ ), 356 ( $\text{M}^+ - \text{C}_7\text{H}_7$ , 5), 226 (100). Anal. Calcd for  $\text{C}_{28}\text{H}_{31}\text{NO}_2$ : C, 81.32; H, 7.55; N, 3.38. Found: C, 81.10; H, 7.60; N, 3.39.

**(1R,2S,4S)-4-Dibenzylamino-1,2-epoxy-1,5-diphenylpentan-3-one (2c)** (87% yield): mp  $106$ – $109^\circ\text{C}$ ;  $R_f$  0.58 (10:1 hexane–ethyl acetate);  $[\alpha]_D^{25} = -97.1^\circ$  ( $c$  0.68,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.01 (dd,  $J = 3.5$ , 13.4 Hz, 1H), 3.28 (dd,  $J = 9.2$ , 13.4 Hz, 1H), 3.55–3.62 (m, 3H), 3.74–3.87 (m, 4H), 7.17–7.49 (m, 20 H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  28.6, 54.3, 59.1, 62.1, 66.8, 126.0, 126.1, 127.3, 128.3, 128.4, 128.5, 128.8, 129.0, 120.5, 135.4, 138.4, 138.8, 202.5; IR (KBr)  $1724$ ,  $3030\text{ cm}^{-1}$ ; MS (EI)  $m/z$  356 ( $\text{M}^+ - \text{C}_7\text{H}_7$ , 5), 300 (70), 91 (100); HMRS calcd for  $\text{C}_{24}\text{H}_{22}\text{NO}_2$  ( $\text{M}^+ - \text{C}_7\text{H}_7$ ) 356.1650, found 356.1650. Chiral HPLC analysis ee  $> 99\%$  (Chiracel OD-H, UV detector 206 nm, 0.8 mL/min, 50:1 hexane/ethanol,  $t_R$  12.3 min).

**(2S,2'S)-2-(Dibenzylamino)-1-(1-oxaspiro[2,4]heptan-2-yl)propan-1-one (2d)** (70% yield):  $R_f$  0.42 (10:1 hexane–ethyl acetate);  $[\alpha]_D^{25} = -120.8^\circ$  ( $c$  0.39,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.44–2.22 (m, 8 H), 3.00 (dd,  $J = 3.5$ , 13.5 Hz, 1 H), 3.25 (dd,  $J = 9.1$ , 13.5 Hz, 1 H), 3.30–3.68 (m, 3 H), 3.80–3.87 (m, 3 H), 7.18–7.41 (m, 15 H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  24.8, 24.9, 28.7, 28.9, 33.9, 54.6, 62.7, 67.1, 72.5, 126.0, 127.4, 128.3, 128.4, 128.6, 129.6, 138.6, 139.0, 204.7; IR (KBr)  $1721$ ,  $3027\text{ cm}^{-1}$ . Anal. Calcd for  $\text{C}_{29}\text{H}_{31}\text{NO}_2$ : C, 81.85; H, 7.34; N, 3.29. Found: C, 81.60; H, 7.40; N, 3.33.

**(2S,2'S)-2-(Dibenzylamino)-1-(1-oxaspiro[2,5]octan-2-yl)propan-1-one (2e)** (68% yield):  $R_f$  0.37 (10:1 hexane–ethyl acetate);  $[\alpha]_D^{25} = -114.9^\circ$  ( $c$  0.47,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.23–2.03 (m and d,  $J = 6.7$  Hz, 13 H), 3.48 (d,  $J = 14.0$  Hz, 2 H), 3.63–3.76 (m, 4 H), 7.28–7.49 (m, 10 H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  6.1, 24.2, 24.4, 25.3, 27.2, 35.2, 54.5, 61.8, 64.9, 66.7, 127.3, 128.3, 128.4, 138.6, 206.3; IR (KBr)  $1721$ ,  $3027\text{ cm}^{-1}$ ; MS (EI)  $m/z$  363 ( $\text{M}^+$ , 7), 348 ( $\text{M}^+ - \text{CH}_3$ , 64), 224 (100); HMRS calcd for  $\text{C}_{24}\text{H}_{29}\text{NO}_2$  363.2200, found 363.2198.

**Synthesis of (S)-(Z)-N,N-Dibenzyl-3-trimethylsilyloxy-4-bromobut-3-en-2-amine (7a).** To a  $-100^\circ\text{C}$  stirred solution of the corresponding  $\alpha$ -bromo ketone **4** (2 mmol) in dry THF (40 mL) was added potassium hexamethyldisilazide (2.6 mL of a 1 M solution in toluene, 2.6 mmol). After the mixture was stirred for 1 h, trimethylchlorosilane (2.4 mmol) was added and the reaction mixture was stirred for another 30 min at this temperature. The solvents were removed at a reduced inert gas pressure, obtaining pure compound **7a** in 87% yield:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.33 (s, 9 H), 1.31 (d,  $J = 7.0$  Hz, 3 H), 3.38 (q,  $J = 7.0$  Hz, 1 H), 3.65 (d,  $J = 14.2$  Hz, 2 H), 3.81 (d,  $J = 14.2$  Hz, 2 H), 5.48 (s, 1 H), 7.28–7.46 (m, 10 H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  1.0, 14.5, 53.8, 57.0, 86.4, 126.7, 128.1, 128.2, 140.1, 154.5. Anal. Calcd for  $\text{C}_{21}\text{H}_{28}\text{BrNOSi}$ : C, 60.28; H, 6.74; N, 3.35. Found: C, 60.01; H, 6.70; N, 3.39.

**Synthesis of (2S,3S,4S,5R)-N,N-Dibenzyl-4,5-epoxy-3,3-(epoxymethane)-5-phenylpentan-2-amine 10a.** To a  $-100^\circ\text{C}$  stirred solution of **5a** (0.51 g, 1.5 mmol) in dry THF (30 mL) was added potassium hexamethyldisilazide (1.95 mL of a 0.5 M solution in toluene, 1.95 mmol). After the mixture was stirred for 1 h, benzaldehyde (0.15 mL, 1.5 mmol) was added and the reaction mixture was stirred for another 30 min at this temperature. Diiodomethane (0.22 mL, 3 mmol) was added, and then methyllithium (2 mL of a 1.5 M solution in

diethyl ether, 3 mmol) was added dropwise at  $-78\text{ }^{\circ}\text{C}$ . After stirring at  $-78\text{ }^{\circ}\text{C}$  for 30 min, the mixture was hydrolyzed with a saturated aqueous solution of  $\text{NH}_4\text{Cl}$  (5 mL) and extracted with diethyl ether. The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated in vacuo. The diepoxide **10a** was examined by  $^1\text{H}$  NMR to give the diastereomeric excess reported in Table 2. Flash column chromatography over silica gel provided pure compound **10a** in 75% yield: mp  $97\text{--}99\text{ }^{\circ}\text{C}$ ;  $R_f$  0.37 (10:1 hexane–ethyl acetate);  $[\alpha]_D^{25} = -24.9^{\circ}$  ( $c$  0.65,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.02 (d,  $J = 6.9$  Hz, 3 H), 2.51 (d,  $J = 5.2$  Hz, 1 H), 2.74 (d,  $J = 5.2$  Hz, 1 H), 3.30–3.39 (m, 4 H), 3.86 (d,  $J = 1.7$  Hz, 1 H), 3.91 (d,  $J = 13.7$  Hz, 2 H), 7.13–7.50 (m, 15 H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  5.0, 45.9, 52.8, 54.2, 56.7, 59.1, 61.4, 126.6, 126.8, 128.1, 128.3, 128.4, 128.6, 136.8, 139.5; IR (KBr) 3007, 3028  $\text{cm}^{-1}$ ; MS (EI)  $m/z$  385 ( $\text{M}^+$ , <1), 224 ( $\text{M}^+ - \text{C}_{10}\text{H}_9\text{O}_2$ , 100); HMRS calcd for  $\text{C}_{26}\text{H}_{27}\text{NO}_2$  385.2042, found 385.2038. Anal. Calcd for  $\text{C}_{26}\text{H}_{27}\text{NO}_2$ : C, 81.01; H, 7.06; N, 3.63. Found: C, 80.90; H, 7.10; N, 3.66.

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**Supporting Information Available:** ORTEP diagrams of **2c** and **10a**, X-ray crystallographic data, atomic coordinates, bond lengths and angles, and torsional angles for structures **2c** and **10a**, and copies of the  $^{13}\text{C}$  NMR spectra for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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