

# Synthesis of Aromatic (*E*)- or (*Z*)- $\alpha,\beta$ -Unsaturated Amides with Total or Very High Selectivity from $\alpha,\beta$ -Epoxyamides and Samarium Diiodide

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**Abstract:** Highly stereoselective synthesis of aromatic  $\alpha,\beta$ -unsaturated amides was achieved by treatment of aromatic  $\alpha,\beta$ -epoxyamides with samarium diiodide. The starting compounds **1** and **3** are easily prepared by the reaction of enolates derived from  $\alpha$ -chloroamides with carbonyl compounds at  $-78\text{ }^{\circ}\text{C}$ . A mechanism to explain this transformation is proposed.

$\alpha,\beta$ -Unsaturated amides have been used as building blocks in organic synthesis<sup>1</sup> to prepare natural products.<sup>2</sup> Moreover,  $\alpha,\beta$ -unsaturated amides show both biological<sup>3</sup> and insecticide activities.<sup>4</sup> Consequently, several preparations of  $\alpha,\beta$ -unsaturated amides have been described. However, the described methodologies afford (*E*)- $\alpha,\beta$ -unsaturated amides and, to the best of our knowledge, only a paper describing the synthesis of (*Z*)- $\alpha,\beta$ -unsaturated amides has been published to date.<sup>5</sup> An important limitation of this last method is that the preparation of the starting phosphonate occurs in low yield (33%).

In addition, transformations of epoxides<sup>6</sup> into alkenes with high diastereoselectivity are very scarce.<sup>7</sup>

Recently, we reported several highly diastereoselective  $\beta$ -elimination reactions, promoted by samarium diiodide,<sup>8</sup> leading (*Z*)-vinyl halides,<sup>9</sup> (*E*)- $\alpha,\beta$ -unsaturated esters,<sup>10</sup> or (*Z*)-vinylsilanes.<sup>11</sup> We also published the preparation of (*E*)- $\alpha,\beta$ -unsaturated amides from 2-chloro-3-hydroxyamides.<sup>12</sup> In addition, more recently we described the transformation of aromatic  $\alpha,\beta$ -epoxyamides into  $\alpha,\beta$ -hydroxyamides by reaction with  $\text{SmI}_2$  in the presence of  $\text{H}_2\text{O}$ .<sup>13</sup>

In this work we wish to describe a new synthesis of aromatic  $\alpha,\beta$ -unsaturated amides starting from the easily available  $\alpha,\beta$ -epoxyamides **1** and **3** by using  $\text{SmI}_2$ . Thus, aromatic (*Z*)- $\alpha,\beta$ -unsaturated amides were obtained from aromatic  $\alpha,\beta$ -epoxyamides, in which the oxirane ring is trisubstituted, and (*E*)- $\alpha,\beta$ -unsaturated amides from aromatic di- and tetrasubstituted  $\alpha,\beta$ -epoxyamides. These preparations take place with total or very high stereoselectivity. A mechanism is proposed to account for the different stereochemistries.

Starting  $\alpha,\beta$ -epoxyamides **1** were prepared by reaction of the corresponding potassium enolates of  $\alpha$ -chloroamides<sup>14</sup> (generated by treatment of  $\alpha$ -chloroamides with potassium hexamethyldisilazide at  $-78\text{ }^{\circ}\text{C}$ ) with different aldehydes at temperatures ranging from  $-78$  to  $25\text{ }^{\circ}\text{C}$ . Disubstituted epoxyamides, compounds **3a** and **3b**, were prepared by reaction of lithium enolate of chloroacetamide (generated by treatment of  $\alpha$ -chloroacetamide with LDA at  $-78\text{ }^{\circ}\text{C}$ ) with different aldehydes at  $-78\text{ }^{\circ}\text{C}$  and further treatment with sodium hydride. Tetrasubstituted epoxyamides, compounds **3c–e**, were obtained by reaction of lithium enolate of chloropropanamide with different ketones at temperatures ranging from  $-78$  to  $25\text{ }^{\circ}\text{C}$  (Scheme 1 and Table 1).

Our first attempts were performed by using *N,N*-diethyl-2-methyl-3-phenyl-2,3-epoxypropanamide as a model substrate, and several reaction conditions were tested. When the elimination reaction was carried out with 4 equiv of  $\text{SmI}_2$ , without cosolvents, a mixture of (*Z*) and (*E*)- $\alpha,\beta$ -unsaturated amides was obtained (roughly

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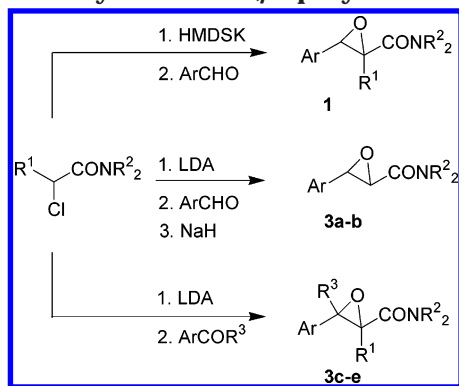
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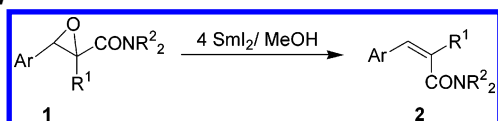
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SCHEME 1. Synthesis of  $\alpha,\beta$ -epoxyamides **1** and **3**TABLE 1. Synthesis of  $\alpha,\beta$ -Epoxyamides **1** and **3**

product	Ar	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	yield (%) <sup>a</sup>
<b>1a</b>	Ph	Me	Et	H	83
<b>1b</b>	Ph	Bu	Et	H	65
<b>1c</b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Me	Et	H	79
<b>1d</b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Me	<i>i</i> -Pr	H	72
<b>1e</b>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	Me	<i>i</i> -Pr	H	74
<b>3a</b>	Ph	H	Et	H	67
<b>3b</b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	H	Et	H	69
<b>3c</b>	Ph	Me	Et	Me	90
<b>3d</b>	Ph	Me	Et	Et	95
<b>3e</b>	Ph	Me	<i>i</i> -Pr	Et	93

<sup>a</sup> Isolated yield after flash column chromatography based on starting carbonyl compound.

SCHEME 2. Synthesis of Trisubstituted Aromatic (*Z*)- $\alpha,\beta$ -Unsaturated Amides **2**

10:1). When 2.5 equiv of SmI<sub>2</sub> was used in the presence of MeOH as a cosolvent,<sup>15</sup> a mixture of the (*Z*)-unsaturated amide and the corresponding 2-hydroxyamide were isolated (roughly 5:1). The best yields and the highest (*Z*)-diastereoselectivity were obtained by using 4 equiv of SmI<sub>2</sub> and MeOH as a cosolvent.<sup>16</sup>

Thus, treatment of  $\alpha,\beta$ -epoxyamides **1a–e** in THF (4 mL) and MeOH (0.5 mL) with a solution of SmI<sub>2</sub><sup>17</sup> (4 equiv) in THF for 30 min at room temperature afforded, after hydrolysis, the corresponding trisubstituted (*Z*)- $\alpha,\beta$ -unsaturated amides **2** with total stereoselectivity (Scheme 2 and Table 2).<sup>18</sup>

This  $\beta$ -elimination reaction was general, and trisubstituted aromatic  $\alpha,\beta$ -unsaturated amides **2** could be obtained bearing electron rich or deficient groups at the aromatic ring or bulky groups R<sup>2</sup> (*i*Pr) on nitrogen (Table 2).

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(17) SmI<sub>2</sub> was very rapidly prepared by sonication of a mixture of samarium powder and diiodomethane in THF: Concellón, J. M.; Rodríguez-Solla, H.; Bardales, E.; Huerta, M. *Eur. J. Org. Chem.* **2003**, 1775–1778.

(18) Minor amounts of 2-hydroxy-2-methyl-3-phenylpropanamide were obtained (11:1). In the other preparations of aromatic trisubstituted  $\alpha,\beta$ -unsaturated amides, no 2-hydroxyamides were detected.

TABLE 2. Synthesis of Trisubstituted Aromatic (*Z*)- $\alpha,\beta$ -Unsaturated Amides **2**

2	Ar	R <sup>1</sup>	R <sup>2</sup>	ed (%)	yield (%) <sup>a</sup>
<b>2a</b>	Ph	Me	Et	>98	75
<b>2b</b>	Ph	Bu	Et	>98	87
<b>2c</b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Me	Et	97	67
<b>2d</b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Me	<i>i</i> -Pr	>98	70
<b>2e</b>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	Me	<i>i</i> -Pr	>98	78

<sup>a</sup> Isolated yield after flash column chromatography based on compound **1**.

SCHEME 3. Synthesis of Di- and Tetrasubstituted (*E*)- $\alpha,\beta$ -Unsaturated Amides **4**TABLE 3. Synthesis of Di- and Tetrasubstituted Aromatic (*E*)- $\alpha,\beta$ -Unsaturated Amides **4**

4	Ar	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	ed (%)	yield (%) <sup>a</sup>
<b>4a</b>	Ph	H	Et	H	>98	75
<b>4b</b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	H	Et	H	>98	80
<b>4c</b>	Ph	Me	Et	Me	>98	95
<b>4d</b>	Ph	Me	Et	Et	>98	84
<b>4e</b>	Ph	Me	<i>i</i> -Pr	Et	>98	91

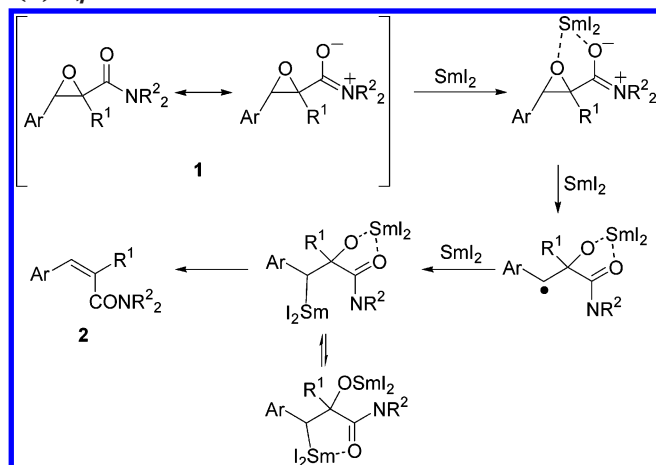
<sup>a</sup> Isolated yield after flash column chromatography or vacuum distillation based on compound **3**.

However, when tetrasubstituted  $\alpha,\beta$ -epoxyamides **3c–e** were used as starting compounds, (*E*)- $\alpha,\beta$ -unsaturated amides were isolated with total stereoselectivity (Scheme 3 and Table 3), instead of (*Z*)-unsaturated amides. When the reactions were performed without MeOH, no differences were observed and similar yields and de were obtained. It is noteworthy that tetrasubstitution of C=C with total diastereoselectivity is very difficult to achieve.

In the case of *N,N*-diethyl-3-phenyl-2,3-epoxypropanamide (disubstituted  $\alpha,\beta$ -epoxyamide), a mixture of *N,N*-diethyl-3-phenyl-2-hydroxypropanamide and its corresponding reduction product (*N,N*-diethyl-3-phenylpropanamide) was obtained. On the basis of these results, the reaction was carried out without MeOH (to avoid both the reduction of the double bond C=C of the  $\alpha,\beta$ -unsaturated amide and the synthesis of  $\alpha$ -hydroxyamides). Thus, treatment of disubstituted  $\alpha,\beta$ -epoxyamides **3a** and **3b** in THF (4 mL) with a solution of SmI<sub>2</sub> (2.5 equiv) in THF for 30 min at room temperature afforded, after hydrolysis, the corresponding disubstituted (*E*)- $\alpha,\beta$ -unsaturated amides **4a–b** with total stereoselectivity (Scheme 3 and Table 3).

It is noteworthy that, although 3:1 mixtures of diastereoisomers of starting compounds **1** and **3** were used in all described reactions, the corresponding  $\alpha,\beta$ -unsaturated amides **2** and **4** were obtained with high stereoselectivity.

The diastereoisomeric excess was determined on the crude reaction products by GC-MS and <sup>1</sup>H NMR spectroscopy.<sup>19</sup> The stereochemistry in the double bond C=C of disubstituted  $\alpha,\beta$ -unsaturated amides **4a,b** was assigned on the basis of the value of <sup>1</sup>H NMR coupling

**SCHEME 4. Mechanistic Proposal for the Synthesis of Trisubstituted Aromatic (*Z*)- $\alpha,\beta$ -Unsaturated Amides **2****


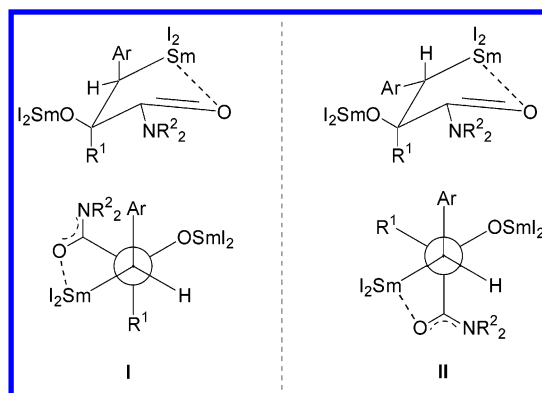
constant between the olefinic protons<sup>20</sup> or by NOESY experiments in the case of the trisubstituted (compounds **2b** and **2d**) and tetrasubstituted (compound **4d**) amides. In addition, in the case of compounds **4c,d**, a comparison with the <sup>1</sup>H and <sup>13</sup>C NMR values described in the literature for the corresponding (*E*)- $\alpha,\beta$ -unsaturated amides<sup>12</sup> was also carried out.

The synthesis of products **2** could be explained (Scheme 4) by assuming the initial double coordination of samarium with both oxygen atoms of **1**. The coordination of samarium with the oxirane ring produces an effect similar to that of a Lewis acid and can open the oxirane ring by reduction of the C <sub>$\beta$</sub> –O bond. The cleavage of the C <sub>$\beta$</sub> –O bond in aromatic  $\alpha,\beta$ -epoxyamides is favored, since it gives rise to a benzylic radical, which is stabilized by resonance.

A very fast second reduction with another equivalent of SmI<sub>2</sub> affords the corresponding anion, which suffers a  $\beta$ -elimination reaction (far faster than the hydrolysis of the anion by MeOH), affording the corresponding  $\alpha,\beta$ -unsaturated amide **2**. Tentatively, we propose an anti elimination process, transition states **I** and **II** being possible (Figure 1), in which the samarium(III) center is coordinated with the oxygen atom of the amide group. **I** would be preferred because there is no steric hindrance between Ar and R<sup>1</sup> and no 1,3-diaxial interactions of Ar are present in the cyclic transition state. Elimination from **I** affords a trisubstituted (*Z*)- $\alpha,\beta$ -unsaturated amide. In the case of disubstituted epoxyamides, transition state **II** would be preferred, with the bulkier group Ar in the equatorial orientation and there is no steric hindrance between Ar and R<sup>1</sup> = H.

When the elimination is carried out from tetrasubstituted epoxyamides, transition state **II** would be also preferred with the bulkier group Ar in the equatorial position.

Synthesis of **2** and **4**, with total stereoselection, from a mixture of diastereoisomers of **1** and **3** could be explained by assuming that after the reaction of epoxyamides **1** and **3** with SmI<sub>2</sub>, only one diastereoisomer is



**FIGURE 1.** Transition states proposal for the synthesis of trisubstituted aromatic (*Z*)- $\alpha,\beta$ -unsaturated amides **2**.

produced with the appropriate conformation for a double coordination of the samarium center with the alcohol oxygen.

The methodology herein described is complementary to the previously reported elimination of aromatic 2-chloro-3-hydroxyamides also promoted by SmI<sub>2</sub>.<sup>12</sup> Thus, the elimination reaction from  $\alpha,\beta$ -epoxyamides to obtain trisubstituted (*Z*)- $\alpha,\beta$ -unsaturated amides or tetrasubstituted (*E*)- $\alpha,\beta$ -unsaturated amides is recommendable, while synthesis of trisubstituted (*E*)- $\alpha,\beta$ -unsaturated amides can be achieved from 2-chloro-3-hydroxyamides. Similar results are obtained from  $\alpha,\beta$ -epoxyamides or 2-chloro-3-hydroxyamides to obtain aromatic disubstituted (*E*)- $\alpha,\beta$ -unsaturated amides.

In conclusion, we have presented an easy, simple, and general methodology to obtain both (*Z*)- $\alpha,\beta$ -unsaturated amides from aromatic trisubstituted  $\alpha,\beta$ -epoxyamides and (*E*)- $\alpha,\beta$ -unsaturated amides from di- or tetrasubstituted  $\alpha,\beta$ -epoxyamides. These elimination reactions proceed with total or high diastereoselectivity.

## Experimental Section

**General.**<sup>21</sup> Samarium diiodide was prepared by reaction of CH<sub>2</sub>I<sub>2</sub> with samarium powder.<sup>17</sup>

**General Procedure for the Synthesis of 2,3-Epoxyamides **1**.** To a –78 °C stirred solution of the corresponding 2-haloamide (2.5 mmol) in dry THF (4 mL) was added dropwise potassium hexamethyldisilazide (6.5 mL of 0.5 M solution in toluene, 3.25 mmol). After stirring for 10 min, a solution of the corresponding aldehyde (2.5 mmol) in dry THF (4 mL) was added dropwise at –78 °C and the mixture was allowed to warm to room temperature. The resulting solution was quenched with aqueous saturated solution of NH<sub>4</sub>Cl (20 mL). Usual workup provided crude 2,3-epoxyamides **1**, and purification by flash column chromatography over silica gel (hexane/ethyl acetate) provided pure compounds.

**General Procedure of Synthesis of  $\alpha,\beta$ -Unsaturated Amides **2**.** A solution of **1** (0.4 mmol) in THF (2 mL) was added to a stirred solution of SmI<sub>2</sub> (1.6 mmol) and MeOH (0.4 mL), under a nitrogen atmosphere, at 25 °C. The mixture was stirred for 30 min at this temperature and then quenched with aqueous HCl (0.1 M, 15 mL). Usual workup afforded crude  $\alpha,\beta$ -unsaturated amides **2**, which were purified by flash column chromatography on silica gel (hexane/AcOEt). Yields are given in Table 1.

**(*Z*)-*N,N*-Diethyl-2-methyl-3-phenylpropenamide (**2a**):** <sup>1</sup>H NMR (400 MHz, [D<sub>6</sub>]DMSO, 373 K)  $\delta$  = 7.32–7.12 (m, 5 H), 6.34 (s, 1 H), 3.36 (q, *J* = 6.9 Hz, 2 H), 3.14 (q, *J* = 6.9 Hz, 2 H),

(19) When the minor diastereoisomer was not detected, *ed* >98% is showed in Tables 2 and 3.

(20) The coupling constant between the olefinic protons of compounds **4a** and **4b** were *J* = 15.3 and 15.5 Hz, respectively, according with the average literature values.

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1.99 (s, 3 H), 1.05 (t,  $J = 6.9$  Hz, 3 H), 0.84 (t,  $J = 6.9$  Hz, 3 H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta = 171.2$  (C), 135.8 (C), 133.4 (C), 128.0 (CH), 127.5 (CH), 127.1 (CH), 126.7 (CH), 41.9 ( $\text{CH}_2$ ), 38.0 ( $\text{CH}_2$ ), 22.4 ( $\text{CH}_3$ ), 13.5 ( $\text{CH}_3$ ), 11.9 ( $\text{CH}_3$ ); MS (70 eV)  $m/z$  (%) 217 [ $\text{M}^+$ ] (81), 202 (32), 145 (100), 117 (97), 91 (40); HRMS calcd for  $\text{C}_{14}\text{H}_{19}\text{NO}$  217.1467, found 217.1461; IR (neat)  $\tilde{\nu} = 2973$ , 1620, 1431  $\text{cm}^{-1}$ ;  $R_f = 0.2$  (hexane/AcOEt 3/1). Anal. Calcd for  $\text{C}_{14}\text{H}_{19}\text{NO}$ : C, 77.38; H, 8.81; N, 6.45. Found: C, 77.51; H, 8.79; N, 6.41.

**(Z)-2-Butyl-N,N-diethyl-3-phenylpropenamide (2b):**  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta = 7.31$ – $7.09$  (m, 5 H), 6.32 (s, 1 H), 3.62–2.92 (m, 4 H), 2.41–2.31 (m, 2 H), 1.60–1.32 (m, 4 H), 1.08 (t,  $J = 6.9$  Hz, 3 H), 0.92 (t,  $J = 6.9$  Hz, 3 H), 0.73 (t,  $J = 6.9$  Hz, 3 H);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta = 170.9$  (C), 138.0 (C), 136.0 (C), 128.0 (CH), 127.7 (CH), 127.1 (CH), 125.8 (CH), 41.8 ( $\text{CH}_2$ ), 37.8 ( $\text{CH}_2$ ), 36.0 ( $\text{CH}_2$ ), 29.7 ( $\text{CH}_2$ ), 22.4 ( $\text{CH}_2$ ), 13.7 ( $\text{CH}_3$ ), 13.3 ( $\text{CH}_3$ ), 11.8 ( $\text{CH}_3$ );  $m/z$  (%) 259 [ $\text{M}^+$ ] (43), 216 (100), 202 (30), 100 (23); IR (neat)  $\tilde{\nu} = 2959$ , 1619, 1430  $\text{cm}^{-1}$ ;  $R_f = 0.3$  (hexane/AcOEt 3/1). Anal. Calcd for  $\text{C}_{17}\text{H}_{25}\text{NO}$ : C, 78.72; H, 9.71; N, 5.40. Found: C, 78.64; H, 9.79; N, 5.42.

**(Z)-N,N-Diethyl-3-[4-methoxyphenyl]-2-methylpropenamide (2c):**  $^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 373 K) 7.21 (d,  $J = 8.8$  Hz, 2 H), 6.84 (d,  $J = 8.8$  Hz, 2 H), 6.26 (s, 1 H), 3.74 (s, 3 H), 3.38 (q,  $J = 6.9$  Hz, 2 H), 3.17 (q,  $J = 6.9$  Hz, 2 H), 1.96 (s, 3 H), 1.08 (t,  $J = 6.9$  Hz, 3 H), 0.87 (d,  $J = 6.9$  Hz, 3 H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta = 171.6$  (C), 158.7 (C), 131.3 (C), 128.9 (CH), 128.7 (C), 126.3 (CH), 113.5 (CH), 55.0 ( $\text{CH}_3$ ), 41.9 ( $\text{CH}_2$ ), 38.1 ( $\text{CH}_2$ ), 22.3 ( $\text{CH}_3$ ), 13.7 ( $\text{CH}_3$ ), 12.0 ( $\text{CH}_3$ ); MS (70 eV)  $m/z$  (%) 247 [ $\text{M}^+$ ] (69), 232 (20), 175 (100), 147 (45), 140 (18); HRMS calcd for  $\text{C}_{15}\text{H}_{21}\text{NO}_2$  247.1572, found 247.1562; IR (neat)  $\tilde{\nu} = 2972$ , 1608, 1513  $\text{cm}^{-1}$ ;  $R_f = 0.3$  (hexane/AcOEt 1/1). Anal. Calcd for  $\text{C}_{15}\text{H}_{21}\text{NO}_2$ : C, 72.84; H, 8.56; N, 5.66. Found: C, 72.71; H, 8.50; N, 5.60.

**(Z)-N,N-Diisopropyl-3-[4-methoxyphenyl]-2-methylpropenamide (2d):**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) 7.31 (d,  $J = 8.8$  Hz, 2 H), 6.80 (d,  $J = 8.8$  Hz, 2 H), 6.21 (s, 1 H), 4.95–4.12 (m, 1 H), 3.79 (s, 3 H), 3.37–3.23 (m, 1 H), 2.03 (s, 3 H), 2.02 (d,  $J = 6.9$  Hz, 6 H), 1.09 (d,  $J = 6.7$  Hz, 3 H), 0.56 (d,  $J = 6.7$  Hz, 3 H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta = 171.4$  (C), 158.7 (C), 133.0 (C), 129.2 (C), 129.1 (CH), 125.2 (CH), 113.4 (CH), 55.1 ( $\text{CH}_3$ ), 50.3 (CH), 45.3 (CH), 22.2 ( $\text{CH}_3$ ), 21.3 ( $\text{CH}_3$ ), 20.6 ( $\text{CH}_3$ ), 20.0 ( $\text{CH}_3$ ), 19.7 ( $\text{CH}_3$ ); MS (70 eV)  $m/z$  (%) 275 [ $\text{M}^+$ ] (8), 260 (13), 175 (75), 91 (53); HRMS calcd for  $\text{C}_{17}\text{H}_{25}\text{NO}_2$  275.3859, found 275.1876; IR (neat)  $\tilde{\nu} = 2981$ , 1616, 1510  $\text{cm}^{-1}$ ;  $R_f = 0.4$  (hexane/AcOEt 3/1). Anal. Calcd for  $\text{C}_{17}\text{H}_{25}\text{NO}_2$ : C, 74.14; H, 9.15; N, 5.09. Found: C, 74.06; H, 9.20; N, 5.01.

**(Z)-N,N-Diisopropyl-3-[4-chlorophenyl]-2-methylpropenamide (2e):**  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ) 7.29 (d,  $J = 8.2$  Hz, 2 H), 7.19 (d,  $J = 7.4$  Hz, 2 H), 6.18 (s, 1 H), 3.99–3.85 (m, 1 H), 3.33–3.20 (m, 1 H), 2.00 (s, 3 H), 1.43 (d,  $J = 5.9$  Hz, 6 H), 1.06 (d,  $J = 6.4$  Hz, 3 H), 0.53 (d,  $J = 6.4$  Hz, 3 H);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta = 170.6$  (C), 135.5 (C), 134.5 (C), 132.5 (C), 129.0 (CH), 128.0 (CH), 124.2 (CH), 50.2 (CH), 45.2 (CH), 22.1 ( $\text{CH}_3$ ), 21.0 ( $\text{CH}_3$ ), 20.2 ( $\text{CH}_3$ ), 19.8 ( $\text{CH}_3$ ), 19.4 ( $\text{CH}_3$ ); MS (70 eV)  $m/z$  (%) 279 [ $\text{M}^+$ ] (47), 264 (29), 179 (100), 168 (11); HRMS calcd for  $\text{C}_{16}\text{H}_{22}\text{NOCl}$  279.1390, found 279.1425; IR (neat)  $\tilde{\nu} = 2984$ , 1612, 1493  $\text{cm}^{-1}$ ;  $R_f = 0.4$  (hexane/AcOEt 3/1). Anal. Calcd for  $\text{C}_{16}\text{H}_{22}\text{ClNO}$ : C, 68.68; H, 7.93; N, 5.01. Found: C, 68.80; H, 7.89; N, 5.11.

**General Procedure for the Synthesis of 2,3-Epoxyamides 3a–e:** To a  $-78$  °C stirred solution of the corresponding 2-haloamide (4.5 mmol) in dry THF (4 mL) was added dropwise lithium diisopropylamide [prepared from MeLi (3.2 mL of 1.5 M solution in diethyl ether, 5 mmol) and diisopropylamine (0.8 mL, 5 mmol) in THF 25 mL) at 0 °C]. After stirring for 10 min, a solution of the corresponding aldehyde or ketone (3.5 mmol)

in dry THF (4.5 mL) was added dropwise at  $-78$  °C and the mixture was stirred for 1 h. In the case of 2,3-epoxyamides **3a,b**, the reaction mixture was quenched with an aqueous saturated solution of  $\text{NH}_4\text{Cl}$  (20 mL). Usual workup provided crude 2-halo-3-hydroxyamides, which were diluted with  $\text{CH}_2\text{Cl}_2$  (20 mL) and treated with sodium hydride (1 g, 45 mmol) at 25 °C. The mixture was stirred for 2.5 h at this temperature and then quenched with  $\text{H}_2\text{O}$ . In the case of 2,3-epoxyamides **3c–e**, the mixture was allowed to warm to room temperature. The resulting solution was quenched with an aqueous saturated solution of  $\text{NH}_4\text{Cl}$  (20 mL). Usual workup afforded crude 2,3-epoxyamides **3a–e**, and purification by flash column chromatography on silica gel (hexane/AcOEt) provided pure compounds.

**General Procedure of Synthesis of  $\alpha,\beta$ -Unsaturated Amides 4.** A solution of **3** (0.4 mmol) in THF (2 mL) was added to a stirred solution of  $\text{SmI}_2$  (1.0 mmol), in THF (12 mL), under a nitrogen atmosphere, at 25 °C. The mixture was stirred for 30 min at this temperature and then quenched with aqueous HCl (0.1 M, 15 mL). Usual workup afforded crude  $\alpha,\beta$ -unsaturated amides **4**, which were purified by flash column chromatography on silica gel (hexane/AcOEt). Yields are given in Table 2.

**(E)-N,N-Diethyl-3-phenylpropenamide (4a).** See ref 12.

**(E)-N,N-Diethyl-3-[4-methoxyphenyl]propenamide (4b):**  $^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 373 K)  $\delta = 7.55$  (d,  $J = 8.5$  Hz, 2 H), 7.42 (d,  $J = 15.5$  Hz, 1 H), 6.95 (d,  $J = 8.5$  Hz, 2 H), 6.84 (d,  $J = 15.5$  Hz, 1 H), 3.81 (s, 3 H), 3.45 (q,  $J = 7.1$  Hz, 4 H), 1.15 (t,  $J = 7.1$  Hz, 6 H);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta = 165.9$  (C), 160.5 (C), 141.7 (CH), 129.1 (CH), 128.0 (C), 115.2 (CH), 114.0 (CH), 55.1 ( $\text{CH}_3$ ), 42.1 ( $\text{CH}_2$ ), 40.9 ( $\text{CH}_2$ ), 14.5 ( $\text{CH}_3$ ), 13.1 ( $\text{CH}_3$ ); MS (70 eV)  $m/z$  (%) 233 [ $\text{M}^+$ ] (21), 218 (6), 161 (100), 133 (25); IR (neat)  $\tilde{\nu} = 2974$ , 1646, 1460  $\text{cm}^{-1}$ ;  $R_f = 0.3$  (hexane/AcOEt 1/1). Anal. Calcd for  $\text{C}_{14}\text{H}_{19}\text{NO}_2$ : C, 72.07; H, 8.21; N, 6.00. Found: C, 72.18; H, 8.29; N, 6.15.

**(E)-N,N-Diethyl-2-methyl-3-phenylbut-2-enamide (4c).** See ref 12.

**(E)-N,N-Diethyl-2-methyl-3-phenylpent-2-enamide (4d).** See ref 12.

**(E)-N,N-Diisopropyl-2-methyl-3-phenylpent-2-enamide (4e):**  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ) 7.34–7.16 (m, 5 H), 3.97–3.84 (m, 1 H), 3.12–2.98 (m, 1 H), 2.32–1.95 (m, 2 H), 1.95 (s, 3 H), 1.36 (d,  $J = 6.9$  Hz, 3 H), 1.06 (d,  $J = 6.9$  Hz, 3 H), 0.99 (d,  $J = 6.7$  Hz, 3 H), 0.94 (t,  $J = 6.7$  Hz, 3 H), 0.37 (d,  $J = 6.7$  Hz, 3 H);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta = 171.9$  (C), 140.8 (C), 136.9 (C), 129.4 (C), 128.5 (CH), 127.6 (CH), 126.6 (CH), 49.7 (CH), 44.9 (CH), 25.8 ( $\text{CH}_2$ ), 21.4 ( $\text{CH}_3$ ), 20.4 ( $\text{CH}_3$ ), 19.7 ( $\text{CH}_3$ ), 19.4 ( $\text{CH}_3$ ), 16.7 ( $\text{CH}_3$ ), 12.4 ( $\text{CH}_3$ ); MS (70 eV)  $m/z$  (%) 273 [ $\text{M}^+$ ] (2), 244 (49), 173 (100), 145 (70), 128 (21); IR (neat)  $\tilde{\nu} = 2967$ , 1619, 1440  $\text{cm}^{-1}$ ;  $R_f = 0.5$  (hexane/AcOEt 3/1). Anal. Calcd for  $\text{C}_{18}\text{H}_{27}\text{NO}$ : C, 79.07; H, 9.95; N, 5.12. Found: C, 79.19; H, 9.84; N, 5.11.

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**Supporting Information Available:** Spectral data of compounds **1** and **3** and  $^{13}\text{C}$  NMR spectra of compounds **2** and **4**. This material is available free of charge via Internet at <http://pubs.acs.org>.

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