

Synthesis of (*E*)- α -Hydroxy- β,γ -Unsaturated Amides with High Selectivity from α,β -Epoxyamides by Using Catalytic Samarium Diiodide or Triiodide

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Abstract: The highly stereoselective synthesis of (*E*)- α -hydroxy- β,γ -unsaturated amides starting from α,β -epoxyamides, by using catalytic SmI₂ or SmI₃, was achieved. This transformation can also be carried out by using SmI₂ generated *in situ* from samarium

powder and diiodomethane. The starting compounds **1** are easily prepared by the reaction of enolates derived

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from α -chloroamides with ketones at -78°C . A mechanism to explain this transformation has been proposed. Cyclopropanation of (*E*)- α -hydroxy- β,γ -unsaturated amides has been performed to demonstrate their synthetic applications.

Introduction

The isomerisation of oxiranes^[1] to allylic alcohols is a valuable transformation in organic synthesis and has been accomplished by a variety of reagents including 1) organoselenium compounds,^[2] 2) dialkylaluminum amides,^[3] 3) alkylboron trifluoromethanesulfonates,^[4] 4) silyl iodides,^[5] 5) boron trifluoride etherate^[6] and 6) various dialkylamides.^[7] These reagents have their own limitations, including poor yields or diastereoselectivity, and failure to react with certain types of oxiranes. However, transformations of α,β -epoxycarbonyl compounds into α -hydroxy- β,γ -unsaturated carbonyl compounds have been very scarcely reported, and in these cases the C=C bond is generated with low diastereoselectivity.^[8] In addition to the best of our knowledge, no transformation of oxiranes into allylic alcohols, with catalytic SmI₂ or SmI₃ has been described, and only two examples of the synthesis of α -hydroxy- β,γ -unsaturated amides have been reported.^[9]

On the other hand, α -hydroxyamides show synthetic potential,^[10] and some possess anticancer properties.^[11] Moreover, the allylic alcohol moiety is an important building block in organic synthesis.^[12] For these reasons, synthesis of α -hydroxy- β,γ -unsaturated amides^[13] are of much interest.

We recently reported a new methodology to obtain aromatic α -hydroxyamides from α,β -epoxyamides,^[14] and α,β -unsaturated esters from α,β -epoxy esters^[15] by using samarium diiodide. We describe a novel synthesis of (*E*)- α -hy-

droxy- β,γ -unsaturated amides starting from readily available α,β -epoxyamides **1**, in which the oxirane ring is tetra- or tri-substituted, by using catalytic amounts of SmI₂ or SmI₃. This transformation can also be carried out by using catalytic amounts of SmI₂ generated *in situ* from a mixture of samarium powder and diiodomethane. The new C=C double bond is generated with high to total regio- and *E* stereoselectivity. A mechanism has been proposed to explain this transformation. Finally, one example of cyclopropanation of the obtained α -hydroxy- β,γ -unsaturated amides, has also been performed to demonstrate their synthetic applications.

Results and Discussion

Preparation of (*E*)- α -hydroxy- β,γ -unsaturated amides by using catalytic samarium diiodide or triiodide: The reaction was first attempted with 2.5 equivalents of SmI₂ in THF at room temperature (RT). Treatment of aromatic α,β -epoxyamides in which the oxirane ring is tri- or tetrasubstituted, with 2.5 equivalents of SmI₂ in THF,^[16] gave a mixture of (*E*)- α -hydroxy- β,γ -unsaturated amides and α,β -unsaturated amides.^[17] When lower amounts of SmI₂ were used, higher yields of (*E*)- α -hydroxy- β,γ -unsaturated amides were obtained, and consequently the yield of α,β -unsaturated amides decreased. Thus, treatment of α,β -epoxyamides with 0.5 equivalents of SmI₂ in THF at RT gave (*E*)- α -hydroxy- β,γ -unsaturated amides as the only product, in high yield, and generated the C=C double bond with high diastereoselectivity (Scheme 1 and Table 1). When the amount of SmI₂ was decreased to 0.2 equivalents, similar results were achieved.^[18]

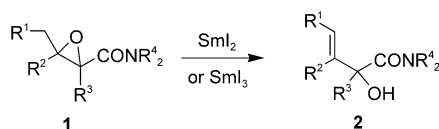
Tri- or tetrasubstituted α,β -epoxyamides **1** were prepared by reacting the lithium enolate of chloroamides (generated

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Table 1. Synthesis of (*E*)- α -hydroxy- β,γ -unsaturated amides **2**.

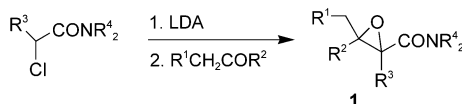
Entry ^[a]	2	R ¹	R ²	R ³	R ⁴	<i>t</i> [h]	<i>T</i> [°C]	<i>de</i> [%] ^[b]	Yield [%] ^[c]
1	2a	H	Ph	H	<i>i</i> Pr	2	25	–	91
2	2b	Et	Ph	H	<i>i</i> Pr	0.166	25	47	76
3	2b	Et	Ph	H	<i>i</i> Pr	0.166	–25	66	74
4	2b	Et	Ph	H	<i>i</i> Pr	0.166	–50	71	74
5 ^[d]	2b	Et	Ph	H	<i>i</i> Pr	2	–78	80	74
6	2c			H	Et	2	25	–	84
7	2d	H	Ph	Me	Et	2	25	–	67
8	2e	Me	Et	Me	Et	2	25	> 98	82
9	2f	Me	Ph	Me	Et	2	25	> 98	71
10 ^[e]	2g	allyl	Me	Me	Et	12	–50	> 98	42
11	2h		–(CH ₂) ₄ –	Me	Et	2	25	–	86
12 ^[e]	2i	C ₅ H ₁₁	Me	Me	Et	12	–50	> 98	45

[a] Unless otherwise noted, reactions were carried out with 0.5 equivalents of SmI₂. [b] Diastereoisomeric excess (*de*) was determined by GC-MS, and 300 MHz ¹H and ¹³C NMR analysis of the crude products. [c] Isolated yield after column chromatography based on compound **1**. [d] The reaction was carried out with 1 equivalent of SmI₂. [e] The reaction was carried out with 2 equivalents of SmI₂.

Scheme 1. Synthesis of (*E*)- α -hydroxy- β,γ -unsaturated amides **2**.

by treatment of α -chloroamides with lithium diisopropylamide at -85°C) with different ketones at -78°C , and warming the reaction mixture to RT (Scheme 2).

The same isomerisation reaction from α,β -epoxyesters, by using SmI₂, was not observed and α,β -unsaturated esters

Scheme 2. Synthesis of α,β -epoxyamides **1**.

were isolated instead of the corresponding α -hydroxy- β,γ -unsaturated esters.^[15] In the case of α,β -epoxyamides the reaction seems to be general and α -hydroxy- β,γ -unsaturated amides **2** can be obtained from tri- or tetrasubstituted α,β -epoxyamides^[19] with the oxirane ring bearing aliphatic or aromatic substituents (Table 1). However, no reaction took

place starting from tetrasubstituted α,β -epoxyamides with R¹=Ph and R⁴=*i*Pr (R²=Me and Et, R³=Me), and the starting compound **1** was recovered.

The diastereoisomeric excess of the generated C=C double bond was determined on the crude reaction products by GC-MS and ¹H NMR spectroscopy, and the *E* stereochemistry of the β,γ -unsaturated amides **2** was assigned by NOESY experiments on products **2e** and **2f**. The stereochemistry of the other compounds **2** was assigned by analogy.

Better diastereoselectivity was obtained when starting from tetrasubstituted rather than trisubstituted α,β -epoxyamides. In this case, higher diastereoselectivity was obtained at lower temperatures (Table 1, entries 2–5). It is worth noting that although 1:1 mixtures of diastereoisomers of starting compounds **1** were used in these reactions, the double bonds of amides **2** were obtained with high or total *E* stereoselectivity.

When R¹ and R² in the epoxyamides **1** have hydrogen atoms at C_γ what can be eliminated, two regioisomers α -hydroxy- β,γ -unsaturated amides are possible. For this reason, the regioselectivity of the reaction was also studied. Thus, when an internal or terminal C=C double bond could be generated, the reaction led to an internal thermodynamically more stable alkene as the major product (Table 2). Higher regioselectivity was also obtained at lower temperatures (Table 2). The regioselectivity of the reactions from **1g** and **1i** and the structure of the major product were determined by NMR spectroscopy.

The reaction of epoxyamides at low temperature (-50°C or -78°C) was carried out using higher amounts of SmI₂ (see Table 1, entries 5, 10 and 12, and Table 2, entries 2, 3 and 5) as very long reaction times were necessary when using lower amounts of SmI₂. The reaction time in the case of tetrasubstituted epoxyamides at low temperatures was longer than those from trisubstituted epoxyamides (Table 1, entries 4 and 10), probably due to steric hindrance.

The transformation of epoxyamides **1** into **2** can also be carried out with SmI₃, instead of SmI₂, and similar yields

Abstract in Spanish: Se describe la síntesis con alta estereoselectividad de (*E*)- α -hidroxiamidas- β,γ -insaturadas a partir de α,β -epoxiamidas, mediante el empleo de diyoduro o triyoduro de samario catalítico. Esta transformación se puede llevar a cabo con diyoduro de samario generado in situ a partir de samario en polvo y diyodometano. Los productos de partida **1** son fácilmente preparados por tratamiento de α -cloroamidas con cetonas a -78°C . Se propone un mecanismo para explicar el proceso. Se ha llevado a cabo la ciclopropanación de (*E*)- α -hidroxiamidas- β,γ -insaturadas para demostrar sus aplicaciones sintéticas.

Table 2. Regioselectivity of the synthesis of (*E*)- α -hydroxy- β,γ -unsaturated amides **2** ($R^2 = R^3 = \text{Me}$, $R^4 = \text{Et}$).

Entry ^[a]	2	R^1	t [h]	T [°C]	Ratio ^[b]	de [%] ^[c]	Yield [%] ^[d]
1	2g	allyl	0.5	25	1:1	> 98	54
2 ^[e]	2g	allyl	12	−50	5:1	> 98	42
3 ^[e]	2i	C_5H_{11}	12	−50	5:1	> 98	45
4	2i	C_5H_{11}	0.5	25	1:1	> 98	61
5 ^[f]	2i	C_5H_{11}	48	−25	3:1	> 98	61

[a] Unless otherwise noted, reactions were carried out with 0.5 equivalents of SmI_2 . [b] Ratio of internal/terminal C=C double bonds. Determined by 300 MHz ^1H and ^{13}C NMR analysis of the crude products. [c] Diastereoisomeric excess (de) determined by GC-MS, and 300 MHz ^1H and ^{13}C NMR analysis of the crude products. [d] Isolated yield after column chromatography based on compound **1**. [e] The reaction was carried out with 2 equivalents of SmI_2 . [f] The reaction was carried out with 1 equivalent of SmI_2 .

were obtained. However, SmI_2 is preferred because cleaner products **2** are obtained. Probably, the lower solubility of SmI_3 in THF relative to that of SmI_2 could explain this result (see below in the section on the mechanism).

Synthesis of (*E*)- α -hydroxy- β,γ -unsaturated amides by using samarium diiodide generated in situ: A limitation of the synthetic applications of SmI_2 is its high sensitivity to oxidation by air that requires careful manipulation and storage. For these reasons, the use of the cheaper and more stable metallic samarium is more desirable. Thus, SmI_2 can be prepared in situ (for example, from diiodomethane and powder metallic samarium) in the presence of the starting organic compound,^[20] and the total reaction time (generation of SmI_2 + reaction of SmI_2) is then shorter than that obtained by using pre-formed SmI_2 .

For this reason, an easier and simpler methodology to prepare (*E*)- α -hydroxy- β,γ -unsaturated amides has been developed, by using SmI_2 generated in situ from a mixture of metallic Sm and diiodomethane. Results in Table 3 show that similar yields and diastereoisomer excess were obtained using this methodology.

Table 3. Synthesis of (*E*)- α -hydroxy- β,γ -unsaturated amides **2** by using SmI_2 generated in situ.

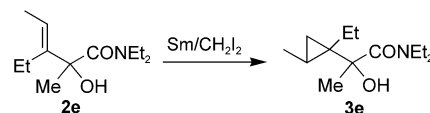
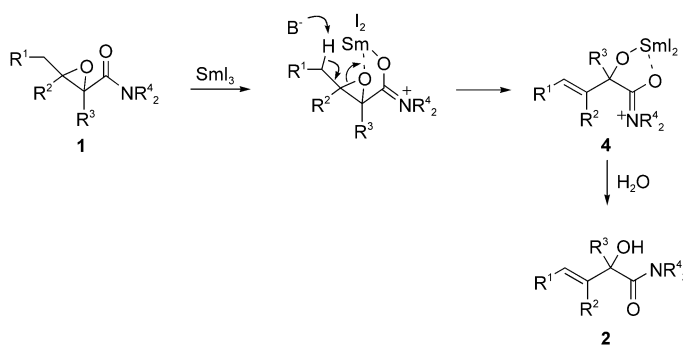
Entry ^[a]	2	R^1	R^2	R^3	R^4	de [%] ^[b]	Yield [%] ^[c]
1	2a	H	Ph	H	<i>i</i> Pr	–	69
2	2c			H	Et	–	85
3	2d	H	Ph	Me	Et	–	72
4	2e	Me	Et	Me	Et	> 98	82
5	2f	Me	Ph	Me	Et	> 98	68

[a] Reactions were carried out with 0.5 equivalents of SmI_2 at 25 °C for 2 h. [b] Diastereoisomeric excess (de) determined by GC-MS, and 300 MHz ^1H and ^{13}C NMR analysis of the crude products. [c] Isolated yield after column chromatography based on compound **1**.

Functional groups of compounds **2** have very different reactivities, and consequently they can be transformed selectively into other products. To illustrate this potential, compound **2e** was cyclopropanated owing to the properties,^[21] synthetic usefulness,^[22] and applications in mechanistic studies^[23] of the cyclopropyl group. Moreover, cyclopropane derivatives with hydroxy and carboxyl functionalities have important biological effects.^[24] Thus, cyclopropanation of the C=C double bond of **2e** was carried out in 71 % yield with a

mixture of Sm and CH_2I_2 by using a stereospecific methodology previously described (Scheme 3).^[25]

Mechanism: The synthesis of product **2** could be explained (Scheme 4) by assuming that it is produced by catalytic SmI_3 .^[26] Thus, the reaction is initiated by the coordination of samari-

Scheme 3. Cyclopropanation of compound **2e**.Scheme 4. Mechanistic proposal for the synthesis of (*E*)- α -hydroxy- β,γ -unsaturated amides.

um with both oxygen atoms of **1**. The coordination of samarium with the oxirane ring produces a similar effect to that of a Lewis acid, and facilitates its opening. This initial chelation is favoured by the electron-donating capacity of the nitrogen atom and could explain the absence of isomerisation of α,β -epoxyesters. An abstraction of a proton bonded to a C_γ atom, by a base (for example alkoxy-samarium species), produces the oxirane ring-opening, affording **4**. Tentatively, we propose an *anti*-elimination process of a proton from the C_γ position resulting in the two possible transition states **I** and **II** (Scheme 4, and Figure 1). Transition state **I** would be preferred due to the lack of steric hindrance between the R^1 and $\text{CR}^3\text{OCONR}^4_2$ groups. Elimination from **I** affords a trisubstituted (*E*)- α -hydroxy- β,γ -unsaturated amide **2**. A product-like transition state could justify the preferential formation of the more thermo-

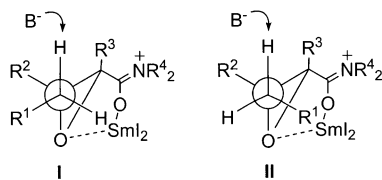


Figure 1. Proposed transition states.

dynamically stable product containing the C=C double bond in an internal position.

Conclusion

We have described a simple and general methodology to obtain (*E*)- α -hydroxy- β,γ -unsaturated amides by treatment of tri- or tetrasubstituted α,β -epoxyamides with catalytic SmI₂ or SmI₃. These elimination reactions proceed with total or high diastereoselectivity and regioselectivity, and a mechanism to explain these results has been proposed. This isomerisation reaction can also be carried out by using SmI₂ generated in situ. Cyclopropanation of the β,γ -unsaturated amides has also been carried out to illustrate their synthetic applications.

Experimental Section

General: Reactions requiring an inert atmosphere were conducted under dry nitrogen, and the glassware was oven dried at 120°C. THF was distilled from sodium/benzophenone immediately prior to use. All reagents were purchased from Aldrich or Merck and were used without further purification. Samarium diiodide was prepared by reaction of CH₂I₂ with samarium powder.^[16] Silica gel for flash chromatography was purchased from Merck (200 $\times$ 450 mesh), and compounds were visualised on analytical thin-layer chromatograms (TLC) by UV light (254 nm). ¹H NMR spectra were recorded at 200 or 300 MHz. ¹³C NMR spectra and DEPT experiments were determined at 50 or 75 MHz. Chemical shifts are given in ppm relative to tetramethylsilane (TMS), which was used as an internal standard, and coupling constants (*J*) are reported in Hz. GC-MS and HRMS were measured at 70 eV or by using FAB conditions. When HRMS could not be measured on molecular ion the HRMS of a significant fragment is given. Only the most important IR absorptions (cm⁻¹) and the molecular ions and/or base peaks in MS are given.

General procedure for the synthesis of 2,3-epoxyamides (1): 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] was added dropwise to a -78°C stirred solution of the corresponding 2-haloamide (4.5 mmol) in dry THF (4 mL). After stirring for 10 min, a solution of the corresponding ketone (3.5 mmol) in dry THF (4.5 mL) was added dropwise at -78°C and the mixture was allowed to warm to RT. The resulting solution was quenched with a saturated aqueous solution of NH₄Cl (20 mL). Crude 2,3-epoxyamides **1** were purified by column flash chromatography over silica gel (hexane/ethyl acetate) eluting compound **1** as a mixture of *cis/trans* diastereoisomers.

2,3-Epoxy-*N,N*-diisopropyl-3-phenylbutanamide (1a): ¹H NMR (200 MHz, CDCl₃): δ = 7.23–6.96 (m, 5H), 3.87–3.74 (m, 1H), 3.40 (s, 1H), 2.97–2.84 (m, 1H), 1.59 (s, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.75 (d, *J* = 6.7 Hz, 3H), 0.60 ppm (d, *J* = 6.4 Hz, 3H); ¹³C NMR (50 MHz, CDCl₃): δ = 163.3 (C), 136.8 (C), 127.1 (CH), 127.0 (CH), 125.7 (CH), 63.3 (CH), 61.6 (C), 47.2 (CH), 44.7 (CH), 22.0 (CH₃), 20.2 (CH₃), 20.0 (CH₃), 19.3 (CH₃), 19.1 ppm (CH₃); IR (neat): $\tilde{\nu}$ = 2967, 1644, 1444, 1335, 1045 cm⁻¹; *R*_f = 0.2 (hexane/AcOEt 3:1); elemental

analysis calcd (%) for C₁₆H₂₃NO₂: C 73.53, H 8.87, N 5.36; found: C 73.47, H 8.79, N 5.38.

2,3-Epoxy-*N,N*-diisopropyl-3-phenylhexanamide (1b): ¹H NMR (200 MHz, CDCl₃): δ = 7.28–7.01 (m, 5H), 4.04–3.90 (m, 1H), 3.45 (s, 1H), 3.04–2.89 (m, 1H), 2.31–1.02 (m, 4H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.95 (t, *J* = 6.7 Hz, 3H), 0.83–0.72 ppm (m, 9H); ¹³C NMR (50 MHz, CDCl₃): δ = 163.7 (C), 135.7 (C), 127.1 (CH), 126.9 (CH), 126.3 (CH), 65.0 (C), 62.1 (CH), 47.2 (CH), 44.9 (CH), 37.5 (CH₂), 20.2 (CH₃), 19.4 (CH₃), 19.1 (CH₃), 17.4 (CH₃), 13.4 ppm (CH₃); IR (neat): $\tilde{\nu}$ = 2968, 1648, 1446, 1371, 1043 cm⁻¹; *R*_f = 0.3 (hexane/AcOEt 3:1); elemental analysis calcd (%) for C₁₈H₂₇NO₂: C 74.70, H 9.40, N 4.84; found: C 74.61, H 9.31, N 4.79.

***N,N*-Diethyl-1,2,3,4-tetrahydronaphthalene-1-spiro-2'-oxirane-3'-carboxamide (1c):** ¹H NMR (200 MHz, CDCl₃): δ = 7.31–6.99 (m, 4H), 3.70 (s, 1H), 3.67–3.00 (m, 4H), 2.99–1.82 (m, 6H), 1.23–1.05 ppm (m, 6H); ¹³C NMR (50 MHz, CDCl₃): δ = 164.3 (C), 138.4 (C), 135.2 (C), 127.8 (CH), 127.1 (CH), 125.5 (CH), 122.5 (CH), 63.5 (CH), 59.7 (C), 40.2 (CH₂), 38.9 (CH₂), 28.4 (CH₂), 26.5 (CH₂), 20.8 (CH₂), 13.4 (CH₃), 12.0 ppm (CH₃); IR (neat): $\tilde{\nu}$ = 2935, 1639, 1460, 1381, 1077 cm⁻¹; *R*_f = 0.4 (hexane/AcOEt 1:1); elemental analysis calcd (%) for C₁₆H₂₁NO₂: C 74.10, H 8.16, N 5.40; found: C 74.18, H 8.13, N 5.46.

2,3-Epoxy-*N,N*-diethyl-2-methyl-3-phenylbutanamide (1d): The data were in agreement with those given in reference [17a].

2,3-Epoxy-*N,N*-triethyl-2-methylpentanamide (1e): ¹H NMR (200 MHz, CDCl₃): δ = 3.66–3.26 (m, 4H), 1.83–1.27 (m, 4H), 1.51 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H), 0.99 (t, *J* = 7.4 Hz, 3H), 0.98 ppm (t, *J* = 7.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 169.3 (C), 67.7 (C), 66.0 (C), 40.9 (CH₂), 39.2 (CH₂), 24.8 (CH₂), 21.6 (CH₂), 16.6 (CH₃), 13.7 (CH₃), 12.0 (CH₃), 8.6 (CH₃), 8.2 ppm (CH₃); IR (neat): $\tilde{\nu}$ = 2972, 1637, 1462, 1380, 1113 cm⁻¹; *R*_f = 0.5 (hexane/AcOEt 1:1); elemental analysis calcd (%) for C₁₂H₂₃NO₂: C 67.57, H 10.87, N 6.57; found: C 65.65, H 10.80, N 6.49.

2,3-Epoxy-*N,N*-diethyl-2-methyl-3-phenylpentanamide (1f): The data were in agreement with those given in reference [17a].

2,3-Epoxy-*N,N*-diethyl-2,3-dimethylhept-6-enamide (1g): Data on a 50:50 mixture of diastereoisomers: ¹H NMR (300 MHz, CDCl₃): δ = 5.95–5.75 (m, 2H), 5.11–4.94 (m, 4H), 3.67–3.27 (m, 8H), 2.47–2.09 (m, 4H), 1.83–1.42 (m, 4H), 1.54 (s, 6H), 1.36 (s, 3H), 1.27 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 6H), 1.14 (t, *J* = 7.0 Hz, 3H), 1.13 ppm (t, *J* = 7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 169.3 (2C), 137.6 (CH), 137.1 (CH), 114.5 (CH₂), 113.9 (CH₂), 65.4 (C), 65.2 (C), 64.0 (C), 63.8 (C), 41.2 (CH₂), 41.0 (CH₂), 39.5 (CH₂), 39.2 (CH₂), 35.2 (CH₂), 32.3 (CH₂), 29.0 (CH₂), 28.6 (CH₂), 19.6 (CH₃), 16.9 (CH₃), 16.6 (CH₃), 16.3 (CH₃), 13.8 (CH₃), 13.7 (CH₃), 12.1 ppm (2CH₃); IR (neat): $\tilde{\nu}$ = 2973, 1636, 1458, 1382, 1114 cm⁻¹; *R*_f = 0.3 (hexane/AcOEt 3:1); elemental analysis calcd (%) for C₁₅H₂₃NO₂: C 69.29, H 10.29, N 6.22; found: C 69.20, H 10.33, N 6.18.

***N,N*-Diethyl-2-methyl-1-oxaspiro[2.5]octane-2-carboxamide (1h):** ¹H NMR (200 MHz, CDCl₃): δ = 3.55–2.98 (m, 4H), 1.68–1.10 (m, 10H), 1.34 (s, 3H), 1.02 (t, *J* = 7.2 Hz, 3H), 0.95 ppm (t, *J* = 7.2 Hz, 3H); ¹³C NMR (50 MHz, CDCl₃): δ = 169.4 (C), 65.9 (C), 65.7 (C), 41.1 (CH₂), 39.3 (CH₂), 32.5 (CH₂), 29.3 (CH₂), 25.0 (CH₂), 24.2 (CH₂), 23.8 (CH₂), 16.2 (CH₃), 13.9 (CH₃), 12.2 ppm (CH₃); IR (neat): $\tilde{\nu}$ = 2934, 1638, 1485, 1380, 1081 cm⁻¹; *R*_f = 0.4 (hexane/AcOEt 1:1); elemental analysis calcd (%) for C₁₃H₂₃NO₂: C 69.29, H 10.29, N 6.22; found: C 69.37, H 10.35, N 6.21.

2,3-Epoxy-*N,N*-diethyl-2,3-dimethylnonanamide (1i): Data on a 50:50 mixture of diastereoisomers: ¹H NMR (200 MHz, CDCl₃): δ = 3.62–3.18 (m, 8H), 1.60–1.37 (m, 26H), 1.47 (s, 6H), 1.26 (s, 6H), 1.07 (t, *J* = 7.0 Hz, 6H), 0.81 ppm (t, *J* = 7.0 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃): δ = 169.7 (2C), 65.7 (C), 65.5 (C), 64.8 (C), 64.6 (C), 41.4 (CH₂), 41.2 (CH₂), 39.6 (CH₂), 39.4 (CH₂), 36.0 (2CH₂), 31.4 (CH₂), 31.3 (CH₂), 29.3 (CH₂), 29.1 (CH₂), 25.0 (CH₂), 24.5 (CH₂), 22.3 (2CH₂), 17.2 (CH₃), 16.8 (CH₃), 16.5 (CH₃), 15.8 (CH₃), 14.1 (CH₃), 13.8 (CH₃), 12.4 (2CH₃), 12.0 ppm (2CH₃); IR (neat): $\tilde{\nu}$ = 2931, 1640, 1462, 1380, 1082 cm⁻¹; *R*_f = 0.3 (hexane/AcOEt 3:1); elemental analysis calcd (%) for C₁₅H₂₉NO₂: C 70.54, H 11.45, N 5.48; found: C 70.49, H 11.36, N 5.41.

General procedure for the synthesis of (*E*)- α -hydroxy- β,γ -unsaturated amides (2): A solution of SmI₂ (0.2 mmol) in THF (2.5 mL) was added, under a nitrogen atmosphere, to a stirred solution of α,β -epoxyamide **1** (0.4 mmol) in THF (2 mL) at 25°C. When the reaction was carried out by using in situ generated SmI₂ (Table 1), CH₂I₂ (0.016 mL, 0.2 mmol)

was added to a stirred solution of α,β -epoxyamide **1** (0.4 mmol) and samarium powder (0.034 g, 0.23 mmol) in THF (2.4 mL). The mixture was stirred for 2 h at 25°C, then quenched with aqueous HCl (0.1 M, 15 mL) and extracted with CH_2Cl_2 (3 $\times$ 5 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in a vacuum affording the crude (E)- α -hydroxy- β , γ -unsaturated amides **2**, which were then purified by flash column chromatography on silica gel (hexane/AcOEt).

N,N-Diisopropyl-2-hydroxy-3-phenylbut-3-enamide (2a): ^1H NMR (300 MHz, CDCl_3): δ = 7.58–7.28 (m, 5H), 5.52 (br, 1H), 5.26 (s, 1H), 4.99–4.96 (m, 1H), 4.88–4.85 (m, 1H), 3.77–3.64 (m, 1H), 3.48–3.35 (m, 1H), 1.46 (d, J = 6.9 Hz, 3H), 1.36 (d, J = 6.9 Hz, 3H), 1.13 (d, J = 6.7 Hz, 3H), 1.03 ppm (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ = 170.2 (C), 147.6 (C), 139.0 (C), 128.3 (CH), 127.9 (CH), 126.3 (CH), 115.7 (CH₂), 71.4 (CH), 47.9 (CH), 46.2 (CH), 20.5 (CH₃), 20.3 (CH₃), 19.5 (CH₃), 18.9 ppm (CH₃); HMS (70 eV): m/z (%): 261 [M^+] (<1), 244 (49), 128 (86), 86 (100), 44 (77); HRMS calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_2$: 261.1729; found: 261.1729; IR (neat): $\tilde{\nu}$ = 3396, 1639, 1446 cm^{-1} ; R_f = 0.2 (hexane/AcOEt 3:1); elemental analysis calcd (%) for $\text{C}_{16}\text{H}_{23}\text{NO}_2$: C 73.53, H 8.87, N 5.36; found: C 73.21, H 8.91, N 5.41.

(E)-N,N-Diisopropyl-2-hydroxy-3-phenylhex-3-enamide (2b): ^1H NMR (200 MHz, CDCl_3): δ = 7.41–7.23 (m, 5H), 5.85 (t, J = 7.4 Hz, 1H), 5.11 (s, 1H), 5.08 (br, 1H), 3.88–3.75 (m, 1H), 3.36–3.22 (m, 1H), 2.46–2.30 (m, 2H), 1.40 (d, J = 6.7 Hz, 3H), 1.13 (t, J = 7.2 Hz, 3H), 1.11 (d, J = 6.7 Hz, 3H), 1.05 (d, J = 6.7 Hz, 3H), 1.00 ppm (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ = 170.7 (C), 140.5 (C), 138.0 (C), 136.7 (CH), 127.8 (CH), 127.1 (CH), 127.0 (CH), 68.4 (CH), 47.5 (CH), 46.2 (CH), 21.4 (CH₂), 20.8 (CH₃), 20.4 (CH₃), 19.3 (2CH₃), 13.9 ppm (CH₃); HMS (70 eV): m/z (%): 289 [M^+] (<1), 272 (100), 128 (95), 77 (28); HRMS calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_2$: 289.2042; found: 289.2160; IR (neat): $\tilde{\nu}$ = 3358, 1633, 1446 cm^{-1} ; R_f = 0.4 (hexane/AcOEt 3:1); elemental analysis calcd (%) for $\text{C}_{18}\text{H}_{27}\text{NO}_2$: C 74.70, H 9.40, N 4.84; found: C 74.99, H 9.46, N 4.77.

N,N-Diethyl-2-(3,4-dihydronaphthalen-1-yl)-2-hydroxyethanamide (2c): ^1H NMR (300 MHz, CDCl_3): δ = 7.54 (d, J = 7.3 Hz, 1H), 7.21–7.02 (m, 3H), 5.97 (t, J = 4.5 Hz, 1H), 5.08 (d, J = 6.3 Hz, 1H), 4.46 (d, J = 6.3 Hz, 1H), 3.64–3.05 (m, 4H), 2.74 (t, J = 8.0 Hz, 2H), 2.32–2.26 (m, 2H), 1.16 (t, J = 7.1 Hz, 3H), 1.06 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ = 171.4 (C), 136.1 (C), 135.8 (C), 132.7 (C), 128.1 (CH), 127.5 (CH), 127.2 (CH), 126.5 (CH), 123.0 (CH), 69.2 (CH), 40.9 (CH₂), 40.3 (CH₂), 27.6 (CH₂), 22.8 (CH₂), 13.3 (CH₃), 12.4 ppm (CH₃); HMS (70 eV): m/z (%): 259 [M^+] (3), 242 (59), 159 (8), 129 (43), 100 (88); HRMS calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_2$: 259.1572; found: 259.1576; IR (neat): $\tilde{\nu}$ = 3387, 1643, 1445 cm^{-1} ; R_f = 0.5 (hexane/AcOEt 1:1); elemental analysis calcd (%) for $\text{C}_{16}\text{H}_{21}\text{NO}_2$: C 74.10, H 8.16, N 5.40; found: C 74.41, H 8.05, N 5.42.

N,N-Diethyl-2-hydroxy-2-methyl-3-phenylbut-3-enamide (2d): ^1H NMR (200 MHz, CDCl_3): δ = 7.44–7.18 (m, 5H), 5.55 (m, 2H), 5.40 (br, 1H), 3.68–3.42 (m, 2H), 3.38–2.81 (m, 2H), 1.65 (s, 3H), 1.04 (t, J = 7.0 Hz, 3H), 0.65 ppm (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ = 173.7 (C), 150.8 (C), 139.6 (C), 127.7 (CH), 127.6 (CH), 127.3 (CH), 114.6 (CH₂), 74.6 (C), 41.1 (CH₂), 40.1 (CH₂), 25.1 (CH₃), 12.3 (CH₃), 11.0 ppm (CH₃); HMS (70 eV): m/z (%): 247 [M^+] (3), 230 (20), 147 (47), 100 (100), 77 (28); HRMS calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_2$: 247.1572; found: 247.1571; IR (neat): $\tilde{\nu}$ = 3346, 1620, 1446 cm^{-1} ; R_f = 0.3 (hexane/AcOEt 3:1); elemental analysis calcd (%) for $\text{C}_{15}\text{H}_{21}\text{NO}_2$: C 72.84, H 8.56, N 5.66; found: C 73.11, H 8.60, N 5.80.

(E)-N,N,3-Triethyl-2-hydroxy-2-methylpent-3-enamide (2e): ^1H NMR (300 MHz, CDCl_3): δ = 5.68 (q, J = 6.8 Hz, 1H), 5.29 (br, 1H), 3.57–3.41 (m, 2H), 3.39–3.23 (m, 2H), 2.19–2.09 (m, 1H), 1.95–1.83 (m, 1H), 1.71 (d, J = 6.8 Hz, 3H), 1.51 (s, 3H), 1.15 (t, J = 7.0 Hz, 3H), 1.11 (t, J = 7.0 Hz, 3H), 1.03 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ = 174.3 (C), 143.2 (C), 120.7 (CH), 76.2 (C), 41.8 (CH₂), 41.0 (CH₂), 23.9 (CH₃), 20.9 (CH₂), 13.9 (CH₃), 13.4 (CH₃), 13.3 (CH₃), 12.2 ppm (CH₃); MS (70 eV): m/z (%): 213 [M^+] (2), 196 (6), 144 (3), 113 (100), 100 (42); HRMS calcd for $\text{C}_{12}\text{H}_{23}\text{NO}_2$: 213.1729; found: 213.1748; IR (neat): $\tilde{\nu}$ = 3384, 1620 cm^{-1} ; R_f = 0.3 (hexane/AcOEt 3:1); elemental analysis calcd (%) for $\text{C}_{12}\text{H}_{23}\text{NO}_2$: C 67.57, H 10.87, N 6.57; found: C 67.32, H 10.80, N 6.72.

(E)-N,N-Diethyl-2-hydroxy-2-methyl-3-phenylpent-3-enamide (2f): ^1H NMR (200 MHz, CDCl_3): δ = 7.32–7.18 (m, 5H), 5.98 (q, J = 6.9 Hz,

1H), 5.40 (br, 1H), 3.84–2.86 (m, 4H), 1.57 (d, J = 6.9 Hz, 3H), 1.55 (s, 3H), 1.15 (t, J = 7.0 Hz, 3H), 0.74 ppm (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ = 173.7 (C), 143.1 (C), 137.1 (C), 129.1 (CH), 127.6 (CH), 126.9 (CH), 123.1 (CH), 75.3 (C), 41.5 (CH₂), 40.3 (CH₂), 24.4 (CH₃), 14.7 (CH₃), 13.4 (CH₃), 11.2 ppm (CH₃); HMS (70 eV): m/z (%): 261 [M^+] (<1), 244 (8), 161 (100), 117 (23), 100 (24); IR (neat): $\tilde{\nu}$ = 3340, 1623, 1442 cm^{-1} ; R_f = 0.3 (hexane/AcOEt 3:1); elemental analysis calcd (%) for $\text{C}_{16}\text{H}_{23}\text{NO}_2$: C 73.53, H 8.87, N 5.36; found: C 73.81, H 8.95, N 5.41.

(E)-N,N-Diethyl-2-hydroxy-2,3-dimethylhepta-3,6-dienamide (2g): ^1H NMR (200 MHz, CDCl_3): δ = 5.91–5.74 (m, 1H), 5.61 (t, J = 7.2 Hz, 1H), 5.33 (br, 1H), 5.09–4.93 (m, 2H), 3.57–3.27 (m, 4H), 2.88–2.82 (m, 2H), 1.59 (s, 3H), 1.54 (s, 3H), 1.18–1.06 ppm (m, 6H); ^{13}C NMR (50 MHz, CDCl_3): δ = 170.4 (C), 137.8 (C), 136.0 (CH), 123.1 (CH), 115.1 (CH₂), 75.6 (C), 41.5 (CH₂), 41.0 (CH₂), 32.2 (CH₂), 23.5 (CH₃), 13.5 (CH₃), 12.7 (CH₃), 12.2 ppm (CH₃); HMS (70 eV): m/z (%): 225 [M^+] (<1), 208 (4), 184 (15), 125 (96), 100 (59); HRMS calcd for $\text{C}_{13}\text{H}_{23}\text{NO}_2$: 225.1729; found: 225.1749; IR (neat): $\tilde{\nu}$ = 3385, 1622 cm^{-1} ; R_f = 0.3 (hexane/AcOEt 3:1); elemental analysis calcd (%) for $\text{C}_{13}\text{H}_{23}\text{NO}_2$: C 69.29, H 10.29, N 6.22; Found: C 68.98, H 10.18, N 6.34.

2-(Cyclohex-1-en-1-yl)-N,N-diethyl-2-hydroxypropanamide (2h): ^1H NMR (200 MHz, CDCl_3): δ = 6.86–5.98 (m, 1H), 5.26 (br, 1H), 3.54–3.17 (m, 4H), 2.03–1.49 (m, 8H), 1.45 (s, 3H), 1.08 ppm (t, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, CDCl_3): δ = 173.7 (C), 138.8 (C), 122.3 (CH), 74.5 (C), 41.1 (CH₂), 40.6 (CH₂), 24.7 (CH₂), 23.5 (CH₂), 23.1 (CH₃), 22.1 (CH₂), 21.6 (CH₂), 13.2 (CH₃), 11.9 ppm (CH₃); MS (70 eV): m/z (%): 225 [M^+] (<1), 208 (5), 125 (100), 100 (51); HRMS calcd for $\text{C}_{13}\text{H}_{23}\text{NO}_2$: 225.1729; found: 225.1759; IR (neat): $\tilde{\nu}$ = 3364, 1621, 1446 cm^{-1} ; R_f = 0.3 (hexane/AcOEt 3:1); elemental analysis calcd (%) for $\text{C}_{13}\text{H}_{23}\text{NO}_2$: C 69.29, H 10.29, N 6.22; found: C 69.40, H 10.18, N 6.41.

(E)-N,N-Diethyl-2-hydroxy-2,3-dimethylnon-3-enamide (2i): ^1H NMR (200 MHz, CDCl_3): δ = 5.57 (t, J = 6.6 Hz, 1H), 5.27 (br, 1H), 3.53–3.20 (m, 4H), 2.09–1.99 (m, 2H), 1.54 (s, 3H), 1.49 (s, 3H), 1.47–0.78 ppm (m, 15H); ^{13}C NMR (75 MHz, CDCl_3): δ = 174.0 (C), 136.2 (C), 126.0 (CH), 75.5 (C), 41.3 (CH₂), 40.8 (CH₂), 31.5 (CH₂), 28.7 (CH₂), 27.7 (CH₂), 23.5 (CH₃), 22.3 (CH₃), 13.8 (CH₃), 13.4 (CH₃), 12.5 (CH₃), 12.1 ppm (CH₃); HMS (70 eV): m/z (%): 255 [M^+] (<1), 238 (4), 155 (67), 100 (35), 57 (28); IR (neat): $\tilde{\nu}$ = 3384, 1623 cm^{-1} ; R_f = 0.3 (hexane/AcOEt 3:1); elemental analysis calcd (%) for $\text{C}_{15}\text{H}_{23}\text{NO}_2$: C 70.54, H 11.45, N 5.48; found: C 70.81, H 11.54, N 5.32.

General procedure for the synthesis of compound 3e: A solution of mercuric chloride (0.2 mmol) in THF (5 mL) was added to a suspension of Sm (2.1 mmol) in THF (5 mL). This mixture was stirred for 10 min and then α -hydroxy- β , γ -unsaturated amide **2e** (0.5 mmol) was added. The mixture was cooled to -78°C , and diiodomethane (2.0 mmol) was added dropwise. The mixture was allowed to warm to RT and stirred for 2 h. The reaction was then quenched with saturated K_2CO_3 and extracted with ethyl ether. The organic layer was washed with brine three times, dried over K_2CO_3 , filtered and concentrated in a vacuum affording the crude compound **3e**, which was purified by flash column chromatography on silica gel (hexane/AcOEt 10/1).

N,N-Diethyl-2-(1-ethyl-2-methylcyclopropyl)-2-hydroxypropanamide (3e): ^1H NMR (200 MHz, CDCl_3): δ = 3.88–3.22 (m, 5H), 1.46–1.02 (m, 11H), 1.02 (s, 3H), 0.95 ppm (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, CDCl_3): δ = 175.4 (C), 77.8 (C), 40.8 (CH₂), 40.5 (CH₂), 30.2 (C), 23.1 (CH₂), 22.8 (CH), 18.8 (CH₃), 16.2 (CH₂), 13.5 (CH₃), 13.3 (CH₃), 12.8 (CH₃), 12.1 ppm (CH₃); HMS (70 eV): m/z (%): 227 [M^+] (<1), 198 (14), 144 (14), 127 (63), 100 (62); IR (neat): $\tilde{\nu}$ = 3385, 1620 cm^{-1} ; R_f = 0.3 (hexane/AcOEt 1:1); elemental analysis calcd (%) for $\text{C}_{13}\text{H}_{25}\text{NO}_2$: C 68.53, H 11.08, N 6.16; found: C 68.70, H 11.19, N 6.27.

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