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The Addition Reaction of Samarium Enolates and 2-Haloenolates Derived from Esters, and Amides to Imines. Totally Stereoselective Synthesis of Enantiopure 3,4-Diamino Esters or Amides

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Abstract: The addition reaction of samarium enolates and 2-haloenolates derived from esters and amides to imines takes place in an efficient manner. A novel protocol to perform the addition reaction of samarium enolates derived from esters or amides to chiral 2-aminoimines, with total stereoselectivity and without racemization, is also reported. The use of samarium enolates in place of other classic metallic enolates (lithium, magnesium, etc.) could be a valuable alternative to obtain enantiopure 3,4-diamino esters or amides, when enolates of low basicity are necessary.

Keywords: addition to carbonyl compounds; enolates; imines; Mannich reaction; samarium

Introduction

3-Amino acid derivatives[1] are important starting materials in organic synthesis,[2] and their functionality is present in compounds with biological[3] or pharmacological[4] activity. In addition, their peptides[5] are present in several drugs.[6]

For this reason, many syntheses of 3-amino acids and their derivatives have been reported.[7] In particular, the Mannich-type reaction (the addition reaction of enolates of acid derivatives to imines) constitutes a method of choice in many cases due to its generality and versatility. Generally, the Mannich reaction is performed using activated aldimines (for example, derived from tosylamides or alkanesulfonamides) and lithium enolates. In recent years, much effort has been focused on the development of novel reagents to perform this transformation under milder reaction conditions and to enhance the generality of the reaction. Thus, alternative, more reactive imines or enolates derived from other metals, without the drawbacks of lithium enolates have been reported. Hence, to overcome the limitations derived from the high basicity, other alternative, less basic enolates derived from metals other than lithium have been developed. In this sense, samarium enolates[8] could be a valuable alternative to the use of lithium enolates due to their lower basicity.

Recently, we have communicated the first protocol to carry out the Mannich reaction with samarium enolates.[9] Here, a range of various 3-amino esters or amides were prepared by the reaction of samarium enolates with imines derived from *p*-toluenesulfonamide. In the same communication, we also reported the reaction of samarium enolate of ethyl acetate with the chiral 2-aminoimine readily available from phenylalaninal and (*R*)-2-methyl-2-propanesulfinamide. Here, the corresponding enantiopure 3,4-diamino ester was obtained with total stereoselectivity and without racemization.

Now, in this paper, our objective is to report the generalization of those previous results and to describe novel addition reactions of samarium enolates to imines. The study of the reaction of samarium enolates with prochiral imines has been completed, and the stereoselective synthesis of enantiopure 3,4-diamino esters has been generalized by preparing two additional examples. The hitherto unreported Mannich reaction of samarium 2-haloenolates of esters or amides and the totally stereoselective synthesis of enantio-

pure 3,4-diamino amides by reaction of samarium enolates from amides with chiral 2-aminoimines is also described.

Firstly, the results obtained from the addition reaction of samarium enolates from esters and amides, or from 2-halo esters and amides to prochiral imines will be described. The chiral version of this samarium-Mannich reaction will additionally be discussed.

Results and Discussion

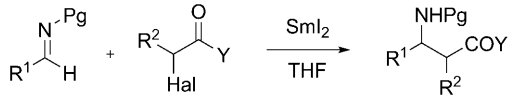
We have previously developed the addition reaction of samarium enolates derived from esters or amides to a range of imines **1** derived from *p*-toluenesulfonamide or benzenesulfonamide. Imines **1** were prepared following a method previously reported in the literature[10] and samarium enolates were prepared under Barbier-type conditions. Thus, the treatment of a solution of the corresponding imine **1** and the 2-halo ester or amide **2** (1 equiv.) in THF at ambient temperature with a solution of 2.5 equiv. of SmI_2 in THF (0.1 M)[11] afforded, after 3.5 h, the 3-amino esters **3** or amides **4** shown in Table 1.

In the case of aldimines derived from benzaldehyde **1e** or phenylacetaldehyde **1f**, by-products derived from the pinacol coupling of the starting aldimines were obtained. To overcome this problem, the samarium enolate was pre-generated (in the absence of the aldimine **1**) by treating the corresponding 2-halo ester **2** with SmI_2 at −20 °C for 30 min. Then, the corresponding imine **1e** or **1f** was added dropwise, and the mixture was stirred for 30 min at the same temperature and for an additional 3.5 h at ambient temperature. The amino esters **3e**, **f** were then obtained in good yields, as shown in Table 1. A similar protocol was followed in the synthesis of products **4h**, **i** derived from *p*-chloro- and *p*-methoxybenzaldimine.

In general terms, as can be seen in Table 1, it is possible to conclude that: (1) the addition reaction of samarium enolates derived from esters or amides is general thus, aliphatic (linear, cyclic, or branched) and aromatic (differently substituted) aldimines **1** can be employed as starting materials. When the starting halo compounds **2** ($R^2 \neq H$) lead to the formation of a diastereoisomeric mixture, the *dr* ranged between 1:1 and 3:1. (2) The 3-amino acids were obtained in good to high yields and, as can be observed in Table 1, higher yields (~10–20% higher) were obtained from amides (entries 7–17) than from esters (entries 1–6). (3) Bromo or chloro derivatives **2** can be utilized as starting materials (Table 1, entries 1–3, and 4–17). (4) The reaction has also been carried out on *N*-benzenesulfonylimines (Table 1, entries 13, and 14) and no differences were observed when compared with the reaction of *N*-tosylimines **1**.

Taking into account the fact that amides derived from morpholine can be readily transformed into ke-

Table 1. Synthesis of 3-amino esters and amides **3** and **4**.

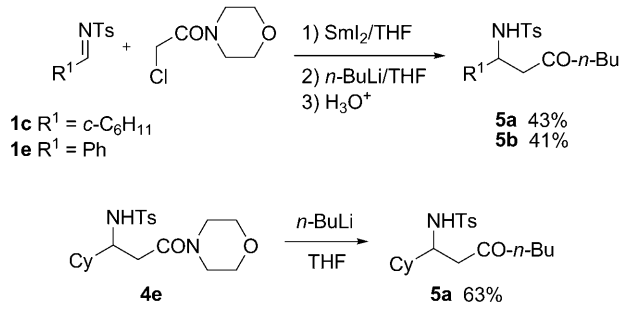


1 **2** **3/4**

Entry	1	3/4	R^1	R^2	Hal	Pg	Y	Yield [%][a]
1	**1a**	**3a**	$PhCH_2CH_2$	H	Br	Ts	OEt[c]	69
2	**1b**	**3b**	*s*-Bu	H	Br	Ts	OEt[c]	63
3	**1c**	**3c**	*c*-C_6H_{11}	H	Br	Ts	OEt[c]	67
4	**1d**	**3d**	*n*-C_7H_{15}	Me	Cl	Ts	OEt	67
5	**1e**	**3e**	Ph	Me	Cl	Ts	OEt	60
6	**1f**	**3f**	$PhCH_2$	*n*-C_5H_{11}	Cl	Ts	OEt	61
7	**1d**	**4a**	*n*-C_7H_{15}	H	Cl	Ts	–[b]	84
8	**1a**	**4b**	$PhCH_2CH_2$	H	Cl	Ts	NEt_2	81
9	**1a**	**4c**	$PhCH_2CH_2$	H	Cl	Ts	–[b]	80
10	**1c**	**4d**	*c*-C_6H_{11}	H	Cl	Ts	NEt_2	84
11	**1c**	**4e**	*c*-C_6H_{11}	H	Cl	Ts	–[b]	85
12	**1e**	**4f**	Ph	H	Cl	Ts	NEt_2	80
13	**1g**	**4g**	*p*-ClC_6H_4	H	Cl	$PhSO_2$	[b]	56
14	**1h**	**4h**	*p*-$MeOC_6H_4$	H	Cl	$PhSO_2$	–[b]	51
15	**1f**	**4i**	$PhCH_2$	Me	Cl	Ts	–[b]	74
16	**1b**	**4j**	*s*-Bu	Me	Cl	Ts	–[b]	73
17	**1d**	**4k**	*n*-C_7H_{15}	Ph	Cl	Ts	–[b]	73

[a] Isolated yield after column chromatography based on compounds **1**.
[b] From morpholine amide.

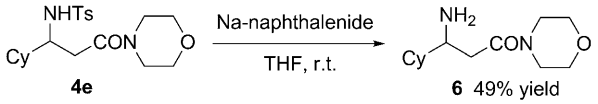
tones by reaction with organolithium reagents,[12] a sequential synthesis of *n*-butyl ketones **5** was carried out from **1c** and **1e**. Thus, the successive treatment of *N*-tosylimines **1c** and **1e** with the samarium enolate derived from 2-chloro-1-morpholinoethanone and subsequently, with *n*-butyllithium at −78 °C for 1 h afforded 3-amino ketones **5a**, **b** in 43 and 41% yield, respectively. When the same reaction was performed from the isolated product **4e** (Scheme 1), a similar



Scheme 1. Synthesis of 3-amino ketones **5**.

yield of *n*-butyl ketone **5a** was obtained (63% yield).

Furthermore, the *N*-substituent on the 3-amino amide **4e** could be easily removed by using sodium naphthalenide, following a method previously reported,[13] furnishing deprotected 3-amino amide **6** in 49% isolated yield after purification (Scheme 2).



Scheme 2. Deprotection of *N*-tosyl-3-amino amide **4e**.

Synthesis of 3-Amino-2-Halo Acid Derivatives 7 and 8

Due to the synthetic possibilities of a C-halogen placed on the α-carbon of a carbonyl group and to generalize the reaction, efforts were next directed towards the synthesis of 3-amino-2-halo esters **7** or amides **8**.

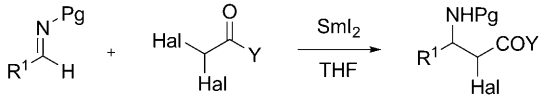
Thus, under similar conditions to those developed for the addition of samarium enolates derived from esters or amides we performed the addition of the corresponding samarium haloenolates. The results are summarized in Table 2.

In a similar manner to the synthesis of compounds **3** and **4**, the addition of haloenolates was general, and no differences were observed in their addition reactions to linear, branched, cyclic aliphatic and aromatic imines. In all these cases, the corresponding 3-amino-2-halo esters or amides were obtained in good to high yields (>51%, after purification by column chromatography). The synthesis of compounds **7b** and **7c** demonstrated that the process was also tolerant to the presence of halogens other than chlorine. As was observed in compounds **3d–f**, and **4i, k**, the 3-amino-2-halo esters **7** and amides **8** were obtained with the *dr* ranging between 1:1 and 3:1.

Synthesis of Enantiopure (3*R*,4*S*)-3,4-Diamino Esters and Amides 10 and 11

3,4-Diamino acids[14] are important compounds due to their pharmacological activity[15] and since they can modify the biological properties of small peptides.[16] From a synthetic point of view, 3,4-diamino acid derivatives are precursors to various interesting organic compounds, such as 2-aminopyrrolidinones or 3-ami-

Table 2. Synthesis of 3-amino-2-halo esters **7** and amides **8**.



Entry	1	7/8	R^1	Hal	Pg	Y	Yield [%][a]
1	**1c**	**7a**	*c*-C_6H_{11}	Cl	Ts	OMe	56
2	**1c**	**7b**	*c*-C_6H_{11}	Br	Ts	OEt	65
3	**1e**	**7c**	Ph	Br	Ts	OEt	68
4	**1d**	**8a**	*n*-C_7H_{15}	Cl	Ts	–[b]	64
5	**1b**	**8b**	*s*Bu	Cl	Ts	NEt_2	63
6	**1c**	**8c**	*c*-C_6H_{11}	Cl	Ts	NEt_2	66
7	**1a**	**8d**	$PhCH_2CH_2$	Cl	Ts	–[b]	60
8	**1g**	**8e**	*p*-ClC_6H_4	Cl	$PhSO_2$	–[b]	54
9	**1h**	**8f**	*p*-$MeOC_6H_4$	Cl	$PhSO_2$	–[b]	51

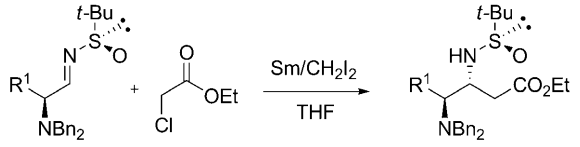
[a] Isolated yield after column chromatography based on compounds **1**.
[b] From morpholine amide.

nopyrrolidines.[17] Despite these applications, only a few preparative methods have been reported,[17,18] and most of these employ multi-step reactions that afford the desired compounds in low overall yields.

We initially performed the synthesis of the enantiopure 3,4-diamino esters by reaction of the samarium ester enolate with the tosylimine derived from *N,N*-dibenzylphenylalaninal.[19] Unfortunately, the addition reaction of the ester samarium enolate afforded the expected 3,4-diamino ester in only 5% yield. In order to improve the yields, we changed the protecting group on the iminic nitrogen. Thus, two changes in the reaction were made: we prepared the imine **9c** by reaction of phenylalaninal with (*R*)-2-methyl-2-propanesulfinamide[20] and the samarium diiodide was generated *in situ*, from a mixture of Sm/CH_2I_2.[21] Thus, the addition of diiodomethane to a mixture of imine **9c** [derived from phenylalaninal, and (*R*)-2-methyl-2-propanesulfinamide], ethyl chloroacetate and samarium powder in THF at 0 °C, and further stirring at ambient temperature for 6 h, afforded the corresponding diamino ester **10c** in 55% yield and as a single diastereoisomer (*dr* > 98/2) (Table 3). The scope of this process was subsequently studied by carrying out the reaction with the tosylimines derived from alaninal and leucinal. The entries in Table 3 demonstrate that, in all cases, similar results were obtained.

Based on the results of the synthesis of 3,4-diamino esters **10**, we tested the synthesis of enantiopure 3,4-diamino amides **11**. Using the same reaction conditions as those used to prepare compounds **10**, enantiopure compounds **11** were obtained as a single diastereoisomer in good yields. The obtained results are summarized in Table 4.

Table 3. Synthesis of enantiopure 3,4-diamino esters **10**

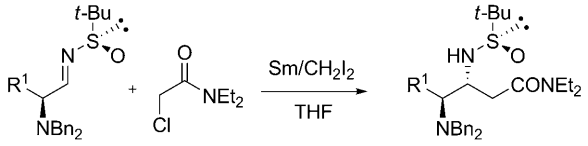


9 **10** *dr* > 98/2

Entry	9	10	R^1	Yield[%][a]
1	**9a**	**10a**	Me	51
2	**9b**	**10b**	*i*-$PrCH_2$	50
3	**9c**	**10c**	$PhCH_2$	55

[a] Isolated yield after column chromatography based on imine **9**.

Table 4. Synthesis of enantiopure 3,4-diamino amides **11**



9 **11** *dr* > 98/2

Entry	9	11	R^1	Yield [%][a]
1	**9a**	**11a**	Me	53
2	**9b**	**11b**	*i*-$PrCH_2$	52
3	**9c**	**11c**	$PhCH_2$	62

[a] Isolated yield after column chromatography based on imine **9**.

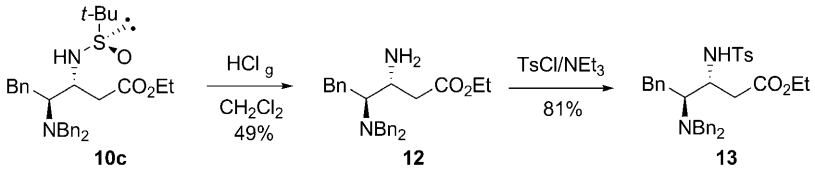
The method for the synthesis of 3,4-diamino acid derivatives **10** and **11** is general and similar results were observed during the synthesis of 3,4-amino ester or amino amide derivatives.

The total stereoselectivity (*dr* > 98/2) of the addition reaction was established on the basis of ^{1}H NMR data of crude reaction products **10** or **11**, which revealed the presence of only one stereoisomer. The absence of the other stereoisomer also proved that no racemization took place in the reaction.

The absolute configuration of the 3,4-diamino esters **10** was established after transformation of **10c** into ethyl (3*R*,4*S*)-5-phenyl-4-(*N,N*-dibenzylamino)-3-(tosylamino)pentanoate **13**, following the synthetic pathway described (Scheme 3). The spectroscopic data of **13** were identical to those reported for the same product, previously prepared and characterized (X-ray analysis) by Reetz.[22]

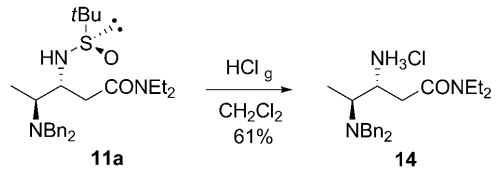
In the case of 3,4-diamino amides **11** the absolute configuration was determined after a deprotection protocol. Hence, after bubbling a stream of HCl to a solution of (3*R*,4*S*)-4-(dibenzylamino)-*N,N*-diethyl-3-[(*R*)-*tert*butanesulfinamide]pentanamide **11a** in dichloromethane, (3*R*,4*S*)-3-amino-4-(dibenzylamino)-*N,N*-diethylpentanamide **14** was isolated as the hydrochloride salt after recrystallization (Scheme 4).

The single-crystal X-ray analysis of compound **14**[23] unambiguously confirmed the absolute configuration of amide **11a**. The absolute configurations of the



10c **12** **13**

Scheme 3. Synthesis of enantiopure 3,4-diamino esters **12** and **13**.



Scheme 4. Deprotection of 3,4-diamino amide **11a**

other 3,4-diamino amides **11b** and **11c** were assigned by correlation.

The absolute configuration of 3,4-diamino esters or amides **10** and **11** is in agreement with that obtained in the previously reported addition of organometallic reagents to 2-dibenzylamino aldehydes,[24] chloromethyl ketones[24] and the reduction of chloromethylketimines.[25] Thus, the stereochemical course of the addition reaction of the samarium enolate **15** could be controlled by the bulky dibenzylamino group. In this case, the addition of samarium enolate to imine **9** could take place under non-chelation control in which the most favoured transition state has the larger substituent (dibenzylamino group) *anti* to the attack of the samarium enolate (Scheme 5). A similar stereochemical course was observed in the addition of other anions to *N*-(3-phenyl-2-dibenzylaminopropylidene)-*tert*-butanesulfilamide.[20,26]

Conclusions

In conclusion, the use of samarium enolates as a valuable alternative to lithium enolates in the Mannich reaction, in special using enantiopure aldimines with high proclivity to racemize, has been proved.

Thus, the addition reaction of samarium enolates (derived from esters, amides, 2-bromo or 2-chloro esters and 2-chloro amides) to prochiral aldimines was carried out in an efficient manner. In addition, enantiopure (3*R*,4*S*)-diamino esters or amides were obtained without racemization and with total stereoselectivity from enolizable chiral 2-aminoaldimines.

The addition reaction of samarium enolates to other compounds with high proclivity to enolize are currently under study in our laboratory.

Experimental Section

General Procedure for the Synthesis of Compounds 1

Imines **1** were synthesized following the method reported in ref.[10] Imine **1a** displayed analytical data in accordance with the published values in ref.[9] Imines **1b–h** displayed analytical data in accordance with the published values.[27]

General Procedure for the Synthesis of Compounds 3 and 4

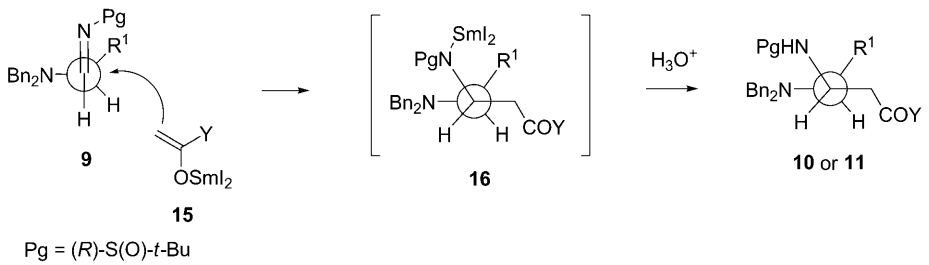
To a stirred solution of the requisite imine **1** (0.4 mmol) and 2-halo ester or amide **2** (0.4 mmol) in THF (2 mL), a solution of SmI_2 in THF (10 mL, 2.5 equiv., 1.0 mmol) was added at ambient temperature. After stirring at the same temperature for 3.5 h, the excess of SmI_2 was removed by bubbling a stream of air through the solution. An aqueous solution of 0.1 N HCl (10 mL) was then added and the aqueous phase was extracted with diethyl ether (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Flash column chromatography on silica gel (hexane/EtOAc, 3:1) provided pure compounds **3** or **4**.

In the case of compounds **3e** and **3f**, the samarium enolate was pre-formed at −20 °C and the imine **1e** or **1f** was added subsequently. The reaction mixture was stirred at the same temperature for 30 min and then it was left to warm to ambient temperature for 3 h. After the corresponding hydrolysis and the purification, the products **3e** and **3f** were isolated pure.

For amino esters **3a–f** and amino amides **4b**, **4e**, **4f**, **4i–k** spectroscopic data have been reported in ref.[9]

1-Morpholino-3-(tosylamino)decan-1-one (4a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 5.77 (d, J = 8.6 Hz, 1H), 3.64–3.51 (m, 8H), 3.35–3.30 (m, 1H), 2.49 (dd, J = 16.1, 4.0 Hz, 1H), 2.41 (s, 3H), 2.38 (dd, J = 16.1, 6.0 Hz, 1H), 1.55–1.45 (m, 2H), 1.42–0.75 (m, 10H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.2 (C), 143.0 (C), 138.1 (C), 129.4 (2CH), 127.0 (2CH), 66.6 (CH_2), 66.3 (CH_2), 51.1 (CH), 45.7 (CH_2), 41.5 (CH_2), 36.6 (CH_2), 34.5 (CH_2), 31.5 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 25.9 (CH_2), 22.5 (CH_2), 21.3 (CH_3), 13.9 (CH_3); MS (70 eV, EI): m/z (%) = 410 (M^+, <1), 311 (17), 255 (100), 155 (25), 114 (57), 91 (71); HR-MS (70 eV); m/z = 311.1060, calcd. for $C_{14}H_{19}N_2O_4S$ ($M^+-C_7H_{15}$): 311.1065, IR (neat): ν = 1614, 1442, 1266, 1160, 738 cm^{-1}; R_f = 0.75 (hexane/EtOAc 1:1).

1-Morpholino-5-phenyl-3-(tosylamino)pentan-1-one (4c): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.3 Hz, 2H),



Scheme 5. Mechanism of the addition to aminoaldimines **9**.

7.31–7.14 (m, 5H), 7.03 (d, $J=8.3$ Hz, 2H), 5.88 (d, $J=6.8$ Hz, 1H), 3.58–3.44 (m, 7H), 3.27–3.16 (m, 2H), 2.65–2.58 (m, 1H), 2.49–2.41 (m, 1H), 2.43 (s, 3H), 2.40–2.38 (m, 2H), 2.02–1.93 (m, 1H), 1.84–1.75 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=169.0$ (C), 143.1 (C), 141.0 (C), 138.2 (C), 129.5 (2CH), 128.2 (4CH), 127.0 (2CH), 125.8 (CH), 66.5 (CH_2), 66.2 (CH_2), 50.7 (CH), 45.6 (CH_2), 41.5 (CH_2), 36.4 (CH_2), 36.0 (CH_2), 32.1 (CH_2), 21.4 (CH_3); MS (ESI$^+$): m/z (%) = 439 ([M+Na]$^+$, 22), 417 ([M+H]$^+$, 100); HR-MS (70 eV): $m/z=311.1059$, calcd. for $C_{14}H_{19}N_2O_4S$ ($M^+-PhCH_2CH_2$): 311.1065; IR (neat): $\nu=2923$, 1628, 1456, 1159, 736 cm^{-1}; $R_f=0.15$ (hexane/EtOAc, 1:1).

3-Cyclohexyl-*N,N*-diethyl-3-(tosylamino)propanamide (4d): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.74$ (d, $J=8.0$ Hz, 2H), 7.26 (d, $J=8.0$ Hz, 2H), 6.21 (d, $J=8.9$ Hz, 1H), 3.29–3.10 (m, 5H), 2.48–2.40 (m, 1H), 2.40 (s, 3H), 2.19 (dd, $J=16.3$, 5.3 Hz, 1H), 1.86–1.49 (m, 6H), 1.08–0.69 (m, 5H), 1.06 (t, $J=7.1$ Hz, 3H), 1.03 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=170.1$ (C), 142.7 (C), 138.5 (C), 129.4 (2CH), 127.0 (2CH), 56.2 (CH), 41.9 (CH_2), 40.5 (CH), 40.0 (CH_2), 32.4 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 26.1 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 21.4 (CH_3), 14.0 (CH_3), 12.8 (CH_3); MS (70 eV, EI): m/z (%) = 380 (M^+, <1), 297 (52), 225 (37), 100 (100), 91 (36), 72 (38); HR-MS (70 eV): $m/z=380.2146$, calcd. for $C_{20}H_{32}N_2O_3S$: 380.2134; IR (neat): $\nu=2931$, 1624, 1266, 1162, 738 cm^{-1}; $R_f=0.22$ (hexane/EtOAc, 2:1).

3-(Benzenesulfonylamino)-3-(4-chlorophenyl)-1-morpholinopropan-1-one (4g): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.68$ (d, $J=7.3$ Hz, 2H), 7.48 (t, $J=7.3$ Hz, 1H), 7.36 (t, $J=7.3$ Hz, 2H), 7.12 (d, $J=8.5$ Hz, 2H), 7.06 (d, $J=8.5$ Hz, 2H), 6.73 (d, $J=7.3$ Hz, 1H), 4.72 (q, $J=5.6$ Hz, 1H), 3.56–3.34 (m, 6H), 3.28–3.14 (m, 2H), 2.82 (dd, $J=15.7$, 5.6 Hz, 1H), 2.67 (dd, $J=15.7$, 5.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=168.4$ (C), 140.3 (C), 138.2 (C), 133.3 (C), 132.3 (CH), 128.7 (2CH), 128.4 (2CH), 128.1 (2CH); 126.9 (2CH), 66.5 (CH_2), 66.1 (CH_2), 54.1 (CH), 45.9 (CH_2), 41.7 (CH_2), 38.5 (CH_2); MS (ESI$^+$): m/z (%) = 433 ([M(^{37}Cl)+Na]$^+$, 17), 431 ([M(^{35}Cl)+Na]$^+$, 19), 411 ([M(^{37}Cl)+H]$^+$, 39), 409 ([M(^{35}Cl)+H]$^+$, 100); HR-MS (70 eV): $m/z=280.0209$, calcd. for $C_{13}H_{11}ClNO_2S$ ($M^+-C_6H_{10}NO_2$): 280.0199; IR (neat): $\nu=2860$, 1622, 1447, 1266, 1162 cm^{-1}; $R_f=0.40$ (EtOAc).

3-(Benzenesulfonylamino)-3-(4-methoxyphenyl)-1-morpholinopropan-1-one (4h): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.69$ (d, $J=7.4$ Hz, 2H), 7.46 (t, $J=7.4$ Hz, 1H), 7.35 (t, $J=7.4$ Hz, 2H), 7.02 (d, $J=8.7$ Hz, 2H), 6.67 (d, $J=8.7$ Hz, 2H), 6.59 (d, $J=6.9$ Hz, 1H), 4.68 (q, $J=5.9$ Hz, 1H), 3.72 (s, 3H), 3.59–3.09 (m, 8H), 2.83 (dd, $J=15.3$, 5.9 Hz, 1H), 2.64 (dd, $J=15.3$, 5.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=168.7$ (C), 158.9 (C), 140.5 (C), 132.1 (CH), 131.6 (C), 128.6 (2CH), 127.7 (2CH), 127.0 (2CH); 113.7 (2CH), 66.4 (CH_2), 66.1 (CH_2), 55.1 (CH_3), 54.3 (CH), 45.9 (CH_2), 41.6 (CH_2), 38.7 (CH_2); MS (ESI$^+$): m/z (%) = 427 ([M+Na]$^+$, 10), 405 ([M+H]$^+$, 21), 248 (100); HR-MS (70 eV): $m/z=276.0692$, calcd. for $C_{14}H_{14}NO_3S$ ($M^+-C_6H_{10}NO_2$): 276.0694; IR (neat): $\nu=2962$, 1616, 1515, 1446, 1265 cm^{-1}; $R_f=0.35$ (EtOAc).

General Procedure for the Synthesis of Compounds 5

To a stirred solution of the requisite imine **1** (0.4 mmol) and 2-chloro-1-morpholinoethanone (0.4 mmol) in THF (2 mL), a solution of SmI_2 in THF (10 mL, 2.5 equiv., 1.0 mmol) was added at ambient temperature. After stirring at the same temperature for 3.5 h, the reaction mixture was cooled at −78 °C and *n*-BuLi (1.6 mmol) was added dropwise. After stirring for an additional hour at −78 °C, the reaction mixture was quenched with an aqueous solution of 0.1 N HCl (10 mL) and the aqueous phase was extracted with diethyl ether (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Flash column chromatography on silica gel (hexane/EtOAc, 3:1) provided pure compounds **5**.

Spectroscopic data for amino ketone **5a** have been reported in ref.[9]

1-Phenyl-1-(tosylamino)heptan-3-one (5b): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.59$ (d, $J=8.2$ Hz, 2H), 7.18–7.07 (m, 7H), 5.75 (d, $J=7.2$ Hz, 1H), 4.67–4.60 (m, 1H), 2.98 (dd, $J=17.0$, 5.6 Hz, 1H), 2.84 (dd, $J=17.0$, 6.2 Hz, 1H), 2.37 (s, 3H), 2.22 (t, $J=7.3$ Hz, 2H), 1.39 (quintuplet, $J=7.3$ Hz, 2H), 1.16 (sixtuplet, $J=7.3$ Hz, 2H), 0.80 (t, $J=7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=209.1$ (C), 143.1 (C), 139.7 (C), 137.2 (C), 129.3 (2CH), 128.4 (2CH), 127.5 (CH), 127.1 (2CH), 126.5 (2CH), 54.1 (CH), 48.5 (CH_2), 43.3 (CH_2), 25.3 (CH_2), 22.0 (CH_2), 21.4 (CH_3), 13.6 (CH_3); MS (70 eV, EI): m/z (%) = 359 (M^+, <1), 260 (37), 204 (87), 155 (44), 120 (40), 91 (100); HR-MS (70 eV): $m/z=359.1565$, calcd. for $C_{20}H_{25}NO_3S$: 359.1555; IR (neat): $\nu=2950$, 1713, 1456, 1160, 738 cm^{-1}; $R_f=0.25$ (hexane/EtOAc, 3:1).

Synthesis of 6 from 4e

Deprotection of compound **4e** was carried out by using the conditions described in ref.[13] Spectra and analytical data of compound **6** have been reported in ref.[9]

General Procedure for the Synthesis of Compounds 7 and 8

To a stirred solution of the requisite imine **1** (0.4 mmol) and 2,2-dihalo ester or amide **2** (0.4 mmol) in THF (2 mL), a solution of SmI_2 in THF (10 mL, 2.5 equiv., 1.0 mmol) was added at 0 °C. After stirring at the same temperature for 2 h, the excess of SmI_2 was removed by bubbling a stream of air through the solution. An aqueous solution of 0.1 N HCl (10 mL) was then added, and the aqueous phase was extracted with diethyl ether (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Flash column chromatography on silica gel (hexane/EtOAc, 3:1) provided pure compounds **7** or **8**.

In the case of compound **7c**, the samarium enolate was pre-formed at −20 °C, and the imine **1e** was added subsequently. The reaction mixture was stirred at the same temperature for 30 min, and then it was left at 0 °C for 2 h. After the corresponding hydrolysis and purification by flash column chromatography, the product **7c** was isolated in the pure state.

Methyl 2-chloro-3-cyclohexyl-3-(tosylamino)propanoate (7a): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.76$ (d, $J=8.1$ Hz, 2H), 7.72 (d, $J=8.3$ Hz, 2H), 7.29–7.26 (m, 4H), 5.36 (d, $J=9.3$ Hz, 1H), 5.08 (d, $J=9.8$ Hz, 1H), 4.56 (d, $J=2.7$ Hz, 1H), 4.41 (d, $J=4.4$ Hz, 1H), 3.82–3.71 (m, 2H), 3.70 (s, 3H), 3.56 (s, 3H), 2.40 (s, 6H), 1.78–1.47 (m, 10H), 1.14–

0.99 (m, 8H), 0.91–0.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.4 (C), 167.9 (C), 143.2 (C), 143.1 (C), 138.4 (C), 138.0 (C), 129.4 (2CH), 129.3 (2CH), 126.9 (2CH), 126.8 (2CH), 60.8 (CH), 60.7 (CH), 59.9 (CH), 58.7 (CH), 53.0 ($2CH_2$), 40.1 (CH), 39.9 (CH), 29.7 (CH_2), 29.4 (CH_2), 29.0 (CH_2), 28.5 (CH_2), 25.8 (CH_2), 25.7 ($5CH_2$), 21.3 ($2CH_3$); HR-MS (ESI$^+$): m/z=374.1187, calcd. for $C_{17}H_{25}ClNO_4S$ $(M+H)^+$: 374.1193; IR (neat): ν=1756, 1449, 1332, 1160, 738 cm^{-1}; R_f=0.32 (hexane/EtOAc, 3:1).

Ethyl 2-bromo-3-cyclohexyl-3-(tosylamino)propanoate (7b): ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.77 (d, J=8.4 Hz, 2H), 7.74 (d, J=8.4 Hz, 2H), 7.29–7.26 (m, 4H), 5.51 (d, J=9.5 Hz, 1H), 4.92 (d, J=9.8 Hz, 1H), 4.51 (d, J=3.6 Hz, 1H), 4.39 (d, J=4.3 Hz, 1H), 4.13 (q, J=7.1 Hz, 2H), 4.07–3.94 (m, 2H), 3.74–3.65 (m, 2H), 2.41 (s, 6H), 1.81–1.45 (m, 10H), 1.26 (t, J=7.1 Hz, 3H), 1.24 (t, J=7.1 Hz, 3H), 1.23–0.71 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.5 (C), 167.3 (C), 143.0 (2C), 138.5 (C), 138.4 (C), 129.2 (4CH), 127.0 (2CH), 126.9 (2CH), 62.6 (CH_2), 62.3 (CH_2), 61.0 (CH), 60.4 (CH), 51.7 (CH), 46.9 (CH), 41.5 (CH), 41.1 (CH), 30.0 (CH_2), 29.6 (CH_2), 28.9 (CH_2), 28.6 (CH_2), 25.9 ($2CH_2$), 25.7 ($2CH_2$), 25.6 ($2CH_2$), 21.4 ($2CH_3$), 13.7 (CH_3), 13.6 (CH_3); MS (ESI$^+$): m/z (%)=456 ([M(^{81}Br)+Na]$^+$, 30), 454 ([M(^{79}Br)+Na]$^+$, 32), 434 ([M(^{81}Br)+H]$^+$, 100), 432 ([M(^{79}Br)+H]$^+$, 99), 352 (12), 181 (9); HR-MS (ES): m/z=432.0838, calcd. for $C_{18}H_{27}BrNO_4S$ $(M+H)^+$: 432.0844; IR (neat): ν=1735, 1449, 1333, 1160, 738 cm^{-1}; R_f=0.25 (hexane/EtOAc, 3:1).

Ethyl 2-bromo-3-phenyl-3-(tosylamino)propanoate (7c): ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.57 (d, J=8.4 Hz, 2H), 7.53 (d, J=8.4 Hz, 2H), 7.19–7.08 (m, 14H), 6.30 (d, J=9.1 Hz, 1H), 5.70 (d, J=7.1 Hz, 1H), 4.90–4.84 (m, 2H), 4.45 (d, J=2.9 Hz, 1H), 4.43 (d, J=4.7 Hz,1H), 4.15–4.04 (m, 2H), 4.03–3.94 (m, 2H), 2.33 (s, 6H), 1.15 (t, J=7.1 Hz, 3H), 1.08 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.2 (C), 166.7 (C), 143.3 (C), 143.1 (C), 137.4 (C), 137.0 (C), 136.4 (C), 136.0 (C), 129.2 (2CH), 129.1 (2CH), 128.5 (2CH), 128.3 (2CH), 128.2 (2CH), 127.4 (2CH), 127.1 (2CH), 127.0 (2CH), 126.9 (2CH), 62.4 (CH_2), 62.3 (CH_2), 60.0 (CH), 59.7 (CH), 50.7 (CH), 46.5 (CH), 21.3 ($2CH_3$), 13.6 ($2CH_3$); MS (ESI$^+$): m/z (%)=450 ([M(^{81}Br)+Na]$^+$, 34), 448 ([M(^{79}Br)+Na]$^+$, 35), 428 ([M(^{81}Br)+H]$^+$, 96), 426 ([M(^{79}Br)+H]$^+$, 100), 255 (26), 257 (25); HR-MS (ESI$^+$): m/z=448.0189, calcd. for $C_{18}H_{20}BrNNaO_4S$ $(M+Na)^+$: 448.0194; IR (neat): ν=3056, 1733, 1265, 1162, 738 cm^{-1}; R_f=0.28 (hexane/EtOAc, 3:1).

2-Chloro-1-morpholino-3-(tosylamino)decan-1-one (8a): ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.76 (d, J=8.2 Hz, 4H), 7.28 (d, J=8.2 Hz, 4H), 6.04 (d, J=8.5 Hz , 1H), 5.79 (d, J=8.5 Hz, 1H), 4.80 (d, J=3.5 Hz, 1H), 4.68 (d, J=3.5 Hz, 1H), 3.72–3.50 (m, 18H), 2.42 (s, 6H), 1.71–1.45 (m, 4H), 1.32–0.92 (m, 20H), 0.86 (t, J=7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=166.0 (2C), 143.2 (2C), 138.1 (2C), 129.5 (4CH), 126.9 (4CH), 66.5 ($2CH_2$), 66.4 ($2CH_2$), 56.8 (2CH), 56.1 (2CH), 46.5 ($2CH_2$), 42.5 ($2CH_2$), 31.6 ($2CH_2$), 31.5 ($2CH_2$), 29.0 ($2CH_2$), 28.9 ($2CH_2$), 25.8 ($2CH_2$), 22.4 ($2CH_2$), 21.4 ($2CH_3$), 13.9 ($2CH_3$); MS (ESI$^+$): m/z (%)=469 ([M(^{37}Cl)+Na]$^+$, 10), 467 ([M(^{35}Cl)+Na]$^+$, 25), 447 ([M(^{37}Cl)+H]$^+$, 42), 445 ([M(^{35}Cl)+H]$^+$, 100); HR-MS (70 eV): m/z=444.1849, calcd. for *para* $C_{21}H_{33}ClN_2O_4S$: 444.1850; IR (neat): ν=1648, 1438, 1266, 1159, 738 cm^{-1}; R_f=0.55 (hexane/EtOAc, 1:1).

2-Chloro-*N*,*N*-diethyl-4-methyl-3-(tosylamino)hexanamide (8b): ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.73 (d, J=8.4 Hz, 4H), 7.20 (d, J=8.4 Hz, 4H), 7.14 (d, J=8.6 Hz, 1H), 6.97 (d, J=8.8 Hz, 1H), 4.46 (d, J=3.5 Hz, 1H), 4.43 (d, J=3.6 Hz, 1H), 3.73–3.60 (m, 2H), 3.47–3.16 (m, 8H), 2.36 (s, 6H), 1.72–1.52 (m, 2H), 1.50–1.35 (m, 1H), 1.25–0.98 (m, 15H), 0.95–0.81 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=167.7 (2C), 142.3 (2C), 139.3 (2C), 128.9 (4CH), 126.9 (4CH), 62.9 (CH), 62.0 (CH), 51.0 (CH), 50.0 (CH), 42.3 ($2CH_2$), 40.8 ($2CH_2$), 39.2 (CH), 38.8 (CH), 26.5 (CH_2), 26.1 (CH_2), 21.3 ($2CH_3$), 15.6 (CH_3), 15.5 (CH_3), 14.3 (CH_3), 14.2 (CH_3), 12.1 ($2CH_3$), 11.3 ($2CH_3$); MS (APCI$^+$): m/z (%)=389 ([M+H]$^+$, 30), 353 (98), 283 (46), 197 (36), 182 (100); HR-MS (ESI$^+$): m/z=389.1660, calcd. for $C_{18}H_{30}ClN_2O_3S$ $(M+H)^+$: 389.1666; IR (neat): ν=1637, 1456, 1330, 1159, 667 cm^{-1}; R_f=0.25, 0.20 (hexane/EtOAc, 3:1).

2-Chloro-3-cyclohexyl-*N*,*N*-diethyl-3-(tosylamino)propanamide (8c): ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.83 (d, J=8.2 Hz, 2H), 7.77 (d, J=7.6 Hz, 2H), 7.31 (d, J=8.2 Hz, 2H), 7.26 (d, J=7.6 Hz, 2H), 5.08 (d, J=9.2 Hz, 2H), 4.50 (d, J=7.9 Hz, 2H), 3.85–3.78 (m, 2H), 3.41–3.15 (m, 8H), 2.43 (s, 3H), 2.40 (s, 3H), 1.82–1.50 (m, 12H), 1.21–1.07 (m, 22H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=166.1 (C), 163.5 (C), 144.2 (C), 142.9 (C), 138.3 (C), 136.6 (C), 129.4 (2CH), 129.2 (2CH), 127.8 (2CH), 127.3 (2CH), 60.8 (2CH), 55.1 (CH), 52.1 (CH), 44.5 (CH_2), 42.2 (CH_2), 42.8 (CH_2), 40.9 (CH_2), 40.1 (CH), 37.8 (CH), 31.3 (CH_2), 30.6 (CH_2), 30.2. (CH_2), 27.6 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 25.9 (CH_2), 25.4 (CH_2), 25.2 (CH_2), 24.9 (CH_2), 21.5 (CH_3), 21.4 (CH_3), 14.4 (CH_3), 14.3. (CH_3), 12.4 (CH_3), 12.3 (CH_3); MS (ESI$^+$): m/z (%)=439 ([M(^{37}Cl)+Na]$^+$, 8), 437 ([M(^{35}Cl)+Na]$^+$, 21), 417 ([M(^{37}Cl)+H]$^+$, 39), 415 ([M(^{35}Cl)+H]$^+$, 100); HR-MS (70 eV): m/z=414.1742, calcd. for $C_{20}H_{31}ClN_2O_3S$: 414.1744; IR (neat): ν=1636, 1450, 1331, 1158, 667 cm^{-1}; R_f=0.25, 0.18 (hexane/EtOAc, 3:1).

2-Chloro-1-morpholino-5-phenyl-3-(tosylamino)pentan-1-one (8d): ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.78 (d, J=7.6 Hz, 2H), 7.30–7.14 (m, 5H), 6.93 (d, J=7.6 Hz, 2H), 6.10 (d, J=8.6 Hz, 1H), 4.66 (d, J=2.9 Hz, 1H), 3.69–3.32 (m, 9H), 2.65–2.55 (m, 1H), 2.45–2.39 (m, 1H), 2.41 (s, 3H), 2.07–1.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=165.5 (C), 143.3 (C), 140.6 (C), 138.1 (C), 129.4 (2CH), 128.2 (2CH), 128.1 (2CH), 126.9 (2CH), 125.9 (CH), 66.3 (CH_2), 66.1 (CH_2), 56.7 (CH), 56.2 (CH), 46.2 (CH_2), 42.4 (CH_2), 33.0 (CH_2), 31.8 (CH_2), 21.4 (CH_3); MS (70 eV, EI): m/z (%)=450 (M$^+$, 30), 415 (18), 327 (22), 224 (37), 191 (59), 155 (51), 114 (100); HR-MS (70 eV): m/z=450.1378, calcd. for $C_{22}H_{27}ClN_2O_4S$: 450.1380; IR (neat): ν=2927, 1644, 1455, 1265, 1158 cm^{-1}; R_f=0.35 (hexane/EtOAc, 1:1).

3-(Benzenesulfonylamino)-2-chloro-3-(4-chlorophenyl)-1-morpholinopropan-1-one (8e): ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.72 (d, J=9.0 Hz, 2H), 7.39–7.18 (m, 8H), 4.94 (dd, J=8.3, 4.4 Hz, 1H), 4.65 (d, J=4.4 Hz, 1H), 3.73–3.47 (m, 4H), 3.46–3.28 (m, 3H), 3.26–3.08 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=165.7 (C), 140.9 (C), 139.4 (C), 135.2 (C), 132.2 (CH), 128.8 (2CH), 128.7 (2CH), 128.6 (2CH), 126.9 (2CH), 66.3 (CH_2), 66.1 (CH_2), 60.7 (CH), 52.2 (CH), 46.6 (CH_2), 42.5 (CH_2); MS (ESI$^+$): m/z (%)=467 ([M(^{37}Cl)+Na]$^+$, 31), 465 ([M(^{35}Cl)+Na]$^+$, 46), 445 ([M(^{37}Cl)+H]$^+$, 70), 443 ([M(^{35}Cl)+H]$^+$, 100), 288 (19), 286 (31), 114 (3); HRMS (ESI$^+$): m/z=465.0400, calcd. for $C_{19}H_{20}Cl_2N_2NaO_4S$

$(M+Na)^+$: 465.0419; IR (neat): ν = 2960, 1645, 1445, 1163, 735 cm^{-1}; R_f = 0.28 (hexane/EtOAc, 3:1)

3-(Benzenesulfonylamino)-2-chloro-3-(4-methoxyphenyl)-1-morpholinopropan-1-one (8f): ^1H NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, J = 8.7 Hz, 2H), 7.47–7.28 (m, 4H), 7.12 (d, J = 8.4 Hz, 2H), 6.73 (d, J = 8.7 Hz, 2H), 4.91 (dd, J = 8.2, 4.4 Hz, 1H), 4.68 (d, J = 4.4 Hz, 1H), 3.76 (s, 3H), 3.61–3.32 (m, 6H), 3.26–3.19 (m, 1H), 3.13–3.06 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1 (C), 159.4 (C), 141.0 (C), 132.0 (C), 128.5 (CH), 128.4 (2CH), 128.3 (2CH), 126.9 (2CH), 113.9 (2CH), 66.3 (CH_2), 66.0 (CH_2), 60.7 (CH), 55.2 (CH_3), 52.2 (CH), 46.5 (CH_2), 42.4 (CH_2); MS (ESI^+) m/z (%) = 463 ([M(^{37}Cl)+Na]$^+$, 41), 461 ([M(^{35}Cl)+Na]$^+$, 100), 441 ([M(^{37}Cl)+H]$^+$, 4), 439 ([M(^{35}Cl)+H]$^+$, 6), 282 (62), 114 (50); HR-MS (ESI^+): m/z = 461.0897, calcd. for $C_{20}H_{23}ClN_2NaO_5S$ $(M+Na)^+$: 461.0914; IR (neat): ν = 3058, 1639, 1448, 1260, 736 cm^{-1}; R_f = 0.20 (hexane/EtOAc, 3:1).

General Procedure for the Synthesis of Compounds 10 and 11

α-Aminoimines **9** were synthesized following the method reported in ref.[20]

To a stirred solution of Sm (0) (3 equiv., 1.2 mmol), previously activated by heating, in THF (2 mL), the imine **9** (0.4 mmol), 2-halo ester or amide (0.4 mmol) and THF (10 mL) were added at ambient temperature. Then, CH_2I_2 (3 equiv., 1.2 mmol) was added, and the reaction mixture was stirred at the same temperature for 6 h. The excess of SmI_2 was removed by bubbling a stream of air through the solution and further treatment with an aqueous solution of 0.1 N HCl (10 mL). The aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Flash column chromatography on silica gel (hexane/EtOAc, 2:1) provided pure compounds **10** and **11**.

For 3,4-diamino ester **10c** spectroscopic data have been previously reported in ref.[9]

Ethyl (3*R*,4*S*)-3-[(*R*)-*tert*butanesulfinamide]-4-(dibenzylamino)pentanoate (10a): ^1H NMR (300 MHz, $CDCl_3$): δ = 7.65–7.17 (m, 10H), 4.03 (q, J = 7.0 Hz, 2H), 3.87–3.64 (m, 2H), 3.76 (d, J = 13.6 Hz, 2H), 3.39 (d, J = 13.6 Hz, 2H), 3.00 (dd, J = 16.4, 3.3 Hz, 1H), 2.95–2.82 (m, 1H), 2.52 (dd, J = 16.4, 8.0 Hz, 1H), 1.48–1.03 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1 (C), 139.1 (2C), 128.8 (4CH), 128.2 (4CH), 126.9 (2CH), 60.2 (CH_2), 57.9 (CH), 56.2 (CH), 55.9 (C), 53.8 (2CH_2), 38.4 (CH_2), 22.4 (3CH_3), 14.0 (CH_3), 9.4 (CH_3); MS (ESI^+): m/z (%) = 467 ([M+Na]$^+$, 100), 445 ([M+H]$^+$, 98); HR-MS (ESI^+): m/z = 445.2519, calcd. for $C_{25}H_{37}N_2O_3S$ $(M+H)^+$: 445.2525; IR (neat): ν = 2981, 1728, 1454, 1266, 1061 cm^{-1}; $[\alpha]_D^{20}$: −15.3 (*c* 1, $CHCl_3$); R_f = 0.35 (hexane/EtOAc, 1:1).

Ethyl (3*R*,4*S*)-3-[(*R*)-*tert*butanesulfinamide]-4-(dibenzylamino)-6-methylheptanoate (10b): ^1H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.17 (m, 10H), 4.27 (d, J = 8.3 Hz, 1H), 4.12–3.99 (m, 2H), 3.89–3.73 (m, 1H), 3.75 (d, J = 14.0 Hz, 2H), 3.61 (d, J = 14.0 Hz, 2H), 3.23–3.16 (m, 1H), 2.59 (dd, J = 15.1, 3.6 Hz, 1H), 2.48 (dd, J = 15.1, 9.4 Hz, 1H), 1.46–1.36 (m, 1H), 1.31–1.11 (m, 14H), 0.92 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.8 (C), 139.0 (2C), 129.1 (4CH), 128.3 (4CH), 127.0 (2CH), 60.4 (CH_2), 60.0 (CH), 56.0 (CH), 55.7 (C), 54.4 (2CH_2), 37.7 (CH_2), 35.9 (CH_2), 25.6 (CH), 23.5 (CH_3), 22.6 (3CH_3), 22.0 (CH_3), 14.1 (CH_3); MS (ESI^+): m/z (%) = 509 ([M+Na]$^+$, 100), 487 ([M+H]$^+$, 96); HR-MS (ESI^+): m/z = 487.2988, calcd. for $C_{28}H_{43}N_2O_3S$ $(M+H)^+$: 487.2994; IR (neat): ν = 2926, 1732, 1455, 1266, 1066 cm^{-1}; $[\alpha]_D^{20}$: −8.9 (*c* 0.70, $CHCl_3$); R_f = 0.23 (hexane/EtOAc, 3:1).

(3*R*,4*S*)-3-[(*R*)-*tert*-butanesulfinamide]-4-(dibenzylamino)-*N*,*N*-diethylpentanamide (11a): ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.21 (m, 10H), 4.55 (d, J = 5.9 Hz, 1H), 3.78 (d, J = 13.6 Hz, 2H), 3.72–3.65 (m, 1H), 3.41 (d, J = 13.6 Hz, 2H), 3.37–3.21 (m, 3H), 3.20–3.09 (m, 2H), 2.99 (dd, J = 16.6, 2.9 Hz, 1H), 2.56 (dd, J = 16.6, 9.3 Hz, 1H), 1.21 (d, J = 6.8 Hz, 3H), 1.15 (s, 9H), 1.15 (t, J = 7.1 Hz, 3H), 1.09 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0 (C), 139.7 (2C), 128.9 (4CH), 128.2 (4CH), 126.9 (2CH), 56.9 (CH), 56.0 (C), 55.3 (CH), 54.0 (2CH_2), 41.9 (CH_2), 40.3 (CH_2), 36.8 (CH_2), 22.6 (3CH_3), 14.1 (CH_3), 13.1 (CH_3), 9.9 (CH_3); MS ($APCI^+$): m/z (%) = 472 ([M+H]$^+$, 99), 382 (15), 224 (100), 175 (33), 91 (11); HR-MS (ESI^+): m/z = 472.2992, calcd. for $C_{27}H_{42}N_3O_2S$ $(M+H)^+$: 472.2998; IR (neat): ν = 2979, 1636, 1266, 1100, 736 cm^{-1}; $[\alpha]_D^{20}$: −18.2 (*c* 0.85, $CHCl_3$); R_f = 0.35 (hexane/EtOAc, 1:2).

(3*R*,4*S*)-3-[(*R*)-*tert*-butanesulfinamide]-4-(dibenzylamino)-*N*,*N*-diethyl-6-methylheptanamide (11b): ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.16 (m, 10H), 4.59 (d, J = 7.7 Hz, 1H), 3.90–3.78 (m, 1H), 3.80 (d, J = 14.0 Hz, 2H), 3.70 (d, J = 14.0 Hz, 2H), 3.34–3.27 (m, 3H), 3.20–3.00 (m, 2H), 2.57 (dd, J = 15.3, 9.0 Hz, 1H), 2.44 (dd, J = 15.3, 3.2 Hz, 1H), 1.88–1.73 (m, 1H), 1.57–1.48 (m, 1H), 1.35–1.26 (m, 1H), 1.17 (s, 9H), 1.07 (t, J = 7.1 Hz, 3H), 1.06 (t, J = 7.1 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4 (C), 139.6 (2C), 129.0 (4CH), 128.2 (4CH), 126.9 (2CH), 59.7 (CH), 56.6 (CH), 55.6 (C), 54.7 (2CH_2), 42.0 (CH_2), 40.4 (CH_2), 36.7 (CH_2), 35.3 (CH_2), 25.3 (CH), 23.1 (CH_3), 22.6 (4CH_3), 14.3 (CH_3), 13.0 (CH_3); MS ($APCI^+$): m/z (%) = 514 ([M+H]$^+$, 100), 399 (13), 298 (11), 266 (26); HR-MS (ESI^+): m/z = 514.3462, calcd. for $C_{30}H_{48}N_3O_2S$ $(M+H)^+$: 514.3467; IR (neat): ν = 2960, 1635, 1455, 1266, 736 cm^{-1}; $[\alpha]_D^{20}$: −21.0 (*c* 1, $CHCl_3$); R_f = 0.25 (hexane/EtOAc, 1:1).

(3*R*,4*S*)-3-[(*R*)-*tert*-butanesulfinamide]-4-(dibenzylamino)-*N*,*N*-diethyl-5-phenylpentanamide (11c): ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.17 (m, 15H), 4.62 (d, J = 6.3 Hz, 1H), 3.91–3.80 (m, 1H), 3.81 (d, J = 13.7 Hz, 2H), 3.64–3.56 (m, 1H), 3.54 (d, J = 13.7 Hz, 2H), 3.32 (q, J = 7.1 Hz, 2H), 3.27–3.05 (m, 3H), 2.94 (dd, J = 14.5, 8.0 Hz, 1H), 2.87 (dd, J = 16.1, 2.9 Hz, 1H), 2.54 (dd, J = 16.1, 9.5 Hz, 1H), 1.15 (s, 9H), 1.10 (t, J = 7.1 Hz, 3H), 1.09 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7 (C), 140.9 (C), 139.4 (2C), 129.5 (2CH), 129.0 (4CH), 128.5 (2CH), 128.1 (4CH), 126.9 (2CH), 126.0 (CH), 62.3 (CH), 56.3 (CH), 55.9 (C), 54.5 (2CH_2), 41.9 (CH_2), 40.3 (CH_2), 36.8 (CH_2), 33.5 (CH_2), 22.5 (3CH_3), 14.1 (CH_3), 13.1 (CH_3); MS ($APCI^+$): m/z (%) = 548 ([M+H]$^+$, 100), 474 (9), 300 (13); HR-MS (ESI^+): m/z = 548.3305, calcd. for $C_{33}H_{46}N_3O_2S$ $(M+H)^+$: 548.3311; IR (neat): ν = 2978, 1625, 1454, 1266, 737 cm^{-1}; $[\alpha]_D^{20}$: −26.7 (*c* 1.08, $CHCl_3$); R_f = 0.25 (hexane/EtOAc, 1:1)

General Procedure for the Synthesis of Compound 12

To a stirred solution of crude material **10c** in CH_2Cl_2, was bubbled a stream of HCl (g) for 15 min. The aqueous phase was extracted with CH_2Cl_2, and the organic layer was washed with $NaHCO_3$ and dried over Na_2SO_4. After removing the solvents, the crude mixture was obtained and purified by flash chromatography on silica gel (hexane/EtOAc. 1:1) to yield analytically pure **12**.

For 3,4-diamino ester **12** spectroscopic data have been reported in ref.[9]

General Procedure for the Synthesis of Compound 13

Triethylamine (1.1 equiv., 0.44 mmol) and tosyl chloride (1.1 equiv., 0.44 mmol) were added to a stirred solution of **12** (0.4 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was left to stir at ambient temperature for 12 h. An aqueous solution of 1 N HCl (10 mL) was then added, and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with aqueous HCl (1 M), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Flash column chromatography on silica gel (hexane/EtOAc, 3:1) provided pure compound **13** with the same spectroscopic data as those shown by the same product prepared by Reetz.[22]

Spectroscopic data of 3,4-diamino ester **13** have been reported in ref.[9]

General Procedure for the Synthesis of Compound 14

To a stirred solution of **11a** in CH_2Cl_2, a stream of HCl (g) was bubbled for 15 min. The reaction mixture was partitioned in H_2O and CH_2Cl_2. The aqueous phase yielded the hydrochloride salt **14**, which was then purified by recrystallization in hexane/EtOAc.

(3*R*,4*S*)-3-Amino-4-(dibenzylamino)-*N*,*N*-diethylpentanamide hydrochloride salt (14): ^{1}H NMR (300 MHz, CD_3OD): $\delta = 7.83$–6.87 (m, 10H), 4.21–4.08 (m, 4H), 3.75–3.59 (m, 1H), 3.39–3.17 (m, 3H), 3.16–3.00 (m, 3H), 2.52 (dd, $J = 9.7$ Hz, 1H), 1.62 (d, $J = 6.5$ Hz, 3H), 0.99 (t, $J = 7.5$ Hz, 3H), 0.94 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.0$ (C), 131.4 (2CH), 131.0 (2CH), 130.2 (2C), 129.5 (CH), 129.4 (CH), 129.1 (2CH), 128.9 (2CH), 61.0 (CH), 54.6 (CH_2), 53.7 (CH_2), 47.1 (CH), 42.6 (CH_2), 40.5 (CH_2), 37.9 (CH_2), 13.3 (CH_3), 12.6 (CH_3), 10.5 (CH_3); MS (APCI$^+$): *m/z* (%) = 368 ($[M+H - HCl]^+$, 100), 171 (12); HR-MS (ESI$^+$): *m/z* = 368.2699, calcd. for $C_{23}H_{34}N_3O$ $(M+H-HCl)^+$: 368.2696; IR (KBr): $\nu = 3423$, 3054, 2984, 1609, 1457, 1387 cm^{-1}; $[\alpha]_D^{20}$: −35.7 (*c* 1.30, $CHCl_3$); $R_f = 0.48$ (dichloromethane/EtOH, 9:1).

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