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# Synthesis of enantiomerically pure 2-(*N*-aryl, *N*-alkyl-aminomethyl) aziridines: a new class of ligands for highly enantioselective asymmetric synthesis

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ABSTRACT

A simple and effective synthesis of enantiomerically pure 2-(*N*-aryl-, *N*-alkyl-aminomethyl)aziridines from (2*S*)-*N*-tritylaziridine-2-carboxylic acid methyl ester has been developed. Treating of this key ester with several primary and secondary amines in the presence of $AlMe_3$ provided the corresponding chiral *N*-trityl-2-carboxamides, and their reduction performed with different reagents resulted in the formation of the expected 2-(aminomethyl)aziridines. The choice of reaction conditions allows to either keep or leave the trityl substituent in the product. Such 2-(aminoalkyl)aziridines have shown very high catalytic efficiency in the asymmetric arylation of aldehydes and in other testing asymmetric reactions. On the other hand, homochiral *N*-trityl-2-carboxamides are interesting building blocks for the synthesis of various biologically active compounds.



## 1. Introduction

Numerous types of 1,2-diamines (primary, secondary, tertiary, cyclic, acyclic) constitute relevant molecules for many scientific sectors such as chemistry, biology, pharmacology and medicine, exhibiting interesting pharmacological properties, such as antitumor, anti-infective, anti-inflammatory, antidiabetic and cardiovascular agents or enzyme inhibitors and immune agents. The typical example of drug containing vicinal diamine subunits is Oxaliplatin and other platinum based drugs.[1] Based on the great importance of such systems, a search for the synthetic approaches leading to these valuable compounds in enantiomerically pure form is one of the most important topics in modern organic synthesis. Additionally, 1,2-diamines are versatile ligand/catalysts in stereocontrolled synthesis, including both transition metal-catalyzed and organocatalytic transformations.[2]

On the other hand, aziridines are a special kind of amine. These nitrogen-containing heterocycles are useful building blocks in synthesis and are important synthetic targets. Interest in these small heterocycles lies either in their biological activity, mainly as antitumor agents, as displayed by some naturally occurring compounds bearing the aziridine subunit, or in their ring strain, which makes these heterocycles useful precursors of more complex systems.[3] Moreover, aziridines (especially aziridine alcohols) can act as sources of chirality in asymmetric transformations working both as chiral ligands and auxiliaries.[4] On the contrary, it is surprising that diamines containing one aziridine ring and another amine function are still only a little known group of organic compounds. The first synthesis of enantiomerically pure aminoalkylaziridines was described by Concellón in 2001.[5] More recently, a new and original method of synthesis of aziridine-containing vicinal diamines from aziridine aldehyde dimers was elaborated by Yudin et al.[6] The obtained amino-aziridine derivatives were then subjected to ring-opening reactions.[7] Interestingly, it should be emphasized, that enantiomerically pure aminoalkylaziridines have never been tested as ligands or organocatalysts in asymmetric synthesis.

The synthetic diversity and broad spectrum of applications of chiral diamines prompted us to explore the synthesis of aziridine-containing diamines and to use them for preliminary research tests as catalysts for stereo-divergent reactions.

## 2. Results and discussion

### 2.1. Synthesis of the ligands

Taking into consideration that a stereogenic center located at the aziridine subunit has a decisive influence on the stereochemical outcome of the asymmetric reaction as we proved earlier,[4d,8] we designed vicinal diamines in which one amine function constitutes an aziridine and the second one is the secondary or tertiary amine. Synthesis of such systems was carried out in two

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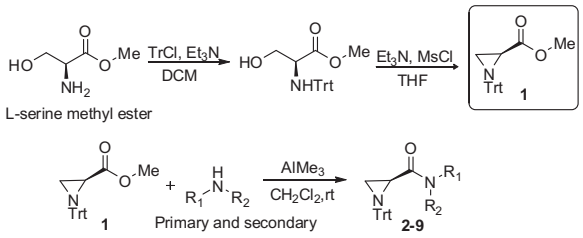
steps, starting from (2*S*)-*N*-tritylaziridine-2-carboxylic acid methyl ester. This key starting material was prepared from homochiral serine methyl ester. Thus, selective protection of the amino group in serine methyl ester as the trityl derivative followed by treatment of the protected serine methyl ester with methanesulfonyl chloride and then with $Et_3N$ in THF using a procedure described by Zwanenburg et al[9] gave the desired methyl (2*S*)-*N*-tritylaziridine-2-carboxylate **1** in essentially quantitative yield (Scheme 1).




**Scheme 1.** Synthesis of aziridine amides **2–9**.

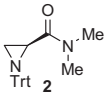
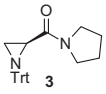
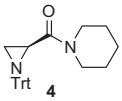
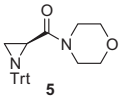
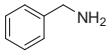
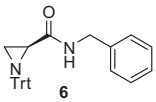
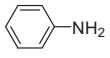
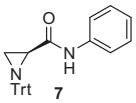
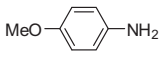
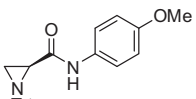
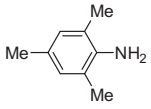
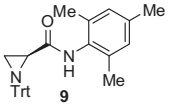
Subsequent treatment of 1 equiv of aziridine ester **1** with 3 equiv of various amines in the presence of 3 equiv of trimethylaluminum in DCM at −10 °C for 1 h and 48–72 h at rt (progress of the reaction was monitored by TLC) resulted in the formation of the corresponding amides **2–9** in good yields (Table 1).

Excluding compounds **2**[10] and **6**[11] (obtained by other methods), the remaining amides were unknown in the literature, thus, their full spectroscopic characterization was performed. It should be noted that our method of synthesis of aziridine carboxamides using amine/$AlMe_3$ reagents afforded products **2** and **6** in a higher total yield (in the literature, **2** and **6** were obtained via cyclisation of the corresponding trityl-L-serine dimethyl- or benzyl amide).

A few hitherto synthesized aziridine carboxamides have been applied to the synthesis of pharmacologically important carbohydrates or peptides, e.g., several α- and β-*O*-glycosyl serine conjugates were obtained stereoselectively via aziridine 2-carboxamide ring-opening reactions with pyranose C1-*O*-nucleophiles.[12] Moreover, the synthesis of new chiral thio-, seleno- and telluropeptides via ring-opening of aziridine carboxamides was described.[11,13]

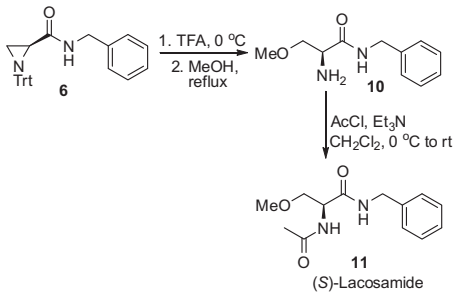
(*R*)-*N*-Benzyl-2-acetamido-3-methoxypropionamide, known as Lacosamide, is a low-molecular-weight antiepileptic drug, which was introduced in both the United States and Europe for adjuvant treatment of partial-onset seizures in adults.[14] There are a few methods that describe its synthesis. The key starting materials for these syntheses were enantiomerically pure methyl *N*-tritylaziridine-2-carboxylate or *N*-tritylaziridine-2-carboxamide that underwent aziridine ring-opening reactions. From the point of view of Lacosamide synthesis, it is more advantageous if the opening of the aziridine ring proceeds in the aziridine ester and the amide group is introduced later than the other way around.[15] Taking into account the above, it seems to be clear that the obtained

**Table 1**
Synthesis of aziridine-2-carboxamides **2–9**

| Entry | Amine ($NR^1R^2$) | Time (h) | Product[a] | Yield (%)[b] | $[\alpha]_D$[c] |
|---|---|---|---|---|---|
| 1 |  | 24 |  **2** | 84 | −69.8 |
| 2 |  | 72 |  **3** | 88 | −74.5 |
| 3 |  | 72 |  **4** | 84 | −55.5 |
| 4 |  | 72 |  **5** | 90 | −71.8 |
| 5 |  | 48 |  **6** | 92 | −101.0 |
| 6 |  | 96 |  **7** | 78 | −115.9 |
| 7 |  | 96 |  **8** | 87 | −118.4 |
| 8 |  | 96 |  **9** | 85 | −104.7 |

[a] Reaction conditions: aziridine ester **1** (1 mmol) and appropriate amine (3 mmol) with $AlMe_3$ (3 mmol) in $CH_2Cl_2$ (5 mL) at 25 °C during the time indicated.
[b] Isolated yields.
[c] In chloroform (*c* 0.3).

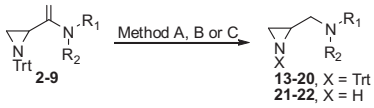
aziridine-2-carboxamides **2**–**9** can be important building blocks for the synthesis of biologically active substances, e.g., amide **6** was transformed into Lacosamide in two simple steps. Treatment of **6** with TFA in a chloroform/methanol mixture at 0 °C for 2 h and then reflux for 6 h afforded primary amine **10** in a good yield (75%). In this 'one pot' reaction, detritylation and opening of the aziridine ring took place sequentially (Scheme 2). This method of preparing of (*S*)-*N*-benzyl-2-amino-3-methoxypropionamide **10** constitutes a new, original and very effective approach to a very important building blocks named C(3)-alkoxy-PAADs (Primary Amino Acid Derivatives).[15c] Acetylation of **10** with AcCl gave (*S*)-Lacosamide **11** in a 87% yield (Scheme 2).




**Scheme 2.** Synthesis of Lacosamide via two steps.

It should be emphasized that although our goal was to synthesize enantiomerically pure aminomethylaziridines as effective ligands/catalysts for asymmetric reactions, synthesized amides may also be very interesting building blocks for the synthesis of many biologically relevant compounds. The ability of influencing the configuration of the stereogenic center (L- or D-serine), the diversity of substituents on the amide nitrogen atom and, the possibility of using different nucleophiles to open the ring, create very wide synthetic possibilities.

All of the obtained amides **2**–**9** were then reduced to amines via three different methods. The first method (Method **A**) was reduction with LAH in boiling THF in a ratio of 1 mol of amide:2 mol of $LiAlH_4$, 3 h of reflux. In the second method (Method **B**), a mixture of triethoxysilane and $Zn(OAc)_2$ in boiling THF was used for reduction. This method is particularly beneficial for the reduction of tertiary amides.[16] And, finally, the third method (**C**) is harsher than **A**, namely LAH in boiling THF in a ratio of 1 mol of amide:4 mol of $LiAlH_4$, 8 h of reflux. The application of this latter method not only resulted in the reduction of amide to amine, but detritylation of the aziridine was also observed (Scheme 3, Table 2).




**Scheme 3.** The reduction of amides **2**–**9** to corresponding amines.

Regardless of the reactions of compounds **6**–**9** using Method **C** (Table 2, entries 9–11), we performed detritylation reactions of amines **16**–**19** using a well-known method with TFA.[17] This reaction provided the same products **20**–**23** in a 70–75% yield, which proves that it is better to use the 'one pot' procedure **C** than **A** and, subsequently, detritylation using TFA. On the other hand, to the best our knowledge, this is the first example of detritylation of aziridines using lithium aluminum hydride.

### 2.2. Asymmetric arylation of *p*-tolualdehyde in the presence of chiral amines 12–22

All amines **12**–**22** were then investigated as catalysts in the asymmetric arylation of *p*-tolualdehyde with phenylboronic acid (Scheme 4). Diarylalcohols may act as precursors of many substances exhibiting biological and pharmacological activities; previously, we reported successful arylation of aldehydes using chiral aziridine alcohols as catalysts.[18] Herein, we demonstrated, that diamines (aziridine amines) exhibit higher catalytic activity in comparison with aziridine carbinols reported by us recently.[18]

The reactions were performed in toluene using phenylboronic acid and *p*-tolualdehyde as starting materials in the presence of ligands **12**–**22** (10 mol %). All the results are summarized in Table 3.

Inspection of Table 3 reveals that all the designed amines **12**–**22** are prone to promote asymmetric model reaction leading to (*S*)-(4-methylphenyl)phenylmethanol in good chemical yields and with very high enantiomeric excess. Among the amines bearing a trityl substituent on the nitrogen atom, system **16** with benzyl group led to the best results in terms of yield and *ee* (Table 3, entry 5). Interestingly, similar results were achieved using NH-aziridines **20**–**22** (without the trityl substituent). The product of arylation was formed in yields 87–90% and with very high enantioselectivity (*ee* up to 98%) (Table 3, entries 9–11). In all cases, (4-methylphenyl)phenylmethanol was formed with (*S*)-absolute configuration which was assigned on the basis of specific rotation measurements and retention times in HPLC chromatograms.[20]

### 2.3. Asymmetric addition of diethylzinc to benzaldehyde promoted by amines 12–22

Catalytic activity of amines **12**–**22** was also checked in the well-known model reaction of addition of diethylzinc to benzaldehyde (Scheme 5), (Table 4). Inspection of Table 4 clearly indicates, that all the ligands **12**–**22** are prone to catalyze this process very efficiently leading to the corresponding chiral alcohol in good chemical yields and with very high enantiomeric excess.

Moreover, it should be emphasized that a chiral alcohol was often formed with higher values of chemical yield and enantiomeric excess than using various aziridine alcohols, as we described earlier.[22]

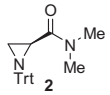
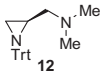
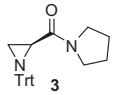
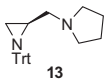
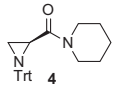
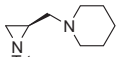
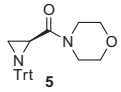
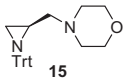
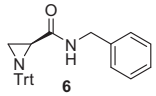
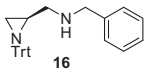
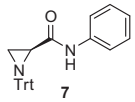
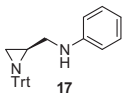
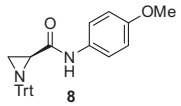
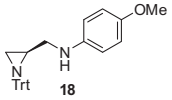
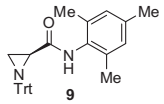
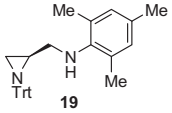
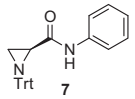
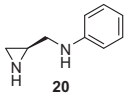
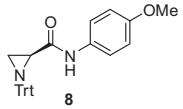
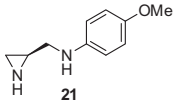
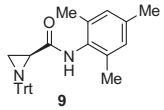
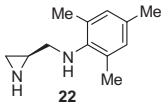
### 2.4. Asymmetric epoxidation of chalcone catalyzed by the most active ligands 13, 16, 20 and 21

Finally, basing on our previous work on the asymmetric synthesis of small three-membered ring heterocycles,[8c,23] the most active ligands **13**, **16**, **20** and **21** in the previous addition, were tested in the asymmetric epoxidation of chalcone (Scheme 6) (Table 5). The reactions were performed in diethyl ether using cumene hydroperoxide (CMHP) as epoxidising agent, diethyl zinc in the presence of the appropriate ligands (20 mol %).

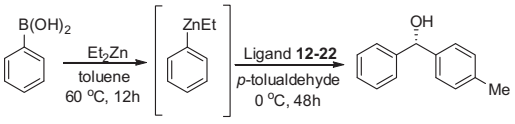
Inspection of Table 5 clearly shows, that all the ligands exhibit a high catalytic activity leading to the corresponding chiral epoxide in good chemical yields and with high enantiomeric excess. In the light of above results, chiral ligands **13**, **16**, **20** and **21** may be used as useful catalysts for the synthesis of chiral epoxides, which consist a structural part of a large variety of natural products, fragrances (epoxides of carvone, β-ionone), pheromones ((+)-disparlure), alkaloids (scopolamine) and many others.

Concerning a transition state model of the enantioselective processes, we assume, that all the asymmetric reactions involving zinc

**Table 2**
Synthesis of aziridine-2-methylamines

| Entry | Amide | Method **A**[a], **B**[b] or **C**[c] Yield (%) | Product | $[\alpha]_D$[d] |
|---|---|---|---|---|
| 1 |  **2** | **A**: 77<br>**B**: 82 |  **12** | −17.4 |
| 2 |  **3** | **A**: 81<br>**B**: 90 |  **13** | −22.3 |
| 3 |  **4** | **A**: 82<br>**B**: 88 |  **14** | −19.7 |
| 4 |  **5** | **A**: 76<br>**B**: 91 |  **15** | −20.5 |
| 5 |  **6** | **A**: 84 |  **16** | −32.6 |
| 6 |  **7** | **A**: 81 |  **17** | −41.3 |
| 7 |  **8** | **A**: 86 |  **18** | −45.8 |
| 8 |  **9** | **A**: 83 |  **19** | −39.7 |
| 9 |  **7** | **C**: 70 |  **20** | +11.9 |
| 10 |  **8** | **C**: 68 |  **21** | +14.0 |
| 11 |  **9** | **C**: 74 |  **22** | +12.7 |

[a] Method **A**: reaction conditions: 1 mmol of amide:2 mmol of $LiAlH_4$, 3 h, reflux.
[b] Method **B**: reaction conditions: $HSi(OEt)_3/Zn(OAc)_2$ in THF, 6 h, reflux, then stirred 3 h in 1 M NaOH at rt.
[c] Method **C**: reaction conditions: 1 mmol of amide:4 mmol of $LiAlH_4$, 8 h, reflux.
[d] In chloroform (*c* 0.3).



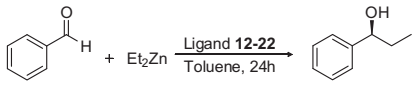

**Scheme 4.** Asymmetric arylation catalyzed by amines **12**–**22**.

ions proceed in accordance with transition state models describing for aziridine alcohols[25] and aziridine sulfides[26] in which zinc atom is complexed by both heteroatoms. It seems probably that in the case of aminoalkylaziridine this interaction is the most effective.

**Table 3**
Asymmetric arylation of *p*-tolualdehyde with phenylboronic acid in the presence of amines **12**–**22**

| Entry | Ligand | Yield (%) | *ee*[a] | Config.[b] | $[\alpha]_D$[c] |
|---|---|---|---|---|---|
| 1 | **12** | 77 | 91 | (*S*) | −2.1 |
| 2 | **13** | 84 | 97 | (*S*) | −2.8 |
| 3 | **14** | 80 | 94 | (*S*) | −2.5 |
| 4 | **15** | 92 | 93 | (*S*) | −2.7 |
| 5 | **16** | 94 | 97 | (*S*) | −3.0 |
| 6 | **17** | 86 | 91 | (*S*) | −3.2 |
| 7 | **18** | 85 | 95 | (*S*) | −3.3 |
| 8 | **19** | 81 | 95 | (*S*) | −3.5 |
| 9 | **20** | 90 | 98 | (*S*) | −3.4 |
| 10 | **21** | 89 | 98 | (*S*) | −2.2 |
| 11 | **22** | 87 | 98 | (*S*) | −2.9 |

[a] Determined using chiral HPLC on Chiralcel OD column.
[b] Absolute configuration was determined as *S* according to literature.[19]
[c] In chloroform (*c* 0.3).

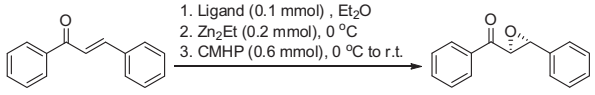



**Scheme 5.** Asymmetric addition of diethylzinc to benzaldehyde promoted by ligands **12**–**22**.

**Table 4**
Asymmetric addition of $Et_2Zn$ to benzaldehyde catalyzed by ligands **12**–**22**

| Entry | Ligand | Yield (%) | *ee*[a] | Config.[b] | $[\alpha]_D$[c] |
|---|---|---|---|---|---|
| 1 | **12** | 82 | 83 | (*S*) | −10.9 |
| 2 | **13** | 93 | 97 | (*S*) | −15.0 |
| 3 | **14** | 89 | 95 | (*S*) | −14.1 |
| 4 | **15** | 90 | 94 | (*S*) | −12.7 |
| 5 | **16** | 95 | 98 | (*S*) | −14.5 |
| 6 | **17** | 84 | 87 | (*S*) | −11.1 |
| 7 | **18** | 87 | 94 | (*S*) | −13.4 |
| 8 | **19** | 92 | 97 | (*S*) | −13.9 |
| 9 | **20** | 91 | 98 | (*S*) | −14.7 |
| 10 | **21** | 88 | 98 | (*S*) | −15.2 |
| 11 | **22** | 86 | 97 | (*S*) | −14.8 |

[a] Determined using chiral HPLC on Chiralcel OD-H column.
[b] Absolute configuration was determined as *S* according to literature.[21]
[c] In chloroform (*c* 0.3).




**Scheme 6.** Asymmetric epoxidation of chalcone in the presence of chiral amines.

**Table 5**
Asymmetric epoxidation of chalcone

| Entry | Ligand | Yield (%) | *ee*[a] | Config.[b] | $[\alpha]_D$[c] |
|---|---|---|---|---|---|
| 1 | **13** | 85 | 87 | (*2R,3S*) | −185.3 |
| 2 | **16** | 94 | 95 | (*2R,3S*) | −190.4 |
| 3 | **20** | 90 | 98 | (*2R,3S*) | −187.8 |
| 4 | **21** | 88 | 98 | (*2R,3S*) | −189.2 |

[a] Determined using chiral HPLC on Chiralcel OD-H column.
[b] Absolute configuration was determined as (*2R,3S*) according to literature.[24]
[c] In chloroform (*c* 0.3).

## 3. Conclusions

A simple synthesis of chiral aziridine amides and three methods of their reduction leading to the corresponding enantiomerically pure 2-(*N*-aryl, *N*-alkyl-aminomethyl)aziridines has been described. We proved that all the newly synthesized aziridine derivatives are versatile catalysts exhibiting high catalytic activity in some asymmetric reaction in the presence of zinc ions like asymmetric arylation, addition of diethylzinc to benzaldehyde or asymmetric epoxidation of chalcone. It should be stressed, that such diamines exhibited higher catalytic activity in comparison with those showed by aziridine alcohols reported previously. The investigations on the use of these new aziridine systems in another asymmetric processes are in progress.

On the other hand, all the obtained chiral aziridine carboxamides, being intermediates, can act as versatile building blocks for the synthesis of biologically relevant compounds, such as Lacosamide (an antiepileptic drug). Taking into account the broad availability of various enantiomerically pure aziridine amides, we can greatly expand a library of Lacosamide analogues.

## 4. Experimental

### 4.1. General

Toluene and tetrahydrofuran were distilled from a sodium benzophenone ketyl radical. Other reagents were purchased from commercial suppliers and used without further purification. $^1H/^{13}C$ NMR spectra were recorded on a Bruker instrument at 600/150 MHz, respectively or Varian-Gemini 200 MHz, using $CDCl_3$ as solvent and TMS as internal standard. Data are reported as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet. Optical rotation measurements were performed on a Anton Paar MCP500 polarimeter with a sodium lamp at room temperature (*c* 0.3). Column chromatography was carried out using Merck 60 silica gel. TLC was performed on Merck 60 $F_{254}$ silica gel plates. Visualization was accomplished with UV light (254 nm) or using iodine vapors. The enantiomeric excess (*ee*) values were determined via chiral HPLC (Chiralcel OD or OD-H column).

### 4.2. Synthesis of amides 2–9—General procedure

To a suspension of corresponding amine (3 mmol) in anhydrous $CH_2Cl_2$ (10 mL) at −10 °C trimethylaluminum (3 mmol) was added dropwise under a nitrogen atmosphere. The reaction mixture was warmed to 25 °C and stirred for 1 h. After this time, the reaction mixture was again cooled to −10 °C and methyl (2*S*)-*N*-tritylaziridine-2-carboxylate **1** (1 mmol) was added dropwise in anhydrous $CH_2Cl_2$ (5 mL). The resulting mixture was stirred at room temperature for the indicated time. Then, the reaction was cooled to 0 °C and carefully quenched with aqueous satd $NaHCO_3$ and extracted with $Et_2O$ (3 × 10 mL), the combined organic layers were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The crude products were purified by flash chromatography on silica gel (AcOEt/hexane 1:4).

#### 4.2.1. (*S*)-*N*,*N*-Dimethyl-1-tritylaziridine-2-carboxamide 2

Yield 84%, colorless solid; mp 96–98 °C; $[\alpha]_D^{23}$ = −69.8 (*c* 0.3, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$: 1.35 (dd, 1H, $J_{H,H}$ = 1.5, $J_{H,H}$ = 6.0 Hz), 1.94 (dd, 1H, $J_{H,H}$ = 3.0, $J_{H,H}$ = 6.0 Hz), 2.36 (dd, 1H, $J_{H,H}$ = 1.5, $J_{H,H}$ = 3.0 Hz), 2.81 (s, 3H), 3.00 (s, 3H), 7.20–7.23 (m, 3H), 7.26–7.29 (m, 6H), 7.54–7.55 (m, 6H) ppm.

$^{13}C$ NMR (151 MHz, $CDCl_3$): $\delta$: 27.2 ($CH_2$ azir), 30.6 (CHazir), 36.0 ($CH_3$), 36.9 ($CH_3$), 74.5 ($C_q$), 126.8 ($C_{ar}$), 127.5 ($C_{ar}$), 129.4 ($C_{ar}$), 144.0 ($C_{q\ ar}$), 169.8 (C=O) ppm.

IR (KBr): 3080, 3054, 3017, 2997, 1655, 1593, 1488, 1449, 1420, 1350, 1242, 1157, 1013, 908, 763, 710 $cm^{-1}$; ESI-MS: *m*/*z*: 358 (40), 379 (100, $[M+Na]^+$), 395 (15, $[M+K]^+$); Anal. Calcd for $C_{24}H_{24}N_2O$ (356.46): C, 80.87; H, 6.79; N, 7.86. Found: C, 80.91; H, 6.68; N, 7.72.

#### 4.2.2. (*S*)-Pyrrolidin-1-yl(1-tritylaziridin-2-yl)methanone 3

Yield 88%, colorless solid; mp 122–124 °C; $[\alpha]_D^{23}$ = −74.5 (*c* 0.3, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$: 1.32 (dd, 1H, $J_{H,H}$ = 1.5, $J_{H,H}$ = 6.0 Hz), 1.78–1.84 (m, 5H), 2.43 (dd, 1H, $J_{H,H}$ = 1.5, $J_{H,H}$ = 3.0 Hz), 3.08–3.11 (m, 1H), 3.22–3.26 (m, 1H), 3.48–3.51 (m, 1H), 3.57–3.61 (m, 1H), 7.20–7.23 (m, 3H), 7.26–7.29 (m, 6H), 7.53–7.54 (m, 6H) ppm; $^{13}C$ NMR (151 MHz, $CDCl_3$): $\delta$ 24.1 ($CH_2$), 26.0 ($CH_2$), 27.1 ($CH_2$ azir), 31.6 (CHazir), 46.0 ($CH_2$), 46.1 ($CH_2$), 74.5 ($C_q$), 126.8 ($C_{ar}$), 127.5 ($C_{ar}$), 129.4 ($C_{ar}$), 144.0 ($C_{q\ ar}$), 168.4 (C=O) ppm; IR (KBr): 3055, 3018, 2981, 2948, 1648, 1597, 1488, 1352, 1228, 1188, 1154, 1081, 1042, 901, 866, 710, 563 $cm^{-1}$; ESI-MS: *m*/*z*: 405 (100, $[M+Na]^+$), 421 (17.5, $[M+K]^+$); Anal. Calcd for $C_{26}H_{26}N_2O$ (382.50): C, 81.64; H, 6.85; N, 7.32. Found: C.81.44;H. 6.90, N. 7.40.

#### 4.2.3. (*S*)-Piperidin-1-yl(1-tritylaziridin-2-yl)methanone 4

Yield 84%, colorless solid; mp 128–130 °C; $[\alpha]_D^{23} = -55.5$ (*c* 0.3, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 1.34–1.35 (m, 3H), 1.54–1.59 (m, 4H), 1.92 (dd, 1H, $J_{H,H}$ = 3.0, $J_{H,H}$ = 6.0 Hz), 2.38 (dd, 1H, $J_{H,H}$ = 1.5, $J_{H,H}$ = 3.0 Hz), 3.19–3.27 (m, 2H), 3.55–3.58 (m, 1H), 3.63–3.66 (m, 1H), 7.20–7.23 (m, 3H), 7.27–7.29 (m, 6H), 7.54–7.56 (m, 6H) ppm; $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$: 24.5 ($2CH_2$), 25.6 ($CH_2$), 26.2 ($CH_2$), 27.0 ($CH_2$ azir), 30.5 (CHazir), 43.4 ($CH_2$), 46.3 ($CH_2$), 74.5 ($C_q$), 126.8 ($C_{ar}$), 127.5 ($C_{ar}$), 129.4 ($C_{ar}$), 144.0 ($C_{q\ ar}$), 168.0 (C=O) ppm; IR (KBr): 3083, 3055, 3032, 2999, 2932, 2854, 1641, 1594, 1488, 1465, 1446, 1351, 1251, 1189, 1141, 1076, 1017, 903, 851, 759, 707, 565 cm$^{-1}$; ESI-MS: *m*/*z*: 419 (100, $[M+Na]^+$), 435 (52.5, $[M+K]^+$); Anal. Calcd for $C_{27}H_{28}N_2O$ (396.52): C, 81.78; H, 7.12; N, 7.06. Found: C, 81.61; H, 7.16; N, 7.10.

#### 4.2.4. (*S*)-Morpholino(1-tritylaziridin-2-yl)methanone 5

Yield 90%, colorless solid; mp 132–134 °C; $[\alpha]_D^{23} = -71.8$ (*c* 0.3, $CHCl_3$); $^1$H NMR(600 MHz, $CDCl_3$) $\delta$: 1.37 (dd, 1H, $J_{H,H}$ = 1.5, $J_{H,H}$ = 6.0 Hz), 1.89 (dd, 1H, $J_{H,H}$ = 3.0, $J_{H,H}$ = 6.0 Hz), 2.41 (dd, 1H, $J_{H,H}$ = 1.5, $J_{H,H}$ = 3.0 Hz), 3.25–3.28 (m, 1H), 3.30–3.33 (m, 1H), 3.43–3.46 (m, 1H), 3.49–3.51 (m, 1H), 3.55–3.58 (m, 1H), 3.66–3.70 (m, 2H), 3.77–3.80 (m, 1H) 7.22–7.24 (m, 3H), 7.28–7.30 (m, 6H), 7.53–7.54 (m, 6H) ppm; $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ 27.2 ($CH_2$ azir), 30.2 (CHazir), 42.5 ($CH_2$), 45.6 ($CH_2$), 66.5 ($CH_2$), 66.9 ($CH_2$), 74.5 ($C_q$), 126.9 ($C_{ar}$), 127.6 ($C_{ar}$), 129.3 ($C_{ar}$), 143.8 ($C_{q\ ar}$), 168.6 (C=O) ppm; IR (KBr): 3056, 3032, 2986, 2968, 2898, 1644, 1595, 1489, 1465, 1447, 1385, 1330, 1233, 1157, 1117, 1068, 1043, 1019, 951, 901, 845, 760, 745, 707, 575 cm$^{-1}$; ESI-MS: *m*/*z*: 421 (100, $[M+Na]^+$), 437 (10, $[M+K]^+$); Anal. Calcd for $C_{26}H_{26}N_2O_2$ (396.52): C, 78.36; H, 6.58; N, 7.03. Found: C, 78.39; H, 6.59; N, 7.05.

#### 4.2.5. (*S*)-*N*-Benzyl-1-tritylaziridine-2-carboxamide 6

Yield 92%, colorless solid; mp 142–144 °C; $[\alpha]_D^{23} = -101.0$ (*c* 0.3, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 1.30 (d, 1H, $J_{H,H}$ = 6.6 Hz), 2.04 (d, 1H, $J_{H,H}$ = 2.6 Hz), 2.11 (dd, 1H, $J_{H,H}$ = 2.6, $J_{H,H}$ = 6.6 Hz), 4.36 (dd, 1H, $J_{H,H}$ = 5.0, $J_{H,H}$ = 15.0 Hz), 4.78 (dd, 1H, $J_{H,H}$ = 7.5, $J_{H,H}$ = 15.0 Hz), 7.11–7.13 (m, 1H), 7.25–7.28 (m, 9H), 7.33–7.35 (m, 1H), 7.37–7.43 (m, 9H) ppm; $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ 29.9 ($CH_2$ azir), 34.2 (CHazir), 43.0 ($CH_2$), 74.6 ($C_q$), 127.2 ($C_{ar}$), 127.5 ($C_{ar}$), 127.6 ($C_{ar}$), 127.7 ($C_{ar}$), 128.8 ($C_{ar}$), 129.3 ($C_{ar}$), 138.5 ($C_{q\ ar}$), 143.2 ($C_{q\ ar}$), 170.7 (C=O) ppm; IR (KBr): 3085, 3057, 3030, 2988, 2927, 1648, 1596, 1545, 1489, 1447, 1357, 1286, 1223, 1187, 1081, 1032, 1011, 965, 903, 745, 708, 632, 592 cm$^{-1}$; ESI-MS: *m*/*z*: 441 (100, $[M+Na]^+$), 457 (5, $[M+K]^+$); Anal. Calcd for $C_{29}H_{26}N_2O$ (418.53): C, 83.22; H, 6.26; N, 6.69. Found: C, 83.10; H, 6.20; N, 6.70.

#### 4.2.6. (*S*)-*N*-Phenyl-1-tritylaziridine-2-carboxamide 7

Yield 78%, colorless solid; mp 133–135 °C; $[\alpha]_D^{23} = -115.9$ (*c* 0.3, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 1.63 (d, 1H, $J_{H,H}$ = 6.6 Hz), 2.16 (d, 1H, $J_{H,H}$ = 2.6 Hz), 2.18 (dd, 1H, $J_{H,H}$ = 2.6, $J_{H,H}$ = 6.6 Hz), 7.16–7.19 (m, 1H), 7.28–7.30 (m, 3H), 7.33–7.35 (m, 6H), 7.39–7.41 (m, 2H), 7.46–7.47 (m, 6H), 7.62–7.64 (m, 2H), 8.69 (s, 1H, NH) ppm; $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ 30.0 ($CH_2$ azir), 34.9 (CHazir), 74.7 ($C_q$), 119.8 ($C_{ar}$), 124.4 ($C_{ar}$), 127.3 ($C_{ar}$), 127.9 ($C_{ar}$), 129.1 ($C_{ar}$), 129.3 ($C_{ar}$), 137.5 ($C_{q\ ar}$), 143.2 ($C_{q\ ar}$), 168.7 (C=O) ppm; IR (KBr): 3315, 3277, 3054, 3031, 2994, 2926, 1690, 1659, 1602, 1533, 1490, 1443, 1411, 1362, 1314, 1263, 1220, 1180, 1034, 1008, 904, 764, 749, 707, 632, 512 cm$^{-1}$; ESI-MS: *m*/*z*: 405 (17.5, $[M+H]^+$), 427 (100, $[M+Na]^+$), 443 (5, $[M+K]^+$); Anal. Calcd for $C_{29}H_{26}N_2O$ (404.50): C, 83.14; H, 5.98; N, 6.93. Found: C, 82.99; H, 6.11; N, 6.97.

#### 4.2.7. (*S*)-*N*-(4-Methoxyphenyl)-1-tritylaziridine-2-carboxamide 8

Yield 87%, colorless solid; mp 144–146 °C; $[\alpha]_D^{23} = -118.4$ (*c* 0.3, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 1.62 (d, 1H, $J_{H,H}$ = 6.6 Hz), 2.15 (d, 1H, $J_{H,H}$ = 2.6 Hz), 2.17 (dd, 1H, $J_{H,H}$ = 2.6, $J_{H,H}$ = 6.6 Hz), 3.84 (s, 3H), 6.93–6.95 (m, 2H), 7.28–7.30 (m, 3H), 7.33–7.35 (m, 6H), 7.46–7.47 (m, 6H), 7.52–7.54 (m, 2H), 8.57 (s, 1H, NH) ppm; $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ 30.0 ($CH_2$ azir), 34.8 (CHazir), 55.5 ($CH_3$), 74.6 ($C_q$), 114.3 ($C_{ar}$), 121.7 ($C_{ar}$), 127.3 ($C_{ar}$), 127.9 ($C_{ar}$), 129.3 ($C_{ar}$), 130.6 ($C_{q\ ar}$), 143.2 ($C_{q\ ar}$), 156.6 ($C_{q\ ar}$), 168.5 (C=O) ppm; IR (KBr): 3304, 3277, 3143, 3051, 2993, 2951, 2830, 1681, 1659, 1608, 1595, 1510, 1462, 1447, 1311, 1244, 1176, 1036, 1002, 905, 828, 707, 634, 514 cm$^{-1}$; ESI-MS: *m*/*z*: 457 (100, $[M+Na]^+$), 473 (7.5, $[M+K]^+$); Anal. Calcd for $C_{29}H_{26}N_2O_2$ (434.53): C, 80.16; H, 6.03; N, 6.45. Found: C, 79.96; H, 6.01; N, 6.48.

#### 4.2.8. (*S*)-*N*-Mesityl-1-tritylaziridine-2-carboxamide 9

Yield 85%, colorless solid; mp 156–158 °C; $[\alpha]_D^{23} = -104.7$ (*c* 0.3, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 1.63 (d, 1H, $J_{H,H}$ = 6.6 Hz), 2.19 (d, 1H, $J_{H,H}$ = 2.6 Hz), 2.27 (dd, 1H, $J_{H,H}$ = 2.6, $J_{H,H}$ = 6.6 Hz), 2.30 (s, 9H), 6.96 (s, 2H), 7.26–7.29 (m, 3H), 7.31–7.34 (m, 6H), 7.50–7.52 (m, 6H), 8.10 (s, 1H, NH) ppm; $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$: 18.5 (2 $CH_3$), 20.9 ($CH_3$), 30.4 ($CH_2$ azir), 34.5 (CHazir), 74.7 ($C_q$), 127.3 ($C_{ar}$), 127.8 ($C_{ar}$), 129.1 ($C_{ar}$), 129.4 ($C_{ar}$), 130.4 ($C_{q\ ar}$), 135.3 ($C_{q\ ar}$), 137.2 ($C_{q\ ar}$), 143.2 ($C_{q\ ar}$), 169.3 (C=O) ppm; IR (KBr): 3085, 3059, 2979, 2952, 2855, 1675, 1660, 1596, 1493, 1447, 1375, 1220, 1188, 1010, 904, 848, 762, 707, 634 cm$^{-1}$; ESI-MS: *m*/*z*: 469 (100, $[M+Na]^+$), 485 (37.5, $[M+K]^+$); Anal. Calcd for $C_{31}H_{30}N_2O$ (446.58): C, 83.37; H, 6.77; N, 6.27. Found: C, 83.32; H, 6.83; N, 6.11.

### 4.3. Synthesis of compounds 10 and 11

#### 4.3.1. (*S*)-2-Amino-*N*-benzyl-3-methoxypropanamide 10

(*S*)-*N*-Benzyl-1-tritylaziridine-2-carboxamide **6** (0.84 g, 2 mmol) was dissolved in a mixture of chloroform (5 mL) and methanol (5 mL). A solution was cooled to 0 °C and TFA (3.2 mL) was added dropwise. The resulting solution was stirred for 2 h at 0 °C. After this time, an additional portion (5 mL) of methanol was added and the mixture was refluxed for 6 h, then cooled to room temperature, neutralized with 3 M aqueous NaOH and extracted with $Et_2O$ (3×). The combined organic layers were dried over anhydrous $MgSO_4$ and the crude product was obtained after evaporation of the solvent in vacuo. Purification via column chromatography ($SiO_2$, $CHCl_3$:MeOH 9/1) gave a pure **10**. Yield 75%, colorless oil, $[\alpha]_D^{23} = 1.3$ (*c* 0.3, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 3.38 (s, 3H), 3.61–3.65 (m, 3H), 4.46 (dd, 2H, $J_{H,H}$ = 6.0, $J_{H,H}$ = 15.0 Hz), 7.25–7.28 (m, 3H), 7.31–7.34 (m, 2H), 7.73 (br s, 1H) ppm. The spectroscopic data are in full agreement with those reported in the literature.[27a]

#### 4.3.2. (*S*)-2-Acetamido-*N*-benzyl-3-methoxypropanamide 11 (*(S)-Lacosamide*)

Acetylation of amine **10** was performed according to literature procedure.[27b] Yield 87%, Colorless oil, $[\alpha]_D^{23} = -7.4$ (*c* 0.3, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 2.03 (s, 3H), 3.38 (s, 3H), 3.44 (dd, 1H, $J_{H,H}$ = 7.5, $J_{H,H}$ = 9.0 Hz), 3.81 (dd, 1H, $J_{H,H}$ = 4.0, $J_{H,H}$ = 9.0 Hz), 4.43–4.51 (m, 2H), 4.51–4.56 (m, 1H), 6.41 (br s, 1H), 6.72 (br s, 1H), 7.22–7.30 (m, 3H), 7.32–7.35 (m, 2H) ppm. The spectroscopic data were in full agreement with those reported in the literature.[27b]

### 4.4. Reduction of amides 2–9 to amines 12–22—General procedures

*Method **A**:* The corresponding amide (1 mmol) was dissolved in anhydrous THF (15 mL). The mixture was cooled to 0 °C and solution of $LiAlH_4$ (2 mmol, 1.0 M in THF) was added under a nitrogen atmosphere. After refluxing for 3 h, the mixture was cooled to room temperature and aqueous 2 M NaOH was added until the

hydrogen bubbling stopped. The resulting mixture was filtered and extracted with $Et_2O$ (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated under vacuum. A crude product was purified by column chromatography (silica gel, hexane with ethyl acetate in gradient 1:9) to afford the corresponding products; *Method* ***B****:* In a round-bottomed flask, zinc acetate (1 mmol), triethoxysilane (3 mmol) and anhydrous THF (5 mL) were mixed. The mixture was stirred for 30 min under argon followed by the addition of corresponding secondary amide (**2**–**5**) (1 mmol) in THF (3 mL). After refluxing for 7 h, the mixture was cooled to room temperature and treated with aqueous 1 M NaOH (5 mL). After stirring for 3 h, the mixture was extracted with ethyl acetate (4 × 10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane with ethyl acetate in gradient 1:9) to afford the corresponding products; *Method* ***C****:* The corresponding amide (1 mmol) was dissolved in anhydrous THF (15 mL). The mixture was cooled to 0 °C and solution of $LiAlH_4$ (4 mmol, 1.0 M in THF) was added under a nitrogen atmosphere. After refluxing for 8 h, the mixture was cooled to room temperature and aqueous 2 M NaOH was added until the hydrogen bubbling stopped. The resulting mixture was filtered and extracted with $Et_2O$ (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated under vacuum. A crude product was purified by column chromatography (silica gel, methanol/ethyl acetate in gradient 1:9) to afford the corresponding products.

#### 4.4.1. (*R*)-*N,N*-Dimethyl-1-(1-tritylaziridin-2-yl)methanamine 12

Yield 82%, colorless solid; mp 159–161 °C; $[\alpha]_D^{23} = -17.4$ (*c* 0.3, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 1.20 (d, 1H, $J_{H,H}$ = 6.0 Hz), 1.36–1.39 (m, 1H), 1.68 (d, 1H, $J_{H,H}$ = 1.5), 2.10–2.14 (m, 1H), 2.19 (s, 6H), 3.09 (d, 1H, $J_{H,H}$ = 12.0 Hz), 7.19–7.22 (m, 3H), 7.25–7.28 (m, 6H), 7.49–7.50 (m, 6H) ppm; $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ 27.7 ($CH_2$ azir), 31.3 (CHazir), 45.9 (2 $CH_3$), 62.7 ($CH_2$), 73.9 ($C_q$), 126.6 ($C_{ar}$), 127.4 ($C_{ar}$), 129.5 ($C_{ar}$), 144.6 ($C_{q\ ar}$) ppm; IR (KBr): 3017, 2995, 2960, 2854, 1487, 1446, 1386, 1231, 1214, 1150, 1041, 1031, 900, 773, 753, 706 cm$^{-1}$; ESI-MS: *m*/*z*: 343 (100, $[M+H]^+$), 365 (32.5 $[M+Na]^+$); Anal. Calcd for $C_{24}H_{26}N_2$ (342.48): C, 84.17; H, 7.65; N, 8.18. Found: C, 84.09; H, 7.71; N, 8.20.

#### 4.4.2. (*R*)-1-((1-Tritylaziridin-2-yl)methyl)pyrrolidine 13

Yield 90%, colorless solid, mp 178–180 °C; $[\alpha]_D^{23} = -22.3$ (*c* 0.3, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 1.18 (d, 1H, $J_{H,H}$ = 6.0 Hz), 1.42–1.44 (m, 1H), 1.68 (d, 1H, $J_{H,H}$ = 3.0 Hz), 1.70–1.75 (m, 4H), 2.21 (dd, 1H, $J_{H,H}$ = 8.5, $J_{H,H}$ = 12.0 Hz), 2.40–2.43 (m, 2H), 2.50–2.52 (m, 2H), 3.34 (dd, 1H, $J_{H,H}$ = 8.5, $J_{H,H}$ = 12.0 Hz), 7.18–7.21 (m, 3H), 7.25–7.27 (m, 6H), 7.49–7.50 (m, 6H) ppm; $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ 23.4 ($CH_2$), 27.5 ($CH_2$ azir), 31.8 (CHazir), 54.5 ($CH_2$), 59.5 ($CH_2$), 73.9 ($C_q$), 126.5 ($C_{ar}$), 127.3 ($C_{ar}$), 129.5 ($C_{ar}$), 144.7 ($C_{q\ ar}$) ppm; IR (KBr): 3053, 3031, 2971, 2956, 2920, 2875, 1595, 1490, 1446, 1349, 1244, 1156, 1143, 1047, 936, 900, 769, 748, 707, 632, 524 cm$^{-1}$; ESI-MS: *m*/*z*: 369 (100, $[M+H]^+$); Anal. Calcd for $C_{26}H_{28}N_2$ (368.51): C, 84.74; H, 7.66; N, 7.60. Found: C, 84.69; H, 7.64; N, 7.58.

#### 4.4.3. (*R*)-1-((1-Tritylaziridin-2-yl)methyl)piperidine 14

Yield 88%, colorless solid, mp 186–188 °C; $[\alpha]_D^{23} = -19.7$ (*c* 0.3, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 1.18 (d, 1H, $J_{H,H}$ = 6.0 Hz), 1.40–1.42 (m, 3H), 1.50–1.53 (m, 4H), 1.66 (d, 1H, $J_{H,H}$ = 3.0 Hz), 2.17 (dd, 1H, $J_{H,H}$ = 8.0, $J_{H,H}$ = 12.5 Hz), 2.28 ($s_{br}$, 2H), 2.41 ($s_{br}$, 2H), 3.10 (dd, 1H, $J_{H,H}$ = 4.0, $J_{H,H}$ = 12.5 Hz), 7.19–7.21 (m, 3H), 7.25–7.27 (m, 6H), 7.48–7.50 (m, 6H) ppm; $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ 24.3 ($CH_2$), 25.9 ($CH_2$), 28.2 ($CH_2$ azir), 30.7 (CHazir), 54.9 ($CH_2$), 62.7 ($CH_2$), 73.9 ($C_q$), 126.5 ($C_{ar}$), 127.4 ($C_{ar}$), 129.6 ($C_{ar}$), 144.7 ($C_{q\ ar}$) ppm; IR (KBr): 3080, 3058, 2982, 2941, 2925, 2853, 2752, 1595, 1489, 1446, 1336, 1257, 1151, 1098, 1043, 1032, 912, 775, 710, 634 cm$^{-1}$; ESI-MS: *m*/*z*: 383 (100, $[M+H]^+$); Anal. Calcd for $C_{27}H_{30}N_2$ (382.54): C, 84.77; H, 7.90; N, 7.32. Found: C, 84.78; H, 7.79; N, 7.29.

#### 4.4.4. (*R*)-4-((1-Tritylaziridin-2-yl)methyl)morpholine 15

Yield 91%, colorless solid, mp 186–188 °C; $[\alpha]_D^{23} = -20.5$ (*c* 0.3, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 1.20 (d, 1H, $J_{H,H}$ = 6.0 Hz), 1.37–1.40 (m, 1H), 1.67 (d, 1H, $J_{H,H}$ = 3.0 Hz), 2.26 (dd, 1H, $J_{H,H}$ = 8.0, $J_{H,H}$ = 12.5 Hz), 2.35–2.36 (m, 2H), 2.47–2.49 (m, 2H), 3.07 (dd, 1H, $J_{H,H}$ = 4.0, $J_{H,H}$ = 12.5 Hz), 3.63–3.68 (m, 4H), 7.19–7.22 (m, 3H), 7.26–7.27 (m, 6H), 7.49–7.51 (m, 6H) ppm; $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ 27.7 ($CH_2$ azir), 30.3 (CHazir), 54.0 ($CH_2$), 62.2 ($CH_2$), 66.9 ($CH_2$), 73.9 ($C_q$), 126.6 ($C_{ar}$), 127.4 ($C_{ar}$), 129.5 ($C_{ar}$), 144.6 ($C_{q\ ar}$) ppm; IR (KBr): 3084, 3031, 2957, 2927, 2853, 2796, 1648, 1596, 1489, 1447, 1330, 1290, 1239, 1155, 1118, 1069, 1010, 910, 866, 747, 707 cm$^{-1}$; ESI-MS: *m*/*z*: 385 (35, $[M+H]^+$), 407 (100, $[M+Na]^+$); Anal. Calcd for $C_{26}H_{28}N_2O$ (384.51): C, 81.21; H, 7.34; N, 7.29. Found: C, 81.10; H, 7.34; N, 7.33.

#### 4.4.5. (*R*)-*N*-Benzyl-1-(1-tritylaziridin-2-yl)methanamine 16

Yield 84%, colorless solid, mp 221–223 °C; $[\alpha]_D^{23} = -32.6$ (*c* 0.3, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 1.01 (d, 1H, $J_{H,H}$ = 6.0 Hz), 1.38–1.39 (m, 1H), 1.46 ($s_{br}$, 1H, NH), 1.67 (d, 1H, $J_{H,H}$ = 3.0 Hz), 2.73 (dd, 1H, $J_{H,H}$ = 5.0, $J_{H,H}$ = 12.0 Hz), 2.87 (dd, 1H, $J_{H,H}$ = 5.0, $J_{H,H}$ = 12.0 Hz), 3.70 (s, 2H), 7.10–7.12 (m, 3H), 7.15–7.19 (m, 9H), 7.22–7.25 (m, 1H), 7.38–7.40 (m, 6H) ppm; $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ 25.5 ($CH_2$ azir), 32.5 (CHazir), 51.5 ($CH_2$), 54.0 ($CH_2$), 73.9 ($C_q$), 126.6 ($C_{ar}$), 126.9 ($C_{ar}$), 127.4 ($C_{ar}$), 128.1 ($C_{ar}$), 128.4 ($C_{ar}$), 129.5 ($C_{ar}$), 140.4 ($C_{q\ ar}$), 144.6 ($C_{q\ ar}$) ppm; IR (KBr): 3057, 3030, 2979, 2922, 2891, 2829, 1680, 1595, 1489, 1448, 1359, 1236, 1153, 1086, 901, 746, 696, 632 cm$^{-1}$; ESI-MS: *m*/*z*: 405 (100, $[M+H]^+$), 427 (27.5, $[M+Na]^+$); Anal. Calcd for $C_{29}H_{28}N_2$ (404.55): C, 86.10; H, 6.98; N, 6.92. Found: C, 86.01; H, 7.21; N, 6.76.

#### 4.4.6. (*R*)-*N*-((1-Tritylaziridin-2-yl)methyl)aniline 17

Yield 81%, colorless oil, $[\alpha]_D^{23} = -41.3$ (*c* 0.3, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 1.18 (d, 1H, $J_{H,H}$ = 6.0 Hz), 1.62–1.65 (m, 1H), 1.87 (d, 1H, $J_{H,H}$ = 3.10 Hz), 3.32–3.34 (m, 1H), 3.42–3.44 (m, 2H), 3.99 (s, 1H, NH), 6.57–6.59 (m, 2H), 6.73–6.75 (m, 1H), 7.18–7.21 (m, 2H), 7.25–7.27 (m, 3H), 7.30–7.33 (m, 6H), 7.52–7.53 (m, 6H) ppm; $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ 25.3 ($CH_2$ azir), 31.8 (CHazir), 45.8 ($CH_2$), 74.0 ($C_q$), 113.0 ($C_{ar}$), 117.4 ($C_{ar}$), 126.8 ($C_{ar}$), 127.5 ($C_{ar}$), 129.2 ($C_{ar}$), 129.5 ($C_{ar}$), 144.4 ($C_{q\ ar}$), 148.3 ($C_{q\ ar}$) ppm; IR (film): 3053, 3019, 2980, 2929, 2893, 1603, 1505, 1489, 1446, 1316, 1253, 1233, 1152, 1032, 902, 869, 747, 708, 693, 633 cm$^{-1}$; HRMS (EI) *m*/*z* calcd for $C_{28}H_{26}N_2$: 390.2099, found 390.2096.

#### 4.4.7. (*R*)-4-Methoxy-*N*-((1-tritylaziridin-2-yl)methyl)aniline 18

Yield 86%, brown solid, mp 216–218 °C; $[\alpha]_D^{23} = -45.8$ (*c* 0.3, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 1.14 (d, 1H, $J_{H,H}$ = 6.0 Hz), 1.58–1.61 (m, 1H), 1.84 (d, 1H, $J_{H,H}$ = 3.0 Hz), 3.23 (dd, 1H, $J_{H,H}$ = 5.5, $J_{H,H}$ = 12.0 Hz), 3.36 (dd, 1H, $J_{H,H}$ = 4.0, $J_{H,H}$ = 12.0 Hz), 3.70 ($s_{br}$, 1H, NH), 3.76 (s, 3H), 6.50–6.52 (m, 2H), 6.76–6.78 (m, 2H), 7.21–7.24 (m, 3H), 7.26–7.29 (m, 6H), 7.49–7.50 (m, 6H) ppm; $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ 25.3 ($CH_2$ azir), 32.0 (CHazir), 47.0 ($CH_2$), 55.9 ($CH_3$), 73.9 ($C_q$), 114.4 ($C_{ar}$), 114.9 ($C_{ar}$), 126.7 ($C_{ar}$), 127.5 ($C_{ar}$), 129.5 ($C_{ar}$), 142.6 ($C_{q\ ar}$), 144.5 ($C_{q\ ar}$), 152.2 ($C_{q\ ar}$) ppm; IR (KBr): 3054, 3030, 2993, 2931, 2901, 2829, 1595, 1513, 1489, 1464, 1447, 1309, 1235, 1179, 1034, 901, 818, 747, 708, 633, 521 cm$^{-1}$; ESI-MS: *m*/*z*: 443 (100, $[M+Na]^+$); Anal. Calcd for $C_{29}H_{28}N_2O$ (420.55): C, 82.82; H, 6.71; N, 6.66. Found: C, 82.67; H, 6.72; N, 6.71.

#### 4.4.8. (*R*)-2,4,6-Trimethyl-*N*-((1-tritylaziridin-2-yl)methyl) aniline 19

Yield 83%, colorless solid, mp 202–204 °C; $[\alpha]_D^{23}$ = −39.7 (*c* 0.3, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 1.12 (d, 1H, $J_{H,H}$ = 6.2 Hz), 1.54–1.57 (m, 1H), 1.68 (d, 1H, $J_{H,H}$ = 3.1 Hz), 2.23 (s, 3H), 2.24 (s, 6H), 3.13 (dd, 1H, $J_{H,H}$ = 4.6, $J_{H,H}$ = 12.4 Hz), 3.27 (dd, 1H, $J_{H,H}$ = 4.6, $J_{H,H}$ = 12.4 Hz), 6.81 (s, 2H), 7.21–7.23 (m, 3H), 7.27–7.29 (m, 6H), 7.51–7.54 (m, 6H) ppm; $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ 18.3 (2 $CH_3$), 20.5 ($CH_3$), 24.8 ($CH_2$ azir), 33.0 (CHazir), 50.3 ($CH_2$), 74.0 ($C_q$), 126.7 ($C_{ar}$), 127.5 ($C_{ar}$), 129.4 ($C_{ar}$), 129.5 ($C_{ar}$), 131.1 ($C_{q\ ar}$), 143.5 ($C_{q\ ar}$), 144.6 ($C_{q\ ar}$) ppm; IR (KBr): 3057, 3032, 2975, 2939, 2897, 1595, 1489, 1448, 1346, 1263, 1236, 1151, 1032, 902, 847, 746, 696, 632 $cm^{-1}$; HRMS (EI) *m/z* calcd for $C_{31}H_{32}N_2$: 432.2599, found 432.2565.

#### 4.4.9. (*S*)-*N*-(Aziridin-2-ylmethyl)aniline 20

Yield 70%, colorless oil, $[\alpha]_D^{23}$ = +11.9 (*c* 0.3, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 1.52 (d, 1H, $J_{H,H}$ = 3.0 Hz), 1.86 (d, 1H, $J_{H,H}$ = 6.0 Hz), 2.30–2.34 (m, 1H), 3.05 (dd, 1H, $J_{H,H}$ = 6.0, $J_{H,H}$ = 13.0 Hz), 3.36 (dd, 1H, $J_{H,H}$ = 4.0, $J_{H,H}$ = 13.0 Hz), 6.64–6.66 (m, 2H), 6.70–6.73 (m, 1H), 7.16–7.19 (m, 2H) ppm; $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ 23.5 ($CH_2$ azir), 29.1 (CHazir), 46.9 ($CH_2$), 113.0 ($C_{ar}$), 117.7 ($C_{ar}$), 129.2 ($C_{ar}$), 148.2 ($C_{q\ ar}$) ppm; IR (film): 3354, 3307, 3108, 3051, 2924, 2850, 1604, 1506, 1435, 1321, 1261, 1180, 1072, 991, 870, 754, 694 $cm^{-1}$; HRMS (EI) *m/z* calcd for $C_9H_{12}N_2$: 148.1003, found 140.1000.

#### 4.4.10. (*S*)-*N*-(Aziridin-2-ylmethyl)-4-methoxyaniline 21

Yield 68%, yellow oil, $[\alpha]_D^{23}$ = +14.0 (*c* 0.3, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 1.51 (d, 1H, $J_{H,H}$ = 3.0 Hz), 1.86 (d, 1H, $J_{H,H}$ = 6.0 Hz), 2.31 (dd, 1H, $J_{H,H}$ = 3.0, $J_{H,H}$ = 6.0 Hz), 2.98 (dd, 1H, $J_{H,H}$ = 6.0, $J_{H,H}$ = 13.0 Hz), 3.31 (dd, 1H, $J_{H,H}$ = 4.0, $J_{H,H}$ = 13.90 Hz), 3.73 ($s_{br}$, 1H, NH), 3.74 (s, 3H), 6.61–6.63 (m, 2H), 6.77–6.79 (m, 2H) ppm; $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ 23.5 ($CH_2$ azir), 29.3 (CHazir), 48.1 ($CH_2$), 55.8 ($CH_3$), 114.4 ($C_{ar}$), 115.0 ($C_{ar}$), 142.5 ($C_{q\ ar}$), 152.4 ($C_{q\ ar}$) ppm; IR (film): 3356, 3309, 3275, 3065, 3033, 2996, 2852, 2830, 1618, 1513, 1465, 1402, 1287, 1234, 1179, 1035, 903, 821, 708, 669, 526 $cm^{-1}$; ESI-MS: *m/z*: 179 (100, $[M+H]^+$); Anal. Calcd for $C_{10}H_{14}N_2O$ (178.23): C, 67.39; H, 7.92; N, 15.72. Found: C, 67.37; H, 7.91; N, 15.69.

#### 4.4.11. (*S*)-*N*-(Aziridin-2-ylmethyl)-2,4,6-trimethylaniline 22

Yield 74%, colorless oil, $[\alpha]_D^{23}$ = +12.7 (*c* 0.3, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 1.48 (d, 1H, $J_{H,H}$ = 3.0 Hz), 1.85 (d, 1H, $J_{H,H}$ = 6.0 Hz), 2.22–2.23 (m, 4H), 2.26 (d, 1H, $J_{H,H}$ = 6.0 Hz), 2.28 (s, 6H), 2.78 (dd, 1H, $J_{H,H}$ = 7.0, $J_{H,H}$ = 13.0 Hz), 3.12 (dd, 1H, $J_{H,H}$ = 4.5, $J_{H,H}$ = 13.0 Hz), 6.82 ($s_{br}$, 2H) ppm; $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ 18.3 (2 $CH_3$), 20.5 ($CH_3$), 23.4 ($CH_2$ azir), 30.1 (CHazir), 52.3 ($CH_2$), 129.4 ($C_{ar}$), 129.9 ($C_{ar}$), 131.5 ($C_{q\ ar}$), 143.0 ($C_{q\ ar}$) ppm; IR (film): 3356, 3301, 2994, 2943, 2915, 2856, 1751, 1593, 1487, 1444, 1375, 1306, 1233, 1157, 1032, 853, 754 $cm^{-1}$; ESI-MS: *m/z*: 189 (100, $[M-H]^-$); Anal. Calcd for $C_{12}H_{18}N_2$ (190.28): C, 75.74; H, 9.53; N, 14.72. Found: C, 75.58; H, 9.40; N, 14.53.

### 4.5. Asymmetric arylation of *p*-tolualdehyde with phenylboronic acid in the presence of $Et_2Zn$—General procedure[18]

A solution of diethylzinc (2.5 mmol) was added dropwise to a solution of phenylboronic acid (0.5 mmol) in toluene (1.5 mL) under nitrogen atmosphere. After stirring for 15 min. at 60 °C, the mixture was cooled to ambient temperature and the solution of the corresponding amine **12**–**22** (10 mol %) in toluene (1 mL) was added. After the complete precipitation of an amorphous white solid, a mixture was cooled to 0 °C and *p*-tolualdehyde (0.5 mmol) was added. After stirring for 24 h, the reaction was quenched with 15 ml of saturated $NH_4Cl$ aqueous solution and the aqueous phase was extracted three times with diethyl ether. The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and the solvents were evaporated in vacuo. (*S*)-(4-Methylphenyl)phenylmethanol was purified via column chromatography (silica gel, hexane with ethyl acetate in gradient). Yield and enantiomeric excess values are listed in Table 3.

#### 4.5.1. (*S*)-(4-Methylphenyl)(phenyl)methanol

Colorless oil; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 2.15 (d, 1H, *J* = 3.6 Hz), 2.34 (s, 3H), 5.83 (d, 1H, *J* = 3.6 Hz), 7.14–7.16 (m, 2H), 7.25–7.27 (m, 3H), 7.32–7.35 (m, 2H), 7.38–7.39 (m, 2H) ppm; *ee* determination conditions: Chiralcel OD, hexane:$^i$PrOH = 95/5, flow = 0.5 mL/min, retention time: 16.4 min (major), 18.4 min (minor).

### 4.6. Asymmetric addition of diethylzinc to benzaldehyde—General procedure[8a]

The corresponding amine **12**–**22** (0.1 mmol) and toluene (10 mL) were placed in a round bottomed flask. To ensure dryness, 5 mL of toluene were distilled off. The solution was cooled to 0 °C and diethylzinc solution (1.0 M in hexane, 3 mmol) was added under argon. After the complete precipitation of an amorphous white solid, benzaldehyde (1 mmol) was added at 0 °C and the mixture was stirred at room temperature overnight. Then, a 5% aqueous solution of hydrochloric acid was added, layers were separated and the aqueous phase was extracted with diethyl ether (4 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous $MgSO_4$. The solvents were evaporated in vacuo to afford a crude (*S*)-1-phenyl-1-propanol, which was purified via column chromatography (silica gel, hexane with ethyl acetate in gradient 95:5). Yield and enantiomeric excess values are listed in Table 4. *(S)-1-Phenyl-1-propanol:* Yellow oil; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 0.96 (t, 3H, *J* = 7.4 Hz), 1.72–1.91 (m, 2H), 1.94 (s, 1H), 4.63 (t, 1H, *J* = 6.6 Hz), 7.29–7.40 (m, 5H) ppm; *ee* determination conditions: Chiralcel OD-H, hexane:$^i$PrOH = 98/2, flow = 0.7 mL/min, retention time: 19.7 min (minor), 23.5 min (major).

### 4.7. Enantioselective epoxidation of chalcone—General procedure[24]

The corresponding amine (0.1 mmol) and anhydrous $Et_2O$ (4 mL) were placed in a round bottomed flask under nitrogen atmosphere. After cooling to 0 °C in an ice-bath, $Et_2Zn$ (0.2 mmol, 1 M solution in toluene) was added while stirring. After the complete precipitation of an amorphous white solid, chalcone (0.5 mmol) and CMHP (0.6 mmol, 80% solution in cumene) were added and the mixture was stirred at 0 °C overnight. The reaction was quenched with aq. sat. $NaHCO_3$ and extracted with $Et_2O$. The organic layer was washed with aqueous $Na_2CO_3$ and brine. The combined organic layers were dried with $MgSO_4$, and the solvent was evaporated in vacuo. A crude product was purified by column chromatography (silica gel, hexane with ethyl acetate in gradient 95:5). Yield and enantiomeric excess values are listed in Table 5.

#### 4.7.1. [(2*R*,3*S*)-3-Phenyloxiran-2-yl]-phenylmethanone

White solid; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 4.09 (d, 1H, *J* = 2.0 Hz), 4.29 (d, 1H, *J* = 2.0 Hz), 7.33–7.46 (m, 5H), 7.49–7.51 (m, 2H), 7.62–7.64 (m, 1H), 8.02–8.03 (m, 2H) ppm; *ee* determination conditions: Chiralcel OD-H, hexane:$^i$PrOH = 95/5, flow = 1.0 mL/min, retention time: 10.0 min (minor), 11.2 min (major).

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## A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetasy.2017.10.018.

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