A new approach towards 1-phenyl and 1-benzyl substituted 2-(aminomethyl)cyclopropanecarboxamides as novel derivatives of the antidepressant Milnacipran†

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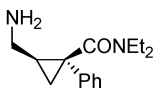
2-(2-Cyano-2-phenylethyl)aziridines were converted into novel *trans*-2-aminomethyl-1-phenylcyclopropanecarboxamides *via* regiospecific ring opening and 3-*exo*-*tet* cyclisation, thus providing the first convenient entry into the *trans*-isomer of Milnacipran as a useful template for further derivatisation. Furthermore, unprecedented 2-aminomethyl-1-benzylcyclopropanecarboxamides have been synthesized using two different routes starting from 2-(2-cyanoethyl)aziridines, both involving α-benzylation with respect to the nitrile group and aziridine to cyclopropane ring transformation.

Introduction

The use of antidepressants and other psychotropic drugs has witnessed an enormous growth in recent years, and antidepressants have become the most commonly prescribed drugs in the US. (±)-Milnacipran **1**, a dual serotonin-noradrenaline reuptake inhibitor, is one of the newer antidepressants used for the routine treatment of patients with major depression.[1] The overall effectiveness and tolerability of Milnacipran is comparable with other antidepressants, and it may even benefit some patient populations who experience adverse effects from other antidepressants in the acute phase of treatment for major depression.[1] Consequently, increasing efforts are devoted to the design and synthesis of analogues of Milnacipran as potential new antidepressants.[2]



***rac*-1** (Milnacipran)

However, the biological study of new Milnacipran derivatives has been limited to modifications at the aminomethyl moiety, the carboxamide group and the phenyl substituent.[2] Two major structural alterations have not been evaluated up to now, *i.e.* *trans*- instead of *cis*-2-(aminomethyl)cyclopropanecarboxamides and the introduction of a 1-benzyl instead of a 1-aryl group, which are direct consequences of the commonly used synthetic approach towards Milnacipran and its derivatives. Indeed, reaction of arylacetonitriles with epichlorohydrin in strong basic medium, followed by lactonisation is known to afford 1-aryl-3-oxabicyclo[3.1.0]hexan-2-ones, which are ring opened by phthalimide and finally converted into *cis*-2-aminomethyl-1-arylcyclopropanecarboxamides using an amine and hydrazine.[3]

By choosing the starting arylacetonitrile (variation of the 1-aryl group) and the amine (variation of the carboxamide moiety), different types of *cis*-2-aminomethyl-1-arylcyclopropanecarboxamides can be prepared.

Via a sequence of reaction steps, different α-alkyl substituted aminomethyl groups can also be obtained starting from 1-aryl-3-oxabicyclo[3.1.0]hexan-2-ones.[2]

In this paper, a short and convenient new approach towards *trans*-2-aminomethyl-1-phenylcyclopropanecarboxamides starting from 2-(2-cyano-2-phenylethyl)aziridines is presented. The preparation of the diastereomeric form of Milnacipran, *i.e.* *trans*-2-aminomethyl-1-phenylcyclopropane-*N*,*N*-diethylcarboxamide, has been neglected so far in the literature, as only one report can be found in which this *trans*-isomer has been synthesized *via* a long and cumbrous approach.[4] Furthermore, the flexibility of the newly developed methodology is demonstrated by the first synthesis of 1-benzyl substituted 2-(aminomethyl)cyclopropanecarboxamides, in addition to the well-known 1-phenyl derivatives. Due to the increasing use of antidepressants in modern medicine, the development of novel approaches towards structurally different 2-(aminomethyl)cyclopropanecarboxamides remains an important challenge for organic and medicinal chemists.

Results and discussion

Aziridines are valuable three-membered ring systems in synthetic organic chemistry[5], *e.g.* as substrates for aziridine to cyclopropane ring transformations.[6,7] In order to introduce a phenyl group into the three-membered carbocycle, the coupling between phenylacetonitrile (1.1 equiv) and 2-(bromomethyl)aziridines **2** was accomplished using lithium diisopropylamide (LDA) in THF, affording novel 2-(2-cyano-2-phenylethyl)aziridines **3** as mixtures of diastereomers in good yields. Subsequently, treatment of the latter aziridines **3** with one equivalent of an arylmethyl bromide in acetonitrile resulted in 5-amino-4-bromo-2-phenylpentanenitriles **5** after reflux for 5 hours through regiospecific ring opening of the *in situ* formed aziridinium salts **4** by bromide. Detailed spectral analysis confirmed the structural identity of these novel

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† Electronic supplementary information (ESI) available: Experimental details and spectral data of compounds **3b–e**, **5b–f**, **6b–f**, **7b–d**, **14b–c** and **15b–c**. CCDC reference number 723556. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b904611a

N-(2-bromo-4-cyano-4-phenylbutyl)amines **5**, excluding the formation of the corresponding regioisomers. The presence of a γ-bromonitrile moiety in aminonitriles **5** allows a formal 1,3-intramolecular ring closure toward cyclopropanecarbonitriles upon α-deprotonation with respect to the nitrile moiety and subsequent bromide expulsion through nucleophilic displacement. In accordance with the previously reported 3-*exo*-*tet* ring closure of *N*-[2-chloro-1-(cyanomethyl)ethyl]benzimidates[6] and 5-amino-4-bromopentanenitriles[7], the premised cyclisation of γ-bromonitriles **5** proceeded very nicely utilizing 1.5 equiv of potassium *tert*-butoxide in THF at rt for 5 hours, affording novel 2-aminomethyl-1-phenylcyclopropanecarbonitriles **6** as *cis*/*trans*-mixtures in good yields.

Due to the synthetic utility of nitriles as precursors of carboxylic acids, esters and amides, the search for novel types of functionalized aminonitriles has become an important challenge in organic synthesis.[8] In a final step, the nitrile group in compounds **6** was transformed into a carboxamide moiety, either by acid or by base hydrolysis. Thus, treatment of cyclopropanecarbonitriles **6** with 26 equiv of concentrated sulfuric acid in CH_2Cl_2 furnished the corresponding cyclopropanecarboxamides **7** after 21 hours at 10 °C as mixtures of *cis*/*trans*-isomers (*cis*/*trans* 42–48/52–58) (Scheme 1, Table 1). However, as the hydrolysis of the *cis*-isomer proceeded more sluggishly than that of the *trans*-isomer, the reaction mixture contained a minor amount of starting *cis*-cyclopropanecarbonitriles **6** as a third constituent (5–36%). Interestingly, the major isomers could be easily isolated from the mixtures by crystallisation from ethanol (32–54%) and were unambiguously assigned as *trans*-2-aminomethyl-1-phenylcyclopropanecarboxamides *trans*-**7** by X-ray analysis (Fig. 1). The minor constituents, *i.e.* *cis*-2-aminomethyl-1-phenylcyclopropanecarboxamides *cis*-**7** were obtained in analytically pure form through column chromatography on silica gel, albeit in lower yields (14–35%). Whereas acid hydrolysis of cyclopropanecarbonitrile **6e** bearing a methoxy group at the aryl moiety only led to complex mixtures, the latter nitrile **6e** was easily converted into the corresponding amide **7e** using 5 equiv of potassium hydroxide in an ethanol/water mixture (3/1) under reflux for 3 days. These prolonged reaction times were necessary in order to drive the reaction to completion.

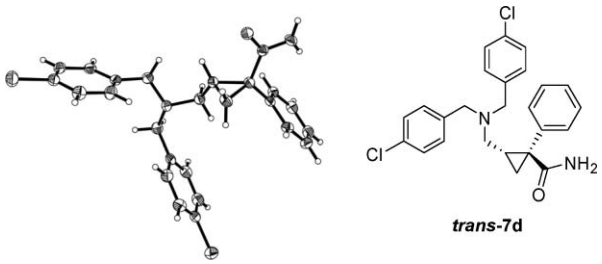


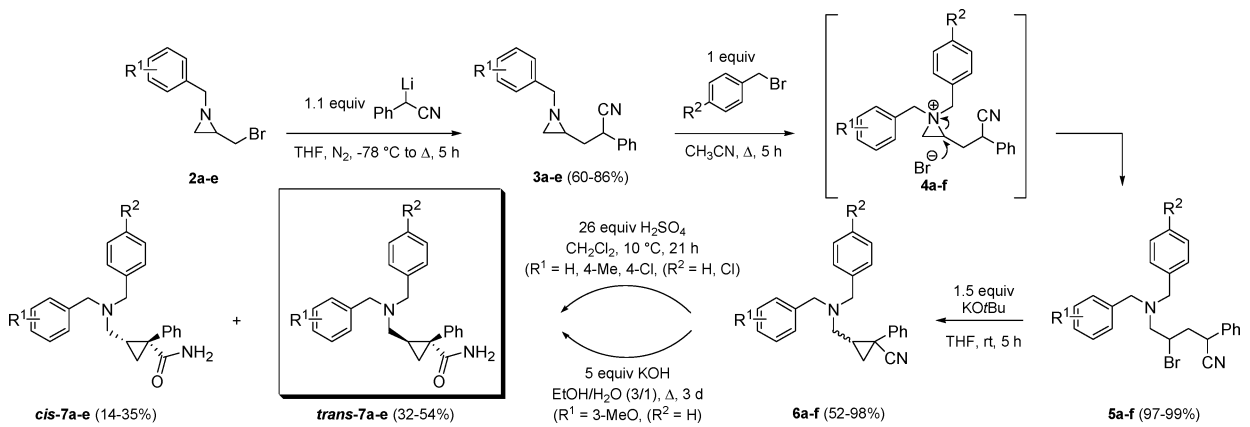
Fig. 1 X-Ray structure of compound ***trans*-7d**.

In order to demonstrate the usefulness of this approach towards the synthesis of Milnacipran analogues, carboxamide ***trans*-7d** was *N*,*N*-diethylated utilizing 4 equiv of sodium hydride and 3 equiv of bromoethane in dry THF, resulting in the corresponding *N*,*N*-diethylcarboxamide **8** in 99% yield. Subsequently, deprotection of the *N*,*N*-di(4-chlorophenylmethyl)amino moiety was achieved upon treatment with palladium on carbon in methanol under reflux in the presence of 5 equiv of ammonium

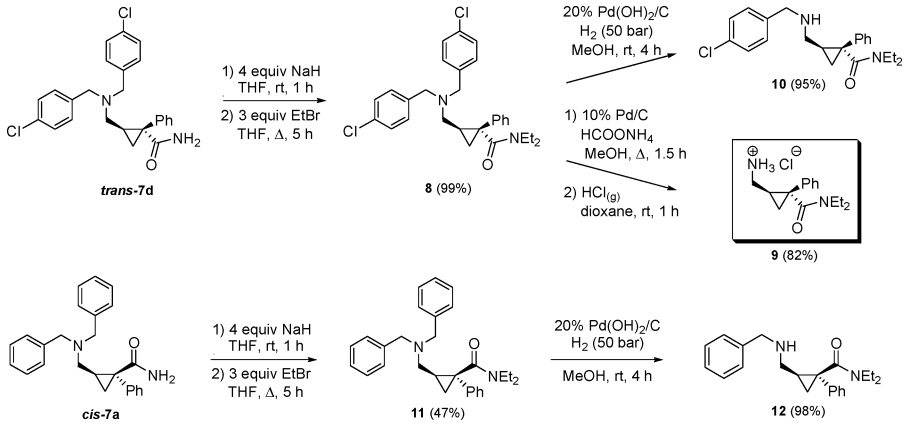
Table 1 Synthesis of aziridines **3**, β-bromoamines **5**, cyclopropanecarbonitriles **6** and cyclopropanecarboxamides **7**

Entry	R^1	Compound **3** (yield, *dr*)[a,b]	R^2	Compounds **5** (yield, *dr*)[c]	Compounds **6** (yield, *cis*/*trans*)[a,b,d]	Compounds **7** (yield, *cis*/*trans*)[a,b]
1	H	**3a** (76%, 51/49)	H	**5a** (99%, 54/46)	**6a** (55%, 48/52)	**7a** (55%, 48/52)
2	4-Me	**3b** (72%, 53/47)	H	**5b** (98%, 55/45)	**6b** (73%, 49/51)	**7b** (49%, 49/51)
3	4-Cl	**3c** (86%, 54/46)	H	**5c** (99%, 53/47)	**6c** (58%, 48/52)	**7c** (54%, 48/52)
4	4-Cl	**3c** (86%, 54/46)	Cl	**5d** (98%, 56/44)	**6d** (85%, 44/56)	**7d** (87%, 44/56)
5	3-MeO	**3d** (60%, 54/46)	H	**5e** (97%, 53/47)	**6e** (98%, 42/58)	**7e** (75%, 43/57)
6	4-MeO	**3e** (69%, 57/43)	H	**5f** (98%, 57/43)	**6f** (52%, 49/51)	—

[a] Isolated yields of the mixtures of diastereomers after column chromatography. [b] Diastereomeric ratio determined by means of GC analysis. [c] Diastereomeric ratio determined by means of ^{1}H NMR. [d] *cis*/*trans* or *vice versa*.



Scheme 1



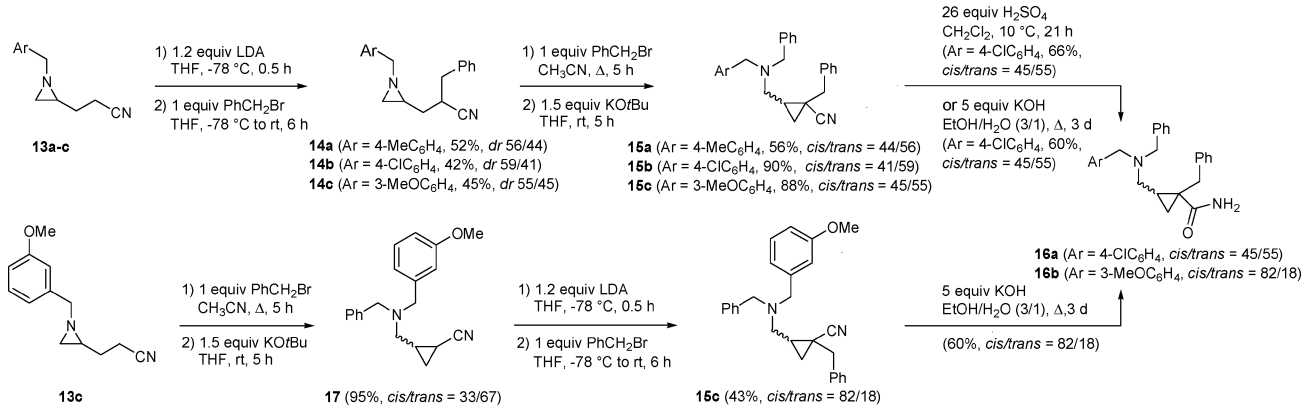
Scheme 2

formate, followed by formation of the hydrochloride salt by means of gaseous hydrogen chloride in dioxane (Scheme 2). In this way, the first convenient entry into *trans*-2-aminomethyl-1-phenyl-*N*,*N*-diethylcyclopropanecarboxamide hydrochloride **9** as the diastereomeric counterpart of Milnacipran is presented. It is worth mentioning that treatment of *N*,*N*-diethylcarboxamide **8** with palladium hydroxide on carbon (20%) in methanol under H_2 atmosphere always resulted in the mono-debenzylated amine **10** as the sole reaction product in excellent yield.

Analogously, *cis*-2-aminomethyl-1-phenylcyclopropanecarboxamide ***cis*-7a** was *N*,*N*-diethylated utilizing 4 equiv of NaH and 3 equiv of EtBr in THF, resulting in the corresponding *N*,*N*-diethylcarboxamide **11** in 47% yield. Due to the unexpected reconversion of amide ***cis*-7a** into nitrile ***cis*-6a** under the given reaction conditions, the isolated yield of *N*,*N*-diethylamide **11** was significantly lower as compared to the *trans*-isomer **8**. The conversion of amide ***cis*-7a** into nitrile ***cis*-6a** using an alkyl halide in basic conditions is remarkable, as no literature precedents can be found.[9] Application of the same reaction conditions to amides ***cis*-7c**,**d** also resulted in partial reconversion to nitriles ***cis*-6c**,**d** (29–72%), whereas surprisingly no nitriles ***trans*-6** were formed upon treatment of amides ***trans*-7** with NaH and EtBr. Apparently, the spacial proximity of the aminomethyl group with regard to the amide moiety in *cis*-2-(aminomethyl)cyclopropanecarboxamides ***cis*-7** is required to facilitate *O*-alkylation after deprotonation of the amide to form an intermediate imidate, followed by a second deprotonation and subsequent expulsion of ethoxide resulting in the corresponding nitriles ***cis*-6**. If no nitrogen atom resides in the proximity of the carboxamide group, for example in *trans*-2-(aminomethyl)cyclopropanecarboxamides ***trans*-7**, exclusive *N*-alkylation occurs after deprotonation of the amide moiety to afford the corresponding *N*,*N*-diethylamides. Furthermore, no nitrile formation was observed upon treatment of, for example, benzamide and *n*-butyramide with NaH and EtBr.

In order to deprotect the *N*,*N*-dibenzylamino moiety, amine **11** was treated with $Pd(OH)_2$ on carbon in methanol under H_2 atmosphere, again resulting in benzylamine **12** as a sole reaction product in excellent yield (Scheme 2). Unfortunately, attempted removal of both benzyl groups of amide **11** utilizing palladium on carbon (10%) in methanol under reflux in the presence of ammonium formate (5 equiv) only resulted in complex reaction mixtures. Extensive efforts towards the *N*,*N*-deprotection of *cis*-2-{[(*N*,*N*-di(arylmethyl)amino]methyl}-1-phenylcyclopropane-*N*,*N*-diethylcarboxamides failed, leading either to the corresponding mono-deprotected 2-(*N*-benzylaminomethyl)cyclopropanecarboxamides in nearly quantitative yield (20% $Pd(OH)_2/C$, 5 bar H_2, MeOH, 48 h or 6 days), to complex reaction mixtures (10% Pd/C, $HCOONH_4$, MeOH, reflux, 5 sec, 10 min, 50 min or 90 min) or to the recovery of the starting material (10% Pd/C, $HCOONH_4$, MeOH, room temperature, 10 min or 90 min). Hydrogenolysis of 2-(*N*-benzylaminomethyl)cyclopropanecarboxamides after isolation and purification did not result in conversion (20% $Pd(OH)_2/C$, 5 bar H_2, MeOH, 48 h), as the starting compound was recovered completely afterwards.

The scope of this synthetic methodology was further extended towards the preparation of 2-aminomethyl-1-benzylcyclopropanecarboxamides, which have not been described in the literature so far. Two different approaches were thus evaluated. In the first method, 2-(2-cyanoethyl)aziridines[7] were α-benzylated upon treatment with 1.2 equiv of LDA and one equiv of benzyl bromide in THF, affording 2-(2-cyano-3-phenylpropyl)aziridines **14** as mixtures of diastereomers (55–59/41–45) after 6 hours at rt. Besides the desired aziridines **14**, the reaction mixtures also contained minor amounts of 2-(2-benzyl-2-cyano-3-phenylpropyl)aziridines due to double alkylation (16–24%). Subsequently, aziridines **14** were transformed into 5-amino-2-benzyl-4-bromopentanenitriles by reaction with one equivalent of benzyl bromide in acetonitrile under reflux—*via* regiospecific ring opening of intermediate aziridinium ions—which were finally cyclised into 2-aminomethyl-1-benzylcyclopropanecarbonitriles **15** as *cis*/*trans*-mixtures (51–52/48–49) utilizing 1.5 equiv of potassium *tert*-butoxide (KO*t*Bu) in THF at rt for 5 hours (Scheme 3). Again, functional group transformation of nitriles **15** to carboxamides **16** was performed either in acidic medium (26 equiv of H_2SO_4 in CH_2Cl_2 at 10 °C for 21 hours) or in basic medium (5 equiv of KOH in EtOH/H_2O 3/1 at reflux for 3 days), furnishing 2-aminomethyl-1-benzylcyclopropanecarboxamides **16** in good yields. Unfortunately, *cis* and *trans* isomers of amides **16** appeared to be inseparable by column chromatography. In an attempt to shorten the reaction time of basic hydrolysis, experiments were conducted using microwave irradiation, resulting in a reduction of the conversion time from 3 days to 30 min at 185 °C (4 equiv of KOH, EtOH/H_2O 3/1, 200 Watt).



Scheme 3

In this case, the same yields and *cis*/*trans* ratios were obtained as compared to the classical methodology (reflux for 3 days). In an alternative approach, 2-(aminomethyl)cyclopropanecarbonitrile **17**, prepared from 2-(2-cyanoethyl)aziridine **13c** *via* a two-step approach[7], was benzylated in α-position with respect to the nitrile group using 1.2 equiv of LDA and 1 equivalent of benzyl bromide in THF (Scheme 3). Thus, *cis*-2-aminomethyl-1-benzylcyclopropanecarbonitrile ***cis*-15c** was obtained in a diastereoselective and convenient way as the major constituent due to steric hindrance by the aminomethyl moiety during alkylation (*cis*/*trans* 82/18). Also the double alkylation of 2-(2-cyanoethyl)aziridines **13** could be avoided *via* this approach. It should be noted that all the indicated yields refer to the pure compounds, obtained after column chromatography. This methodology enables the first short and easy synthesis of 1-benzyl substituted precursors of novel Milnacipran derivatives.

In conclusion, a short and efficient approach towards *trans*-2-aminomethyl-1-phenylcyclopropanecarboxamides is reported starting from 2-(2-cyano-2-phenylethyl)aziridines, thus providing the first convenient entry into the *trans*-isomer of Milnacipran as a useful template for further evaluation. In a second part, 2-aminomethyl-1-benzylcyclopropanecarboxamides have been synthesized using two different routes starting from 2-(2-cyanoethyl)aziridines, in which the benzyl moiety was incorporated by α-alkylation with respect to the nitrile group. This is the first report on the synthesis of 1-benzyl substituted cyclopropanecarboxamides as novel derivatives of Milnacipran.

Experimental section

Synthesis of 2-(2-cyano-2-phenylethyl)aziridines 3

As a representative example, the synthesis of 1-benzyl-2-(2-cyano-2-phenylethyl)aziridine **3a** is described here. To a solution of diisopropylamine (11 mmol, 1.1 equiv) in dry THF (10 mL), *n*-BuLi (4.4 mL, 11 mmol, 1.1 equiv, 2.5M) was added *via* a syringe at −78 °C under nitrogen atmosphere, and the resulting solution was stirred for 30 min at −78 °C. Subsequently, a solution of phenylacetonitrile (11 mmol, 1.1 equiv) in THF (10 mL) was added *via* a syringe at −78 °C, and the resulting solution was stirred for 1 hour at −78 °C. Then, a solution of 1-benzyl-2-(bromomethyl)aziridine **2a** (10 mmol) in THF (10 mL) was added *via* a syringe at −78 °C, followed by heating under reflux for 5 hours. Afterwards, the reaction mixture was poured into water (50 mL) and extracted with Et_2O (3 × 50 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 1-benzyl-2-(2-cyano-2-phenylethyl)aziridine **3a**, which was purified by means of column chromatography on silica gel (hexane/EtOAc 3/1).

1-Benzyl-2-(2-cyano-2-phenylethyl)aziridine 3a

Spectral data derived from the mixture of diastereomers.

Major isomer. Yellow oil. $R_f = 0.05$ (Hexane/EtOAc 3/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.58–1.67 (1H, m, (*H*CH)CHCN); 1.60 (1H, d, J = 6.6 Hz, (H_{cis}CH)CHN); 1.74 (1H, d, J = 3.3 Hz, (HCH_{trans})CHN); 1.79–1.86 (1H, m, CHN); 2.14 (1H, d × d × d, J = 13.8, 10.7, 4.1 Hz, (HC*H*)CHCN); 3.36 and 3.56 (2H, 2 × d, J = 12.7 Hz, N(HCH)$C_{arom, quat}$); 3.67 (1H, d × d, J = 10.7, 4.7 Hz, CHCN); 7.11–7.16 and 7.28–7.38 (10H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$); δ 34.70, 36.15, 36.76, 39.86, 64.85, 120.63, 127.21, 127.45, 128.61, 128.72, 129.18, 135.76, 138.89. IR (ATR, cm^{-1}): ν_{CN} = 2240. MS (70 eV): *m*/*z* (%): 263 (M^++1, 100).

Minor isomer. Yellow oil. $R_f = 0.05$ (Hexane/EtOAc 3/1).^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44–1.48 (2H, m, (H_{cis}CH)CHN and CHN); 1.71 (1H, d, J = 3.3 Hz, (HCH_{trans})CHN); 2.01–2.07 (2H, m, CH_2CHCN); 3.32 and 3.42 (2H, 2 × d, J = 13.2 Hz, N(HCH)$C_{arom, quat}$); 3.79 (1H, t, J = 7.2 Hz, CHCN); 7.11–7.16 and 7.28–7.38 (10H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$); δ 34.00, 35.48, 36.29, 39.05, 64.62, 120.95, 127.56, 127.64, 128.15, 128.28, 128.34, 135.15, 139.07. IR (ATR, cm^{-1}): ν_{CN} = 2240. MS (70 eV): *m*/*z* (%): 263 (M^++1, 100).

Anal. Calcd for $C_{18}H_{18}N_2$: C 82.41; H 6.92; N 10.68. Found: C 82.58; H 7.07; N 10.55.

Synthesis of 5-amino-4-bromo-2-phenylpentanenitriles 5

As a representative example, the synthesis of 4-bromo-5-dibenzylamino-2-phenylpentanenitrile **5a** is described here. To a stirred solution of 1-benzyl-2-(2-cyano-2-phenylethyl)aziridine **3a** (7.5 mmol) in acetonitrile (10 mL), benzyl bromide (7.5 mmol, 1.0 equiv) was added, and the resulting mixture was heated under reflux for 5 hours. Evaporation of the solvent afforded 4-bromo-5-dibenzylamino-2-phenylpentanenitrile **5a** in high purity (> 95% based on ^{1}H NMR).

4-Bromo-5-dibenzylamino-2-phenylpentanenitrile 5a

Spectral data derived from the mixture of diastereomers.

Yellow-orange oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.70 (1H, d × d × d, J = 14.9, 11.2, 4.1 Hz, (HC*H*)CHCN); 2.03 (1H, d × d × d, J_{gem} = 14.7, 10.6, 4.1 Hz, (HC*H*)CHCN); 2.52–2.66 (2 × 1H, 2 × m, 2×(*H*CH)CHCN); 2.73–2.86 (3H, m, N(*H*CH)CH and NC*H*$_2$CH); 2.97 (1H, d × d, J = 13.5, 5.8 Hz, N(HC*H*)CH); 3.32, 3.52, 3.56 and 3.69 (2 × 4H, 2 × 2 × d, J = 13.5, 13.2 Hz, 4 × N(HCH)C_{arom}); 3.42–3.54 (1H, m, CHBr); 4.03 (1H, d × d, J = 11.3, 4.1 Hz, CHCN); 4.16 (1H, d × d, J = 11.8, 4.1 Hz, CHCN); 4.17–4.26 (1H, m, CHBr); 7.15–7.39 (30H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 35.11, 36.44, 41.83, 42.74, 49.17, 50.68, 59.11, 59.31, 60.59, 60.81, 119.96, 121.06, 127.30, 127.47, 127.93, 128.39, 128.51, 128.83, 128.92, 129.07, 129.16, 129.25, 129.31, 129.46, 134.28, 135.35, 138.46, 138.61. IR (ATR, cm^{-1}): ν_{CN} = 2241. MS (70 eV): *m*/*z* (%): 433/5 (M^++1, 10), 353 (100). Anal. Calcd for $C_{25}H_{25}BrN_2$: C 69.28; H 5.81; N 6.46. Found: C 69.41; H 6.03; N 6.39.

Synthesis of 2-aminomethyl-1-phenylcyclopropanecarbonitriles 6

As a representative example, the synthesis of 2-[(dibenzylamino)methyl]-1-phenylcyclopropanecarbonitrile **6a** is described here. To a solution of 4-bromo-5-dibenzylamino-2-phenylpentanenitrile **5a** (7.5 mmol) in dry THF (15 mL) was added potassium *tert*-butoxide (11.25 mmol, 1.5 equiv) at room temperature. After stirring for 5 hours at room temperature, the reaction mixture was poured into water (50 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with water (2 × 50 mL) and brine (1 × 50 mL). Drying ($MgSO_4$), filtration of the drying agent and removal of the solvent afforded 2-[(dibenzylamino)methyl]-1-phenylcyclopropanecarbonitrile **6a** as a mixture of *cis*/*trans*-isomers. The *cis*-isomer was isolated in pure form by means of column chromatography on silica gel (hexane/EtOAc 2/1).

***cis*-2-[(Dibenzylamino)methyl]-1-phenylcyclopropanecarbonitrile *cis*-6a**

Yellow oil. R_f = 0.18 (Hexane/EtOAc 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (1H, d × d, J = 7.4, 5.2 Hz, CH(*H*CH)CN); 1.56 (1H, d × d, J = 8.5, 5.2 Hz, CH(*H*CH)CN); 1.64–1.74 (1H, m, CH); 2.82 and 2.94 (2H, 2 × d × d, J = 13.6, 6.3, 6.1 Hz, NC*H*$_2$CH); 3.65 and 3.76 (2 × 2H, 2 × d, J = 13.5 Hz, 2 × NCH_2C_{arom}); 7.18–7.40 (15H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 19.81, 23.45, 28.82, 55.43, 58.70, 120.66, 125.56, 127.15, 127.62, 128.41, 128.84, 128.99, 136.28, 139.36. IR (ATR, cm^{-1}): ν_{CN} = 2232. MS (70 eV): *m*/*z* (%): 353 (M^++1, 100). Anal. Calcd for $C_{25}H_{24}N_2$: C 85.19; H 6.86; N 7.95. Found: C 85.43; H 7.06; N 8.07.

***trans*-2-[(Dibenzylamino)methyl]-1-phenylcyclopropanecarbonitrile *trans*-6a**

Spectral data derived from the mixture of diastereomers.

Yellow oil. R_f = 0.18 (Hexane/EtOAc 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (1H, d × d, J = 7.4, 5.2 Hz, CH(*H*CH)CN); 1.64–1.73 (1H, m, CH(HC*H*)CN); 1.83 (1H, d × d, J = 13.5, 8.0 Hz, N(*H*CH)CH); 1.94–2.04 (1H, m, CH); 2.40 (2H, d × d, J = 13.5, 5.2 Hz, N(*H*CH)CH); 3.41 and 3.57 (2 × 2H, 2 × d, J = 13.5 Hz, 2 × NCH_2C_{arom}); 7.11–7.39 (15H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 18.30, 18.36, 26.93, 51.98, 58.61, 123.50, 127.16, 128.12, 128.40, 128.90, 131.80, 139.21. IR (ATR, cm^{-1}): ν_{CN} = 2232. MS (70 eV): *m*/*z* (%): 353 (M^++1, 100).

Synthesis of 2-aminomethyl-1-phenylcyclopropanecarboxamides 7

As a representative example, the synthesis of 2-[(dibenzylamino)methyl]-1-phenylcyclopropanecarboxamide **7a** is described here. To an ice-cooled solution of 2-[(dibenzylamino)methyl]-1-phenylcyclopropanecarbonitrile **6a** (3 mmol) in dry CH_2Cl_2 (10 mL), concentrated sulfuric acid (4.35 mL, 26 equiv) was added, and the resulting solution was stirred for 21 hours at 10 °C. The reaction mixture was poured into ice water (25 mL), followed by extraction using a saturated solution of aqueous ammonium hydroxide and EtOAc (3 × 50 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 2-[(dibenzylamino)methyl]-1-phenylcyclopropanecarboxamide **7a**. Isolation of the *trans* isomer ***trans*-7a** was realized by means of a selective crystallisation from absolute ethanol, whereas the *cis* isomer ***cis*-7a** was obtained by column chromatography on silica gel (hexane/EtOAc 2/1).

***cis*-2-[(Dibenzylamino)methyl]-1-phenylcyclopropanecarboxamide *cis*-7a**

Yellow oil. R_f = 0.16 (Hexane/EtOAc 2/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (1H, d × d, J_{gem} = 9.1, 4.4 Hz, CH(HC*H*)C_{quat}); 1.58 (1H, d × d, J = 7.2, 4.4 Hz, CH(*H*CH)C_{quat}); 1.71–1.81 (1H, m, CH); 2.83 and 2.88 (2H, 2 × d × d, J = 13.6, 6.9, 6.1 Hz, N(*H*CH)CH); 3.64 and 3.69 (2 × 2H, 2 × (2 × d), J = 13.8 Hz, 2 × NCH_2C_{arom}); 5.58 and 6.02 (2H, 2 × s, NH_2); 7.18–7.39 (15H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 19.52, 27.00, 35.40, 52.06, 58.43, 127.04, 127.83, 128.40, 129.06, 129.13, 130.26, 139.81, 141.64, 174.39. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1671, ν_{NH2} = 3479. MS (70 eV): *m*/*z* (%): 371 (M^++1, 100).

***trans*-2-Aminomethyl-1-phenylcyclopropanecarboxamide *trans*-7a**

White crystals. R_f = 0.10 (Hexane/EtOAc 2/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (1H, d × d, J = 6.6, 3.9 Hz, CH(HC*H*)C_{quat}); 1.55 (1H, d × d, J = 13.2, 9.4 Hz, N(HC*H*)CH); 1.74 (1H, d × d, J = 8.8, 3.9 Hz, CH(*H*CH)C_{quat}); 2.15–2.24 (1H, m, CH); 2.68 (1H, d × d, J = 13.2, 3.9 Hz, N(*H*CH)CH); 3.48 and 3.66 (2 × 2H, 2 × d, J = 13.8 Hz, 2 × NCH_2C_{arom}); 5.26 and 5.81 (2H, 2 × s, NH_2); 7.16–7.29 (15H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 22.4, 23.9, 33.6, 54.4, 58.0, 126.8, 128.0, 128.2, 128.8, 129.0, 131.4, 136.3, 139.6, 176.6. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1670, ν_{NH} = 3477. MS (70 eV): *m*/*z* (%): 371 (M^++1, 100). Mp. 118.7 °C. Anal. Calcd for $C_{25}H_{26}N_2O$: C 81.05; H 7.07; N 7.56. Found: C 81.28; H 7.32; N 7.44.

Synthesis of 2-{[(*N*-benzyl-*N*-(3-methoxybenzyl)amino]methyl}-1-phenylcyclopropanecarboxamide 7e

To a solution of 2-{[(*N*-benzyl-*N*-(3-methoxybenzyl)amino]-methyl}-1-phenylcyclopropanecarbonitrile **6e** (3 mmol) in ethanol/water (3/1) (30 mL), potassium hydroxide (15 mmol, 5 equiv) was added at room temperature, and the resulting mixture was heated under reflux for 3 days.

The reaction mixture was poured into water (30 mL) and extracted with EtOAc (3 × 50 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 2-{[(*N*-benzyl-*N*-(3-methoxybenzyl)amino]methyl}-1-phenylcyclopropanecarboxamide **7e**. Isolation of both isomers was realized by means of column chromatography on silica gel (hexane/EtOAc 3/1).

cis-2-{[(*N*-Benzyl-*N*-(3-methoxybenzyl)amino]methyl}-1-phenylcyclopropanecarboxamide *cis*-7e

Yellow oil. R_f = 0.15 (Hexane/EtOAc 3/1).^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (1H, d × d, J = 9.1, 4.1 Hz, CH(HC*H*)C_{quat}); 1.60 (1H, d × d, J = 7.4, 4.1 Hz, CH(*H*CH)C_{quat}); 1.73–1.83 (1H, m, CH); 2.87 (2H, d, J = 6.6 Hz, N(*H*C*H*)CH); 3.63, 3.65, 3.69 and 3.71 (2 × 2H, 2×(2 × d), J = 13.8 Hz, 2 × NCH_2C_{arom}); 3.80 (3H, s, CH_3); 5.42 and 5.64 (2H, 2 × s, NH_2); 6.76–6.80, 6.96–6.98 and 7.20–7.41 (14H, m, CH_{arom}).^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 19.49, 27.06, 35.35, 52.10, 55.26, 58.35, 58.44, 112.32, 114.52, 121.31, 127.01, 127.80, 128.34, 129.01, 129.10, 129.28, 130.20, 139.71, 141.56, 159.73, 174.00. IR (ATR, cm^{-1}): $\nu_{C=O}$= 1671, ν_{NH2}= 3478. MS (70 eV): *m*/*z* (%): 401 (M^++1, 100).

trans-2-{[(*N*-Benzyl-*N*-(3-methoxybenzyl)amino]methyl}-1-phenylcyclopropanecarboxamide *trans*-7e

Yellow oil. R_f = 0.05 (Hexane/EtOAc 3/1).^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (1H, d × d, J = 6.6, 3.9 Hz, CH(HC*H*)C_{quat}); 1.56 (1H, d × d, J = 13.2, 9.4 Hz, N(HC*H*)CH); 1.76 (1H, d × d, J = 8.8, 3.9 Hz, CH(*H*CH)C_{quat}); 2.15–2.25 (1H, m, CH); 2.68 (1H, d × d, J = 13.2, 3.9 Hz, N(*H*CH)CH); 3.47, 3.48, 3.65 and 3.66 (2 × 2H, 2 × (2 × d), J = 13.8 Hz, 2 × NCH_2C_{arom}); 3.78 (3H, s, OCH_3); 5.28 and 5.85 (2H, 2 × s, NH_2); 6.72–6.76, 6.85–6.87 and 7.14–7.39 (14H, m, CH_{arom}).^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 22.39, 23.99, 33.57, 54.49, 55.25, 58.00, 112.52, 114.14, 121.22, 126.92, 127.06, 127.97, 128.06, 128.26, 128.87, 129.02, 129.19, 131.19, 131.38, 136.12, 139.51, 141.32, 159.65, 177.38. IR (ATR, cm^{-1}): $\nu_{C=O}$= 1671, ν_{NH2}= 3479. MS (70 eV): *m*/*z* (%): 401 (M^++1, 100). Anal. Calcd for $C_{26}H_{28}N_2O_2$: C 77.97; H 7.29; N 6.99. Found: C 78.14; H 7.46; N 6.89.

Synthesis of *trans*-2-{[(*N*,*N*-di(4-chlorobenzyl)amino]methyl}-1-phenylcyclopropane-*N*,*N*-diethylcarboxamide 8

To a solution of *trans*-2-{[(*N*,*N*-di(4-chlorobenzyl)amino]-methyl}-1-phenylcyclopropanecarboxamide ***trans*-7d** (1.5 mmol) in dry THF (10 mL), sodium hydride (6 mmol, 4 equiv) was added at room temperature, and the resulting solution was stirred for 1 hour at room temperature. Subsequently, a solution of ethyl bromide (4.5 mmol, 3 equiv) in THF (5 mL) was added at room temperature, and the resulting mixture was heated under reflux for 5 hours. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3 × 50 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded *trans*-2-{[(*N*,*N*-di(4-chlorobenzyl)amino]methyl}-1-phenylcyclopropane-*N*,*N*-diethylcarboxamide **8** (purity >95% based on ^{1}H NMR).

trans-2-{[(*N*,*N*-Di(4-chlorobenzyl)amino]methyl}-1-phenylcyclopropane-*N*,*N*-diethylcarboxamide 8

Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.54 (3H, t, J = 7.2 Hz, CH_3); 1.05 (3H, t, J = 7.2 Hz, CH_3); 1.14 (1H, d × d, J = 8.5, 5.8 Hz, CH(HC*H*)C_{quat}); 1.25–1.33 (1H, m, CH(*H*CH)C_{quat}); 1.78 (1H, d × d, J = 14.7, 9.6 Hz, N(HC*H*)CH); 2.20 (1H, d × d, J = 14.7, 4.4 Hz, N(*H*CH)CH); 2.15–2.27 (1H, m, CH); 3.13 (1H, d × q, J = 14.3, 7.2 Hz, N(*H*CH)CH_3); 3.24–3.41 (3 × 1H, m, N(HC*H*)CH_3 and NCH_2CH_3); 3.34 and 3.56 (2 × 2H, 2 × (2 × d), J = 13.8 Hz, 2 × NCH_2C_{arom}); 7.03–7.28 (13H, m, CH_{arom}).^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 12.45, 12.67, 15.46, 22.21, 35.60, 39.75, 41.36, 52.20, 57.30, 126.69, 128.11, 128.31, 128.41, 130.12, 132.38, 136.69, 138.28, 171.84. IR (ATR, cm^{-1}): $\nu_{C=O}$= 1632. MS (70 eV): *m*/*z* (%): 495/7 (M^++1, 100). Anal. Calcd for $C_{29}H_{32}Cl_2N_2O$: C 70.30; H 6.51; N 5.65. Found: C 70.47; H 6.66; N 5.54.

Synthesis of *trans*-2-aminomethyl-1-phenyl-*N*,*N*-diethylcyclopropanecarboxamide hydrochloride 9

To a solution of *trans*-2-{[(*N*,*N*-di(4-chlorobenzyl)amino]-methyl}-1-phenylcyclopropane-*N*,*N*-diethylcarboxamide **8** (1.5 mmol) in methanol (20 mL), ammonium formate (7.5 mmol, 5 equiv) and 10% Pd/C (0.15 mmol, 0.1 equiv) were added at room temperature, and the resulting mixture was heated under reflux for 1.5 hours. Afterwards, the reaction mixture was filtered over celite®. Evaporation of the solvent afforded *trans*-2-aminomethyl-1-phenyl-*N*,*N*-diethylcyclopropanecarboxamide, which was subsequently dissolved in dioxane, and gaseous hydrochloric acid was bubbled through the solution for one hour. Filtration of the resulting reaction mixture afforded *trans*-2-aminomethyl-1-phenyl-*N*,*N*-diethylcyclopropanecarboxamide hydrochloride **9** (purity >95% based on ^{1}H NMR).

trans-2-Aminomethyl-1-phenyl-*N*,*N*-diethylcyclopropanecarboxamide hydrochloride 9

White-yellow crystals. ^{1}H NMR (300 MHz, MeOD): δ 0.59 and 1.06 (2 × 3H, 2 × t, J = 7.2 Hz, 2 × CH_3); 1.38 and 1.84 (2 × 1H, 2 × d × d, J = 8.3, 5.9, 5.8 Hz, CH(*H*C*H*)C_{quat}); 2.01–2.15 (2 × 1H, m, CH and N(*H*CH)CH); 2.77–2.82 (1H, m, N(HC*H*)CH); 3.20–3.39 (3 × 1H, m, NCH_2CH_3 and N(*H*CH)CH_3); 3.50–3.64 (1H, m, N(HC*H*)CH_3); 7.34–7.44 (5H, m, CH_{arom}).^{13}C NMR (75 MHz, ref = MeOD): δ 12.5, 12.9, 15.7, 22.4, 37.0, 41.0, 41.3, 43.0, 129.0, 129.5, 130.3, 136.2, 172.9. IR (ATR, cm^{-1}): $\nu_{C=O}$= 1600, ν_{NH2}= 3381. MS (70 eV): *m*/*z* (%): 247 (M^++1-HCl, 100). Mp. 128.3 °C. Anal. Calcd for $C_{15}H_{23}ClN_2O$: C 63.70; H 8.20; N 9.91. Found: C 63.87; H 8.37; N 10.06.

Synthesis of *trans*-2-[(4-chlorobenzylamino)methyl]-1-phenylcyclopropane-*N*,*N*-diethylcarboxamide 10

A solution of *trans*-2-{[(*N*,*N*-di(4-chlorobenzyl)amino]methyl}-1-phenylcyclopropane-*N*,*N*-diethylcarboxamide **8** (1.5 mmol) in methanol (6 mL) was hydrogenated (50 bar H_2) in the presence of 20% palladium hydroxide on active charcoal (0.15 mmol, 0.1 equiv) at room temperature for 4 hours. The reaction mixture was then filtered over celite®, and evaporation of

the solvent afforded *trans*-2-[(4-chlorobenzylamino)methyl]-1-phenylcyclopropane-*N*,*N*-diethylcarboxamide **10** (purity >95% based on ^{1}H NMR).

trans-2-[(4-Chlorobenzylamino)methyl]-1-phenylcyclopropane-*N*,*N*-diethylcarboxamide 10

Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.56 (3H, t, J = 7.2 Hz, CH_3); 1.03 (3H, t, J = 7.2 Hz, CH_3); 1.23–1.34 (1H, m, CH(HC*H*)C_{quat}); 1.80 (1H, d × d, J = 5.5 CH(*H*CH)C_{quat}); 2.21–2.35 (2 × 1H, m, CH and N(HC*H*)CH); 2.45–2.54 (1H, m, N(*H*CH)CH); 3.15 (1H, d × q, J = 14.3, 7.2 Hz, N(*H*CH)CH_3); 3.21–3.30 (2 × 1H, m, N(HC*H*)CH_3 and N(*H*CH)CH_3); 3.40 (1H, d × q, J = 14.3, 7.2 Hz, N(HC*H*)CH_3); 3.83 and 3.88 (2H, 2 × d, J = 13.2 Hz, NCH_2C_{arom}); 7.15–7.36 (9H, m, CH_{arom}).^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 12.38, 12.64, 15.23, 21.48, 36.15, 39.94, 41.48, 46.49, 51.25, 127.47, 128.25, 128.48, 128.84, 128.95, 129.57, 128.95, 129.57, 171.07. IR (ATR, cm^{-1}): $\nu_{C=O}$= 1615, ν_{NH}= 3418. MS (70 eV): *m*/*z* (%): 337 (M^++1-Cl, 100). Anal. Calcd for $C_{22}H_{27}ClN_2O$: C 71.24; H 7.34; N 7.55. Found: C 71.12; H 7.41; N 7.58.

Synthesis of *cis*-2-[(benzylamino)methyl]-1-phenylcyclopropane-*N*,*N*-diethylcarboxamide 12

A solution of *cis*-2-[(*N*,*N*-dibenzylamino)methyl]-1-phenylcyclopropane-*N*,*N*-diethylcarboxamide **11** (1.5 mmol) in methanol (6 mL) was hydrogenated (50 bar H_2) in the presence of 20% palladium hydroxide on active charcoal (0.15 mmol, 0.1 equiv) at room temperature for 4 hours. The reaction mixture was then filtered over celite®, and evaporation of the solvent afforded *cis*-2-[(benzylamino)methyl]-1-phenylcyclopropane-*N*,*N*-diethylcarboxamide **12** (purity >95% based on ^{1}H NMR).

cis-2-[(Benzylamino)methyl]-1-phenylcyclopropane-*N*,*N*-diethylcarboxamide 12

Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (3H, t, J = 7.2 Hz, CH_3); 1.06 (3H, t, J = 7.2 Hz, CH_3); 1.54 (1H, d × d, J = 5.8, 5.6 Hz, CH(*H*CH)C_{quat}); 1.80 (1H, d × d, J = 8.8, 5.6 Hz, CH(HC*H*)C_{quat}); 1.83–1.93 (2 × 1H, m, CH); 2.43 (1H, d × d, J = 12.1, 10.5 Hz, N(*H*CH)CH); 3.17–3.55 (5 × 1H, m, 2 × NCH_2CH_3 and N(HC*H*)CH); 3.94 and 4.24 (2H, 2 × d, J = 12.7 Hz, NCH_2C_{arom}); 7.14–7.55 (9H, m, CH_{arom}).^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 12.42, 13.02, 18.83, 25.08, 34.82, 39.77, 42.24, 50.27, 51.75, 125.76, 127.41, 129.13, 129.88, 138.45 170.89. IR (ATR, cm^{-1}): $\nu_{C=O}$= 1626, ν_{NH}= 3406. MS (70 eV): *m*/*z* (%): 337 (M^++1, 100). Anal. Calcd for $C_{22}H_{28}N_2O$: C 78.53; H 8.39; N 8.33. Found: C 78.71; H 8.56; N 8.14.

Synthesis of 2-(2-cyano-3-phenylpropyl)aziridines 14

As a representative example, the synthesis of 2-(2-cyano-3-phenylpropyl)-1-(4-methylbenzyl)aziridine **14a** is described here. To solution of diisopropylamine (6 mmol, 1.2 equiv) in dry THF (10 mL), *n*-BuLi (2.4 mL, 6 mmol, 1.2 equiv, 2.5M) was added *via* a syringe at −78 °C under nitrogen atmosphere, and the resulting solution was stirred for 30 min at −78 °C. Subsequently, a solution of 1-(4-methylbenzyl)-2-(2-cyanoethyl)aziridine **13a** (5 mmol) in THF (10 mL) was added *via* a syringe at −78 °C, and the resulting solution was stirred for 1 hour at −78 °C. Then, a solution of benzyl bromide (5 mmol, 1 equiv) in THF (10 mL) was added *via* a syringe at −78 °C. After stirring for 6 hours at room temperature, the reaction mixture was poured into water (50 mL) and extracted with diethyl ether (3 × 50 mL). Drying ($MgSO_4$), filtration of the drying agent and removal of the solvent afforded 2-(2-cyano-3-phenylpropyl)-1-(4-methylbenzyl)aziridine **14a**, which was purified by means of column chromatography on silica gel (hexane/EtOAc 3/1).

2-(2-Cyano-3-phenylpropyl)-1-(4-methylbenzyl)aziridine 14a

Spectral data derived from the mixture of diastereomers.

Yellow oil. R_f = 0.06 (Hexane/EtOAc 3/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (1H, d × d × d, J = 13.7, 8.1, 4.3 Hz, CH(*H*CH)CH_{minor}); 1.51 (1H, d, J = 6.1 Hz, (H_{cis}CH)CHN_{major}); 1.57 (1H, d, J = 6.3 Hz, (H_{cis}CH)CHN_{minor}); 1.66 (1H, d, J = 2.8 Hz, (H_{trans}CH)CHN_{major}); 1.68–1.75 (5 × 1H, m, ((HCH_{trans})CHN_{minor}, (*H*CH)$CHCH_{major}$ and CHN_{major} and CHN_{minor}); 1.85 (1H, d × d × d , J = 13.7, 10.3, 3.6 Hz, CH(HC*H*)CH_{minor}); 2.32 (3H, s, $CH_{3,minor}$); 2.35 (3H, s, $CH_{3,major}$); 2.62–2.80 (6 × 1H, m, (CH(*H*CH)$C_{arom,quat})_{major}$, (CH(*H*CH)$C_{arom,quat})_{minor}$, $CHCN_{minor}$ and $CHCN_{major}$); 3.26 and 3.51 (2H, 2 × d, J = 12.7 Hz, (N(HCH)$C_{arom,quat})_{minor}$); 3.29 and 3.53 (2H, 2 × d, J = 12.8 Hz, (N(HCH)$C_{arom,quat})_{major}$); 7.06–7.34 (18H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$); δ 21.37, 32.06, 32.50, 33.81, 34.52, 35.11, 35.83, 36.36, 36.87, 37.51, 38.39, 64.55, 64.64, 121.70, 127.31, 128.55, 128.63, 128.70, 128.81, 128.89, 129.18, 129.25, 129.44, 130.75, 130.83, 136.14, 137.04, 137.19. IR (ATR, cm^{-1}): ν_{CN}= 2233. MS (70 eV): *m*/*z* (%): 291 (M^++1, 100). Anal. Calcd for $C_{20}H_{22}N_2$: C 82.72; H 7.64; N 9.65. Found: C 82.96; H 7.94; N 9.78.

Synthesis of 1-benzyl-2-(aminomethyl)cyclopropanecarbonitriles 15

As a representative example, the synthesis of 1-benzyl-2-{[*N*-benzyl-*N*-(4-methylbenzyl)amino]methyl}cyclopropanecarbonitrile **15a** is described here. To a stirred solution of 2-(2-cyano-3-phenylpropyl)-1-(4-methylbenzyl)aziridine **14a** (2.5 mmol) in acetonitrile (10 mL), benzyl bromide (2.5 mmol, 1.0 equiv) was added, and the resulting mixture was heated under reflux for 5 hours. Evaporation of the solvent afforded the corresponding 5-amino-2-benzyl-4-bromopentanenitrile, which was dissolved in dry THF (30 mL). Subsequently, potassium *tert*-butoxide (3.75 mmol, 1.5 equiv) was added at room temperature. After stirring for 5 hours at room temperature, the reaction mixture was poured into water (50 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with water (2 × 50 mL) and brine (50 mL). Drying ($MgSO_4$), filtration of the drying agent and removal of the solvent afforded 1-benzyl-2-{[*N*-benzyl-*N*-(4-methylbenzyl)amino]methyl}cyclopropanecarbonitrile **15a** as a mixture of *cis*/*trans*-isomers, which was purified by means of column chromatography on silica gel (hexane/EtOAc 9/1).

1-Benzyl-2-{[*N*-benzyl-*N*-(4-methylbenzyl)amino]methyl}-cyclopropanecarbonitrile 15a

Spectral data derived from the mixture of diastereomers.

Yellow oil. R_f = 0.15 (Hexane/EtOAc 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.73 (1H, d × d, J = 7.0, 5.3 Hz, CH(HC*H*)CN$_{trans}$); 0.91 and 1.06 (2 × 1H, 2 × d × d, J = 8.7, 6.7, 5.6 HzCHCH_2CN$_{cis}$); 1.24–1.37 (1H, m, CH$_{cis}$); 1.44 (1H, d × d, J = 9.4, 5.3 Hz, CH(*H*CH)CN$_{trans}$); 1.74–1.84 (1H, m, CH$_{trans}$); 2.33 (3H, s, CH_3); 2.47 (1H, d × d, J = 13.5, 6.6 Hz, N(HC*H*)CH$_{trans}$); 2.31 and 2.80 (2H, 2 × d, J = 15.1 Hz, (C$_{quat}$(*H*CH)C$_{arom,quat}$)$_{trans}$, (C$_{quat}$(HC*H*)C$_{arom,quat}$)$_{trans}$); 2.61–2.90 (5 × 1H, m, N(*H*CH)CH$_{trans}$, (C$_{quat}$(*H*CH)C$_{arom,quat}$)$_{cis}$, (C$_{quat}$(HC*H*)C$_{arom,quat}$)$_{cis}$ and NCH_2CH$_{cis}$); 3.48–3.69 (8H, m, 2×(NCH_2C$_{arom}$)$_{cis}$ and 2×(NCH_2C$_{arom}$)$_{trans}$); 7.03–7.40 (2 × 14H, m, (CH$_{arom}$)$_{cis}$ and (CH$_{arom}$)$_{trans}$).^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 15.06, 17.34, 19.31, 19.51, 21.35, 23.95, 24.13, 35.03, 40.85, 51.62, 55.10, 58.32, 58.43, 58.62, 121.76, 123.91, 127.13, 127.18, 127.39, 127.42, 128.43, 128.55, 128.81, 128.90, 129.09, 129.15, 129.25, 136.03, 136.43, 136.67, 136.93, 137.64, 139.30, IR (ATR, cm^{-1}): ν_{CN}= 2231. MS (70 eV): *m*/*z* (%): 381 (M^++1, 100). Anal. Calcd for $C_{27}H_{28}N_2$: C 85.22; H 7.42; N 7.36. Found: C 85.44; H 7.67; N 7.22.

Synthesis of 2-{[*N*-benzyl-*N*-(4-chlorobenzyl)amino]methyl}-1-benzylcyclopropanecarboxamide 16a

To an ice-cooled solution of 1-benzyl-2-{[*N*-benzyl-*N*-(4-chlorobenzyl)amino]methyl}cyclopropanecarbonitrile **15b** (2.2 mmol) in dry CH_2Cl_2 (10 mL), concentrated sulfuric acid (4.2 mL, 26 equiv) was added, and the resulting solution was stirred for 21 hours at 10 °C. The reaction mixture was poured into ice water (30 mL), followed by extraction using a saturated solution of aqueous ammonium hydroxide and EtOAc (3 × 50 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 2-{[*N*-benzyl-*N*-(4-chlorobenzyl)amino]methyl}-1-benzylcyclopropanecarboxamide **16a**, which was purified by means of column chromatography on silica gel (hexane/EtOAc 9/1).

cis- and *trans*-2-{[*N*-benzyl-*N*-(4-chlorobenzyl)amino]methyl}-1-benzylcyclopropanecarboxamide 16a

Spectral data derived from the mixture of diastereomers.

Yellow oil. R*f* = 0.15 (Hexane/EtOAc 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.64 (1H, d × d, J = 6.6, 4.0 Hz, CH(HC*H*)CN$_{trans}$); 0.92–1.02 (2H, m, CHCH_2CN$_{cis}$); 1.25–1.39 (1H, m, CH$_{cis}$); 1.66 (1H, d × d, J = 9.1, 4.0 Hz, CH(*H*CH)CN$_{trans}$); 1.79–1.90 (1H, m, CH$_{trans}$); 2.41 (1H, d × d, J = 13.2, 7.2 Hz, N(HC*H*)CH$_{trans}$); 2.50–2.73 (5H, m, N(*H*CH)CH$_{trans}$, (C$_{quat}$(*H*CH)C$_{arom,quat}$)$_{cis}$, (C$_{quat}$(*H*CH)C$_{arom,quat}$)$_{trans}$ and NCH_2CH$_{cis}$); 2.89 (1H, d, J = 18.2 Hz, (C$_{quat}$(*H*CH)C$_{arom,quat}$)$_{trans}$); 3.09 (1H, d, J = 14.9 Hz, (C$_{quat}$(HC*H*)C$_{arom,quat}$)$_{cis}$); 3.26, 3.27, 3.51, 3.55, 3.65 and 3.69 (6 × 1H, 3×(2 × d), J = 13.2 Hz, 3×(NCH_2C$_{arom}$); 3.49–3.82 (2H, m, NCH_2C$_{arom}$); 5.18, 5.46, 5.59 and 5.66 (4 × 1H, 4 × s, 2 × NH$_{2,cis}$ and 2 × NH$_{2,trans}$); 7.05–7.35 (2 × 14H, m, (CH$_{arom}$)$_{cis}$ and (CH$_{arom}$)$_{trans}$).^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 18.4, 21.5, 23.1, 23.9, 26.7, 31.8, 34.2, 42.7, 52.6, 57.4, 57.4, 58.2, 57.5, 58.3, 126.7, 126.9, 127.2, 127.4, 128.1, 128.4, 128.5, 128.7, 128.8, 128.9, 129.0, 129.3, 130.3, 130.6, 132.7, 138.2, 138.5, 139.3, 132.9, 137.3, 138.3, 138.8, 174.5, 176.9. IR (ATR, cm^{-1}): $\nu_{C=O}$= 1630, ν_{NH2}= 3386. MS (70 eV): *m*/*z* (%): 419/21 (M^++1, 100). Anal. Calcd for $C_{26}H_{27}ClN_2O$: C 74.54; H 6.50; N 6.69. Found: C 74.81; H 6.76; N 6.45.

Synthesis of *cis*- and *trans*-2-{[*N*-benzyl-*N*-(3-methoxybenzyl)-amino]methyl}-1-benzylcyclopropanecarboxamide 16b

To a solution of 1-benzyl-2-{[*N*-benzyl-*N*-(3-methoxybenzyl)-amino]methyl}cyclopropanecarbonitrile **15c** (2 mmol) in ethanol/water (3/1, 20 mL), potassium hydroxide (10 mmol, 5 equiv) was added at room temperature, and the resulting mixture was heated under reflux for 3 days. The reaction mixture was poured into water (30 mL) and extracted with EtOAc (3 × 50 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 2-{*N*-benzyl-*N*-(3-methoxybenzyl)amino]-methyl}-1-benzylcyclopropanecarboxamide **16b**, which was purified by means of column chromatography on silica gel (Hexane/EtOAc 9/1).

Alternative procedure: To a solution of 1-benzyl-2-{[*N*-benzyl-*N*-(3-methoxybenzyl)amino]methyl}cyclopropanecarbonitrile **15c** (2 mmol) in ethanol/water (3/1, 20 mL), potassium hydroxide (8 mmol, 4 equiv) was added at room temperature, and the resulting mixture was heated for 30 min at 185 °C under microwave conditions (200 Watt). The reaction mixture was poured into water (30 mL) and extracted with EtOAc (3 × 50 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 2-{*N*-benzyl-*N*-(3-methoxybenzyl)amino]methyl}-1-benzylcyclopropanecarboxamide **16b**, which was purified by means of column chromatography on silica gel (Hexane/EtOAc 9/1).

cis- and *trans*-2-{*N*-benzyl-*N*-(3-methoxybenzyl)amino]methyl}-1-benzylcyclopropanecarboxamide 16b

Spectral data derived from the mixture of diastereomers.

Orange oil. R_f = 0.15 (Hexane/EtOAc 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.67 (1H, d × d, J = 6.9, 4.1 Hz, CH(HC*H*)CN$_{trans}$); 0.91–0.98 (2H, m, CHCH_2CN$_{cis}$); 1.25–1.41 (1H, m, CH$_{cis}$); 1.68–1.72 (1H, m, CH(*H*CH)CN$_{trans}$); 1.82–1.92 (1H, m, CH$_{trans}$); 2.43–2.56 (2H, m, NCH_2CH$_{trans}$); 2.52 (1H, d × d, J = 13.2, 8.8 Hz, N(*H*CH)CH$_{cis}$); 2.58 (1H, d, J = 14.6 Hz, (C$_{quat}$(*H*CH)C$_{arom,quat}$)$_{cis}$); 2.65–2.74 (1H, m, (C$_{quat}$(HC*H*)C$_{arom,quat}$)$_{trans}$); 2.71 (1H, d × d, J = 13.2, 5.5 Hz, N(HC*H*)CH$_{cis}$); 2.95 (1H, d, J = 17.6 Hz, (C$_{quat}$(*H*CH)C$_{arom,quat}$)$_{trans}$); 3.14 (1H, d, J = 14.6 Hz, (C$_{quat}$(HC*H*)C$_{arom,quat}$)$_{cis}$); 3.24 and 3.26 (2H, 2 × d, J = 13.2 Hz, (NCH_2C$_{arom,quat}$)$_{cis}$); 3.54 and 3.56 (2H, 2 × d, J = 13.5 Hz, (NCH_2C$_{arom,quat}$)$_{trans}$); 3.66–3.81 (2 × 2H, m, (NCH_2C$_{arom,quat}$)$_{cis}$ and (NCH_2C$_{arom,quat}$)$_{trans}$); 3.77 (OCH$_{3,cis}$); 3.79 (OCH$_{3,trans}$); 4.90, 5.13 and 5.34 (4 × 1H, 4 × s, 2 × NH$_{2cis}$ and 2 × NH$_{2trans}$); 6.71–6.79, 6.91–6.96 and 7.12–7.38 (2 × 14H, m, (CH$_{arom}$)$_{cis}$ and (CH$_{arom}$)$_{trans}$).^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 18.19, 21.28, 22.93, 24.04, 26.87, 31.93, 34.21, 42.62, 52.62, 54.41, 55.25, 58.12, 58.21, 58.29, 58.32, 112.37, 114.50, 115.04, 126.66, 126.77, 127.09, 127.30, 128.12, 128.37, 128.64, 128.99, 129.04, 129.35, 138.52, 138.77, 139.53, 140.25, 141.33, 159.64, 159.71, 174.72, 177.15. IR (ATR, cm^{-1}): $\nu_{C=O}$= 1663. MS (70 eV): *m*/*z* (%): 415 (M^++1, 100). Anal. Calcd for $C_{27}H_{30}N_2O_2$: C 74.54; H 6.50; N 6.69. Found: C 74.48; H 6.65; N 6.74.

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