Ti(II)-Mediated Conversion of α-Heterosubstituted (O, N, S) Nitriles to Functionalized Cyclopropylamines. Effect of Chelation on the Cyclopropanation Step

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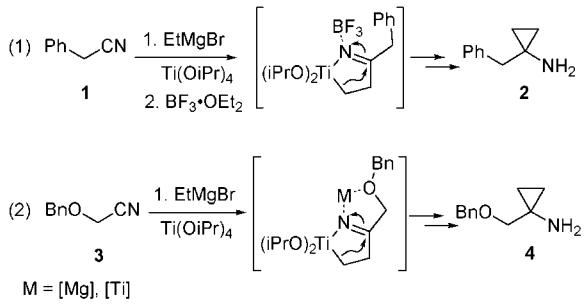
Abstract: α-Alkoxy, amino-, and thio nitriles undergo a Ti(II)-mediated coupling with Grignard reagents to afford heterofunctionalized cyclopropylamines. A chelation effect appears to be generally responsible for the spontaneous contraction of the intermediate azatitanacycle leading to cyclopropane. By using the described reaction, 1-aminocyclopropanecarboxylic acids were prepared in four steps, in good overall yields, from the readily available benzyloxyacetonitrile.

Cyclopropylamines have attracted much attention due to their synthetic potential[1] and biological properties.[2] In particular, 1-(alkoxymethyl)-substituted cyclopropylamines can be considered as useful intermediates for the synthesis of 1-aminocyclopropanecarboxylic acids (ACCs).[3] Furthermore, the 1-(1-aminoalkyl)-substituted cyclopropylamine moiety is encountered in biologically active compounds.[4] Here, we present a new straightforward access to such O-, N-, and also S-heterofunctionalized cyclopropylamines.

Despite their interest, most of the synthetic approaches to cyclopropylamines are rather specific and require multistep reactions.[1] Among the simpler methods, two titanium-mediated reactions have been reported. Thus, the de Meijere[5] variant of the Kulinkovich reaction[6] makes it possible to synthesize *N*,*N*-dialkylcyclopropylamines from amides. Recently, we have reported a new access to primary amines from nitriles.[7] In our reaction, the cyclopropane ring is formed efficiently via a Lewis acid mediated contraction of the intermediate azatitanacycle (Scheme 1, eq 1).[8]

Scheme 1



For example, cyclopropylamine **2** was obtained in 70% yield from benzyl cyanide (**1**) in THF or Et_2O when BF_3•OEt_2 was used. Interestingly, in the absence of BF_3•OEt_2, **2** was also formed but the yields were markedly lower, i.e., 7% in THF and 31% in Et_2O. We anticipated that weak acid species (Mg, Ti) always present in the reaction mixture would operate slightly in this case.

By studying the feasibility of preparing 1-(alkoxymethyl)-substituted cyclopropylamines from α-alkoxy nitriles (O-protected cyanohydrins), we noticed that these reactions proceeded efficiently *even* in the absence of an additional Lewis acid. This contrasted not only with the reactions involving the nonfunctionalized nitriles,[7] but also those involving *β*-alkoxy nitriles. A striking example is given through the comparison of the two reactions using α- and *β*-benzyloxy nitriles **3** and **5** (Table 1, entries 1 and 2).

Both reactions were carried out in Et_2O or THF and employed 1.1 equiv of Ti(O-*i*-Pr)$_4$ and 2 equiv of EtMgBr. Thus, in the absence of BF_3•OEt_2, α-benzyloxy nitrile **3** was converted to **4** in 74% yield, while only 5% yield of **6** was obtained starting from the *β*-benzyloxy nitrile **5** in Et_2O.[9] Similar yields of **4** and **6** were obtained in THF. Significantly, the subsequent addition of BF_3•OEt_2 did not increase the yield of **4** (entry 1) but markedly increased the yield of **6** (54%, entry 2).

The formation of **4** from **3** in the absence of BF_3•OEt_2 can be rationalized by assuming a five-membered chelate, as depicted in Scheme 1 (eq 2). When the chelation is involved, the intermediate azatitanacycle would contract efficiently even in the presence of weak Lewis acid species. In contrast, when a five-membered chelate cannot be formed, the contraction step would be efficient neither for **5** nor for the nonfunctionalized nitriles. It should be noticed that analogous chelation-promoted addition of Grignard reagents to α-alkoxy imines is known.[10] Moreover, the dialkylation of nitriles similarly operates from O-protected cyanohydrins.[11]

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(6) (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevsky, D. A.; Prityckaja, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244−2245. (b) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevsky, D. A. *Synthesis* **1991**, 234. (c) Kukinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789−2834.

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(8) In contrast to the Kulinkovich and de Meijere reactions, in which the intermediate oxatitanacycle contracts spontaneously without requiring an additional Lewis acid, see refs 5 and 6.

(9) Starting from **5**, 1-benzyloxy-3-pentanone was the major product formed (60% yield) on hydrolysis.

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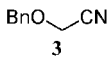
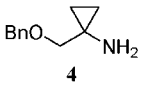
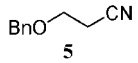
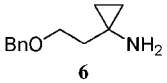
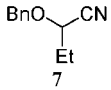
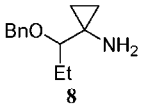
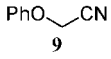
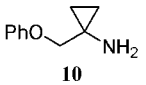
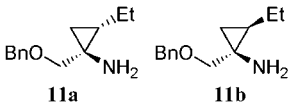
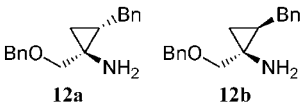
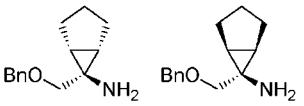
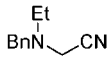
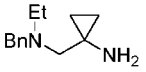
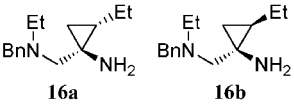
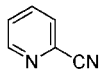
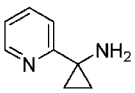
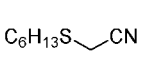
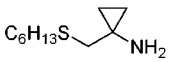
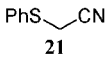
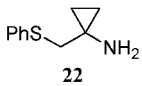
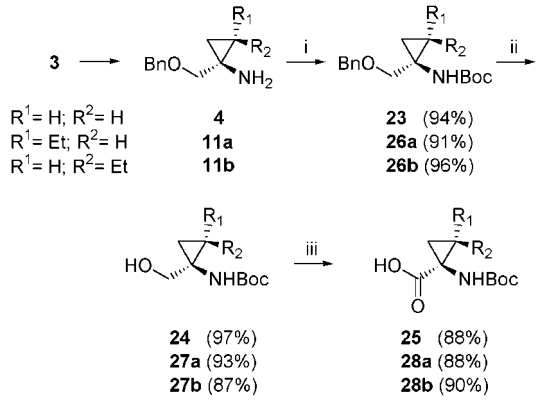
Table 1. Synthesis of Cyclopropylamines from Nitriles

Entry	Nitrile	RMgX	Product (isomer ratio)	Yield[a,b] (%)
1	 **3**	EtMgBr	 **4**	74 (75)
2	 **5**	EtMgBr	 **6**	5 (54)
3	 **7**	EtMgBr	 **8**	73
4	 **9**	EtMgBr	 **10**	49 (80)
5	**3**	*n*BuMgBr	 **11a** **11b** (70 : 30)	61
6	**3**	$Ph(CH_2)_3MgBr$	 **12a** **12b** (64 : 36)	64
7	**3**	cC_5H_9MgCl	 **13a** **13b** (86 : 14)	45
8	 **14**	EtMgBr	 **15**	64
9	**14**	*n*BuMgBr	 **16a** **16b** (63 : 37)	72
10	 **17**	EtMgBr[c]	 **18**	57
11	 **19**	EtMgBr	 **20**	20 (54)
12	 **21**	EtMgBr	 **22**	5 (39)

[a] Isolated yields. [b] Yields in parentheses refer to an addition of 2 equiv of $BF_3{\cdot}OEt_2$, 30 min after the addition of Grignard reagent. [c] Reaction performed in THF.

Different α-alkoxy or -aryloxy nitriles and Grignard reagents can be employed to perform the reaction. The cyclopropanation occurred smoothly, in the absence of a Lewis acid, with the O-protected propanal cyanohydrin **7** (entry 3, Table 1). Starting from the less coordinating α-phenoxy nitrile **9**, however, a better yield was achieved when $BF_3{\cdot}OEt_2$ was added (entry 4). The reactions

Scheme 2[a]



[a] Reagents: (i) $(Boc)_2O$, NaOH, *t*-BuOH, H_2O; (ii) H_2, Pd 5% on C, MeOH; (iii) $KMnO_4$, NaOH, *t*-BuOH, H_2O.

employing α-alkoxy nitriles and higher Grignard reagents proceeded without an additional Lewis acid as well. The examples are given in entries 5−7 of Table 1. Noteworthy is the easy preparation of the bicyclic cyclopropylamine **13**. In such cases, mixtures of diastereomeric cyclopropylamines **11**−**13a**,**b** can easily be separated by flash chromatography.[12]

The described method also allows to prepare N-functionalized cyclopropylamines (1,2-diamines bearing a cyclopropane ring) directly from α-aminonitriles. Different compounds can be obtained as depicted in Table 1 (entries 8−10), among them pyridine-containing diamine **18**. Finally, the title reaction could also be applied to the synthesis of alkyl- and arylthio-substituted cyclopropylamines **20** and **22** (entries 11 and 12). For these reactions, however, synthetically useful yields require the use of an additional Lewis acid, likely due to the relative softness of the thio nitriles **19** and **21** (Mg and Ti species being supposed weak and hard Lewis acids).

By using the title reaction, the readily available benzyloxyacetonitrile (**3**)[13] is revealed to be suitable starting material for the synthesis of natural and non-natural 1-aminocyclopropanecarboxylic acids.[14] Three examples are given in Scheme 2.

Boc-protected ACC (**25**)[15a] was obtained in four steps, in 59% total yield from **3**, by cyclopropanation, protection of the amino group, debenzylation, and oxidation of the resulting alcohol.[16] In an analogous way, Boc-protected coronamic (**28a**)[15b] and *allo*-coronamic (**28b**)[15c] acids were

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(12) The relative stereochemistry of the diastereoisomers was established by NOE experiments as well as by transformation of **11a**,**b** to the known products **27a**,**b**.

(13) Benzyloxyacetonitrile can be obtained in one step from sodium cyanide, formaldehyde, and benzyl cyanide; see ref 17a.

(14) Similarly, 3-benzyloxypropionitrile (**5**) can be used to prepare *β*-aminocyclopropanecarboxylic acids.

(15) (a) Naturally occurring ACC is the precursor of ethylene, a phytohormone responsible for fruit ripening; see: Pirrung, M. C. *Acc. Chem. Res.* **1999**, *32*, 711−718. (b) Coronamic acid is the constituent of the bacterial toxin coronatine in *Pseudomonas coronafacience* var. *atropurpurea*; see: Ichiara, A.; Shiraishi, K.; Sato, H.; Sakamura, S.; Nishiyama, K.; Sakai, R. Furusaki, A.; Matsumoto, T. *J. Am. Chem. Soc.* **1977**, *99*, 636−637. (c) *allo*-Coronamic acid is a competitive inhibitor of the ethylene biosynthesis, producing 1-butene; see: Hoffman, N. E.; Yang, S. F.; Ichiara, A.; Sakamura, S. *Plant Physiol.* **1982**, *70*, 195−199.

simply obtained from **3** through the diastereomeric benzyloxy cyclopropylamines **11a** and **11b**. Other 1-(benzyloxymethyl)-substituted cyclopropylamines, readily available by our method, are potentially useful for the syntheses of various 1-aminocyclopropanecarboxylic acids.

In summary, in the presence of Ti(O-*i*-Pr)$_4$, α-alkoxy, amino, and thio nitriles readily react with Grignard reagents to afford functionalized cyclopropylamines. The chelation effect appears as responsible for the spontaneous contraction of the intermediate azatitanacycle leading to cyclopropane. The described procedure should be a method of choice for the easy preparation of these useful series of compounds.

Experimental Section

General Methods. Et_2O and THF were distilled from sodium benzophenone ketyl under argon. All Grignard reagents were titrated in THF by menthol in the presence of *o*-phenanthroline prior to use. Commercially available Ti(O-*i*-Pr)$_4$, BF_3·OEt_2, and nitrile **17** were distilled under argon. Nitriles **3**, **5**, **7**, **9**, **14**, **19**, and **21** were prepared following the reported procedures.[17]

General Procedure for the Synthesis of Cyclopropylamines 4, 8, 11−13, 15−16, and 18. To a solution of the nitrile (2 mmol) in Et_2O (6 mL) were added successively, at room temperature, Ti(O-*i*-Pr)$_4$ (0.65 mL, 2.2 mmol) and a Grignard reagent (4 mmol, 1−2 M in ether). After the mixture was stirred for 0.5 h, water (ca. 1 mL) was added and the mixture extracted with ether. The combined ether layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting crude material was purified by flash chromatography on silica gel.

General Procedure for the Synthesis of Cyclopropylamines 6, 10, 20, and 22. Addition of a Lewis Acid. To a solution of the nitrile (2 mmol) in Et_2O (6 mL) were added successively at room temperature Ti(O-*i*-Pr)$_4$ (0.65 mL, 2.2 mmol) and a Grignard reagent (4 mmol, 1−2 M in ether). After the mixture was stirred for 0.5 h, BF_3·OEt_2 (0.51 mL, 4 mmol) was added at once. Stirring was continued over a period of 10 min. A solution of 10% NaOH (ca. 1 mL) was added, and the mixture was treated as above.

1-(Benzyloxymethyl)cyclopropylamine (4): colorless oil; 74% yield (262 mg); R_f 0.18 (Et_2O); IR (neat) 3361, 2855, 1453 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.46−0.55 (m, 2 H), 0.55−0.68 (m, 2 H), 1.75 (s, 2 H, NH_2), 3.38 (s, 2 H), 4.58 (s, 2 H), 7.28−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 12.4, 33.8, 72.7, 78.1, 127.4, 127.6, 128.3, 138.2; MS (EI 70 eV) *m*/*z* 177 ($M^{\bullet+}$, 1), 105 (8), 91 (100). Anal. Calcd for $C_{11}H_{15}ON$·HCl: C, 61.82; H, 7.55; N, 6.55. Found: C, 61.58; H, 7.44; N, 6.45.

1-(2-Benzyloxyethyl)cyclopropylamine (6): yellow oil; 54% yield (206 mg); R_f 0.24 (acetone); IR (neat) 3357, 2857, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.43−0.46 (m, 2 H), 0.56−0.59 (m, 2 H), 1.69 (s, 2 H, NH_2), 1.74 (t, J = 6.3 Hz, 2 H), 3.69 (t, J = 6.3 Hz, 2 H), 4.52 (s, 2 H), 7.29−7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.4, 33.1, 40.0, 69.1, 73.1, 127.6, 127.8, 128.4, 138.4; MS (CI^+, NH_3) *m*/*z* 192 (M + 1, 1), 106 (9), 84 (100).

1-(1-Benzyloxypropyl)cyclopropylamine (8): colorless oil; 73% yield (299 mg); R_f 0.21 (Et_2O); IR (neat) 3372, 2961, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.25−0.35 (m, 1 H), 0.52−0.61 (m, 2 H), 0.74−0.81 (m, 1 H), 1.02 (t, J = 7.4 Hz, 3 H), 1.55−1.81 (m, 2 H), 1.75 (s, 2 H, NH_2), 2.65 (dd, J = 8.6, 4.7 Hz, 1 H), 4.52 (d, J = 11.8 Hz, 1 H), 4.78 (d, J = 11.8 Hz, 1 H), 7.24−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.5, 11.0, 15.9, 25.3, 34.8, 71.0, 86.0, 127,5, 127.6, 128.3, 138.9; MS (EI 70 eV) *m*/*z* 177 (4), 114 (64), 91 (100). Anal. Calcd for $C_{13}H_{19}NO$·HCl: C, 64.59; H, 8.34; N, 5.79. Found: C, 64.57; H, 8.27; N, 5.68.

1-(Phenoxymethyl)cyclopropylamine (10): pale yellow oil; 80% yield (261 mg); R_f 0.30 (acetone); IR (neat) 3363, 1599, 1495, 1241 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.60−0.68 (m, 2 H), 0.71−0.78 (m, 2 H), 2.00 (s, 2 H, NH_2), 3.82 (s, 2 H), 6.85−7.00 (m, 3 H), 7.23−7.32 (m, 2 H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 12.6, 33.7, 76.1, 114.5, 120.8, 129.5; MS (EI 70 eV) *m*/*z* 163 ($M^{\bullet+}$, 47), 146 (12), 108 (32), 77 (42), 70 (100). Anal. Calcd for $C_{10}H_{13}NO$·HCl: C, 60.15; H, 7.07; N, 7.01. Found: C, 60.05; H, 6.96; N, 6.72.

(*E*)-1-(Benzyloxymethyl)-2-ethylcyclopropylamine (11a): pale yellow oil; 43% yield (175 mg); R_f 0.16 (Et_2O); IR (neat) 3362, 2958, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.14 (t, J = 5.2 Hz, 1 H), 0.70 (dd, J = 8.8, 4.7 Hz, 1 H), 0.86−0.92 (m, 1 H), 0.97 (t, J = 7.3 Hz, 3 H), 1.10−1.20 (m, 1 H), 1.36−1.42 (m, 1 H), 1.90 (s, 2 H, NH_2), 3.41 (d, J = 9.9 Hz, 1 H), 3.48 (d, J = 9.9 Hz, 1 H), 4.52 (d, J = 12.0 Hz, 1 H), 4.55 (d, J = 12.0 Hz, 1 H), 7.23−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 18.5, 22.7, 27.8, 37.4, 72.9, 75.0, 127.4, 127.5, 128.2, 138.3; MS (EI 70 eV) *m*/*z* 176 (12, M − Et), 114 (27), 91 (100). Anal. Calcd for $C_{13}H_{19}NO$·HCl: C,64.59; H,8.34; N, 5.79. Found: C,64.60; H, 8.24; N, 5.82. **(*Z*)-1-(Benzyloxymethyl)-2-ethylcyclopropylamine (11b):** pale yellow oil; 18% yield (75 mg); R_f 0.38 (Et_2O); IR (neat) 3372, 2958, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.22 (t, J = 5.1 Hz, 1 H), 0.59 (dd, J = 8.9, 4.4 Hz, 1 H), 0.60−0.68 (m, 1 H), 0.99 (t, J = 7.5 Hz, 3 H), 1.40−1.55 (m, 2 H), 1.78 (s, 2 H, NH_2), 3.25 (d, J = 9.9 Hz, 1 H), 3.35 (d, J = 9.9 Hz, 1 H), 4.56 (s, 2 H), 7.23−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 14.3, 17.3, 21.2, 25.0, 37.4, 72.5, 79.3, 127.4, 127.6, 128.2, 138.4; MS (EI 70 eV) *m*/*z* 176 (11, M − Et), 114 (28), 91 (100).

(*E*)-1-(Benzyloxymethyl)-2-benzylcyclopropylamine (12a): pale yellow oil; 41% yield (219 mg); R_f 0.19 (Et_2O); IR (neat) 3363, 1603, 1453 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.40 (t, J = 5.6 Hz, 1 H), 0.88 (dd, J = 9.1, 5.0 Hz, 1 H), 1.22−1.35 (m, 1 H), 1.90 (s, 2 H, NH_2), 2.48 (dd, J = 15.2, 8.3 Hz, 1 H), 2.83 (dd, J = 15.2, 6.3 Hz, 1 H), 3.50 (d, J = 10.0 Hz, 1 H), 3.59 (d, J = 10.0 Hz, 1 H), 4.58 (d, J = 12.0 Hz, 1 H), 4.62 (d, J = 12.0 Hz, 1 H), 7.15−7.40 (m, 10 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.0, 26.5, 35.2, 37.8, 73.1, 75.1, 125.8, 127.6, 127.7, 128.2, 128.3, 128.4, 138.3, 141.6; MS (EI 70 eV) *m*/*z* 267 ($M^{\bullet+}$, 2), 176 (56), 146 (24), 91 (100). **(*Z*)-1-(Benzyloxymethyl)-2-benzylcyclopropylamine (12b):** pale yellow oil; 23% yield (123 mg); R_f 0.67 (Et_2O); IR (neat) 3373, 1603, 1453 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.47 (t, J = 5.4 Hz, 1 H), 0.73 (dd, J = 9.1, 5.0 Hz, 1 H), 1.00−1.11 (m, 1 H), 1.80 (s, 2 H, NH_2), 2.88 (dd, J = 15.2, 6.7 Hz, 1 H), 2.89 (dd, J = 15.2, 7.5 Hz, 1 H), 3.29 (d, J = 9.9 Hz, 1 H), 3.46 (d, J = 9.9 Hz, 1 H), 4.53 (s, 2 H), 7.15−7.40 (m, 10 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.5, 24.1, 33.7, 37.6, 72.6, 79.3, 125.7, 127.5, 127.7, 128.2, 128.3, 128.3, 138.4, 142.3; MS (EI 70 eV) *m*/*z* 267 ($M^{\bullet+}$, 2), 176 (60), 146 (18), 91 (100).

(*E*)-6-(Benzyloxymethyl)bicyclo[3.1.0]hex-6-ylamine (13a): pale yellow oil; 39% yield (168 mg); R_f 0.45 (MeOH); IR (neat) 3362, 2949, 1453 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.25−2.00 (m, 10 H), 3.51 (s, 2 H), 4.57 (s, 2 H), 7.22−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.8, 27.3, 33.7, 41.3, 71.7, 73.1, 127.6, 127.8, 128.4, 138.4; MS (CI^+, NH_3) *m*/*z* 218 (M + 1, 42), 112 (100).

(*Z*)-6-(Benzyloxymethyl)bicyclo[3.1.0]hex-6-ylamine (13b): pale yellow oil; 6% yield (27 mg); R_f 0.33 (Ether); ir (neat) 3374, 2926, 1453 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.20−1.95 (m, 10 H), 3.26 (s, 2 H), 4.55 (s, 2 H), 7.23−7.41 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.9, 27.4, 29.1, 41.3, 72.7, 78.8, 127.6, 127.7, 128.4, 138.5; MS (CI^+, NH_3) *m*/*z* 218 (M + 1, 12), 112 (100).

1-(*N*-Benzyl-*N*-ethylaminomethyl)cyclopropylamine (15): pale yellow oil; 64% yield (261 mg); R_f 0.30 (Acetone); IR (neat) 3357, 2963, 1261 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.34−0.36 (m, 2 H), 0.58−0.60 (m, 2 H), 1.05 (t, J = 7.1 Hz, 3 H), 1.86 (s, 2 H, NH_2), 2.39 (s, 2 H), 2.63 (q, J = 7.1 Hz, 2 H), 3.65 (s, 2 H), 7.24−7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 11.3, 12.9, 32.0, 47.2, 58.1, 62.1, 126.7, 128.2, 128.7, 140.2; MS (EI 70 eV) *m*/*z* 204 ($M^{\bullet+}$, 5), 148 (60), 134 (71), 91 (100).

(*E*)-1-(*N*-Benzyl-*N*-ethylaminomethyl)-2-ethylcyclopropylamine (16a): pale yellow oil; 45% yield (210 mg); R_f 0.19

(16) The synthesis of 1-aminocyclopropanecarboxylic acids from *N*,*N*-dialkylamides was recently reported by de Meijere et al. (see ref 5d). The method we described here is short (see ref 13), high yielding, and may be applied to the preparation of diastereomerically pure compounds.

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(acetone); IR (neat) 2962, 1677 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.08 (dd, J = 4.9, 3.7 Hz, 1 H), 0.71−0.85 (m, 2 H), 0.95 (t, J = 7.1 Hz, 3 H), 1.02 (t, J = 7.1 Hz, 3 H), 1.05−1.15 (m, 1 H), 1.42−1.57 (m, 1 H), 1.98 (s, 2 H, NH_2), 2.30 (d, J = 12.7 Hz, 1 H), 2.48−2.62 (m, 2 H), 2.68 (d, J = 12.7 Hz, 1 H), 3.45 (d, J = 13.7 Hz, 1 H), 3.77 (d, J = 13.7 Hz, 1 H), 7.25−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 11.4, 14.2, 20.4, 22.3, 26.3, 35.4, 46.8, 57.8, 57.9, 126.7, 128.1, 128.7, 140.2; MS (CI^+) m/z 233 (M + 1, 40), 136 (100). **(*Z*)-1-(*N*-Benzyl-*N*-ethylaminomethyl)-2-ethylcyclopropylamine (16b):** pale yellow oil; 27% yield (126 mg); R_f 0.33 (acetone); IR (neat) 2962, 1677 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.15 (t, J = 5.0 Hz, 1 H), 0.43 (dd, J = 9.0, 4.3 Hz, 1 H), 0.48−0.58 (m, 1 H), 0.95 (t, J = 7.4 Hz, 3 H), 1.02 (t, J = 7.1 Hz, 3 H), 1.40−1.54 (m, 2 H), 1.79 (s, 2 H, NH_2), 2.18 (d, J = 12.6 Hz, 1 H), 2.52 (d, J = 12.6 Hz, 1 H), 2.48−2.70 (m, 2 H), 3.50 (d, J = 13.6 Hz, 1 H), 3.70 (d, J = 13.6 Hz, 1 H), 7.25−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 11.2, 14.3, 17.3, 21.5, 26.2, 35.7, 46.9, 57.9, 63.6, 126.7, 128.1, 128.7, 140.2; MS (EI 70 eV) m/z 232 ($M^{\bullet+}$, <1), 148 (10), 134 (26), 91 (100).

1-(Pyridin-2-yl)cyclopropylamine (18): yellow oil; 57% yield (153 mg); R_f 0.23 (acetone); IR (neat) 3361, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.10−1.16 (m, 2 H), 1.20−1.28 (m, 2 H), 2.20 (s, 2 H, NH_2), 7.20 (d, J = 8.2 Hz, 1 H), 7.35 (t, J = 6.3 Hz, 1 H), 7.82 (t, J = 7.6 Hz, 1 H), 7.20 (d, J = 4.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 19.7, 37.6, 118.0, 120.2, 136.1, 148.6, 165.2; MS (EI 70 eV) m/z 134 ($M^{\bullet+}$, 34), 133 (100), 105 (35), 79 (85). Anal. Calcd for $C_8H_{10}N_2 \cdot HCl$: C, 56.31; H, 6.50; N, 16.42. Found: C, 56.16; H, 6.63; N, 16.11.

1-(Hexylthiomethyl)cyclopropylamine (20): yellow oil; 54% yield (202 mg); R_f 0.27 (Et_2O); IR (neat) 3353, 2926, 1592, 1458 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.45−0.55 (m, 2 H), 0.61−0.73 (m, 2 H), 0.88 (t, J = 6.8 Hz, 3 H), 1.25−1.45 (m, 6 H), 1.51−1.65 (m, 2 H), 1.95 (s, 2 H, NH_2), 2.58 (t, J = 7.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 13.8, 14.1, 22.4, 28.4, 29.6, 31.2, 32.0, 32.9, 44.1; MS (EI 70 eV) m/z 187 ($M^{\bullet+}$, 2), 118 (14), 102 (62), 71 (100). Anal. Calcd for $C_{10}H_{21}NS \cdot HCl$: C, 53.67; H, 9.91; N, 6.26. Found: C, 53.33; H, 10.28; N, 6.15.

1-(Phenylthiomethyl)cyclopropylamine (22): yellow oil; 39% yield (140 mg); R_f 0.39 (acetone); IR (neat) 3358, 1583, 1480, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.42−0.52 (m, 2 H), 0.59−0.69 (m, 2 H), 1.82 (s, 2 H, NH_2), 3.08 (s, 2 H), 7.15−7.30 (m, 3 H), 7.35−7.42 (m, 2 H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 14.6, 33.6, 47.3, 126.4, 128.8, 130.4, 136.4; MS (EI 70 eV) m/z 179 ($M^{\bullet+}$, 72), 146 (54), 110 (100).

(*N*-*tert*-Butoxycarbonyl)-1-(benzyloxymethyl)cyclopropylamine (23). To a solution of cyclopropylamine **4** (1.18 g, 5.8 mmol) in *t*-BuOH (7 mL) and water (10 mL) were added successively NaOH (0.3 g, 7.5 mmol) and Boc_2O (1.63 g, 7.5 mmol). After being stirred for 1 h, the mixture was extracted with ether. The combined organic layers were dried ($MgSO_4$) and concentrated. The resulting crude material was purified by flash chromatography giving a white solid (94% yield, 1.51 g): mp = 61 °C; R_f 0.22 (petroleum ether/ethyl acetate 95:5); IR (neat) 3369, 1687, 1508 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.70−0.85 (m, 4 H), 1.43 (s, 9 H), 3.48 (s, 2 H), 4.55 (s, 2 H), 5.10 (s, 1 H, NH), 7.25−7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 12.1, 28.3, 33.2, 73.0, 74.4, 79.3, 127.6, 127.8, 128.4, 138.3, 155.6; MS (CI^+, NH_3) m/z 278 (M + 1, 2), 221 (44), 204 (100). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.51; H, 8.31; N, 4.97.

[1-(*N*-*tert*-Butoxycarbonylamino)cyclopropyl]methanol (24).[5d] To a solution of benzyl ether **23** (1.36 g, 4.9 mmol) in methanol (20 mL) was added palladium 5% on charcoal (60 mg). The suspension was stirred overnight under an atmospheric pressure of H_2. After filtration and evaporation of the solvent, an analytically pure solid was obtained (97% yield, 887 mg): mp = 86 °C; R_f 0.22 (petroleum ether/ethyl acetate 95:5); IR (neat) 3341, 1695, 1532 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.82 (s, 4 H), 1.43 (s, 9 H), 3.56 (s, 2 H), 5.05 (s, 1 H, NH); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 12.8, 28.3, 35.2, 69.8, 80.2; MS (CI^+, NH_3) m/z 188 (M + 1, 3), 149 (16), 131 (26), 72 (100). Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.66; H, 9.43; N, 7.19.

(*E*)-(*N*-*tert*-Butoxycarbonyl)-1-(benzyloxymethyl)-2-ethylcyclopropylamine (26a). The title compound was prepared from **11a** (1.43 g, 7 mmol) using the procedure described for **23**: colorless oil; 91% yield (1.94 g); R_f 0.33 (petroleum ether/ethyl acetate 9:1); IR (neat) 3335, 1717 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.43 (t, J = 5.4 Hz, 1 H), 0.93−1.06 (m, 2 H), 1.01 (t, J = 7.1 Hz, 3 H), 1.12−1.21 (m, 1 H), 1.42 (s, 9 H), 1.51−1.56 (m, 1 H), 3.48 (d, J = 9.8 Hz, 1 H), 3.62−3.68 (m, 1 H), 4.50 (d, J = 12.2 Hz, 2 H), 4.55 (d, J = 12.2 Hz, 2 H), 5.15 (s, 1 H, NH), 7.26−7.36 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9, 18.3, 22.5, 27.4, 28.4, 36.8, 71.7, 73.1, 79.1, 127.5, 127.6, 128.3, 138.4, 155.5; MS (CI^+, NH_3) m/z 306 (M + 1, 2), 250 (8), 249 (14), 232 (62), 100 (100).

(*Z*)-(*N*-*tert*-Butoxycarbonyl)-1-(benzyloxymethyl)-2-ethylcyclopropylamine (26b). The title compound was prepared from **11b** (315 mg, 1.54 mmol) using the procedure described for **23**: colorless oil; 96% yield (425 mg); R_f 0.33 (petroleum ether/ethyl acetate 9:1); IR (neat) 3335, 1716 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.48−0.50 (m, 1 H), 0.83−0.89 (m, 2 H), 1.01 (t, J = 7.3 Hz, 3 H), 1.19−1.26 (m, 1 H), 1.43 (s, 9 H), 1.55−1.62 (m, 1 H), 3.42 (d, J = 10.1 Hz, 1 H), 3.48−3.52 (m, 1 H), 4.54 (s, 2 H), 4.95 (s, 1 H, NH), 7.26−7.36 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8, 16.9, 21.4, 24.9, 28.3, 37.2, 72.8, 75.1, 79.2, 127.5, 127.6, 128.3, 138.5, 156.0; MS (CI^+, NH_3) m/z 306 (M + 1, 3), 250 (20), 249 (38), 232 (100).

(*E*)-[1-(*N*-*tert*-Butoxycarbonylamino)-2-ethylcyclopropyl]methanol (27a).[18] The alcohol **27a** was prepared from **26a** (1.70 mg, 5.6 mmol) using the procedure described for **24**: white solid; 93% yield (1.11 g); mp = 81−82 °C; R_f 0.22 (petroleum ether/ethyl acetate 7:3); IR (KBr) 3402, 3283, 1686, 1051 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.50 (t, J = 5.9 Hz, 1 H), 0.88 (dd, J = 9.2, 5.3 Hz, 1 H), 0.93−0.98 (m, 1 H), 1.01−1.12 (m, 1 H), 1.03 (t, J = 7.2 Hz, 3 H), 1.22−1.40 (m, 1 H), 1.43 (s, 9 H), 1.50−1.68 (m, 1 H), 3.62−3.80 (m, 3 H), 5.09 (s, 1 H, NH); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 13.9, 18.7, 22.7, 28.3, 28.8, 38.5, 66.8, 80.1, 157.8; MS (CI^+, NH_3) m/z 216 (M + 1, 3), 160 (10), 159 (30), 100 (100). Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.70; H, 10.06; N, 6.28.

(*Z*)-[1-(*N*-*tert*-Butoxycarbonylamino)-2-ethylcyclopropyl]methanol (27b).[18] The alcohol **27b** was prepared from **26b** (377 mg, 1.24 mmol) using the procedure described for **24**: white solid; 87% yield (230 mg); mp = 40−42 °C; R_f 0.23 (petroleum ether/ethyl acetate 7:3); IR (neat) 3331, 1690, 1172 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.40 (t, J = 5.1 Hz, 1 H), 0.93−0.98 (m, 1 H), 1.00−1.06 (m, 1 H), 1.01 (t, J = 7.3 Hz, 3 H), 1.21−1.30 (m, 1 H), 1.44 (s, 9 H), 1.49−1.58 (m, 1 H), 3.44−3.50 (m, 1 H), 3.67 (d, J = 11.4 Hz, 1 H), 3.75 (s, 1 H, OH), 4.92 (s, 1 H, NH); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 13.8, 18.2, 21.6, 25.5, 28.2, 39.5, 71.1, 80.2, 158.2; MS (CI^+, NH_3) m/z 216 (M + 1, 5), 160 (34), 159 (36), 100 (100). Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.66; H, 10.07; N, 6.30.

Boc-protected amino acids **25** and **28** were obtained by oxidation;[5d] the spectroscopic data for compounds **25** (88% yield), **28a** (88% yield), and **28b** (90% yield) are in accordance with the literature data.[5d,18]

Supporting Information Available: Copies of ^1H and ^{13}C spectra for **4**, **6**, **8**, **10**−**13**, **15**, **16**, **18**, **20**, **22**−**24**, **26**, and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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