Articles

Synthesis of 4,4-Disubstituted β-Lactams by Regiospecific Electrophile- and Silver-Induced Ring Expansion of 2,2-Disubstituted 1-Methoxycyclopropylamines

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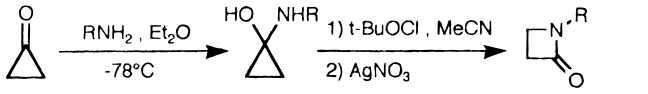
2,2-Disubstituted 1-methoxycyclopropylamines underwent regiospecific ring expansion to 1,4,4-trisubstituted 2-azetidinones by N-chlorination with *tert*-butyl hypochlorite and subsequent rearrangement with silver tetrafluoroborate. Upon thermolysis, 4,4-disubstituted β-lactams suffer a characteristic ring opening to afford β,γ-unsaturated carboxylic amides. The reduction of 1,4,4-trisubstituted 2-azetidinones with lithium aluminum hydride afforded 1,2,2-trisubstituted azetidines.

Introduction

The synthesis of monocyclic β-lactams received considerable attention in recent years due to their potential antibacterial activity.[1−6] Several synthetic entries toward monocyclic β-lactams have been developed,[2−6] the most important routes being the (1) ester enolate−imine condensation, (2) cyclization of β-amino carboxylic acids and esters, (3) cyclocondensation of ketenes, ketenimines, and keteniminium salts with imines, (4) cycloaddition of chromium−carbene complexes with imines, (5) cyclization of β-functionalized amides, imidates, and hydroxamates, and (6) oxidation of azetidines.[1−6]

Some ring transformations to form β-lactams have been reported, the most appealing one being the ring expansion of amine adducts across cyclopropanones.[7−9] The addition of primary amines to cyclopropanone **1** afforded labile carbinolamines **2** which were suitable sources for β-lactams **3** via a synthetic procedure involving N-chlorination with *tert*-butyl hypochlorite and subsequent reaction with silver salts (Scheme 1).[7,8] This elegant synthesis suffers from a major drawback, *i.e.*, the difficult accessibility of cyclopropanone, which is prepared by the low-temperature cycloaddition of diazomethane across ketene.[10] Despite this drawback, major efforts have been made to generalize the ring expansion of cyclopropanone adducts. In this respect, α-amino acid derivatives and hydroxylamines have been used with success to generate cyclopropanone adducts and to induce the rearrangement to β-lactams.[7,8]

Scheme 1



No ring-substituted cyclopropanones were ever shown to undergo the ring transformation of amine adducts. However, the addition product of azide across cyclopropanone underwent spontaneous rearrangement into 2-azetidinone in very low yield.[11] Up to now, only three ring substituted cyclopropanones, *i.e.*, bicyclo[4.1.0]heptan-7-one (generated from the hemiacetal),[12] *trans*-2,3-di-*tert*-butylcyclopropanone,[13] and *cis*-2,3-bis(trimethylsilyl)-cyclopropanone,[14] rearranged via their azide adducts to the corresponding β-lactams. The latter three peculiar and bulky examples, in addition to the cyclopropanone case itself, demonstrate the limitation of the methodology to only certain substrates. In the present paper, a new entry into previously inaccessible 4,4-disubstituted 2-azetidinones from α-chloro ketones via α-chloro imines and 1-methoxycyclopropylamines is disclosed.

Results and Discussion

2,2-Dialkyl-1-methoxycyclopropylamines **5** are accessible from 3-chloro-2-alkanones **4** in a three-step proce-

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dure involving (1) imination with primary amines in the presence of stoichiometric amounts of titanium(IV) chloride, (2) regiospecific deprotonation with LDA and alkylation with an alkyl bromide or iodide, and (3) ring closure of the resulting α-chloro ketimine and concomitant addition of sodium methoxide across the double bond of a transient Favorskii-type cyclopropylideneamine.[15−18] The addition of methoxide ion across the imino bond of the intermediate cyclopropylideneamine, *i.e.*, the N-analogue of cyclopropanone, showed almost no stereoselectivity.

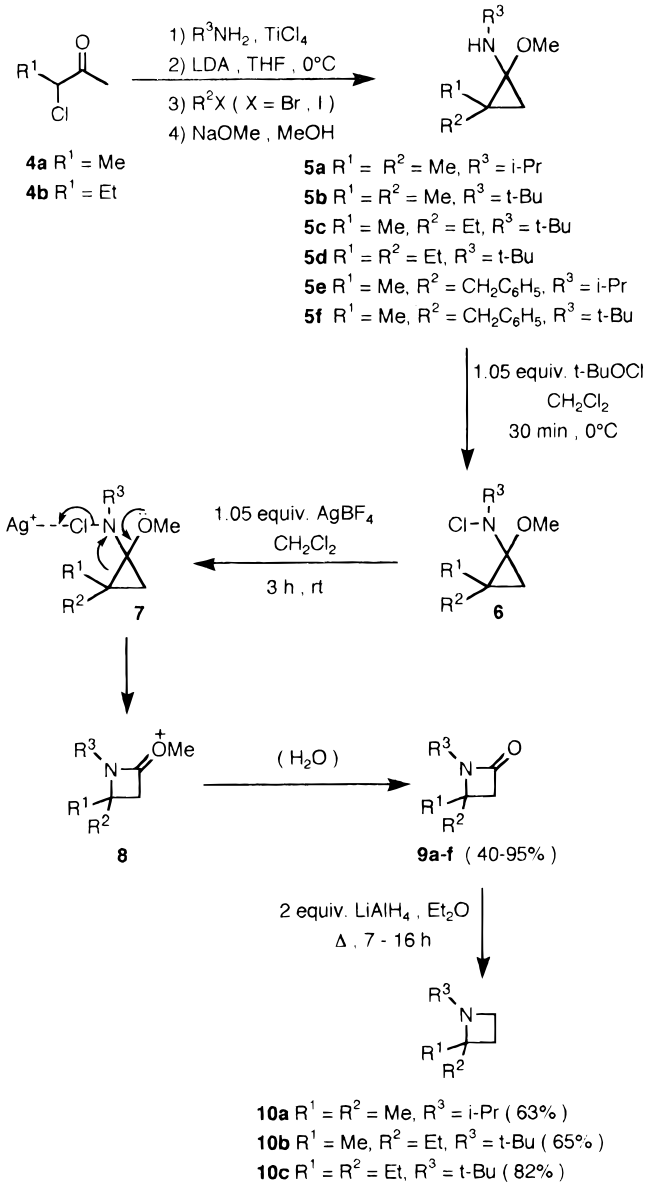
It was found that 1-methoxycyclopropylamines **5** can undergo ring enlargement in a regiospecific way via N-chlorination and subsequent silver-induced rearrangement. 2,2-Disubstituted 1-methoxycyclopropylamines **5** reacted with *tert*-butyl hypochlorite in dichloromethane at 0 °C for 30 min to give the corresponding *N*-chlorocyclopropylamines **6** *in situ*, which underwent ring expansion into β-lactams **9** by reaction with silver tetrafluoroborate in dichloromethane at ambient temperature in 3 h (Scheme 2). All β-lactams **9** were formed in good to excellent yields (75−95%), except **9c** which was isolated in 40% yield (small scale experiment), although no side products were detected (Table 1), and **9e** which was isolated in 41% yield (starting material was still present in the reaction mixture).

The novelty of this β-lactam synthesis consists of (1) the use of 1-alkoxycyclopropylamines **5** for the first time, (2) the use of geminally dialkylated cyclopropanone adducts for the first time, (3) the synthesis of previously almost inaccessible (cfr. only one recent report[19]) 1,4,4-trialkyl- 2-azetidinones,[20] (4) the regiospecific nature of this transformation, and (5) the use of α-chloro ketones as a new source of β-lactams.

The mechanism of the conversion of cyclopropanone adducts **5** into β-lactams **9** is interpreted by N-chlorination of **5** to give **6** and silver-assisted rearrangement, by which the electron pair of the methoxy oxygen atom is pushing the electrons toward ring-opening and expulsion of chloride (push-pull mechanism).[7,8] The resulting oxonium species **8** undergoes further hydrolytic cleavage during workup. Efforts to intercept the oxonium species **8** under water-free conditions by methanolic workup did not lead to any other products than β-lactams **9**. The regiospecificity of this process arises from the better migratory aptitude of the *gem*-disubstituted ring carbon to neutralize the intermediate pseudonitrenium species.

It is known that β-lactams are reduced by nucleophilic hydrides to afford the corresponding azetidines.[21] However, this reaction cannot be generalized because many transformations of 2-azetidinones with reducing agents, *e.g.*, diborane, do not lead to azetidines, but instead give rise to γ-amino alcohols.[22] Because of the recent promising results of chloroalanes in the reductive conversion of

Scheme 2



β-lactams into azetidines,[21b−e] monochloroalane was tried out with 1,4,4-trisubstituted 2-azetidinones **9** because it could give rise to the rare 1,2,2-trisubstituted azetidines **10**. All our efforts to utilize chloroalane, generated from lithium aluminum hydride and aluminum(III) chloride, failed completely. Instead, lithium aluminum hydride (2 molar equiv) in diethyl ether under reflux for 7−16 h converted 2-azetidinones **9a,c,d** into azetidines **10a,c,d** in 63−82% yield.

All substrates **5**, **9**, and **10** were subject to thermal transformations. It was previously reported that aliphatic 1-methoxycyclopropylamines **5** undergo thermal fragmentation into olefins, α,β-unsaturated imines, methanol, and an aliphatic isonitrile upon gas chromatography.[18] This reaction was also observed for benzyl de-

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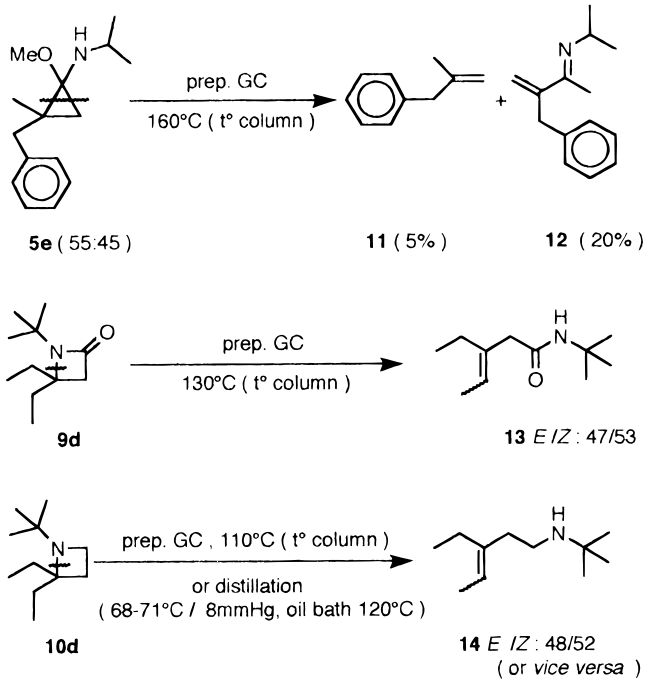
Table 1. Synthesis of β-Lactams 9 and Azetidines 10

R^1	R^2	R^3	2-azetidinone **9**[a]	yield from **5** (%)	bp of **9** (°C/mmHg)	azetidines **10**[b]	yield from **9** (%)
Me	Me	*i*-Pr	**9a**	86	25−27/0.01	**10a**	63
Me	Me	*t*-Bu	**9b**	75	70−75/2		
Me	Et	*t*-Bu	**9c**	40[c]	31−33/0.01	**10c**	65
Et	Et	*t*-Bu	**9d**	87	74−80/0.25	**10d**	82
Me	CH_2Ph	*i*-Pr	**9e**	41	84−85/0.01		
Me	CH_2Ph	*t*-Bu	**9f**	95	91−95/0.01		

[a] Reaction of cyclopropanone adducts **5** with 1.05 equiv of *tert*-BuOCl in dichloromethane (0 °C, 30 min) and subsequent addition of 1.05 equiv of $AgBF_4$ (rt; 3 h). [b] Reaction of β-lactams **9** with 2 molar equiv of $LiAlH_4$ in ether under reflux for 7 h (**7c**) or 16 h (**7a** and **7d**). [c] No other side products were detected.

Scheme 3



rivative **5e** which was converted into 2-methyl-3-phenyl-1-propene (**11**) and α,β-unsaturated ketimine **12** upon preparative gas chromatographic analysis. The imine hydrolyzed readily to the corresponding ketone in $CDCl_3$ solution.

The little known 1,4,4-trisubstituted 2-azetidinones **9** and 1,2,2-trisubstituted azetidines **10** underwent a typical thermal rearrangement in which 2-azetidinones **9** and 1,2,2-trisubstituted azetidines **10** were cleaved at the more substituted N−C(4) and N−C(1) bond, respectively, to afford a mixture of (*E*)- and (*Z*)-β,γ-unsaturated carboxylic amides or 3-alkenamines, respectively. It seems that this rearrangement is more typical for more heavily substituted derivatives, as exemplified for the thermal conversion during preparative gas chromatography of 1-*tert*-butyl-4,4-diethyl-2-azetidinone (**9d**) and 1-*tert*-butyl-2,2-diethylazetidine (**10d**) (Scheme 3). This rupture of the carbon−nitrogen double bond is certainly favored by the adjacent geminal substitution at carbon, which facilitates the development of a carbenium ion or radical.

In conclusion, a regiospecific rearrangement of 1-methoxycyclopropylamines into β-lactams was developed. Both bulky substituted β-lactams and the corresponding azetidines were shown to undergo thermal rearrangement into β,γ-unsaturated carboxylic amides or 3-alkenamines, respectively.

Experimental Section

^1H NMR spectra were recorded at 60 and 270 MHz. ^{13}C NMR spectra were recorded at 20 and 67.8 MHz. Mass spectra were obtained on a mass spectrometer (70 eV) using direct inlet or GC-MS coupling (RSL 200, 20 m glass capillary column, i.d. 0.53 mm, He carrier gas). Gas chromatographic analyses were performed with glass columns (RSL 150, 20 m, i.d. 0.53 mm, N_2 carrier gas and 1.5 m, i.d. 4 mm, 5−10% SE-30, Chromosorb W 60−80, H_2 carrier gas). THF and diethyl ether were distilled from benzophenone ketyl and sodium, while dichloromethane was distilled from calcium hydride. The α-chloro ketimines and 2,2-dialkyl-1-methoxycyclopropylamines **5** were synthesized according to the method previously described.[15−17] Spectral data for cyclopropylamines **5a**−**f** and the corresponding α-chloro ketimines (*i.e.* precursors to cyclopropylamines **5e,f**) are given in the supporting information.

General Procedure for the Synthesis of β-Lactams 9. A stirred solution of 2,2-disubstituted 1-methoxycyclopropylamine **5** (5 mmol) in dry dichloromethane (5 mL) was cooled to 0 °C and treated dropwise with *tert*-butyl hypochlorite (0.57 g, 5.3 mmol) in dichloromethane (2 mL). The solution was stirred at 0 °C for 30 min, after which silver tetrafluoroborate (0.98 g, 5.3 mmol) was added. The reaction mixture was further stirred at room temperature for 3 h in the dark. After filtration of the precipitated silver chloride, the filtrate was treated with water (10 mL) and the organic layer was isolated. The aqueous layer was extracted with dichloromethane (5 mL × 2), and the combined organic extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The remaining residue consisted of β-lactam **9** in a purity of 90−95%. Purification was performed by vacuum distillation, because flash chromatography on silica gel gave a complete decomposition of the labile β-lactams **9**. An analytical sample of compound **9e** was obtained by preparative gas chromatography. Yields and boiling points of β-lactams **9** are compiled in Table 1.

4,4-Dimethyl-1-isopropyl-2-azetidinone (9a): ^1H NMR (270 MHz, $CDCl_3$) δ 1.31 (6H, d, J = 6.60 Hz), 1.42 (6H, s), 2.66 (2H, s), 3.58 (1H, septet, J = 6.93 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.74, 26.18, 44.37, 50.24, 55.96, 165.69; IR (NaCl, cm^{-1}) $\nu_{C=O}$ = 1725; MS (70 eV) m/z (rel int) 141 (M^+, 28), 126 (7), 98 (6), 84 (35), 70 (21), 56 (100), 43 (21), 42 (100). Anal. Calcd (Found) for **9a**, $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92 (C, 68.12; H, 10.79; N, 9.79). This compound was recently prepared for the first time by intramolecular rhodium(II)-catalyzed insertion of α-diazo carboxylic amides.[19]

1-*tert*-Butyl-4,4-dimethyl-2-azetidinone (9b): ^1H NMR (270 MHz, $CDCl_3$) δ 1.40 (9H, s), 1.51 (6H, s), 2.59 (2H, s); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 27.53, 28.61, 50.15, 54.60, 57.21, 166.34; IR (NaCl, cm^{-1}) $\nu_{C=O}$ = 1730; MS (70 eV) m/z (rel int) 155 (M^+, 12), 140 (17), 112 (1), 100 (4), 99 (4), 98 (7), 84 (100), 71 (2), 70 (2), 59 (2), 58 (13), 57 (49), 56 (100), 55 (13), 51 (4), 49 (9), 44 (7), 43 (7), 42 (20). Anal. Calcd (Found) for **9b**, $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02 (C, 69.50; H, 11.11; N, 9.10).

1-*tert*-Butyl-4-ethyl-4-methyl-2-azetidinone (9c): ^1H NMR (270 MHz, $CDCl_3$) δ 0.95 (3H, t, J = 7.43 Hz), 1.39 (9H, s), 1.49 (3H, s), 1.73 and 1.84 (2H, d × d × q, J = 7.16 Hz, J_{gem} = 14.31 Hz), 2.40 and 2.65 (2H, 2 × d, AB, J = 14.19 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 9.89, 25.91, 29.18, 32.83, 47.06, 55.42, 61.58, 167.26; IR (NaCl, cm^{-1}) $\nu_{C=O}$ = 1725; MS (70 eV) m/z (rel int) 169 (M^+, 11), 154 (18), 140 (5), 112 (6), 98 (9), 84 (100), 71 (14), 70 (84), 58 (29), 57 (55), 56 (20), 55 (62), 43 (16),

42 (53). Anal. Calcd (Found) for **9c**, $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.27 (C, 71.10; H, 11.24; N, 8.15).

1-*tert*-Butyl-4,4-diethyl-2-azetidinone (9d): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.97 (6H, t, J = 7.42 Hz), 1.39 (9H, s), 1.72 and 1.86 (4H, d × d × q, J = 7.28 Hz, J_{gem} = 14.51 Hz), 2.50 (2H, s); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 8.90, 28.30, 30.28, 42.17, 54.70, 64.89, 166.92; IR (NaCl, cm^{-1}) $\nu_{C=O}$ = 1735; MS (70 eV) m/z (rel int) 183 (M^+, 15), 168 (22), 154 (11), 126 (3), 112 (11), 98 (31), 85 (8), 84 (100), 70 (6), 69 (49), 67 (2), 58 (31), 57 (42), 56 (36), 55 (20), 54 (4), 53 (3), 43 (9), 42 (13). Anal. Calcd (Found) for **9d**, $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64 (C, 71.95; H, 11.51; N, 7.75). Upon preparative gas chromatographic analysis (235 °C, 30 μL), azetidinone **9d** rearranged partially into β,γ-unsaturated carboxylic amide **12** (*E*/*Z* 47/53 determined by capillary GC).

4-Benzyl-1-isopropyl-4-methyl-2-azetidinone (9e): ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.37 (3H, d, J = 5.94 Hz), 1.38 (3H, s), 1.41 (3H, d, J = 6.93 Hz), 2.49 and 2.92 (2H, 2×d, AB, J = 14.51 Hz), 2.97 and 3.00 (2H, 2 × d, AB, J = 13.53 Hz), 3.50 (1H, septet, J = 6.43 Hz), 7.1−7.4 (5H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.89, 22.01, 23.58, 44.78, 45.37, 47.98, 59.08, 126.88, 128.50, 129.77, 136.91, 165.77; IR (NaCl, cm^{-1}) $\nu_{C=O}$ = 1725; MS (70 eV) m/z (rel int) 217 (M^+, 3), 174 (2), 160 (3), 159 (2), 132 (10), 131 (6), 130 (10), 127 (14), 126 (100), 117 (24), 91 (20), 84 (72), 77 (4), 65 (9), 43 (22), 42 (95). Anal. Calcd (Found) for **9e**, $C_{14}H_{19}NO$: N, 6.45 (N, 6.57).

4-Benzyl-1-*tert*-Butyl-4-methyl-2-azetidinone (9f): ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.48 (9H, s), 1.48 (3H, s), 2.33 and 2.89 (2H, 2 × d, AB, J = 14.52 Hz), 2.99 and 3.20 (2H, 2 × d, AB, J = 13.20), 7.1−7.4 (5H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 25.10, 28.95, 46.47, 47.22, 55.26, 60.88, 126.83, 128.46, 129.92, 137.16, 166.45; IR (NaCl, cm^{-1}) $\nu_{C=O}$ = 1730; MS (70 eV) m/z (rel int) 231 (M^+, 7), 216 (3), 190 (6), 174 (5), 160 (5), 159 (7), 140 (69), 132 (19), 117 (27), 91 (27), 84 (100), 77 (6), 65 (11), 57 (78), 43 (19), 42 (34). Anal. Calcd (Found) for **9f**, $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05 (C, 77.69; H, 9.04; N, 6.11).

Reduction of 1,4,4-Trisubstituted Azetidinones 9 to 1,2,2-Trisubstituted Azetidines 10. To an ice-cooled solution of β-lactam **9** (1 mmol) in diethyl ether (2 mL) was added lithium aluminum hydride (0.08 g, 2 mmol). This solution was stirred under reflux for 7−16 h after which the reaction mixture was cooled in an ice bath and the reaction was quenched by a few drops of water. Filtration over a potassium carbonate layer and evaporation *in vacuo* yielded azetidines **10** in a purity of 87−92%. Azetidine **10d** was distilled (bp 68−71 °C/8 mmHg, oil bath 120 °C) but suffered from a considerable amount of ring opening, resulting in the formation of homoallylamine **13**. Vacuum distillation led also to partial decomposition of azetidines **10a**,**c**. However, a purified sample could be obtained by utilization of a high vacuum distillation and by trapping of the most volatile fraction in a cold finger.

2,2-Dimethyl-1-isopropylazetidine (10a): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.91 (6H, d, J = 6.27 Hz), 1.24 (6H, s), 1.77 (2H, t, J = 6.93 Hz), 2.60 (1H, septet, J = 6.27 Hz), 3.05 (2H, t, J = 6.93 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.10, 25.44, 31.16, 46.95, 50.10, 62.73; IR (NaCl, cm^{-1}) ν_{max} = 1460, 1378, 1362, 1332, 1290, 1266, 1222, 1203, 1048; MS (70 eV) m/z (rel int) 128 (M^+ + 1, 5), 127 (M^+, 24), 113 (10), 112 (61), 98 (10), 84 (29), 72 (12), 71 (13), 70 (60), 69 (13), 57 (12), 56 (100), 55 (20), 44 (28), 43 (38), 42 (65). Anal. Calcd (Found) for **10a**, $C_8H_{17}N$: N, 11.01 (N, 11.19).

1-*tert*-Butyl-2-ethyl-2-methylazetidine (10c): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.81 (3H, t, J = 7.42 Hz), 1.00 (9H, s), 1.23 (3H, s), 1.45−1.58 (2H, m), 1.60−1.72 (1H, m), 1.89−1.97 (1H, m), 3.04−3.09 (1H, m), 3.11−3.23 (1H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 8.82, 27.58, 28.50, 35.09, 41.35, 52.92, 68.57; IR (NaCl, cm^{-1}) ν_{max} = 1450, 1365, 1360, 1235, 1146, 1137, 1100, 1067; MS (70 eV) m/z (rel int) 156 (M^+ + 1, 3), 155 (M^+, 16), 140 (38), 126 (20), 112 (4), 98 (6), 84 (19), 83 (10), 70 (100), 58 (27), 57 (26), 55 (24), 42 (21). Anal. Calcd (Found) for **10c**, $C_{10}H_{21}N$: N, 9.02 (N, 8.85).

1-*tert*-Butyl-2,2-diethylazetidine (10d): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.43 Hz), 0.99 (9H, s), 1.4−1.6 (2H, m), 1.68 (2H, t, J = 6.93 Hz), 3.11 (2H, t, J = 6.93 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 9.04, 23.23, 27.62, 29.87, 41.53, 52.47, 71.57; IR (NaCl, cm^{-1}) ν_{max} = 1455, 1350, 1250, 1233; MS (70 eV) m/z (rel int) 169 (M^+, 12), 154(26), 140(33), 112(4), 86(30), 84(100), 70(20), 58(29), 57(36), 56(19), 55(35), 44(4), 43(4), 42(9). Anal. Calcd (Found) for **10d**, $C_{11}H_{23}N$: N, 8.27 (N, 8.40).

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Supporting Information Available: Full spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, and MS) and physical data for the α-chloro ketimines (precursors to cyclopropylamines **5e**,**f**), compounds **5a**−**f**, **11**−**13**, and 3-benzyl-3-buten-2-one (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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