Syntheses and Reactions of 1-Amino-2,2-dialkylcyclopropane-1-carbonitriles and -carboxamides – Potential Precursors of ACC Derivatives

Wim Aelterman,[a] Kourosch Abbaspour Tehrani,[a] Wim Coppens,[a] Tom Huybrechts,[a] Norbert De Kimpe,*[a] Dirk Tourwé,[b] and Jean-Paul Declercq[c]

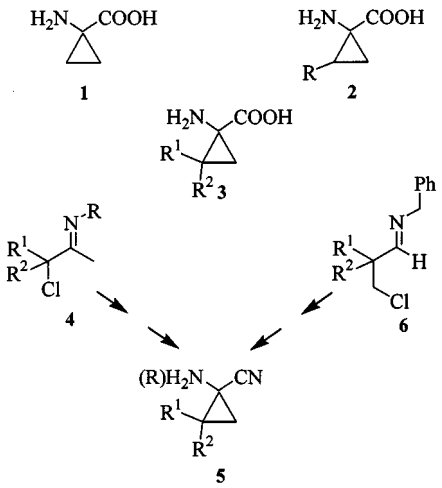
Keywords: Cyclopropanes / Rearrangements / Cyanohydrins / Schiff bases / Small ring systems

The direct cyclization of 2-amino-4-chloro-3,3-dimethylbutanenitrile with potassium *tert*-butoxide in THF afforded 1-amino-2,2-dimethylcyclopropane-1-carbonitrile and a dimerization product. Various new *cis*- and *trans*-1-(*tert*-butylamino)-2-benzyl-2-methylcyclopropane-carbonitriles and the corresponding cyclopropanecarboxamides have been synthesized, with focus on the isolation of the pure stereoisomeric cyclopropanecarboxamides. The relative configuration of the stereoisomers was established by X-ray crystallographic analysis of one of the model compounds. A new route to the latter functionalized cyclopropanes was developed by reaction of 1-methoxycyclopropylamines with potassium cyanide. Some remarkable rearrangements of 1-aminocyclopropane-1-carbonitriles into azetidine and oxazine derivatives via Favorskii-derived intermediates are reported. Various aspects of the chemistry of geminally functionalized cyclopropanes are discussed.

Introduction

1-Aminocyclopropane-1-carboxylic acid (ACC) (**1**) is omnipresent in the plant kingdom as the precursor of the plant growth regulator ethylene, which is responsible for the leaf and fruit drop, the flowering, the ripening of fruits, and the senescence of plants.[1] Various ACC derivatives **2** and **3**, substituted at the ring carbons with alkyl groups, have been synthesized as potential plant growth regulators (Scheme 1).[2−5] Major focus was given to 2-substituted and 2,2-disubstituted 1-aminocyclopropane-1-carboxylic acids in recent years. 1-Aminocyclopropanecarboxylic acid derivatives have also been studied in the light of the construction of peptides containing these sterically constrained α-amino acids in order to gain defined conformational changes, the ultimate goal being the design of enzyme inhibitors.[6−8]

2,2-Dialkyl-1-aminocyclopropanecarboxylic acids **3** were previously synthesized from α-chloroketimines **4**[9] or β-chloroaldimines **6**[10] via the corresponding 1-aminocyclopropane-1-carbonitriles **5** (Scheme 1). Each of these routes had several drawbacks in the generation of these cyclopropane carbonitriles in such a way that it was desirable to evaluate new ways of their generation. In the present report, several potential methods for the synthesis of 1-amino-2,2-dialkylcyclopropane-1-carbonitriles **5** are disclosed, each originating from a strategy which avoids previously encountered problems. In addition, novel aspects of the chemistry of these functionalized cyclopropanes, e.g. dimerization reactions and ring transformations into heterocycles, are unraveled.



Scheme 1

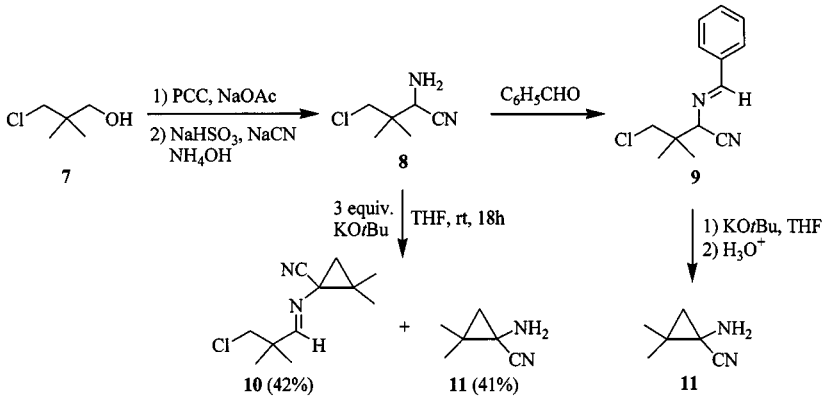
Results and Discussion

2-Amino-4-chloro-3,3-dimethylbutanenitrile (**8**), easily accessible from the γ-chloroalcohol **7** via oxidation with pyridinium chlorochromate and subsequent reaction with ammonium hydroxide in the presence of sodium cyanide and sodium bisulfite,[11,12] was found to react with benzaldehyde to give the functionalized aldimine **9**, which was conveniently 1,3-dehydrochlorinated by potassium *tert*-butoxide and subsequently hydrolyzed in acid medium to afford 1-amino-2,2-dimethylcyclopropane-1-carbonitrile (**11**) (Scheme 2).[10]

It was never investigated before if the α-amino-γ-chloronitrile **8** could directly give rise to 1-amino-2,2-dimethylcy-

[a] Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, University of Gent, Coupure Links 653, B-9000 Gent, Belgium
[b] Free University of Brussels, Department of Organic Chemistry, Pleinlaan 2, B-1050 Brussels, Belgium
[c] Laboratoire de Chimie Physique et de Crystallographie, Université Catholique de Louvain, Place L. Pasteur 1, B-1348 Louvain-la-Neuve, Belgium

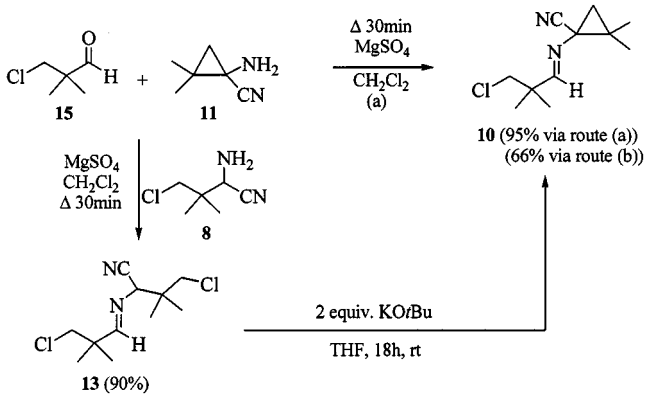
  1434−193X/99/0101−0239 $ 17.50+.50/0



Scheme 2

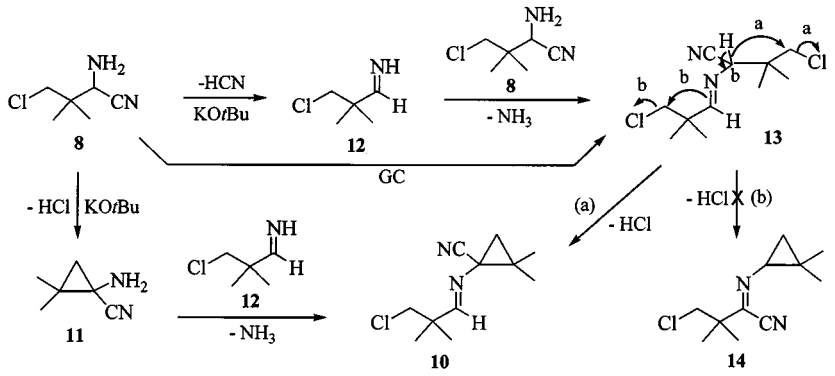
clopropane-1-carbonitrile (**11**) by treatment with potassium *tert*-butoxide, avoiding the amino protection−deprotection protocol. To this end, 2-amino-4-chloro-3,3-dimethylbutanenitrile (**8**) was treated with three equivalents of potassium *tert*-butoxide in tetrahydrofuran at room temperature for 18 h to give rise to 1-amino-2,2-dimethylcyclopropane-1-carbonitrile (**11**) and 1-[(3-chloro-2,2-dimethyl-1-propylidene)amino]-2,2-dimethylcyclopropane-1-carbonitrile (**10**) in 41% and 42% yield, respectively (Scheme 2). Both compounds were easily separated by flash chromatography. The surprising formation of this "dimerization product" **10** is postulated to proceed via an initial dehydrocyanation step to give the labile *N*-unsubstituted aldimine **12**. Condensation of the latter imine with the starting α-aminonitrile **8** may then give rise to the transimination product **13** which can suffer 1,3-dehydrochlorination to form the *N*-cyclopropylimine **10** (route a, Scheme 3). Alternatively, the starting material may undergo 1,3-dehydrochlorination to afford 1-amino-2,2-dimethylcyclopropane-1-carbonitrile (**11**), the more bulky amino group of which is also able to give a transimination with the reactive *N*-unsubstituted β-chloroimine **12** (Scheme 3).

Since the reaction was performed under anhydrous conditions, hydrolysis of the unsubstituted aldimine **12** to the corresponding aldehyde, prior to condensation with either amine **8** or amine **1**, was not considered. Although deprotonation at the α_N-position of the β-chloroaldimine **13** generates an ambident 2-azaallylic anion, only 1,3-dehydrochlorination at the nitrile side occurs. No trace of the imidoylcyanide **14**, resulting from a 1,5-dehydrochlorination process, was detected (route b, Scheme 3). The structure of the "dimeric" compound **10** was unequivocally proven by the synthesis of this compound from β-chloroaldehyde **15** and 1-amino-2,2-dimethylcyclopropane-1-carbonitrile (**11**) in dichloromethane in the presence of magnesium sulfate (reflux 30 min) (Scheme 4).



Scheme 4

1-(Alkylideneamino)cyclopropylideneamine **10** was obtained in 95% yield after flash chromatography. Remarkably, pure 2-amino-4-chloro-2,2-dimethylbutanenitrile (**8**) is converted by preparative gas chromatography (injector temperature 230°C) into 4-chloro-3,3-dimethyl-2-[(3-chloro-



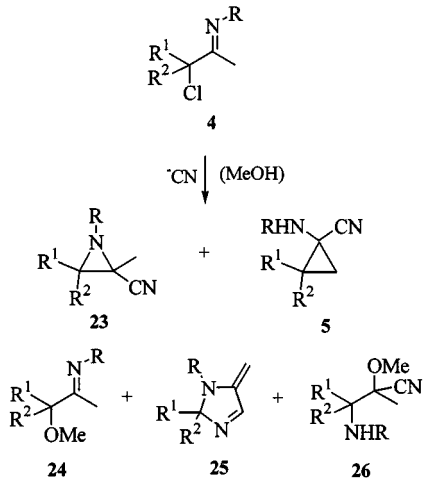
Scheme 3

2,2-dimethyl-1-propylidene)amino]butanenitrile (**13**) via dehydrocyanation of **8**, followed by transimination with the latter. Compound **10**, a stable distillable compound, was also prepared by condensation of β-chloroaldehyde **15** with 2-amino-4-chloro-2,2-dimethylbutanenitrile (**8**). Treatment of the resulting β-chloroaldimine **13** with two equivalents of potassium *tert*-butoxide in THF at room temperature for 18 h afforded β-chloroaldimine **10** in 66% yield (route b, Scheme 4).

Another remarkable reaction took place with the cyanoborohydride reduction product of β-chloroaldimine **10**, i.e. γ-chloroamine **16**, upon treatment with potassium *tert*-butoxide in THF under reflux for 60 h. This reaction gave rise to 1-pivaloylazetidine **17** (50%) and the cyclic imidate **18** (40%). The formation of both heterocycles **17** and **18** from cyclopropane **10** can be explained by the generation of the Favorskii intermediate **19** by dehydrocyanation,[13] opening of the cyclopropylideneamine **19** by *tert*-butoxide with subsequent loss of isobutene[14] and following intramolecular *N*-alkylation or *O*-alkylation of the amide anion **22** (Scheme 5).

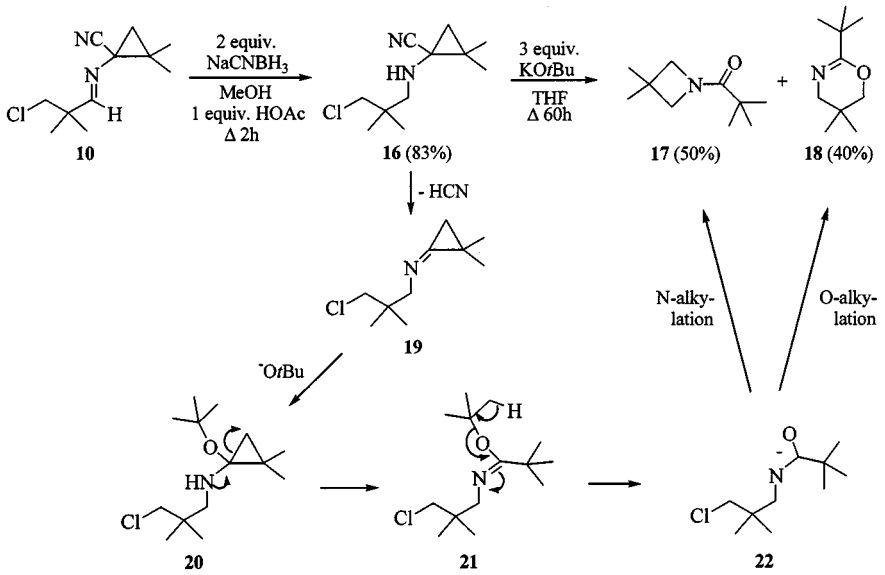
From a practical viewpoint, the direct ring closure of α-amino-γ-chloronitrile **8** offers no real advantage and therefore this process was not optimized. It is clear however that on aqueous acid hydrolysis of the reaction mixture, 1-amino-1-cyclopropanecarbonitrile **11** can be obtained as a pure compound by subsequent acid and base extraction. The protection of the amino function is thus not really a requisite for the cyclopropane forming process (Scheme 2; **8** → **9** → **11**).

Attention was then turned to the generation of 1-aminocyclopropanecarbonitriles **5** from α-chloroketimines **4**. It was found previously that the outcome of the reaction of α-haloketimines with cyanide was greatly dependent upon various reaction parameters, such as the nitrogen substituent, the solvent, the type of cyanide (the counter ion), the nature of the carbon skeleton and the α-halogen. Besides to α-cyanoaziridine formation several other reactions occurred, including Favorskii-type rearrangement, solvolysis, nucleophilic substitution, 1,2-dehydrochlorination, and the formation of heterocyclic compounds (Scheme 6).[15] Previously, an extensive investigation on the reactivity of cyanide towards α-haloimines enabled to differentiate between the parameters influencing the reaction path.[15] Depending on the conditions used the reaction could be directed towards α-cyanoaziridines **23** or cyclopropanecarbonitriles **5**.[9] Putting together all requirements and tracing them back to the starting α-haloimines, *N*-*tert*-butyl tertiary α-chlorinated methylketimines were used to synthesize 1-amino-2,2-dialkyl-1-cyclopropanecarboxylic acids **3** via reaction with cyanide in methanol.

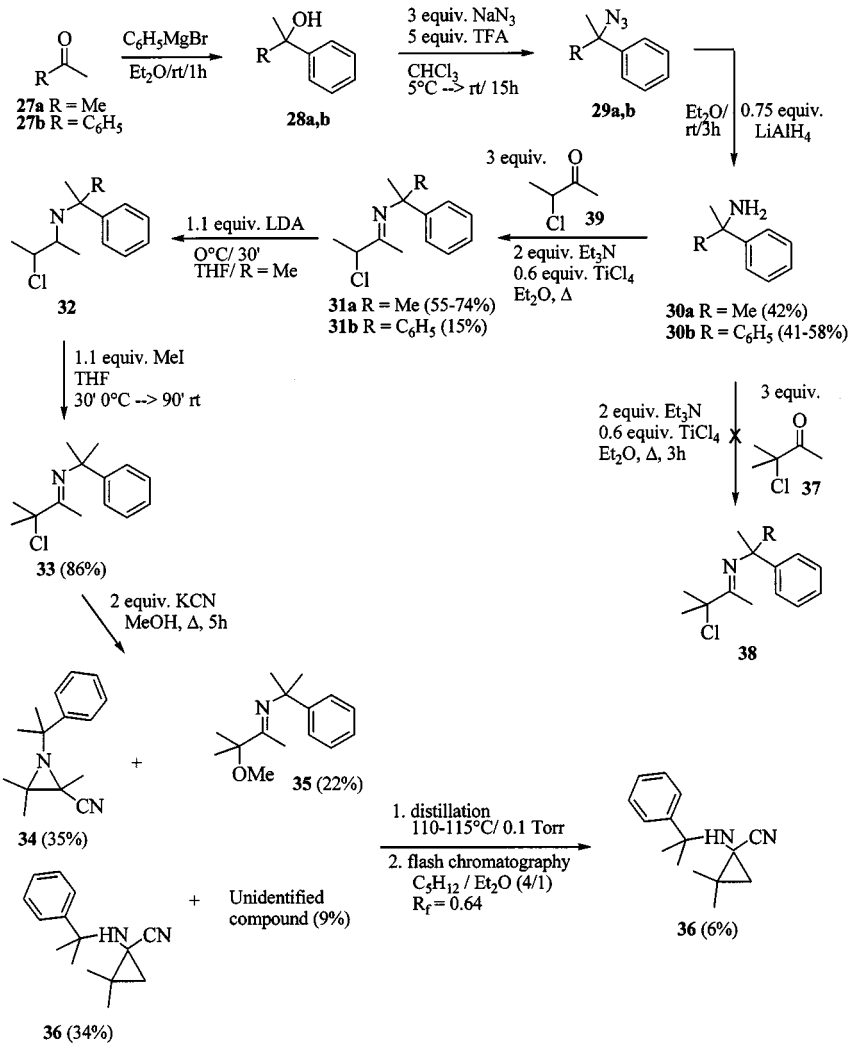


Scheme 6

In the present paper, attention is paid to the cyclopropanation of α-haloimines carrying a tertiary *N*-benzylic substituent. The goal of this selected substituent is twofold. Primarily, a further decrease of the aziridine formation is put forward as a result of the increased steric hindrance at the



Scheme 5



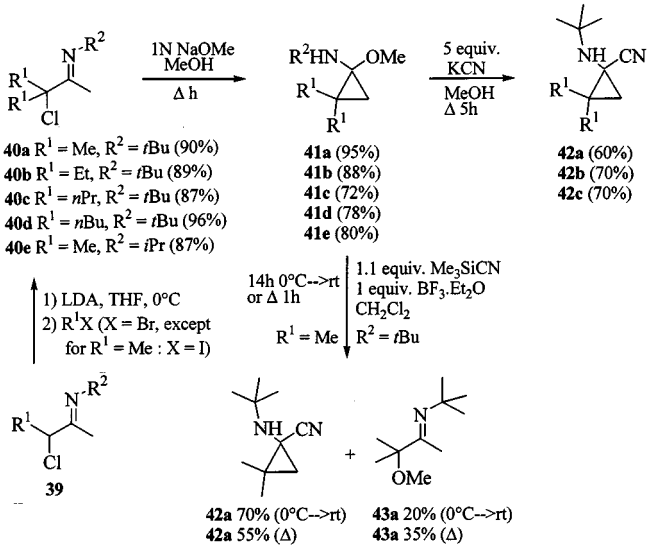
Scheme 7

α_N-position. This effect would be especially important regarding the dimethyl compound. Second, the presence of an aryl group is expected to facilitate the nitrogen−carbon bond scission by stabilization of the transient carbenium ion formed in the deprotection step (executed in acid medium). The tertiary amines **30a**, **b**, necessary for this purpose, were prepared following a three step reaction sequence involving (a) addition of phenylmagnesium bromide to ketones **27a**, **b**, (b) replacement of the hydroxyl group by azide through reaction with sodium azide in the presence of trifluoroacetic acid, and (c) subsequent reduction of the azides **29a**, **b** by lithiumaluminium hydride in ether.[16] As could be expected, the direct condensation of amines **30** with 3-chloro-3-methyl-2-butanone (**37**) in the presence of titanium(IV) chloride did not give rise to the tertiary α-chloroketimine **38**. Therefore, an alternative synthetic route was applied in which the tertiary amine **30** was condensed with 3-chloro-2-butanone (**39**) followed by regiospecific methylation with iodomethane of the resulting secondary α-chloroketimine **31**. In the case of α,α-dimethylbenzylamine (**30a**), both reactions occurred smoothly and in good yields. For 1,1-diphenylethylamine (**30b**) the condensation with the secondary α-chloroketone **39** could not be established in a selective way since the corresponding α-chloroketimine **31b** was always accompanied by an elimination type of product. Even though the imine **31b** could be isolated in pure form by means of flash chromatography and recrystallization, it did not seem an attractive preparative way because of the low yield after purification (15%).

Having in hands *N*-(3′-chloro-3′-methyl-2-butylidene)-1,1-dimethylbenzylamine (**33**), this imine was treated with potassium cyanide in methanol under reflux. In contrast to other *N*-*tert*-alkyl tertiary α-chloroketimines, this reaction did not lead to the corresponding cyclopropanecarbonitrile **36** as the major or sole reaction product. Instead, a reaction mixture was obtained, out of which the derived compound **36** was isolated in a disappointing 6% yield by distillation and subsequent flash chromatography. Next to the α-aminonitrile **36**, the α-cyanoaziridine **34** (35%) and the α-methoxyketimine **35** (22%) were identified by GC-MS analysis. A fourth compound comprising about 10% of the reaction mixture remained unidentified. Since the reaction of α-chloroimines with cyanide was investigated already quite extensively,[15] no further attempts were made to further evaluate

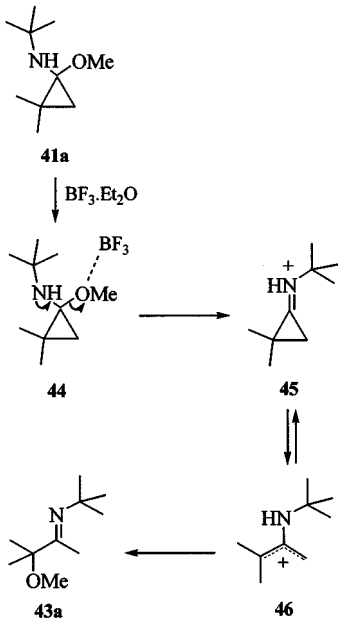
this type of reaction towards the synthesis of geminally dialkylated ACC analogues.

Because 1-aminocyclopropane-1-carbonitriles **5** have been used for the synthesis of ACC analogues[9,10] and because they are valuable cyclopropanone adducts,[17] efforts were undertaken to make them accessible via 1-methoxycyclopropylamines **41**. The cyclopropanone adducts **41** are easily available from α-chloroketimines **39** and **40**, by reaction of the latter with 1 N sodium methoxide in methanol under reflux (Scheme 8).[18]



Scheme 8

The reaction of 1-methoxycyclopropylamines **41a–c** with potassium cyanide (5 equiv.) in methanol for 5 days gave rise to 2,2-dialkyl-1-(*tert*-butyl)aminocyclopropane-1-carbonitriles **42a–c** in 60–70% yield. The cyclopropanecarbonitriles **42** are formed by expulsion of methoxide from cyclopropanone adduct **41**, the intermediate cyclopropaniminium ion or cyclopropylidenamine being trapped by cyanide. This synthetic route offers a new useful entry to 1-aminocyclopropanecarbonitriles **42** via a two-step-reaction from α-chloroketimines **40** (Scheme 8). It offers the advantage that the undesired α-cyanoaziridine formation in some reactions (e.g. with gem. dimethyl derivatives) does not occur. The use of cyanide in the presence of Lewis acids was less successful. Accordingly, *N*-*tert*-butyl-2,2-dimethyl-1-methoxycyclopropylamine (**41a**) reacted with trimethylsilyl cyanide in the presence of borontrifluoride etherate in dichloromethane, either at 0°C to room temperature or at reflux, to give a mixture of the derived 1-aminocyclopropanecarbonitrile **42a** (55%–70%) and the less expected α-methoxyketimine **43a** (20–35%) (Scheme 8). Under these conditions, the transient cyclopropylideniminium ion **45** is apparently in equilibrium with the ring-opened delocalized 2-aminoallylic carbenium ion **46**, which is trapped by methanol at the more substituted carbon to give compound **43a** (Scheme 9).

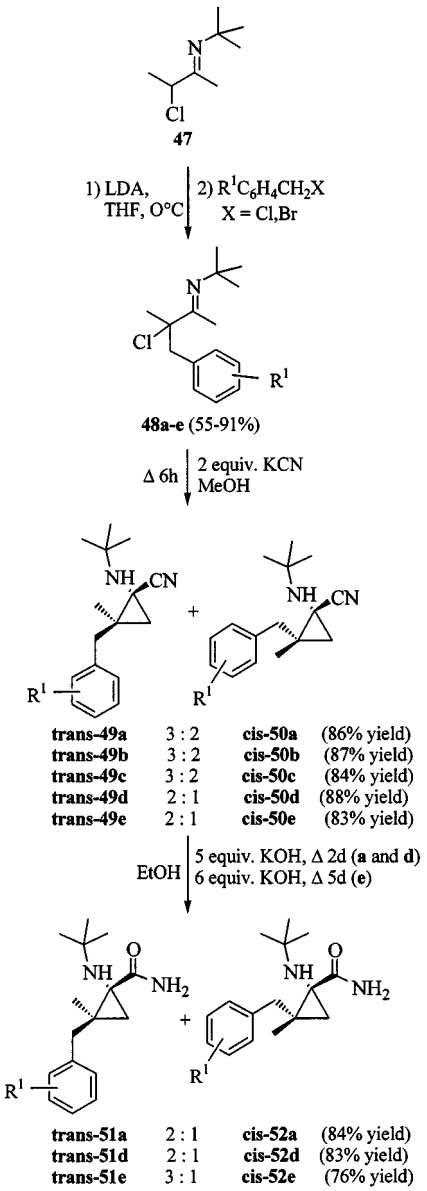


Scheme 9

Next, major attention was given to the stereoselectivity of the cyclopropane-forming process from α-chloroketimines. The purpose was to get access to *cis* and/or *trans* isomers of ACC derivatives, e.g. 1-aminocyclopropanecarbonitriles and 1-aminocyclopropanecarboxamides, in pure form. To this end, a whole range of *N*-(3-chloro-4-aryl-2-butylidene)-*tert*-butylamines **48** were synthesized by regiospecific α-benzylation of *N*-(3-chloro-2-butylidene)-*tert*-butylamine (**47**).[19] It proved to be advantageous to use slightly less than one equivalent of the electrophile (0.90–0.95 equiv.), affording the new α-chloro ketimines **48a–e** in 55 to 91% yield (Scheme 10; Table 1).

Reaction of *N*-(3-chloro-4-aryl-2-butylidene)-*tert*-butylamines **48** with 2 equivalents of potassium cyanide in methanol under reflux for 6 h gave rise to a mixture of *cis*-1-aminocyclopropanecarbonitriles **50** and *trans*-1-aminocyclopropanecarbonitriles **49** in a 2:3 or 1:2 ratio. No side products were observed in this clean reaction leading to the cyclopropanes **49** and **50** in combined yields of 83–88%. Treatment of these mixtures of stereoisomeric 1-aminocyclopropane-1-carbonitriles **49a**, **d**, **e** and **50a**, **d**, **e** with an excess of potassium hydroxide in ethanol for 2–5 days under reflux afforded a mixture of *cis*-1-aminocyclopropane-1-carboxamides **52a**, **d**, **e** and *trans*-1-aminocyclopropane-1-carboxamides **51a**, **d**, **e** in a 1:2 or 1:3 ratio. While the stereoisomeric cyclopropanecarbonitriles **49** and **50** were not separable by vacuum distillation, flash chromatography or preparative gas chromatography, the corresponding stereoisomeric cyclopropanecarboxamides **51** and **52** were easily separable by crystallization or flash chromatography.

The reaction of the *cis*- and *trans*-1-(*tert*-butylamino)-2-(4-chlorobenzyl)-2-methylcyclopropanecarbonitriles (**49d**) and (**50d**) with an excess (8 equiv.) of lithium hydroxide in



Scheme 10

dioxane in the presence of hydrogen peroxide (8 equiv.)[20] gave only a low yield of the corresponding carboxamides.

The structure of the cyclopropanecarbonitriles **49** and **50** and the corresponding cyclopropanecarboxamides **51** and **52** was established by ^{1}H NMR, ^{13}C NMR, IR, and mass spectrometry. The relative configuration was determined by X-ray crystallographic analysis of *trans*-1-*tert*-butylamino-2-benzyl-2-methylcyclopropane-1-carboxamide (**51a**). (see Figure 1). This result enabled to determine the stereochemical assignments of all the other compounds **49**, **50**, **51**, and **52**.

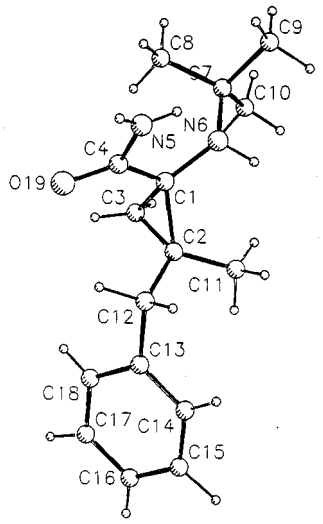


Figure 1. X-ray crystallographic picture of *trans*-1-*tert*-butylamino-2-benzyl-2-methylcyclopropane-1-carboxamide **57a**

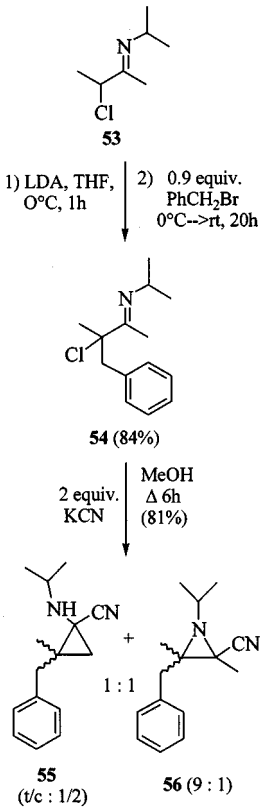
The clean conversion of α-benzyl-α-chloroketimines **48** seems to be limited to *N*-*tert*-butyl derivatives. The *N*-isopropyl α-benzyl-α-chloroketimine **54**, accessible from α-chloroketimine **53** in 94% yield, reacted with two equivalents of potassium cyanide in methanol (reflux 6 h) to give a 1:1 mixture of cyclopropanecarbonitrile **55** and aziridine-2-carbonitrile **56** in a combined yield of 81%. The cyclopropanecarbonitrile **55** consisted of a 2:1 mixture of the *trans*- and the *cis*-isomer, respectively, while the aziridine-2-carbonitrile **56** proved to be a 9:1 stereoisomeric mixture (c/t or vice versa) (Scheme 11).

Attempts to hydrolyze the 1-aminocyclopropane-1-carboxamides **51** and **52** with aqueous acid did not lead to the corresponding 1-aminocyclopropanecarboxylic acids. As examplified for *trans*-1-(*N*-*tert*-butylamino)-2-(4-chlorophenyl)-2-methylcyclopropane-1-carboxamide (**51d**), the reaction with excess 6 N hydrogen chloride at reflux for 3 hours, or with excess 2 N HCl at reflux for 20 hours, gave rise to the corresponding hydrochloride **57d** in 86% yield (Scheme 12). Longer reaction times led to unidentified reaction products.

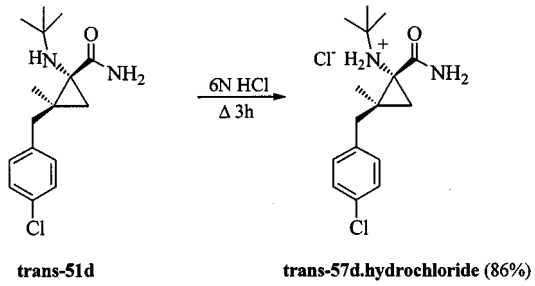
In conclusion, several new entries towards cyclopropanecarbonitriles and cyclopropanecar-boxamides have been unraveled.

Table 1. Synthesis of α-Chloroketimines **48** from **47**

	$R^1C_6H_4CH_2X$ R^1	X	Deprotonation of **47** (1.2 equiv. LDA)	Benzylation	Equiv. of $R^1C_6H_4CH_2X$	Yield of **48**
a	H	Br	0°C, 1 h	0°C → r.t., 20 h	0.9	84%
b	*m*-OCH_3	Cl	0°C, 45 min	0°C, 1 h	0.95	91%
c	*p*-Br	Br	0°C, 45 min	0°C, 1 h	0.9	83%
d	*p*-Cl	Cl	0°C, 1 h	0°C → r.t., 20 h	0.9	86%
e	*m*-F	Br	0°C, 1 h	0°C → r.t., 20 h	0.9	55%



Scheme 11



Scheme 12

Experimental Section

IR spectra were recorded with a Perkin Elmer 1310 spectrophotometer. – ^{1}H NMR and ^{13}C NMR spectra were measured with Jeol PMX60SI (^{1}H NMR 60 MHz), Jeol JNM EX 270 (^{1}H NMR 270 MHz and ^{13}C NMR 67 MHz), Varian T-60 (^{1}H NMR 60 MHz) and Varian FT-80 (^{13}C NMR 20 MHz) NMR spectrometers. – Mass spectra were obtained with a Varian MAT 112 mass spectrometer (70 eV) using GC-MS coupling with a Varian 2700 gas chromatograph (RSL 200, 20 m glass capillary column, i.d. 0.53 mm, He carrier gas). – Melting points were measured with a Reichert Jung (Kofler type) hotbench and a Büchi 535 melting point apparatus.

Reaction of 2-Amino-4-chloro-3,3-dimethylbutanenitrile (8) with Potassium *tert*-Butoxide in THF: To a solution of 2-amino-4-chloro-3,3-dimethylbutyronitrile hydrochloride (**8×HCl**) (0.91 g, 5 mmol) in THF (20 mL) was added potassium *tert*-butoxide (1.68 g, 15 mmol). The reaction mixture was stirred for 18 h, poured into water (50 mL) and extracted with diethyl ether (3× 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to yield 0.47 g (72%) of a mixture consisting of 1-amino-2,2-dimethylcyclopropanecarbonitrile (**11**) (81%)[10] and 1-[(3-chloro-2,2-dimethyl-1-butylidene)amino]-2,2-dimethylcyclopropanecarbonitrile (**10**) (19%). Flash chromatography (silica gel, eluent: Et_2O/C_5H_{12}, 1:1) yielded both products **10** (R_f = 0.94, 42%) and **11** (R_f = 0.49, 41%), indicating hydrolysis of the imino functionality during chromatography.

[(3-Chloro-2,2-dimethyl-1-propylidene)amine]-2,2-dimethylcyclopropyl-1-carbonitrile (10): ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.17 and 1.18 (6 H, 2 s, Me_2CCH_2Cl); 1.29 and 1.39 (6 H, 2 s, Me_2); 1.38 and 1.47 (2 H, AB, J = 5.13 Hz, CH_2 ring); 3.53 and 3.55 (2 H, AB, J = 10.98 Hz, CH_2Cl); 7.89 (1 H, s, HC=N). – ^{13}C NMR (67 MHz, $CDCl_3$): δ 19.57 and 23.81 (Me_2); 23.27 (Me_2CCH_2Cl); 29.51 (CMe_2); 31.81 (CH_2 ring); 41.47 and 44.69 (*C*CN and CCH_2Cl); 52.51 (CH_2Cl); 117.39 (*C*N); 166.75 (H*C*=N). – IR (NaCl): $\tilde{\nu}$ 2225 cm^{-1} (C≡N) and 1660 cm^{-1} (C=N). – MS, *m*/*z* (%): 212/214 [M$^+$] (0.4), 197/199 (4), 177 (4), 171 (3), 169 (2), 163 (26), 131 (3), 121 (100), 109 (5), 107 (25), 94 (12), 82 (4), 80 (5), 79 (4), 69 (8), 68 (5), 67 (11), 66 (4), 65 (3), 56 (14), 55 (20), 53(9), 52 (4), 43 (5), 41 (19), 40 (7). – $C_{11}H_{17}ClN_2$ (212.7):: Calcd. C 62.11, H 8.06, N 13.17; found C 61.94, H 8.17, N 13.26.

Synthesis of *N*-(3-Chloro-2,2-dimethyl-1-propylidene)-1-cyano-2,2-dimethylcyclopropylamine (10): To a solution of 1.10 g (0.01 mol) of 1-amino-2,2-dimethylcyclopropanecarbonitrile (**11**) in 10 mL of dry dichloromethane was added 3.54 g (0.02 mol) of $MgSO_4$ followed by 1.21 g (0.01 mol) of 3-chloro-2,2-dimethylpropanal (**15**). The mixture was refluxed for 1.5 h, the drying agent was filtered off and washed with 5 mL of dry ether. After evaporation of the solvent in vacuo 2.02 g (95%) of crude **10** was obtained which was purified by flash chromatography (ether/pentane, 5:95; R_f = 0.71) to yield pure **10** (1.34 g; 69%).

Synthesis of *N*-(3-chloro-2,2-dimethyl-1-propylidene)-3-chloro-1-cyano-2,2-dimethylbutylamine (13): Propylideneamine **13** was prepared in an analogous way (30 min at reflux) as described for compound **10**. – ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.09; 1.20; 1.21; 1.22 (12 H, 4 s, 2 Me_2); 3.45 and 3.64 (2 H, AB, J = 11.21 Hz, CH_2Cl); 3.59 (2 H, s, CH_2Cl); 4.54 (1 H, d, J = 1.65 Hz, C*H*CN); 7.83 (1 H, d, J = 1.65 Hz, H*C*=N). – ^{13}C NMR (67 MHz, $CDCl_3$): δ 21.28; 22.77; 23.16 (2 Me_2); 39.87 and 41.98 (2 CMe_2); 51.86 and 52.11 (2 CH_2Cl); 63.99 (*C*HCN); 116.37 (*C*N); 172.04 (H*C*=N). – IR: $\tilde{\nu}$ 2240 cm^{-1} (C≡N) and 1665 cm^{-1} (C=N). – MS *m*/*z* (%): no M$^+$; 213/215 (26), 201 (3), 199 (10), 160 (20), 159 (32), 158 (61), 157 (79), 133 (17), 132 (9), 131 (52), 130 (14), 123 (30), 109 (24), 107 (8), 105 (8), 104 (5), 103 (23), 95 (5), 94 (25), 93 (14), 91 (28), 83 (15), 82 (98), 81 (43), 80 (12), 77 (6), 75 (9), 70 (5), 69 (11), 68 (20), 67 (47), 66 (17), 65 (13), 63 (16), 57 (9), 56 (100), 55 (82), 54 (14), 53 (26), 52 (5), 51 (10), 49 (15), 43 (7), 42 (10), 41 (57), 40 (7). – $C_{11}H_{18}Cl_2N_2$ (249.2): Calcd. C 53.02, H 7.28%, N 11.24; found C 53.19, H 7.39, N 11.05.

Cyclization of *N*-(3-Chloro-2,2-dimethyl-1-propylidene)(3-chloro-1-cyano-2,2-dimethylbutyl)amine (13) to Cyclopropanecarbonitrile 10: A solution of 1.25 g (0.005 mol) of β-chloro aldimine **13** in 10 mL of dry THF was treated with 1.12 g (0.01 mol) of potassium *tert*-butoxide. The reaction mixture was stirred for 24 h at room temperature, poured into 20 mL of water and extracted with dichloromethane (3× 10 ml). The combined extracts were dried ($MgSO_4$) and concentrated to provide crude **10** which was distilled in vacuo to afford 0.52 g (49%) of pure cyclopropanecarbonitrile **10**, b.p. 51–54°C/0.07 Torr.

Synthesis of 1-(3-Chloro-2,2-dimethylpropyl)amino-2,2-dimethylcyclopropanecarbonitrile (16): To a solution of 0.57 g (0.0027 mol) of aldimine **10** in 5 mL of dry methanol was added 0.36 g (0.0054

mol) of sodium cyanoborohydride followed by 0.16 g (0.0027 mol) of acetic acid. The mixture was refluxed for 2 hours and subsequently poured into 20 mL of water and extracted with CH_2Cl_2 (3× 10 ml). After drying ($MgSO_4$), filtration, and evaporation of the solvent in vacuo 0.48 g (83%) of the cyclopropanecarbonitrile **16** (purity > 95%) was obtained. This compound was used as such in the next experiment. – ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.97 and 0.98 (6 H, 2 s, *Me*$_2$); 0.83 and 1.04 (2 H, AB, *J* = 4.88 Hz, C*H*$_2$ ring); 1.25 and 1.30 (6 H, 2 s, *Me*$_2$); 1.59 (1 H, broad s, N*H*); 2.66 (2 H, broad s, C*H*$_2$NH); 3.35 and 3.41 (2 H, AB, *J* = 10.62 Hz, C*H*$_2$Cl). – ^{13}C NMR (67 MHz, $CDCl_3$): δ 18.87; 23.54; 23.63 and 23.72 (2 *Me*$_2$); 26.83 (*C*Me$_2$); 28.50 (*C*H$_2$ ring); 36.14 and 38.04 (*C*CN and *C*CH$_2$Cl); 53.06 (*C*H$_2$Cl); 55.06 (*C*H$_2$NH); 120.90 (*C*N). – IR (NaCl): ṽ 3330 cm^{-1} (NH); 2220 cm^{-1} (C≡N). – MS *m*/*z* (%): 214/216 [M$^+$] (3), 199/201 (8), 179 (0.2); 171/173 (4), 165 (3), 158/160 (10), 143/145 (4), 132 (2), 124 (11), 123 (100), 109 (6), 108 (3), 107 (9), 106 (2), 96 (5), 95 (11), 94 (5), 93 (3), 82 (6), 81 (8), 69 (10), 68 (7), 67 (16), 56 (13), 55 (10), 53 (6), 43 (6), 42 (6), 41 (24), 40 (6).

Ring transformation of Cyclopropanecarbonitrile 16 into Azetidine 17 and Oxazine Derivative 18: A solution of 0.64 g (0.003 mol) of cyclopropanecarbonitrile **10** in 10 mL dry THF was treated with 1.01 g (0.009 mol) of potassium *tert*-butoxide. After reflux of the stirred mixture for 60 h, the reaction mixture was poured in water and extracted three times with ether. The combined extracts were dried ($MgSO_4$) and evaporated to give a reaction mixture which consisted (^{1}H NMR, GC) mainly of two compounds, as judged by preparative GC, which allowed the isolation of azetidine **17** (50%) and oxazine derivative **18** (40%) in pure form.

1-(2,2-Dimethylpropanoyl)-3,3-dimethylazetidine (17): ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.19 (9 H, s, *Me*$_3$); 1.26 (6 H, s, *Me*$_2$); 3.67 and 4.01 (4 H, broad s, C*H*$_2$-N-C*H*$_2$). – ^{13}C NMR (67 MHz, $CDCl_3$): δ 26.97 (*Me*$_2$); 27.19 (*Me*$_3$); 30.98 (*C*Me$_2$); 38.53 (*C*Me$_3$); 61.13 and 65.44 (*C*H$_2$-N-*C*H$_2$); 178.00 (*C*=O). – IR (NaCl): ṽ 1630 cm^{-1} (C=O). – MS *m*/*z* (%): 169 [M$^+$] (24), 168 (3), 154 (12), 127 (32), 126 (2), 114 (48), 112 (23), 86 (3), 85 (18), 84 (9), 83 (7), 82 (2), 72 (3), 71 (2), 70 (33), 69 (32), 68 (2), 67 (2), 58 (8), 57 (100), 56 (32), 55 (12), 54 (1), 53 (2), 44 (4), 43 (11), 42 (9), 41 (48), 40 (14). – $C_{10}H_{19}NO$ (169.3): Calcd. C 70.96, H 11.31, N 8.27; found C 70.81, H 11.39, N 8.16.

Oxazine Derivative 18: ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.92 (6 H, s, *Me*$_2$); 1.15 (9 H, s, *Me*$_3$); 3.07 (2 H, s, CH_2N); 3.68 (2 H, s, CH_2O). – ^{13}C NMR (67 MHz, $CDCl_3$): δ 23.36 (*Me*$_2$); 27.15 (*C*Me$_2$); 27.78 (*Me*$_3$); 37.18 (*C*Me$_3$); 55.27 (CH_2N); 74.00 (OCH_2); 164.47 (O*C*=N). – IR (NaCl): ṽ 1673 cm^{-1} (C=N). – MS *m*/*z* (%): 169 [M$^+$] (26), 168 (13), 155 (7), 154 (56), 128 (2), 127 (27), 114 (23), 112 (3), 98 (20), 86 (13), 85 (14), 84 (13), 83 (12), 82 (2), 72 (2), 71 (3), 70 (9), 69 (56), 68 (3), 67 (2), 58 (8), 57 (100), 56 (44), 55 (23), 53 (3), 44 (3), 43 (6), 42 (11), 41 (73), 40 (9). – $C_{10}H_{19}NO$ (169.3): Calcd. C 70.96, H 11.31, N 8.27; found C 70.91, H 11.50, N 8.36.

Synthesis of α-Chloroketimines 31a, b: α,α-Dimethylbenzylamine (**30a**) and 1,1-diphenylethylamine (**30b**) were synthesized from the corresponding ketones **27a**, **b** via Grignard reaction with phenylmagnesium bromide, azidation of the tertiary alcohols **28** with sodium azide in the presence of trifluoroacetic acid and reduction of the tertiary azides with lithiumaluminium hydride.[16] The synthesis of α-chloroketimine **31a** (R = Me) is representative. To an ice cooled solution of 1,1-dimethylbenzylamine (**30a**) (8.1 g, 0.06 mol), 3-chloro-2-butanone (**39**) (19.17 g, 0.18 mol) and triethylamine (12.12 g, 0.12 mol) in diethyl ether (150 mL) was added dropwise $TiCl_4$ (6.84 g, 0.36 mol), dissolved in pentane (10 mL). The resulting suspension was stirred for 2 h at reflux and poured into 0.5 N NaOH. The organic phase was separated and the aqueous layer was extracted two times additionally with Et_2O (2× 75 mL). The combined organic extracts were dried (K_2CO_3), filtered, and evaporated in vacuo. The residual oil was distilled to yield 7.3 g (55%) of pure α-chloro imine **31a**, b.p. 62–64°C/0.4 Torr. This imine was used as such in the next alkylation step.

***N*-(3-Chloro-2-butylidene)-1-methyl-1-phenylethylamine (31a):** ^{1}H NMR ($CDCl_3$, 60 MHz): δ 1.46 (3 H, s, N=C*Me*); 1.58 (6 H, s, *Me*$_2$); 1.60 (3 H, d, *J* = 6.8 Hz, C*H*$_3$CHCl); 4.58 (1 H, q, *J* = 6.8 Hz, CH$_3$C*H*Cl); 7.32 (5 H, s, C$_6$*H*$_5$). – ^{13}C NMR ($CDCl_3$, 90 MHz): δ 16.07 (q, N=C*Me*); 22.13 (q, *C*H$_3$CHCl); 30.90 and 31.12 (each q, C*Me*$_2$); 60.17 (s, *C*Me$_2$); 64.01 (d, *C*HCl); 125.24 and 128.41 (each d, Co and Cm); 126.03 (d, Cp); 149.20 (s, Cq); 167.76 (s, *C*=N). – IR (NaCl, cm^{-1}) ṽ 1659 (C=N). – MS (70 eV) *m*/*z* (rel. int.) 223/225 [M$^+$] (0.5), 208/210 (1), 188 (7), 172 (2), 160 (3), 131 (1), 119 (100), 118 (7), 117 (6), 116 (1), 115 (3), 107 (1), 105 (2), 104 (3), 103 (6), 102 (1), 91 (36), 89 (1), 80 (1), 79 (6), 78 (4), 77 (7), 70 (2), 65 (1), 63 (1), 58 (1), 55 (1), 53 (1), 51 (2), 44 (2), 43 (1), 42 (4), 41 (10).

***N*-(3-Chloro-2-butylidene)-1,1-diphenylethylamine (31b):** Purification was performed by means of flash chromatography [R_f (Et_2O/C_5H_{12}/Et_3N, 88:5:7) = 0.72] and subsequent recrystallization in pentane at –20°C, mp 79°C. Yield 0.43 g (15%). – ^{1}H NMR δ ($CDCl_3$, 60 MHz) 1.55 (3 H, s, N=C*Me*); 1.69 (3 H, d, *J* = 7 Hz, C*H*$_3$CHCl); 1.81 (3 H, s, NC*Me*); 4.67 (1 H, q, *J* = 7 Hz, CH$_3$C*H*Cl); 7.1–7.7 [10 H, m, C(C$_6$*H*$_5$)$_2$]. – ^{13}C NMR δ ($CDCl_3$, 90 MHz) 17.15 (q, N=C*Me*); 22.04 and 27.07 (each q, *C*H$_3$CHCl and NC*Me*); 64.00 (d, *C*HCl); 65.83 (s, N-*C*); 126.04 (d, 2 Cp); 126.98 and 128.08 (each d, 2 Co and Cm); 149.54 and 149.72 (each s, 2 Cq); 166.90 (s, *C*=N). – IR (NaCl, cm^{-1}) ṽ 1660 (C=N). – MS (70 eV) *m*/*z* (rel. int.) no M$^+$, 182 (8), 181 (53), 180 (100), 179 (58), 178 (47), 177 (9), 176 (11), 166 (19), 165 (74), 153 (5), 152 (10), 151 (6), 150 (4), 115 (6), 104 (7), 103 (33), 102 (9), 89 (48), 88 (10), 79 (8), 78 (39), 77 (33), 76 (5), 63 (12), 51 (23), 79 (8).

Synthesis of *N*-(3-Chloro-3-methyl-2-butylidene)-1-methyl-1-phenylethylamine (33): This experiment was run under a N_2-atmosphere. All reagents were added dropwise via a glass syringe. To an ice cooled solution of diisopropylamine (2.42 g, 0.024 mol) in THF was added *n*BuLi (8.8 mL 2.5 M solution in hexane, 0.022 mol) followed after 10 min by *N*-(3′-chloro-2′-butylidene)-1,1-dimethylbenzylamine (**31a**) (4.46 g, 0.02 mol). The reaction mixture was stirred for 30 min at 0°C. MeI (1.1 equiv.) was then added, the mixture was stirred additionally for 30 min at 0°C and gradually warmed to ambient temperature during 1.5 h. The reaction mixture was poured into 0.5 N NaOH, extracted with Et_2O (3× 50 mL) and the combined organic extracts were dried (K_2CO_3). Evaporation yielded 4.07 g (86%) of *N*-(3′-chloro-3′-methyl-2′-butylidene)-1,1-dimethylbenzylamine (**33**). Distillation led to partial decomposition (1 g of this imine only yielded 0.35 g), b.p. 69–71°C/0.1 Torr. – ^{1}H NMR δ ($CDCl_3$, 60 MHz) 1.56 (6 H, s, *Me*$_2$); 1.58 (3 H, s, N=C*Me*); 1.73 (6 H, s, *Me*$_2$CCl); 7.32 (5 H, s, C$_6$*H*$_5$). – ^{13}C NMR δ ($CDCl_3$, 90 MHz) 16.72 (q, N=C*Me*); 30.70 and 31.12 (each q, each *Me*$_2$); 59.90 (s, Me$_2$C); 73.85 (s, *C*Cl); 125.31 and 128.34 (each d, Co and Cm); 125.91 (d, Cp); 149.58 (s, Cp); 168.28 (s, N=*C*). – IR (NaCl, cm^{-1}) ṽ 1659 (C=N). – MS (70 eV) *m*/*z* (rel. int.) 237/239 [M$^+$] (1), 222/224 (1), 202 (2), 186 (1), 160 (1), 119 (100), 118 (7), 117 (5), 115 (3), 104 (2), 103 (4), 91 (29), 84 (4), 79 (4), 78 (3), 77 (4), 42 (3), 41 (11), 40 (11). – $C_{14}H_{20}ClN$ (237.8): Calcd. C 70.72, H 8.48, N 5.89; found C 70.90, H 8.59, N 5.71.

Reaction of α-Chloroketimine 33 with Potassium Cyanide in Methanol: To a solution of potassium cyanide (1.48 g, 22.8 mmol) in

methanol (30 mL) was added *N*-(3′-chloro-3′-methyl-2′-butylidene)-1,1-dimethylbenzylamine (**33**) (2.7 g, 11.4 mmol). The mixture was stirred for 5 h under reflux, poured into water, and extracted with CH_2Cl_2 (3× 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to yield a mixture consisting of four components out of which 2,2-dimethyl-1-(1′,1′-dimethylbenzylamino)cyclopropane-carbonitrile (**36**) was isolated by means of distillation and flash chromatography, b.p. 110−115°C/0.1 Torr; R_f (Et_2O/C_5H_{12}, 8:2) = 0.64. All other compounds were isolated by preparative gas chromatography.

2,2-Dimethyl-1-(1-methyl-1-phenylethyl)aminocyclopropanecarbonitrile (36): ^{1}H NMR ($CDCl_3$, 60 MHz): δ 0.64 and 0.92 (2 H, AB, J = 5.2 Hz, CH_2 ring); 1.23 and 1.27 (6 H, each s, C*Me*$_2$); 1.59 and 1.72 (6 H, each s, C*Me*$_2$ ring); 1.93 (1 H, s br, N*H*); 7.2−7.7 (5 H, m, C_6H_5). − ^{13}C NMR δ ($CDCl_3$, 90 MHz) 19.59 and 23.32 (each q, C*Me*$_2$ ring); 26.26 and 33.30 (each s, Me$_2$*C* ring and *C*CN); 28.25 and 30.55 (each q, C*Me*$_2$); 29.35 (t, CH_2); 56.76 (s, *C*Me$_2$); 122.93 (s, *C*=N); 125.86 and 128.02 (each d, Co en Cm); 126.63 (d, Cp); 148.56 (s, Cq). − IR (NaCl, cm^{-1}) ν_{NH} = 3330, $\nu_{C=N}$ = 2220 cm^{-1}. − MS (70 eV) *m*/*z* (rel. int.) no M$^+$, 119 (100), 118 (19), 117 (13), 115 (6), 110 (12), 103 (9), 95 (8), 91 (46), 79 (8), 78 (7), 77 (9), 44 (17). − $C_{15}H_{20}N_2$ (228.3): Calcd. C 78.90, H 8.83, N 12.27; found C 78.75, H 8.69, N 12.34.

Synthesis of 1-Aminocyclopropanecarbonitriles 42 by Reaction of 1-Methoxycyclopropylamines 41 with Potassium Cyanide: 1-Methoxycyclopropylamines **41** were synthesized by cyclization of α-chloroketimines **40**[23] with 1 N sodium methoxide (1.1 equivalents) in methanol under reflux.[18] 1-Methoxycyclopropylamines **41a−c** (0.05 mol) were dissolved in 10 mL of dry methanol to which 0.25 mol of potassium cyanide was added. The reaction mixture was refluxed for 5 h after which it was poured in water and extracted with dichloromethane. After drying ($MgSO_4$), the combined extracts were evaporated in vacuo to afford crude 1-*N*-*tert*-butylamino-2,2-dialkylcyclopropanecarbonitriles **42a−c** (purity > 90%; GC) in 60−70% yield. Pure samples of compounds **42** were obtained by preparative gas chromatography. The spectroscopic data of 1-*tert*-butylamino-2,2-dimethylcyclopropane-1-carbonitrile (**42a**), 1-*tert*-butylamino-2,2-diethylcyclopropane-1-carbonitrile (**42b**), and 1-*tert*-butylamino-2,2-dipropylcyclopropane-1-carbonitrile (**42c**) have been described previously.[9]

Reaction of *N*-*tert*-Butyl-2,2-dimethyl-1-methoxycyclopropylamine (41a) with Trimethylsilyl Cyanide in the Presence of Boron Trifluoride−Diethyl Ether: A solution of 0.003 mol of cyclopropylamine **41a** in 3 mL of dichloromethane was treated successively with 0.0033 mol of trimethylsilyl cyanide and 0.003 mol of boron trifluoride−diethyl ether. This solution was either refluxed for 1 h or stirred for 14 h during which the temperature rose from 0°C to room temperature. The reaction mixture was then poured in 0.5 N sodium hydroxide, stirred for 10 minutes, extracted with dichloromethane, dried (K_2CO_3), and evaporated in vacuo. ^{1}H NMR and GC analysis revealed that the composition of cyclopropanecarbonitrile **42a** and α-methoxyketimine **43a** was 70% and 20%, respectively, for the room temperature experiment, while it changed to 55% and 35%, respectively, under reflux conditions. Both compounds were isolated by preparative gas chromatography.

***N*-(3-Methoxy-3-methyl-2-butylidene)-*tert*-butylamine (43a):** ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.26 (15 H, s, Me_3 and Me_2); 1.93 (3 H, s, MeC=N); 3.10 (3 H, s, OMe). − IR (NaCl): ṽ 1169 cm^{-1} (C=N) and 2822 cm^{-1} (OMe). − MS *m*/*z* (%): 171 [M$^+$] (1), 141 (5), 98 (54), 84 (9), 73 (54), 57 (100), 43 (3), 42 (8).

Synthesis of *N*-(4-aryl-3-chloro-3-methyl-2-butylidene)-*tert*-butylamines 48: The synthesis of α-chloroketimine **48a** is representative.

To an ice-cooled solution of diisopropylamine (5.25 g, 52 mmol) in 50 mL of dry THF was subsequently added dropwise *n*-butyllithium (19.2 mL, 48 mmol; 2.5 M in hexane) and *N*-(3-chloro-2-butylidene)-*tert*-butylamine **(47)** (6.46 g, 40 mmol), dissolved in dry THF (40 mL). After 1 h at 0°C, benzyl bromide (6.16 g, 36 mmol, ***Caution:*** lacrimatory substance!) in 20 mL THF was added and the reaction mixture was stirred for 20 h at room temperature and subsequently poured into 300 mL of aqueous sodium hydroxide (1 N). The α-chloroketimine **48a** was extracted with diethyl ether (3× 75 mL) and the combined extracts were dried (K_2CO_3). The solvent was evaporated under reduced pressure and the crude imine **48a** was distilled in vacuo (8.45 g, 84%, b.p. 74−76°C/0.03 Torr).

***N*-(3-Chloro-3-methyl-4-phenyl-2-butylidene)-*tert*-butylamine (48a):** ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.20 (9 H, s, Me_3); 1.53 (3 H, s, MeCCl); 2.04 (3 H, s, MeC=N); 3.18 (2 H, s, CH_2); 7.08 (5 H, s, C_6H_5). − ^{13}C NMR (20 MHz, $CDCl_3$) δ 17.06 (*Me*C=N); 28.25 (*Me*CCl); 30.03 (Me_3); 47.82 (CH_2); 54.88 (*C*Me$_3$); 77.35 (CCl); 126.56; 127.65 and 130.85 (=CH′s); 137.9 (=C_{quat}); 163.94 (C=N). − IR (NaCl): ṽ 1669 cm^{-1} (C=N). − MS *m*/*z* (%): 251/253 [M$^+$] (0.2), 236/238 (2), 216 (19), 215 (5), 200 (3), 180 (4), 179 (4), 178 (2), 160 (14), 158 (15), 144 (6), 117 (8), 115 (7), 98 (21), 91 (27), 77 (3), 65 (5), 63 (2), 58 (7), 57 (100), 51 (4), 43 (4), 42 (14), 41 (20). − $C_{15}H_{22}ClN$ (251.8): Calcd. C 71.55, H 8.81, N 5.56; found C 71.70, H 8.94, N 5.41.

***N*-[3-Chloro-4-(3-methoxyphenyl)-3-methyl-2-butylidene]-*tert*-butylamine (48b):** ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.24 (9 H, s, Me_3); 1.58 (3 H, s, MeCCl); 2.09 (3 H, s, MeC=N); 3.25 (2 H, s, CH_2); 3.73 (3 H, s, OMe); 6.6−7.4 (4 H, m, C_6H_4). − ^{13}C NMR (20 MHz, $CDCl_3$): δ 17.03 (*Me*C=N); 28.41 (*Me*CCl); 30.10 (Me_3); 47.95 (CH_2); 54.95 (*C*Me$_3$); 54.95 (OMe); 77.39 (CCl); 112.01; 116.90; 123.39 and 128.54 (=CH′s); 138.71 (=C_{quat}); 159.28 (=C_{quat} OMe); 164.01 (C=N). − IR (NaCl): ṽ 2835 cm^{-1} (OMe) and 1660 cm^{-1} (C=N). − $C_{16}H_{24}ClNO$ (281.8): Calcd. C 68.19, H 8.58, N 4.97; found C 68.05, H 8.49, N 5.10.

***N*-[4-(4-Bromophenyl)-3-chloro-3-methyl-2-butylidene]*tert*-butylamine (48c):** ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.22 (9 H, s, Me_3); 1.53 (3 H, s, MeCCl); 2.06 (3 H, s, MeC=N); 3.20 (2 H, s, CH_2); 7.07 (2 H, d, J = 8 Hz, 2 =CH); 7.29 (2 H, d, J = 8 Hz, 2 =CH). − ^{13}C NMR (20 MHz, $CDCl_3$): δ 17.01 (*Me*C=N); 28.37 (*Me*CCl); 30.07 (Me_3); 46.98 (CH_2); 54.95 (*C*Me$_3$); 76.87 (CCl); 120.60 (=C_{quat} Br); 130.69 and 132.66 (=CH′s); 136.33 (=C_{quat}); 163.85 (C=N). − MS *m*/*z* (%): no M$^+$, 294/6 (M$^+$−Cl, 3), 278/280 (1), 236/238 (4), 224/226 (1), 169/171 (2), 158 (8), 143 (2), 116 (2), 115 (2), 98 (9), 84 (2), 57 (100). − IR (NaCl): ṽ 1665 cm^{-1} (C=N). − $C_{15}H_{21}BrClN$ (330.7): Calcd. C 54.48, H 6.40, N 4.24; found C 54.59, H 6.55, N 4.20.

***N*-[3-Chloro-4-(4-chlorophenyl)-3-methyl-2-butylidene]*tert*-butylamine (48d):** ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.25 (9 H, s, Me_3); 1.54 (3 H, s, MeCCl); 2.08 (3 H, s, MeC=N); 3.21 and 3.26 (2× 1 H, AB, J = 16.0 Hz, CH_2); 7.17 and 7.22 (2× 1 H, AB, J = 8.0 Hz, =CH′s). − ^{13}C NMR (68 MHz, $CDCl_3$): δ 17.11 (*Me*C=N); 28.23 (*Me*CCl); 30.03 (Me_3); 46.78 (CH_2); 54.98 (*C*Me$_3$); 77.11 (CCl); 127.76 and 132.34 (=CH′s); 128.25 (=CCl); 135.79 (=C_{quat} CH_2); 163.92 (C=N). − MS *m*/*z* (%): no M$^+$, 250/252 (3), 234/236 (2), 192/194/196 (6), 159 (5), 141 (4), 125/127 (6), 117 (2), 115 (4), 98 (11), 57 (100), 53 (2), 44 (4). − IR (NaCl): ṽ 1666 cm^{-1} (C=N). − B.p. 96−98°C/0.03 Torr. − $C_{15}H_{21}Cl_2N$ (286.2): Calcd. C 62.94, H 7.39, N 4.89; found C 63.09, H 7.49, N 4.77.

***N*-[3-Chloro-4-(3-fluorophenyl)-3-methyl-2-butylidene]*tert*-butylamine (48e):** ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.25 (9 H, s, C*Me*$_3$); 1.57 (3 H, s, *Me*CCl); 2.10 (3 H, s, *Me*C=N); 3.28 (2 H, s, C*H*$_2$C$_6$H$_4$); 6.88−7.02 (3 H, m, Ar, 2× *H*$_{ortho}$, *H*$_{para}$); 7.17−7.25 (1 H, m, Ar, *H*$_{meta}$). − ^{13}C NMR (68 MHz, $CDCl_3$): δ 17.07 (*Me*C=N); 28.32 (*Me*CCl); 30.03 (C*Me*$_3$); 47.26 (*C*H$_2$C$_6$H$_4$); 55.02 (*C*Me$_3$); 76.98 (*C*-Cl); 113.43 (d, J_{C-F} = 20.7 Hz, C-2 aryl); 117.81 (d, J_{C-F} = 20.7 Hz, C-4 aryl); 126.74 (d, J_{C-F} = 2.4 Hz, C-6 aryl); 128.96 (d, J_{C-F} = 8.5 Hz, C-5 aryl); 139.84 (d, J_{C-F} = 6.4 Hz, C-1 aryl); 162.31 (d, J_{C-F} = 245.4 Hz, *C*F); 163.86 (C=N). − IR (NaCl) (C=N) ṽ 1660 cm^{-1}. − MS (70 eV) *m*/*z* (%): no M$^+$, 234 (7), 178 (7), 176 (5), 162 (2), 161 (2), 147 (1), 146 (2), 145 (2), 135 (2), 133 (2), 115 (1), 110 (1), 109 (7), 99 (1), 98 (17), 96 (1), 83 (2), 57 (100), 56 (3), 55 (2), 53 (2), 43 (1), 42 (11), 41 (16). − $C_{15}H_{21}ClFN$ (269.8): Calcd. C 66.78, H 7.85, N 5.19; found C 66.71, H 7.72, N 5.30.

Cyclization of α-Chloroketimines 48 with Potassium Cyanide in Methanol: The synthesis of cyclopropanecarbonitriles **49a** and **50a** is representative. To a solution of α-chloroketimine **48a** (7.54 g, 30 mmol) in methanol (80 ml) was added 60 mmol (3.90 g) of potassium cyanide. The stirred mixture was refluxed for 6 h, poured into H_2O (300 mL) and extracted with CH_2Cl_2 (3× 50 mL). The combined extracts were dried ($MgSO_4$), concentrated in vacuo, and purified by distillation (yield **49a** + **50a**: 6.24 g, 86%, b.p. 105−108°C/0.15 Torr).

1-*tert*-Butylamino-2-benzyl-2-methylcyclopropane-1-carbonitriles (49a/50a) (ratio 3:2): ^{1}H NMR (60 MHz, $CDCl_3$): δ 0.88 (1 H, d, *J* = 4.7 Hz, *H*CH$_{ring}$); 1.20 and 1.27 (total 9 H, 2× s, Me$_3$); 1−1.3 (4 H, m, Me and HC*H*$_{ring}$); 2.8 (2 H, broad s, CH$_2$); 7.15−7.4 (5 H, broad s, C$_6$H$_5$). − ^{13}C NMR (20 MHz, $CDCl_3$): δ 17.17 and 21.07 (Me); 29.75 and 29.90 (CH$_2$ ring); 30.39 and 30.48 (Me$_3$); 31.06 (N*C*C≡N); 33.39 and 33.75 (CH$_2$*C*Me); 38.23 and 42.29 (*C*H$_2$C$_6$H$_5$); 52.48 and 52.73 (*C*Me$_3$); 120.57 and 123.65 (C≡N); 131.19; 131.34 and 131.69 (CH=′s); 138.00 and 138.87 (=C$_{quat}$). − MS *m*/*z* (%): 242 [M$^+$] (1), 227 (3), 185 (3), 151 (30), 118 (22), 117 (10), 115 (4), 95 (100), 91 (12), 57 (70), 41 (26), 40 (22). − IR (NaCl): ṽ 3325 cm^{-1} (NH) and 2218 cm^{-1} (C≡N). − $C_{16}H_{22}N_2$ (242.4): Calcd. C 79.29, H 9.15, N 11.56; found C 79.12, H 9.28, N 11.69.

1-*tert*-Butylamino-2-(3-methoxybenzyl)-2-methylcyclopropane-1-carbonitriles (49b/50b) (ratio 3:2): B.p. 125−130°C/0.1 Torr. ^{1}H NMR (60 MHz, $CDCl_3$): δ 0.88 (1 H, d, *J* = 5 Hz, *H*CH$_{ring}$); 1.17 and 1.27 (total 9 H, 2× s, Me$_3$); 1−1.3 (4 H, m, Me and HC*H*$_{ring}$); 2.77 (2 H, broad s, CH$_2$); 3.73 (3 H, s, OMe); 6.6−7.4 (4 H, m, C$_6$H$_4$). − ^{13}C NMR (20 MHz, $CDCl_3$): δ 17.03 and 20.94 (Me); 29.69 (CH$_2$ ring); 30.15 and 30.23 (Me$_3$); 31.09 (N*C*C≡N); 33.26 and 33.56 (CH$_2$*C*Me); 38.60 and 42.72 (*C*H$_2$C$_6$H$_4$); 52.30 and 52.55 (*C*Me$_3$); 55.04 (OMe); 111.35; 111.84; 115.25; 115.31; 121.52 and 121.73 (CH=′s); 122.89 and 123.56 (C≡N); 129.95 and 129.31 (CH=′s); 140.25 and 141.07 (=C$_{quat}$); 159.76 (=*C*OMe). − MS *m*/*z* (%): 272 [M$^+$] (2), 257 (1), 216 (2), 162 (2), 152 (26), 148 (20), 147 (4), 122 (3), 121 (6), 117 (3), 95 (100), 91 (5), 78 (2), 77 (2), 68 (3), 57 (55), 55 (3), 44 (2), 42 (3), 41 (21). − IR (NaCl): ṽ 3325 cm^{-1} (NH) and 2220 cm^{-1} (C≡N). − $C_{17}H_{24}N_2O$ (272.4): Calcd. C 74.96, H 8.88, N 10.28; found C 74.81, H 9.01, N 10.36.

2-(4-Bromobenzyl)-1-*tert*-butylamino-2-methylcyclopropane-1-carbonitriles (49c/50c) (ratio 3:2): Bp 134−140°C/0.35 Torr. − ^{1}H NMR (60 MHz, $CDCl_3$): δ 0.90 (1 H, d, *J* = 5 Hz, *H*CH$_{ring}$); 1.22 and 1.28 (total 9 H, 2× s, Me$_3$); 1−1.4 (4 H, m, Me and HC*H*$_{ring}$); 2.80 (2 H, broad s, CH$_2$); 7.0−7.6 (4 H, m, C$_6$H$_4$). − MS *m*/*z* (%): 320/2 [M$^+$] (0.5), 305/7(1), 196/8(4), 169/71(2), 151(23), 117(3), 116(4), 115 (4), 95(100), 68(4), 57(89), 56(3), 55(3), 41(23). − IR: ṽ 3225 cm^{-1} (NH) and 2215 cm^{-1} (C≡N). − $C_{16}H_{21}BrN_2$ (321.3): Calcd. C 59.82, H 6.59, N 8.72; found C 59.98, H 6.42, N 8.65.

1-*tert*-Butylamino-2-(4-chlorobenzyl)-2-methylcyclopropane-1-carbonitriles (49d) and (50d) (ratio 2:1): B.p. 109−110°C/0.04 Torr. *trans*-**49d**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.95 (1 H, d, *J* = 5.1 Hz, *H*CH$_{ring}$); 1.07 (3 H, s, Me); 1.22 (9 H, s, Me$_3$); 1.36 (1 H, d, *J* = 5.1 Hz, HC*H*$_{ring}$); 1.44−1.48 (1 H, broad s, NH); 2.77 and 2.87 (2 H, AB, *J* = 14.5 Hz, C*H*$_2$C$_6$H$_4$); 7.21 and 7.27 (4 H, AB, *J* = 8.6 Hz, C$_6$H$_4$). − ^{13}C NMR (68 MHz, $CDCl_3$): δ 16.87 (Me); 29.49 (CH$_{2\ ring}$); 30.12 (Me$_3$); 31.09 (N*C*C≡N); 33.06 (CH$_2$*C*Me); 41.96 (*C*H$_2$C$_6$H$_4$); 52.38 (*C*Me$_3$); 123.65 (C≡N); 128.46 and 130.64 (=CH′s); 132.27 (=CCl); 137.10 (=*C*CH$_2$). − MS *m*/*z* (%): 276/8 [M$^+$] (2), 261/263 (3), 220/222 (1), 219/121 (2), 205/207 (1), 168 (1), 167 (1), 166 (1), 154 (6), 153 (4), 152 (17), 151 (31), 125/7 (8), 117 (8), 115 (6), 95 (100), 89 (2), 68 (7), 58 (8), 57 (88), 41 (31). − IR (NaCl): ṽ 3325 cm^{-1} (NH) and 2218 cm^{-1} (C≡N).

cis-**50d**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.16 and 1.26 (2 H, AB, *J* = 5.6 Hz, CH$_{2\ ring}$); 1.22 (3 H, s, Me); 1.22 (9 H, s, Me$_3$); 1.52−1.56 (1 H, broad s, NH); 2.73 and 2.93 (2 H, AB, *J* = 14.5 Hz, C*H*$_2$C$_6$H$_4$); 7.11 and 7.20 (4 H, AB, *J* = 8.6 Hz, C$_6$H$_4$). − ^{13}C NMR (68 MHz, $CDCl_3$): δ 20.75 (Me); 29.34 (CH$_{2\ ring}$); 30.21 (Me$_3$); 31.09 (N*C*C≡N); 33.42 (CH$_2$*C*Me); 37.88 (*C*H$_2$C$_6$H$_4$); 52.65 (*C*Me$_3$); 122.93 (C≡N); 128.52 and 130.44 (=CH′s); 132.04 (=CCl); 137.91 (=*C*CH$_2$). − MS *m*/*z* (%): identical to *trans*-**49d**. − IR (NaCl): ṽ 3325 cm^{-1} (NH) and 2218 cm^{-1} (C≡N). − $C_{16}H_{21}ClN_2$ (276.8) (**49d**, **50d**): Calcd. C 69.42, H 7.65, N 10.12; found C 69.60, H 7.61, N 10.28.

1-*tert*-Butylamino-2-(3-fluorobenzyl)-2-methylcyclopropane-1-carbonitriles (49e) and (50e) (ratio 2:1): B.p. 89−102°C/0.05 Torr. *trans*-**49e**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.98 (1 H, d, *J* = 5.27 Hz, C*H* ring); 1.10 (3 H, s, *Me*); 1.23 (9 H, s, C*Me*$_3$); 1.39 (1 H, d, *J* = 5.3 Hz, C*H* ring); 1.43−1.47 (1 H, broad s, N*H*); 2.76 and 2.98 (each 1 H, AB, J_{AB} = 14.52 Hz, C*H*$_2$C$_6$H$_4$); 6.87−7.06 (3 H, m, Ar, 2× *H*$_{ortho}$, *H*$_{para}$); 7.23−7.31 (1 H, m, Ar, *H*$_{meta}$). − ^{13}C NMR δ (67.5 MHz, $CDCl_3$); 16.93 (*Me*); 29.61 (*C*H$_2$ ring); 30.24 (C*Me*$_3$); 31.00 (HN*C*C≡N); 33.08 (*C*Me); 42.37 (*C*H$_2$C$_6$H$_4$); 52.72 (*C*Me$_3$); 113.52 (d, J_{C-F} = 20.7 Hz, Ar, *C*$_{para}$); 116.07 (d, J_{C-F} = 20.7 Hz, Ar, C$_{quat}$*C*HCF); 123.61 (*C*≡N); 124.78 (d, J_{C-F} = 2.5 Hz, Ar, C$_{quat\ C}$HCH); 129.83 (d, J_{C-F} = 8.6 Hz, Ar, *C*$_m$H); 141.18 (d, J_{C-F} = 7.3 Hz, Ar, *C*$_{quat}$); 162.81 (d, J_{C-F} = 245.3 Hz, Ar, *C*F). − IR (NaCl): ṽ 3300 cm^{-1} (NH) and 2219 cm^{-1} (C=N). − MS *m*/*z* (%): 260 [M$^+$] (1), 245 (2), 204 (1), 203 (2), 189 (1), 186 (1), 176 (2), 175 (1), 163 (2), 162 (1), 161 (1), 152 (3), 151 (22), 150 (2), 149 (2), 137 (2), 136 (11), 124 (2), 121 (1), 115 (1), 110 (2), 109 (12), 107 (2), 96 (8), 95 (100), 84 (1), 78 (1), 75 (1), 69 (2), 68 (5), 67 (1), 63 (1), 58 (6), 57 (82), 56 (4), 53 (3), 51 (1), 49 (1), 43 (1), 42 (5), 41 (27).

cis-**50e**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.19 and 1.29 (2 H, AB, J_{AB} = 5.27 Hz, CH$_2$ ring); 1.19 (3 H, s, *Me*); 1.23 (9 H, s, C*Me*$_3$); 1.52−1.56 (1 H, broad s, N*H*); 2.80 and 2.91 (each 1 H, AB, J_{AB} = 14.52 Hz, C*H*$_2$C$_6$H$_4$); 6.87−7.06 (3 H, m, Ar, 2× *H*$_{ortho}$, *H*$_{para}$); 7.23−7.31 (1 H, m, Ar, *H*$_{meta}$). − ^{13}C NMR δ (67.5 MHz, $CDCl_3$): 20.83 (*Me*); 29.47 (*C*H$_2$ ring); 30.15 (C*Me*$_3$); 31.00 (HN*C*C≡N); 33.44 (*C*Me); 38.31 (*C*H$_2$C$_6$H$_4$); 52.45 (*C*Me$_3$); 113.41 (d, J_{C-F} = 20.7 Hz, Ar, *C*$_{para}$); 116.59 (d, J_{C-F} = 20.7 Hz, Ar, C$_{quat\ C}$HCF); 122.96 (*C*≡N); 125.35 (d, J_{C-F} = 2.4 Hz, Ar, C$_{quat\ C}$HCH); 129.80 (d, J_{C-F} = 8.5 Hz, Ar, *C*$_{meta}$ H); 142.05 (d, J_{C-F} = 7.3 Hz, Ar, *C*$_{quat}$); 162.86 (d, J_{C-F} = 245.0 Hz, Ar, *C*F). − IR (NaCl) and MS: identical to *trans*-**49e**. − $C_{16}H_{21}FN_2$ (260.3): Calcd. C 73.81, H 8.13, N 10.76; found C 73.70, H 8.26, N 10.71.

Synthesis of 1-Aminocyclopropane-1-carboxamides 51 and 52: The synthesis of 1-aminocyclopropanecarboxamides **51d** and **52d** is rep-

resentative. To a solution of 1-aminocyclopropanecarbonitriles **49d**/**50d** (ratio 2:1; 0.91 g, 3.3 mol) in ethanol (10 mL) was added potassium hydroxide (0.93 g, 16.5 mmol). The solution was refluxed for 50 h, cooled, poured into water (20 mL) and extracted with dichloromethane (3× 20 mL). After drying of the combined extracts with $MgSO_4$ and evaporation of the solvent *in vacuo*, a mixture of *trans*- and *cis*-carboxamides **51d**/**52d** was obtained (ratio 2:1, 0.79 g, 83%). Recrystallization from CCl_4 (−20°C) yielded 0.35 g of *trans*-**51d** (37%). Purification of the mother liquor by flash chromatography (ethyl acetate/hexane: 60/40) yielded 0.16 g of *cis*-**52d** (17%).

1-*tert*-Butylamino-2-benzyl-2-methylcyclopropane-1-carboxamides (51a) and (52a): *trans*-**51a**: m.p. 142°C. − ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.02 (1 H, d, J = 9.4 Hz, HCH_{ring}); 1.10 (3 H, s, Me); 1.14 (9 H, s, Me_3); 1.2−1.4 (1 H, broad s, $NHCMe_3$); 1.97 (1 H, d, J = 4.9 Hz, HCH_{ring}); 2.79 (2 H, s, $CH_2C_6H_5$); 5.23 (1 H, s, CONH); 7.1−7.3 (5 H, m, C_6H_5); 7.64 (1 H, s, CONH). − ^{13}C NMR (20 MHz, $CDCl_3$): δ 19.21 (Me); 23.49 (CH_2 ring); 29.85 (s, $MeCCH_2$); 30.65 (Me_3); 38.42 ($CH_2C_6H_5$); 47.03 ($NCCONH_2$); 52.56 (CMe_3); 125.81, 128.04, and 129.36 (=CH′s); 140.46 (=C_{quat}); 178.62 (C=O). − MS *m*/*z* (%): 260 [M^+] (4), 245 (7), 203 (71), 186 (50), 169 (11), 160 (18), 159 (11), 158 (32), 143 (100), 118 (21), 117 (21), 115 (14), 113 (36), 96 (36), 91 (29), 73 (14), 72 (11), 68 (18), 57 (89), 56 (11), 55 (14), 44 (14), 41 (57). − $C_{16}H_{24}N_2O$ (260.4): Calcd. C 73.81, H 9.29, N 10.76; found C 73.68, H 9.11, N 10.89.

cis-**52a**: ^{13}C NMR (20 MHz, $CDCl_3$): δ 17.20 (Me); 30.62 (Me_3); 40.82 ($CH_2C_6H_5$); 47.45 ($NCCONH_2$); 52.70 (CMe_3); 126.07, 128.14 and 128.87 (=CH′s); 139.30 (=C_{quat}); 178.17 (C=O).

1-*tert*-Butylamino-2-(4-chlorobenzyl)-2-methylcyclopropane-1-carboxamides (51d) and (52d): *trans*-**51d**: m.p. 151°C. − ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.02 (1 H, d, J = 5.2 Hz, HCH); 1.08 (3 H, s, Me); 1.14 (9 H, s, CMe_3); 1.25 (1 H, broad s, Me_3CNH); 1.94 (1 H, d, J = 5.42 Hz, HCH_{ring}); 2.71 (2 H, s, $CH_2C_6H_4$); 5.99 (1 H, broad s, CONH); 7.11 and 7.21 (4 H, AB, J = 7.4 Hz, C_6H_4); 7.65 (1 H, broad s, CONH). − ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 19.28 (Me); 23.77 (CH_2 ring); 29.94 (CMe); 30.60 (Me_3); 37.61 ($CH_2C_6H_4$); 46.85 ($NCCO$); 52.63 (CMe_3); 128.17 and 130.67 (=CH′s); 131.61 (=C-Cl); 138.81 (=C-CH_2); 178.33 (C=O). − IR (NaCl): ṽ 3410, 3375, and 3050−3280 (NH and NH_2); 1655 cm^{-1} (C=O). − MS *m*/*z* (%): 294/296 [M^+] (44), 238/240 (14), 237/239 (83), 220/222 (51), 203/205 (10), 192/194 (20), 177/179 (52), 157 (23), 152 (10), 149 (18), 142 (12), 125 (16), 115 (13), 133 (31), 96 (36), 68 (16), 57 (100), 44 (49).

cis-**52d**: m.p. 126.5−128°C. Hexane/ethyl acetate, 60:40. R_f = 0.26. − ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.99 (3 H, s, Me); 1.15 (9 H, s, CMe_3); 1.15 (1 H, d, J = 5.3 Hz, HCH_{ring}); 1.43 (1 H, broad s, Me_3CNH); 1.66 (1 H, d, J = 5.3 Hz, HCH_{ring}); 2.71 and 2.89 (2 H, AB, J = 15.2 Hz, $CH_2C_6H_4$); 6.05 (1 H, broad s, CONH); 7.15 and 7.28 (4 H, AB, J = 8.4 Hz, C_6H_4); 7.26 (1 H, broad s, CONH). − ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 16.87 (Me); 23.88 (CH_2 ring); 27.83 (CMe); 30.69 (Me_3); 40.34 ($CH_2C_6H_4$); 47.35 ($NCCO$); 52.83 ($NCMe_3$); 128.57, 128.57 and 130.19 (=CH′s); 132.00 (=CCl); 137.46 (=CCH_2); 177.84 (C=O). − IR (NaCl): ṽ 3425, 3382, and 3100−3280 cm^{-1} (NH and NH_2); 1670 cm^{-1} (C=O). − MS identical to *trans* isomer **51d**. − $C_{16}H_{23}ClN_2O$ (294.8): Calcd. C 65.18, H 7.86, N 9.50; found C 65.30, H 7.82, N 9.41.

1-*tert*-Butylamino-2-(3-fluorobenzyl)-2-methylcyclopropane-1-carboxamides (51e) and (52e): *trans*-**51e**: m.p. 103.5−104°C. Hexane/ethyl acetate, 75:25, R_f = 0.26. − ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.04 (d, J = 5.28 Hz, CH ring); 1.09 (3 H, s, Me); 1.14 (9 H, s, CMe_3); 1.26 (1 H, broad s, Me_3CNH); 1.94 (1 H, d, J = 5.28 Hz, CH ring); 2.80 (2 H, s, $CH_2C_6H_4$); 6.18 (1 H, broad s, $CONH$); 6.82−6.97 (3 H, m, Ar, 2× H_{ortho}, H_{para}); 7.15−7.27 (1 H, m, Ar, H_{meta}); 7.67 (1 H, broad s, $CONH$). − ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 19.26 (Me); 23.82 (CH_2 ring); 29.83 (CMe); 30.62 (Me_3); 38.06 ($CH_2C_6H_4$); 46.83 ($NCCO$); 52.63 ($NCMe_3$); 112.68 (d, J_{C-F} = 20.8 Hz, Ar, C_{para}); 116.02 (d, J_{C-F} = 20.7 Hz, Ar, $C_{quat}CHCF$); 125.03 (d, J_{C-F} = 2.5 Hz, Ar, $C_{quat}CHCH$); 129.39 (d, J_{C-F} = 8.5 Hz, Ar, $C_{meta}H$); 142.03 (d, J_{C-F} = 7.4 Hz, Ar, C_{quat}); 162.76 (d, J_{C-F} = 244.1 Hz, Ar, CF); 178.38 (C=O). − IR (KBr) ṽ 3416, 3374, 3241, 2976 (NH and NH_2), 1663 (C=O). − MS *m*/*z* (%): 278 [M^+] (32), 222 (12), 221 (79), 204 (50), 178 (10), 176 (36), 162 (18), 161 (100), 135 (16), 113 (34), 109 (26), 96 (41), 86 (10), 72 (11), 68 (16), 58 (10), 57 (92), 55 (10), 44 (16), 43 (8), 42 (20), 41 (50). − $C_{16}H_{23}FN_2O$ (278.4): Calcd. C 69.04, H 8.33, N 10.06; found C 68.90, H 8.51, N 9.95.

cis-**52e**: m.p. 121.5−122°C. Hexane/ethyl acetate, 75:25, R_f = 0.16. − ^{1}H NMR δ (270 MHz, $CDCl_3$): 1.01 (3 H, s, Me); 1.16 (1 H, d, J = 5.28 Hz, CH ring); 1.16 (9 H, s, CMe_3); 1.62 (1 H, broad s, Me_3CNH); 1.69 (1 H, d, J = 5.28 Hz, CH ring); 2.74 and 2.93 (2 H, AB, J_{AB} = 15.18 Hz, $CH_2C_6H_4$); 5.91−7.01 (3 H, m, Ar, 2× H_{ortho}, H_{para}); 7.22−7.31 (1 H, m, Ar, H_{meta}). − ^{13}C NMR δ (68 MHz, $CDCl_3$): 16.89 (Me); 23.95 (CH_2 ring); 27.85 (CMe); 30.71 (Me_3); 40.77 ($CH_2C_6H_4$); 47.33 (NCC=O); 52.87 (CMe_3); 113.19 (d, J_{C-F} = 22.0 Hz, Ar, C_{para}); 115.69 (d, J_{C-F} = 20.8 Hz, Ar, $C_{quat}CHCF$); 124.54 (d, J_{C-F} = 3.6 Hz, Ar, $C_{quat}CHCH$); 129.89 (d, J_{C-F} = 8.5 Hz, Ar, $C_{meta}H$); 141.63 (d, J_{C-F} = 7.3 Hz, Ar, C_{quat}); 162.95 (d, J_{C-F} = 245.3 Hz, Ar, CF); 177.75 (C=O). − IR (KBr) cm^{-1} ṽ 3412 (NH, NH_2), 1668 (C=O). − MS (70 eV) *m*/*z* (%): 278 [M^+] (26), 222 (11), 221 (75), 204 (46), 178 (11), 176 (41), 162 (18), 161 (94), 135 (19), 113 (37), 109 (38), 96 (43), 86 (10), 72 (11), 68 (19), 58 (11), 57 (100), 55 (13), 44 (20), 43 (11), 42 (26), 41 (62). − $C_{16}H_{23}FN_2O$ (278.4): Calcd. C 69.04, H 8.33, N 10.06; found C 68.98, H 8.44, N 10.15.

X-Ray Crystallographic Data of *trans*-1-*tert*-butylamino-2-benzyl-2-methylcyclopropane-1-carboxamide (51a): Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101364. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code +44 (1223) 336-033; E-mail: deposit@ccdc.cam.ac.uk]. − $C_{16}H_{24}N_2O$: Mr = 260.4, monoclinic, $C2/c$, a = 23.468(3), β = 6.236(1), c = 24.008(3) Å, β = 117.6(1)°, V = 3113.1(6) $Å^3$, Z = 8, D_x = 1.11 $g{\cdot}cm^{-3}$, Cu-$K\alpha$, λ = 1.54178 Å, μ = 5.5 cm^{-1}, F(000) = 1136, T = 291 K, R = 0.051 for 2319 observed reflections. A parallelepiped crystal with dimensions 0.2 × 0.3 × 0.4 mm was used. Lattice parameters were refined using 30 reflections in the range 2° ≤ 2θ ≤ 39° (Huber diffractometer, graphite monochromatized Cu-$K\alpha$ radiation). 2878 Independent reflections with $\sin\theta/\lambda \leq 0.6$ $Å^{-1}$; $-28 \leq h \leq 28$, $0 \leq k \leq 7$, $0 \leq l \leq 28$, 2319 with $I \geq 2.5\sigma(I)$ were measured. The standard reflection (−5,1,5) was checked every 50 reflections: no significant deviation. The structure was solved by direct methods using SHELXS-86.

Reaction of α-Chloroketimine 54 with Potassium Cyanide in Methanol: A solution of 2.37 g (10 mol) of α-chloroketimine **54**, prepared in analogous way as the corresponding *N*-*tert*-butyl derivative **48a**, in 25 mL of dry methanol was treated with 1.30 g (20 mol) of potassium cyanide. The mixture was refluxed for 6 h, then cooled, evaporated to half of its volume, poured in water, and extracted with dichloromethane (3× 25 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo to yield 1.85 g (81%) of a 50:50 mixture of the cyclopropanecarbonitriles **55** and

aziridine-2-carbonitriles **56** which could be separated by preparative gas chromatography.

1-Isopropylamine-2-benzyl-2-methylcyclopropane-1-carbonitriles *cis*- and *trans* (55) (TLC: 2/1): *trans*-**55**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.88 (1 H, d, J = 5.3 Hz, HCH_{ring}); 1.01 and 1.13 (6 H, 2× d, J = 6.6 Hz, $CHMe_2$); 1.10 (3 H, s, MeC); 1.55−1.70 (1 H, broad s, NH); 2.79 and 2.91 (2 H, AB, J = 14.7 Hz, $CH_2C_6H_5$); 3.23 (1 H, sept, J = 6.3 Hz, $CHMe_2$); 7.17−7.34 (5 H, broad s, C_6H_5). − ^{13}C NMR (68 MHz, $CDCl_3$): δ 16.86 (MeC); 22.95 (Me_2); 28.36 (CH_2 ring); 31.07 ($NCC{\equiv}N$); 36.62 (CMe); 42.93 ($CH_2C_6H_5$); 47.51 ($CHMe_2$); 121.29 (C≡N); 126.51, 128.37 and 129.31 (=CH′s); 138.51 (=C-CH_2). − IR (NaCl): $\tilde{\nu}$ 3320 cm^{-1} (NH) and 2220 cm^{-1} (C≡N). − MS m/z (%): 228 [M$^+$] (2), 213 (2), 175 (2), 168 (4), 137 (100), 118 (22), 117 (26), 116 (6), 115 (13), 109 (9), 96 (8), 95 (88), 91 (24), 84(6), 77(6), 70 (28), 69 (5), 68 (6), 65 (8), 55 (6), 53 (6), 44 (8), 43(44).

cis-**55**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.09 and 1.12 (6, 2× d, J = 6.7 Hz, $CHMe_2$); HCH_{ring} invisible; 1.25 (3 H, s, MeC); 1.55−1.70 (1 H, broad s, NH); 2.74 and 2.96 (2 H, AB, J = 14.8 Hz, $CH_2C_6H_5$); 3.26 (1 H, sept, J = 6.3 Hz, $CHMe_2$); 7.17−7.35 (5 H, broad s, C_6H_5). − ^{13}C NMR (68 MHz, $CDCl_3$): δ 21.06 (MeC); 22.70 (Me_2CH); 28.30 (CH_2 ring); 30.42 ($NCC{\equiv}N$); 36.91 (CMe); 38.44 ($CH_2C_6H_5$); 47.71 ($CHMe_2$); 120.73 (C≡N); 126.30, 128.42 and 129.14 (=CH′s); 139.33 (=CCH$_2$). − MS and IR: identical to *trans*-**55**. − $C_{15}H_{20}N_2$ (228.3): Calcd. C 78.90, H 8.83, N 12.27; found C 79.06, H 8.80, N 12.15.

3-Benzyl-1-isopropyl-2,3-dimethylaziridine-2-carbonitrile 56 (major isomer): ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.91 and 1.19 (2× 3 H, 2× d, J = 6.0 Hz, $CHMe_2$); 1.28 and 1.62 (2× 3 H, 2× s, 2× Me); 2.55 (1 H, sept, J = 6.0 Hz, $CHMe_2$); 2.69 and 2.70 (2 H, AB, J = 14.2 Hz, $CH_2C_6H_5$); 7.18−7.34 (5 H, m, C_6H_5). − ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 19.21 ($MeCCH_2$); 22.12 and 22.60 (Me_2CH); 30.94 ($MeCCN$); 36.85 (CCN); 41.99 ($CH_2C_6H_5$); 49.83 ($CHMe_2$); 49.97 ($MeCCH_2$); 119.57 (C≡N); 126.72, 128.33 and 129.63 (=CH′s); 137.19 (=C-CH_2). − IR (NaCl): $\tilde{\nu}$ 2230 cm^{-1} (C≡N). − MS m/z (%): 228 [M$^+$] (12), 227 (10), 185 (41), 174 (18), 158 (27), 144 (37), 130 (9), 117 (100), 115 (27), 112 (20), 105 (30), 95 (24), 91 (55), 85 (9), 84 (11), 77 (10), 68 (22), 54 (9), 49 (17), 44 (34), 42 (68). − $C_{15}H_{20}N_2$ (228.3): Calcd. C 78.90, H 8.93, N 12.27; found C 79.08, H 8.99, N 12.38.

Acknowledgments

The authors are indebted to the Fund for Scientific Research − Flanders (F. W. O. − Vlaanderen), the I.W.T. and the Flemish Ministry of Science and Technology (Bilateral Scientific and Technological Cooperation Flanders-Hungary) for financial support.

[1] S. F. Yang, in *Plant Nitrogen Metabolism*, Chapter 8, (Eds.: J. E. Poulton, J. T. Romeo, E. E. Conn), Plenum Press; New York, **1989**.
[2] [2a] M. C. Pirrung, G. M. McGeehan, *Angew. Chem.* **1985**, *97*, 1074−1075. − [2b] M. C. Pirrung, G. M. McGeehan, *J. Org. Chem.* **1986**, *51*, 2103−2106.
[3] F. L. Switzer, H.Van Halbeek, E. M. Holt, C. H. Stammer, M. E. Saktveit, Jr. *Tetrahedron* **1989**, *45*, 6091−6100.
[4] C. H. Stammer, U. S. US 4,954,158 (Cl. 71−76; A01N43/38), Sept. 4, **1990**, US Appl. 523,080, Aug. 16, **1983**; *Chem. Abstr.* **1991**, *114*, 143132.
[5] [5a] H. Toshima, Y. Niwayama, H. Nagata, F. Greulich, A. Ichihara, *Biosci. Biotech. Biochem.* **1993**, *57*, 1394−1395. − [5b] C. Cativiela, M. Diaz-de-Villegas, A. Jimenez, *Tetrahedron Asym.* **1995**, *6*, 2067−2072 and refs. cited therein. − [5c] A. Hercouet, B. Bessières, M. Le Corre, *Tetrahedron Asym.*, **1996**, *7*, 283−284 and references cited therein.
[6] [6a] C. H. Stammer, *Tetrahedron* **1990**, *46*, 2231−2254 and references cited therein. [6b] A. Alami, M. Calmas, J. Daunis, R. Jacquier, *Bull. Soc. Chim. Fr.* **1993**, 5−24.
[7] K. Burgess, K.-K. Ho, *Tetrahedron Lett.* **1992**, *33*, 5677−5680.
[8] D. Mendel, J. Ellman, P. G. Schultz, *J. Am. Chem. Soc.* **1993**, *115*, 4359−4360.
[9] N. De Kimpe, P. Sulmon, P. Brunet, *J. Org. Chem.* **1990**, *55*, 5777−5784.
[10] N. De Kimpe, P. Sulmon, C. Stevens, *Tetrahedron* **1991**, *47*, 4723−4738.
[11] P. Sulmon, N. De Kimpe, R. Verhé, L. De Buyck, N. Schamp, *Synthesis* **1986**, 192−195.
[12] N. De Kimpe, M. Boeykens, L. Lazar, G. Bernath, *Natural Prod. Lett.* **1994**, *5*, 1−6.
[13] N. De Kimpe, P. Sulmon, L. Moëns, N. Schamp, J.-P. Declercq, M. Van Meerssche, *J. Org. Chem.* **1986**, *51*, 3839−3848.
[14] N. De Kimpe, R. Verhé, L. De Buyck, L. Moëns, N. Schamp, *Tetrahedron Lett.* **1981**, *22*, 1837−1840.
[15] [15a] N. De Kimpe, P. Sulmon, R. Verhé, L. De Buyck, N. Schamp, *J. Org. Chem.* **1983**, *48*, 4320−4326. − [15b] N. De Kimpe, P. Sulmon, N. Schamp, *Bull. Soc. Chim. Belg.* **1986**, *95*, 567−586.
[16] [16a] P. Geneste, P. Hermann, J. M. Kamenka, A. Pons, *Bull. Soc. Chim. Fr.* **1975**, *7*, 1619−1626. − [16b] A. Thurkauf, B. de Costa, S. Yamaguchi, M. V. Mattson, A. E. Jacobson, K. C. Rice, M. A. Rogawski, *J. Med. Chem.* **1990**, *33*, 1452−1458.
[17] N. De Kimpe, in *Methods of Organic Chemistry* (Houben-Weyl), Vol. E17B "Carbocyclic Three-Membered Ring Compounds", Chapters 5.2.3.4. up to 5.2.3.7., pp. 1603−1694, Ed. A. de Meijere, G. Thieme Verlag, Stuttgart, **1997**.
[18] N. De Kimpe, P. Brunet, R. Verhé, N. Schamp, *J. Chem. Soc. Chem. Commun.* **1988**, 825−827.
[19] N. De Kimpe, P. Sulmon, N. Schamp, *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 881−882.
[20] [20a] A. Fadel, *Synlett*. **1993**, 503−505. − [20b] A. Fadel, A. Khesrani, *Tetrahedron Asym.* **1998**, *9*, 305−320 and refs. cited therein.

Received July 28, 1998
[O98365]