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Review

Titanium-mediated syntheses of cyclopropylamines

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Abstract

The transformations of *N*,*N*-dialkylcarboxamides and nitriles with 1,2-dicarbanionic organometallics in situ generated from organomagnesium (Grignard) as well as organozinc reagents in the presence of stoichiometric or substoichiometric (semi-catalytic) quantities of a titanium alkoxide derivative of type $XTi(OR)_3$ with X = OR, Cl, Me and OR = O*i*Pr, OEt are described. The key step in the transformation of a monocarbanionic into a 1,2-dicarbanionic organotitanium species is a disproportionation of a dialkyltitanium intermediate to form an alkane and a titanium alkene complex which has the reactivity of a titanacyclopropane derivative. The latter are able to undergo insertion of the carbonyl group of an *N*,*N*-dialkylcarboxamide or a cyano group to furnish, after ring contraction and hydrolysis, dialkylcyclopropylamines or cyclopropylamines, respectively. The titanium alkene complexes can also undergo ligand exchange with alkenes to afford new titanacyclopropanes, which subsequently react as 1,2-dicarbanionic equivalents. In many cases, these titanium-mediated formations of a wide range of synthetically and/or pharmacologically important cyclopropylamines proceed in good to very good yields (from 20% to 98% for dialkylcyclopropylamines from *N*,*N*-dialkylcarboxamides and from 27% to 73% for primary cyclopropylamines from nitriles) and with high chemo- and stereoselectivity. These circumstances in conjunction with the simplicity of the experimental handling and inexpensiveness of the reagents favor these reactions for an ever increasing range of applications in organic synthesis.
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Keywords: Aminocyclopropanes; Amino acids; Cyclopropanations; Amides; Nitriles; Grignard reagents; Titanium

1. Introduction

Among the wide variety of organometallic compounds, the relatively inexpensive and safely handled non-transition-metal derivatives, in particular organolithium, organomagnesium, organozinc, and organoaluminum reagents, are definitely the most widely used ones in organic synthesis [1]. The majority of synthetically useful transformations of these reagents, including carbon–carbon bond forming reactions, may sometimes dramatically change their rates or even modes when conducted in the presence of a transition-metal compound [2–9]. The use of the latter, especially of group(IV) transition-metal derivatives, sometimes not only allows one to modify the reactivity of non-transition organometallics, but also to perform new kinds of transformations due to a structural reorganization of the carbanionic moiety. Among group(IV) metal derivatives, titanium mediators or catalysts, such as titanium chlorides, titanium alkoxides, and titanocene derivatives, are especially attractive for practical use, as they are the least expensive ones, and they are conveniently handled. In the form of the Sharpless-epoxidation [10–15] and the McMurry-coupling reagents [16–21], chemo- and stereoselective reactions of carbonyl compounds [22–24] as well as olefin metathesis reactions [25], titanium derivatives have found numerous synthetic applications, and all of these have been reviewed extensively.

This contribution compiles some of the synthetic applications of an important class of rather novel low-valent titanium reagents which are in situ formed from titanium alkoxides and organometallic compounds, especially organomagnesium halides, leading to cyclopropylamines from *N*,*N*-dialkylcarboxamides and nitriles, all of which have been developed in the last 10

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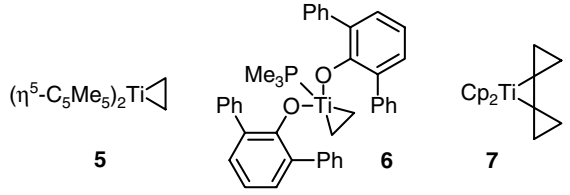
years (the analogous syntheses of cyclopropanols from carboxylic acid esters (lactones) and chemical transformations of cyclopropanols have been exhaustively reviewed [26,27]). These discoveries have led to synthetically extremely useful transformations of organic compounds that could not even have been thought of in classical organic chemistry, yet are well on their way to being routinely applied in modern organic synthesis. The increasing importance of these reactions is demonstrated by the first successful applications in the syntheses of natural products and syntheses of compounds with potentially useful properties, which will also be discussed.

2. Reaction modes of alkyltitanium derivatives possessing β-hydrogen atoms

Alkyl derivatives of titanium and other transition metals having β-hydrogen atoms are known to be prone to β-hydride elimination reactions as the most characteristic transformation [23,28–33], and this occurs particularly easily, when two or more alkyl groups are bound to the metal. This leads to the formation of the corresponding alkanes and low valent titanium derivatives [34–39]. The latter intermediates which may be formed by a bimolecular disproportionation, are essentially 1,2-dimetalloalkylene derivatives [36]. The thermal decomposition of alkyltitanium derivatives may also occur by β-elimination of metal hydride [3,40–43]. The mechanism of this includes a ligand dissociation step from **1** with formation of a coordinatively unsaturated dialkyltitanium derivative, followed by elimination of metal hydride from one of the alkyl groups in **2** with concomitant transfer of the resulting alkene to the vacant coordination site to form an alkenealkylhydrido complex **3** (Scheme 1). Readdition of a ligand to **3** accompanied by reductive elimination of an *n*-alkane eventually leads to the alkenetitanium complex **4** (Scheme 1) [28,44–48].

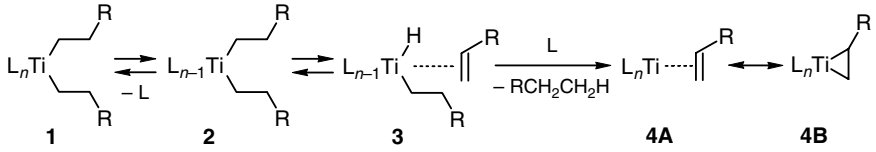
The question, whether a transition-metal complex of type **4** is best described as an alkene π-complex **4A** or a metallacyclopropane **4B**, which is of practical importance, has been addressed in several computational studies on the relation between alkene π-complexes and three-membered rings [49–53]. It has been concluded that the titanium complexes of type **4** are best represented as titanacyclopropanes, i.e., resonance structure **4B**, if one is willing to accept the notion that **4A** and **4B** are limiting resonance forms [53].

The first isolable alkenetitanium complex, the bis-(pentamethylcyclopentadienyl)-titanium-ethylene complex **5**, was prepared by Bercaw and co-workers [43] by sodium amalgam reduction of bis(pentamethylcyclopentadienyl)titanium dichloride in toluene under an atmosphere of ethylene (ca. 700 Torr) or from $\{[(\eta\text{-}C_5Me_5)_2Ti]_2(\mu\text{-}N_2)_2\}$ by treatment with ethylene. The X-ray crystal structure analysis of **5** and of the ethylenebis(aryloxy)-trimethylphosphinotitanium complex **6** [54] disclosed that the coordination of ethylene causes a substantial increase in the carbon–carbon double bond length from 1.337(2) Å for free ethylene to 1.438(5) and 1.425(3) Å, respectively. Considerable bending of the hydrogen atoms out of the plane of the ethylene molecule is also observed. By comparison with structural data of other ethylene complexes and three-membered heterocyclic compounds, the structures of **5** and **6** would appear to be intermediate along the continuum between a Ti(II)-ethylene (**4A**) and a Ti(IV)-metallacyclopropane (**4B**) (Scheme 1) as limiting structures [43]. No crystal structure analysis, but full NMR-spectroscopic characterization has been reported for the interesting bisspirocyclopropanated titanacyclopropane **7**, which was readily formed upon reaction of $Cp_2Ti(PMe_3)_2$ with bicyclopropylidene [55].



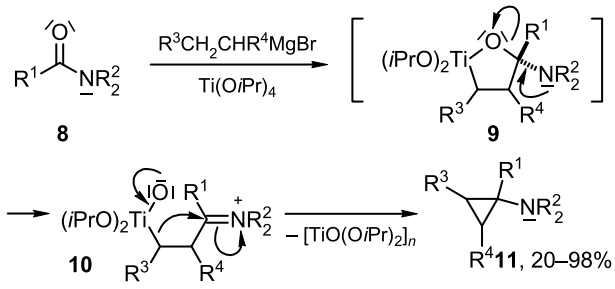
3. Preparation of cyclopropylamines from amides via organomagnesium precursors

The first synthetically useful reaction of titanium complexes of type **4** leading to the formation of two new carbon–carbon bonds has been developed by Kulinkovich and co-workers [26,56]. They found that treatment of a carboxylic acid ester with a mixture of one equivalent of titanium tetraisopropoxide and an excess of ethylmagnesium bromide at −78 to −40 °C, affords 1-alkylcyclopropanols in good to excellent



Scheme 1. Thermal decomposition of dialkyltitanium derivatives by β-elimination of metal hydride.

yields [26,27]. As reported by the same group, this efficient transformation can also be carried out with substoichiometric amounts of $Ti(OiPr)_4$ (5–10 mol%) [57,58]. Four years later, development of a very useful and highly versatile preparation of cyclopropylamines was initiated by de Meijere et al. [59–68]. *N*,*N*-Dialkylaminocyclopropanes (**11**) with up to three additional substituents are readily obtained from carboxylic acid *N*,*N*-dialkylamides (**8**) and ethyl- as well as substituted ethylmagnesium halides in the presence of titanium tetraisopropoxide or, even better, methyltitanium triisopropoxide. These transformations were also possible with substoichiometric amounts of the titanium reagent, but the yields were significantly higher with stoichiometric amounts. In some cases, extended reaction times and/or slightly elevated temperatures did also lead to better yields. Particularly, high yields were obtained from *N*,*N*-dialkylformamides (Scheme 2, and selected examples in Table 1); yields are consistently lower from amides with bulky substituents next to the carbonyl group or on the nitrogen, but even the overcrowded *N*,*N*-di-*tert*-butylformamide could be converted to di-*tert*-butylcyclopropylamine (Table 1, entry 8), albeit in only 20% yield [60]. The diastereoselectivities in the formation of 2-substituted and 1,2-disubstituted *N*,*N*-dialkylcyclopropylamines are generally lower than those for the corresponding cyclopropanols formed from esters.

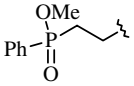


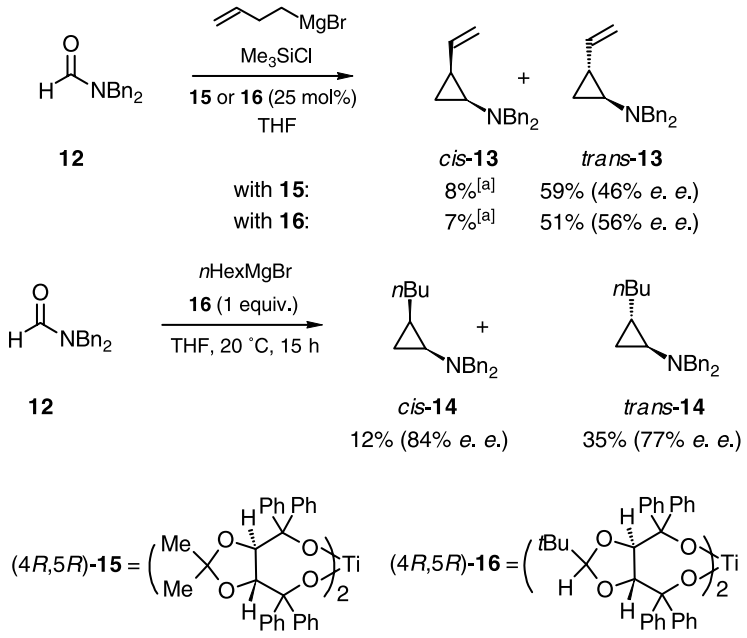
Scheme 2. Preparation of *N*,*N*-dialkylaminocyclopropanes **11** from carboxylic acid *N*,*N*-dialkylamides **8**. For details see Table 1.

As far as the mechanism is concerned, this transformation of carboxamides to cyclopropylamines is different in some important details from that of esters to cyclopropanols (cf. [26a]; this mechanism was recently probed with density functional theory calculations at the B3LYP/6-31G* level of theory [69a] and experimentally [69b]). Due to the poorer leaving group ability of the dialkylamino group in the oxatitanacyclopentane intermediate **9**, which is initially formed by insertion of the carbonyl group of the amide into the titanium–carbon bond of a titanacyclopropane, **9** does not undergo ring contraction like the corresponding oxatitanacyclopentane from an ester, but ring opening to an iminium–titanium oxide zwitterion **10** which cyclizes to the cyclopropylamine **11** with loss of an oxotitanium diisopropoxide species (Scheme 2). Recent experiments with *trans*-β-deuterostyrene have proved that the ring closing fragmentation of **10** occurs with inversion of configuration of the titanium-bearing carbon which requires a W-shaped transition state structure [69c].

In the presence of substoichiometric amounts (25 mol%) of titanium bistaddolates like **15** and **16** (25 mol%), generated from titanium tetraisopropoxide

Table 1
N,*N*-Dialkylcyclopropylamines **11** from *N*,*N*-dialkylcarboxamides **8** and ethyl- as well as substituted ethylmagnesium bromides in the presence of titanium tetraisopropoxide (selected examples)

Entry	R^1	R^2_2	R^3	R^4	Yield (%) (d.r.)	Ref.
1	Me	Bn_2	H	H	60	[60]
2	Et	Bn_2	H	H	63	[60]
3	*n*Pr	Bn_2	H	H	52	[60]
4	*n*Pr	Bn_2	*n*Bu	H	35	[60]
5	H	Bn_2	H	H	73	[60]
6	H	$-(CH_2)_5-$	H	H	74	[60]
7	H	$-(CH_2)_2O(CH_2)_2-$	H	H	74	[60]
8	H	tBu_2	H	H	20	[60]
9	H	Bn_2	Me	H	63 (1:1)	[60]
10	H	Bn_2	*n*Bu	H	52 (1:2.3)	[60]
11	Me	Bn_2	Et	H	47	[59]
12		Me_2	Et	H	42 (10:1)	[61]
13	H	Bn_2	$-(CH_2)_4-$		34	[59]
14	Me	Me_2	*n*Bu	H	38 (>25:1)	[65]
15	H	Bn_2	$CH_2{=}CH-$	H	42 (>25:1)	[65]
16	$-(CH_2)_2-$,Bn		H	H	21	[65]
17	$-(CH_2)_5-$,Me		H	H	33	[65]

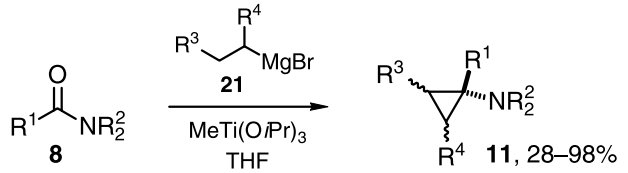


Scheme 3. Preparation of enantiomerically enriched *trans*-1-dibenzylamino-2-ethenyl-cyclopropane *trans*-**13** and *cis*- and *trans*-1-dibenzylamino-2-*n*-butylcyclopropanes *cis*-**14** and *trans*-**14** [68]. [a]Enantiomeric excess not determined.

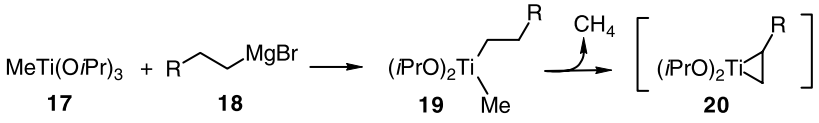
and the corresponding TADDOL, as well as one equivalent of trimethylsilyl chloride, 1-dibenzylamino-2-ethenylcyclopropanes *cis*-**13** and *trans*-**13** could be prepared in 67% yield from dibenzylformamide **12** and 1-buten-4-ylmagnesium bromide in a ratio of 1:7 [68]. The latter were obtained with an enantiomeric excess (e.e.) of up to 56% for the major *trans*-isomer (Scheme 3, the absolute configuration was not determined). With a substoichiometric amount of the titanium bistaddolate present, but no trimethylsilyl chloride, the yields of *cis*- and *trans*-**13** were only 6% and 41%, respectively, with an e.e. for *trans*-**13** of only 24%. The trimethylsilyl chloride most probably converts the oxotitanium diisopropoxide, which tends to be oligomeric and not well soluble, into a soluble titanium(IV) derivate which can participate in the reaction again. With a stoichiometric amount of (4*R*,5*R*)-**16** present, the reaction of **12** with *n*-hexylmagnesium bromide gave a separable mixture of the *n*-butyl derivatives *cis*-**14** and *trans*-**14** (ratio 1:3) with an e.e. of 84% for the minor and 77% for the major isomer.

Since benzyl groups can be removed from *N*,*N*-dibenzylcyclopropylamines by catalytic hydrogenation over palladium catalysts, primary cyclopropylamines are also accessible by this methodology. Thus, the theoretically interesting tricyclopropylamine [63,64] could be prepared from benzylcyclopropylformamide in a sequence of reductive cyclopropanation of the formyl group, hydrogenolytic debenzylation, *N*-formylation and repeated reductive cyclopropanation [63,64].

Improved yields of cyclopropylamines **11** were obtained by using methyltitanium triisopropoxide (**17**) instead of titanium tetraisopropoxide [65], as well as by adding the Grignard reagent to the mixture of the amide and the titanium reagent at ambient instead of low temperature (Schemes 4, 5 and Table 2) [61,70]. It is presumed that at room temperature, the rate of formation of the reactive titanacyclopropane intermediate and of its consumption by reaction with the amide are better balanced that at low temperature. Methyltitanium

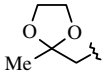
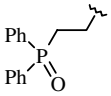
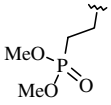
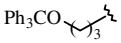
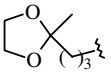


Scheme 5. Preparation of *N*,*N*-dialkylcyclopropylamines **11** in the presence of methyltitanium triisopropoxide. For details see Table 2.



Scheme 4. Formation of the reactive titanacyclopropane intermediate **20** from methyltitanium triisopropoxide and a Grignard reagent.

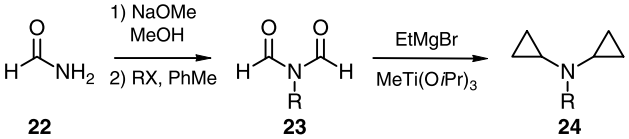
Table 2
N,*N*-Dialkylcyclopropylamines **11** from *N*,*N*-dialkylcarboxamides **8** and ethyl- as well as substituted ethylmagnesium bromides **21** in the presence of methyltitanium triisopropoxide

Entry	R^2_2	R^1	R^3	R^4	Yield (%) (d. r.)	Ref.
1	Bn_2	H	H	H	95	[66,70]
2	Bn_2	H	Me	H	89 (1:1.1)	[70]
3	Bn_2	Et	H	H	70	[66,70]
4	Bn_2	*n*Pr	H	H	62	[66,70]
5	Me_2		$-(CH_2)_3-$	H	28	[59,65]
6	Bn_2	H	CH_2=CH	H	98 (1:7)	[70]
7	Bn_2	$BnOCH_2$	Et	H	48 (1:5)	[67,68]
8	Bn_2	$BnOCH_2$	*i*Pr	H	42 (1:3)	[67]
9	Bn_2	*i*Pr	H	H	44	[66,70]
10	iPr_2	H	H	H	86	[70]
11	Bn_2	H	Ph	H	98 (1:2.3)	[70]
12	Bn_2	H	$tBuO(CH_2)_3$	H	59 (1:2)	[70]
13	Bn_2	H		H	92 (1:1.5)	[70]
14	$-(CH_2)_5-$	H	Ph	H	92 (1:1.5)	[70]
15	Bn_2	$ClCH_2CH_2$	H	H	49	[66]
16	Bn_2	$BnOCH_2CH_2$	Me	H	33 (1:3)	[66]
17	Bn_2		CH_2=CH	H	61	[70]
18	Bn_2	$BnCH_2O$	$BnOCH_2CH_2$	H	40 (1:3)	[66]
19	Me_2		CH_2=CH	H	83 (1:3)	[61,70]
20	Me_2		Ph	H	82 (1:1.4)	[61,70]
21	Bn_2	H	$-CH_2CH_2CH_2-$		89	[70]
22	Me_2	H	CH_2=CH	H	57 (17:1)	[65]
23	Me_2	H	$BnOCH_2CH_2$	H	54 (1.1:1)	[65]
24	Bn_2	H	$THPO(CH_2)_2$	H	34 (2.1:1)	[65]
25	Me_2	H		H	53 (1.8:1)	[65]
26	$-(CH_2)_5-$	Ph	H	H	73	[70]
27	Et_2	H	H	H	83	[70]
28	Bn_2		H	H	85	[70]
29	Me_2	H	$-CH_2CH_2-$		72	[70]
30	Bn_2	H	$-CH_2CH_2-$		87	[70]
31	Bn_2	H	$-CH(CH_3)CH_2-$		87	[70]

triisopropoxide in principle requires only one equivalent of the alkylmagnesium halide to provide a dialkyltitanium diisopropoxide intermediate **19**, and in this particular case β-hydride elimination can only occur at the non-methyl substituent so that methane is liberated selectively. This is an advantage – also for the production of certain cyclopropanols from esters – with valuable, e.g., functionally substituted, Grignard reagents, since one does not sacrifice one equivalent of it as an alkane in the formation of the corresponding titanacyclopropane **20** (Scheme 4). By using an excess of the alkylmagnesium halide in spite of having the sacrificial methyl substituent on the titanium reagent, the yields based on the substrate carboxamide can be raised to as high as 92–98% (Table 2, entries 1, 6, 11, 13, 14). This is beneficial especially whenever the carboxamide is more precious than the Grignard reagent. This modification has also successfully been applied towards the intramolecular reductive cyclopropanation of *N*,*N*-dialkylcarboxamides in which the Grignard reagent **21** was generated in situ from an ω-bromocarboxamide and metallic magnesium (Table 2, entry 5).

It is remarkable that even cyclobutylmagnesium bromides cleanly react with titanium alkoxides to yield reactive titanacyclopropane intermediates which reductively cyclopropanate *N*,*N*-dialkylformamides. Although the first synthesis of such a highly strained *N*,*N*-dialkylbicyclo[2.1.0]pent-5-ylamine was published as early as 1989 by Vilsmeier et al. [71], this approach makes a large variety of derivatives more easily available (Table 2, entries 29–31).

The reductive cyclopropanation with in situ generated titanacyclopropanes can also be applied to alkyldiformylamines **23** which are easily prepared from inexpensive formamide (**22**). Both formyl groups are converted to cyclopropyl groups, and the alkyldicyclopropylamines **24** are obtained in good to very good yields (Scheme 6) [70]. This new method for the preparation of dicyclopropylamines compares favorably with the previously published [72] reductive amination of cyclopropanone alkyl silyl acetals with primary amines,



22 **23** **24**

RX	R	**23** (%)	**24** (%)
$(MeO)_2SO_2$	Me	70	67
$(EtO)_2SO_2$	Et	71	82
*n*BuOMs	*n*Bu	74	53
All-Br	All	52	0
BnBr	Bn	97	57

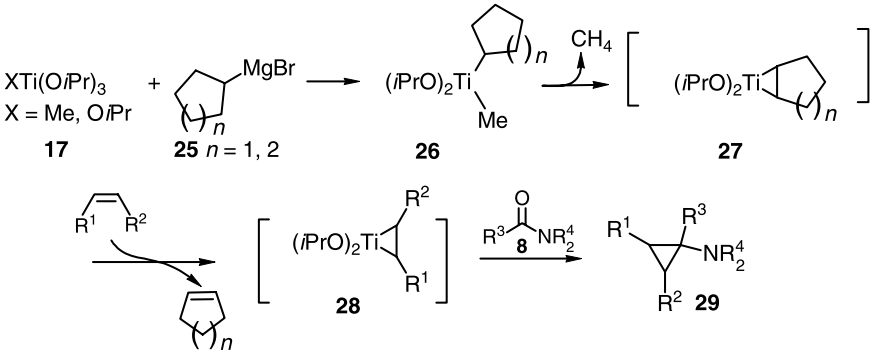
Scheme 6. The twofold reductive cyclopropanation of alkyldiformylamines **23** [70].

as the reagents used in this current protocol are commercially available and are far less expensive.

4. Cyclopropylamines from amides via ligand-exchanged titanium–alkene complexes

In view of the versatile new general synthesis of dialkylcyclopropylamines from *N*,*N*-dialkylcarboxamides by way of titanacyclopropane intermediates generated from Grignard reagents and $XTi(OiPr)_3$ (X = O*i*Pr, Me) [60,65], de Meijere et al. also turned their attention to the additional synthetic potential of titanacyclopropane intermediates generated by ligand exchange (Scheme 7) applying cyclohexylmagnesium halides as Grignard reagents [61,62,73]. This approach, which was also simultaneously developed by Cha and co-workers [74–76], applying a number of alkenes and favoring the use of cyclopentylmagnesium halides [77], has since been established as an efficient method for the formal dialkylaminocyclopropanation not only of a whole range of mono-, but also of some disubstituted alkenes and cycloalkenes (for selected examples see Table 3).

The diastereoselective and efficient cyclopropanations with tributylvinylstannane (Table 3, entries 24 and 25)



Scheme 7. Ligand exchange of titanacyclopropanes **27** with added alkenes [61,62,73–76].

Table 3
N,*N*-Dialkylcyclopropylamines **29** from *N*,*N*-dialkylcarboxamides and alkenes via ligand-exchanged titanium intermediates from Grignard reagents and $XTi(OiPr)_3$ (X = O*i*Pr, Cl, Me, OR) [61,62b,73,75,76,78,79]

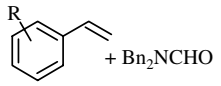
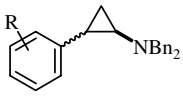
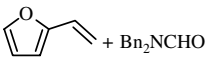
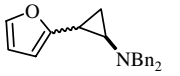
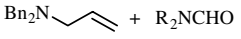
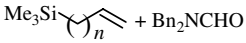
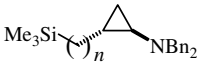
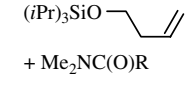
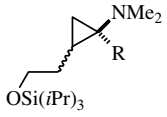
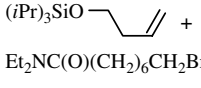
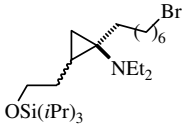
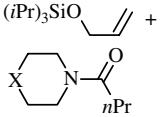
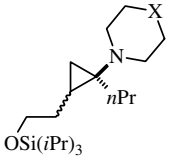
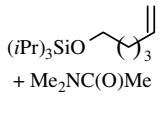
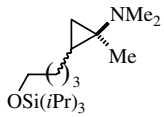
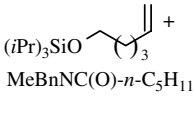
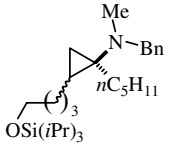
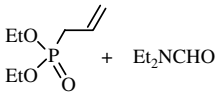
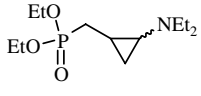
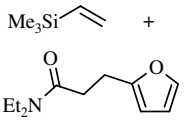
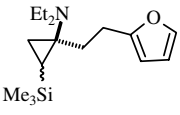
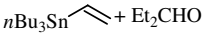
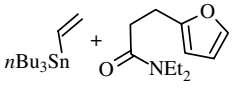
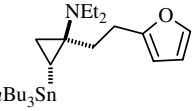
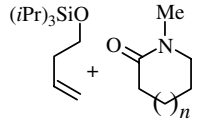
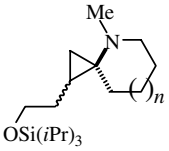
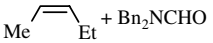
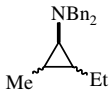
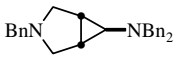
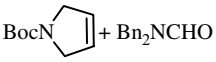
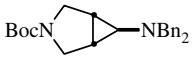
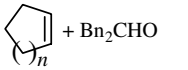
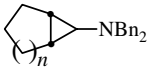
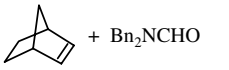
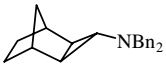
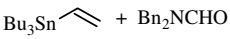
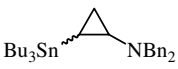
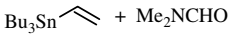
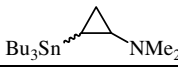
Entry[a]	Alkene, Starting Amide	Product	Yield (%) (d. r.)	Ref.
				
1	R = H	R = H	66 (1:3.1)	[62b, 73]
2	R = 4-OMe	R = 4-OMe	45[b] (1:1.2)	[62b]
3	R = 2-CF_3	R = 2-CF_3	11[b] (1:4)	[62b]
4	R = 3-CF_3	R = 3-CF_3	46 (1:11.5)	[62b]
5	R = 4-CF_3	R = 4-CF_3	18[b] (0:1)	[62b]
6			43 (1:4)	[62b]
7[c]			44[b] (R = Me) (1:5) 39[b] (R = Bn) (1:4)	[62b]
8[c]			59[b] (*n* = 0) (0:1) 28[b] (*n* = 1) (0:1)	[62b]
9[d]			61 (R = H) (1:2.2) 68 (R = Me) (6.3:1) 56 (R = *n*-Pr) (5.3:1)	[76]
10			60 (7.6:1)	[78]
11			69 (X = CH_2) (7.3:1) 77 (X = O) (3.1:1)	[76,78]
12			n. r.[e]	[79]
13			n. r.[e]	[79]
14			36[b] (1.6:1)	[61]
15[d]			68 (1:6.5)	[75]
16[d]			57	[75]
17[d]			68	[75]

Table 3 (*continued*)

Entry[a]	Alkene, Starting Amide	Product	Yield (%) (d. r.)	Ref.
18			21 ($n = 0$) (1.0:0) 79 ($n = 1$) (6.2:1)	[75]
19			26[b] (1:2:6)	[62b]
20			87 (<2:98)	[62b, 73a]
21			90 (<2:98)	[62b, 73a]
22			88 ($n = 1$) 27 ($n = 2$) 33 ($n = 4$)	[62b, 73a]
23			43 (<2:98)	[62b]
24[c]			92 (1:45)	[73b]
25[c]			88 (<1:50)	[73b]

[a] The reaction was performed with $Ti(OiPr)_4$, if not otherwise specified.

[b] Not optimized.

[c] Reaction with $MeTi(OiPr)_3$.

[d] Reaction with $ClTi(OiPr)_3$.

[e] n. r. = Not reported.

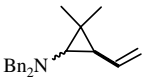
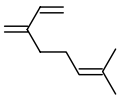
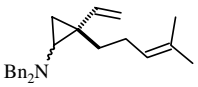
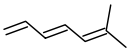
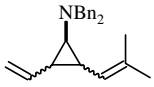
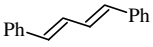
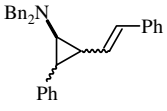
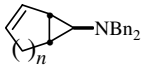
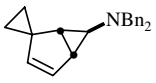
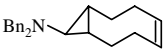
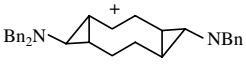
are of special interest, as the resulting dialkylaminocyclopropylstannanes could favorably be applied in Stille cross-coupling reactions with aryl iodides yielding the pure *trans*-2-aryl-(*N*,*N*-dialkylaminocyclopropanes) in yields ranging from 45% to 67% [73b].

The optimized protocol was also applied to a whole range of open-chain and cyclic dienes (Table 4, selected examples) [62b,80]. The latter generally give higher yields than non-terminal alkenes and cycloalkenes except for strained ones like *N*-benzylpyrroline, *N*-*tert*-butoxycarbonylpyrroline, cyclopentene and norbornene (Table 3, entries 20–23).

Surprisingly, the reaction with substituted 1,3-dienes such as isoprene, 4-methyl-1,3-pentadiene and myrcene all gave the alkenyldibenzylaminocyclopropanes derived from putative attack on the more highly substituted double bond of the conjugated diene unit rather than the expected product which would have been formed by attack on the least substituted double bond (entries 1–4, Table 4). As these expected products were not detected in any case, and control experiments with 2,3-dimethylbutadiene and 2,5-dimethyl-2,4-hexadiene did not yield any cyclopropylamines, it must be concluded that the alkenyldiisopropyloxy-titanacyclopropane **30** with the least substituted double bond of the conjugated diene attached to the titanium is kinetically – and possibly thermodynamically – favored. The formamide **12** then cycloadds to this alkenyltitanacyclopropane **30** by way of a metallaene reaction with a six-center transition state to yield an oxatitanacycloheptene **31**. This intermediate can cyclorevert to an iminiumallyltitanium oxide 1,8-zwitterion **32**, which subsequently can only cyclize to a cyclopentenylamine or to the observed, more highly substituted cyclopropylamine **33** (Scheme 8) [62b,80].

The formation of the same cyclopropylamine from 2-methyl-1,3-pentadiene as from 4-methyl-1,3-pentadiene (entries 2 and 3 in Table 4) most probably arises by initial isomerization of the former to the latter under the conditions employed. The fact that the conjugated 6-methyl-1,3,5-heptatriene yields only the 2,3-dialkenylcyclopropylamine (entry 5) arising from attack at the central double bond in the triene is in full accord with the notion that the reacting species are actually the less substituted titanacyclopropanes of type **30** and that the transformation to the oxatitanacycloheptene of type **31** occurs as a metallaene reaction [62b].

Table 4
2-Alkenyl-1-(*N*,*N*-dibenzylamino)cyclopropanes formed from *N*,*N*-dibenzylformamide (**12**) and titanium–diene complexes in situ generated by ligand exchange

Entry	Alkene	Product	Yield (%) (d. r.)	Ref.
1			56 (R = H) (>2:98) 59 (R = Me) (>2:98)	[62b,80]
2			64 (1:5.3)	[62b,80]
3			27 (1:3)	[62b,80]
4			51 (>2:98)	[62b,80]
5			54 (1:1.5:1.5)	[62b,80]
6			9 (1:0)	[62b]
7			(n = 1): No conversion (n = 2): 58 (2:98)	[62b]
8			trace	[62b]
9		 	11 (<2:98) 1.5 (>2:98)	[62b]

In the analogous reactions of 1-ethenylcycloalkenes **34** only the endocyclic double bond was involved in the aminocyclopropanation to furnish the $(n+3)$-(dialkylamino)-1-ethenylbicyclo[n.1.0]alkanes **36**. It is particularly remarkable that 1-ethenylcyclobutene **34a** is converted to *exo*-5-dibenzylaminobicyclo[2.1.0]pentane (**36a**) without any problem in 63% yield. This is another facile formation of a highly strained bicyclo[2.1.0]pentylamine [71] (Scheme 9) [70,81].

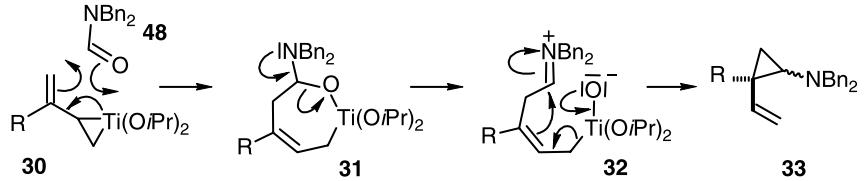
These aminocyclopropanations of terminal alkenes can also be applied intramolecularly in several versions [74,82–87]. Terminally, ethenyl-substituted *N*,*N*-dialkylcarboxamides like **37** yield 1-(dialkylamino)bicyclo[4.1.0]alkanes like **38** [74,82], while (ω-alkenylamino)carboxamides like **39** lead to 1-alkyl-2-azabicyclo[$(n+3)$.1.0]alkanes like **40** [83,87], and *N*-allylaminoacid *N*,*N*-dialkylamides **41** furnish bicyclic diamines **42** [84–86] (Scheme 10, for selected examples see Table 5).

1,2-Disubstituted alkenes bearing an acetamide group were found to undergo intramolecular cyclopropanations in low or moderate yield, but almost complete diastereoselectivity [87].

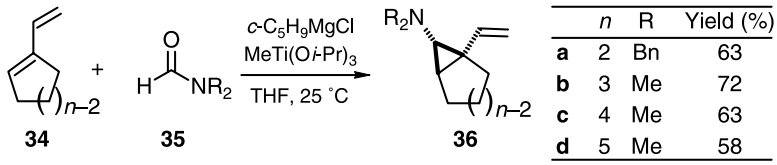
In the hydroxycyclopropanation of alkenes, certain esters may be more reactive than certain *N*,*N*-dialkylcarboxamides, as is illustrated by the exclusive formation of the disubstituted cyclopropanol **45** from the succinic acid monoester monoamide **43** (Scheme 11) [88]. However, the reactivities of both ester- as well as amide-carbonyl groups can significantly be influenced by steric bulk around them [88,89]. Thus, in intermolecular competitions for the reaction with the titanacyclopropane intermediate from an alkylmagnesium halide and titanium tetraisopropoxide or methyltitanium triisopropoxide, between *N*,*N*-dibenzylformamide (**12**) and *tert*-butyl acetate (**46**), the former won to yield only the corresponding cyclopropylamine **47**, and only the cyclopropylamino derivative **49** was isolated from the reaction of the succinic acid *tert*-butyl monoester monoamide **48** (Scheme 11) [59,90].

5. Cyclopropylamines from nitriles

Early attempts to convert aliphatic nitriles into primary cyclopropylamines, just like *N*,*N*-dialkylcarboxamides **8** are transformed to *N*,*N*-dialkylcyclopropylamines **11** upon treatment with Grignard reagents in the presence of Ti(O*i*Pr)$_4$, were unfruitful [91]. Szymoniak et al. [92a], however, found out that addition of a Lewis acid like boron trifluoride etherate is necessary to activate the azatitanacyclopentene **51**

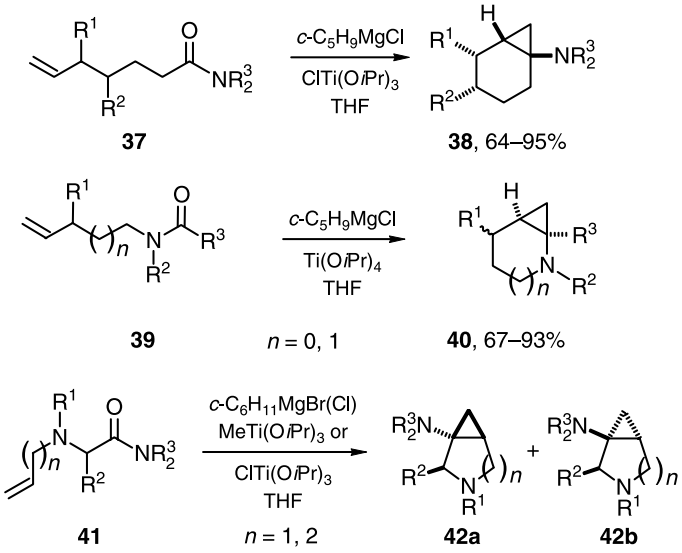


Scheme 8. Aminocyclopropanation of the more highly substituted double bond in a conjugated diene: a mechanistic rationalization [62b,80].



	n	R	Yield (%)
a	2	Bn	63
b	3	Me	72
c	4	Me	63
d	5	Me	58

Scheme 9. Aminocyclopropanation of 1-ethenylcycloalkenes **34**.



Scheme 10. Intramolecular aminocyclopropanations of terminal alkenes [73,82–87]. For further details see Table 5.

resulting by insertion of the nitrile **50** into the titanium–carbon bond of the first formed reactive titanacyclopropane intermediate (Scheme 12 and selected examples in Table 6). Under the action of BF_3, the ring contraction of **52** occurs readily, and after basic work-up, the unprotected primary cyclopropylamines **53** are isolated in good yields (Table 6, entries 1–6) [92–95].

Starting from aliphatic nitriles [92a], this methodology was extended by Szymoniak et al. to a wide variety of functionally substituted nitriles [93–96], upon which two important observations were made. Firstly, in intermolecular competitions for the reaction with the titanacyclopropane intermediate from ethylmagnesium bromide and titanium tetraisopropoxide, between the benzyl cyanide **54** and ethyl phenylacetate **55** as well as benzyl cyanide **54** and dibenzylformamide **12**, the nitrile **54** always won to furnish mainly the corresponding cyclopropylamine **56** in 59–60% yield; only 4% of the cyclopropanol **57** and no dibenzylcyclopropylamine **58** was isolated from these reactions (Scheme 12) [95]. This indicates that a cyano group reacts with a titanacyclopropane intermediate more rapidly than an ester as well as an amide and thus can be converted selectively into an aminocyclopropyl moiety in the presence of such functionalities (Table 6, entries 13–17). Secondly, α-alkoxy- and α-alkylthionitriles undergo reductive cyclopropanations even in the absence of added $BF_3 \cdot Et_2O$ (Table 6, entries 7–11); apparently, the possible α-alkoxy- or α-alkylthio-chelation of the titanium in the intermediate plays the role of the Lewis acid in the other cases [93]. Aromatic nitriles and alkenylnitriles did not yield 1-arylcyclopropylamines under these conditions. As was recently found, however, these conversions could be brought about by adding the Grignard reagent to the mixture of such a nitrile and titanium tetraisopropoxide at −70 °C [94] (Table 6, entries 18–24).

The intramolecular version of these aminocyclopropanations, which was elaborated by de Meijere and coworkers [85] and soon further developed by Szymoniak and co-workers [96] makes azabicyclo[3.1.0]hexyl-, azabicyclo[4.1.0]heptyl- and even azabicyclo[5.1.0]octylamines **61** readily accessible from unsaturated nitriles **59** (Scheme 13 and selected examples in Table 7).

Interestingly, lithium or sodium iodide can also be used in these reactions as a Lewis acid to promote ring contraction of the intermediate of type **60** [85]. In several cases, however, the reaction was performed without any additive, and the yields of bicycles **61** were only a few percent lower [96]. Whereas *N*,*N*-dialkylcarboxamides were commonly best converted to cyclopropylamines in

Table 5
Intramolecular aminocyclopropanations of dialkylcarboxamides **37**, **39** and **41** (selected examples)

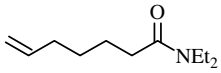
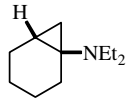
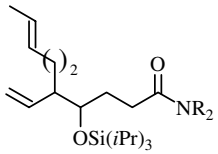
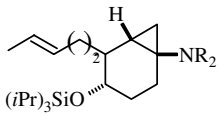
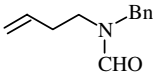
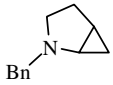
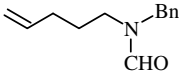
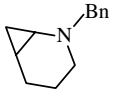
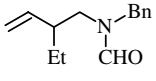
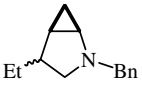
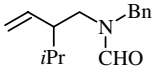
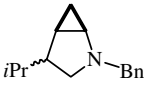
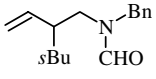
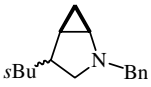
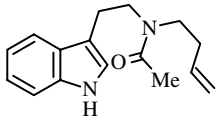
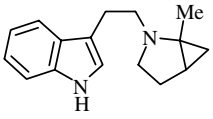
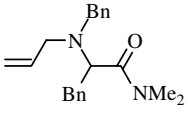
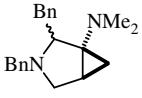
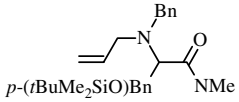
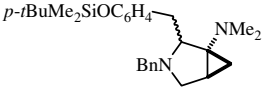
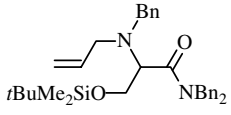
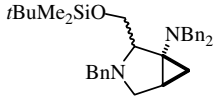
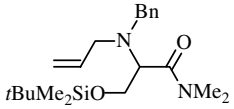
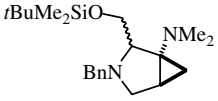
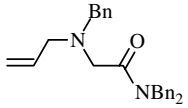
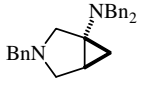
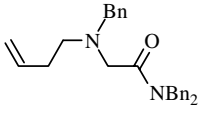
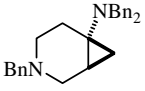
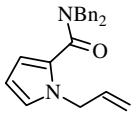
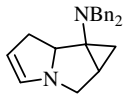
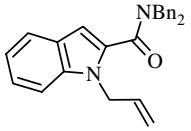
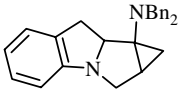
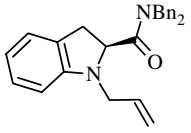
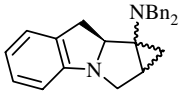
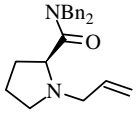
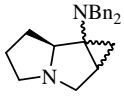
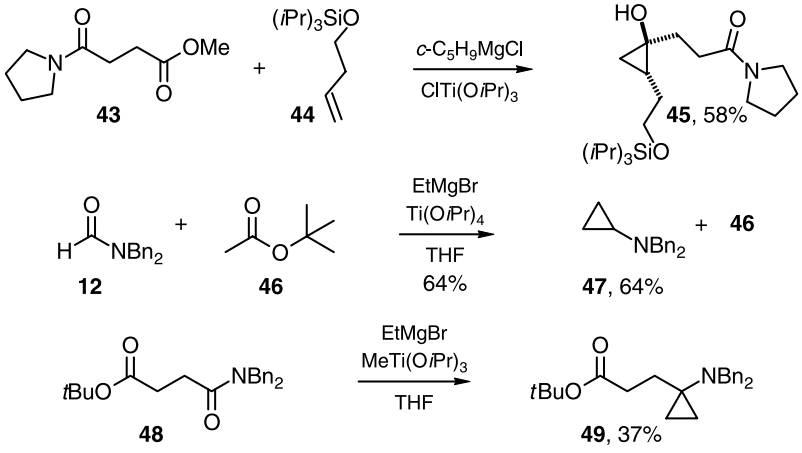
Entry	Starting Material	Product	Yield (%) (*exo*:*endo*)	Ref.
1			64	[74]
2			80–95 (not detailed for different R = Me, Et, Ph, Bn)	[82]
3			84	[83]
4			67 (>2:98)	[83]
5			82 (3:1)	[83]
6			77 (8:1)	[83]
7			74 (10:1)	[83]
8			93	[87]
9			83 (1:2.6)	[84]
10			83 (1:2.6)	[84]
11			83 (1:2.5)	[85]
12			89 (1:2)	[85]
13			58	[85]
14			59	[85]

Table 5 (*continued*)

Entry	Starting Material	Product	Yield (%) (*exo*:*endo*)	Ref.
15			78	[86]
16			79	[86]
17			61 (1:1)	[86]
18			70 (1:2.9)	[86]



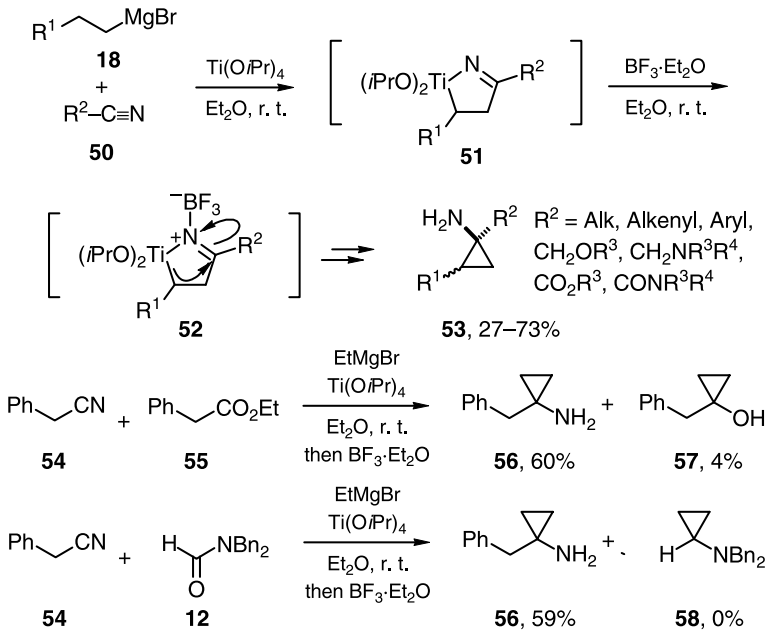
Scheme 11. Competition between ester and amide attack by titanacyclopropane intermediates [59,88,90].

tetrahydrofuran, diethyl ether turned out to be the solvent of choice for reductive cyclopropanations of nitriles in most cases [92–96].

6. Cyclopropylamines from organozinc precursors

As diorganylzinc reagents are less nucleophilic than organomagnesium compounds and can easily be prepared with a variety of functional groups, including ester moieties [97], their potential application in the preparation of functionalized aminocyclopropanes appears to be very promising. In the first attempt, it was found that diethylzinc in the presence of methyltitanium triisopropoxide did react with dibenzylformamide (**12**) under conditions commonly applied for alkylmagnesium halides, to give *N*,*N*-dibenzylaminocyclopropane (**47**), but in only 21% yield [70]. A systematic study of this reaction revealed that the yield could be improved significantly by addition of alkali metal alkoxides, the optimum was reached with 89% when 2 equiv. of NaO*i*-Pr and 2 equiv. of Et_2Zn were used (Scheme 14) [90a,98].

However, under the conditions optimized for diethylzinc, the reductive cyclopropanations of *N*,*N*-dialkylcarboxamides could not be carried out with differently functionalized organozinc reagents. Yet, monoalkylation of dichlorotitanium diisopropoxide with a diorganozinc reagent **62** followed by treatment with methylmagnesium chloride to substitute the second chlorine atom in **63** with a methyl group, provided the



Scheme 12. Preparation of cyclopropylamines **53** from nitriles **50** and intermolecular competition between a nitrile, an ester and a formamide for the reaction with a titanacyclopropane intermediate [92–95]. For selected examples, see Table 6.

titanium intermediates of type **64** which exhibited essentially the same reactivity pattern as the titanium intermediates generated from Grignard reagents, and transformed *N*,*N*-dialkylformamide to yield the correspondingly substituted dialkylaminocyclopropane derivatives **65**. The reagent **64** can also be prepared directly from **62** and dimethyltitanium diisopropoxide (Scheme 15 and Table 8) [90].

This new protocol provides an easy access to various functionally substituted aminocyclopropanes including cyclopropylamino acid derivatives [90], albeit the yields as well as the diastereoselectivities of this approach leave room for further improvement.

The application of diethylzinc in the presence of methyltitanium triisopropoxide and lithium isopropoxide also provided a complementary method, as developed by de Meijere et al., for the transformation of aromatic nitriles into 1-arylcyclopropylamines. While aliphatic nitriles **50** with this reagent mixture gave primary cyclopropylamines **53** in only 12–16% yield, aromatic nitriles **66**, **68** furnished 1-arylcyclopropylamines **67**, **69** in good yields (47–75%) for substituted benzonitriles **66** and 82% for 3-cyanopyridine (**68**) (Scheme 16) [90a,98].

7. Application of cyclopropylamines towards the synthesis of natural products and other compounds with potentially useful properties

Several applications of cyclopropylamines prepared by the described methodologies towards the syntheses of natural products, biologically active as well as compounds of other practical use have been reported since the discoveries of these approaches. For example, a large variety of *N*-cyclopropyl-*N*-arylamines of type **70** and their isotopically labeled analogues have been prepared from the corresponding formamides for mechanistic studies of Cytochrome P450-catalyzed *N*-dealkylations and autocatalytic radical ring-opening reactions under aerobic conditions [99–101].

Cha and co-workers [76,82] have demonstrated the synthetic potential of such oxidation reactions, as photoinitiated aerobic oxidation of bicyclic cyclopropylamines **71**, **73** results in a domino ring-opening-cyclization sequence to give cyclohept-2-enone (**72**) or substituted bicyclo[5.3.0]-decan-3-one **74** in preparatively useful yields (53% and 59%, respectively; for the preparation of starting materials **71**, **73**, see Table 5, entries 1 and 2) (Scheme 17). Iwata and co-workers [79] have transformed a number of cyclopropylamines of type **75** into substituted bicyclo[3.3.0]octylamines **76** using ceric ammonium nitrate (CAN)-mediated oxidative ring-opening followed by 5-*exo*-*trig* radical cyclizations in moderate to good yields, however, with low stereoselectivities (Scheme 17).

The aminocyclopropyl moiety plays a significant role in a variety of naturally occurring amino acids [102] and quite a number of biologically active non-natural compounds such as the antidepressant tranylcypromine (**77**) [103], the widely used broad spectrum antiinfectant ciprofloxacin **78** [104] and the once successful antibiotic trovafloxacin **79** [105,106].

Table 6
Cyclopropropylamines **53** from nitriles **50**, Grignard reagents as well as $Ti(OiPr)_4$ upon subsequent treatment with $BF_3 \bullet Et_2O$ (selected examples, see Scheme 12)

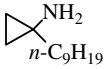
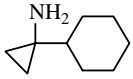
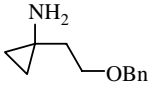
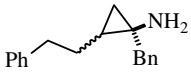
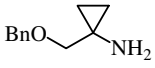
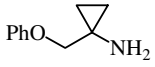
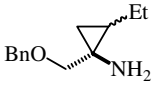
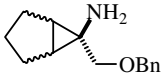
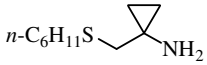
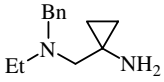
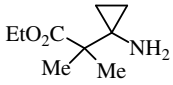
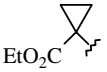
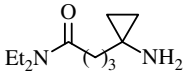
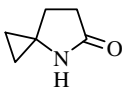
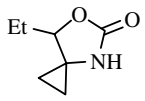
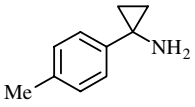
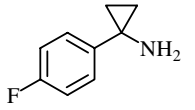
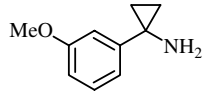
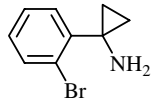
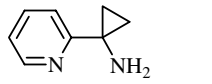
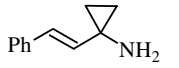
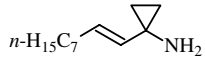
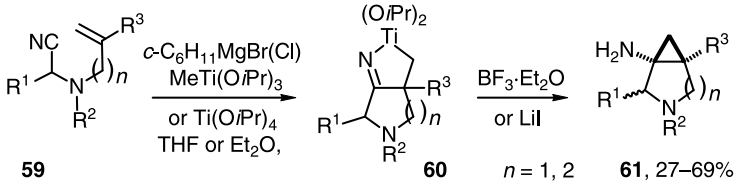
Entry	Grignard Reagent R^1	Starting Nitrile **50** R^2	Product	Yield[a] (%) [d. r.[b]]	Ref.
1	H	Bn		70	[92a]
2	H	n-C_9H_{19}		70	[92a]
3	H	Cyclohexyl		52	[92a]
4	Et	Bn		57 [64:36]	[92a]
5	H	$BnO(CH_2)_2$		54 (5)	[92a,93]
6	$Ph(CH_2)_2$	Bn		51 [68:34]	[92a]
7	H	$BnOCH_2$		75 (74)	[93]
8	H	$PhOCH_2$		80 (49)	[93]
9	Et	$BnOCH_2$		61 [70:30]	[93]
10	c-C_5H_9MgBr	$BnOCH_2$		45 [86:14]	[93]
11	H	n-$C_6H_{13}SCH_2$		54 (20)	[93]
12	H	$BnEtNCH_2$		64	[93]
13	H	$EtO_2CC(Me_2)$		35	[95]
14	H			51	[95]
15	H	$Et_2NC(O)(CH_2)_3$		46	[95]
16	H	$EtO_2C(CH_2)_2$		(68)	[95]

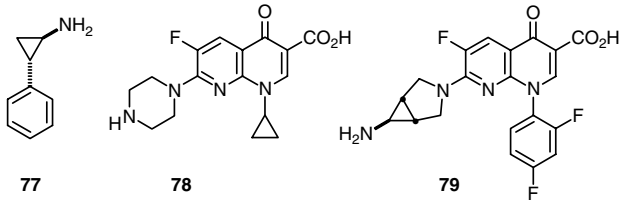
Table 6 (*continued*)

Entry	Grignard Reagent R^1	Starting Nitrile **50** R^2	Product	Yield[a] (%) [d. r.[b]]	Ref.
17	H	EtO_2C-O-CH(Et)		(72)	[95]
18	H	*p*-Me-C_6H_4		73	[94]
19	H	*p*-F-C_6H_4		64	[94]
20	H	*m*-MeO-C_6H_4		73	[94]
21	H	*o*-Br-C_6H_4		71	[94]
22	H	2-Py		57	[95]
23	H	(*E*)-PhCH=CH		65	[94]
24	H	(*E*)-*n*-C_7H_{15}CH=CH		50	[94]

[a] Yields in parentheses refer to the corresponding transformations without the use of $BF_3{\cdot}Et_2O$.
[b] d. r. = diastereomeric ratio.



Scheme 13. Intramolecular aminocyclopropanations of unsaturated nitriles [85,96]. For selected examples, see Table 7.

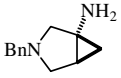
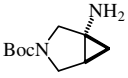
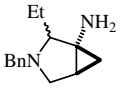
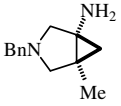
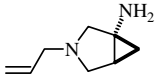
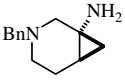
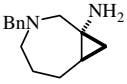


77 **78** **79**

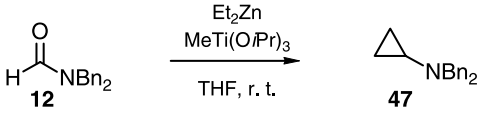
Using the aminocyclopropanation of styrene with dibenzylformamide, *N*,*N*-dibenzylprotected **77** can be prepared in one step, however, with low diastereoselectivity (Table 3, entry 1). The *trans*-stereoselectivity can be improved by applying the stereoselective and efficient aminocyclopropanation of tributylvinylstannane with dibenzylformamide (**12**) (see Table 3, entries 24 and 25) followed by Stille cross-coupling reactions of stannylcyclopropylamines **80** with aryl iodides yielding the pure *trans*-2-aryl-(*N*,*N*-dialkylaminocyclopropanes) (**81**) in yields ranging from 45% to 67% (Scheme 18) [73b].

Among the pharmacologically significant cyclopropylamines, one of the important targets was 3-azabicyclo-

Table 7
Bicyclic primary cyclopropylamines **61** from unsaturated nitriles **59**, Grignard reagents and $Ti(OiPr)_4$ by intramolecular aminocyclopropanations in the presence of $BF_3 \cdot Et_2O$ (selected examples, see Scheme 13)

Entry	Starting Nitrile **59**				Product **61**	Yield[a] (%) [d. r.[b]]	Ref.
	n	R^1	R^2	R^3			
1	1	H	Bn	H		48 69 (66)	[85] [96]
2	1	H	Boc	H		41	[85]
3	1	Et	Bn	H		67 (59) [2.6:1]	[96]
4	1	H	Bn	Me		69 (62)	[96]
5	1	H	Allyl	H		67 (58)	[96]
6	2	H	Bn	H		60 (11)	[96]
7	3	H	Bn	H		27	[96]

[a] Yields in parentheses refer to the corresponding transformation without the use of $BF_3 \cdot Et_2O$.
[b] d. r. = diastereomeric ratio.



Base Additive (equiv.)	Et_2Zn (equiv.)	Yield (%)
None	2	21
NaO*i*Pr (1)	2	52
NaOEt (2)	2	82
NaO*i*Pr (2)	2	89
NaO*i*Pr (2)	1	82
NaO*i*Pr (2)	0.5	43

Scheme 14. Reactions of diethylzinc with dibenzylformamide **12** in the presence of methyltitanium triisopropoxide and an added alkoxide base [90a,98].

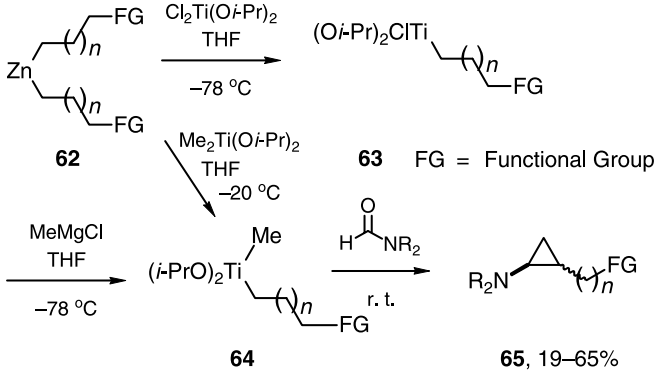
[3.1.0]hexylamine **85**-H, a key component in the once commercial antibiotic trovafloxacin **79**. Quite fortunately, *N*-protected 2,5-dihydropyrroles (pyrrolines) **82** turned out to rapidly undergo ligand exchange especially with the titanacyclopropane generated from cyclohexylmagnesium halides and $XTi(OiPr)_3$ (X = O*i*Pr, Me), and the resulting intermediates efficiently reacted with *N*,*N*-disubstituted formamides **83** to give the tris-protected *exo*-6-amino-3-azabicyclo[3.1.0]hexanes **84a** in up to 90% yield (Scheme 19) [62b,73a]. While the unprotected bicyclic diamine **85**-H can be prepared by hydrogenolytic debenzylation of **84a** under appropriate conditions, the mono- and bis-protected versions **85**-Boc and **85**-Bn_2, respectively, can be obtained at wish from the orthogonally tris-protected **84b**. This is particularly noteworthy, as it makes this bicyclic diamine skeleton of **85** with an interesting nitrogen–nitrogen distance of 4.28 Å [62b] a versatile scaffold for various combinations of pharmacophoric groups as in compounds of type **88** (Scheme 19).

The same holds true for the structurally related 1-amino-3-azabicyclo[3.1.0]hexane (**87**-H) which is accessible by intramolecular aminocyclopropanation of the corresponding amides or nitriles (see above, Schemes 10, 13 and Table 5, entries 9–14, and Table 7, entries 1 and 2), and subsequent catalytic hydrogenation [85]. This scaffold features a nitrogen–nitrogen distance of 3.68 Å [85]; especially the mono-protected version of this bicyclic diamine **87**-Boc would be a suitable precursor to a library of compounds of type **89** with one or two pharmacophoric groups attached (Scheme 19).

Applying only a few simple operations, the dibenzylaminocyclopropanes **90**-R, prepared as described above from *N*,*N*-dibenzyl-α-benzyloxyacetamide in 33–48% yield (see Scheme 5 and Table 2), have been transformed into *N*-Boc-protected methyl esters of some interesting amino acids **95**-R containing a cyclopropane moiety (Scheme 20) [66,67]. Several such analogues of natural amino acids, also referred to as methanoamino acids, exhibit important biological activities [102c,102d].

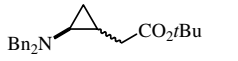
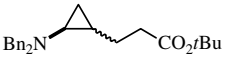
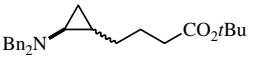
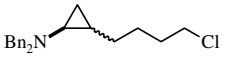
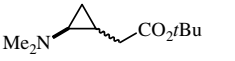
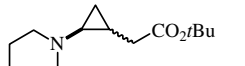
This approach has been used for the synthesis of the main building block **101** [66,107] for the preparation of methano-β-amino acid analogue **102** [66] of the parent dipeptide antiinfectant TAN-1047 [108] (Scheme 21). A similar strategy has recently been developed by Szymoniak and co-worker [93]. Starting from benzyloxyacetonitrile (**103**), they prepared Boc-protected 1-aminocyclopropanecarboxylic (ACC, **107a**), coronamic (**107b**) and *allo*-coronamic (**107c**) acids in 80%, 74% and 75% overall yield, respectively (Scheme 22; for the preparation of starting materials, see Table 6, entries 7 and 9).

Two potentially biologically active analogues of the important γ-aminobutyric acid, the *N*-Boc-protected methyl 3,4-methano-γ-aminobutyrate **110** and the 4-spirocyclopropane-γ-butyrolactam **114**, have been obtained in 55% and 44% overall yield, respectively (Scheme 23) [66,67]. The access to **114**,

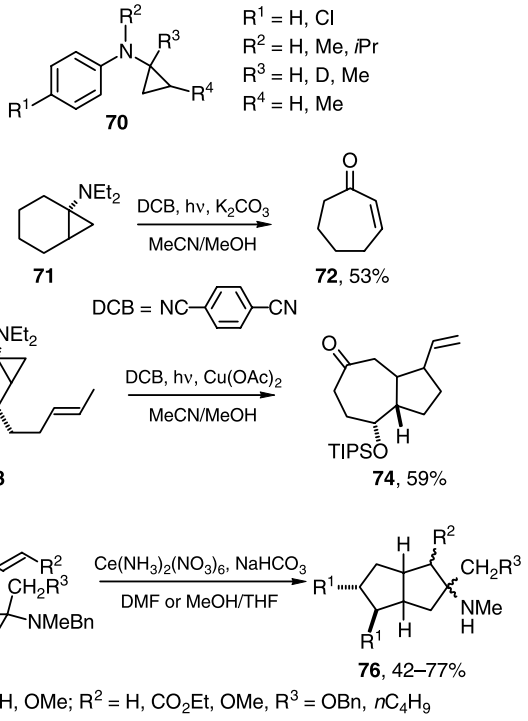


Scheme 15. Preparation of various functionally substituted aminocyclopropanes from diorganozinc reagents **62** and *N*,*N*-dialkylcarboxamides [90].

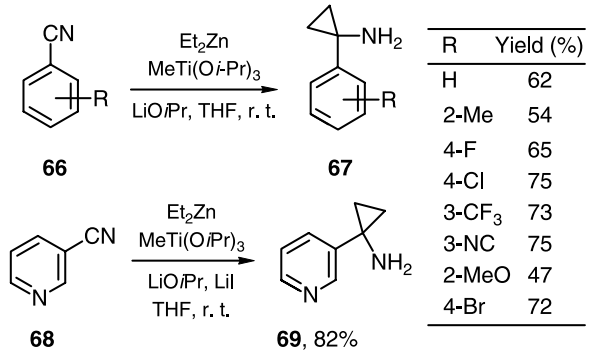
Table 8
Functionally substituted *N*,*N*-dibenzylcyclopropylamines **65** from *N*,*N*-dialkylformamides and organozinc precursors (see Scheme 15)

Product	Conditions[a]	Yield (%)	(*E*/*Z*) Ratio
	A	49	1.1:1
	B	60	1.8:1
	A	36	1.2:1
	B	40	1.2:1
	B	24	1.1:1
	A	19	1.1:1
	B	27	1.2:1
	A	61	1.2:1
	B	65	1.2:1
	A	57	1.1:1
	B	61	1.1:1
	B	60	2.0:1
	B	63	1.3:1
	B	60	1.8:1

[a] A: 1) $Zn(CH_2CH_2FG)_2$, $Cl_2Ti(Oi\text{-}Pr)_2$, THF, –30 °C, 1 h; 2) VMeMgCl (5 equiv.), THF, –30 to 20 °C, 8 h. B: 1) $Zn(CH_2CH_2FG)_2$, $Me_2Ti(Oi\text{-}Pr)_2$, MeMgCl (2 equiv.); 2) R2NCHO, THF,–30 to 20 °C, 8 h.



Scheme 17. Three examples of oxidatively initiated rearrangements of aminocyclopropanes [76,79,82].



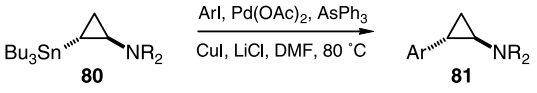
R	Yield (%)
H	62
2-Me	54
4-F	65
4-Cl	75
3-CF_3	73
3-NC	75
2-MeO	47
4-Br	72

Scheme 16. Synthesis of 1-arylcyclopropylamines from aromatic nitriles by reaction with diethylzinc in the presence of $MeTi(OiPr)_3$ and NaO*i*Pr [90a,98].

however, has recently been further improved by a one-step preparation with 68% yield (see Table 6, entry 16) [95].

Using the aminocyclopropanation of *N*-Boc-protected *tert*-butyl (2*S*)-3,4-dehydroprolinate **116** with dibenzylformamide (**12**), the 3-azabicyclo[3.1.0]hexylamine derivative **117** was obtained in 50% yield [107] (Scheme 23). This compound possesses an additional functionality as compared to its analogues **85** and **87** (see Scheme 19) and, therefore, should be an even more versatile scaffold for various combinations of pharmacophoric groups.

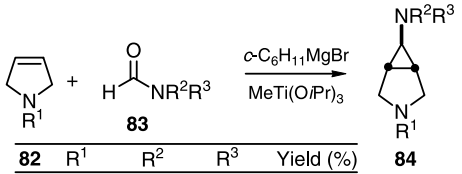
A variety of 2-ethenyl-substituted cyclopropylamines **118** upon flash vacuum pyrolysis or under silver



80 **81**

R	Bn	Bn	Me	Bn	Bn
Ar	Ph	4-MeC_6H_4	4-MeC_6H_4	4-$MeO_2CC_6H_4$	4-$MeOC_6H_4$
Yield (%)	67	65	63	45	49

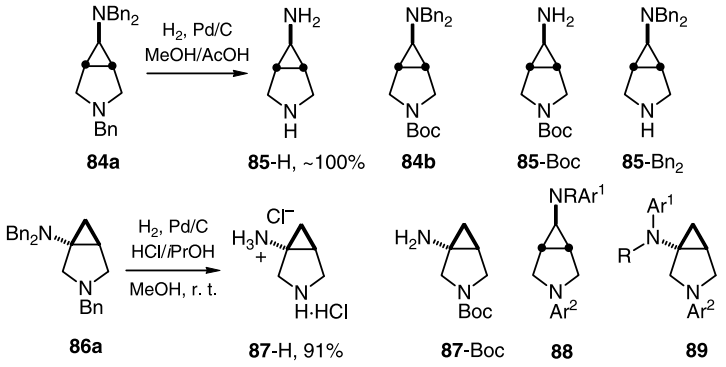
Scheme 18. Palladium-catalyzed cross coupling of 2-(trialkylstannyl)-*N*,*N*-dialkylcyclopropylamines (**80**) with various aryl iodides [73b].



83 **84**

82	R^1	R^2	R^3	Yield (%)
a	Bn	Bn	Bn	87
b	Boc	Bn	Bn	90
c	PMB[a]	Bn	Bn	68
d	Bn	PMB	PMB	37
e	Bn	Bn	PMB	67

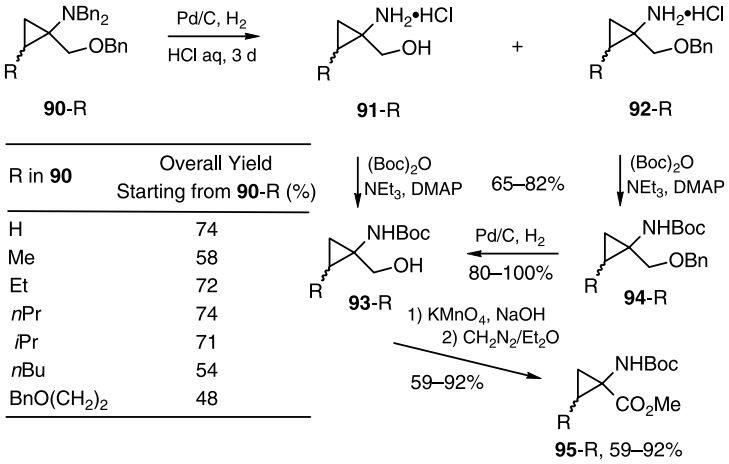
[a] PMB = *p*-methoxybenzyl



84a **85**-H, ~100% **84b** **85**-Boc **85**-Bn_2

86a **87**-H, 91% **87**-Boc **88** **89**

Scheme 19. Aminocyclopropanation of *N*-protected 2,5-dihydropyrroles **82** and debenzylation of the *exo*-6-amino-3-azabicyclo[3.1.0]hexanes **84** as well as the structurally related 1-dibenzylaminoazabicyclo[3.1.0]hexane **86** [62b,85].



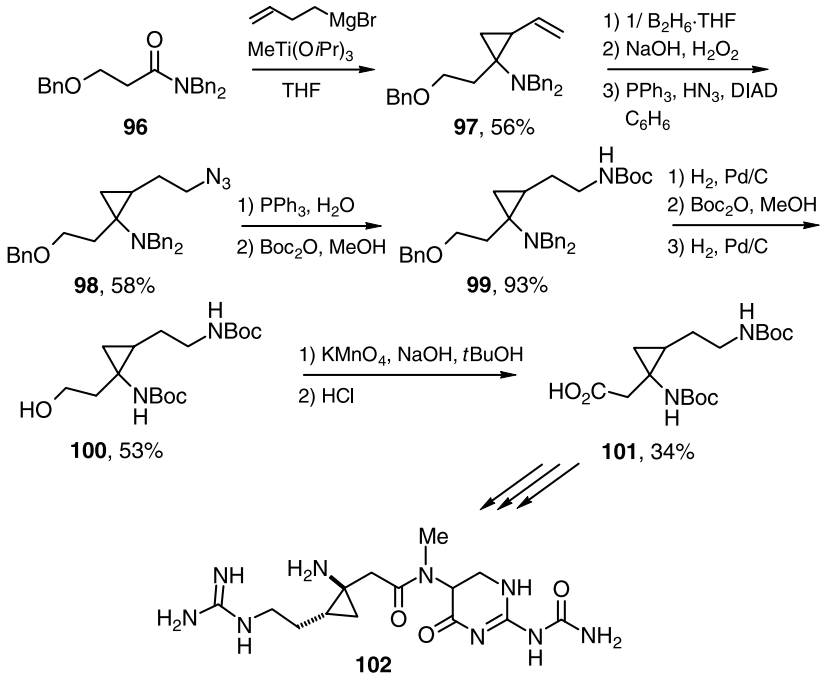
90-R **91**-R **92**-R

R in **90**	Overall Yield Starting from **90**-R (%)
H	74
Me	58
Et	72
*n*Pr	74
*i*Pr	71
*n*Bu	54
$BnO(CH_2)_2$	48

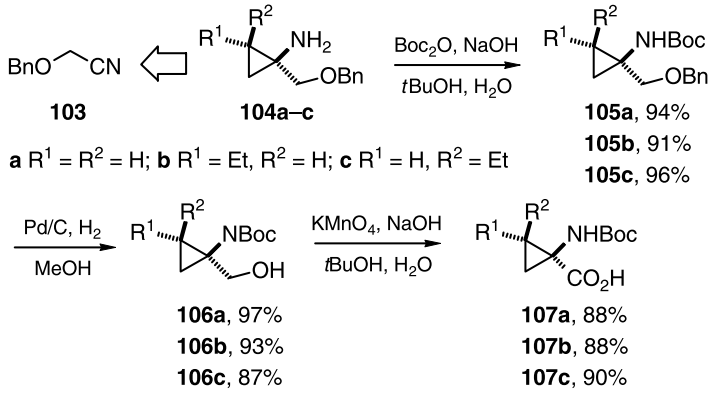
93-R **94**-R

95-R, 59–92%

Scheme 20. Preparation of various protected substituted 1-aminocyclopropanecarboxylic acid (ACC) derivatives **95**-R from *N*,*N*-dibenzylamino(benzyloxymethyl)cyclopropanes **90**-R [66,67].



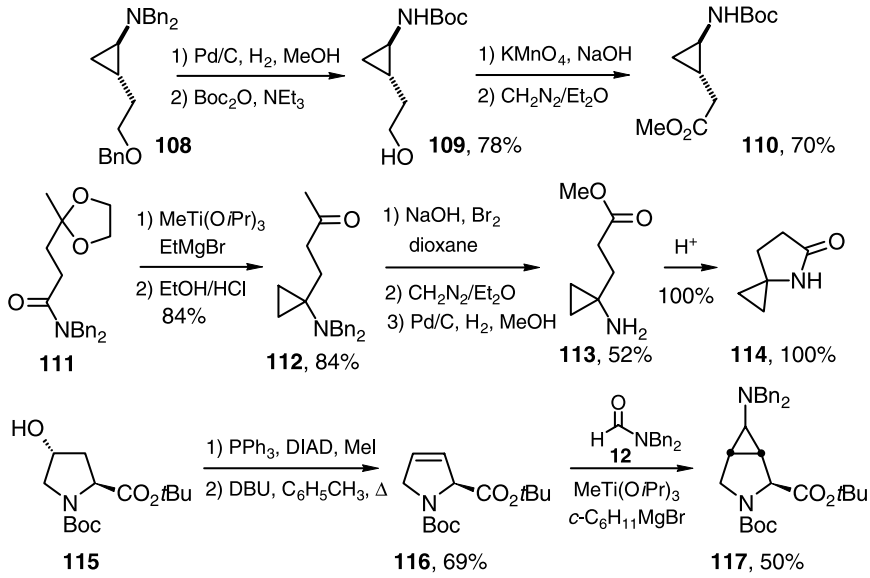
Scheme 21. Synthesis of the methano-β-aminoacid analogue **102** of the natural dipeptide antiinfectant TAN-1047.



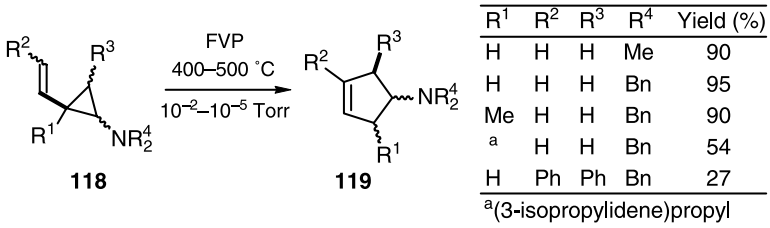
Scheme 22. Preparation of various *N*-protected substituted 1-aminocyclopropanecarboxylic acid (ACC) derivatives **107** from benzyloxyacetonitrile (**103**) [93].

nitrate catalysis cleanly undergo a vinylcyclopropane to cyclopentene rearrangement [109] and afford high yields (up to 95%) of 4-aminocyclopent-1-enes **119**, some of which have unprecedented substitution patterns (Scheme 24) [62a].

Analogously, the $(n + 3)$-(dimethylamino)-1-ethenylbicyclo[n.1.0]alkanes **36b–d** (see Scheme 9) under similar conditions undergo ring enlargement to $(n + 1)$-dimethylamino-bicyclo[n.3.0]alkenes **120b–d** (Scheme 25) [81]. As was demonstrated for **120c**, **d** ($n = 4$, 5), this thermal rearrangement can more cleanly be brought about by heating of the starting materials **36c**, **d** in decalin at 220 °C for 1 h (90% and 84% yield, respectively). The overall sequence starting from a cycloalkanone via a 1-ethenylcycloalkene to yield bicyclo[n.3.0]alkenes **120** constitutes a new cyclopentene-annealation methodology. Through quaternization with methyl iodide followed by Hofmann elimination, compounds **120** could be transformed into mixtures of fused cyclopentadienes **122**, **123** in 64–78% overall yield (Scheme 25) [81,110].



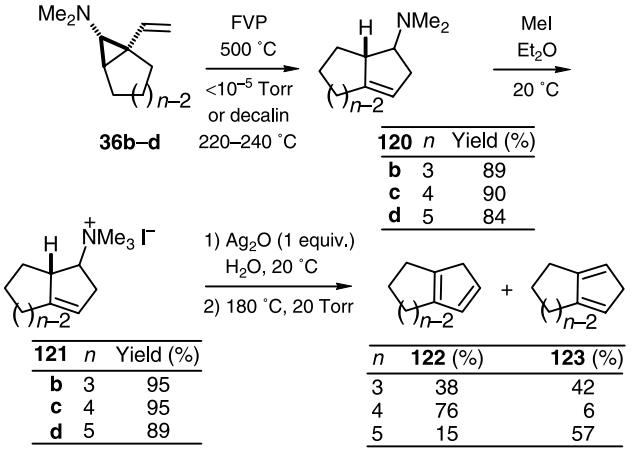
Scheme 23. Preparation of methyl 3,4-methano-γ-aminobutyrate acid **110**, 4-spirocyclopropane-γ-butyrolactam **114** and the protected bicyclic diaminoacid **117** [66,67,107].



R^1	R^2	R^3	R^4	Yield (%)
H	H	H	Me	90
H	H	H	Bn	95
Me	H	H	Bn	90
[a]	H	H	Bn	54
H	Ph	Ph	Bn	27

[a](3-isopropylidene)propyl

Scheme 24. Vinylcyclopropane to cyclopentene rearrangement of 2-alkenyl-substituted cyclopropylamines **118** [62a].



Scheme 25. Vinylcyclopropane to cyclopentene rearrangement in $(n+3)$-(dimethylamino)-1-ethenylbicyclo[n.1.0]alkanes **36** [81].

8. Conclusion

Dicarbanionic dialkoxytitanium organometallics in situ generated from organomagnesium (Grignard) and organozinc reagents in the presence of $Ti(OiPr)_4$ and $MeTi(OiPr)_3$ have established their versatility for the facile preparation of a wide range of aminocyclopropane derivatives from *N*,*N*-dialkylcarboxamides and nitriles. In many cases, these titanium-mediated reactions of nontransition organometallics proceed in good yields and with high chemo- and stereoselectivity. These circumstances in conjunction with the simplicity of the experimental handling and inexpensiveness of the reagents favor these reactions for an ever increasing range of applications in organic synthesis.

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