1,*n*-Dicarbanionic Titanium Intermediates from Monocarbanionic Organometallics and Their Application in Organic Synthesis

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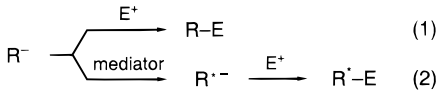
I. Introduction

Among the wide variety of organometallic compounds, the relatively cheap and safely handled nontransition-metal derivatives, in particular organolithium, organomagnesium, organozinc, and organoaluminum reagents, are definitely the most widely used ones in organic synthesis.[1] The electron density of a metal−carbon bond in any organometallic compound is shifted to the more electronegative carbon atom, and the majority of synthetically useful transformations of these reagents, including carbon−carbon bond forming reactions, in a formal sense correspond to a recombination of the corresponding monocarbanionic equivalent[2] R^- of an organometallic reagent $R^{\delta-}M^{\delta+}$ with an electrophilic substrate (Scheme 1, eq 1). These reactions may sometimes dramatically change their rates or even modes when conducted in the presence of a transition-metal compound.[3−10] Thus, their use sometimes allows one not only to modify the reactivity of nontransition organometallics, but also to perform new kinds of transformations due to a structural reorganization of the carbanionic moiety. These transformations may be formally expressed by eq 2 in Scheme 1, where R^- and R^{*-} are structurally different carbanionic equivalents of the same starting organometallic reagent $R^{\delta-}M^{\delta+}$.

Scheme 1



A continuously increasing interest in the reactions of nontransition organometallics with group(IV) transition-metal derivatives has persisted ever since the discovery[11] that the dark solid product from the reaction between aluminum alkyls and titanium halides is an active catalyst for the polymerization of ethylene at low pressure. Most of the proposed mechanisms for the action of these catalysts infer formation of unstable organotitanium intermediates which initiate any further transformations of the reactants.[12−16] Some reactions of nontransition organometallics catalyzed by zirconium compounds, which are important for organic synthesis, have also been found in the past decade and have been reviewed extensively.[10,17] The properties of organotitanium compounds and their applications in organic synthesis have been reviewed in great detail by Reetz.[18,19] Among group(IV) metal derivatives, titanium catalysts or mediators, 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 convenient to handle. In the form of the Sharpless-epoxidation[20−25] and the McMurry-coupling reagents,[26−31] titanium derivatives have found numerous synthetic applications, and all these have been reviewed. However, there are no reviews specifically addressing those reactions of nontransition organometallics which are catalyzed or mediated by titanium compounds and depend on formal transformation of the starting organometallic monocarbanionic equivalents into dicarbanionic species. The simplest conversions of this type are the formal disproportion of methyl anion into

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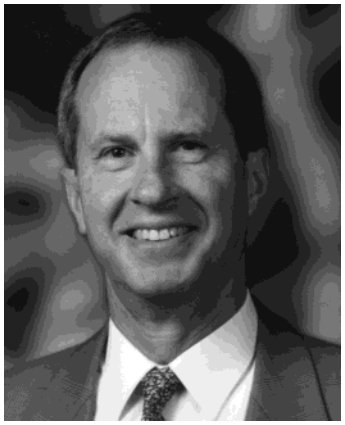
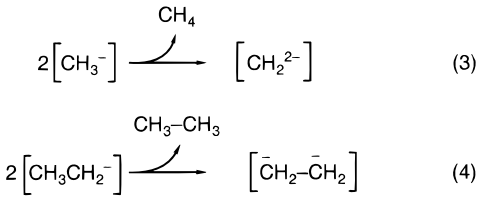
Oleg G. Kulinkovich was born in Estonia in 1948. He graduated from the Belorussian State University (BSU) in Minsk in 1971 with an honors diploma. After obtaining his Doctoral degree in Organic Chemistry in 1975 under the direction of Professor I. G. Tishchenko, he performed his research permanently at the BSU. He received his Doctor of Science (D.Sc.) degree in 1987 for his work on the chemistry of halogenated cyclopropyl ketones. Since 1991 he has been Head of the Department of Organic and Polymer Chemistry at the BSU. His research interests center on organic synthesis, including the development of new catalytic and noncatalytic synthetic methods based on transformations of strained molecules, and the elaboration of simple ways for the preparation of compounds which may be used for maintaining the environmental equilibrium.



Armin de Meijere, born 1939 in Homberg (Niederrhein), Germany, studied chemistry at the universities of Freiburg and Göttingen and obtained his doctorate (Dr. rer. nat.) at the University of Göttingen under the guidance of Wolfgang Lüttke. Following postdoctoral training under Kenneth B. Wiberg at Yale University in New Haven, CT, he fulfilled the requirements for his "Habilitation" in 1971 at the University of Göttingen. He became Full Professor of Organic Chemistry at the University of Hamburg in 1977, and returned to the University of Göttingen to succeed his former mentor in the chair of Organic Chemistry in October 1989. He has been Visiting Professor at the University of Wisconsin in Madison, WI, the IBM Research Laboratory in San José, CA, the Technion in Haifa, Israel, Princeton University in Princeton, NJ, the Université de Aix-Marseille III, France, the Università degli Studi, Firenze, Italy, the Ecole Normale Supérieur, Paris, France, the University of Colorado, Boulder, CO, and the University of Florida, Gainesville, FL. He received a fellowship from the Studienstiftung des Deutschen Volkes, obtained the award "Dozentenstipendium" from the Fonds der Chemischen Industrie in 1972, and was elected a member of the Norwegian Academy of Sciences and Letters in 1992, and in 1996 he received the Alexander-von-Humboldt-Gay-Lussac Prize of the French Ministry for Higher Education and Research. In 1997 he was elected as a member of the Braunschweigische Wissenschaftliche Gesellschaft, as an Honorary Professor of the St. Petersburg State University in St. Petersburg, Russia, and nominated as a Fellow of the Japan Society for the Promotion of Science. He is Editor or member of the Editorial Board of a number of scientific journals, including *Chemical Reviews*, periodicals, and books. His scientific achievements have been published in over 430 original publications, review articles, and chapters in books. His current research interests include the development of new cascade reactions for the efficient construction of complex skeletons and new small-ring building blocks to be applied in the synthesis of natural and nonnatural compounds, new highly strained polycyclic compounds with interesting properties, as well as the development of new synthetic methodology based on metal-mediated and -catalyzed transformations of organic compounds.

methylene dianion and methane (Scheme 2, eq 3) and of ethyl anion into ethylene 1,2-dianion and ethane (Scheme 2, eq 4).

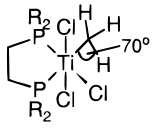
Scheme 2



Certain titanium compounds do indeed bring about such transformations of monocarbanionic nontransition organometallics, and they can also mediate the formal conversion of dicarbanionic organometallics into 1,3- as well as 1,4-dicarbanionic equivalents. This article therefore compiles the contributions to this branch of chemistry mainly made in the last 10−20 years, several of which have led to synthetically extremely useful transformations of organic compounds that could not even be thought of in classical organic chemistry, yet are on their way to being routinely applied in organic synthesis. The increasing importance of these organometallic dicarbanion equivalents is enhanced by successful application in the syntheses of natural products, leading examples of which will also be discussed in this review.

II. 1,1-Dicarbanionic Equivalents

Crystalline PhTi(O*i*-Pr)$_3$ was the first isolated and fully characterized organotitanium compound.[32,33] Methyl- and other monoalkyltitanium derivatives are also reasonably stable, but di-, tri-, and tetraalkylated derivatives all appear to be considerably less stable. Quantitative data were obtained for the thermal decompositions of methyl-,[34−40] benzyl-,[41−43] and neopentyltitanium(IV) derivatives[41,44−46] to evidence that free radicals are not formed in these decomposition reactions, at least not in noncoordinating solvents. The relatively lower stability of the organotitanium compounds[47] is definitely not connected with a particular weakness of the carbon−titanium σ-bonds (in fact, these bond energies usually exceed 60 kcal mol^{-1})[48] but rather with the readiness of titanium to provide its low-lying empty d-orbitals for so-called agostic interactions[49] with neighboring σ-bonds.[18,50−53] In the trichloro(methyl)titanium ethylenediphosphine chelate **1**, R = Me, the methyl



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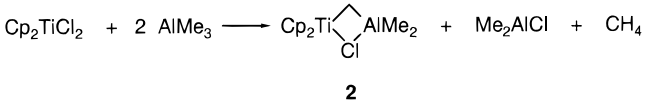
group displays a pronounced distortion with a Ti−C−H angle of 70(2)°,[49,54] and this phenomenon has been explained with an agostic interaction between the titanium atom and the C_α−H bond.[49]

It is accepted knowledge that decomposition of organotitanium compounds that do not contain any hydrogen atom in the β-position of the organyl group is initiated by an intramolecular α-hydrogen abstraction from the alkyl group to afford the corresponding alkylidenetitanium species.[37,55−57] In alkylated titanocene derivatives, a hydrogen abstraction from the cyclopentadienyl moiety can also take place.[37,43] The agostic interaction between titanium and the C_α−H bond may assist the α-elimination reaction, which possibly proceeds as a 1,2-hydrogen shift to the metal atom to form a hydridotitanium species or in a concerted mode via a four-center transition state with direct elimination of an alkane molecule.[18,50,51] A certain analogy between α-agostic interactions and hyperconjugative stabilization of carbenium ions by β-hydrogen has been pointed out[12,50,51,58] and used to explain the kinetic isotope effects that have been observed in olefin insertion reactions involving d^0-metallocene complexes.[50]

A. Organoaluminum Precursors

Up to the end of the 1970s, the use of titanium-catalyzed transformations of nontransition organometallics in organic synthesis was limited mainly to chemo- and stereoselective reactions of carbonyl compounds[17r,18,19] as well as olefin metathesis reactions.[59] The first synthetically important reaction of an organotitanium compound, accompanied by a structural modification of an alkyl group in the organometallic reagent, was discovered by Tebbe et al.[60,61] They found that the methylene-bridged bismetallic compound **2** is able to transform carbonyl compounds into terminal alkenes similar to the Wittig[62] and other[63−65] carbonyl-olefinating reagents. Tebbe's reagent **2** is a crystalline product from the reaction of titanocene dichloride with 2 equiv of trimethylaluminum, to which the structure of a four-membered dimetallacycle has been assigned (Scheme 3).[60] The preparation of Tebbe's reagent is

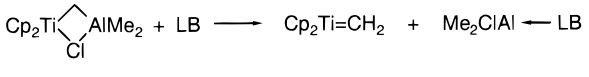
Scheme 3



accompanied by formation of an equivalent amount each of methane and dimethylaluminum chloride, and it can be purified by crystallization.[60] The same product is also formed by reaction of Cp_2TiMe_2 with Me_2AlCl.

The presence of the Lewis acid dimethylaluminum chloride formed in the initial step of the reaction dictates the abstraction of hydrogen from the methyl rather than the cyclopentadienyl groups in the initially formed methyltitanocene chloride and thus inhibits formation of dimethyltitanocene from Cp_2TiCl_2 and $AlMe_3$.[37,39,40,45,66] Under the action of a Lewis base (LB), compound **2** can be transformed into the transient methylenetitanocene **3** which most probably is the reactive intermediate that interacts with organic compounds (Scheme 4).[60]

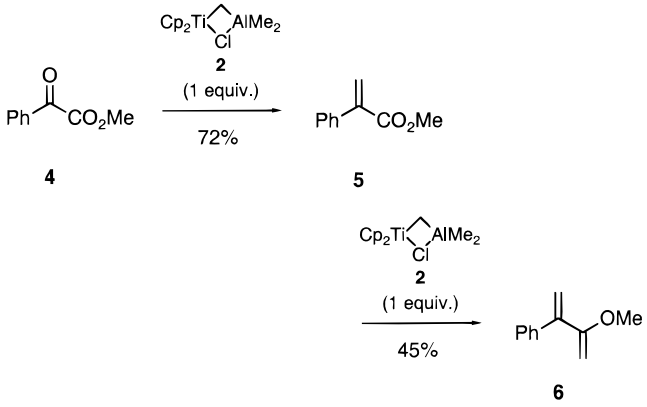
Scheme 4[a]



[a] LB = Lewis Base

The intermediate **3** has not been isolated as a pure compound;[67] however, its phosphine complexes are known and have been characterized spectroscopically.[68−73] In accordance with theoretical considerations, the methylenetitanocene **3** is a 16-electron species with an empty orbital on titanium lying in the plane bisecting the Cp−Ti−Cp bond angle. Any ligand with unpaired electrons, such as a carbonyl group, may coordinate.[74−76] The carbonyl olefinations with the Tebbe reagent **2** have been reviewed extensively.[7,77] The reaction of **2** with cyclohexanone, for example, in toluene solution proceeds at −15 °C to room temperature to produce methylenecyclohexane in 65% yield.[60] Since the Wittig methylenation can only be applied to aldehydes and ketones, it is a particular advantage of Tebbe's reagent **2** that it also smoothly reacts with carboxylic acid derivatives such as esters and lactones. Grubbs et al.[78] and Pine et al.[79] found that Tebbe's reagent **2** converts esters between −40 °C and room temperature to enol ethers in high yield. Reactions are rapid when a Lewis base such as THF or a tertiary amine capable of complexing the aluminum moiety and releasing the methylenetitanocene **3** is present in the reaction mixture. In the absence of such a Lewis base, the reaction of **2** with an ester proceeds considerably more slowly. Ketones usually react with Tebbe's reagent much faster than esters, and thus, selective methylenations of only one carbonyl group in a keto ester are possible. For example, methyl benzoylformate **4** was cleanly converted to methyl phenylacrylate **5** by treatment with 1 equiv of Tebbe's reagent **2** and to 2-methoxy-3-phenylbutadiene **6** with an additional equivalent of **2** (Scheme 5).[79]

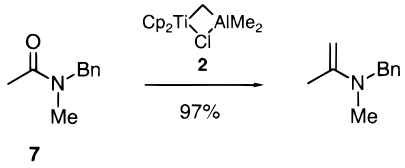
Scheme 5



Tebbe's reagent **2** is also effective to methylenate some other carboxylic acid derivatives;[78−80] for example, *N*,*N*-dialkylcarboxamides can be transformed to enamines. The latter reactions are rapid even

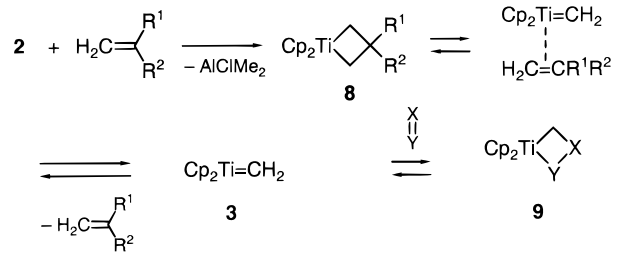
without an added Lewis base; they present a convenient alternative for the preparation of enamines derived from methyl ketones as exemplified by the almost quantitative conversion of the amide **7** to the corresponding enamine (Scheme 6).[79]

Scheme 6



One of the serious drawbacks of Tebbe's reagent **2** is the fact that a highly reactive organoaluminum compound, which may initiate side reactions of sensitive compounds, is released during the reaction. Grubbs et al. found that the titanium−aluminum complex **2** reacts with alkenes to form reasonably stable, crystalline titanacyclobutane derivatives **8**. The latter can serve as a source of an aluminum-free reagent of the type $Cp_2Ti{=}CH_2$ **(3)**[81−83]as well as to initiate the ring-opening metathesis polymerization of norbornene.[84] Labeling and kinetic studies have shown that the rate-limiting step in reactions of titanacyclobutanes **8** with unsaturated compounds X=Y is the opening of the four-membered ring with liberation of an alkene complex of the methylenetitanocene **3**, which rapidly traps any unsaturated compound X=Y with heteroatoms to form a new four-membered titanacycle **9** (Scheme 7).[69,81−83,85]

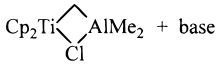
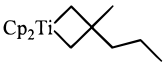
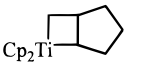
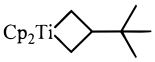
Scheme 7



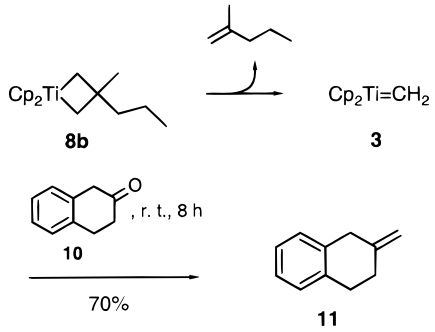
The stability of titanacyclobutanes **8** is considerably influenced by the substituents on the four-membered metallacycle[81] as well as on the cyclopentadienyl ligands.[82] Thus, the recommended temperatures for the generation of the methylenetitanium intermediate **3** from different titanacyclobutanes **8** vary considerably (Table 1).[81]

When the methylenetitanocene **3** is generated by thermal cleavage of a titanacyclobutane **8** in the presence of aldehydes, ketones, esters, or *N*,*N*-dialkylcarboxamides, the same products as with Tebbe's reagent **2** are obtained.[81] For preparative applications, the crystalline titanacyclobutane **8b**, which is readily prepared from **2** and 2-methylpentene, is most convenient, and the yields of the products are comparable to those obtained with Tebbe's reagent **2**. Thus, the choice of either **2** or **8b** as a source of the carbonyl-methylenating intermediate **3** is dictated by experimental convenience and the necessity for selectivity. In contrast to Wittig reagents, which react with enolizable ketones predominantly by proton abstraction, the reactive methylenetitanocene **3** produces good yields of the corresponding methylenation products.[86] Thus, even the easily enolizable *β*-tetralone **10** could be converted to 2-methylenetetraline **11** by the titanacyclobutane **8b** in 70% yield (Scheme 8).[86]

Table 1. Recommended Temperatures for the Generation of $Cp_2Ti{=}CH_2$ (3) from Various Titanacycles[81]

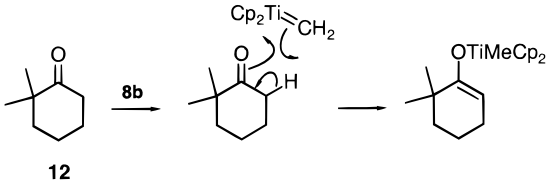
Titanacycle	Temperature [°C]
	−40
 **8a**	5
 **8b**	0
 **8c**	45
 **8d**	60

Scheme 8



With most α,α-disubstituted ketones such as 2,2-dimethylcyclohexanone (**12**), however, the titanacyclobutane **8b** does react with proton abstraction to form titanium enolates instead of terminal alkenes (Scheme 9). Obviously the preferred enolization is due to the steric overcrowding that blocks the methylene transfer from **3** via an oxametallacycle.[86]

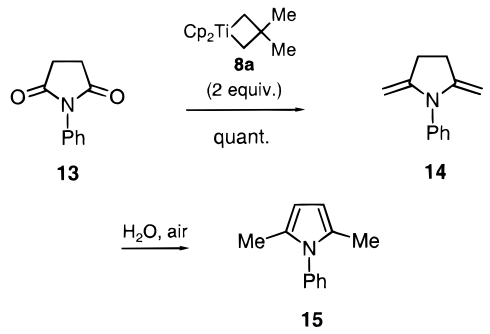
Scheme 9



The reactions of titanacyclobutanes **8** with five- and six-membered cyclic imides may proceed by two pathways: while 2,6-piperidinediones are predominantly enolized, 2,5-pyrrolidinediones undergo methylenation exclusively.[80] Thus, for example, the treatment of 1-phenyl-2,5-pyrrolidinedione (**13**) with 2 equiv of **8a** leads to a quantitative formation of the bismethylenated product **14** which rapidly isomerizes upon contact with moisture in the air to the 2,5-dimethylpyrrole **15** (Scheme 10).[80] These differences

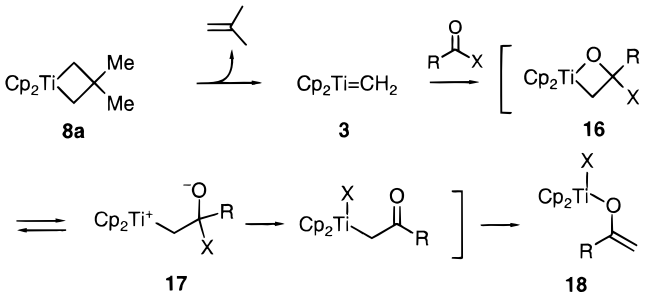
in the reactivity of five- and six-membered heterocycles have been attributed to the distinctions in spatial orientation of the protons α to the carbonyl group which are prone to be abstracted.

Scheme 10



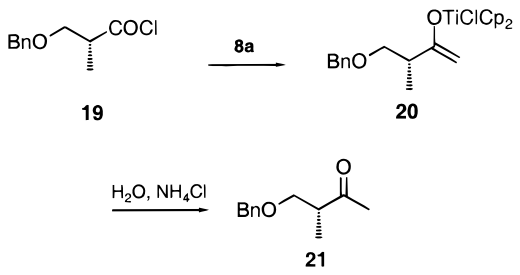
The methylenetitanocene complex **3** generated from the dimethyltitanacyclobutane **8a** reacts with acid chlorides[81,87,88] and anhydrides[81] to yield the corresponding methyltitanocene ketone enolates **18**. It has been suggested that this transformation also proceeds through an oxatitanacyclobutane **16**[87] or ring-opened 1,4-zwitterionic form **17**[88] in which an alkanoate or chloride anion is transferred to the titanium atom to produce the titanium enolate **18** (Scheme 11).

Scheme 11



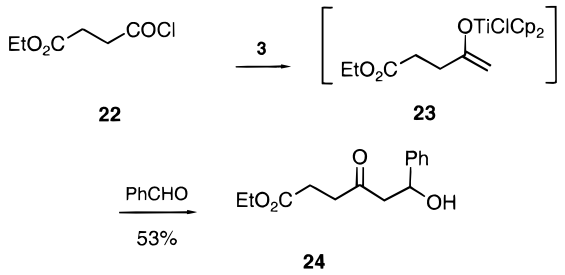
It is particularly important that these transformations produce the terminal enolates in high yield and without isomerization into the thermodynamically more stable enolates. Thus, the optically active acid chloride **19** with an α-stereogenic center under action of dimethyltitanacyclobutane **8a** is converted to the methyl ketone **21** via titanium enolate **20** without racemization (Scheme 12).[87]

Scheme 12



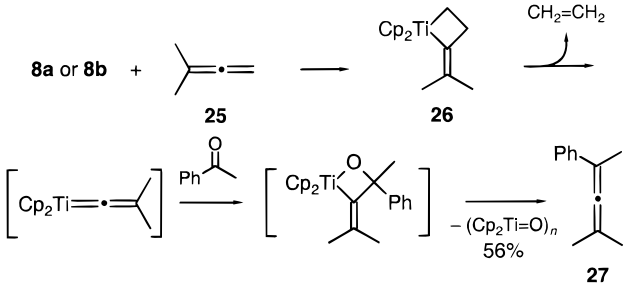
Titanium enolates of methyl ketones prepared by this way show the typical enolate behavior, such as undergoing aldol reactions[87] or alkylations.[80] This demonstrates the possibility to use the methylenetitanocene complex **3** as a synthetic equivalent of a methylene dicarbanion in consecutive reactions with two different electrophiles (see also refs 89−92). Since an acid chloride is more reactive toward **3** than an ester, the succinic acid monoester monochloride **22** is converted into aldol **24** via methyl ketone enolate **23** with high chemoselectivity (Scheme 13).[87]

Scheme 13



Titanacyclobutane reagents of type **8** can only be used to accomplish methylenation of carbonyl compounds. Attempts to prepare higher homologues of alkenes with homologous 2-alkyltitanacyclobutanes have been unsuccessful. This has been attributed to decomposition of the corresponding organotitanium intermediates by *β*-hydride elimination.[61,93] However, alkenylidenetitanium complexes can be successfully prepared via the corresponding alkenyltitanium[94] or alkylidenetitanacyclobutane intermediates.[95] Thus, isopropylidenetitanacyclobutane **26** was formed upon reaction of either titanacyclobutane **8a** or **8b** with 1 equiv of 1,1-dimethylallene (**25**) in quantitative yield, and **26** gave the tetrasubstituted allene **27** by treatment with acetophenone (Scheme 14).[96]

Scheme 14



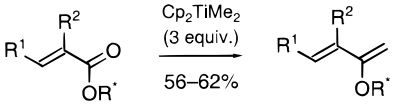
When alkylidenetitanacyclobutanes were used as a source of the corresponding alkenylidenetitanocenes as olefinating agents, the corresponding allenes were usually formed in good yields. In contrast, the use of Tebbe's reagent to olefinate the respective carbonyl compounds generally led to less clean reactions and lower yields.[96,97]

B. Organolithium and Organomagnesium Precursors

An alternative and more practical method for the titanium-mediated olefination of carbonyl compounds that avoids difficulties associated with the handling of organoaluminum compounds has more recently been developed by Petasis et al.[98−101] This method

makes use of Cp_2TiMe_2 which can readily be prepared from Cp_2TiCl_2 and methyllithium.[102,103] Clean conversions of carbonyl compounds or esters to the corresponding alkenes or enol ethers by treatment with Cp_2TiMe_2 and heating in toluene solution are usually observed.[17t,98−101,103−108] Even α,β-unsaturated esters **28** with a chiral alcohol moiety could be transformed to the chirally modified 2-alkoxydiene **29** with Cp_2TiMe_2 in toluene (Scheme 15).[109]

Scheme 15



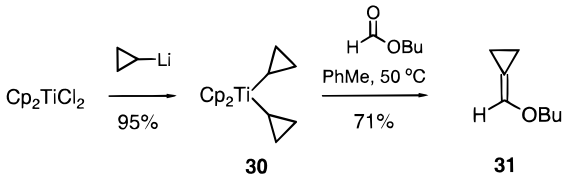
28 **29**

29	R^1	R^2	R*	%
(−)-**29a**	Ph	H	Menth	60
(±)-**29b**	Ph	H	PC	56
(−)-**29c**	Ph	H	PC	56
(±)-**29d**	H	Me	PC	62

PC = *trans*-2-phenylcyclohexyl

Other carboxylic acid derivatives including silyl esters, thioesters, selenoesters, anhydrides, carbonates, and imides also react with Cp_2TiMe_2 to give the corresponding heterosubstituted alkenes in moderate to good yields.[110] It is noteworthy that Cp_2TiMe_2 survived prolonged heating in the presence of carbonyl substrates,[111] in contrast to dimethyltitanocene which is easily fragmented thermally to yield methane and methylenetitanocene (**3**). The authors proposed that this may be due to complexation of Cp_2TiMe_2 with the carbonyl compound, which eventually will undergo migratory insertion and reductive elimination to yield the alkene products. Under similar conditions, heating of dibenzyltitanocene with ketones, esters, lactones, and amides afforded the corresponding phenyl-substituted alkenes.[112] Analogous olefination may also successfully be performed with various substituted dibenzyltitanocenes in which electron-withdrawing groups enhance the efficiency of olefinations. Since 1,2-diphenylethane and its substituted derivatives are formed as byproducts, homolytic cleavage of the dibenzyltitanocenes has been considered but only as a competing pathway not precluding an alternative mechanism for the olefinations as suggested for the methylenation with Cp_2TiMe_2.[112] Bis(trimethylsilylmethyl)titanocene has also successfully been applied to prepare alkenylsilanes.[113] The conversion of carbonyl compounds to alkenylsilanes can be performed under milder conditions when using the titanacyclobutene formed from $Cp_2Ti{=}CHSiMe_3$ and bis(trimethylsilyl)acetylene as an olefinating agent.[114] Dicyclopropyltitanocene (**30**) can also easily be prepared from Cp_2TiCl_2 and cyclopropyllithium, and it also cleanly reacts with carbonyl compounds to give methylenecyclopropane derivatives in high yields. Apparently, β-hydride elimination to yield a highly strained cyclopropene complex is retarded.[110,114] For example, butyl formate reacts with dicyclopropyltitanocene (**30**) to afford the cyclopropylidenemethyl butyl ether **31** in 71% yield (Scheme 16).[115]

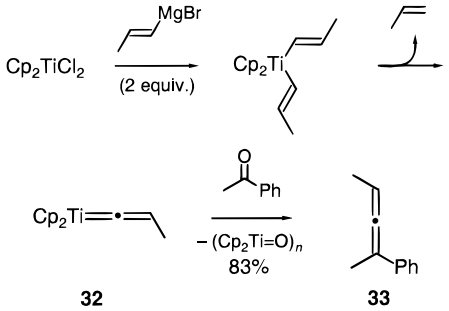
Scheme 16



30 **31**

Alkenylidenetitanocene intermediates formed in situ from bis(alkenyl)titanocene precursors are efficient allenating agents for ketones (Scheme 17).[116]

Scheme 17

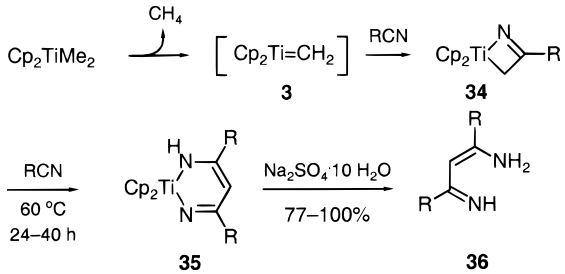


32 **33**

Upon heating, e.g., bis(1-propenyl)titanocene with acetophenone, the trisubstituted allene **33** is obtained via the in situ formed propenylidenetitanocene intermediate **32**.

An additional example to demonstrate the possibility of consecutively forming two carbon−carbon bonds between a methylene dicarbanion equivalent and two carbon electrophiles is the reaction of Cp_2TiMe_2 with nitriles which gives very good yields of 4-amino-1-azadienes **36**.[117] This reaction probably proceeds via intermediary formed titanaheterocycles **34** and **35** (Scheme 18).[91,110,117,118]

Scheme 18



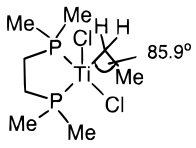
3 **34** **35** **36**

36	R	%
a	Ph	~100
b	C_6H_4-4-Me	77
c	2-Furyl	88
d	*i*Pr	~100
e	*t*Bu	~100
f	$MeOCH_2$	~100

III. Generation of 1,2-Dicarbanionic Equivalents

The α-hydride elimination reactions in dialkyltitanocene derivatives considered in the previous section, which lead to the generation of 1,1-dicarbanionic equivalents, usually occur only in cases in which no hydrogen atoms are present in the β-position of the alkyl substituents. For alkyl derivatives of transition

metals having β-hydrogen atoms, β-hydride elimination reactions are more characteristic.[18,119−124] Nevertheless, ethyltitanium derivatives and their homologues can be prepared in solution by monoalkylation of titanium(IV) halides and can be stabilized with bidentate ligands such as bipyridyl[18] and others. The X-ray crystal structure of the diphosphine adduct **37**

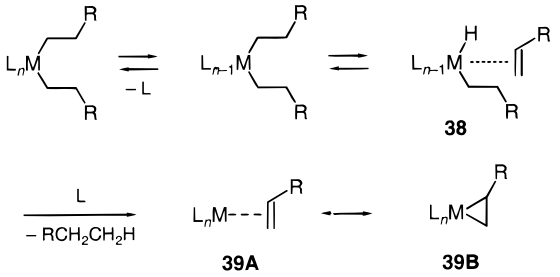


37

of ethyltitanium(IV) chloride indicates quite clearly that the methyl group is being drawn toward the titanium center and the Ti−C−C angle is only 85.9(6)°.[125] One of the hydrogens in the methyl group points toward titanium, and the distance between these atoms (Ti−H 2.29 Å) is shorter than the sum of the van der Waals radii. Interestingly, the signals in the ^{1}H NMR spectrum of the complex **37** at −90 °C may be assigned in agreement with the crystal structure, but the spectrum shows no features unambiguously assignable to an anomalous β-hydrogen. The authors infer that the three methyl hydrogens would become equivalent in the NMR experiment owing to a fluxional process, e.g., rotation about the carbon−carbon bond.[125] However, the IR spectra of [TiEt(Cp)Cl_2] and its deuterated isotopomers indicated that the terminal methyl group is markedly asymmetric with one weak and two stronger C−H bonds.[126] The same has been observed in the IR spectra of [TiEtCl_3] and its isotopomers.[127] The dissociation enthalpy of the agostic β-C−H bond has been estimated to be 31 kcal mol^{-1} smaller than that of a nonagostic counterpart. On the basis of computational evidence, which is consistent with spectroscopical data, the authors concluded that the Ti−C_α bonding electrons are delocalized over both C_α and C_β atoms as well as their appended hydrogen atoms and that the decrease of the Ti−C−C valence angle allows the establishment of covalent bonding between Ti and C_β and, to a lesser extent, one of its hydrogen atoms.[127] These data are consistent with a strong agostic interaction between the titanium atom and a C_β−H moiety and in turn may promote the β-elimination of a hydrogen atom.[49,128−131]

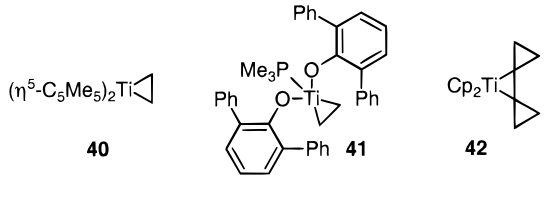
β-Hydride elimination reactions occur particularly easily when two or more alkyl groups are bound to titanium and yield the corresponding alkanes, polyolefins, and low-valence titanium derivatives.[32,34,35,132−134] The original proposition that the formation of hydrocarbons would proceed via alkyl-radical intermediates formed by homolytic dissociation of titanium−carbon bonds[34,135,136] could not be confirmed. Upon decomposition of alkyltitanium derivatives in dilute hydrocarbon solution, no evidence has been obtained for the formation of free alkyl radicals.[134] These findings as well as the observed considerable kinetic isotope effect $k_{\beta-H}/k_{\beta-D} \approx 8$ in decomposition reactions of organotitanium derivatives allows one to propose a bimolecular disproportionation and formation of 1,2-dimetalloalkylidene derivatives as intermediates.[35] For the thermal decomposition of alkyltitanium derivatives, a mechanism based on β-elimination of metal hydride has also been postulated.[4,137−140] This mechanism includes a ligand elimination step with formation of a coordinatively unsaturated dialkyltitanium derivative, followed by elimination of metal hydride from one of the alkyl groups with concomitant transfer of the resulting alkene to the vacant coordination site to form an alkenealkylhydrido complex **38** (Scheme 19). Readdition of a ligand to **38** accompanied by reductive elimination of an *n*-alkane eventually leads to the alkenetitanium complex **39** (M = Ti, Scheme 19).[119,129,141−144]

Scheme 19



The question of whether a transition-metal complex of type **39** is best described as an alkene π-complex **39A** or a metallacyclopropane **39B**, which is of practical importance, has been addressed in several computational studies on the relation between alkene π-complexes and three-membered rings.[145−149] It has been concluded that the titanium complexes of type **39** (M = Ti) are best presented as titanacyclopropanes, i.e., resonance structure **39B**, if one is willing to accept the notion that **39A** and **39B** are limiting resonance forms.[149]

The first isolable alkenetitanium complex was the ethylene adduct **40** which was synthesized by Bercaw et al. by sodium amalgam reduction of bis(pentamethylcyclopentadienyl)titanium dichloride in toluene under an atmosphere of ethylene (ca. 700 Torr).[140] The lime-green complex **40** was also rapidly and quantitatively formed from {[(η-$C_5Me_5)_2$Ti]$_2$(μ-$N_2)_2$} by treatment with ethylene. The X-ray crystal structure analysis disclosed that the coordination of ethylene to the decamethyltitanocene fragment causes a substantial increase in the carbon−carbon double bond length from 1.337(2) Å for free ethylene to 1.438(5) Å in complex **40**.[140] The crystal structure of



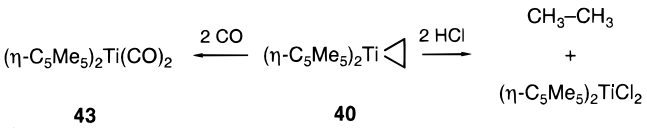
the ethylenebis(aryloxy)trimethylphosphinotitanium complex **41**[150] shows that the C_2H_4 unit lies approximately coplanar with the Ti−PMe_3 bond and has a slightly shorter carbon−carbon bond of 1.425(3) Å than that in the metallocene complex **40**. Considerable bending of the hydrogen atoms out of the planar ethylene geometry is also observed. By

comparison with structural data of other ethylene complexes and three-membered heterocyclic compounds, the structures of **40** and **41** would appear to be intermediate along the continuum between Ti(II) ethylene (**39A**, M = Ti) and Ti(IV) metallacyclopropane (**39B**, M = Ti) (Scheme 19) as limiting structures.[140]

No crystal structure analysis, but full NMR-spectroscopic characterization has been reported for the interesting bisspirocyclopropanated titanacyclopropane **42**, which was readily formed upon reaction of $Cp_2Ti(PMe_3)_2$ with bicyclopropylidene.[151]

The chemical reactivity of complex **40** is consistent with the conclusion that it is somewhere intermediate between a Ti(II) ethylene and a Ti(IV) metallacyclopropane. With carbon monoxide above −78 °C, for example, **40** reacts as a metal olefin complex to produce the dicarbonyltitanocene complex **43**, whereas upon reaction with anhydrous HCl, **40** demonstrates the typical properties of an organometallic compound with covalent metal−carbon bonds and quantitatively liberates ethane (Scheme 20).[140]

Scheme 20

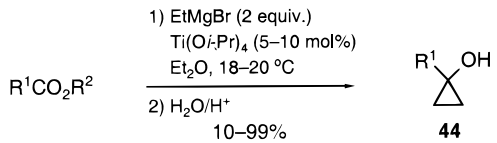


Quite a number of other reactions of alkenes and acetylenes that are mediated or catalyzed by low-valent titanium derivatives have been described.[152−171] Although some of these reactions may also formally be considered as transformations involving dicarbanionic equivalents, all of them in practice make use of the organometallic intermediates only as monocarbanionic equivalents, because the second electrophile always is a proton and thus only one carbon−carbon or carbon−heteroatom bond is formed. On the other hand, ethylene could be displaced from titanacyclopropane compounds of type **40** by electron-donating ligands, and they thus are useful starting materials for the synthesis of titanium(II) complexes.[140,163,167,172−175]

A. Organomagnesium Precursors

The first synthetically useful reaction in which a titanacyclopropane intermediate in a formal sense acts as a 1,2-dicarbanionic equivalent, and thus leads to the formation of two new carbon−carbon bonds, has been developed by Kulinkovich et al.[176] They found that treatment of a carboxylic acid ester with a mixture of 1 equiv of titanium tetraisopropoxide and an excess of ethylmagnesium bromide at −78 to −40 °C affords 1-alkylcyclopropanols **44** in good to excellent yields (Scheme 21 and Table 2).[176,177] This

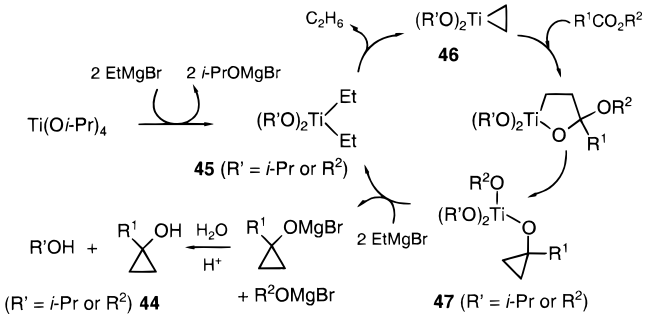
Scheme 21



efficient transformation can also be carried out with substoichiometric amounts of $Ti(O\textit{i}\text{-}Pr)_4$ (5−10 mol %).[178,179] In this case, an ether solution of 2 equiv of ethylmagnesium bromide is added at room temperature to the solution of the ester and the titanium tetraisopropoxide.

Mechanistically this reaction can be rationalized as depicted in Scheme 22. It is assumed that 2 equiv

Scheme 22



of the Grignard reagent reacts with $Ti(O\textit{i}\text{-}Pr)_4$ to form the thermally unstable diethyltitanium intermediate **45**, which rapidly undergoes β-hydride elimination (see Scheme 19) and reductive elimination to yield ethane and the reactive intermediate titanacyclopropane **46**. The putative titanacyclopropane **46** then acts as a 1,2-dicarbanionic equivalent in that it performs an overall 2-fold alkylation of the alkoxycarbonyl group. This most probably happens by insertion of the ester carbonyl group into one of the titanium−carbon bonds to give an oxatitanacyclopentane and subsequent ring contraction, most probably initiated by attack of an alkoxide moiety from a titanium or magnesium alkoxide or even attack of another molecule of ethylmagnesium bromide on titanium, with concurrent loss of the alkoxide group from the former carbonyl carbon atom to yield the titanium cyclopropanolate **47** or an analogue with one ethyl group on Ti. The latter reacts with one or two more molecules of the Grignard reagent to reform the intermediate **45**—completing a catalytic cycle—and give the magnesium cyclopropanolate that is eventually hydrolyzed to **44**.

This cyclopropanol formation also proceeds smoothly with alkenyl-,[194] cycloalkyl-,[179−181,193] and arylcarboxylates[177,179] as well as with carboxylates containing β-[186,195] or γ-halogen,[187] acetal,[192,196] and quite a number of other functional substituents including dialkoxyphosphonyl groups (see Table 2). This methodology offers the best way to prepare the key precursors to bicyclopropylidene (**48**)[180,181] and its bisspirocyclopropanated analogue **49**,[180] since methyl cyclopropanecarboxylate and ethyl dispiro[2.0.2.1]-heptane-7-carboxylate are virtually quantitatively converted to 1-cyclopropylcyclopropanol and 1-(dispiro-[2.0.2.1]hept-7-yl)cyclopropanol (Scheme 23).[180] The same approach has successfully been applied toward the preparation of other strained bicyclopropylidene derivatives.[193,197]

Diesters and even triesters have been converted to bis- and triscyclopropanols, respectively. Dimethyl

Table 2. 1-Alkylcyclopropanols 44 from Carboxylic Acid Esters and Ethylmagnesium Bromide in the Presence of Titanium Tetraisopropoxide (see Scheme 21)

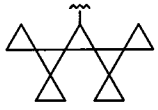
Entry	Starting Ester	Conditions[a]	Product	Yield	Ref.
	R^2	(mol% $Ti(O\textit{i}\text{-}Pr)_4$	R^1	(%)	
1	Me	A	Me	74	(176, 177)
	Me	B (5–10)	Me	76	(178)
	Et	B (4–10)	Me	84	(179)
2	Me	A	Et	82	(176, 177)
	Me	B (5–10)	Et	79	(178)
3	Me	A	*n*-Pr	90	(176, 177)
	Me	B (4–10)	*n*-Pr	91	(178, 179)
4	Me	A	*n*-Bu	88	(176, 177)
	Me	B (4–10)	*n*-Bu	90	(178, 179)
5	Me	A	$n\text{-}C_5H_{11}$	93	(176, 177)
	Me	B (4–10)	$n\text{-}C_5H_{11}$	94	(178, 179)
6	Me	A	$n\text{-}C_7H_{15}$	91	(177)
	Me	B (4–10)	$n\text{-}C_7H_{15}$	94	(179)
7	Me	A	$n\text{-}C_9H_{19}$	98	(176, 177)
	Me	B (5–10)	$n\text{-}C_9H_{19}$	95	(178)
8	Me	A	*i*-Pr	88	(176, 177)
	Me	B (4–10)	*i*-Pr	88	(179)
9	Me	B (22)	*c*-Pr	99	(180, 181)
10	Me	B (4–10)	*c*-Hex	85	(179)
11	Et	B (20)	1-(*trans*-4-*n*-Pr-*c*-Hex)	95	(182)
12	Et	B (20)	1-(*trans*-4-*n*-Bu-*c*-Hex)	95	(182)
13	Et	B (20)	1-(*trans*-4-$n\text{-}C_5H_{11}$-*c*-Hex)	95	(182)
14	Me	B (10)	$CH{=}CH_2$	11	(183)
15	Me	B (10)	$C(Me){=}CH_2$	10	(183)
16	Me	B (10)	$CH{=}C(Me)_2$	23	(183)
17	Me	B (10)	$(CH_2)_{14}CH{=}CH_2$	>90	(184)
18	Et	A	Ph	93	(176,177)
	Et	B (4–10)	Ph	64	(179)
19	Et	B (22)		97	(180) (181)
20	Et	B (22)		38	(180)
21	Et	B (22)		56	(180)
22	Et	B (22)		99	(180)
23	Et	B (22)		93	(185)

Table 2 (Continued)

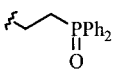
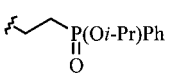
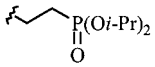
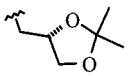
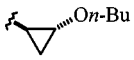
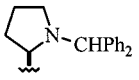
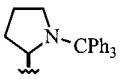
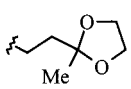
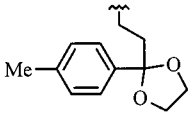
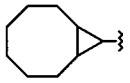
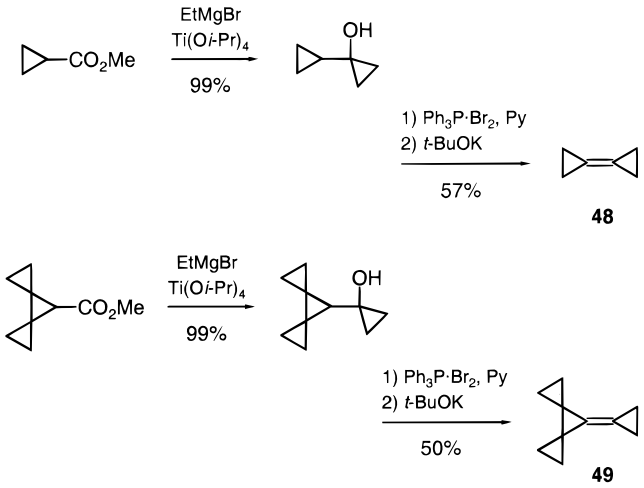
Entry	Starting Ester	Conditions[a]	Product	Yield	Ref.
	R^2	(mol% $Ti(Oi\text{-}Pr)_4$	R^1	(%)	
24	Me	B (10)	$ClCH_2CH_2$	76	(186)
25	Me	B (10)	$BrCH_2CH_2$	86	(186)
26	Et	B (10)	$ClCH_2CH_2CH_2$	85	(187)
27		C	$c\text{-}Pr_2NCH_2$	28	(188)
28	*i*-Pr	B (14)	$i\text{-}PrOCH_2$	50	(189)
29	Me	B (14)	$PhOCH_2$	30	(189)
30	Me	B (10)	Me_3SiCH_2	67	(183)
31	*i*-Pr	B (14)	EtCH(O*i*-Pr)	55	(189)
32	*i*-Pr	B (14)	PrCH(O*i*-Pr)	67	(189)
33	*i*-Pr	B (14)	$n\text{-}C_{12}H_{25}CH(Oi\text{-}Pr)$	69	(189)
34	*i*-Pr	B (14)	$n\text{-}C_{14}H_{29}CH(Oi\text{-}Pr)$	70	(189)
35	*i*-Pr	B (14)	PhCH(OMe)	55	(189)
36	Me	B (10)	$Me_3SiCH(Me)$	38	(183)
37	Me	A		64	(190)
38	Me	A		37	(190)
39	Me	A		67	(190)
40		B		85	(196)
41	*t*-Bu	B (22)		52	(180)
42		B (20)	Bn_2NCH_2	90	(191)
43		B (20)	L-$Bn_2NCH(Me)$	87	(191)
44		B (20)	D,L-$Bn_2CH(Et)$	85	(191)
45		B (20)	L-$Bn_2CH(i\text{-}Pr)$	92	(191)
46	Et	B (25)		40	(191)
47	Et	B (25)		60	(191)
48	Et	B (20)		98	(191)
49	Me	B (20)		99	(191)
50	Me	B (10)		84	(192)

Table 2 (Continued)

Entry	Starting Ester R^2	Conditions[a] (mol% $Ti(Oi\text{-}Pr)_4$)	Product R^1	Yield (%)	Ref.
51	Me	B (10)		78	(192)
52	Et	B (24)		84	(193)
53	Et	B (24)		81	(193)

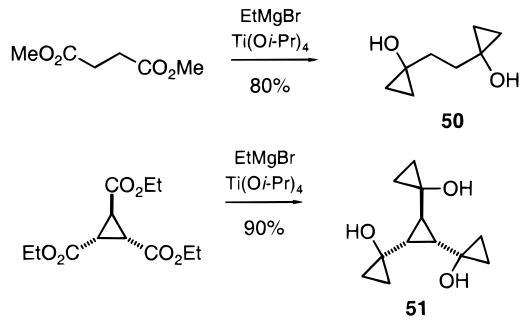
[a] A: 3 equiv of EtMgBr, 1 equiv of $Ti(Oi\text{-}Pr)_4$. B: 2−4 equiv of EtMgBr, 0.05−0.5 equiv of $Ti(Oi\text{-}Pr)_4$. C: 3 equiv of EtMgBr, $MeTi(Oi\text{-}Pr)_3$.

Scheme 23



succinate gave the biscyclopropanol derivative **50** in 80% yield, and triethyl *trans*-cyclopropanetricarboxylate yielded the triscyclopropanol **51** (90%) (Scheme 24 and Table 3).[198] Higher dicarboxylic acid diesters

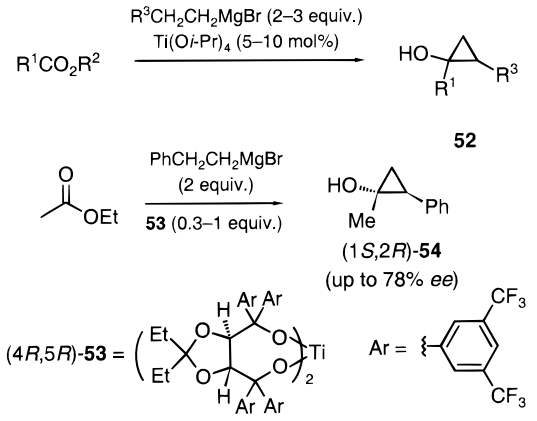
Scheme 24



also smoothly converted with ethylmagnesium bromide in the presence of $Ti(Oi\text{-}Pr)_4$ to provide the corresponding biscyclopropanols, which have been utilized as ideal precursors to α,ω-divinyl ketones.[192,199]

1,2-Disubstituted cyclopropanols **52** can be prepared from esters and appropriately 2-substituted ethylmagnesium halides in the presence of titanium tetraisopropoxide.[177,201,202] In the absence of any chelating substituents in the substrate, the products **52** are formed with high diastereoselectivity, i.e., the two substituents on the 1,2-disubstituted cyclopropanol preferentially end up in a cis relationship with one another (Scheme 25 and Table 4).[201,203] Yet the sequence of events in the formal bisalkylation of an alkoxycarbonyl group with 2-substituted titanacyclopropane intermediates is not at all clear.[198,203] In the presence of certain titanium bistaddolates **53**, generated in situ from chlorotriisopropyloxytitanium and the corresponding taddol, 2-phenyl-1-methylcyclopropanol **54** was obtained from ethyl acetate and (2-phenylethyl)magnesium bromide (64%) with an enantiomeric excess of up to 78%.[201]

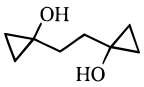
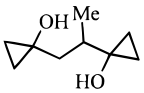
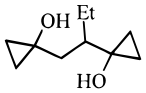
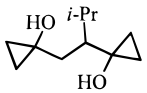
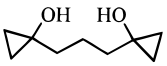
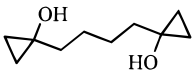
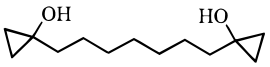
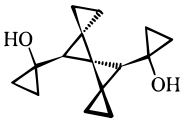
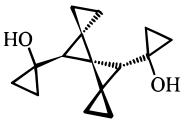
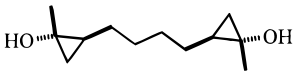
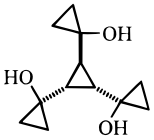
Scheme 25



An interesting application of a 1,2-disubstituted cyclopropanol toward a seven-membered ring-annelation methodology has been developed by Cha et al.[202] The cyclopropanol **55**, obtained from methyl 1-cyclopentenecarboxylate and 4-(triisopropylsilyl)-oxybutylmagnesium chloride, was converted to a 1,2-dialkenylcyclopropanol bissilyl ether which by a subsequent facile Cope rearrangement afforded the cycloheptadienyl-annelated cyclopentane derivative **56** in 32% overall yield (Scheme 26).

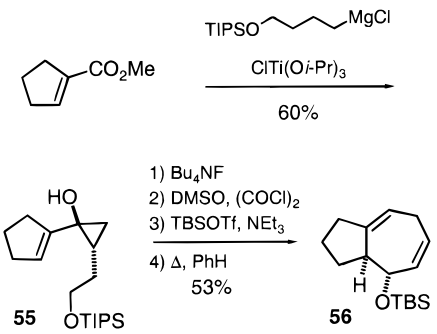
A very useful adaptation of the original protocol for the conversion of esters to cyclopropanols with

Table 3. Bis- and Triscyclopropanols from Di- and Tricarboxylic Acid Ethyl Esters and Titanacyclopropanes Generated from Ethylmagnesium Bromide in the Presence of Titanium Tetraisopropoxide or by Ligand Exchange with 1,7-Octadiene

Entry	Conditions[a] (mol% $Ti(OR)_4$)	Product	Yield (%)	Ref.
1	A (20)		80	(192)
2	A (20)		68	(199)
3	A (20)		64	(199)
4	A (20)		85	(199)
5	A (20)		90	(199)
6	A (20)		90	(199)
7	A (20)		85	(199)
8	A (22)		47	(180)
9	A (22)		51	(180)
10	A, B (50)[b]		10	(200)
11	A (30)		90	(198)

[a] A: $Ti(Oi\text{-}Pr)_4$. B: $ClTi(Oi\text{-}Pr)_3$. [b] The reaction was carried out in the presence of 1,7-octadiene using *i*-PrMgBr.

Scheme 26



titanacyclopropane 1,2-dicarbanionic equivalents toward a highly versatile preparation of cyclopropylamines has been developed by de Meijere et al.[207−211] *N*,*N*-Dialkylaminocyclopropanes **58** with up to three additional substituents are readily obtained from carboxylic acid *N*,*N*-dialkylamides and ethyl- as well as substituted ethylmagnesium bromide in the presence of titanium tetraisopropoxide. These transformations were also possible with substoichiometric amounts of $Ti(Oi\text{-}Pr)_4$, but the yields were significantly better with stoichiometric amounts. In some cases, longer reaction times and/or higher temperatures were also beneficial. Particularly high

Table 4. 1,2-Disubstituted Cyclopropanols 52 from Carboxylic Acid Esters and 2-Substituted Ethylmagnesium Halides in the Presence of Titanium Tetraisopropoxide or Chlorotitanium Triisopropoxide

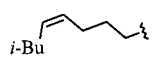
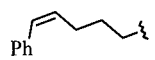
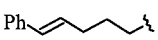
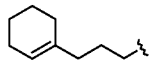
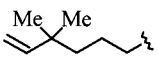
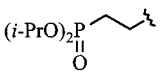
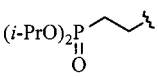
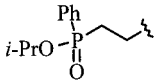
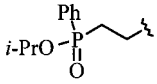
Entry	Starting Ester	Product		Conditions[a] (mol%	Yield (%)	Ref.
	R^2	R^1	R^3	$Ti(OR)_4$)	(d. r. Z/E[b])	
1	Et	H	*n*-Bu	B (10)	37	(183)
2	Me	H	*n*-C_6H_{13}	C (10)	72	(201)
3	Me	H	Ph	C (10)	60	(201)
4	Me	Me	Me	A	67	(182)
	Et	Me	Me	B (4–10)	57	(179)
	Et	Me	Me	B (10)	74	(183)
	Me	Me	Me	C[c] (10)	80	(199)
5	Et	Me	Et	B (4–10)	73	(179)
	Et	Me	Et	B (10)	72	(183)
6	Et	Me	*n*-Bu	B (10)	75	(183)
7	Me	Me	*t*-Bu	A	2.2	(183)
8	Et	Me	$CH{=}CMe_2$	A	2.4	(183)
9	Me	Me	Ph	A	62	(177)
	Et	Me	Ph	B (10)	85	(183)
	Me	Me	Ph	C (10)	83	(201)
10	Me	Et	Me	A	78	(177)
11	Me	Et	Et	A	74	(177)
	Me	Et	Et	B (4–10)	74	(179)
12	Me	Et	*n*-Pr	A, B (10)	n. r.[d]	(205)
13	Me	Et	Ph	B (10)	73	(183)
14	Me	*n*-Pr	Et	C[c] (10)	79	(201)
15	Me	*n*-Bu	Me	A, B (10)	n. r.[d]	(205)
16	Me	*n*-C_5H_{11}	*n*-C_5H_{11}	A, B (10)	n. r.[d]	(205)
17	Me	*n*-C_6H_{13}	Et	C[c] (10)	81	(201)
18	Me	*n*-C_6H_{13}	*n*-Bu	A, B (10)	n. r.[d]	(205)
19	Me	*n*-C_6H_{13}	*n*-C_6H_{13}	C[c] (10)	88	(201)
20	Me	*n*-C_7H_{15}	Me	A	94	(177)
	Me	*n*-C_7H_{15}	Me	B (4–10)	90	(189)
21	Me	*i*-Pr	Me	B (10)	44 (1:1)	(183)
22	Me	*t*-Bu	Me	B (10)	61 (2.5:1)	(183)
23	Me	*c*-Pr	Me	B (10)	57 (2.2:1)	(183)
24	Me	*c*-Pr	Et	B (10)	49 (2:1)	(183)
25	Me	*c*-Pr	Ph	B (10)	65	(183)
26	Me		Et	C (50)	–[e]	(206)
27	Me		Et	C (50)	–[e]	(206)
28	Me		Et	C (50)	–[e]	(206)
29	Me		Et	C (50)	–[e]	(206)
30	Me		Et	C (50)	61	(206)

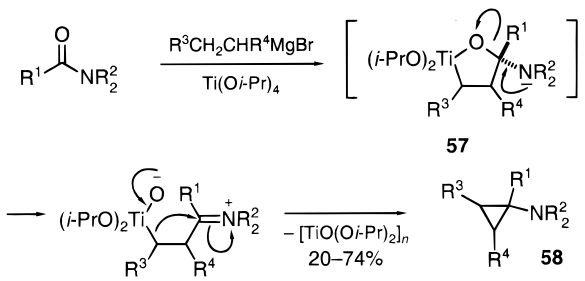
Table 4 (Continued)

Entry	Starting Ester	Product		Conditions[a] (mol%	Yield (%)	Ref.
	R^2	R^1	R^3	$Ti(OR)_4$)	(d. r. Z/E[b])	
31	Me	$PhCH_2CH_2$	Me	C[c] (10)	83	(201)
32	Me	$PhCH_2CH_2$	Et	C[c] (10)	79	(201)
33	Et	Ph	Me	A	62	(177)
	Me	Ph	Me	B (10)	27 (1:1)	(183)
34	Me	Ph	Et	B (10)	52 (1:1)	(183)
35	Et	Ph	Ph	A, B (4–10)	26	(177)
	Et	Ph	Ph		31	(179)
36	Me	$Me_2C{=}CH$	Me	B (10)	24	(183)
37	Me	Me_3SiCH_2	Ph	A	44	(183)
38	Me	$Me_3SiCHMe$	Ph	A	43	(183)
39	Me		Me	A	60	(190)
40	Me		Et	A	71	(190)
41	Me		Me	A	40 (1:1)	(190)
42	Me		Et	A	41 (1:1)	(190)
43	Me		$THPOCH_2CH_2$	C (catal.)	46	(200)
44	Me		$TIPSOCH_2CH_2$	C (catal.)	77	(200)
45	Me		$TIPSOCH_2CH_2$	C (catal.)	60	(200)
46	Me	$Br(CH_2)_5$	$MeO_2C(CH_2)_3$	D[c]	16	(183)

[a] A: 3 equiv EtMgBr/$Ti(Oi\text{-}Pr)_4$ (stoichiometric method); B: 2−4 equiv EtMgBr/0.05−0.5 equiv $Ti(Oi\text{-}Pr)_4$ (catalytic version); C: 3 equiv EtMgBr/$ClTi(Oi\text{-}Pr)_3$; D: $MeTi(Oi\text{-}Pr)_3$. [b] d.r. = diastereomeric ratio, quoted only when reported in the original paper. [c] Reaction was carried out by addition of alkyl halide to the mixture containing magnesium turnings. [d] n.r. = not reported. [e] Report only quotes "good yield".

yields were obtained from *N*,*N*-dialkylformamides (Scheme 27 and Table 5); yields are consistently

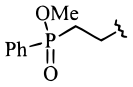
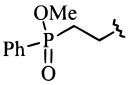
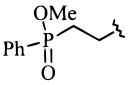
Scheme 27



lower from amides with bulky substituents next to the carbonyl groups or on the nitrogen, but even the overcrowded *N*,*N*-di-*tert*-butylformamide could be converted to di-*tert*-butylcyclopropylamine (Table 5, entry 13), albeit in only 20% yield. The diastereoselectivities in the production of 2-substituted and 1,2-disubstituted *N*,*N*-dialkylcyclopropylamines are generally lower than those in the formation of the corresponding cyclopropanols from esters.

Since benzyl groups can be removed from *N*-benzylcyclopropylamines by catalytic hydrogenation with palladium catalysts, primary cyclopropylamines are accessible by this methodology. Thus, the theoretically interesting tricyclopropylamine[209,210] could be prepared from benzylcyclopropylformamide in a sequence of reductive cyclopropanation of the formyl group, hydrogenolytic debenzylation, *N*-formylation, and repeated reductive cyclopropanation.[209,210]

Table 5. *N,N*-Dialkylcyclopropylamines 58 from *N,N*-Dialkylcarboxamides and Ethyl- as Well as Substituted Ethylmagnesium Halides in the Presence of Titanium Tetraisopropoxide

Entry	R^1	R^2	R^3	R^4	Yield (%) (d. r.)	Ref.
1	Me	Me	H	H	56	(207)
2	Me	Bn	H	H	60	(207)
3	Et	Bn	H	H	63	(207)
4	*n*-Pr	Bn	H	H	52	(207)
5	Me	Bn	Me	H	50	(207)
6	Me	Bn	Me_2[a]	H	51	(207)
7	Et	Bn	Me	H	38	(207)
8	*n*-Pr	Bn	*n*-Bu	H	35	(207)
9	H	Bn	H	H	73	(207)
10	H	$-(CH_2)_5-$	H	H	74	(207)
11	H	$-(CH_2)_2O(CH_2)_2-$	H	H	74	(207)
12	H	Bn	H	H	69	(207)
13	H	*t*-Bu	H	H	20	(207)
14	H	Bn	Me	H	63 (1:1)	(207)
15	H	Bn	*n*-Bu	H	52 (1:2.3)	(207)
16	Me	Me	*n*-Bu	H	37	(183)
17	Me	Bn	Et	H	47	(183)
18		Me	H	H	47	(190)
19		Me	Me	H	39 (8.5:1)	(190)
20		Me	Et	H	42 (10:1)	(190)
21	H	Bn	$-(CH_2)_4-$		34	(183)
22	Me	Me	*n*-Bu	H	38 (>25:1)	(211)
23	*n*-Pr	Bn	*n*-Bu	H	35 (10:1)	(211)
24	H	Bn	CH_2=CH–	H	42 (>25:1)	(211)
25	$-CH_2CH_2-$	$-CH_2CH_2-$, Bn	H	H	21	(211)
26	$-(CH_2)_4-$	$-(CH_2)_4-$, Me	H	H	33	(211)

[a] 2,2-Dimethylcyclopropyl derivative.

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. Due to the poorer leaving group ability of the dialkylamino group in the oxatitanacyclopentane intermediate **57** which is initially formed by insertion of the carbonyl group of the amide into the titanium−carbon bond of a titanacyclopropane, **57** does not undergo ring contraction like the corresponding oxatitanacyclopentane **46** from an ester (see Scheme 22) but ring opening to an iminium−titanium oxide zwitterion which cyclizes to the cyclopropylamine **58** with loss of an oxotitanium diisopropoxide species (Scheme 27).

Table 6. *N,N*-Dialkylcyclopropylamines 58 from *N,N*-Dialkylcarboxamides and Ethyl- as Well as Substituted Ethylmagnesium Halides in the Presence of Methyltitanium Triisopropoxide

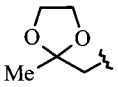
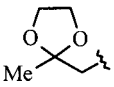
Entry	R^2	R^1	R^3	R^4	Yield (%) (d. r.)	Ref.
1	Bn	H	H	H	95	(188, 212)
2	Bn	H	Me	H	89 (1:1.1)	(188)
3	Bn	Me	H	H	77	(188, 212)
4	Bn	Et	H	H	70	(188, 212)
5	Bn	Pr	H	H	62	(188, 212)
6	Me	$-CH_2CH_2CH_2-$		H	28	(183, 211)
7	Bn	H	CH_2=CH	H	54	(183)
					98 (1:7)	(188)
8	Bn	$BnOCH_2$	H	H	48	(212, 213)
9	Bn	$BnOCH_2$	Me	H	37 (1:3)	(212, 213)
10	Bn	$BnOCH_2$	Et	H	48 (1:5)	(212, 213)
11	Bn	$BnOCH_2$	Pr	H	34 (1:3)	(213)
12	Bn	$BnOCH_2$	*i*-Pr	H	42 (1:3)	(213)
13	Bn	$BnOCH_2$	Bu	H	33 (1:2)	(212, 213)
14	Bn	*i*-Pr	H	H	44	(188, 212)
15	Bn	*t*-Bu	H	H	25	(188, 212)
16	*i*-Pr	H	H	H	86	(188)
17	Bn	H	*n*-Pr	H	85 (1:2.1)	(188)
18	Bn	H	*n*-Bu	H	87 (1:2.2)	(188)
19	Bn	H	Ph	H	98 (1:2.3)	(188)
20	Bn	H	*t*-$BuO(CH_2)_3$	H	59 (1:2)	(188)
21	Bn	H		H	92 (1:1.5)	(188)
22	Bn		H	H	57	(188)
23	$(CH_2)_5$	H	Ph	H	92 (1:1.5)	(188)
24	Bn	*i*-Bu	H	H	52	(212)
25	Bn	$PhCH_2CH_2$	H	H	63	(212)
26	Bn	$PhCH_2$	H	H	47	(212)
27	Bn	$BnOCH_2CH_2$	H	H	38	(212)
28	Bn	$ClCH_2CH_2$	H	H	49	(212)
29	Bn		H	H	63	(188)
30	Bn		H	H	56	(188)
31	Bn	$BnOCH_2CH_2$	Me	H	33 (1:3)	(212)
32	Bn		Et	H	58	(188)
33	Bn		CH_2=CH	H	61	(188)
34	Bn	$BnCH_2O$	$BnOCH_2CH_2$	H	40 (1:3)	(212)

Table 6 (Continued)

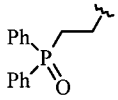
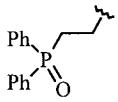
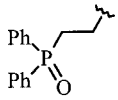
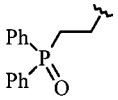
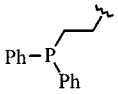
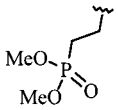
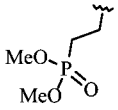
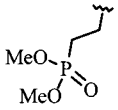
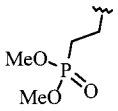
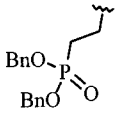
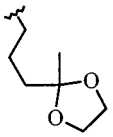
Entry	R^2	R^1	R^3	R^4	Yield (%) (d. r.)	Ref.
35	Bn		H	H	83	(188, 190)
36	Me		Me	H	80 (1:3.5)	(188, 190)
37	Me		CH_2=CH	H	83 (1:3)	(188, 190)
38	Me		Ph	H	67	(188, 190)
39	Ph		H	H	21	(188)
40	Me		H	H	79	(188, 190)
41	Me		Me	H	81 (1:6)	(188, 190)
42	Me		CH_2=CH	H	86 (1:1.6)	(188, 190)
43	Me		Ph	H	82 (1:1.4)	(188, 190)
44	Bn		H	H	62	(188, 190)
45	Me	H	$-CH_2CH_2-$		72	(188)
46	Bn	H	$-CH_2CH_2-$		87	(188)
47	Bn	H	$-CH(Me)CH_2-$		82	(188)
48	Bn	H	$-CH_2CH_2CH_2-$		89	(188)
49	Me	Me	*n*-Bu	H	51 (>25:1)	(211)
50	Bn	*n*-Pr	*n*-Bu	H	47 (10:1)	(211)
51	Me	H	CH_2=CH	H	57 (17:1)	(211)
52	Bn	H	CH_2=CH	H	54 (>25:1)	(211)
53	Me	H	Ph_3COCH_2-	H	18 (>25:1)	(211)
54	Me	H	$BnOCH_2CH_2$	H	54 (1.1:1)	(211)
55	Bn	H	$THPO(CH_2)_2$	H	34 (2.1:1)	(211)

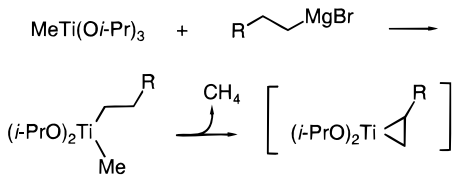
Table 6 (Continued)

Entry	R^2	R^1	R^3	R^4	Yield (%) (d. r.)	Ref.
56	Me	H		H	53 (1.8:1)	(211)
57	$-(CH_2)_5-$	Ph	H	H	73	(188)
58	Et	H	H	H	83	(188)
59	Bn		H	H	85	(188)
60[a]	$-(CH_2)_5-$		H	H	47	211
	$R^{2'}$ = Me					

[a] $NR_2^2 = NR^2R^{2'}$.

Improved yields of cyclopropylamines **58** were obtained by using methyltitanium triisopropoxide instead of titanium tetraisopropoxide,[211] as well as by adding the Grignard reagent to the mixture of the amide and the titanium reagent at ambient instead of low temperature.[188,190] Methyltitanium triisopropoxide requires only 1 equiv of the alkylmagnesium halide to generate a dialkyltitanium diisopropoxide intermediate, and in this particular case, β-hydride elimination can only occur at the nonmethyl 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 (Scheme 28). By using an excess of the alkyl-

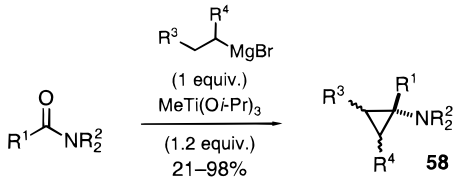
Scheme 28



magnesium halide despite having the sacrificial methyl substituent on the titanium reagent, the yields based on the substrate carboxamide can be raised to as high as 90% (Table 6, entries 1, 7, 19, 21, 23). This is beneficial especially whenever the carboxamide is more precious than the Grignard reagent. This modification has also successfully been applied toward the intramolecular reductive cyclopropanation of *N*,*N*-dialkylcarboxamides in which the Grignard reagent was generated in situ from ω-bromocarboxamides and metallic magnesium (Scheme 29 and Table 6).

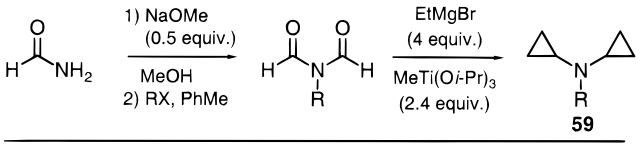
The reductive cyclopropanation with in situ generated titanacyclopropanes can also be applied to alkyldiformylamines which are readily prepared from inexpensive formamide. Both formyl groups are converted to cyclopropyl groups, and the alkyldicy-

Scheme 29



clopropylamines **59** were obtained in good to very good yields (Scheme 30).[188] This new method for the

Scheme 30



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

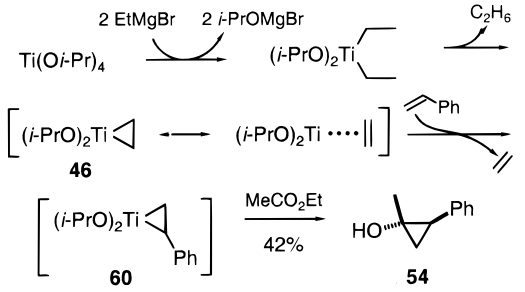
preparation of dicyclopropylamines compares favorably with the recently published[214] reductive amination of cyclopropanone hemiacetals with primary amines, as the reagents used in this current protocol are commercially available and are less expensive.

B. Ligand Exchange with Alkenes

As noted above (see Scheme 19), a titanacyclopropane is just the dominating resonance structure of an alkenetitanium complex. It is quite understandable then that such titanacyclopropanes **46** formed from dialkyltitanium diisopropoxides can undergo ligand exchange with other added alkenes. The consequence of such a ligand exchange has first been drawn by Kulinkovich et al. and applied to develop an alternative economic method for the preparation of 1,2-disubstituted cyclopropanols.[203] In a first attempt, (*E*)-1-methyl-2-phenylcyclopropanol (**54**) was

obtained in 42% yield by addition of 2 equiv of ethylmagnesium bromide in ether to a boiling ether solution of styrene (2 equiv) and a catalytic (0.05 equiv) amount of titanium tetraisopropoxide (Scheme 31).[203] The gaseous products from the reaction of

Scheme 31



ethylmagnesium bromide with titanium tetraisopropoxide in the presence as well as in the absence of ethyl acetate and styrene were analyzed and identified as ethane and ethylene.[203] The standard procedure for the preparation of 1-methylcyclopropanol from ethyl acetate carried out in the absence of styrene leads only to ethane evolution; however, the same reaction in the presence of styrene produces ethane and ethene (Table 7). Apparently, the titanacyclopropane intermediate **46** formed from ethylmagnesium bromide and Ti(O*i*-Pr)$_4$ undergoes a rapid ligand exchange with styrene to give the phenyl-substituted titanacyclopropane **60**, which subsequently reacts with ethyl acetate to give **54**.

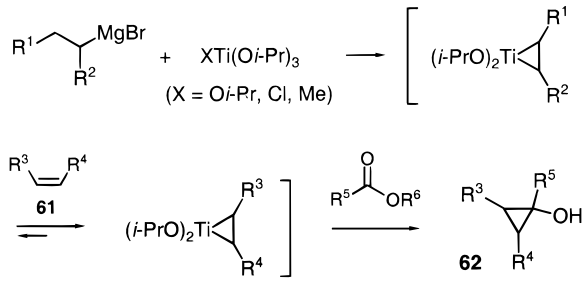
Table 7. Composition of the Gaseous Products from the Reaction of 2 Equiv of Ethylmagnesium Bromide with 0.05 Equiv of Titanium Tetraisopropoxide in the Presence and the Absence of Ethyl Acetate as Well as Styrene[203]

EtOAc (equiv)	PhCH=CH$_2$ (equiv)	C$_2$H$_6$ (equiv)	C$_2$H$_4$ (equiv)	yield (%)
		1.1	0.5	80
1		1.0	0.0	45
1	2	0.9	0.6	75

In contrast to styrene, 1-heptene, and some other alkenes when added to the reaction mixture did not undergo rapid enough ligand exchange with the parent titanacyclopropane intermediate **46** in the presence of only catalytic quantities of Ti(O*i*-Pr)$_4$ to afford the corresponding 1,2-disubstituted cyclopropanols in satisfactory yields. Sato et al.[215] as well as Cha et al.[200,204,206] independently found that upon treatment of esters with an excess of an organomagnesium compound in the presence of close to equimolar amounts of titanium tetraisopropoxide as well as 1 equiv of various terminal alkenes, 1,2-disubstituted cyclopropanols bearing substituents from the respective alkene are obtained in moderate to good yields (Scheme 32 and Table 8).[215−224] The best results have been achieved using isopropyl-,[215] butyl-,[217] cyclopentyl-, or cyclohexylmagnesium halides.[200,206,216]

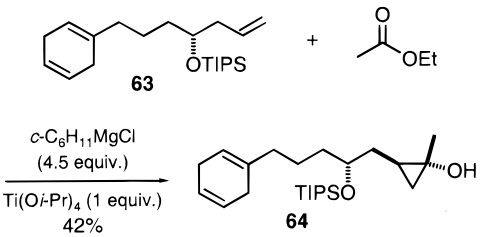
In a formal sense, the reaction of an ester with organotitanium 1,2-dicarbanionic equivalents generated by ligand exchange with an alkene to give a 1,2-disubstituted cyclopropanol may be considered as a hydroxycyclopropanation of an alkene **61**.[200,206,215−228]

Scheme 32



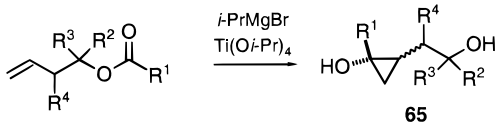
With the exception of norbornene[223] only terminal alkenes have been hydroxycyclopropanated in this way (Table 8). The presence of remote other functional groups such as di- and trisubstituted alkenyl,[200,206,225,226] bromo,[200] hydroxy,[218] silyloxy,[200,204,206,219,225,226] alkoxy,[226] acetal,[220] dialkylamino,[204,227,228] and acyloxy groups[215] is tolerated. Thus, the triene **63** can be cyclopropanated selectively at the terminal monosubstituted double bond to give the 1,2-disubstituted cyclopropanol **64** with the two alkyl groups in *cis*-relationship (Scheme 33).[200]

Scheme 33



Functional substituents on the terminal alkene may have a significant influence on the stereochemistry of the hydroxycyclopropanation.[200,204,206,215,218,225] For example, homoallyl acetate gives the 2-(2′-hydroxyethyl)-1-methylcyclopropanol **65** with a slight excess of the *trans*-diastereomer (trans/cis = 58:42) in excellent yield (93%) (Scheme 34 and Table 9).[215]

Scheme 34



Other homoallyl esters yield the corresponding 1-substituted 2-(2′-hydroxyethyl)methylcyclopropanols with much higher preference for the (*E*)-diastereomer (*E*/*Z* up to >97:3). These reactions have been classified by the authors as intramolecular nucleophilic acyl substitution (INAS) reactions; however, the possibility of an initial transesterification of the starting compounds catalyzed by titanium tetraisopropoxide[229] has not been excluded by any experimental evidence.

This hydroxycyclopropanation of a terminal double bond also works perfectly well intramolecularly with terminally alkenyl-substituted esters to yield 1-hydroxybicyclo[*n*.1.0]alkanols and heterocyclic analogues when five- and six-membered rings can be formed (Table 10).

Sato et al. developed an interesting enantioselective synthesis of bicyclic cyclopropanols from *N*-

Table 8. Substituted Cyclopropanols 62 from Carboxylic Acid Esters and Titanium Reagents Generated by Ligand Exchange on Intermediate Titanacyclopropanes from Grignard Reagents and XTi(O*i*-Pr)$_3$ (X = O*i*-Pr, Cl, Me)

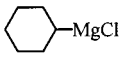
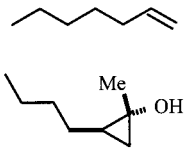
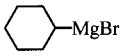
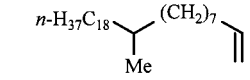
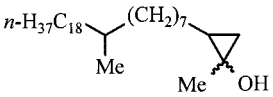
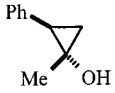
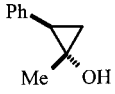
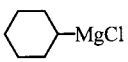
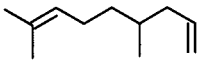
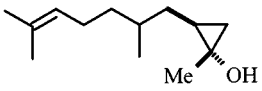
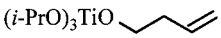
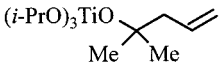
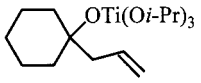
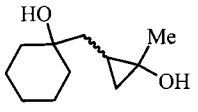
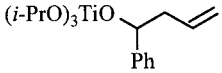
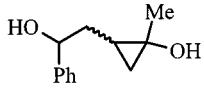
Entry	Starting Ester		Grignard Reagent (Equiv.)	Alkene	Conditions [a] (mol%)	Yield (%) (cis:trans[b])	Ref.
	R^5	R^6		Product			
1	Me	Et	 (4.5)		A, B	95 (>98:2)	(200)
2	Me	Et	 (7.1)	 	A (140)	64	(216)
3	Me	Et	EtMgBr (2)	 	A (10)	42 (>98:2)	(203)
4	Me	Et	RMgBr (2–4.5); R = Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *c*-Hex	 	A (10–100)	30–78[c] (>98:2)	(217)
6	Me	Et	 (4.5)	 	A, B	87 (>98:2)	(200)
7	Me	Et	EtMgBr (4)	 	A	42	(218)
8	Me	Et	EtMgBr (4)	 	A	56	(218)
9	Me	Et	EtMgBr (4)	 	A	26	(218)
10	Me	Et	EtMgBr (4)	 	A	58	(218)

Table 8 (Continued)

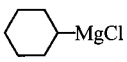
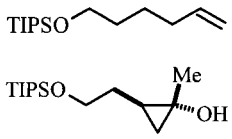
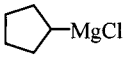
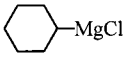
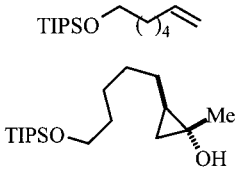
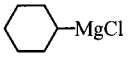
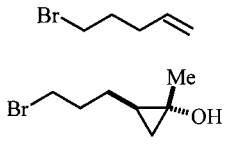
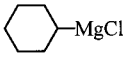
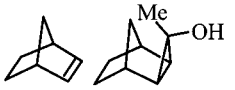
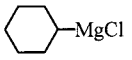
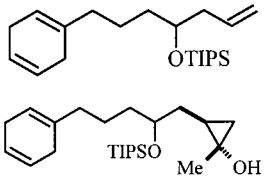
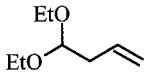
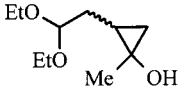
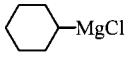
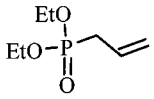
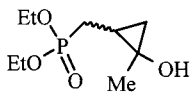
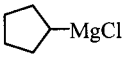
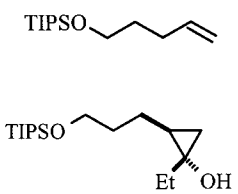
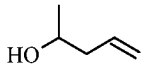
Entry	Starting Ester		Grignard Reagent (Equiv.)	Alkene Product	Conditions[a] (mol%)	Yield (%) (cis:trans[b])	Ref.
	R^5	R^6					
11	Me	Et	 (4.5)		A, B	75 (>98:2)	(200)
			 (4.5)			81 (>98:2)	(219)
12	Me	Et	 (4.5)		A, B	71 (>98:2)	(200)
13	Me	Et	 (4.5)		A, B	64 (>98:2)	(200)
14	Me	Et	 (4.5)		A, B	37	(200)
15	Me	Et	 (4.5)		A, B	42 (>98:2)	(200)
16	Me	Et	*i*-PrMgBr (2)		A	54	(220)
			n-BuMgBr (3)		A	80	(221)
17	Me	Me			A	54 (3:1)	(190)
							
18	Et	Et	 (4.5)		A, B	65 (>98:2)	(219)
19	Et	Et	*i*-PrMgBr (4)		A	71	(222)

Table 8 (Continued)

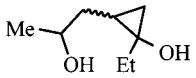
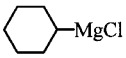
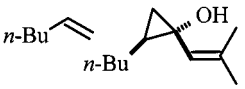
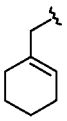
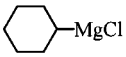
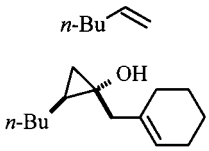
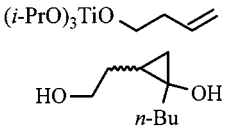
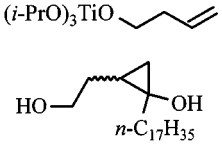
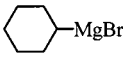
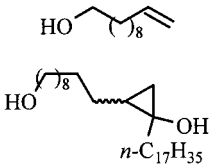
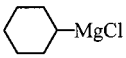
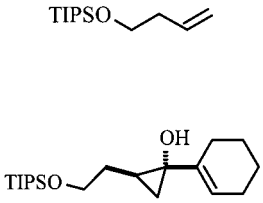
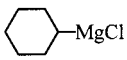
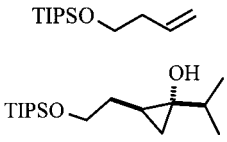
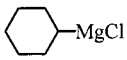
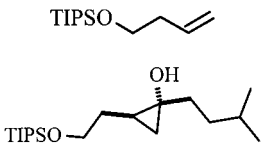
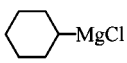
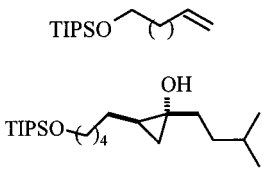
Entry	Starting Ester R^5	R^6	Grignard Reagent (Equiv.)	Alkene Product	Conditions[a] (mol%)	Yield (%) (cis:trans[b])	Ref.
							
20		Me	 (4.5)		A, B	37 (>98:2)	(200)
21		Me	 (4.5)		A, B	56 (>98:2)	(200)
22	*n*-Bu	Et	EtMgBr (4)		A	37	(218)
23	*n*-$C_{17}H_{35}$	Et	EtMgBr (4)		A	41	(218)
24	*n*-$C_{17}H_{35}$	Et	 (6)		A	>56	(216)
25		Me	 (4.5)		A, B	55 (>98:2)	(200)
26	*i*-Pr	Me	 (4.5)		A, B	62 (>98:2)	(200)
27	*i*-C_5H_{11}	Me	 (4.5)		A, B	65 (>98:2)	(200)
28	*i*-C_5H_{11}	Me	 (4.5)		A, B	72 (>98:2)	(200)

Table 8 (Continued)

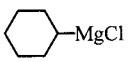
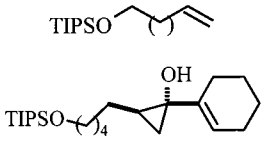
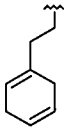
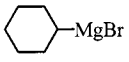
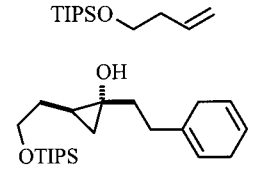
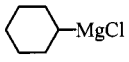
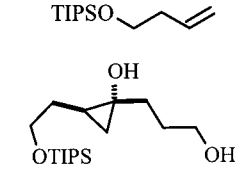
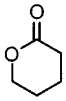
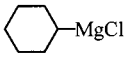
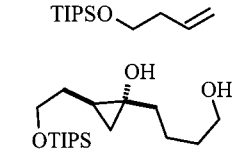
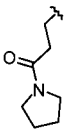
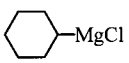
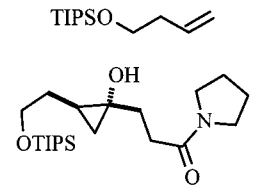
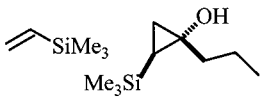
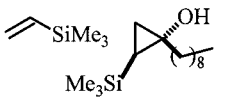
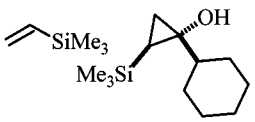
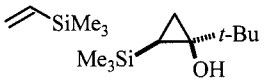
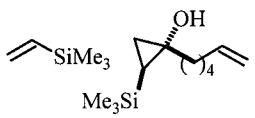
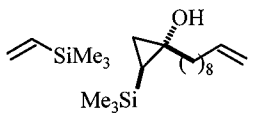
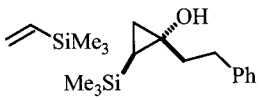
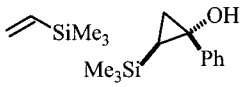
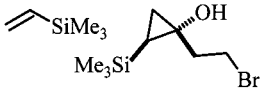
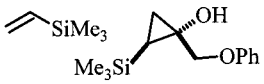
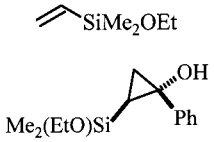
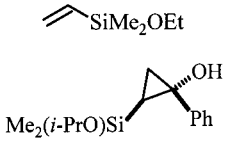
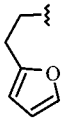
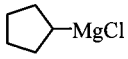
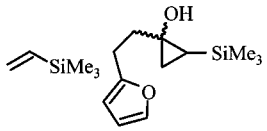
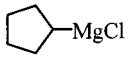
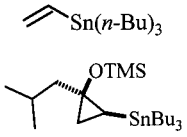
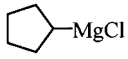
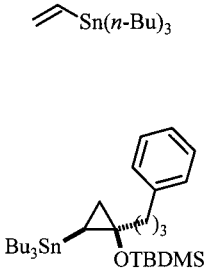
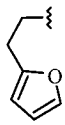
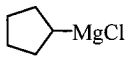
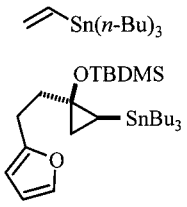
Entry	Starting Ester		Grignard Reagent (Equiv.)	Alkene	Conditions [a]	Yield (%)	Ref.
	R^5	R^6		Product	(mol%)	(cis:trans[b])	
29		Me	 (4.5)		A, B	46 (>98:2)	(200)
30		Me	 (4.5)		A, B	64 (>98:2)	(200)
31			 (4.5)		A, B	33 (>98:2)	(200)
32			 (4.5)		A, B	52 (>98:2)	(200)
33		Me	 (4.5)		A, B (80)	58 (>98:2)	(219)
34	*n*-Pr	Me	*i*-PrMgCl (2.9)		B (150)	80 (87:13)	(223)
35	*n*-Non	Me	*i*-PrMgCl (2.9)		B (150)	74 (88:12)	(223)
36	*c*-Hex	Me	*i*-PrMgCl (2.9)		B (150)	62 (81:19)	(223)
37	*t*-Bu	Me	*i*-PrMgCl (2.9)		B (150)	82 (7:93)	(223)
38		Me	*i*-PrMgCl (2.9)		B (150)	62 (88:12)	(223)
39		Me	*i*-PrMgCl (2.9)		B (150)	81 (87:13)	(223)

Table 8 (Continued)

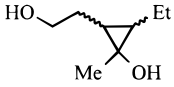
Entry	Starting Ester R^5	R^6	Grignard Reagent (Equiv.)	Alkene Product	Conditions[a] (mol%)	Yield (%) (cis:trans[b])	Ref.
40		Et	*i*-PrMgCl (2.9)		B (150)	76 (81:19)	(223)
41	Ph	Et	*i*-PrMgCl (2.9)		B (150)	88 (93:7)	(223)
42		Et	*i*-PrMgCl (2.9)		B (150)	42 (77:23)	(223)
43		Et	*i*-PrMgCl (2.9)		B (150)	55 (88:12)	(223)
44	Ph	Et	*i*-PrMgCl (2.9)		B (150)	31 (65:35)	(223)
45	Ph	Et	*i*-PrMgCl (2.9)		B (150)	62 (85:15)	(223)
46		Me	 (3.9)		B (110)	30 (1:1.7)	(224)
47	*i*-Bu	Me	 (3.9)		B (110)	14[d]	(224)
48		Me	 (3.9)		B (110)	43[d]	(224)
49		Me	 (3.9)		B (110)	51[d]	(224)

[a] B = $Ti(O\text{-}i\text{-}Pr)_4$. [b] Determined by ^1H NMR. [c] Determined by GC. [d] Isolated yield.

Table 8 (Footnotes)

[a] A: Ti(O*i*-Pr)$_4$. B: ClTi(O*i*-Pr)$_3$. [b] Cis and trans are with respect to the relative positions of the alkyl substituents. [c] Yield of the crude crystalline product is given. [d] As the respective cyclopropanols were found to be unstable, they were isolated as TMS or TBDMS ethers by protection under standard conditions.

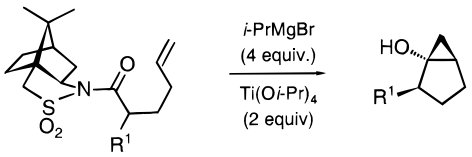
Table 9. 1,2-Disubstituted Cyclopropanols of Type 65 from Homoallyl and 3-Butenyl Carboxylates by Intramolecular Nucleophilic Acyl Substitution (INAS) Reaction (see Scheme 34)

Entry	R^1	R^2	R^3	R^4	Grignard Reagent (Equiv.)	Conditions (mol%)[a]	Yield (%) (*cis*:*trans*[b])	Ref.
1	Me	H	H	H	*i*-PrMgBr (4)	A (200)	93 (42:58)	(215)
2	Me	H	H	H	*i*-PrMgBr (4)	A (200) up to 20 °C	61 (55:45)	(215)
3	Me	Et	H	H	*i*-PrMgBr (4)	A (200) up to 0 °C	33 (59:41)	(215)
						A (200) up to 20 °C	70 (5:95)	
4	Me	H	H	Me	*i*-PrMgBr (4)	A (200)	74 (>3:97)	(215)
5	Me	Me	Me	H	*i*-PrMgBr (4)	A (200) up to 0 °C	28	(215)
						A (200) up to 20 °C	78	(215)
6	*n*-C_5H_{11}	H	H	H	*i*-PrMgBr (4)	A (200)	95 (12:88)	(215)
7	*i*-Pr	H	H	H	*i*-PrMgBr (4)	A (200)	88 (12:88)	(215)
8	1-Propenyl	H	H	H	*i*-PrMgBr (4)	A (200)	78 (7:93)	(215)
9	Ph	H	H	H	*i*-PrMgBr (4)	A (200)	85 (>3:97)	(215)
					n-BuMgCl (5)	B (50)	78 (1:7)	(206)
10	Ph	H	H	H	*n*-BuMgCl (5)	B (50)	15	(206)
11					*i*-PrMgBr (4)	A (200)	<5	(215)

[a] A: Ester (1.0 equiv), Ti(O*i*-Pr)$_4$ (2.0 equiv), *i*-PrMgBr (4.0 equiv), Et_2O, −45 to −40 °C, 1 h or −40 to 20 °C, 2 h, then 20 °C, 2 h. B: Ester (1.0 equiv), ClTi(O*i*-Pr)$_3$ (0.5 equiv), *n*-BuMgCl (5.0 equiv), Et_2O, r. t., 1−2 h. [b] Cis and trans are with respect to the relative positions of the alkyl substituents.

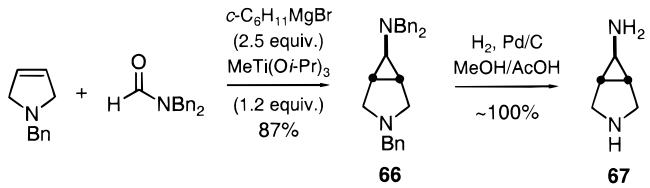
acylcamphorsultame derivatives. Enantiomeric excesses in the products were up to >98% (Scheme 35 and Table 11).[230]

Scheme 35



In view of their versatile new synthesis of dialkylcyclopropylamines from *N*,*N*-dialkylcarboxamides by way of titanacyclopropane intermediates generated from Grignard reagents and XTi(O*i*-Pr)$_3$ (X = O*i*-Pr, Me),[207,211] de Meijere et al. had also soon turned their attention to the additional synthetic potential of titanacyclopropane intermediates generated by ligand exchange. Their first target in mind was the 3-azabicyclo[3.1.0]hexylamine **67**, an essential building block for the commercial antibiotic trovafloxacin.[231] In fact, *N*-benzyl-2,5-dihydropyrrole turned out to rapidly undergo ligand exchange especially with the titanacyclopropane generated from cyclohexylmagnesium halides and XTi(O*i*-Pr)$_3$ (X = O*i*-Pr, Me), and the resulting intermediate efficiently reacted with *N*,*N*-dibenzylformamide to give the tribenzyl-protected *exo*-6-amino-3-azabicyclo[3.1.0]hexane **66** in up to 87% yield.[232] The unprotected diamine **67** was obtained from **66** by catalytic hydrogenation under appropriate conditions (Scheme 36 and Table 12).[232]

Scheme 36



The optimized protocol was applied to a whole range of alkenes and has since been established as

Table 10. Substituted Cyclopropanols by Intramolecular Hydroxycyclopropanation of a Terminally Alkoxycarbonyl-Substituted Alkene via Intermediate Titanacyclopropane Reagents Generated by Ligand Exchange

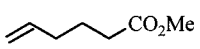
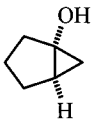
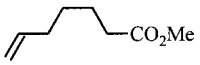
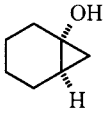
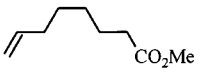
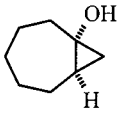
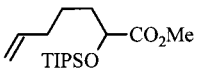
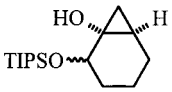
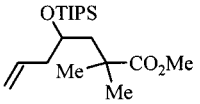
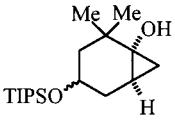
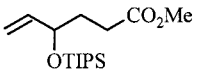
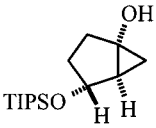
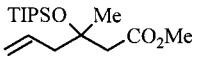
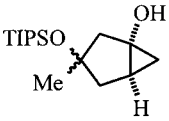
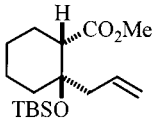
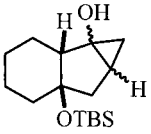
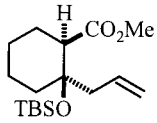
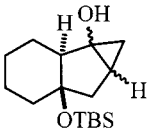
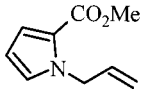
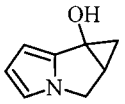
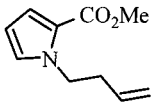
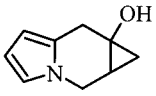
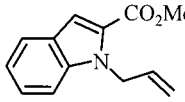
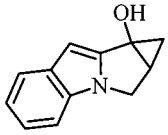
Entry	Starting Unsaturated Ester	Grignard Reagent (Equiv.)	Conditions[a] (mol % $XTi(O\textit{i}\text{-}Pr)_3$[a])	Product	Yield (%) (d. r.)[b]	Ref
1		*n*-BuMgCl (3) (5)	B (50) B (50)		48 55	(206)
2		*n*-BuMgCl (3) (5)	B (50) B (50)		55 62	(206)
3		*n*-BuMgCl (5)	B (50)		11	(206)
4		*n*-BuMgCl (5)	B (50)		76 (2:1)	(206)
5		*n*-BuMgCl (5)	B (50)		75 (1:1)	(206)
6		*n*-BuMgCl (5)	B (50)		14 (1:0)	(206)
7		*n*-BuMgCl (5)	B (50)		58 (7:2)	(206)
8		*n*-BuMgCl (5)	B (50)		70 (2:1)	(206
9		*n*-BuMgCl (5)	B (50)		42 (3:2)	(206)
10		*i*-PrMgBr (2.6)	A (130)		80	(227)
11		*i*-PrMgBr (2.6)	A (130)		80	(227)
12		*i*-PrMgBr (4.0) (2.6)	A (200) A (130)		75 94	(228) (227)

Table 10 (Continued)

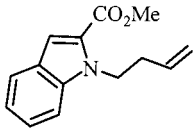
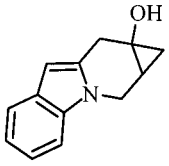
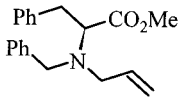
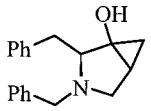
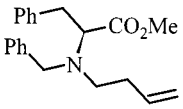
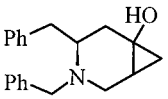
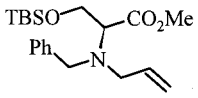
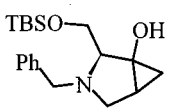
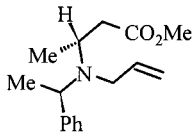
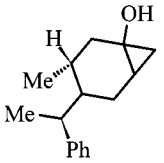
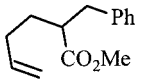
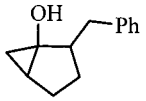
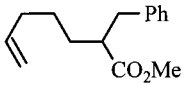
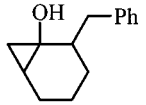
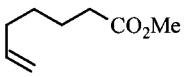
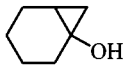
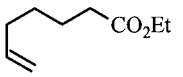
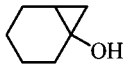
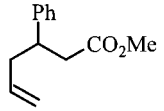
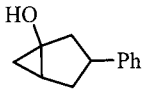
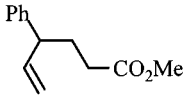
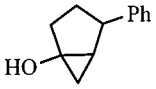
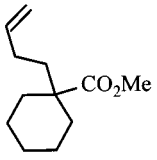
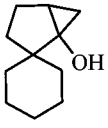
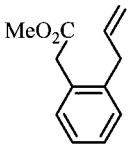
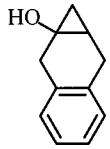
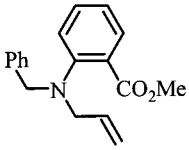
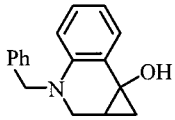
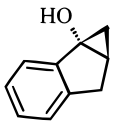
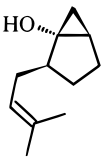
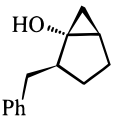
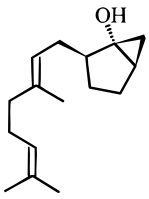
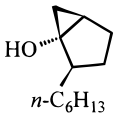
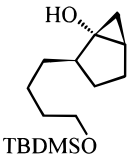
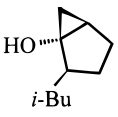
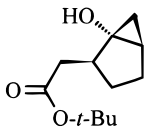
Entry	Starting Unsaturated Ester	Grignard Reagent (Equiv.)	Conditions[a] (mol % $XTi(O\textit{i}\text{-}Pr)_3$[a])	Product	Yield (%) (d. r.)[b]	Ref
13		*i*-PrMgBr (2.6)	A (130)		74	(227)
14		*i*-PrMgBr (2.6)	A (130)		75 (73:27)	(227)
15		*i*-PrMgBr (2.6)	A (130)		76 (92:8)	(227)
16		*i*-PrMgBr (2.6)	A (130)		86	(227)
17		*i*-PrMgBr (2.6)	A (130)		73 (56:44)	(227)
18		*i*-PrMgBr (4.0)	A (200)		77 (66:34)	(228)
19		*i*-PrMgBr (4.0)	A (200)		73 (89:11)	(228)
20		*i*-PrMgBr (4.0)	A (200)		57	(228)
21		*i*-PrMgBr (4.0)	A (200)		52	(228)
22		*i*-PrMgBr (4.0)	A (200)		83 (61:39)	(228)
23		*i*-PrMgBr (4.0)	A (200)		76 (55:45)	(228)
24		*i*-PrMgBr (4.0)	A (200)		88	(228)

Table 10 (Continued)

Entry	Starting Unsaturated Ester	Grignard Reagent (Equiv.)	Conditions[a] (mol % $XTi(Oi\text{-}Pr)_3$[a])	Product	Yield (%) (d. r.)[b]	Ref
25		*i*-PrMgBr (4.0)	A (200)		98	(228)
26		*i*-PrMgBr (4.0) (2.6)	A (200) A (130)		94	(228) (227)

[a] A: $Ti(Oi\text{-}Pr)_4$. B: $ClTi(Oi\text{-}Pr)_3$. [b]Diastereomeric ratio given only when reported in the original literature.

Table 11. Substituted Cyclopropanols from *N*-Acylcamphorsultame and Titanium Reagents Generated by Ligand Exchange on Intermediate Titanacyclopropanes from *i*-PrMgBr and $Ti(Oi\text{-}Pr)_4$ (see Scheme 35)[230]

Entry	Product	Yield (%)	D. r. (*ee*)	Entry	Product	Yield (%)	D. r. (*ee*)
1		90	– (33%)	5		87	>95:5 (>98%)
2		38–86	99:1 (>98%)	6		74	>95:5 (>98%)
3		58	>95:5 (>98%)	7		84	>95:5 (>98%)
4		80	>95:5 (>98%)	8		56	>92:8 (>98%)

an efficient method for the formal dialkylaminocyclopropanation not only of mono- but also of some disubstituted alkenes and cycloalkenes (Table 12) as well as open-chain and cyclic dienes (Table 13).[232] The latter generally give higher yields than nonterminal alkenes and cycloalkenes, except for cyclopentene and norbornene.

Surprisingly, the reaction with substituted 1,3-dienes such as isoprene, 4-methyl-1,3-pentadiene, and myrcene all gave the alkenyldibenzylaminocyclopropanes derived from 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 2−5, Table 13). 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 (entries 9, 10), it must be concluded that only the alkenyldiisopropyloxytitanacyclopropane **68** is initially formed from a substituted conjugated diene by complexation at the least substituted double bond. It is conceivable that **68** then undergoes a titanium shift to the more highly substituted titanacyclopropane **70** before it reacts with the carbonyl group in the formamide. This shift might occur via a

Table 12. *N,N*-Dialkylcyclopropylamines 58 from *N,N*-Dialkylcarboxamides and Titanium Reagents Generated by Ligand Exchange on Intermediate Titanacyclopropanes from Grignard Reagents and XTi(O*i*-Pr)$_3$ (X = O*i*-Pr, Cl, Me, OR)

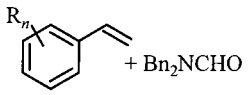
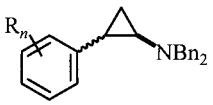
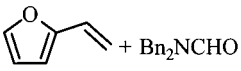
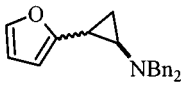
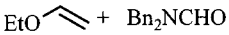
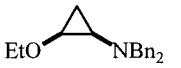
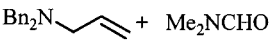
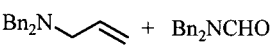
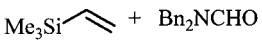
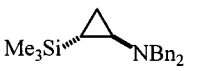
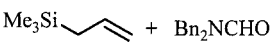
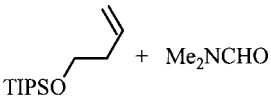
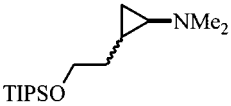
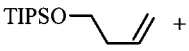
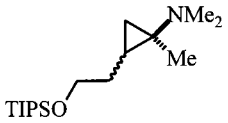
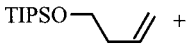
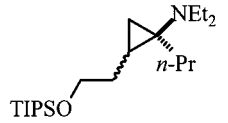
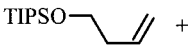
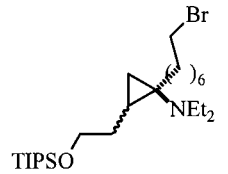
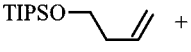
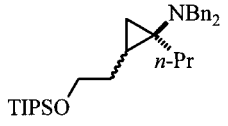
Entry	Alkene, Starting Amide	Product	Yield (%) (d. r.)	Ref.
				
1	R_n = H	R_n = H	66 (1:3.2)	(208, 232)
2	R_n = 4-OMe	R_n = 4-OMe	45[a] (1:1.2)	(232)
3	R_n = 2-CF_3	R_n = 2-CF_3	13[a] (1:4)	(232)
4	R_n = 3-CF_3	R_n = 3-CF_3	56 (1:11)	(232)
5	R_n = 4-CF_3	R_n = 4-CF_3	18[a] (0:1)	(232)
6	R_n = 3,5-$(CF_3)_2$	R_n = 3,5-$(CF_3)_2$	12[a] (1:16)	(232)
7	R_n = 2-Br	R_n = 2-Br	30[a] (1:99)	(232)
8			43 (1:4)	(232)
9			4[a] (1:0)	(232)
10			44[a] (1:5)	(232)
11			39[a] (1:4)	(232)
12			38[a] (0:1)	(232)
13			28[a] (0:1)	(232)
14			61 (1:2.2)	(204)
15	 $Me_2NC(O)Me$		68 (6.3:1)	(204)
16	 $Et_2NC(O)$-*n*-Pr		56 (5.3:1)	(204, 233)
17	 $Et_2NC(O)(CH_2)_6CH_2Br$		60 (7.6:1)	(204)
18	 $Bn_2NC(O)$-*n*-Pr		54 (1.3:1)	(204)

Table 12 (Continued)

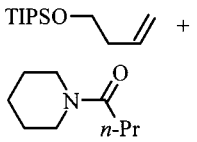
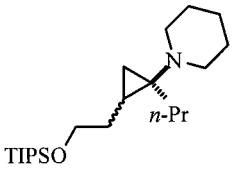
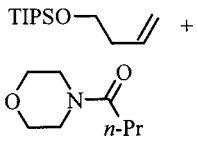
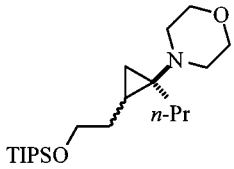
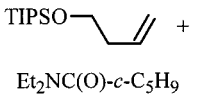
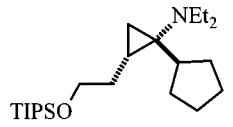
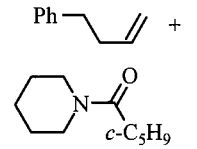
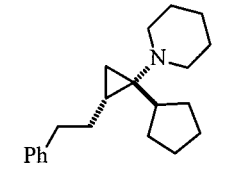
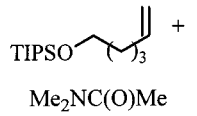
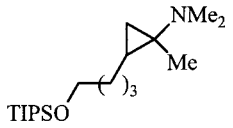
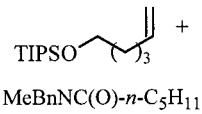
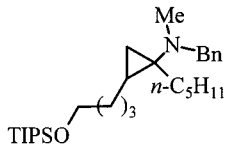
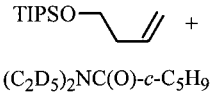
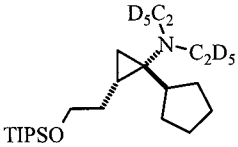
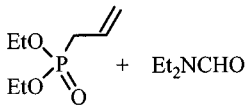
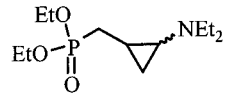
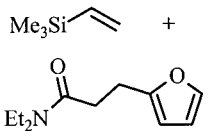
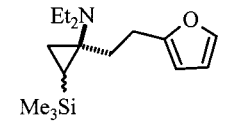
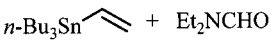
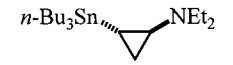
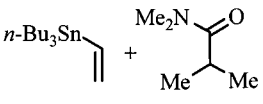
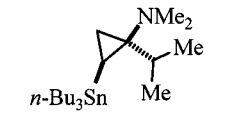
Entry	Alkene, Starting Amide	Product	Yield (%) (d. r.)	Ref.
19			69 (7.3:1)	(204)
20			77 (3.1:1)	(204, 233)
21			n. r.[b]	(233)
22			n. r.	(233)
23			n. r.	(234)
24			n. r.	(234)
25			n. r.	(233)
26			36[a] (1.6:1)	(190)
27			68 (1:6.5)	(224)
28			57	(224)
29			48	(224)

Table 12 (Continued)

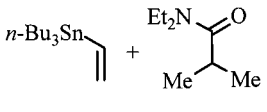
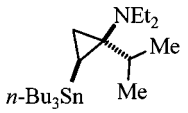
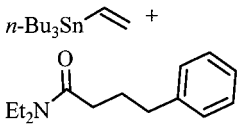
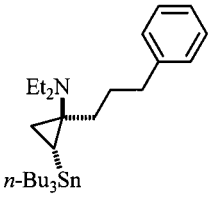
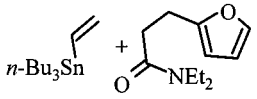
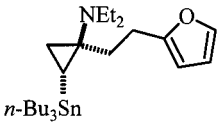
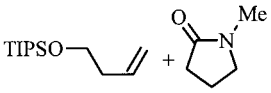
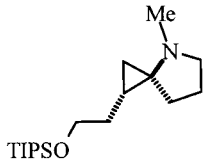
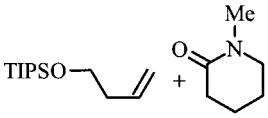
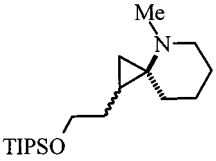
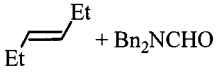
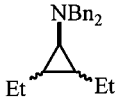
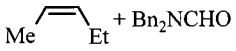
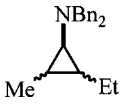
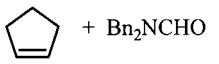
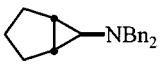
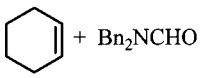
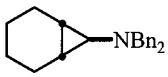
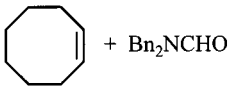
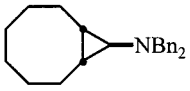
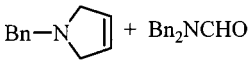
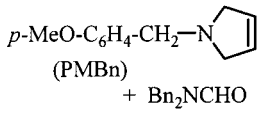
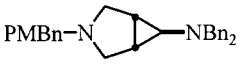
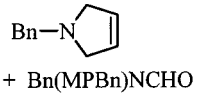
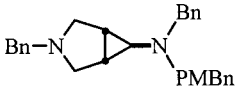
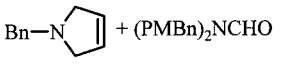
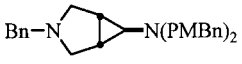
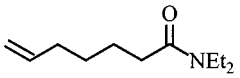
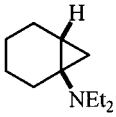
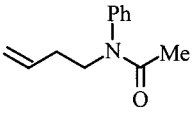
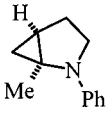
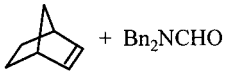
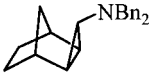
Entry	Alkene, Starting Amide	Product	Yield (%) (d. r.)	Ref.
30			14	(224)
31			43	(224)
32			68	(224)
33			21 (1.0:0)	(204)
34			79 (6.2:1)	(204)
35			13 (1:14:15)	(232)
36			26[a] (1:2:6)	(232)
37			28[a] 92	(232)
38			28 (<4:96)	(232)
39			33	(232)
40			87 (<2:98)	(208b, 232)
41			68	(208b)
42			67	(208b)

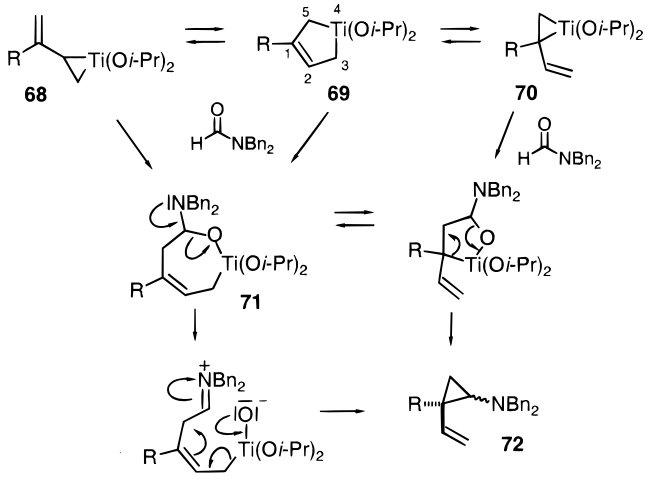
Table 12 (Continued)

Entry	Alkene, Starting Amide	Product	Yield (%) (d. r.)	Ref.
43			37	(208b)
44			64	(204, 233)
45			93	(204)
46			43 (<2:98)	(204)

[a] Not optimized. [b] n.r. = not reported.

1-alkenyltitanacyclopropane **68** to 4-titanacyclopentene **69** rearrangement—corresponding to an intramolecular carbotitanation of an alkene by an allyltitanium species—with subsequent ring contraction to give **70**. Only if **70** were much more reactive than **68** this route would lead to the selective formation of the more highly substituted cyclopropylamine **72** via the corresponding oxatitanacyclopentane. More likely, though, the formamide reacts with the kinetically favored and also thermodynamically more stable **68** via a six-center transition structure to yield the oxatitanacycloheptene **71**, which can only cyclorevert to the observed more highly substituted cyclopropylamine **72**. The seven-membered ring intermediate **71** could also be formed by addition of formamide to **69** via a four-centered transition structure or by ring enlargement of the vinyloxatitanacyclopentane (Scheme 37).[235]

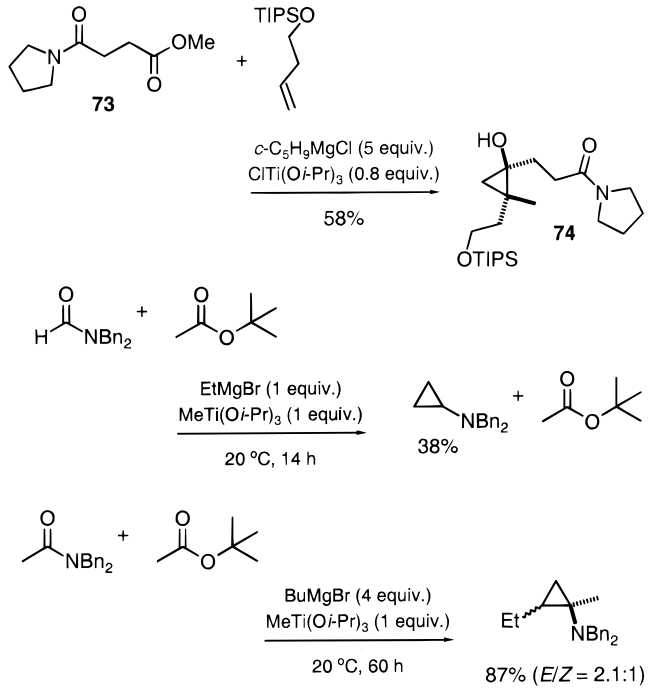
Scheme 37



The formation of the same cyclopropylamine from 2-methyl-1,3-pentadiene as from 4-methyl-1,3-pentadiene (entries 4, 3 in Table 13) 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 6) arising from attack at the central double bond in the triene may be taken to indicate that the reacting species is actually the less substituted titanacyclopropane of type **68** or a titanacyclopentene of type **69** rather than the most highly substituted titanacyclopropane of type **70**.[235]

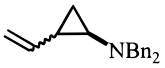
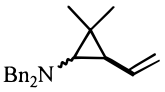
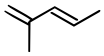
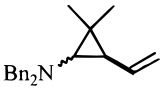
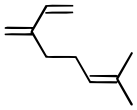
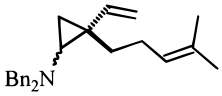
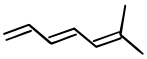
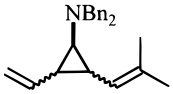
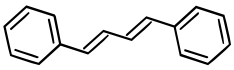
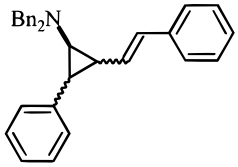
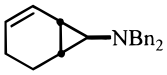
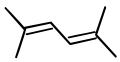
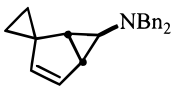
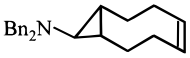
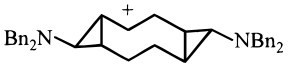
In the hydroxycyclopropanation of alkenes, esters may be more reactive than *N*,*N*-dialkylcarboxamides, as is illustrated by the exclusive formation of the trisubstituted cyclopropanol **74** from the succinic acid monoester monoamide **73** (Scheme 38).[219] However,

Scheme 38



the reactivities of both ester- as well as amide-carbonyl groups can significantly be influenced by steric bulk around them.[201,219] Thus, in an intermolecular competition for reaction with a titanacyclopropane generated from an alkylmagnesium halide and methyltitanium triisopropoxide, between *N*,*N*-

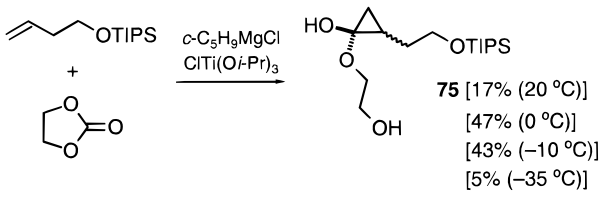
Table 13. 2-Alkenyl-1-(*N*,*N*-dibenzylamino)cyclopropanes Formed from *N*,*N*-Dibenzylformamide and Titanium−Diene Complexes in Situ Generated by Ligand Exchange[232,235]

Entry	Alkene	Product	Yield (%) (d. r.)	Ref.
1			56 (1:2.7)	(232, 235)
2			59 (>98:2)	(232, 235)
3			64 (1:5.3)	(232, 235)
4			27 (1:3)	(232, 235)
5			51 (>98:2)	(232, 235)
6			54 (1:1.5:1.5)	(232, 235)
7			9 (1:0)	(232)
8			58 (2:98)	(232)
9		No conversion	–	(232)
10		No conversion	–	(232)
11		No conversion	–	(232)
12			trace	(232)
13			11 (<2:98)	(232)
			2.2 (>2:98)	

dibenzylformamide and *tert*-butyl acetate as well as between *N*,*N*-dibenzylacetamide and *tert*-butyl acetate, the amide both times won to yield only the corresponding cyclopropylamine (Scheme 38).[236]

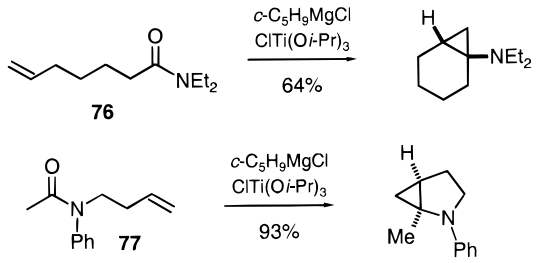
Dialkyl carbonates and cyclic carbonates can be converted to cyclopropanone hemiacetals in moderate yields with titanacyclopropane intermediates generated by ligand exchange with terminal alkenes.[219,225] The best yields have been obtained with cyclic carbonates at −10 to 0 °C. Higher reaction temperatures (even ambient) lead to a considerable decrease of the yield (Scheme 39).[225]

Scheme 39



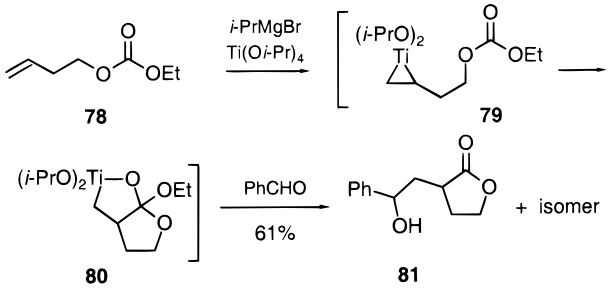
These aminocyclopropanations of terminal alkenes also work intramolecularly in two versions: Terminally ethenyl-substituted *N*,*N*-dialkylcarboxamides such as **76** yield 1-(dialkylamino)bicyclo[*n*.1.0]alkanes, while (*ω*-alkenylamino)carboxamides such as **77** lead to 1-alkyl-2-azabicyclo[*n*.1.0]alkanes (Scheme 40 and Table 12).[204]

Scheme 40



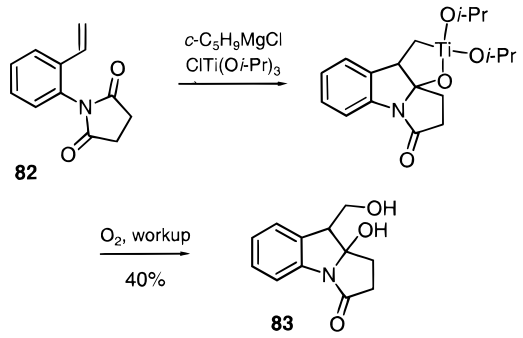
In all of the above-mentioned reactions of organotitanium 1,2-dicarbanionic equivalents leading to the formation of cyclopropane compounds, both new carbon−carbon bonds are formed with the same carbon atom of a single electrophile. The synthetic potential of 1,2-dicarbanionic organotitanium intermediates, however, should be considerably expanded if effective reactions for two consecutive C,C-bond formations with two different electrophiles will be elaborated. Some recent reports indicate that this reaction principle can possibly be realized[225,237−239] in the form of intramolecular new carbon−carbon bond formations in terminally ethenyl-substituted carbonates such as **78**,[225,239−241] ketones,[159,242] esters,[243] and imines.[244] For example, the bicyclic oxatitanacyclopentane intermediate **80** of the primary adduct **79** has successfully been intercepted intermolecularly with benzaldehyde to form 2-(2′-hydroxy-2-phenylethyl)-4-butyrolactone (**81**) and an isomer thereof in good total yield (Scheme 41).[237]

Scheme 41



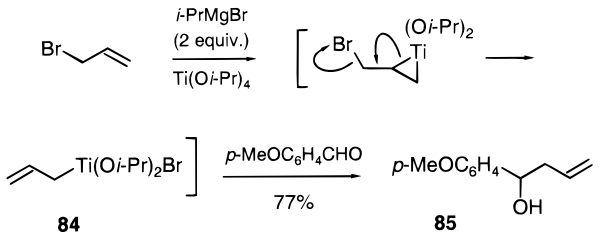
The intramolecular trapping of an oxatitanacyclopentane intermediate formed from readily available *N*-(2′-ethenylphenyl)succinimide (**82**) and analogous (*ω*-ethenylalkyl)imides is the key step in an elegant new approach to the frameworks of the mithomycine antibiotic as well as pyrrolizidine and indolizine alkaloids.[238] The oxatitanacyclopentane intermediate formed from **82** upon treatment with cyclopentylmagnesium chloride in the presence of chlorotitanium triisopropoxide readily reacts with oxygen bubbled through the solution and is subsequently hydrolyzed to the azatricyclic compound **83** having the characteristic skeleton and functionalities of mithomycine (Scheme 42).

Scheme 42



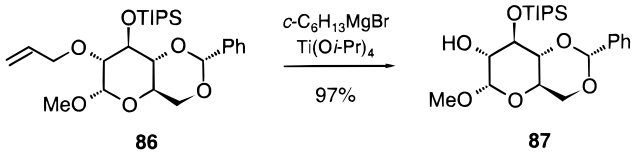
Formally, dicarbanionic titanacyclopropane intermediates with a *β*-leaving group preferentially undergo an intramolecular *β*-elimination to form an allyltitanium species with monocarbanionic reactivity.[245−247] This type of transformation has first been reported by Sato et al., who generated allyltitanium reagents from allyl halides, carboxylates, and sulfides.[245−247] The allyltitanium reagents thus prepared showed a similar reactivity pattern in terms of chemo- and stereoselectivities in their additions to carbonyl groups of aldehydes, saturated as well as α,*β*-unsaturated ketones,[245,246] and imines[246,248] as the allyltriisopropoxytitanium species obtained from allyllithium or -magnesium compounds with ClTi(O*i*-Pr)$_3$. For example, *p*-methoxybenzaldehyde, when treated with the allyltitanium reagent **84** generated from allyl bromide, isopropylmagnesium bromide, and titanium tetraisopropoxide, gave the homoallyl alcohol **85** in good yield (Scheme 43).

Scheme 43



This type of transformation of titanacyclopropane intermediates generated by ligand exchange also is the basis for a new method that allows the selective cleavage of allyl ethers and allyl carboxylates.[249] Acetal and trialkylsilyloxy groups are not affected under the mildly basic reaction conditions as demonstrated by the quantitative deprotection of the allyl ether **86** to the alcohol **87** (Scheme 44).[249]

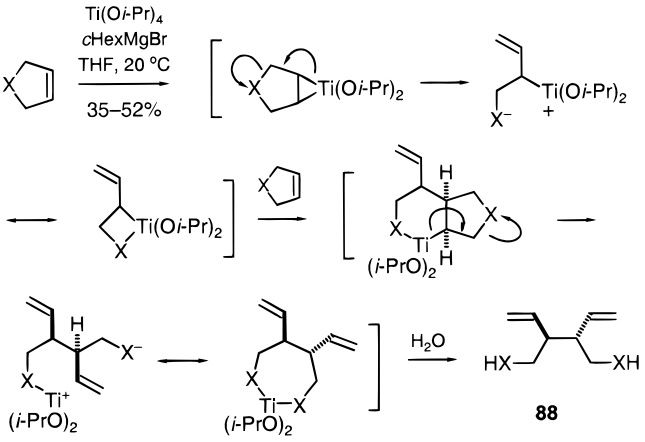
Scheme 44



86 **87**

The cyclic allyl ether 2,5-dihydrofuran is also cleaved upon treatment with the low-valent titanium species generated from titanium tetraisopropoxide and cyclohexylmagnesium bromide, but another molecule of dihydrofuran subsequently inserts into the Ti−C bond of the allyltitanium intermediate formed, and the 4,5-diethenyl-2,7-dioxatitanacycloheptane formed after ring opening of the second furan ring upon hydrolysis yields 2,3-diethenylbutane-1,4-diol. This dihydrodimerization occurs with complete diastereoselectivity to yield the D,L-isomer, and in the presence of titanium bis(4*R*,5*R*)-taddolate instead of Ti(O*i*-Pr)$_4$, the diol is formed with up to 94% enantiomeric excess. *N*-Sulfonyl-2,5-dihydropyrroles react analogously to yield *N*,*N*′-disulfonyl-2,3-diethenylbutane-1,4-diamines **88** (Scheme 45).[250]

Scheme 45



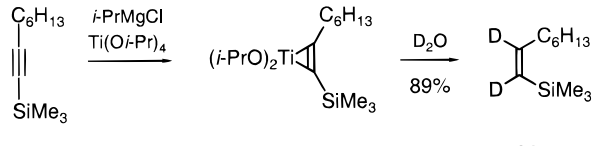
88

X = O, NSO_2R (R = Me, *p*-Tol, *o*-Tol, *p*-ClC_6H_4, β-Naphth)
d,*l*/*meso* ≥ 96:4
X = O: 94% *ee* with Ti-bis(4*R*,5*R*)-taddolate

C. Ligand Exchange with Alkynes

Disubstituted acetylenes react rapidly with titanacyclopropane intermediates, generated from Grignard reagents and titanium tetraisopropoxide, liberating an alkene to form titanacyclopropenes which are ethylene 1,2-dicarbanionic equivalents.[251] For example, the terminally trimethylsilyl-substituted alkyne **89** readily gives the titanacyclopropene intermediate **90** as evidenced by its reaction with deuterium oxide to yield the *cis*-dideuterated alkene **91** (89%) (Scheme 46). By analogy, an efficient access to (*Z*)-vinyltinacetals from easily available alkynyltin derivatives via corresponding titanacyclopropene intermediates has recently been elaborated.[252]

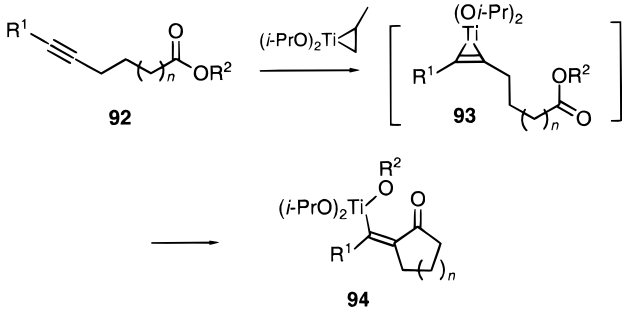
Scheme 46



89 **90** **91**

The titanacyclopropene intermediates are also reactive toward carbonyl compounds,[242,251,253,254] esters,[227,239,255] imines,[244,256−258] carbon dioxide,[258] and carbon monoxide.[256] These reactions can be interrupted at the stage of a single coupling with an electrophile, and the resulting 1:1 adduct can then intercept another electrophile at its Ti−C bond.[239,251,253,256,258] In a titanacyclopropene intermediate such a **93** generated from an acetylenic ester **92**, intramolecular carbon−carbon bond formation readily occurs to yield α-(titaniumalkylidene)cyclopentanones and -cyclohexanones **94**, which can be intercepted with various electrophiles (Scheme 47).[159,239] Chirally modified

Scheme 47

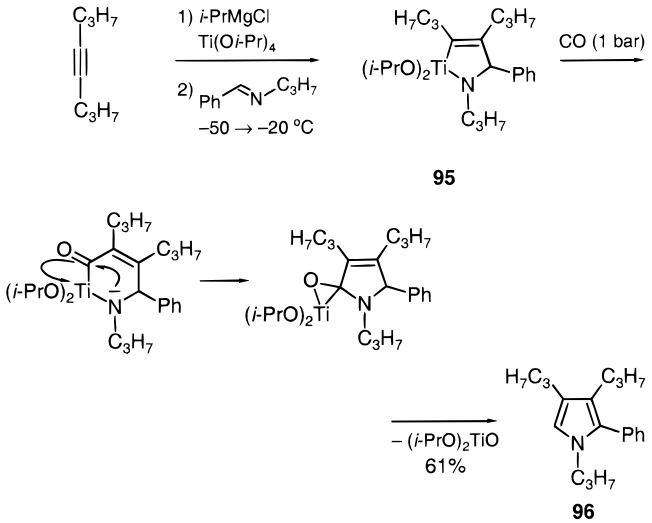


92 **93** **94**

titanacyclopropenes generated from chlorotris[(−)-menthyloxy]titanium, *i*-PrMgBr, and disubstituted acetylenes add to carbonyl compounds with moderate enantiofacial selectivity.[254]

Azatitanacyclopentene intermediates of type **95** are formed by insertion of imines into titanacyclopropenes,[244,256−258] and they react with carbon monoxide[256] and carbon dioxide[219] under atmospheric pressure to eventually afford the correspondingly substituted pyrroles, e.g., **96**, and 1,5-dihydro-2*H*-pyrrol-2-ones, respectively. The formation of **96** can be rationalized as a sequence of carbon monoxide inserting into the titanium−carbon bond of the azatitanacyclopentene **95** followed by intramolecular nucleophilic attack of the nitrogen at the carbonyl carbon

Scheme 48

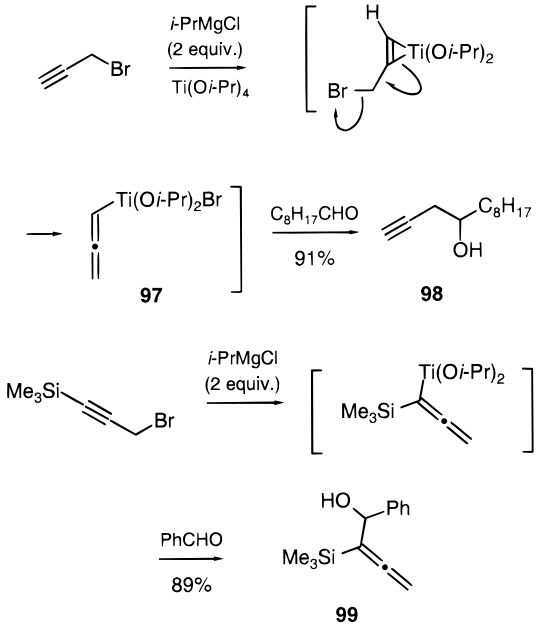


95 **96**

to form an azaoxatitanaspiro[2.4]heptene which, by elimination of diisopropyloxytitanium oxide and hydrogen migration, eventually yields the tetrasubstituted pyrrole **96** (Scheme 48). In view of the operational simplicity of the procedure and the ready availability of the starting materials, this appears to be an attractive new method for the preparation of highly substituted five-membered nitrogen heterocycles.

Alkynes with a leaving group such as halide or acetate in the propargylic position react with isopropylmagnesium chloride in the presence of $Ti(O\textit{i}\text{-}Pr)_4$ to yield allenyltitanium reagents by β-elimination in the titanacyclopropene intermediates initially formed by ligand exchange.[259,260] Propargyl bromide is thus very efficiently converted to the unsubstituted allenyltitanium reagent **97** which, upon reaction with an aldehyde such as nonanal, gives the homopropargyl alcohol **98** in excellent yield without contamination by the corresponding allenyl alcohol (Scheme 49),

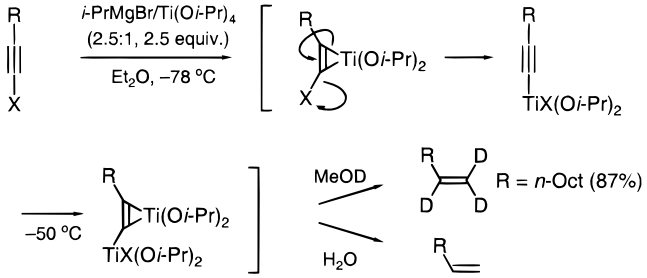
Scheme 49



while the titanium reagent derived from 1-trimethylsilyl-3-bromo-1-propyne reacts with benzaldehyde to afford (1′-trimethylsilylallenyl)benzyl alcohol **99** exclusively. An intramolecular version of this type of reaction allows one to efficiently prepare cyclopentenols with an ethenylidene or alkynyl moiety at the β-position.[260]

Treatment of a 1-halo- or a 1-phenylthio-substituted alkyne with 2.5 equiv of a 2.5:1 mixture of isopropylmagnesium bromide and titanium tetraisopropoxide in ether at −78 to −50 °C led to the ready formation of a titanotitanacyclopropene in high yield, as evidenced by the isolation of the corresponding 1,1,2-trideuterated terminal alkene upon solvolysis with [D_1]methanol and the terminal alkene, respectively, upon hydrolysis (Scheme 50).[261] The titanotitanacyclopropene intermediate is an interesting alkene 1,1,2-tricarbanion equivalent, and it remains to be seen which types of electrophiles will selectively react with it.

Scheme 50



R	X	%
Oct	Cl	90
Hex	Br	75
Hex	I	65
Hex	SPh	70
p-Tol	Cl	95
t-AmylO$(CH_2)_2$	Cl	93

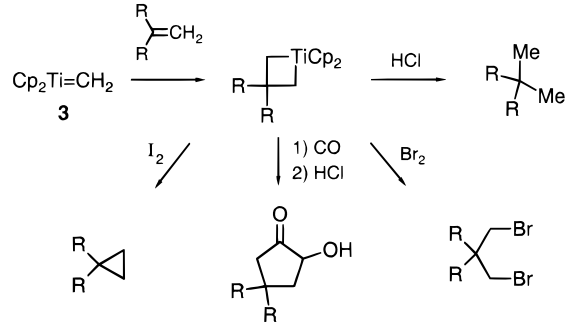
IV. Interconversion of Dicarbanionic Equivalents

The transformations of organometallic monoanionic building blocks into their dicarbanionic counterparts considered above are all based on disproportionation reactions of the corresponding dialkyltitanium intermediates. Modifications of 1,1- and 1,2-dicarbanionic equivalents can be achieved by metathesis and alkene exchange reactions. The capability of dianionic organotitanium compounds to add to alkenes and alkynes under mild conditions to yield carbometalation products can also serve as a tool for the generation of dicarbanionic organotitanium intermediates with the two carbanionic centers separated by one or more carbon atoms. This indirect access to dicarbanionic equivalents has at least been realized for the generation of 1,3- and 1,4-dicarbanionic organometallic reagents.

A. 1,3-Dicarbanionic Equivalents

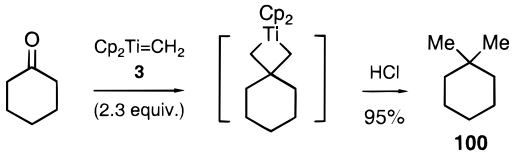
The [2+2] cycloaddition of a titaniumcarbene complex, usually generated by dissociation of Tebbe's reagent **2**, to an alkene affords the corresponding titanacyclobutane intermediate.[76,82,83,262−264] Such titanacyclobutanes, besides being able to undergo cycloreversion to form a titanaalkylidene intermediate,[69,82,83,96,265−273] can also react as usual 1,3-dicarbanionic organometallics[81,96,274,275] as, for example, their reactions with hydrogen chloride, halogens and carbon monoxide demonstrate (Scheme 51)

Scheme 51



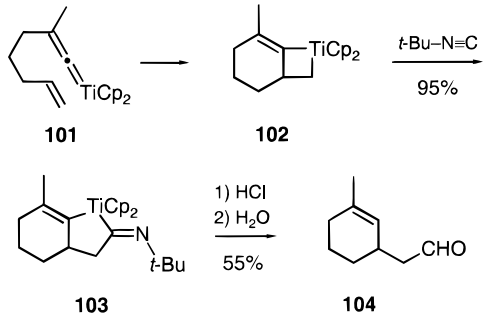
Since terminal alkenes can be prepared from carbonyl compounds with Tebbe's reagent, the sequence of a [2+2] cycloaddition with another equivalent of the titanaalkylidene and subsequent protiodemetalation may be used as a method for the 2-fold alkylation of a carbonyl carbon. Thus, protonolysis of the titanacyclobutane intermediate prepared from cyclohexanone and an excess of Tebbe's reagent gave 1,1-dimethylcyclohexane (**100**) in excellent yield (Scheme 52).[54]

Scheme 52



Bicyclic methylenetitanacyclobutane **102**, formed by an intramolecular [2+2] cycloaddition of the titanocenealkenylidene complex **101**, also reacts as a 1,3-dicarbanionic equivalent with various electrophiles. Thus, insertion of *tert*-butyl isocyanide into **102** occurred regioselectively to afford the imino complex **103**, which gave aldehyde **104** upon acidic work up (Scheme 53).[95b] Titanacyclobutenes, formed

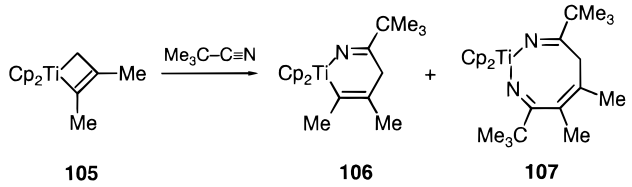
Scheme 53



by intermolecular [2+2] cycloadditions of in situ generated titaniumalkenylidene complexes to alkynes, react with isocyanides in an analogous way and afford alkenylketeneimines in high yields.[276]

2,3-Dialkyltitanacyclobutenes, as for example **105**, react with nitriles with lower regioselectivity to yield single-insertion **106** and double-insertion **107** products in a ratio of 40:60 (Scheme 54).[91,277] Control

Scheme 54



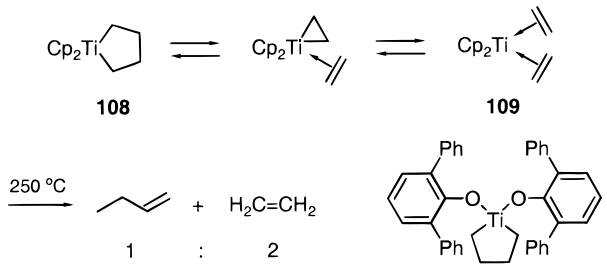
experiments have shown that the double-insertion product **107** cannot be formed by further reaction of the single-insertion product **106**. The authors therefore suggest that **107** results from an insertion of another nitrile molecule into an isomeric single-insertion intermediate formed by insertion of the first nitrile molecule into the metal−vinyl carbon bond or may be connected with proceeding of cascade pericyclic organometallic reactions.

Titanacyclobutenes can react as 1,3-dicarbanionic organometallics also with certain other electrophiles;[91,92,278−281] in particular, they may be transformed into four-membered phosphorus heterocycles by reaction with dichloro(phenyl)phosphine and related phosphorus dichlorides.[92]

B. Interconversion of 1,2- and 1,4-Dicarbanionic Equivalents

Tetramethylenetitanocene **108**, prepared from titanocene dichloride by reaction with 1,4-dilithiobutane, is significantly more stable than the acyclic di-*n*-butyltitanocene analogue. The latter decomposes rapidly at −50 °C, while the titanacyclopentane **108** is reasonably stable at 0 °C.[282] In contrast to the thermal decomposition of the dibutyl derivative, that of the titanacyclopentane **108** (0 °C, 4 h) does not only yield C_4 hydrocarbons but considerable amounts of ethene (Scheme 55). The increased stability of the

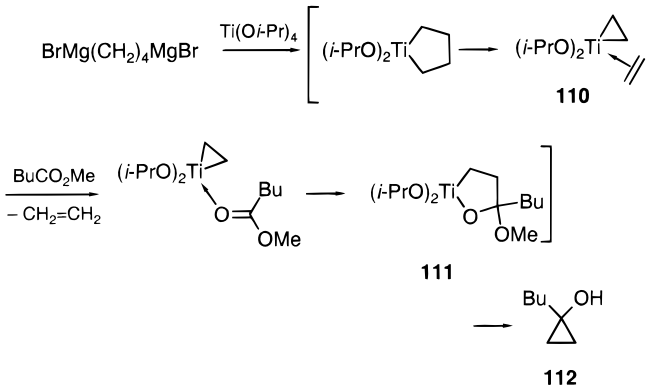
Scheme 55



titanacyclopentane apparently results from a retarded β-elimination of metal hydride in the metallacycle, and the formation of ethylene from **108** has been rationalized as a straightforward reductive elimination via the bisethylenetitanocene intermediate **109**.[282] A pure sample of tetramethylenetitanocene **108** upon warming to above −35 °C produced ethylene as the major product. The 2,2,5,5-tetradeuterio-labeled analogue at −45 °C underwent isomerization of the butene fragment more rapidly than fragmentation to give ethene.[283] These results led to the conclusion that the intramolecular reorganization with reversible carbon−carbon bond cleavage to an intermediate bisethylene complex **109** is faster than the decomposition to produce ethylene.[283] The molecular structure of [Ti(OC_6H_3-2,6-Ph_2)$_2$-(CH_2)$_4$] (Scheme 55) in the crystal is clearly that of a titanacyclopentane, and the $^{13}C-H$ coupling constants in the NMR spectrum are also inconsistent with a bisethylene complex.[150] There is, however, evidence in the ^1H NMR spectrum of this titanacyclopentane at elevated temperature (60 °C) for a facile, reversible reorganization into a bisethylene species. The reverse transformation of the bisethylene complex **109** into the titanacyclopentane **108** may be viewed as a four-electron insertion process. The ring strain in titanacyclopropane intermediates as well as the participation of the metal d-orbitals in the covalent metal−carbon bond probably plays an important role in their transformation into titanacyclopentanes by simple [2_s+2_s] reactions.[149]

The observation that 1-substituted cyclopropanols are obtained, albeit in moderate yields, upon reaction of esters such as methyl pentanoate with 1,4-di(bromomagnesium)butane in the presence of titanium tetraisopropoxide also corroborates the formation of titanacyclopropane **110** from titanacyclopentane derivatives (Scheme 56).[284] Apparently, an ester

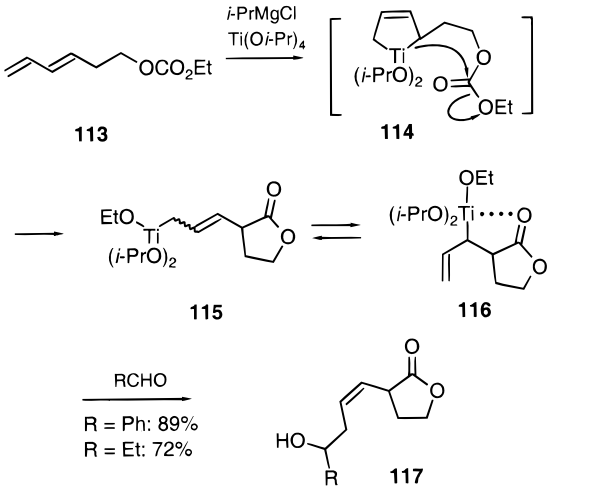
Scheme 56



readily displaces an ethylene ligand in **110**, and a subsequent intramolecular [2_s+2_π] cycloaddition leads to the oxatitanacyclopentane **111**, the precursor to 1-butylcyclopropanol **112**.

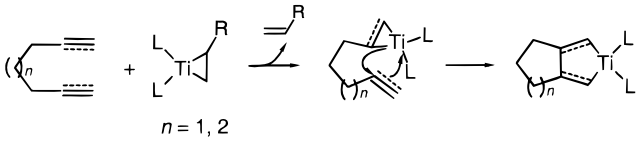
The transformation of monoanionic organometallics into titanacyclopropane intermediates with a dicarbanionic reactivity pattern, followed by [2_s+2_π] cycloaddition to an alkene or an alkyne,[150,285−292] is a convenient and flexible access to 1,4-dicarbanionic equivalents. For example, the treatment of hexa-3,5-dienyl ethyl carbonate **113** with isopropylmagnesium chloride in the presence of Ti(O*i*-Pr)$_4$ must give the titanacyclopentene intermediate **114**, which intramolecularly reacts with the ester group to afford the equilibrating allyltitanium species **115**, **116** with a γ-butyrolactone moiety. The latter adds regio- and diastereoselectively to aldehydes to give the homoallyl alcohols **117** (Scheme 57).[293]

Scheme 57



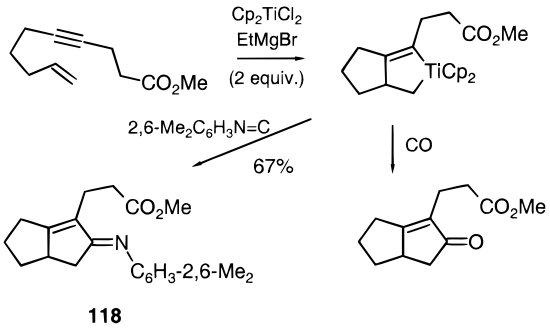
This approach has mainly been used to generate titanabicycles by intramolecular [2_s+2_π] cycloaddition[294] of intermediate titanacyclopropanes[295] generated from the corresponding enynes[290,296−298] as well as diynes (Scheme 58).[297,299]

Scheme 58



Thus, Buchwald et al. found that the combination of Cp_2TiCl_2 with EtMgBr provides an efficient reagent for the reductive cyclization of enynes.[290] It is noteworthy that, in contrast to the analogous procedures with low-valent zirconium reagents,[294] enynes with ester groups could also be cyclized in good yields with retention of the functionality.[290] The titanabicycles formed may then be transformed into functionalized bicyclic iminocyclopentenes as, for example, bicyclic imine **118** by the reaction with an isocyanide[290] or cyclopentenones with carbon monoxide (Scheme 59).[300,301]

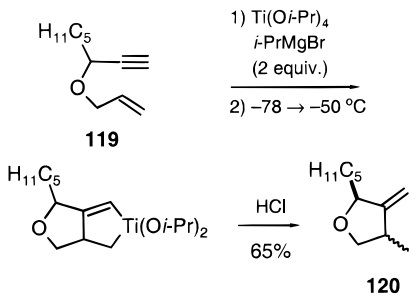
Scheme 59



Intramolecular reductive cyclizations of 1,7-octadienes as well as intermolecular regio- and stereoselective C,C-coupling reactions of some alkenes and cycloalka-1,3-dienes via the corresponding titanacyclopropane intermediates as a sacrificed source of 1,2-dicarbanionic building blocks generated from titanium tetraaryloxides and 2 equiv of *n*-butyllithium have also been reported.[285,288,302−304] As a more convenient reagent system in a practical sense for the generation of titanacyclopentanes by intramolecular [2_s+2_π] cycloaddition of a titanacyclopropane intermediate to a multiple bond, Sato et al.[289,293,296−299] recommend use of isopropylmagnesium halide and titanium tetraisopropoxide. The reactions are conducted by adding *i*-PrMgBr [two equivalents with respect to Ti(O*i*-Pr)$_4$] to a mixture of the bis-unsaturated substrate and a slight excess of Ti(O*i*-Pr)$_4$ in ether at −78 °C, then keeping the reaction mixture at −50 °C for a few hours. This *i*-PrMgBr/Ti(O*i*-Pr)$_4$ reagent was successfully applied even for the cyclization of enynes with an unprotected terminal triple bond. Thus, the substituted allyl propargyl ether **119** could be smoothly transformed into the corresponding 3-methylenetetrahydrofuran **120** by subsequent acidic work up of the reaction mixture (Scheme 60).[297]

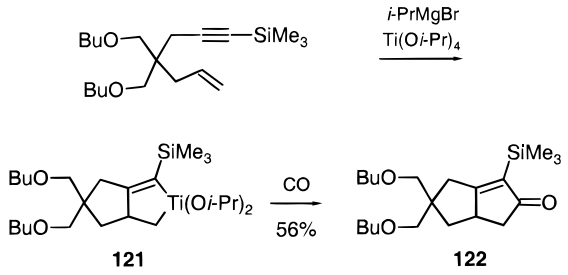
In contrast, unprotected diynes with two terminal triple bonds gave complex mixtures of products. Yet after protection of the acetylenic termini with trimethylsilyl groups, the cyclizations could be per-

Scheme 60



formed in excellent yields.[289,296−299] Titanacyclopentadienes with a 1,4-dicarbanionic reactivity pattern generated by this way have been quenched with deuterium oxide,[289,296,297] iodine,[297,298] aldehydes,[289,296,297,299] ketones,[289,296] carbon monoxide and carbon dioxide.[297] An example is the preparation of the substituted bicyclo[3.3.0]oct-1-en-3-one **122** by reaction of the intermediate titanacyclopentene **121** with carbon monoxide (Scheme 61).[297] An interesting

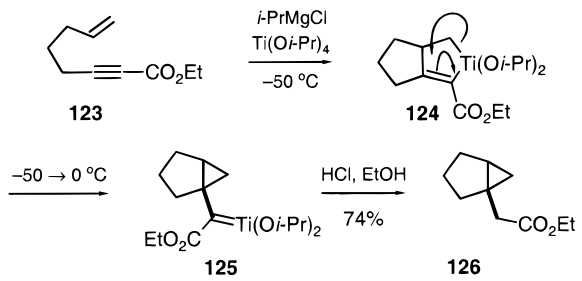
Scheme 61



modification of this convenient method for the construction of bicyclic skeletons uses bisunsaturated substrates containing an α,*β*-unsaturated ester moiety.[289,296,305] The second ring closure in this case occurs by intramolecular attack of one of the carbanionic centers on the titanium intermediate at the ester group which leads to a titanium enolate that can be trapped with an added external electrophile. This methodology circumvents the use of carbon monoxide for the preparation of bicyclic ketones.

1,6-Enynes with a terminal propargylic moiety underwent reductive cyclization to a titanacyclopentene intermediate, but this subsequently underwent ring contraction to a cyclopropylmethylidenetitanium complex which was diprotiodemetalated. For example, ethyl oct-7-en-2-ynoate **123**, upon treatment with *i*-PrMgCl and Ti(O*i*-Pr)$_4$ at −50 °C, afforded, after acidic hydrolysis, ethyl 2-(1′-bicyclo[3.1.0]hexyl)-acetate **126** (Scheme 62).[296]

Scheme 62



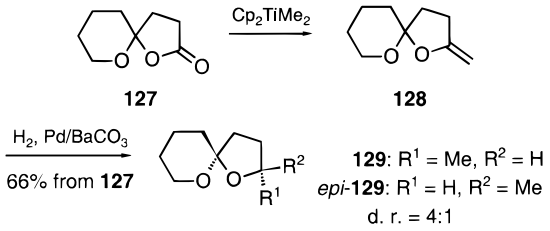
The formation of the cyclopropane ring in this reaction has been rationalized as an intramolecular Michael-type addition of the alkyl-carbon−titanium bond onto the α,*β*-unsaturated ester moiety of the intermediate titanabicyclo[3.3.0]octenecarboxylate **124**. The intermediacy of the titaniumcarbene complex **125** (or the corresponding biscyclopentadienyl species) has been confirmed by deuteriolysis with DCl to yield the ester, which was completely deuterated in the two α-positions as well as by reaction with diethyl ketone to give the α-(diethylmethylene)-carboxylate. This original transformation of a 1,4-dicarbanionic organotitanium intermediate has successfully been applied toward the construction of the bicyclo[3.3.0]octane skeletons of terpenic hydrocarbons (see below).

V. Applications in Natural Product Syntheses

A. 1,1-Dicarbanionic Equivalents

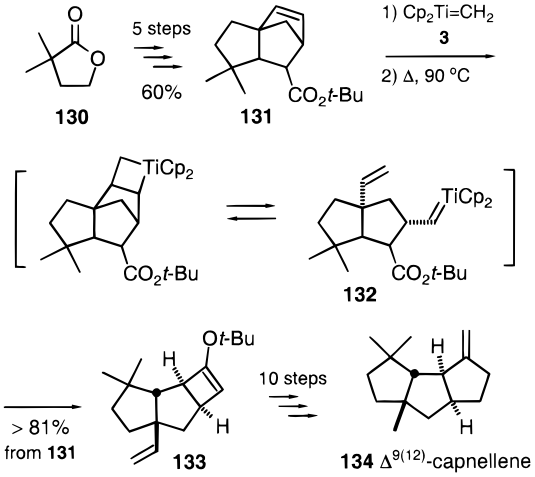
The organotitanium 1,1-dicarbanionic equivalents have found several applications in the synthesis of natural products mainly for methylenations of carbonyl compounds[305,306] and esters.[49,89,307] Total syntheses of the pheromones **129** of the common wasp and the olive fruit fly by methylenation of the spirolactone **127** in the key step have been accomplished.[308] Attempts to methylenate the spirolactone **127** to the enol ether **128** using Tebbe's reagent had been unsuccessful and led to fragmentation of the spiroketal moiety, but treatment of **127** with Petasis' reagent afforded the enol ester **128** in excellent yield. Catalytic hydrogenation of the latter gave a 4:1 mixture of the racemic pheromones **129** and *epi*-**129**. The natural pheromone is a 1:1 mixture of **129** and *epi*-**129** (Scheme 63).

Scheme 63



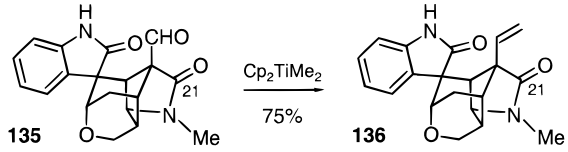
An elegant 3-fold application of alkylidenetitanium intermediates as reagents to build up the skeleton of linear triquinane sesquiterpenes has been elaborated by Grubbs et al. Starting from α,α-dimethylbutyrolactone **130**, they performed an efficient synthesis of (±)-$\Delta^{9(12)}$-capnellene **134** using a metathesis-type reaction of the tricyclic substrate **131** to generate the functionalized alkylidenetitanocene **132** as a key step.[265,309] The intramolecular trapping of the alkylidenetitanocene moiety in **132** by the *endo*-ester functionality yielded the substituted tricyclo[5.3.0.0^{2,5}]-dec-3-ene **133**, which could be transformed to the target product **134** in 10 additional steps in good yield. The final introduction of the methylene group in **134** was achieved in 93% yield by methylenation of a carbonyl group at this position in a corresponding precursor using Tebbe's reagent **2** (Scheme 64).

Scheme 64



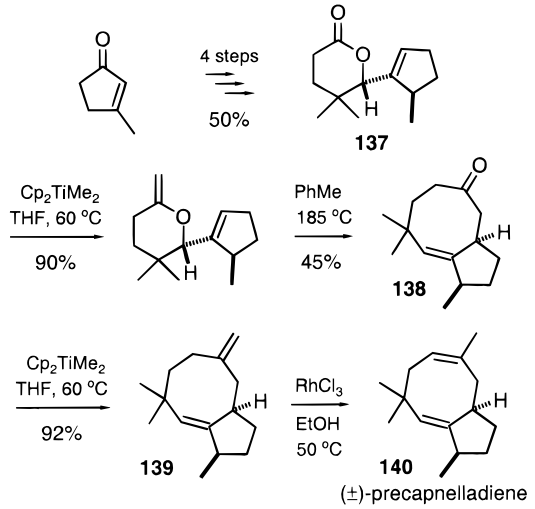
In an approach to the 21-oxo derivative **136** of the alkaloid gelesemnine, the bridgehead vinyl group was established by selective methylenation of the bridgehead aldehyde functionality (75% yield) in the tetracyclic bisamide **135** using dimethyltitanocene (Scheme 65).[306]

Scheme 65



In a total synthesis of the sesquiterpene precapnelladiene **140** in racemic form, Petasis et al. applied the titanium-mediated methylenation of the δ-cyclopentenyl-substituted lactone **137** to obtain a bicyclic allyl vinyl ether which, by a Claisen rearrangement, yielded the key intermediate for the cyclooctanoid natural product **140**.[99,110,307,310] The olefination was not only applied to the intermediate lactone **137**, prepared from 3-methylcyclopent-2-enone in four steps, but also to the cyclooctenone **138**, and both transformations proceeded smoothly, yet the isomerization of the methylenecyclooctene derivative **139** with $RhCl_3$ in ethanol only led to a 1:1 mixture of the starting material **139** and (±)-precapnelladiene **140** (Scheme 66).[99]

Scheme 66

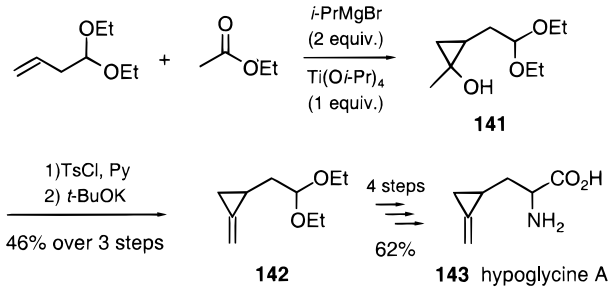


B. 1,2-Dicarbanionic Equivalents

Several applications of organotitanium 1,2-dicarbanionic equivalents in syntheses directed at natural products, e.g., for the construction of a cyclopropane ring present in the target molecule,[220] the elaboration of a branched carbon skeleton,[216] or α,β-unsaturated ketone key intermediates[195] as well as stereoselective hydrogenation of acetylenes to *cis*-1,2-disubstituted alkenes[311] have been reported in recent years.

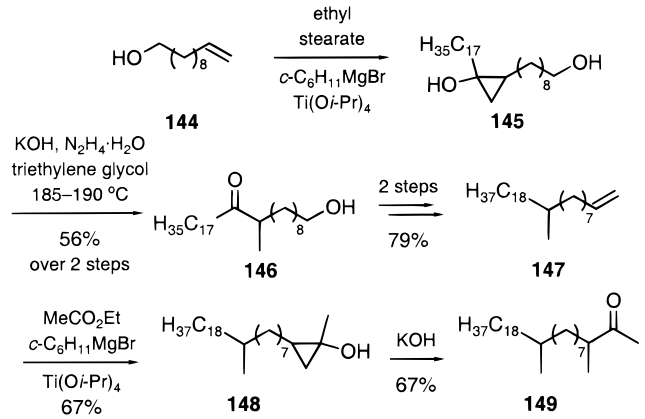
Thus, in a novel synthesis of hypoglycine A **143**, hydroxycyclopropanation of ethenylacetaldehyde diethyl acetal followed by formal dehydration of the cyclopropanol **141** via its intermediate tosylate, gave the methylenecyclopropane key precursor **142** to the target amino acid (Scheme 67).[220]

Scheme 67



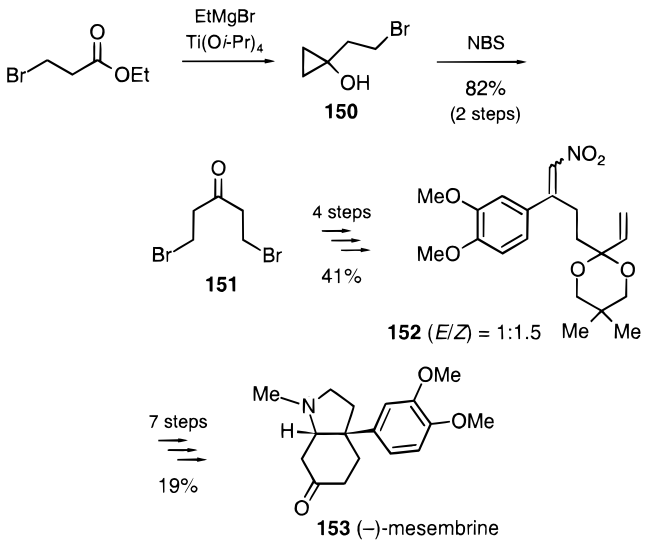
A new convenient approach to 3,11-dimethylnonacosan-2-one (**149**), a component of the sex pheromone of the German cockroach *Blattella germanica*, using 1,2-disubstituted cyclopropanols as key intermediates has been elaborated.[216] The construction of the branched chain of **149** is based on the regioselective base-induced cleavage of 1,2-disubstituted cyclopropanols **145** and **148** to the corresponding α-methyl ketones **146** and **149**.[312] The key compounds **145** and **148** were prepared by hydroxycyclopropanation of the alkenes **144** and **147** with ethyl stearate and ethyl acetate, respectively (Scheme 68).

Scheme 68



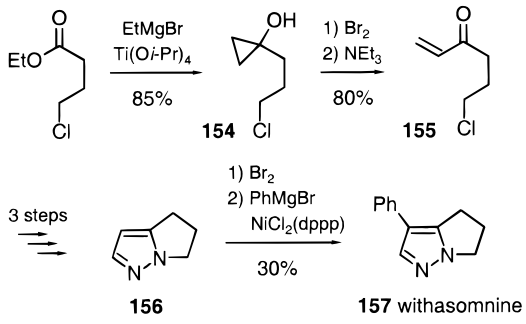
An effective total synthesis of the *Sceletium* alkaloid (−)-mesembrine **153** has been accomplished in seven steps and 19% overall yield from the functionally substituted nitroalkene **152** applying a domino [4+2]/[3+2]-cycloaddition sequence as a key step for the construction of the quaternary carbon center in the target molecule.[195] The key nitroalkene **152** was prepared in four steps (43% overall yield) from 1,5-dibromopentan-3-one (**151**) for which the previously reported approach[186] to 1,5-dihalopentan-3-ones based on the transformation of alkyl 3-haloalkanoates with the Ti(O*i*-Pr)$_4$/EtMgBr reagent and subsequent ring-opening bromination of the substituted cyclopropanol, in this case **150**, with *N*-bromosuccinimide was applied (Scheme 69).

Scheme 69



The transformation of ethyl 4-chlorobutyrate with the Ti(O*i*-Pr)$_4$/EtMgBr reagent also proceeds with high yield (85%) to give 1-(3-chloropropyl)cyclopropanol (**154**), which by ring-opening bromination with bromine and subsequent dehydrobromination gave the vinyl ketone **155** as a key intermediate in the synthesis of the pyrazole alkaloid withasomnine **157**

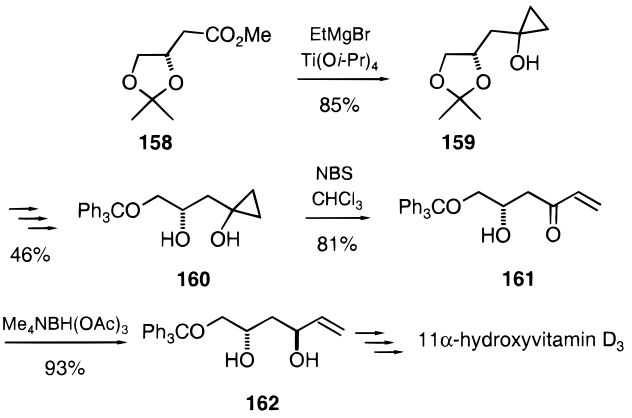
Scheme 70



by selective bromination and subsequent nickel-catalyzed cross-coupling with phenylmagnesium bromide (Scheme 70).[187]

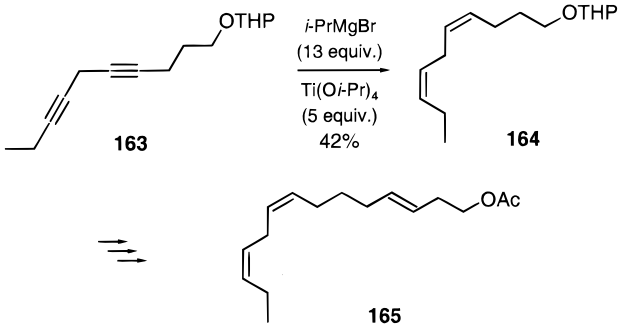
The transformation of an ester group into a vinyl ketone moiety has also been used for the preparation of the *anti*-diol **162** as a key intermediate in the synthesis of the 11α-hydroxyvitamin D$_3$.[196] Toward **162**, from L-(+)-malic acid ester, easily accessible **158** was used as the chiral enantiomerically pure starting material, which by reaction with ethylmagnesium bromide in the presence of titanium tetraisopropoxide gave the cyclopropanol derivative **159**. After appropriate manipulations of the protecting groups on the 1,2-diol unit, the cyclopropanol derivative **160** was transformed into the vinyl ketone **161**. The latter by diastereoselective reduction with Me$_4$NBH(OAc)$_3$ gave the key intermediate **162** in high yield (Scheme 71).

Scheme 71



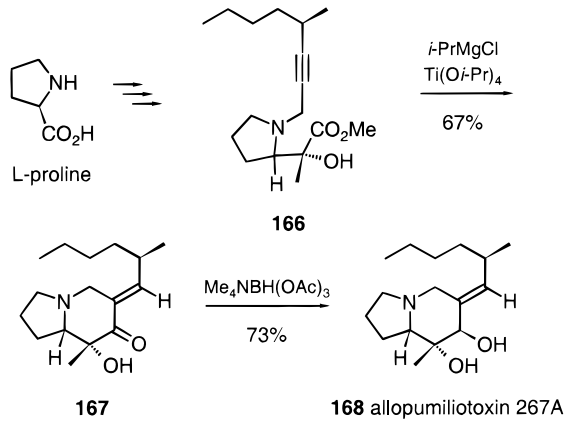
Kitching et al. applied a titanacyclopropane-mediated stereoselective reduction of the methylenescipped diyne **163** to the (*Z*,*Z*)-1,4-diene **164** in a one-pot procedure as a key step in the total synthesis of (*E*,*Z*,*Z*)-3,8,11-tetradecatrienyl acetate **165**, the major sex attractant of *Scrobipalpuloides absoluta*, a destructive pest of tomatoes (Scheme 72).[311]

Scheme 72



A highly efficient total synthesis of allopumiliotoxin 267A **168** has recently been accomplished.[227] The *N*-propargylated pyrrolidine derivative **166** prepared from L-proline in six steps was treated with isopropylmagnesium bromide in the presence of titanium tetraisopropoxide to afford the indolizidinone **167** in 67% yield and in turn **167** could be converted to the target alkaloid **168** following a previously established procedure (Scheme 73).[313]

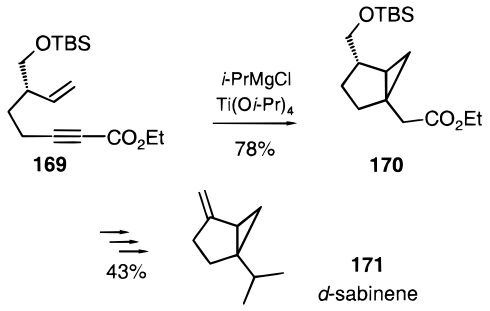
Scheme 73



C. 1,4-Dicarbanionic Equivalents

Despite their broad synthetic potential, the synthesis equivalents of 1,3- and 1,4-dicarbanionic organometallic reagents, to our knowledge, so far have only been applied in a single natural product synthesis. Sato et al. used the titanium-mediated generation of a 1,4-dicarbanionic equivalent in an efficient synthesis of D-sabinene **171** from the enantiopure ethyl hept-6-en-1-ynecarboxylate **169** (Scheme 74).[296]

Scheme 74



Upon treatment with *i*-PrMgCl in the presence of titanium tetraisopropoxide, **169** reacted analogous to **123** via a titanabicyclo[3.3.0]octene intermediate (Scheme 62) to give, after hydrolysis, the ethyl bicyclo[3.1.0]hexyl acetate **170**, which was eventually transformed to D-sabinene. Nearly complete chirality transfer to the two new stereogenic centers was achieved in this transformation.

VI. Conclusion

Monocarbanionic organometallic reagents in the presence of stoichiometric or catalytic quantities of certain titanium derivatives may act as dicarbanionic equivalents in reactions with electrophiles. The key steps in the transformations of monocarbanionic into dicarbanionic organometallics are disproportionation reactions of dialkyltitanium intermediates to form alkylidenetitanium or titanacyclopropane derivatives. These highly reactive organometallic compounds apparently have properties of reagents with two carbon−metal σ-bonds and are able to react as equivalents of 1,1- and 1,2-dicarbanionic moieties with various electrophiles. They can also react with alkenes and alkynes to afford new titanoalkylidene or titanacyclopropane and titanacyclopropene, respectively, intermediates by reaction or displacement of the dicarbanionic ligand on titanium. [2_s+2_π]-Cycloadditions of alkylidenetitanium and titanacyclopropane intermediates onto alkenes and alkynes yield titanacyclobutane, titanacyclopentane, and titanacyclopentene derivatives which may react as 1,3- and 1,4-dicarbanionic organometallics, respectively. In many cases these titanium-catalyzed or -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.

VII. Acknowledgments

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