Alkylation of carboxylic acid derivatives with dialkoxytitanacyclopropane reagents*

O. G. Kulinkovich

Belarussian State University,
4 av. F. Skaryny, 220050 Minsk, Belarus.
Fax: +375 (17) 226 5609. E-mail: kulinkovich@bsu.by

Methods for the generation of dialkoxytitanacyclopropanes (dialkoxytitanium olefin complexes) are surveyed. Alkylation of carboxylic acid derivatives with these reagents giving rise to β-titanio ketones and related species, which are spontaneously transformed into the corresponding cyclopropane compounds or react with external electrophiles, are considered.

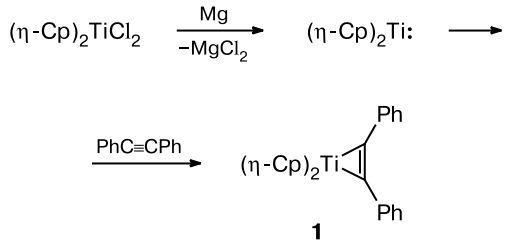
Key words: titanium alkoxides, Grignard reagents, titanacyclopropanes, carboxylic acid derivatives, alkylation, cyclopropanols, cyclopropylamines.

Introduction

Organic compounds of low-valent titanium have found wide application in industrial and laboratory chemical syntheses. A large-scale industrial process based on the use of such compounds is exemplified in the olefin polymerization on the Ziegler—Natta catalysts.[1,2] The formation of carbon—carbon bonds in complexes of tri- or divalent titanium derivatives with olefins plays a key role in the mechanism of action of these catalysts.[3—5] Complexes of divalent titanium derivatives with olefins or other unsaturated compounds are predominantly used as reagents or catalysts for the formation of carbon—carbon bonds in preparative organic synthesis (see the reviews[6—17]). In 1963, it was hypothesized[18] that divalent titanium compounds exhibit carbenoid properties in reactions with alkenes and acetylenes and form three-membered metallacycles. However, these compounds could be synthesized and characterized many years later. For instance, substituted titanacyclopropene **1** was synthesized for the first time in the early 1980s by reduction of titanocene dichloride with magnesium in the presence of tolan apparently through cycloaddition of titanocene at the C≡C bond (Scheme 1).[19]

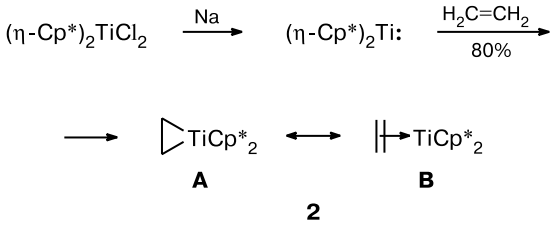
In the same year, a crystalline adduct of ethylene with bis(pentamethylcyclopentadienyl)titanium (**2**) was synthesized[20] by reduction of the corresponding dichloride $(\eta\text{-Cp}^*)_2TiCl_2$ with sodium amalgam in an atmosphere of ethylene (Scheme 2). Adduct **2** was also prepared in quantitative yield by the replacement of nitrogen in the $[(\eta\text{-Cp}^*)_2Ti]_2(\eta\text{-}N_2)_2$ complex by ethylene.[20]

Scheme 1



1

Scheme 2



A **B**

2

An X-ray diffraction study has demonstrated[20] that the distance between the C atoms of the methylene groups in compound **2** is 0.1 Å longer than the carbon—carbon bond in ethylene and the mutual arrangement of these groups is substantially nonplanar. Comparison of these data with the geometric parameters of other three-membered cyclic compounds and transition metal olefin complexes led to the conclusion that the structure of complex **2** corresponds to the resonance hybrid with compa-

* Materials were presented at the VII International Conference on the Chemistry of Carbenes and Related Intermediates (Kazan, 2003).

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 5, pp. 1022—1043, May, 2004.

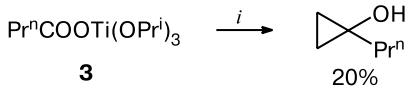
1066-5285/04/5305-1065 © 2004 Plenum Publishing Corporation

rable contributions of the Ti^{IV}-metallacyclopropane (**A**) and Ti^{II}-ethylene (**B**) limiting structures[20] (see Scheme 2) and a substantial back electron transfer from the metal atoms to the π* orbital of the ethylene ligand takes place.[21–23] Theoretical study of the electronic structure of the adduct of titanium(II) chloride with ethylene demonstrated that it better corresponds to the titanacyclopropane limiting structure although it was assumed that this species can also exhibit properties of a metal olefin complex.[24]

In the next two decades, practically valuable chemical reactions were discovered in which cyclopentadienyl derivatives of titanacyclopropane (titanocene olefin complexes) served as reagents or catalysts.[8,10–17] However, the introduction of these compounds into the practice of organic synthesis was impeded by difficulties in preparing these reagents and separating titanocene derivatives from the target reaction products.

About 15 years ago, when studying model reactions in the presence of the Ziegler—Natta-type catalytic systems, our research group found[25] that the reaction of ethylmagnesium bromide with triisopropoxytitanium butyrate (**3**) afforded 1-propylcyclopropanol in low yield (Scheme 3). This unusual transformation have attracted our attention not only as a new procedure for the synthesis of cyclopropane compounds but also due to the prospects for substantially extending the field of application of organomagnesium reagents in organic synthesis because ethylmagnesium bromide acts in these reactions as a 1,2-dicarbanionic equivalent.[25,26]

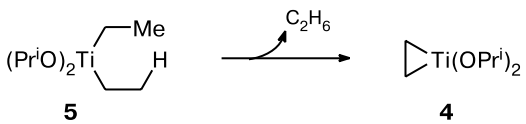
Scheme 3



i. 1) EtMgBr (3 equiv.), 2) H_3O^+.

By analogy with a known ability of dialkyl derivatives of metallocenes to undergo disproportionation giving rise to alkanes and metallocene olefin complexes,[8,11,27] we hypothesized that diisopropoxytitanacyclopropane (**4**), which is generated upon elimination of ethane from a thermally unstable diethyltitanium precursor **5** (Scheme 4), serves as an alkylating agent in the process under consideration.[25,26]

Scheme 4

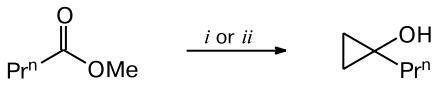


Shortly thereafter, studies with the use of this relatively inexpensive and handy combination of the reagents were performed in several laboratories, which provided abundant data on the useful chemical properties of dialkoxytitanacyclopropanes, including their ability to promote the intermolecular and intramolecular formation of covalent bonds between sp^2- or sp-hybridized C atoms. Various aspects of these investigations were generalized in several reviews.[14–17,28–30] The present review covers the state-of-the-art studies of reactions of dialkoxytitanacyclopropanes with carboxylic acid derivatives which have been initiated by our research group[31,32] and then served as the basis for the development of new efficient procedures for the synthesis of important classes of functional organic compounds.

Reactions with carboxylic esters

Our attempts to increase the yields of 1-substituted cyclopropanols by varying the conditions of reactions of ethylmagnesium bromide with titanium acylates, for example, with compound **3**, have met with only limited success. Nevertheless, we found that the addition of carboxylic esters to a solution of 3 equiv. of ethylmagnesium bromide and 1 equiv. of $Ti(OPr^i)_4$ in Et_2O at −78 °C afforded the target products in high or even quantitative yields.[25,26,31] We succeeded in developing a catalytic version of this transformation by changing the order of addition of the reagents, *e.g.*, by adding ethylmagnesium bromide to a solution of the ester and catalytic amounts of $Ti(OPr^i)_4$ in the same solvent.[32,33] This procedure allowed us to prepare the corresponding cyclopropanols in high yields by the reactions at room temperature, no excess of the Grignard reagent (with respect to the stoichiometric amount) was needed (Scheme 5).

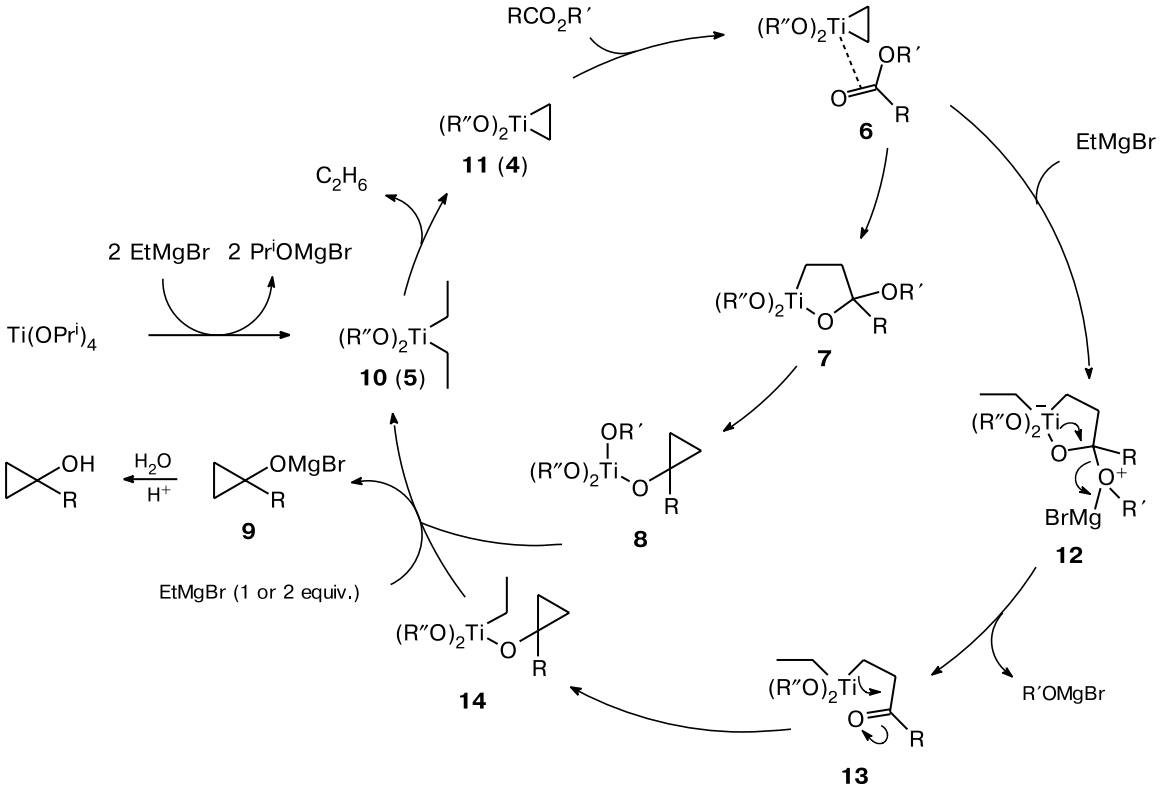
Scheme 5



Reagents and conditions: *i*. 1) EtMgBr (3 equiv.), $Ti(OPr^i)_4$ (1 equiv.), −78 °C → 0 °C, 2) H_3O^+, 90% yield; *ii*. 1) EtMgBr (2 equiv.), $Ti(OPr^i)_4$ (0.1 equiv.), ~20 °C, 2) H_3O^+, 91% yield.

The mechanism of this reaction was initially assumed[25,26,33] to involve the formation of the carbon—carbon bond in the diisopropoxytitanacyclopropane—ester complex (**6**) (Scheme 6) followed by the migration of the alkoxide group in oxatitanacyclopentane intermediate **7** to the oxophilic Ti atom with the simultaneous closure of the three-carbon ring to form titanium cyclopropanolate **8**. In the absence of a catalyst, hydrolysis of the latter gave the corresponding 1-substituted

Scheme 6



cyclopropanol. Under catalytic conditions, titanium cyclopropanolate **8** is transformed into magnesium cyclopropanolate **9**, which is accompanied by regeneration of diethyltitanium intermediate **10** serving as a precursor for the key dialkoxytitanacyclopropane **11**. If R″ = Pr^i, compounds **10** and **11** are identical to compounds **4** and **5**, respectively (see Scheme 4).

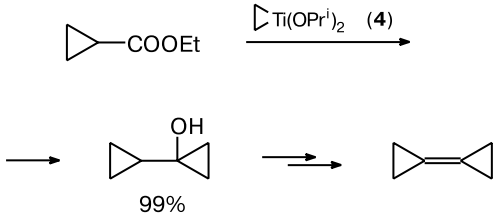
Taking into account that it is necessary to use an additional equivalent of the Grignard reagent to achieve high yields of the cyclopropanation products of esters in the absence of catalysts as well as of ethylation products of allylic alcohols with dialkoxytitanacyclopropane **4** discovered later,[34] it was hypothesized[28] that the additional equivalent of the Grignard reagent initiates the key step of formation of the covalent bond between the C atom of the titanacyclopropane fragment and the C atom of the carbonyl group in complex **6**. Actually, if the alkoxide groups are considered as the 6e ligands, the addition of ethylmagnesium bromide to the 18e titanacyclopropane complex with ester (**6**) can give 18e-ate complex **12**, while oxatitanacyclopentane **7** is an organometallic species with the unfilled 16e shell (see Scheme 6). This hypothesis provides an explanation for a substantial increase in the yield of the product when the reactions of equimolar amounts of titanium alkoxide and an ester are carried out with the use of an additional equivalent of an organomagnesium compound. Under catalytic conditions, an organomagnesium compound is present in an excess with respect to titanium alkoxide and, hence, there is no need to consume its additional equivalent for the formation of oxatitanacyclopentane ate complex **12**. Apparently, alkylation of the Ti atom in complex **6** increases nucleophilicity of the C atoms in the titanacyclopropane fragment and favors its involvement in the formation of the carbon—carbon bond with the ester group, which is inert with respect to organotitanium compounds under standard conditions.[7] Elimination of alkoxymagnesium bromide from oxatitanacyclopentane ate complex **12** gives rise to β-titanio ketone **13**, which undergoes isomerization to cyclopropanolate **14**. As in the initially proposed mechanism, alkylation of the latter is accompanied by regeneration of diethyltitanium derivative **10** and liberation of magnesium cyclopropanolate **9** (see Scheme 6).[28]

Recently,[35] a detailed theoretical study of the mechanism of a model reaction of 1,1-dimethoxytitanacyclopropane with methyl formate has been carried out. According to the results of geometry optimization of this titanacyclopropane reagent, the distance between the C atoms of the methylene groups is 1.482 Å, which is more consistent with the carbon—carbon single bond length rather than with the double bond length. In addition, according to the results of calculations, the oxatitana-

cyclopentane intermediate is formed from the complex of methyl formate with dimethoxytitanacyclopropane (compounds corresponding to structures **6** and **7** in Scheme 6; R = H, R′ = R″ = Me) in an exothermic process with low activation energy, whereas the subsequent migration of the alkoxide group to the Ti atom and the formation of the three-carbon ring are energetically much less favorable and their rates are comparable.[35]

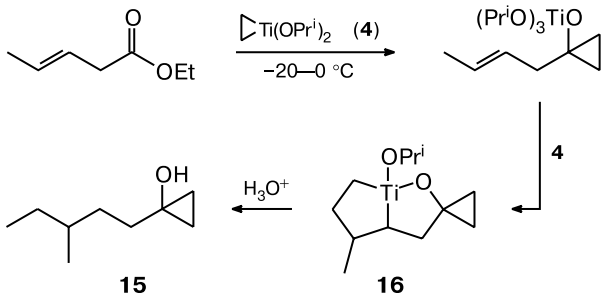
Cyclopropanation of esters of aliphatic, cycloaliphatic, and aromatic carboxylic acids with ethylmagnesium bromide in the presence of titanium alkoxides usually occurs smoothly to give the corresponding 1-substituted cyclopropanols (see the reviews[14,36,37]). For instance, cyclopropanation of methyl cyclopropanecarboxylate with this system of reagents afforded 1-cyclopropylcyclopropanol in quantitative yield.[38] The latter is a key intermediate in the synthesis of bicyclopropylidene, which is a highly strained unsaturated hydrocarbon possessing unusual chemical properties[39—41] (Scheme 7).

Scheme 7



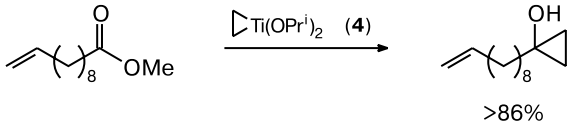
The reactions of α,β-unsaturated acyclic carboxylic esters with titanacyclopropane **4** afford the corresponding 1-alkenylcyclopropanols in low yields,[14,42,43] whereas cyclopropanation of the ester group in methyl cyclopent-1-ene- and cyclohex-1-enecarboxylates occurs rather smoothly.[44—46] The reactions of β,γ-unsaturated acid esters with titanacyclopropane **4** are complicated by reductive ethylation of the double bond. For example, the reaction of ethyl pent-3-enoate with an excess of ethylmagnesium bromide and Ti(OPr^i)$_4$ gave 1-(3-methylpentyl)cyclopropanol **15** in high yield (Scheme 8).[47] In this process, ethylation proceeds more slowly than cyclopropanation and involves the formation of bicyclic oxatitanacyclopentane **16** as an intermediate.

Scheme 8



The coordination effect of the O atom of the functional group on the formation of compound **15** plays a decisive role because cyclopropanation of unsaturated acid esters in which the double bond is remote from the ester group with reagent **4** occurs without complications. Under standard conditions, catalytic cyclopropanation of methyl undec-10-enoate affords 1-(dec-9-enyl)cyclopropanol in high yield (Scheme 9).[48]

Scheme 9

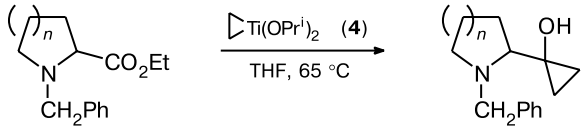


The reaction of butylmagnesium bromide with ethyl propiolate in the presence of Ti(OPr^i)$_4$ proceeds much less smoothly and produces the corresponding ethynylcyclopropanol in low yield.[43] Alkynoic and alkenoic acid esters containing the carbon—carbon multiple bond in a favorable position undergo intramolecular alkylation under the action of dialkoxytitanacyclopropanes. Examples of such transformations are considered below.

Although chloro- and bromocyclopropanes undergo hydrodehalogenation with ethylmagnesium bromide in the presence of Ti(OPr^i)$_4$,[49,50] the alkoxycarbonyl group in halocarboxylic esters is generally more reactive with respect to this combination of reagents. Under these conditions, esters of β-chloro- and β-bromo-substituted carboxylic acids and halocarboxylic esters in which the halogen atom is more spatially remote from the ester group are smoothly transformed into the corresponding haloalkyl-substituted cyclopropanols.[14,36] Generally, esters containing other functional groups resistant against organomagnesium compounds can also be subjected to cyclopropanation with diisopropoxytitanacyclopropane.[14,36] However, the presence of additional complex-forming substituents in the substrate can cause complications associated with the formation of precipitates insoluble in ethers. Sometimes, this problem can be overcome by using solvents possessing better solvation characteristics.[51—53] For example, *N*,*N*-dibenzyl-α-amino acid ethyl esters smoothly react with ethylmagnesium bromide in the presence of Ti(OPr^i)$_4$ in diethyl ether to give the corresponding 1-(1-dibenzylaminoalkyl)cyclopropanols in good yields. Under analogous conditions, cyclopropanation of ethyl esters of *N*-benzylproline and *N*-benzylpipecolinic acid is accompanied by the formation of a copious precipitate and gives a complex mixture of products, whereas the reaction in refluxing THF proceeds un-

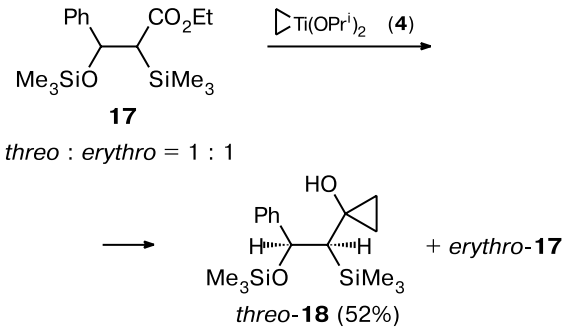
der homogeneous conditions to give the target products in relatively high yields (Scheme 10).[52]

Scheme 10



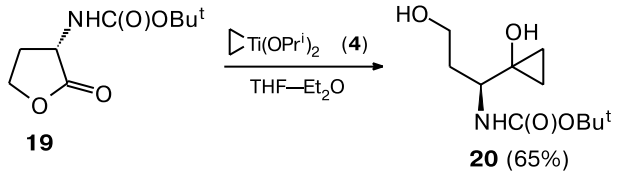
In the reaction of titanacyclopropane **4** with *erythro*/*threo* diastereomeric ethyl 2-trimethylsilyl-3-(trimethylsilyloxy)-3-phenylpropionates **17**, only the *threo* isomer is subjected to cyclopropanation, whereas the *erythro* isomer remains intact (Scheme 11).[54] The difference in the reactivity of these compounds was accounted for[54] by the difference in the energies of the corresponding oxatitanacyclopentane intermediates estimated theoretically.

Scheme 11



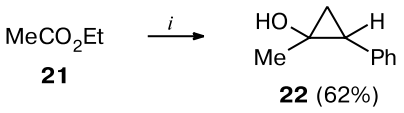
The reactions of lactones with titanacyclopropane **4** produce the corresponding hydroxyalkyl-substituted cyclopropanols.[53,55] It should be noted that the reactions with α- and β-aminobutyrolactones containing the protecting alkoxycarbonyl groups also afford products in rather high yields. For example, cyclopropanation of chiral lactone **19** gives the corresponding cyclopropanol **20** (Scheme 12).[53]

Scheme 12



The reactions of alkyl- and aralkylmagnesium halides with esters in the presence of $Ti(OPr^i)_4$ yield the corresponding 1,2-disubstituted cyclopropanols.[14,25,36] The stereochemical characteristic feature of these reactions is that they afford predominantly products containing the *cis*-arranged hydrocarbon substituents in the cyclopropane ring. For instance, ethyl acetate (**21**) reacts with phenethylmagnesium bromide in the presence of $Ti(OPr^i)_4$ to form *cis*-1-methyl-2-phenylcyclopropanol (**22**) (Scheme 13).[25]

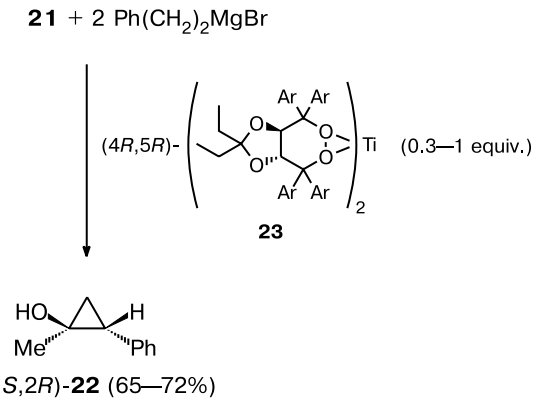
Scheme 13



i. 1) $Ph(CH_2)_2MgBr$ (3 equiv.), 2) H_3O^+.

Under catalytic conditions, the same transformation occurs in the presence of $ClTi(OPr^i)_3$ instead of $Ti(OPr^i)_4$, the product being prepared in somewhat higher yield.[56] The *cis*-diastereoselectivity of this reaction was unambiguously established by chromatograpy, X-ray diffraction study, and ^1H NMR spectroscopy. Cyclopropanation of ethyl acetate (**21**) with phenethylmagnesium bromide in the presence of 0.3—1 equiv. of chiral titanium alkoxide **23** gave (1*S*,2*R*)-cyclopropanol **22** in 65—72% yields with an enantiomeric excess of 85—89% (Scheme 14).[56]

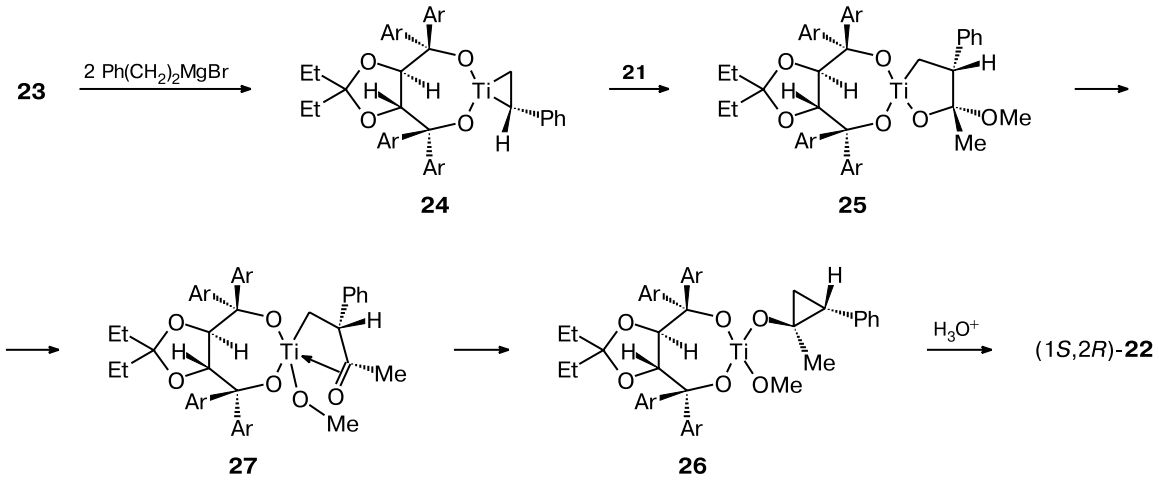
Scheme 14



Ar is 3,5-bis(trifluoromethyl)phenyl

The observed stereoselectivity of the formation of (1*S*,2*R*)-**22** was explained by the fact that titanium alkoxide **23** is transformed into sterically less hindered titanacyclopropane **24**, which undergoes ring expansion due to insertion of the ester carbonyl group of ethyl acetate (**21**) between the Ti atom and the more substituted

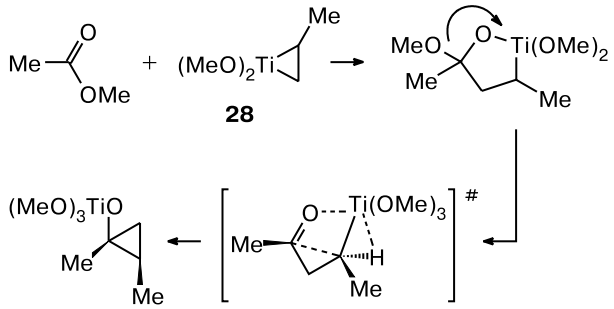
Scheme 15



C atom of the titanacyclopropane ring to give oxatitanacyclopentane **25** in which the bulky Ph and Me groups are in *trans* positions with respect to each other. Compound **25** is stereoselectively transformed into titanium cyclopropanolate **26** through β-organotitanium compound **27** (Scheme 15).[56]

In the above-considered model, stereoselectivity of cyclopropanation is determined by all steps of formation of carbon—carbon bonds. An alternative stereochemical model of cyclopropanation of esters with dialkoxytitanacyclopropanes was proposed[35] based on the results of quantum-chemical calculations for the model reaction of methyl-substituted titanacyclopropane **28** with methyl acetate. According to the results of this study, the formation of the bond between the least substituted C atom of the titanacyclopropane ring and the carbonyl C atom of the ester group is kinetically more favorable, and the selective formation of *cis*-isomeric cyclopropanols is associated with an agostic interaction between the Ti atom and the H atom in the α position with respect to Ti in the corresponding transition state (Scheme 16). This stabilizing agostic interaction is absent in the transition state of the cyclization step giving rise to *trans*-isomeric cyclopropanolate.[35]

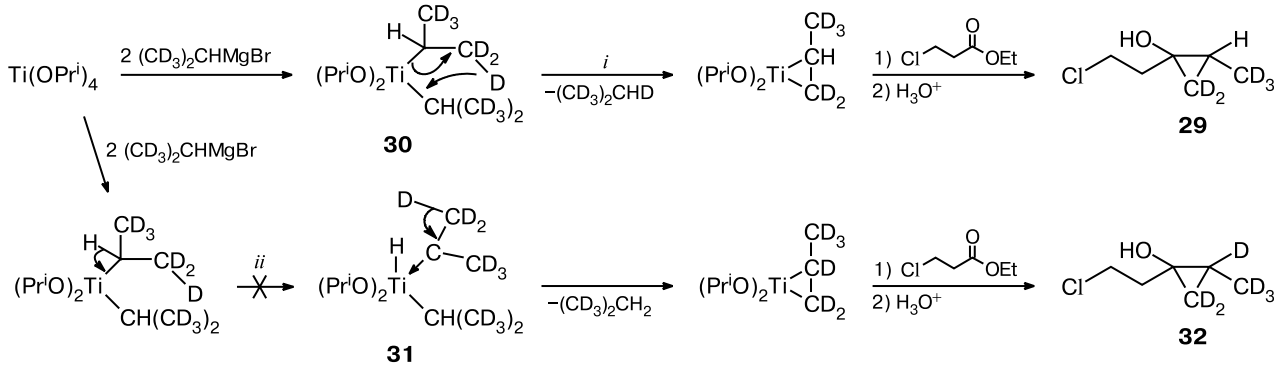
Scheme 16



The distribution of deuterium labels in 1,2-disubstituted cyclopropanol **29** (Scheme 17), which was prepared by the titanium-catalyzed reaction of ethyl 3-chloropropionate with 1,1,1,3,3,3-hexadeuterioisopropylmagnesium bromide in the presence of $Ti(OPr^i)_4$, confirms the mechanism of disproportionation of dialkyltitanium intermediate **30** through β-elimination of the D atom.[57] These data argue against the mechanism of formation of titanacyclopropane reagents involving successive α-elimination of the H atom of the alkyl fragment and the carbene-olefin rearrangement of alkylidenetitanium complex **31**, because this pathway should afford hexadeuterated cyclopropanol **32**.[57]

Many studies were devoted to the synthesis of 1-substituted and 1,2-disubstituted cyclopropanols by alkylation of esters with dialkoxytitanacyclopropanes. However, data on the formation of compounds containing a larger number of substituents in the three-carbon ring are scarce. Cyclopropanation of ethyl acetate with cyclohexylmagnesium bromide and $Ti(OPr^i)_4$ was described for the first time by de Meijere and coworkers.[58] However, the corresponding bicyclanol was isolated in low yield. Recently, the reactions of ethyl 2-chloropropionate with cycloalkylmagnesium bromides in the presence of $Ti(OPr^i)_4$ have been systematically investigated.[59] It appeared that cyclobutyl-, cyclopentyl-, and cycloheptylmagnesium bromides gave annelated cyclopropanols in moderate yields, the reaction with cyclohexylmagnesium bromide afforded the product in 17% yield, whereas cyclopropylmagnesium bromide remained inert. Cyclopropanation occurred most smoothly with the use of cyclopentylmagnesium bromide, and bicyclic cyclopropanol **33** was isolated as a mixture of *exo* and *endo* isomers (Scheme 18). Other reactions afforded ex-

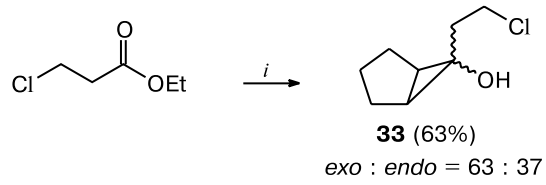
Scheme 17



i. β-Elimination; *ii*. α-Elimination.

clusively bicyclic cyclopropanols containing the hydroxy group in the *exo* position.[59]

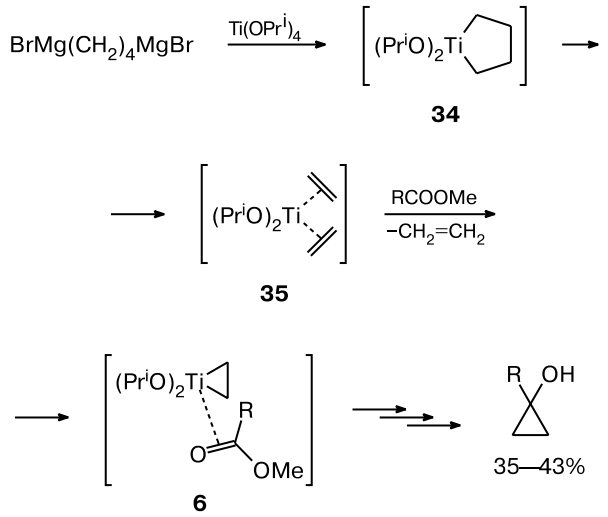
Scheme 18



i. *cyclo*-C_5H_9MgBr (4 equiv.), $Ti(OPr^i)_4$ (1 equiv.).

When studying the $Ti(OPr^i)_4$-catalyzed reaction of esters with 1,4-di(bromomagnesium)butane, we found an alternative method for the generation of dialkoxytitanacyclopropanes.[60] In this reaction, titanacyclopentane **34** (Scheme 19) that formed upon alkylation with the Grignard reagent is rearranged into bis-ethylene complex **35**. The replacement of the ethylene molecule in this complex by ester affords titanacyclopropane ester complex **6**, which is transformed into the corresponding 1-substituted cyclopropanol according to the usual scheme.

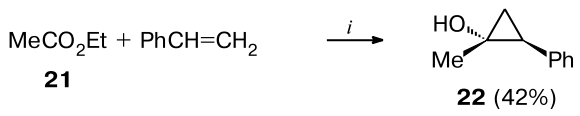
Scheme 19



R = Pr, Bu, C_5H_{11}

The exchange of olefinic ligands at the Ti atom provides an alternative procedure for the generation of a broad spectrum of dialkoxytitanacyclopropanes containing substituents in the three-membered ring. In these transformations, dialkoxytitanacyclopropanes exhibit properties of titanium(II) olefin complexes. That this exchange was possible was exemplified for the first time by the synthesis of *cis*-1-methyl-2-phenylcyclopropanol (**22**) using the reaction of ethylmagnesium bromide with a mixture of ethyl acetate and styrene in the presence of catalytic amounts of $Ti(OPr^i)_4$ (Scheme 20).[61]

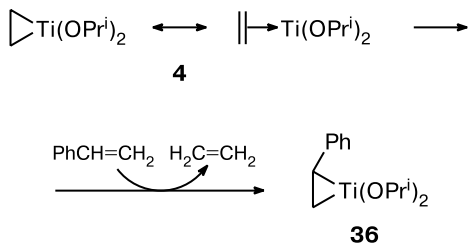
Scheme 20



i. EtMgBr (2.5 equiv.), $Ti(OPr^i)_4$ (0.1 equiv.), Et_2O, refluxing.

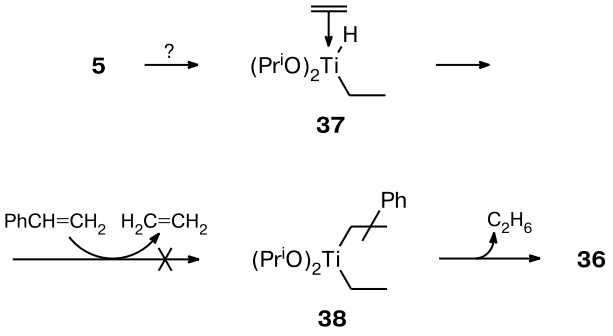
We believed that this reaction gives phenyl-substituted titanacyclopropane **36** due to the replacement of ethylene in the coordination sphere of the metal atom in titanacyclopropane (titanium ethylene complex) **4** with styrene (Scheme 21). Actually, ethylene was detected among gaseous reaction products, whereas cyclopropanation of ethyl acetate with reagent **4** in the absence of styrene was accompanied by elimination of ethane as the major gaseous product, which is indirect evidence for the proposed mechanism of olefin ligand exchange.[61]

Scheme 21



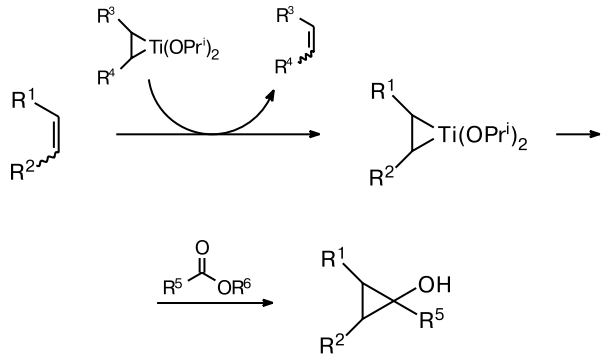
It should be noted that disproportionation of diethyltitanium derivative **5** can also proceed *via* intermediate titanium hydride **37**, which assumes an alternative mechanism of formation of titanacyclopropane **36** involving the addition of hydride **37** to styrene followed by elimination of ethane from intermediate **38** (Scheme 22). However, this mechanism is inconsistent with the formation of nondeuterated cyclopropanol **22** in the reaction of $(CD_3)_2CHMgBr$ with ethyl acetate, styrene, and $Ti(OPr^i)_4$.[62]

Scheme 22



It was proposed[55,63] to employ sterically more hindered titanacyclopropane substrates generated by the reactions of $Ti(OPr^i)_4$ with cyclohexyl-,[55,64] *n*-butyl-,[55] or isopropylmagnesium halide[63] in the olefin ligand exchange (Scheme 23). In some cases, the reactions of equivalent or excess amounts of these reagents with a mixture of an ester and an olefin give the corresponding cyclopropanols in high yields. This procedure for the preparation of the latter compounds is also referred to as hydroxycyclopropanation of olefins.[55]

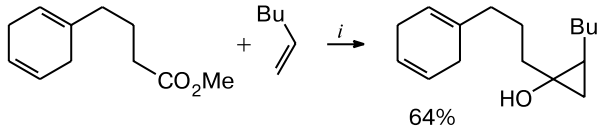
Scheme 23



R^1, R^2, R^5, R^6 = Alk, Ar; R^3+R^4 = (CH$_2$)$_4$; R^3 = Me, R^4 = H; R^3 = Et; R^4 = H

Intermolecular hydroxycyclopropanation occurs, as a rule, smoothly only with terminal olefins, which allows one to transform exclusively the vinyl group in the case of olefins containing several nonconjugated double bonds with different degrees of substitution[14,36] or to use unsaturated carboxylic esters containing di- and tri-substituted double bonds as a hydroxycyclopropanating agent, as exemplified by Scheme 24.[55,65]

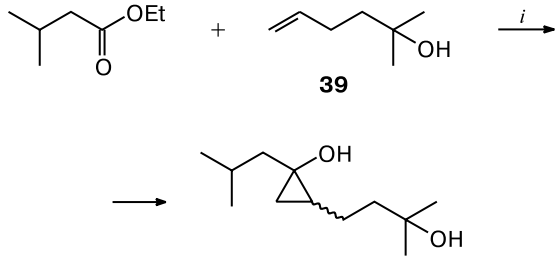
Scheme 24



i. *cyclo*-$C_6H_{11}MgCl$ (4.5 equiv.), $Ti(OPr^i)_4$ (1 equiv.).

Comparison of the efficiency of various Grignard reagents in hydroxycyclopropanation of styrene with ethyl acetate in the presence of $Ti(OPr^i)_4$ demonstrated that the yield of compound **22** decreases in the series Bu^nMgBr > > $Pr^iMgBr \approx Pr^nMgBr$ > *cyclo*-$C_6H_{11}MgBr \approx EtMgBr$.[62] However, it is difficult to give unambiguous recommendations for choosing a particular Grignard reagent for hydroxycyclopropanation of olefins catalyzed by titanium alkoxides or involving the latter. For example, the dialkoxytitanacyclopropane-induced reaction of unsaturated alcohol **39** with ethyl isopentanoate affords the target products in better yields when titanacyclopropane precursors are generated by the reaction of $Ti(OPr^i)_4$ with ethylmagnesium bromide (Scheme 25).[66] It was also reported

Scheme 25



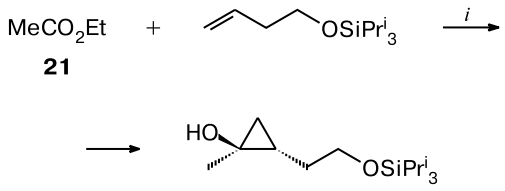
i. 1) RMgBr (5 equiv.), $Ti(OPr^i)_4$ (1 equiv.), 2) H_3O^+.

R	Et	Pr^i	Bu	*cyclo*-C_6H_{11}
Yield (%)	72	63	62	33

that the titanacyclopropane reagent prepared by the reaction of $Ti(OPr^i)_4$ with cyclopentylmagnesium chloride[67] is more efficient in hydroxycyclopropanation of homoallylic alcohols than an analogous intermediate generated by the reaction of ethylmagnesium bromide with $Ti(OPr^i)_4$.[68]

The yields of the cyclopropanation products of methyl cyclohexanecarboxylate in the reaction with ethylmagnesium bromide in the presence of various titanium alkoxides and aryloxides were demonstrated to be independent of the structure of the latter reagents, whereas the reaction of 1-triisopropylsilyloxybut-3-ene with ethyl acetate proceeds most smoothly with the use of the cyclopentylmagnesium chloride—$Ti(OPr^i)_3Cl$ and(or) cyclopentylmagnesium chloride—$MeTi(OPr^i)_3$ system (Scheme 26).[55]

Scheme 26



i. *cyclo*-C_5H_9MgCl, $XTi(OPr^i)_3$, THF, ~20 °C.

X	Pr^iO	Cl	Me
Yield (%)	71	78	84

The 1,3-diastereoselectivity of hydroxycyclopropanation of titanates of homoallylic alcohols with esters in the presence of cyclopentylmagnesium chloride and $Ti(OPr^i)_4$ (15 reactions were examined) varies from 3.3 : 1 to 12.2 : 1 and is maximum for titanate of 1-phenylbut-3-en-1-ol (Scheme 27).[67] In the authors' opinion, diastereomeric 1,3-bicyclic titanacyclopropane intermediate **41** is more reactive than diastereomer **40** existing in equilibrium with **41**, which is responsible for the predominant formation of cyclopropanol **42**. It should be noted that, although intramolecular hydroxycyclopropanation (see below) of 1-phenylbut-3-en-1-yl acetate affords almost exclusively *trans*-isomeric cyclopropanols, the formation of compound **42** proceeds with low 1,3-stereoselectivity.[67]

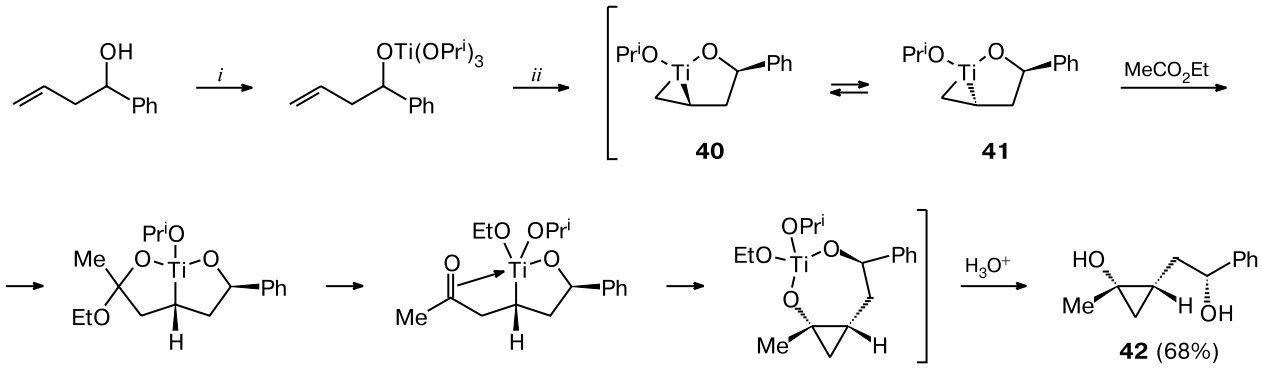
Besides, dialkoxytitanacyclopropanes successfully induce intermolecular hydroxycyclopropanation of trialkylvinylsilanes,[69,70] trialkylvinylstannanes,[71] and terminal olefins containing acetal[72—74] and diethylphosphine functional groups.[75]

Carbonates and ethyl chloroformate react with bicyclic dialkoxytitanacyclopropanes in the presence of alkenes to form the corresponding 2-substituted cyclopropanone hemiacetals in low or moderate yields. The best results were obtained for cyclic carbonates, for example, in the reaction of hex-1-ene with ethylene carbonate (Scheme 28).[64]

Intramolecular cyclization of alk-4-enoic and alk-5-enoic acid esters with dialkoxytitanacyclopropanes affords the corresponding bicyclic cyclopropanols in moderate or high yields.[76—80] For example, the reaction of titanabicycloheptane **43** generated from cyclohexylmagnesium chloride and $ClTi(OPr^i)_3$ with methylhept-6-enoate gave bicyclo[4.1.0]heptan-1-ol in moderate yield (Scheme 29).[76,77]

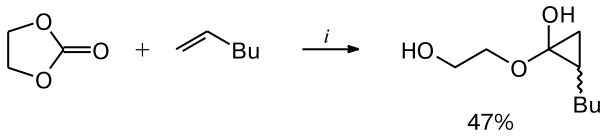
In the reactions of dialkoxytitanacyclopropanes with unsaturated acid esters in which the vinyl group is more remote from the ester group, the yields of bicyclanols are substantially lower or intramolecular cyclopropanation products are not formed at all. Attempts to perform intramolecular hydroxycyclopropanation of trisubstituted double bonds and the vinyl group bound to the quaternary C atom also failed.[76] In contrast, analogous reactions of esters of unsaturated oxacarboxylic acids produce cyclopropanols fused to seven- and eight-membered rings in satisfactory yields. For example, oxabicyclononanol **44** was synthesized by the reaction of unsubstituted diiso-

Scheme 27



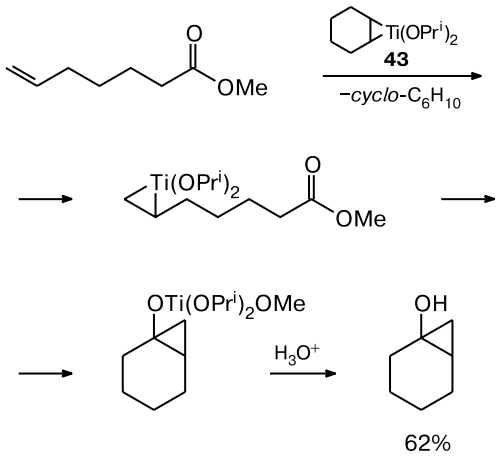
Reagents and conditions: *i*. 1) $Ti(OPr^i)_4$, toluene, 1 h, 2) 40 °C, *in vacuo*; *ii*. $MeCO_2Et$, *cyclo*-C_5H_9MgCl, THF.

Scheme 28



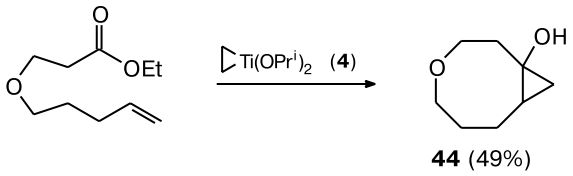
i. *cyclo*-C_5H_9MgCl (5 equiv.), $ClTi(OPr^i)_3$ (1 equiv.), THF, 0 °C.

Scheme 29



propoxytitanacyclopropane **4** with ethyl 4-oxanon-8-enoate (Scheme 30).[80]

Scheme 30



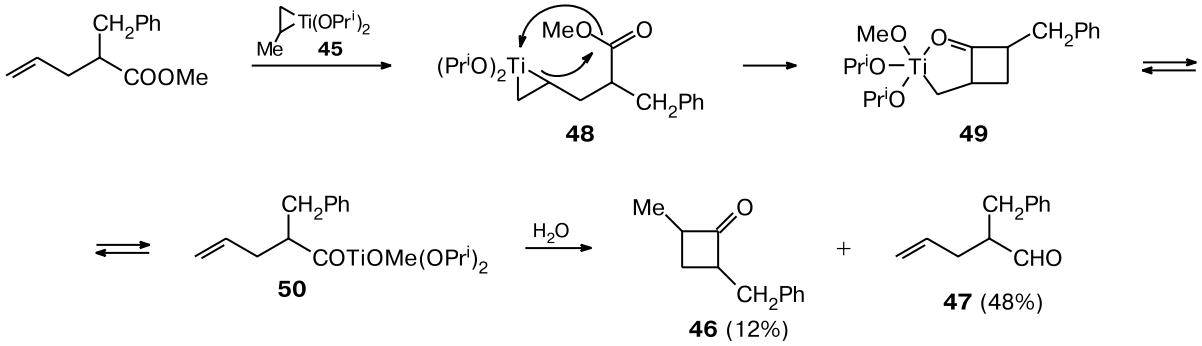
Attempts to prepare bicyclic cyclopropanols by the reactions of γ,δ-unsaturated acid esters with titanacyclopropane **45** generated by the reaction of isopropylmagnesium chloride with $Ti(OPr^i)_4$ were also unsuccessful. These reactions afforded the corresponding α-methylcyclobutanones (for example, **46**) and γ,δ-unsaturated aldehydes (for example, **47**) (Scheme 31) as the major products.[81] Apparently, the role of functionalized titanacyclopropane intermediate **48** generated as a result of ligand exchange is reduced exclusively to intramolecular monoalkylation of the ester group giving rise to β-titanio ketone **49**, which exists in equilibrium with acyltitanium derivative **50**. Their hydrolysis affords cyclobutanone **46** and γ,δ-unsaturated aldehyde **47**, respectively (see Scheme 31). Deuterolysis gives compound **47** containing the deuterated aldehyde group (the deuterium content was >95%), which is consistent with the proposed mechanism. The reaction of dialkoxytitanacyclopropane **45** with γ,δ-alkenoic acid esters proceeds predominantly as reduction of the ester group to the aldehyde group.[81]

Presumably, hydroxycyclopropanation of homoallyl carboxylates also occurs intramolecularly, which accounts for the fact that this reaction produces the corresponding *trans*-1,2-disubstituted cyclopropanols with moderate or high selectivity.[43,63] For example, the reaction of homoallyl crotonate with titanacyclopropane **45** affords *trans*-1,2-disubstituted cyclopropanol **51** *via* bicyclic titanate **52** (Scheme 32).[42,43]

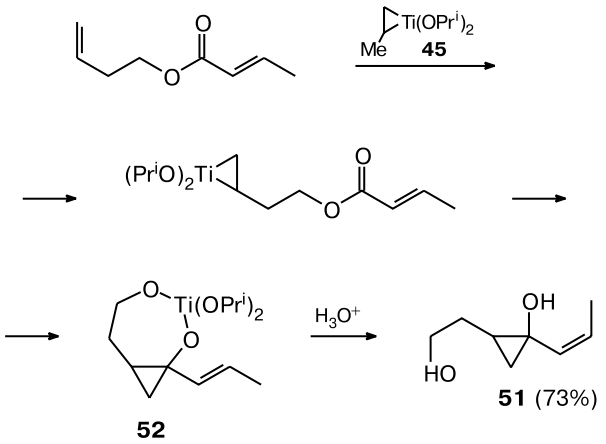
It should be noted that the stereochemistry of 1,2-disubstituted cyclopropanols depends substantially on the reaction conditions. At low temperature, the reaction of alkenyl acetate **53** with titanacyclopropane **45** produces stereoisomeric cyclopropanols **54** and **55** with low stereoselectivity. However, exposure of the reaction mixture at room temperature affords almost exclusively cyclopropanol **54** (Scheme 33).[63] Presumably, the formation of the latter occurs due to thermodynamic control, and the step of the formation of the three-membered ring is reversible.

Intramolecular hydroxycyclopropanation of the vinyl group in *N*-allyl-substituted amino acid esters smoothly results in the corresponding bicyclic cyclopropanols, which are valuable intermediates in the synthesis of nitro-

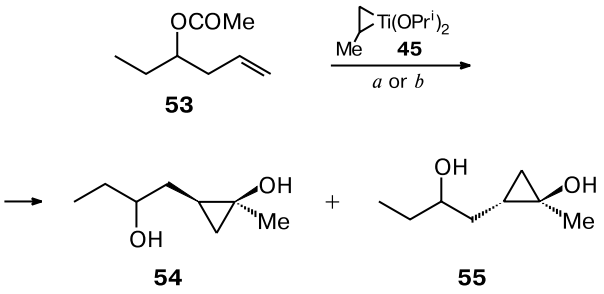
Scheme 31



Scheme 32

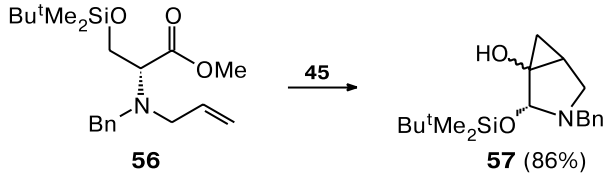


Scheme 33



Conditions: *a*. –40 °C → 20 °C, 33% yield, **54** : **55** = 41 : 59; *b*. –40 °C, 70% yield, **54** : **55** > 97 : 3.

Scheme 34

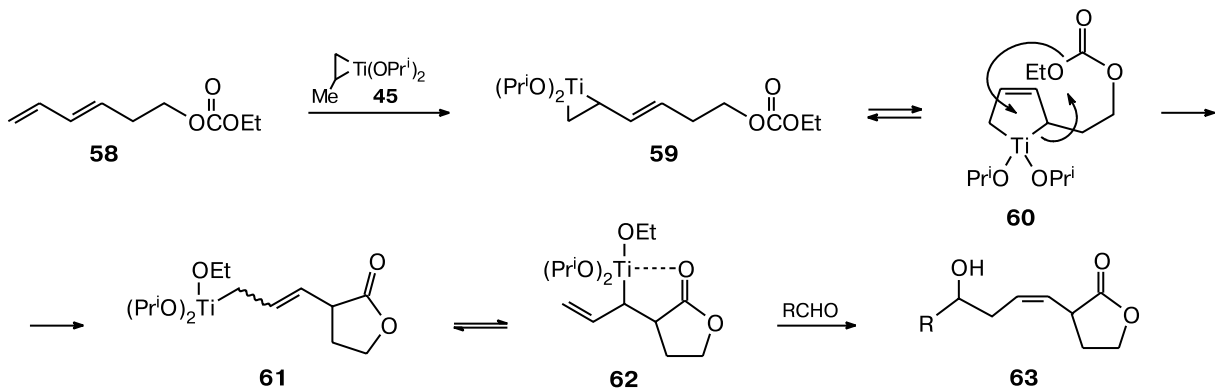


gen-containing heterocyclic compounds.[79,82] For example, the reaction of D-serine derivative **56** with dialkoxytitanacyclopropane **45** gives bicyclic amino alcohol **57** in high yield (Scheme 34).[79]

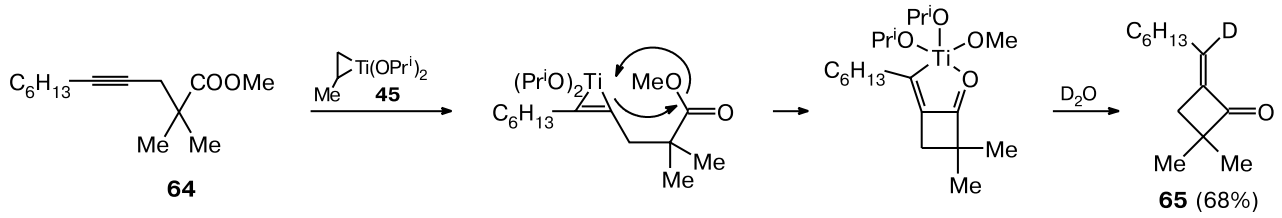
In the reactions with dialkoxytitanacyclopropanes, ω-1,3-diene esters of carboxylic acids undergo monoalkylation of the C atom of the ester group. The ligand exchange between titanacyclopropane **45** and dienyl carbonate **58** (Scheme 35) affords vinyltitanacyclopropane intermediate **59** existing in equilibrium with titanacyclopentene **60**. The intramolecular electrophilic substitution of the Ti atom in the latter gives allyltitanium derivatives of lactones **61** and **62**, which react with aldehydes to form (*Z*)-alk-2-enyllactones **63** with high regio- and stereoselectivity.[83] The reactions of dialkoxytitanacyclopropanes with ω-1,3-dienoic acid esters proceed analogously.[84]

The ligand exchange of dialkoxytitanacyclopropanes with alkynes also occurs readily to form the corresponding titanacyclopropenes.[85–87] The chemistry of dialkoxytitanacyclopropenes thus formed was covered in detail in the reviews.[15,17,29,30] The reactions of dialkoxytitanacyclopropanes with alkynoates in which the C≡C bond is remote from the ester group generally begin with the alkene-alkyne ligand exchange to form the corresponding dialkoxytitanacyclopropenes, their intramolecular addition to the ester group is stopped in the step of the formation of only one carbon—carbon bond. The resulting bicyclic oxatitanacyclopentene intermediates smoothly react with electrophilic reagents to form the corresponding α-alkylidenecycloalkanones.[79,81] For example, the reaction of γ,δ-acetylenic ester **64** with dialkoxytitanacyclopropane **45** followed by deuterolysis of the reaction mixture affords deuterated α-heptylidenecyclobutanone **65** (Scheme 36).[81]

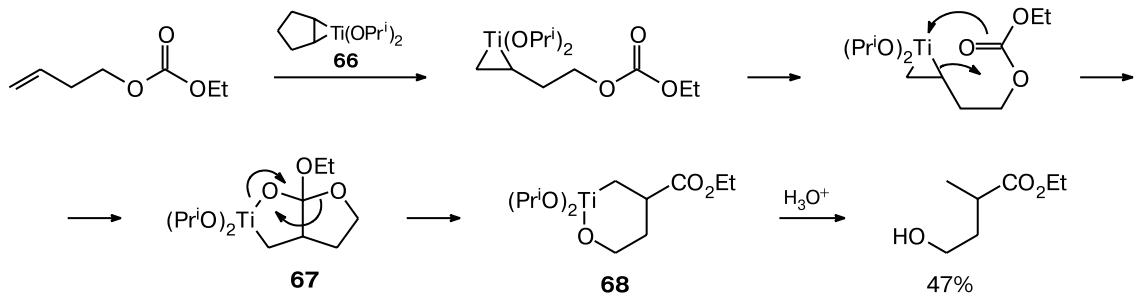
Scheme 35



Scheme 36



Scheme 37

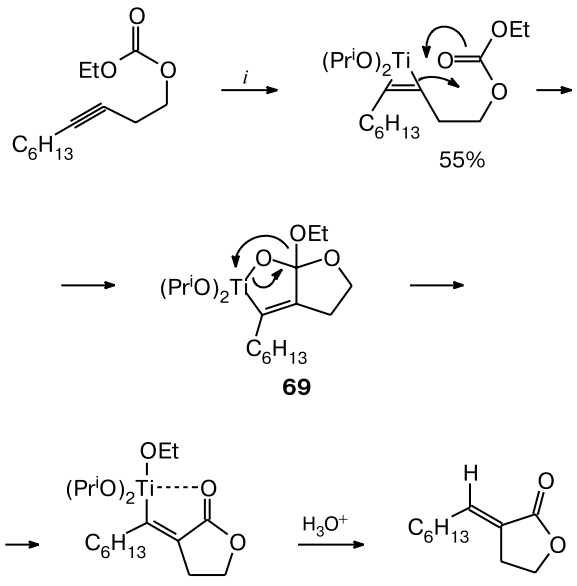


Unlike but-3-enyl acetate, which undergoes hydroxycyclopropanation in the reactions with dialkoxytitanacyclopropanes,[63] ethyl but-3-enyl carbonate reacts with titanabicyclohexane **66**, which is generated from cyclopentylmagnesium chloride and $Ti(OPr^i)_4$, to give ethyl 4-hydroxy-2-methylbutanoate through the rearrangement of bicyclic derivative **67** into oxatitanacyclohexane derivative **68** (Scheme 37).[64]

The reactions of dialkoxytitanacyclopropanes with ethyl carbonates of homopropargylic alcohols proceed analogously,[88–90] the ethoxy group migrating to the metal atom in bicyclic intermediate **69** (Scheme 38).[88,89] From the viewpoint of the final result, *viz.*, hydroalkoxycarbonylation of the multiple bond in the starting compound, the above-mentioned differences in the proposed mechanisms of these two reactions are not significant.

In the reactions with dialkoxytitanacyclopropane **45**, carbonates of homoallenic alcohols behave analogously to esters of homoallylic and homopropargylic alcohols. The formation of the corresponding alkylidenetitanacyclopropane intermediates and electrophilic substitution with the replacement of the Ti atom by the C atom of the carbonyl group lead to the stereoselective formation of (*Z*)-β,γ-unsaturated carboxylic esters. For instance, intramolecular ethoxycarbonylation of optically active allene **70** (Scheme 39) initiated by titanacyclopropane **45** affords α-substituted (*Z*)-β,γ-unsaturated acid ester **72** with high optical purity. It was hypothesized[91] that the reaction proceeds *via* sterically less hindered alkylidenetitanacyclopropane intermediate **71**, in which the electrophilic substitution of the metal atom occurs with retention of the configuration of the carbanionic center.

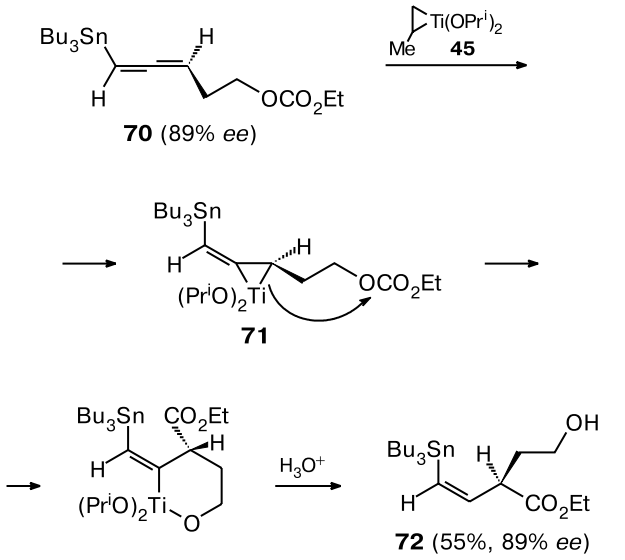
Scheme 38



i. Pr^iMgBr (2 equiv.), $ClTi(OPr^i)_3$.

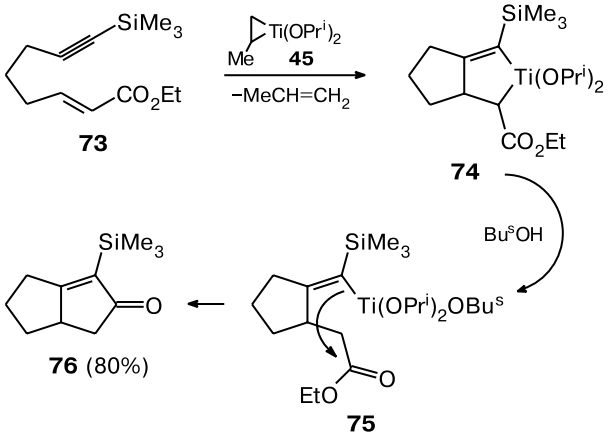
Interesting results were obtained[92,93] in the studies of the reactions of diisopropoxytitanacyclopropane intermediates with esters of carboxylic acids containing double and triple bonds in positions favorable for intramolecular cyclization. It appeared that essentially different products are formed depending on whether the double or triple bond is conjugated with the ester group. The reaction of titanacyclopropane **45** with ethyl alkynylacrylate **73** (Scheme 40) followed by treatment of the reaction mix-

Scheme 39



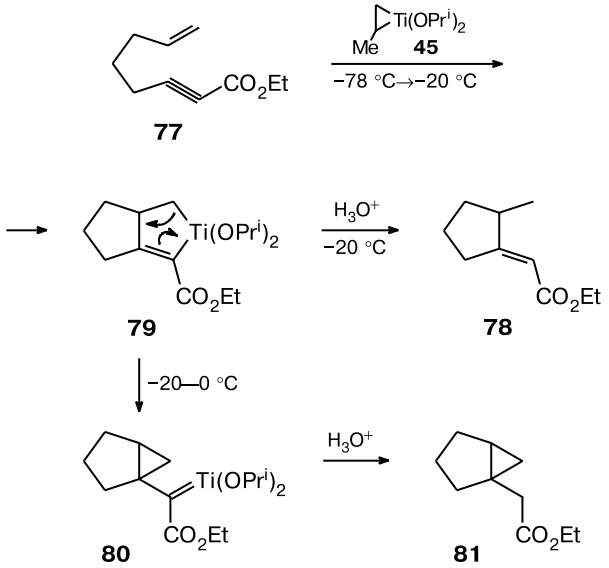
ture with *sec*-butyl alcohol gives bicyclic ketone **76**. It was assumed that the regioselective protonation of titanabicyclooctene **74** followed by the intramolecular replacement of the ethoxy group with the vinyl carbanion are the key steps of this reaction. Bicyclo[3.3.0]octane derivatives are formed also by dialkoxytitanacyclopropane-induced cyclization of alkynyl-substituted vinyl esters with the same mutual arrangement of the multiple bonds.[94]

Scheme 40



The reaction of ethyl alkenylpropargylate **77** characterized by the opposite arrangement of the double and triple bonds affords α,β-unsaturated acid ester **78** (Scheme 41), the ethoxycarbonyl group remaining intact. A comparatively small variation in the reaction conditions, *viz.*, an increase in the temperature of the reaction mixture to 0 °C before its acid treatment, results in the formation of ethyl bicyclohexylacetate **81**. The authors hypothesized that protonation of bicyclic titanacyclopentene intermediate **79** at low temperatures affords ester **78**. An increase in the temperature causes the rearrangement of compound **79** to bicyclic titanium carbene complex **80**, which is a precursor of derivative **81**.[92,93]

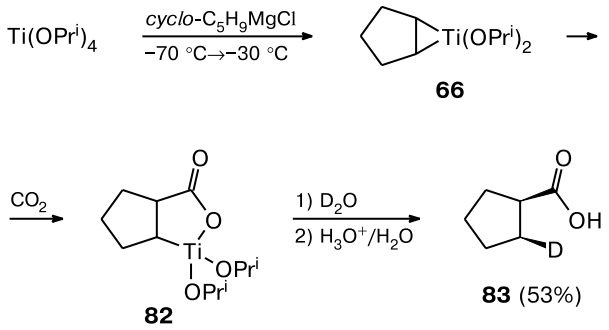
Scheme 41



Alkylation of carbon dioxide

Carbon dioxide reacts with titanabicyclohexane **66** in diethyl ether to give titanium acylate **82**, whose deuterolysis affords *cis*-2-deuteriocyclopentanecarboxylic acid **83** (Scheme 42) in moderate yield, whereas oxidation of compound **82** with oxygen produces an equimolar mixture of diastereomeric 2-hydroxycyclopentanecarboxylic acids.[95]

Scheme 42

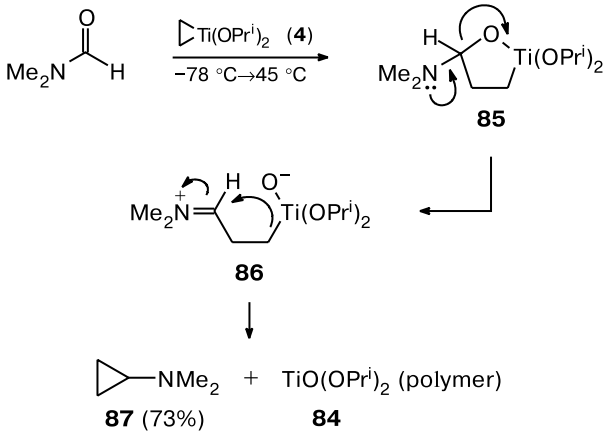


Reactions with *N*,*N*-dialkylcarboxamides

Intermolecular cyclopropanation of *N*,*N*-dialkylcarboxamides with dialkoxytitanacyclopropanes was investi-

gated.[96,97] Unlike the analogous transformation of esters, cyclopropanation of tertiary amides requires, as a rule, longer time or higher temperature.[14] Attempts to perform cyclopropanation of tertiary amides with dialkoxytitanacyclopropanes in the presence of catalysts failed due apparently to the transformation of $Ti(OPr^i)_4$ into polymeric titanium oxide **84** (Scheme 43), which cannot be again transformed into the corresponding titanacyclopropane reagents under the action of Grignard reagents. The reactions of titanacyclopropane **4** with *N*,*N*-dialkylformamides usually give *N*,*N*-dialkylcyclopropylamines in higher yields.[96] In these reactions, oxatitanacyclopentane intermediates (for example, **85**) are apparently transformed into nitrogen analogs of β-oxoalkyl anions (for example, **86**), which then close the three-carbon ring with elimination of titanium oxide **84**.

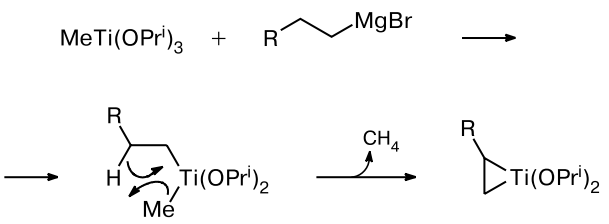
Scheme 43



A comparative study of the reactions of dialkoxytitanacyclopropanes with various carboxylic acid derivatives was carried out.[98] Tertiary amides are less reactive than esters. The opposite chemoselectivity is observed only for sterically hindered *tert*-butyl carboxylates, whereas the reactivity of ethylene carbonate is intermediate between those of *N*,*N*-dialkylcarboxamides and esters. The reactions of dialkoxytitanacyclopropanes with anhydrides, carboxylic acid chlorides, and thiocarboxylic esters were studied.[98] In all cases, the corresponding cyclopropanols were prepared as the major products. However, the conclusions about the relative reactivities of these carboxylic acid derivatives should be treated with caution because they can be transformed into the corresponding esters under the reaction conditions.

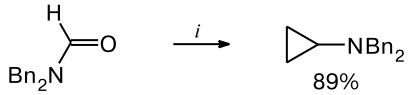
The reactions of *N*,*N*-dialkylcarboxamides with alkyl-substituted dialkoxytitanacyclopropanes give the corresponding 1,2-disubstituted *N*,*N*-dialkylcyclopropylamines, which are, as a rule, formed with low *cis*/*trans* stereoselectivity.[14] The generation of dialkoxytitanacyclopropanes containing substituents in the three-membered ring by the reactions of alkylmagnesium halides with $MeTi(OPr^i)_3$ instead of $Ti(OPr^i)_4$ allows one to perform cyclopropanation of *N*,*N*-dialkylcarboxamides in higher yields.[58] Besides, these reactions require only one equivalent of alkylmagnesium halide, which is a considerable advantage in the case of reactions with difficultly accessible Grignard reagents (Scheme 44).

Scheme 44



The generation of dialkoxytitanacyclopropanes by the reactions of organozinc compounds with titanium alkoxides is also of interest. First attempts to use these reagents led to the formation of the target products in low yields. However, the yields were substantially increased by performing the reactions in the presence of alkali metal alkoxides, whose complexes with organozinc reagents exhibit higher nucleophilic activity. For example, the cyclopropanation product of *N*,*N*-dibenzylformamide was prepared in high yield using a twofold excess of the diethyzinc complex with sodium isopropoxide in the presence of an equimolar amount of $MeTi(OPr^i)_3$ (Scheme 45).[99]

Scheme 45

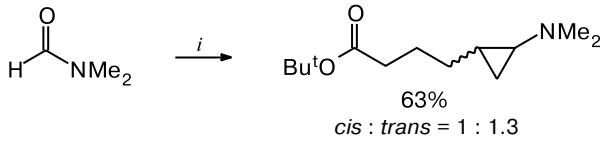


i. $MeTi(OPr^i)_3$ (1 equiv.), Et_2Zn (2 equiv.), $NaOPr^i$ (2 equiv.).

Dialkoxytitanacyclopropanes are less reactive with respect to sterically hindered *tert*-butyl carboxylates[98] due to which *tert*-butoxycarbonyl-substituted dialkoxytitanacyclopropanes prepared from the corresponding organozinc compounds were successfully used for cyclopropanation of *N*,*N*-dialkylcarboxamides (Scheme 46).[100] Since these reactions proceed with low stereoselectivity, give products in moderate yields, and require organometallic compounds of three different metals, this approach is of limited usefulness.

***N*-Substituted carboximides** give no cyclopropanation products in the reactions with dialkoxytitanacyclopropanes due apparently to weak electron-donating character of

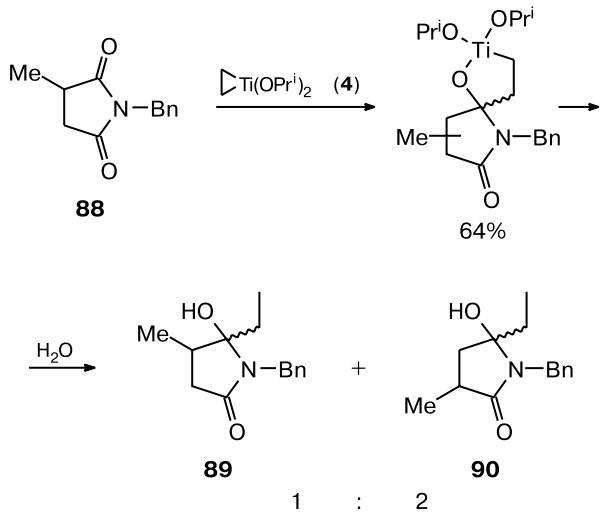
Scheme 46



i. $Zn[(CH_2)_3CO_2Bu^t]_2$, $Me_2Ti(OPr^i)_2$, MeMgCl.

the N atom, which does not favor heterolysis of the C—O bond in the corresponding oxatitanacyclopentane intermediates.[101,102] For example, alkylation of methyl-substituted succinimide **88** with titanacyclopropane **4** affords hydroxy lactams **89** and **90** in moderate yields with low regio- and stereoselectivity (Scheme 47). The latter are readily dehydrated to form the corresponding enamides. It should be noted that the regioselectivity of this reaction is opposite to that observed in the case of addition of Grignard reagents to compound **88**.[102]

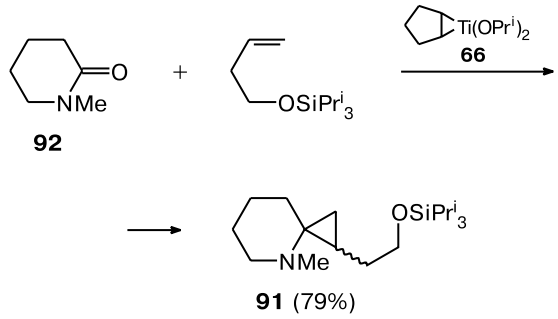
Scheme 47



The ligand exchange of dialkoxytitanacyclopropanes with olefins can also be efficiently used for the transformation of *N*,*N*-dialkylcarboxamides into the corresponding cyclopropylamines.[103,104] Synthesis of substituted spirocyclic amine **91** from silylated but-3-enol and *N*-methylpiperidone **92** represents an example (Scheme 48).[103]

Aminocyclopropanation of monosubstituted aryl-, hetaryl-, silyloxyalkyl-, dibenzylaminomethyl-, trimethylsilyl-, trimethylsilylmethyl-, diethylphosphinyl-, and tributylstannylethenes with dialkoxytitanacyclopropanes gives rise to the corresponding cyclopropylamines in moderate yields.[14] It was noted[104] that the use of titanabicycloheptane **43** in ligand exchange increases the yields

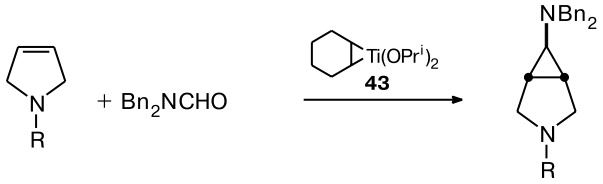
Scheme 48



of aminocyclopropanation products of terminal olefins compared to other dialkoxytitanacyclopropanes.

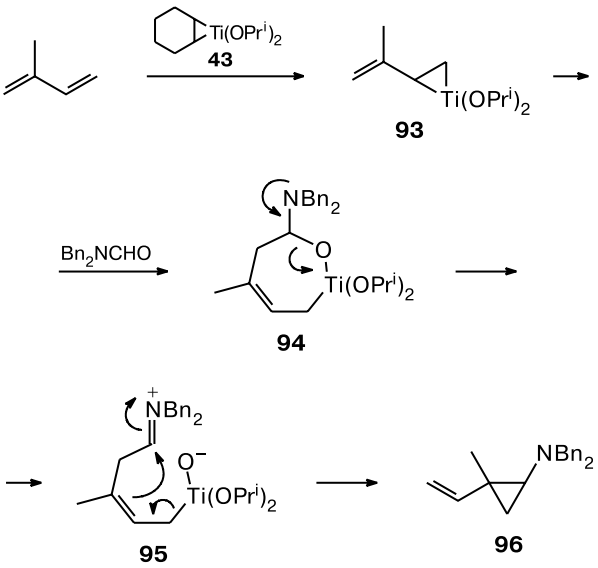
Generally, aminocyclopropanation of the majority of nonterminal olefins and nonconjugated dienes studied afforded products in moderate or low yields.[104] However, the reaction of titanabicycloheptane **43** prepared from cyclohexylmagnesium chloride and $MeTi(OPr^i)_3$, with *N*-benzyl- and *N*-*tert*-butoxycarbonyl-2,5-dihydropyrrols gives the corresponding *exo*-6-dibenzylamino-3-azabicyclo[3.1.0]hexanes in high yields (Scheme 49).[104] Titanacyclopropanes **4** and **45** or titanabicyclohexane **66** are less efficient as promoters of this reaction.

Scheme 49



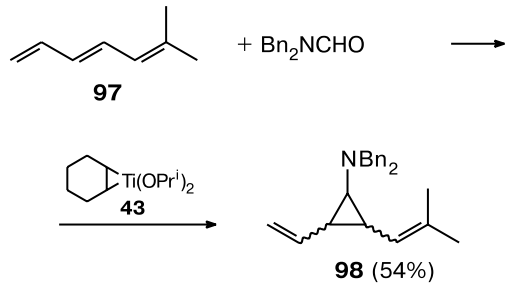
It should be noted that conjugated dienes containing multiple bonds with different degrees of substitution (for example, of isoprene) give products aminocyclopropanated at a more substituted double bond (Scheme 50).[104—106] Under analogous conditions, 2,3-dimethylbutadiene and 2,5-dimethylhexa-2,4-diene do not undergo aminocyclopropanation. Apparently, the sterically less hindered multiple bond in isoprene is involved in the ligand exchange to give isopropenyltitanacyclopropane intermediate **93**, which undergoes the allylic rearrangement under the action of dibenzylformamide to form oxatitanacycloheptene **94**.[104—106] Heterolysis of the C—O bond in the latter and the intramolecular addition of the allyltitanium fragment to the iminium group of the resulting zwitterion **95** affords 2,2-disubstituted *N*,*N*-dibenzylcyclopropylamine **96** (see Scheme 50).[104]

Scheme 50



Cyclopropanation of conjugated triene **97** with *N*,*N*-dibenzylformamide induced by titanabicycloheptane **43** occurs across the central double bond, its stereochemical configuration being not transferred to the three-membered ring. The reaction produces three diastereomeric dibenzylcyclopropylamines **98** in comparable amounts (Scheme 51).[104]

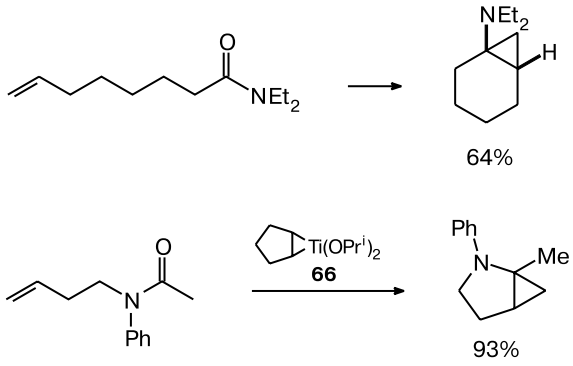
Scheme 51



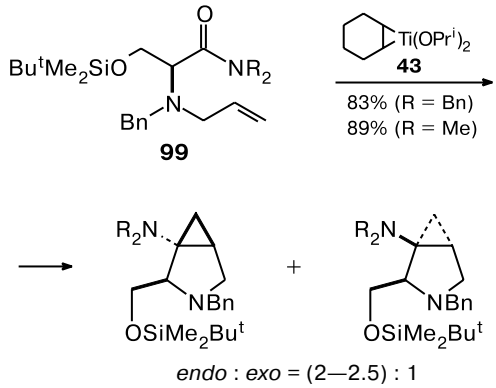
Intramolecular alkylation of tertiary amide in unsaturated *N*,*N*-dialkylcarboxamides is a convenient procedure for the synthesis of annelated cyclopropylamines.[103,107—111] Typical examples of the use of this procedure for the preparation of carbocyclic and heterocyclic amines from hept-6-enoic acid diethylamide and *N*-homoallyl-*N*-phenylacetamide, respectively, are presented in Scheme 52.[103,111]

This approach was successfully extended to the synthesis of annelated cyclopropylamines from *N*,*N*-dialkylamides of *N*-allylated aliphatic[108] and arylaliphatic[112] amino acids. The yields of 3-azabicyclo[3.1.0]hexanes and 3-azabicyclo[4.1.0]heptanes, which were prepared by reactions of titanabicycloheptane **43** with the corresponding tertiary amides of *N*-allylated α-amino carboxylic acids (for example, with compound **99**), varied from moderate to high. In these transformations, the dialkoxytitanacyclopropane reagent was generated from cyclohexylmagnesium chloride and MeTi(OPr^i)$_3$ (Scheme 53).[108] The stereoselectivity of this reaction, like that of cyclopropanation of arylaliphatic α-amino acids *N*,*N*-dialkylamides,[112] is low.

Scheme 52



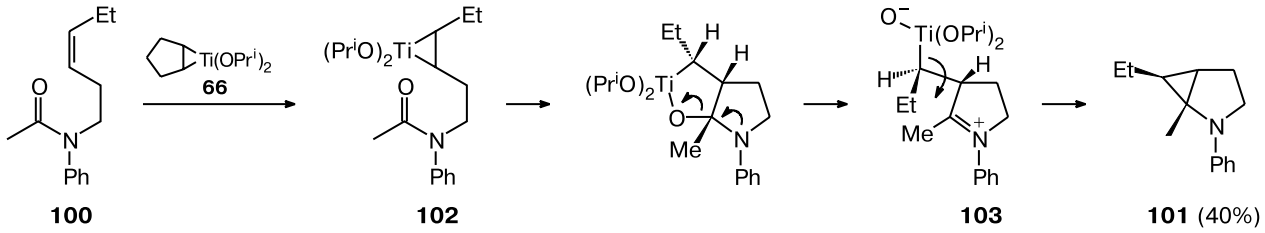
Scheme 53



1,2-Disubstituted ethenes were also subjected to intramolecular aminocyclopropanation.[110] Unlike intermolecular reactions proceeding nonstereoselectively to give 2,3-disubstituted dialkylcyclopropylamines in low yields,[14] intramolecular aminocyclopropanation of tertiary *N*-homoallylacetamides is almost completely diastereoselective. For example, unsaturated acetanilide **100** is transformed into 2-azabicyclohexane containing *trans* substituents in the three-membered ring (**101**) *via* intermediate disubstituted dialkoxytitanacyclopropane **102**, which suggests the inversion of the configuration of the carbanionic center upon closure of the three-membered ring in zwitterionic intermediate **103** (Scheme 54).[110]

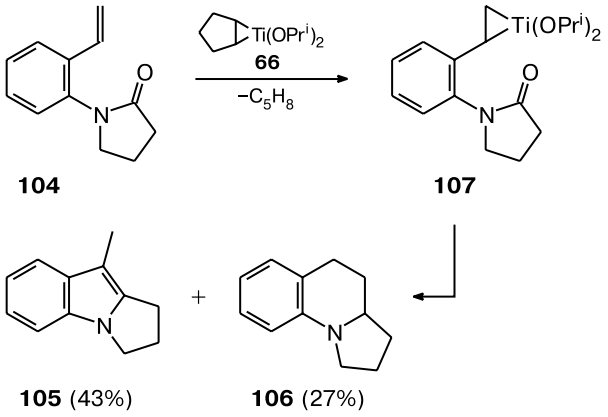
The reaction of dialkoxytitanabicyclohexane **66** with lactam **104** affords tricyclic products **105** and **106**

Scheme 54



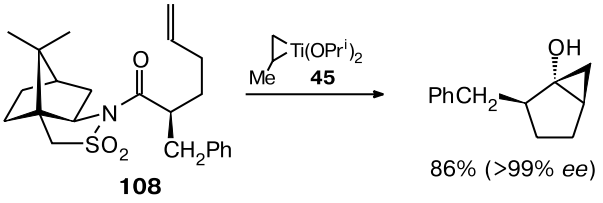
(Scheme 55), which indicates that each carbanionic center of metallacycle **107** can be involved in the intramolecular formation of the carbon—carbon bond.[101] Closure of three-membered rings is apparently hindered due to steric strain in the transition states of the corresponding reactions. In the cited study,[101] reduction of the precursor of compound **106** was not discussed.

Scheme 55



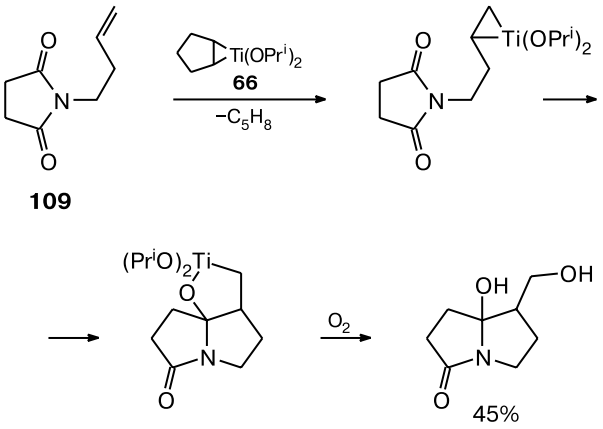
The reactions of dialkoxytitanacyclopropanes with ***N*-acylcamphorsultam derivatives** are accompanied by the cleavage of the C—N bond to form the corresponding annelated cyclopropanols. The reaction is characterized by high diastereoselectivity and allows one to transform chiral sultams (for example, **108**) into optically pure target products (Scheme 56).[113]

Scheme 56



Intramolecular cyclization of ***N*-alkenylimides** initiated by diisopropoxytitanacyclopropanes is of considerable synthetic value because it provides a convenient approach to the construction of skeletons of important alkaloids.[101,114–116] In particular, dialkoxytitanacyclopropanes efficiently induce cyclization of *N*-but-3-enylsuccinimide **109** (Scheme 57) and *N*-but-3-enylglutarimide. Oxidation of the intermediate oxazatitanatricycles was efficiently employed for the introduction of a hydroxy group into the alkyl substituent, which is present in many natural pyrrolizidine and indolizidine alkaloids.[101]

Scheme 57

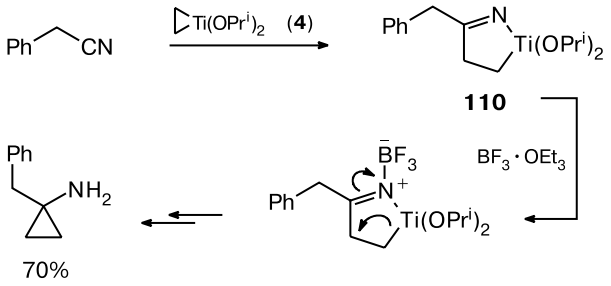


Reactions with carbonitriles

Intermolecular cyclopropanation of carbonitriles is of practical interest because this reaction opens a direct route to primary cyclopropylamines, some of which exhibit important biological activities.[117] Aliphatic carbonitriles were subjected to cyclopropanation[118] with dialkoxytitanacyclopropanes to afford products in high or moderate yields. It was found that the formation of the three-membered ring in this reaction is promoted by Lewis acids. For example, 1-benzylcyclopropylamine was synthesized in 31% yield by slowly adding an ethereal solution of ethylmagnesium bromide (2 equiv.) to a mixture of equimolar amounts of phenylacetonitrile and Ti(OPr^i)$_4$. Treatment of the reaction mixture with 2 equiv. of $BF_3 \cdot Et_2O$ prior to hydrolysis led to an increase in the yield of the target product to 70%, which is apparently

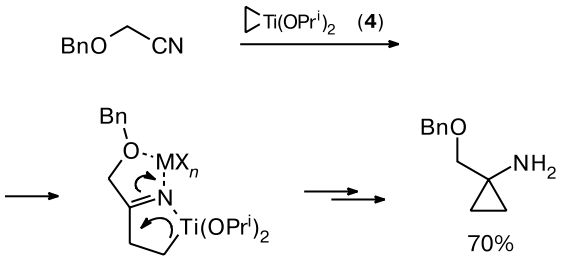
due to the fact that the Lewis acid activates closure of the three-membered carbocycle in azatitanacyclopentene intermediate **110** (Scheme 58). The reactions of phenylacetonitrile with titanacyclopropanes generated by the reactions of $Ti(OPr^i)_4$ with *n*-butyl-, *sec*-butyl-, and phenethylmagnesium bromide produce mixtures of the corresponding *cis*- and *trans*-1,2-disubstituted cyclopropylamines in moderate yields. Under these conditions, cyclopentylmagnesium chloride gives mixtures of bicyclohexylamines with the isomers having the *exo* configuration of the amino group substantially predominating.[118] A slight modification of this procedure, *viz.*, mixing of the reagents at low temperature, made it possible to perform cyclopropanation of aromatic and α,β-unsaturated carbonitriles.[119]

Scheme 58



The reactions of dialkoxytitanacyclopropanes with nitriles containing the alkoxy, phenoxy, or dialkylamino groups in the α position give cyclopropylamines in high yields, no additional treatment of the reaction mixture with Lewis acid being required.[120] High susceptibility of the nitrile group in these compounds to cyclopropanation was attributed to activation of the imine group in the corresponding azatitanacyclopentene intermediates due to the formation of chelate magnesium or titanium complexes, as exemplified by cyclopropanation of benzyloxyacetonitrile in Scheme 59.

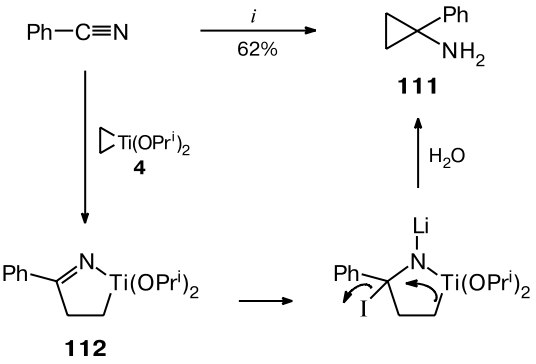
Scheme 59



M = Mg, Ti

The reactions of nitriles with dialkoxytitanacyclopropanes are most often accompanied by the addition of an additional equivalent of the organometallic compound across the C=N bond of azatitanacyclopentene intermediates as a side process.[99,118,121] To overcome this problem, it was suggested that the reaction should be carried out in the presence of lithium iodide.[99] Actually, the reactions of benzonitrile with diethylzinc, $MeTi(OPr^i)_3$, and lithium isopropoxide afforded 1-phenylcyclopropylamine **111** in 25% yield, whereas the yield of compound **111** in the presence of lithium iodide increased to 62% (Scheme 60).[99] Apparently, lithium iodide adds at the C=N bond of azatitanacyclopentene intermediate **112** thus preventing its further alkylation. Under these conditions, aromatic carbonitriles containing electron-donating and electron-withdrawing substituents are transformed into the corresponding cyclopropylamines in 40—82% yields. However, cyclopropanation of aliphatic carbonitriles using this procedure gives unsatisfactory results.

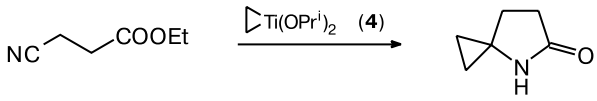
Scheme 60



i. $MeTi(OPr^i)_3$ (1—2 equiv.), Et_2Zn (1.2 equiv.), $LiOPr^i$ (2.5 equiv.), LiI (2.5 equiv.).

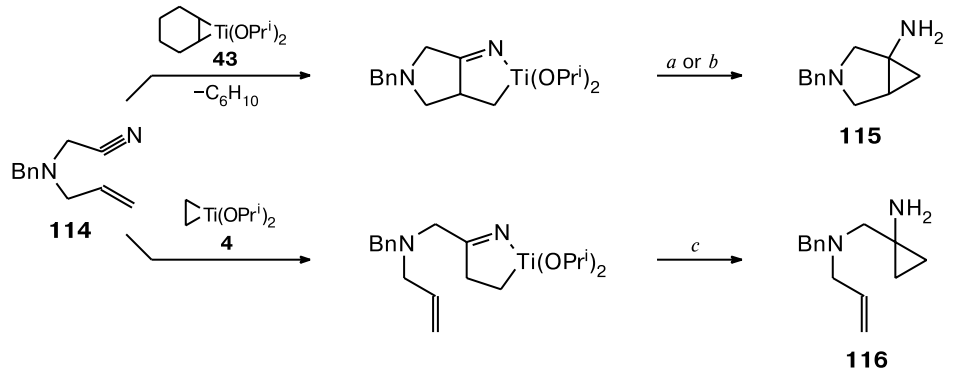
Compared to ethyl phenylacetate and *N*,*N*-dibenzylformamide, phenylacetonitrile is substantially more reactive in the reaction with ethylmagnesium bromide in the presence of $Ti(OPr^i)_4$, which made it possible to perform chemoselective cyclopropanation of the nitrile group in esters and tertiary amides of a series of cyanocarboxylic acids. For example, the reaction of ethyl β-cyanopropionate with titanacyclopropane **4** afforded spirocyclic lactam **113** in good yield (Scheme 61). This reaction also does not require activation of the the three-carbon ring clousure with Lewis acids.[122]

Scheme 61



113 (68%)

Scheme 62

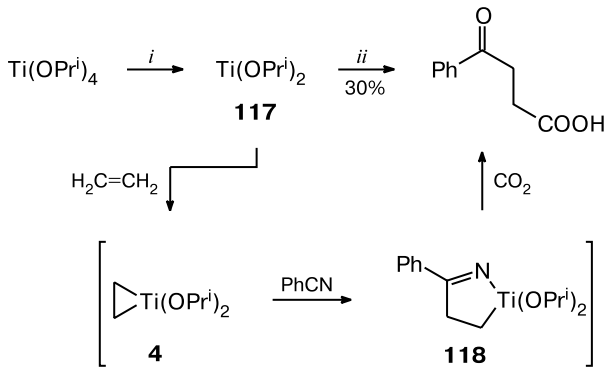


Reagents and conditions: *a*. LiI (2 equiv.), 70 °C, 43—48% yield;[108] *b*. $BF_3 \cdot Et_2O$ (2 equiv.), 20 °C, 69% yield; [121] *c*. $BF_3 \cdot Et_2O$ (2 equiv.), ~20 °C, 60% yield.

Intramolecular aminocyclopropanation of *N*-allylated α-amino nitrile **114**, its *N*-*tert*-butoxycarbonyl derivative, and certain of the nearest homologs of these compounds, which contain the double bond more remote from the functional group, with dialkoxytitanacyclopropanes was performed by promoting the closure of the three-carbon ring with $BF_3 \cdot Et_2O$ or LiI.[108,121] In the study,[121] the authors compared the efficiency of titanacyclopropanes, which have been generated by the reactions of EtMgBr, BuMgBr, Pr^{i}MgBr, *cyclo*-C_5H_9MgCl, or *cyclo*-$C_6H_{11}MgCl$ with Ti(OPr^i)$_4$, in ligand exchange with unsaturated aminonitrile **114**. It appeared that only the reaction of dialkoxytitanabicycloheptane **43**, which was prepared by the reaction of cyclohexylmagnesium chloride with Ti(OPr^i)$_4$, led exclusively to intramolecular aminocyclopropanation of the double bond of compound **114** giving rise to azabicyclohexylamine **115** in 69% yield. The use of this procedure also made it possible to perform for the first time intramolecular aminocyclopropanation of an analog of compound **114** containing the *gem*-disubstituted double bond.[121] It should be noted that dialkoxytitanacyclopropane **4** containing the unsubstituted three-membered ring is not involved in ligand exchange under these reaction conditions; instead, it acts as a cyclopropanating agent to form 1-substituted cyclopropylamine **116** (Scheme 62).[121] The reactions with other Grignard reagents involved intramolecular aminocyclopropanation of the double bond and intermolecular cyclopropanation of the nitrile group with the latter process predominating.

Monoalkylation of benzonitrile with low-valent titanium alkoxides has been carried out recently.[123,124] Diisopropoxytitanium (**117**) was prepared by the reaction of *n*-butyllithium with Ti(OPr^i)$_4$ in THF at −78 °C followed by removal of the solvent under reduced pressure. It was demonstrated that reagent **117** can promote reactions of alkenes and alkynes as equivalents of 1,2-dicarbanions. For example, ethylene was passed through a solution of titanium alkoxide **117** in THF followed by the addition of benzonitrile, carbon dioxide, and water to give 3-benzoylpropionic acid in a total yield of 30% (Scheme 63). It was hypothesized that diisopropoxytitanacyclopropane **4**, which is generated in the reaction of ethylene with titanium alkoxide **117**, serves as the key organometallic reagent in these transformations. By analogy with the Prilezhaev epoxidation of olefins with peroxy acids, this reaction was classified as epimetallation. It was hypothesized that the addition of diisopropoxytitanacyclopropane **4** to benzonitrile should afford the corresponding azatitanacyclopentene **118**, which is transformed into 3-benzoylpropionic acid after scavenging with carbon dioxide and protonation.[123,124]

Scheme 63



Reagents and conditions: *i*. BuLi (2 equiv.), THF, −78 °C → 25 °C; *ii*. 1) $H_2C{=}CH_2$, 2) PhCN, 3) CO_2, 4) H_2O.

Although the scheme proposed in the study[123] is simple and seemingly realistic, such an interpretation of the results is doubtful. For instance, it is not inconceivable that

this process involves species which can be formed due to electron transfer from low-valent titanium alkoxide to the nitrile group or the addition of diisopropoxytitanium (**117**) in the singlet or triplet electronic state to the nitrile group. In the recent study,[125] the same authors adduced arguments in favor of the mechanism of epimetallation through transfer of titanium diisopropoxide (**117**) to the unsaturated substrate directly from the corresponding dialkyl derivative. This hypothetical mechanism, which is classified as the coordination-induced carbenoid transfer, is a modification of the mechanism of direct alkene ligand exchange in dialkoxytitanacyclopropane intermediates.[61,62]

Conclusion

The development of convenient procedures for the generation of highly reactive dialkoxytitanacyclopropane intermediate species (titanium(II) olefin complexes) by the reactions of organomagnesium compounds with inexpensive and low-toxic titanium tetraisopropoxide in combination with their ability to act as equivalents of 1,2-dicarbanions[25,26] made it possible to devise new useful methods for preparative organic synthesis. Alkylation of carboxylic acid derivatives with dialkoxytitanacyclopropanes giving rise to intermediate β-titanio ketones or other products promising in organic synthesis were, in particular, successfully used for the preparation of natural cyclopropane-containing amino acids,[43,72,97,120,126,127] alkaloids,[79,101,114—116,128—131] antibiotics,[101,115,132] pheromones,[66,73,133,134] and other natural compounds or their analogs.[42,93,100,104,108,135—140] Considerable study has been directed to the use of dialkoxytitanacyclopropanes for initiation of other types of chemical transformations, in particular, intra- and intermolecular cyclizations of alkenes and alkynes,[14—17,30,141] as well as their intermolecular alkylation[28,34,142] or coupling.[143,144] In spite of certain progress, the possibilities of the use of dialkoxytitanacyclopropanes in the synthesis of chiral compounds are far from being exhausted. Transformation of dialkoxytitanacyclopropanes into organotitanium and other organometallic reagents containing metals in different oxidation states[145,146] is a promising field of application of these compounds in organic synthesis. Undoubtedly, such investigations will give interesting results and can be of practical importance.

References

1. K. Ziegler, E. Holzkamp, H. Breil, and H. Martin, *Angew. Chem.*, 1955, **67**, 541.
2. G. Natta, P. Pino, P. Corradini, F. Danusso, E. Mantica, G. Mazzanti, and G. Moraglio, *J. Am. Chem. Soc.*, 1955, **77**, 1708.
3. L. Bohm, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 5010.
4. P. Margl, L. Deng, and T. Ziegler, *J. Am. Chem. Soc.*, 1999, **121**, 154.
5. S. Niu and M. B. Hall, *Chem. Rev.*, 2000, **100**, 353.
6. U. Klabuda, F. N. Tebbe, G. W. Parshall, and R. L. Harlow, *J. Mol. Catal.*, 1980, **8**, 37.
7. M. T. Reetz, *Organotitanium Reagents in Organic Synthesis*, Springer Verlag, Berlin—Heidelberg, 1986, 236 p.
8. S. L. Buchwald and R. B. Nielsen, *Chem. Rev.*, 1988, **88**, 1047.
9. S. H. Pine, *Organic Reactions*, 1993, **43**, 1.
10. U. M. Dzhemilev, O. S. Vostrikova, and G. A. Tolstikov, *Usp. Khim.*, 1990, **59**, 1972 [*Russ. Chem. Rev.*, 1990, **59**, 1157 (Engl. Transl.)].
11. E. Negishi and D. Y. Kondakov, *Chem. Soc. Rev.*, 1996, **26**, 417.
12. A. H. Hoveyda and J. P. Morken, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1263.
13. U. M. Dzhemilev and A. G. Ibragimov, *Izv. Akad. Nauk. Ser. Khim.*, 1998, 816 [*Russ. Chem. Bull.*, 1998, **47**, 786 (Engl. Transl.)].
14. O. G. Kulinkovich and A. de Meijere, *Chem. Rev.*, 2000, **100**, 2789.
15. F. Sato, H. Urabe, and S. Okamoto, *Chem. Rev.*, 2000, **100**, 2835.
16. F. Sato, H. Urabe, and S. Okamoto, *Synlett*, 2000, 753.
17. F. Sato and S. Okamoto, *Adv. Synth. Catal.*, 2001, **343**, 759.
18. M. E. Vol´pin, V. A. Dubovitskii, O. V. Nogina, and D. N. Kursanov, *Dokl. Akad. Nauk SSSR,* 1963, **151**, 1100 [*Dokl. Chem.*, 1963, **151**, 1103 (Engl. Transl.)].
19. V. B. Shur, S. Z. Bernadyuk, V. V. Burlakov, V. G. Andrianov, A. I. Yanovsky, Yu. T. Struchkov, and M. E. Vol´pin, *J. Organomet. Chem.*, 1983, **243**, 157.
20. S. A. Cohen, P. R. Auburn, and J. E. Bercaw, *J. Am. Chem. Soc.*, 1983, **105**, 1136.
21. J. W. Lauher and R. Hoffman, *J. Am. Chem. Soc.*, 1976, **98**, 1729.
22. M. J. S. Dewar and G. P. Ford, *J. Am. Chem. Soc.*, 1979, **101**, 783.
23. T. A. Albright, R. Hoffman, J. C. Thibeault, and D. L. Thorn, *J. Am. Chem. Soc.*, 1979, **101**, 3801.
24. M. L. Steigerwald and W. A. Goddard, *J. Am. Chem. Soc.*, 1985, **107**, 5027.
25. O. G. Kulinkovich, S. V. Sviridov, D. A. Vasilevskii, A. I. Savchenko, and T. S. Pritytskaya, *Zh. Org. Khim.*, 1991, **27**, 294 [*J. Org. Chem. USSR*, 1991, **27**, 250 (Engl. Transl.)].
26. O. G. Kulinkovich, S. V. Sviridov, D. A. Vasilevskii, and T. S. Pritytskaya, *Zh. Org. Khim.*, 1989, **25**, 2244 [*J. Org. Chem. USSR*, 1989, **25**, 2027 (Engl. Transl.)].
27. E. Negishi and T. Takahashi, *Acc. Chem. Res.*, 1994, **21**, 1277.
28. O. G. Kulinkovich, *Pure Appl. Chem.*, 2000, **72**, 1715.
29. F. Sato and H. Urabe, in *Titanium and Zirconium in Organic Synthesis*, Ed. I. Marek, Wiley-VCH, Weinheim, 2002, p. 319.
30. F. Sato, H. Urabe, and S. Okamoto, *Pure Appl. Chem.*, 1999, **71**, 1511.
31. USSR Inventor's Certificate No. 1525140; *Byul. Izobr.* [*Invention Bulletin*], 1989, 44 (in Russian).
32. USSR Inventor's Certificate No. 1594162; *Byul. Izobr.* [*Invention Bulletin*], 1990, 35 (in Russian).

33. O. G. Kulinkovich, S. V. Sviridov, and D. A. Vasilevski, *Synthesis*, 1991, 234.
34. O. G. Kulinkovich, O. L. Epstein, V. E. Isakov, and E. A. Khmel´nitskaya, *Synlett*, 2001, 49.
35. Y.-D. Wu and Z.-H. Yu, *J. Am. Chem. Soc.*, 2001, **123**, 5777.
36. O. G. Kulinkovich, *Chem. Rev.*, 2003, **103**, 2597.
37. O. G. Kulinkovich, *Polish J. Chem.*, 1997, **71**, 849.
38. A. de Meijere, S. Kozhushkov, T. Spaeth, and N. S. Zefirov, *J. Org. Chem.*, 1993, **58**, 502.
39. N. S. Zefirov, T. S. Kuznetsova, and A. N. Zefirov, *Izv. Akad. Nauk. Ser. Khim.*, 1995, 1613 [*Russ. Chem. Bull.*, 1995, **44**, 1543 (Engl. Transl.)].
40. A. de Meijere, S. I. Kozhushkov, and A. F. Khlebnikov, *Zh. Org. Khim.*, 1996, **32**, 1607 [*Russ. J. Org. Chem.*, 1996, **32**, 1555 (Engl. Transl.)].
41. A. de Meijere, S. I. Kozhushkov, and A. F. Khlebnikov, *Top. Curr. Chem.*, 2000, **207**, 89.
42. S. Racouchot, J. Ollivier, and J. Salaün, *Synlett*, 2000, 1729.
43. S. Racouchot, I. Silvestre, J. Ollivier, Yu. Yu. Kozyrkov, A. Pukin, O. G. Kulinkovich, and J. Salaün, *Eur. J. Org. Chem.*, 2002, 2160.
44. J. Lee, H. Kim, and J. K. Cha, *J. Am. Chem. Soc.*, 1995, **117**, 9919.
45. J. Lee and J. K. Cha, *Org. Lett.*, 2002, **4**, 3707.
46. S. Y. Cho and J. K. Cha, *Org. Lett.*, 2000, **2**, 1337.
47. K. N. Prokhorevich and T. A. Chevtchouk, *Abstrs. of Papers of Third Youth School-Conf. on Organic Synthesis "Organic Synthesis in the New Century" (St.-Petersburg, June 24—27, 2002)*, St.-Petersburg, 2002, 82a.
48. V. I. Dolgopalets, S. M. Volkov, M. A. Kisel´, A. N. Kozhevko, and O. G. Kulinkovich, *Zh. Org. Khim.*, 1999, **35**, 1469 [*Russ. J. Org. Chem.*, 1999, **35**, 1436 (Engl. Transl.)].
49. O. G. Kulinkovich, I. I. Astapovich, and N. V. Masalov, *Zh. Org. Khim.*, 1998, **34**, 1327 [*Russ. J. Org. Chem.*, 1998, **34**, 1266 (Engl. Transl.)].
50. (a) J. R. Al Dulayymi, M. S. Baird, I. G. Bolesov, V. V. Tverezovsky, and A. V. Nizovtsev, *J. Chem. Soc., Perkin Trans. 2*, 2000, 1603; (b) J. R. Al Dulayymi, M. S. Baird, I. G. Bolesov, V. Tveresovsky, and M. Rubin, *Tetrahedron Lett.*, 1996, **37**, 8933.
51. M. V. Raiman, N. A. Il´ina, and O. G. Kulinkovich, *Synlett*, 1999, 1053.
52. I. L. Lysenko and O. G. Kulinkovich, *Zh. Org. Khim.*, 2001, **37**, 1306 [*Russ. J. Org. Chem.*, 2001, **37**, 1238 (Engl. Transl.)].
53. A. Esposito and M. Taddei, *J. Org. Chem.*, 2000, **65**, 9245.
54. D. Hazelard, J. Ollivier, R. Paugam, and J. Salaun, *Synlett*, 2003, 1155.
55. J. Lee, H. Kim, and J. K. Cha, *J. Am. Chem. Soc.*, 1996, **118**, 4198.
56. E. J. Corey, S. A. Rao, and M. C. Noe, *J. Am. Chem. Soc.*, 1994, **116**, 9345.
57. O. L. Epshtein, A. I. Savchenko, and O. G. Kulinkovich, *Izv. Akad. Nauk. Ser. Khim.*, 2000, 376 [*Russ. Chem. Bull., Int. Ed.*, 2000, **49**, 378].
58. V. Chaplinski, H. Winsel, M. Kordes, and A. de Meijere, *Synlett*, 1997, 111.
59. F. Lecornue and J. Ollivier, *Chem. Commun.*, 2003, 584.
60. O. G. Kulinkovich, S. V. Sviridov, and A. I. Savchenko, *Metalloorg. Khim.,* 1990, **3**, 881 [*Organomet. Chem. USSR*, 1990, **3** (Engl. Transl.)].
61. O. G. Kulinkovich, A. I. Savchenko, S. V. Sviridov, and D. A. Vasilevsky, *Mendeleev Commun.*, 1993, 230.
62. O. L. Epstein, A. I. Savchenko, and O. G. Kulinkovich, *Tetrahedron Lett.*, 1999, **40**, 5935.
63. A. Kasatkin and F. Sato, *Tetrahedron Lett.*, 1995, **36**, 6079.
64. J. Lee, H. Kim, J. G. Bae, and J. K. Cha, *J. Org. Chem.*, 1996, **61**, 4878.
65. J.-H. Youn, J. Lee, and K. Cha, *Org. Lett.*, 2001, **3**, 2935.
66. O. L. Epstein and O. G. Kulinkovich, *Tetrahedron Lett.*, 2001, **42**, 3757.
67. L. G. Quan, S.-H. Kim, J. C. Lee, and J. K. Cha, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 2160.
68. A. I. Savchenko and O. G. Kulinkovich, *Zh. Org. Khim.*, 1997, **33**, 913 [*Russ. J. Org. Chem.*, 1997, **33**, 846 (Engl. Transl.)].
69. R. Mizojiri, H. Urabe, and F. Sato, *J. Org. Chem.*, 2000, **65**, 6217.
70. R. Mizojiri, H. Urabe, and F. Sato, *Tetrahedron Lett.*, 1999, **40**, 2557.
71. K. Lee, S.-I. Kim, and J. K. Cha, *J. Org. Chem.*, 1998, **63**, 9135.
72. O. G. Kulinkovich, A. I. Savchenko, and T. A. Shevchuk, *Zh. Org. Khim.*, 1999, **35**, 244 [*Russ. J. Org. Chem.*, 1999, **35**, 225 (Engl. Transl.)].
73. T. A. Chevtchouk, V. E. Isakov, and O. G. Kulinkovich, *Tetrahedron*, 1999, **55**, 13205.
74. Yu. Yu. Kozyrkov and O. G. Kulinkovich, *Synlett*, 2002, 443.
75. H. Winsel, V. Gazizova, O. Kulinkovich, V. Pavlov, and A. de Meijere, *Synlett*, 1999, 1999.
76. J. Lee, C. H. Kang, H. Kim, and J. K. Cha, *J. Am. Chem. Soc.*, 1996, **118**, 291.
77. J. S. U, J. Lee, and J. K. Cha, *Tetrahedron Lett.*, 1997, **38**, 5233.
78. A. Kasatkin, K. Kobayashi, S. Okamoto, and F. Sato, *Tetrahedron Lett.*, 1996, **37**, 1849.
79. S. Okamoto, M. Iwakubo, K. Kobayashi, and F. Sato, *J. Am. Chem. Soc.*, 1997, **119**, 6984.
80. F. Lecornue and J. Ollivier, *Org. Biomol. Chem.*, 2003, **1**, 3600.
81. A. Kasatkin, T. Yamazaki, and F. Sato, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1966.
82. M. Shirai, S. Okamoto, and F. Sato, *Tetrahedron Lett.*, 1999, **40**, 5331.
83. P. K. Zubaidha, A. Kasatkin, and F. Sato, *Chem. Commun.*, 1996, 197.
84. L. G. Quan and J. K. Cha, *Org. Lett.*, 2001, **3**, 2745.
85. N. L. Hungerford and W. Kitching, *Chem. Commun.*, 1996, 1697.
86. N. L. Hungerford and W. Kitching, *J. Chem. Soc., Perkin Trans. 1*, **1998**, 1839.
87. N. Morlender-Vias, N. Solodovnikova, and I. Marek, *Chem. Commun.*, 2000, 1849.
88. A. Kasatkin, S. Okamoto, and F. Sato, *Tetrahedron Lett.*, 1995, **36**, 6075.
89. S. Okamoto, A. Kasatkin, P. K. Zubaidha, and F. Sato, *J. Am. Chem. Soc.*, 1996, **118**, 2208.

90. K. Kim, S. Okamoto, Y. Takayama, and F. Sato, *Tetrahedron Lett.*, 2002, **43**, 4237.
91. Y. Yoshida, S. Okamoto, and F. Sato, *J. Org. Chem.*, 1996, **61**, 7826.
92. K. Suzuki, H. Urabe, and F. Sato, *J. Am. Chem. Soc.*, 1996, **118**, 8729.
93. H. Urabe, K. Suzuki, and F. Sato, *J. Am. Chem. Soc.*, 1997, **119**, 10014.
94. H. Urabe, D. Suzuki, M. Sasaki, and F. Sato, *J. Am. Chem. Soc.*, 2003, **125**, 4036.
95. (a) Y. Six, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1159; (b) Y. Six, *Eur. J Org. Chem.*, 2003, 1157.
96. V. Chaplinski and A. de Meijere, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 413.
97. M. Kordes, H. Winsel, and A. de Meijere, *Eur. J. Org. Chem.*, 2000, 3235.
98. S. Y. Cho, J. Lee, R. K. Lammi, and J. K. Cha, *J. Org. Chem.*, 1997, **62**, 8235.
99. S. Wiedemann, D. Frank, H. Winzel, and A. de Meijere, *Org. Lett.*, 2003, **5**, 753.
100. S. Wiedemann, I. Marek, and A. de Meijere, *Synlett*, 2002, **5**, 879.
101. J. Lee, J. D. Ha, and J. K. Cha, *J. Am. Chem. Soc.*, 1997, **119**, 8127.
102. S.-H. Kim, Y. Park, H. Choo, and J. K. Cha, *Tetrahedron Lett.*, 2002, **43**, 6657.
103. J. Lee and J. K. Cha, *J. Org. Chem.*, 1997, **62**, 1584.
104. A. de Meijere, C. M. Williams, A. Kourdioukov, S. V. Sviridov, V. Chaplinski, M. Kordes, A. Savchenko, C. Stratmann, and M. Noltemeyer, *Chem. Eur. J.*, 2002, **8**, 3789.
105. G. M. Williams, V. Chaplinski, P. R. Schreiner, and A. de Meijere, *Tetrahedron Lett.*, 1998, **39**, 7695.
106. T. Voigt, H. Winsel, and A. de Meijere, *Synlett*, 2002, 1362.
107. H. B. Lee, M. J. Sung, S. C. Blackstock, and J. K. Cha, *J. Am. Chem. Soc.*, 2001, **123**, 11322.
108. M. Gensini, S. I. Kozhushkov, D. S. Yufit, J. A. K. Howard, M. Es-Sayed, and A. de Meijere, *Eur. J. Org. Chem.*, 2002, 2499.
109. G.-D. Tebben, K. Rauch, C. Strattmann, C. M. Williams, and A. de Meijere, *Org. Lett.*, 2003, **5**, 483.
110. N. Ouhamou and I. Six, *Org. Biomol. Chem.*, 2003, **1**, 3007.
111. J. Lee, J. S. U, S. C. Blackstock, and J. K. Cha, *J. Am. Chem. Soc.*, 1997, **119**, 10241.
112. B. Cao, D. Xiao, and M. M. Joullie, *Org. Lett.*, 1999, **1**, 1799.
113. R. Mizojiri, H. Urabe, and F. Sato, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 2666.
114. M. J. Sung, C.-W. Lee, and J. K. Cha, *Synlett*, 1999, 561.
115. S.-H. Kim, S.-I. Kim, S. Lai, and J. K. Cha, *J. Org. Chem.*, 1999, **64**, 6771.
116. L. Oller, G. Mentic, F. P. J. T. Rutjes, W. N. Speckamp, and H. Hiemstra, *Org. Lett.*, 1999, **1**, 1331.
117. J. Salaün, *Top. Curr. Chem.*, 2000, **207**, 1.
118. P. Bertus and J. Szymoniak, *Chem. Commun.*, 2001, 1792.
119. P. Bertus and J. Szymoniak, *J. Org. Chem.*, 2003, **68**, 7133.
120. P. Bertus and J. Szymoniak, *J. Org. Chem.*, 2002, **67**, 3965.
121. C. Laroche, P. Bertus, and J. Szymoniak, *Tetrahedron Lett.*, 2003, **44**, 2485.
122. P. Bertus and J. Szymoniak, *Synlett*, 2003, 265.
123. J. J. Eisch, J. N. Gitua, P. O. Otieno, and X. Shi, *J. Organomet. Chem.*, 2001, **624**, 229.
124. J. J. Eisch, *J. Organomet. Chem.*, 2001, **617—618**, 148.
125. J. J. Eisch and G. N. Gitua, *Organometallics*, 2003, **22**, 24.
126. Yu. Yu. Kozyrkov, A. Pykin, O. G. Kulinkovich, J. Ollivier, and J. Salaün, *Tetrahedron Lett.*, 2000, **41**, 6399.
127. A. Esposito, P. P. Piras, D. Ramazotti, and M. Taddei, *Org. Lett.*, 2001, **3**, 3273.
128. O. G. Kulinkovich, N. Masalov, V. Tyvorskii, and N. De Kimpe, *Tetrahedron Lett.*, 1996, **37**, 1095.
129. S. E. Denmark and L. R. Marcin, *J. Org. Chem.*, 1997, **62**, 1675.
130. I. L. Lysenko, A. V. Bekish, and O. G. Kulinkovich, *Zh. Org. Khim.*, 2002, **38**, 918 [*Russ. J. Org. Chem.*, 2002, **38**, 875 (Engl. Transl.)].
131. I. L. Lysenko and O. G. Kulinkovich, *Zh. Org. Khim.*, 2004, **40**, No. 8 [*Russ. J. Org. Chem.*, 2004, **40**, No. 8 (Engl. Transl.)].
132. T. A. Shevchuk and O. G. Kulinkovich, *Zh. Org. Khim.*, 2000, **36**, 1160 [*Russ. J. Org. Chem.*, 2000, **36**, 1124 (Engl. Transl.)].
133. O. L. Epstein and O. G. Kulinkovich, *Tetrahedron Lett.*, 1998, **39**, 1823.
134. V. I. Tyvorskii, D. A. Astasko, and O. G. Kulinkovich, *Tetrahedron*, 2004, **60**, 1473.
135. B. Achmatowicz, P. Jankowski, and J. Wicha, *Tetrahedron Lett.*, 1996, **37**, 5589.
136. M. Brandl, S. I. Kozhushkov, D. S. Yufit, J. A. K. Howard, and A. de Meijere, *Eur. J. Org. Chem.*, 1998, 2785.
137. M. Shirai, S. Okamoto, and F. Sato, *Tetrahedron Lett.*, 1999, **40**, 5331.
138. T. A. Shevchuk and O. G. Kulinkovich, *Zh. Org. Khim.*, 2000, **36**, 515 [*Russ. J. Org. Chem.*, 2000, **36**, 491 (Engl. Transl.)].
139. H. Venkatesan, M. C. Davic, Y. Altas, J. P. Snyder, and D. C. Liotta, *J. Org. Chem.*, 2001, **66**, 3653.
140. M. V. Raiman, A. V. Pukin, V. I. Tyvorskii, N. De Kimpe, and O. Kulinkovich, *Tetrahedron*, 2003, **59**, 5265.
141. M. J. Sung, J.-H. Pang, S.-B. Park, and J. K. Cha, *Org. Lett.*, 2003, **5**, 2173.
142. E. A. Matyushenkov, D. G. Churikov, N. A. Sokolov, and O. G. Kulinkovich, *Zh. Org. Khim.*, 2003, **39**, 514 [*Russ. J. Org. Chem.*, 2003, **39**, 478 (Engl. Transl.)].
143. A. de Meijere, B. Stecker, A. Kourdioukov, and C. M. Williams, *Synthesis*, 2000, 929.
144. V. E. Isakov and O. G. Kulinkovich, *Synlett*, 2003, 967.
145. Y. Obora, H. Moriya, M. Tokunaga, and Y. Tsuji, *Chem. Commm.*, 2003, 2820.
146. E. A. Matiushenkov, N. A. Sokolov, and O. G. Kulinkovich, *Synlett*, 2004, 77.

Received December 9, 2003;
in revised form March 1, 2004