Bicyclization of dienes, enynes, and diynes with Ti(ɪɪ) reagent. New developments towards asymmetric synthesis*

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Abstract: The title bis-unsaturated compounds undergo bicyclization with (η^2-propene)Ti(O-*i*-Pr)$_2$ to give dialkoxytitanacycles, the characteristic reactions of which are highlighted. Substrate-controlled asymmetric cyclizations starting from optically active allenes, enynes having a chiral acetal as a leaving group, and optically active enynoates were found promising to give cyclic compounds with high enantiopurity.

INTRODUCTION

In 1989, Kulinkovich and co-workers reported the generation of a dialkoxytitanacyclopropane (and/or an olefin-titanium complex, *vide infra*) from Ti(O-*i*-Pr)$_4$ and two equivalents of an alkyl Grignard reagent and that it reacts with esters to afford cyclopropanols (Eqn 1) [1]. In this reaction, the carbon framework of the titanacyclopropane is derived from the Grignard reagent and participates in the reaction with esters as a vicinal dianion equivalent. This unique and synthetically useful reaction has attracted considerable interest and brought about the development of its further utility as a vicinal di-carbanionic reagent by several research groups [2]. Another important feature of this titanium species that was also mentioned by Kulinkovich is that it behaves as an (η^2-alkene)titanium(ɪɪ) complex. Thus, they reported that the reaction of EtMgBr, styrene, and ethyl acetate in the presence of a catalytic amount of Ti(O-*i*-Pr)$_4$ afforded 1-methyl-2-phenycyclopropanol rather than 1-methylcyclopropanol and they proposed that the catalytic cycle involved the ligand (olefin) exchange of the ethylene in (η^2-ethylene)Ti(O-*i*-Pr)$_2$ with styrene [3]. However, no further light had been shed on the second aspect of this titanium species prior to our report in 1995.
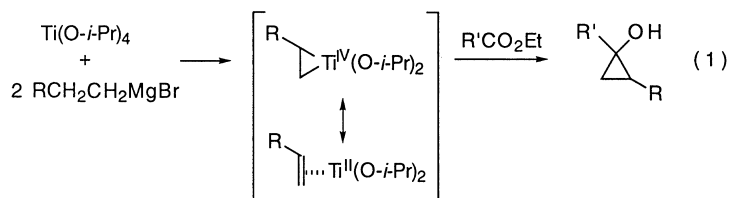
In mid-1994, we found that the aforementioned (η^2-alkene)titanium(ɪɪ) complex derived from Ti(O-*i*-Pr)$_4$ and 2 equiv of *i*-PrMgX reacts with an alkyne to afford (η^2-alkyne)Ti(O-*i*-Pr)$_2$ (and/or the corresponding titanacyclopropene) through the ligand exchange from propene to the alkyne. This newly formed alkyne–titanium complex is hydrolyzed or reacts with aldehydes or ketones to give *cis*-olefin or allylic alcohol in good to excellent yields (Eqn 2) [4]. This finding demonstrates that (η^2-propene)Ti(O-*i*-Pr)$_2$ (**1**), in fact, serves as a synthetically useful titanium(ɪɪ) reagent, where the ligating propene should play

an important role to protect the Ti(O-*i*-Pr)$_2$ moiety, but does not participate in the following reactions. It should be noted that the combination of Ti(O-*i*-Pr)$_4$ and *i*-PrMgX is crucial to generate the reagent which works as a divalent titanium, because the use of other Grignard reagents involving EtMgX, *n*-PrMgX, or *i*-BuMgX in place of *i*-PrMgX gave far less satisfactory results [5]. Since then, we have been devoting our efforts to develop new synthetic methodology based on this particular combination. The results so far obtained have indicated that the reagent is unimaginably versatile. Typical reactions based on the reagent **1** can be classified into the following four categories [6]: (i) formation of an (alkyne)Ti(O-*i*-Pr)$_2$ complex and its utilization as a vicinal vinylic dianion; (ii) generation of allyl-, propargyl, and allenyltitanium reagents from allyl or propargyl alcohol derivatives via the ligand exchange followed by the β-elimination, and their synthetic application; (iii) intramolecular nucleophilic acyl substitution reaction of olefinic and acetylenic esters and the related cyclopropanol formation; (iv) inter- or intramolecular coupling reaction of olefins and acetylenes. This paper outlines a survey on recent progress in the fourth reaction, especially bicyclization of bis-unsaturated compounds, with special focus on its application in asymmetric synthesis.
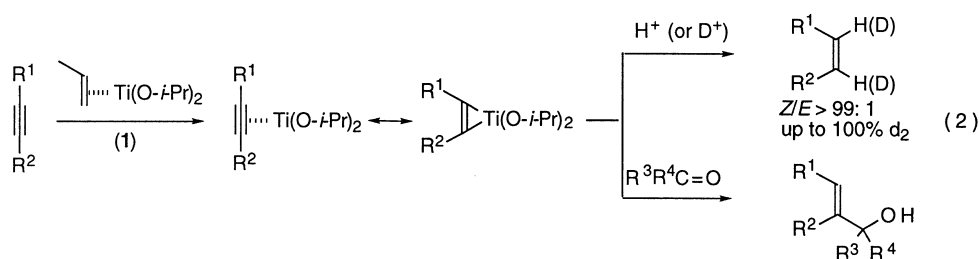

BICYCLIZATION OF DIENES, ENYNES AND DIYNES

Bicyclization of dienes, enynes and diynes with a catalytic or a stoichiometric amount of a metallic reagent is a potential method for the preparation of cyclic compounds. One advantage of the stoichiometric reactions is the generation of metallacycles as the primary product, because such organometallic reagents are useful for the subsequent functionalization or carbon-carbon bond formation from the resultant cyclic compound. (η^2-Propene)Ti(O-*i*-Pr)$_2$ (**1**) nicely effects the cyclization of these substrates. The intermediate dialkoxytitanacycles are metallacycles of a quite new class, because most group 4 metallacycles so far utilized in organic synthesis have a bis(η^5-cyclopentadienyl)titanium or -zirconium moiety [7], which is distinctive from the dialkoxytitanium portion. Several new reactions developed by **1** and by the resultant titanacycles will be highlighted in the following discussion.

Cyclization of 1,6-diene with **1** afforded the bicyclic titanacyclopentane which, upon hydrolysis, gave a cyclopentane derivative (Eqn 3) [8]. The stereoselection found in the **1**- and Cp$_2$Zr-mediated cyclizations of a certain 1,6-bis-olefinic substrate was reported to be reversed to each other [9]. 1,6- or 1,7-Enynes analogously undergo the cyclization to give the titanacyclopentenes which, upon addition of deuteriochloric acid, iodine, or carbon monoxide, give the corresponding addition products as do other group 4 metallacycles (Eqn 4) [8].
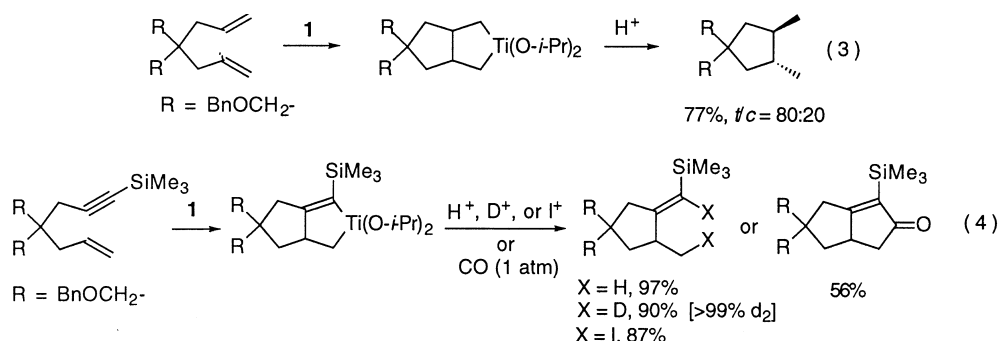
Addition of organometallic reagents to carbonyl compounds is an important synthetic process. The above titanacycle could be utilized in this type of reaction, and aldehydes are selectively inserted into the alkenyl-metal bond of the titanacycle as shown in Eqn 5 [10,11], This is in marked contrast to and complementary with a similar reaction of Cp_2-zirconacyclopentenes which add to aldehydes at their alkyl-metal bond [7a,12], The aldehyde addition of 2-silyl-1-titana-2-cyclopentenes, where the presence of an extra equivalent of $Ti(O-i-Pr)_2Cl_2$ increases the product yields, shows very high 1,4-diastereoselectivity (>96 : 4) with respect to the hydroxy and methyl groups [10,11].
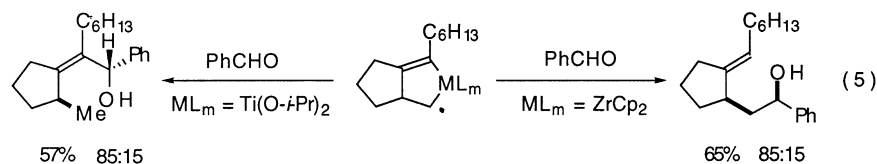
In addition to the homocoupling [13] and crosscoupling reaction of two acetylenes [14] effected by **1**, the intramolecular cyclization of 1,6- or 1,7-diynes proceeds readily to afford the bicyclic titanacycle as well, which could be protonated, deuterated, and iodinated as other group 4 metallacyclopentadienes (Eqn 6) [8]. Although the coupling reaction of Cp_2-titanacyclopentadiene and its zirconium counterpart with aldehydes has not been reported [15], dialkoxytitanacyclopentadienes obtained here undergo the addition to aldehydes, preferably in the presence of an additional equivalent of $TiCl_2(O-i-Pr)_2$, to furnish the adducts in good yields with high regioselectivity (Eqns 6 and 7) [10,11].
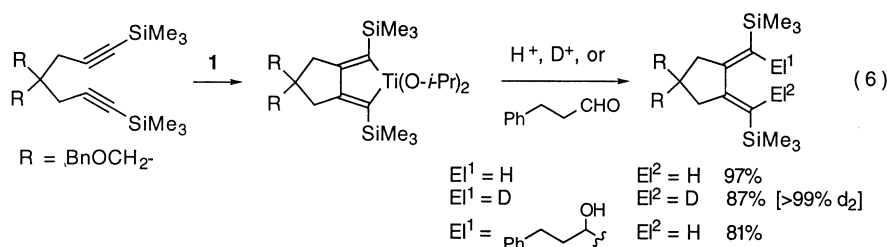

Besides the reaction with aldehydes, a carbon-carbon bond elongation from the titanacycles can be executed by alkylation with allyl bromide in the presence of a copper salt to give the products in a highly regioselective manner [11]. A titanacyclopentadiene having both silyl and alkyl side chains showed good regioselectivity as high as 9 : 1 (Eqn 7). The reaction stopped at the mono-allylation stage, and the other remaining carbon-titanium bond could be identified by deuteration. The extension of a carbon chain at each carbon-titanium bond of the titanacyclopentadiene shown in Eqn 7 was possible by simply switching the kind of electrophile. As transmetallation of titanium compounds to other metallic species such as copper reagents has not been so far studied in detail, this is an informative observation.
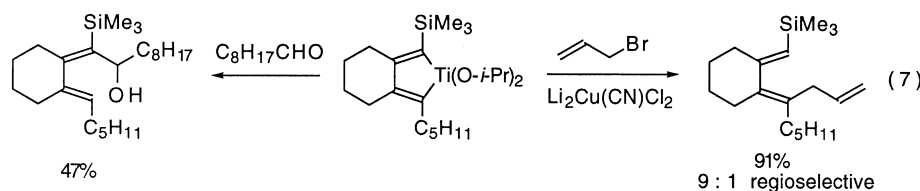

Stereoselective cyclization is often required in the synthesis of naturally occurring products. Although the substrate-controlled methods are frequently encountered in group 4 metal-mediated cyclization, it is usually difficult to control the stereochemistry of the cyclization by a remote substituent to the reaction center [7]. The **1**-mediated reaction provides an answer to this issue: the cyclization of the substrates shown in Eqn 8 proceeded in a highly stereoselective manner provided that the hydroxy group is converted to magnesium alkoxide prior to the cyclization [16]. When the same reaction was attempted

with substrates having a TBS protecting group to their hydroxy group, only inferior stereoselectivity was observed.
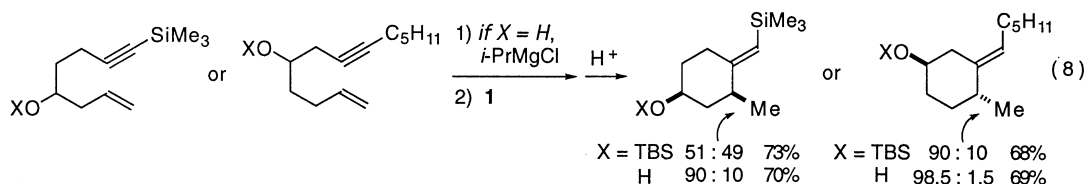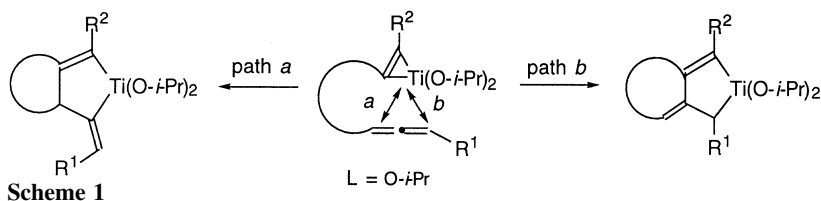

The bicyclization between the acetylene and diene groups proceeded equally well to give intermediate titanacycles, which have an allyltitanium moiety in the molecule [17]. Aldehydes attacked this allytitanium moiety selectively at its terminal position to furnish a cyclopentane ring having a side chain with *trans*-olefinic configuration (Eqn 9).
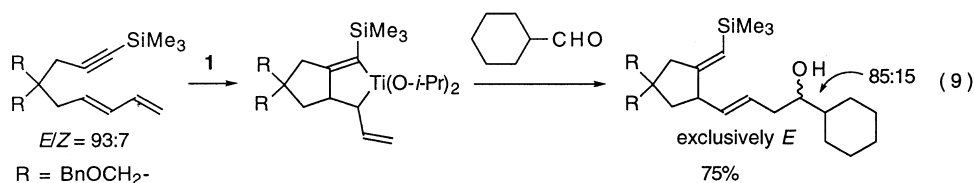

ASYMMETRIC CYCLIZATION OF OPTICALLY ACTIVE ALLENES

Homocoupling of allenes [18] and intermolecular coupling of allene and acetylene with **1** [18] have been already reported. The latter reaction was readily extended to the intramolecular version. There are two modes of cyclization, path *a* or *b*, dependent upon the structure of allenynes as shown in Scheme 1.
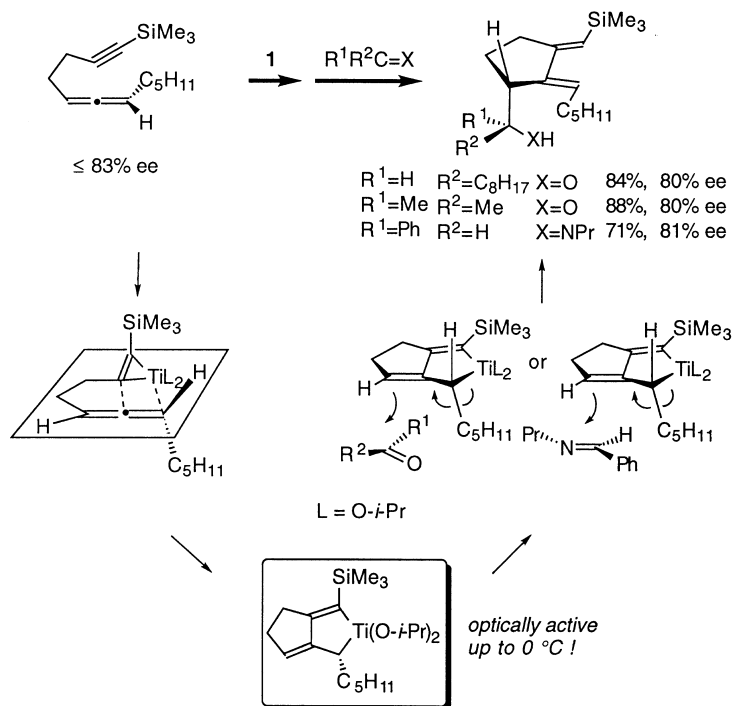

Scheme 1

The bicyclization of 1,2-dien-7-ynes smoothly proceeds via path *a* in Scheme 1 in accord with the aforementioned intermolecular reaction of allene and acetylene (Eqns 10, 11) [19]. If this reaction starts with an optically active allene as shown in Eqn 10, the optically active titanacycle was generated. As the bulky silyl group effectively controls the direction of the approach of the intermediate acetylene-titanium complex to the allene plane, the virtually complete transfer of chirality was observed (Eqn 10). The cyclization of an optically active allene followed by carbonylation of the titanacycle afforded a bicyclic ketone with the predictable stereochemistry without loss of the enantiopurity of the starting allene (Eqn 11) [19].

Intramolecular cyclization of 1,2-dien-6-ynes shows a different mode of ring closure to give a new titanacycle (path *b* in Scheme 1), which has not been reported before [19]. The reaction is illustrated in Eqn 12, where a tri-substituted olefinic bond in the allene participated in the cyclization to form the titanacycle which, upon reaction with an aldehyde, gave the exo-cyclic diene including an isopropylidene group. More importantly, when the cyclization is initiated from an optically active allene, the optically active titanabicycle having no chiral auxiliary such as the one in Scheme 2, which belongs to a rare class of optically active allyltitanium species [20], is generated. The subsequent reaction of the titanacycle with aldehyde, ketone, or imine proceeded without loss of the enantiopurity of the starting allene to give an optically active cyclopentane skeleton (Scheme 2). As the diene portion enables further elaboration of the ring structure by Diels–Alder reaction, this reaction would be a convenient way to prepare optically active cyclic compounds.

$$(10)$$

80%, 80-83% ee

$$(11)$$

EI = H 68%, 86% ee
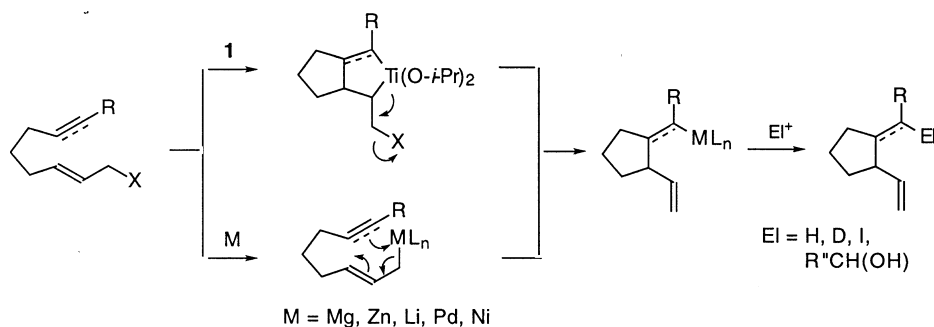EI = D 67%

$$(12)$$

77% >95:5
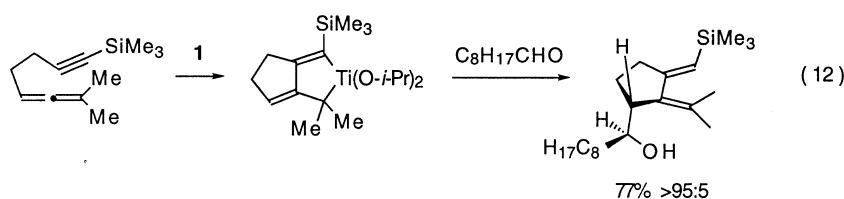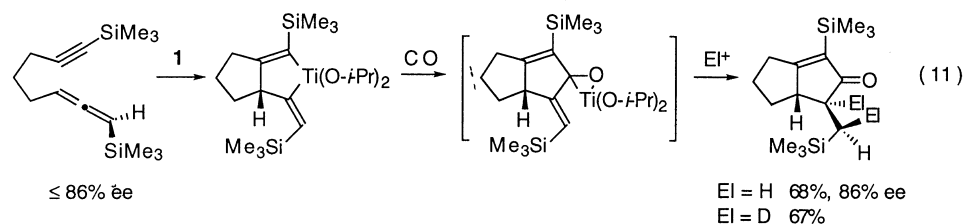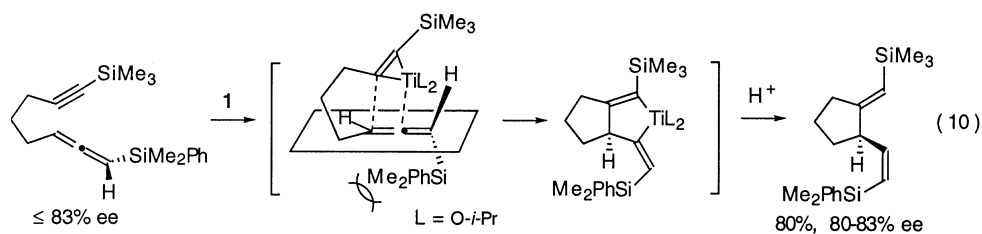
ASYMMETRIC CYCLIZATION OF ENYNES HAVING A CHIRAL ACETAL

If dienes, enynes, and diynes being subjected to the **1**-mediated reaction have a leaving group at an appropriate position, the resulting titanacycles undergo the elimination of such a group as shown in Scheme 3 [21]. The overall outcome of this transformation can be considered as an equivalent of the metallo-ene reaction [22,23], The vinyltitanium species remaining in the product could be intercepted

R^1=H R^2=C_8H_{17} X=O   84%, 80% ee
R^1=Me R^2=Me X=O   88%, 80% ee
R^1=Ph R^2=H   X=NPr 71%, 81% ee

L = O-*i*-Pr

optically active
up to 0 °C !

Scheme 2

Scheme 3

$$(13)$$
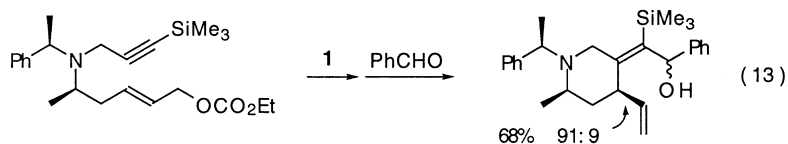
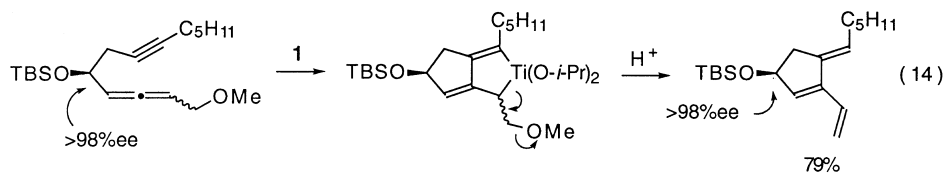with electrophiles including aldehydes. Preparation of heterocyclic compounds (Eqn 13) [24,25] and cross-conjugated trienes useful for the diene-transmissive Diels–Alder reaction (Eqn 14) [26] has been achieved based on this method.

$$(14)$$

The use of a chiral acetal as the leaving group made the above reaction a very efficient asymmetric cyclization as shown in Scheme 4 [27]. Similarly, tetrahydrofuran and cyclohexane skeletons are also prepared with excellent enantiopurity (Eqn 15).

Scheme 4

$$(15)$$
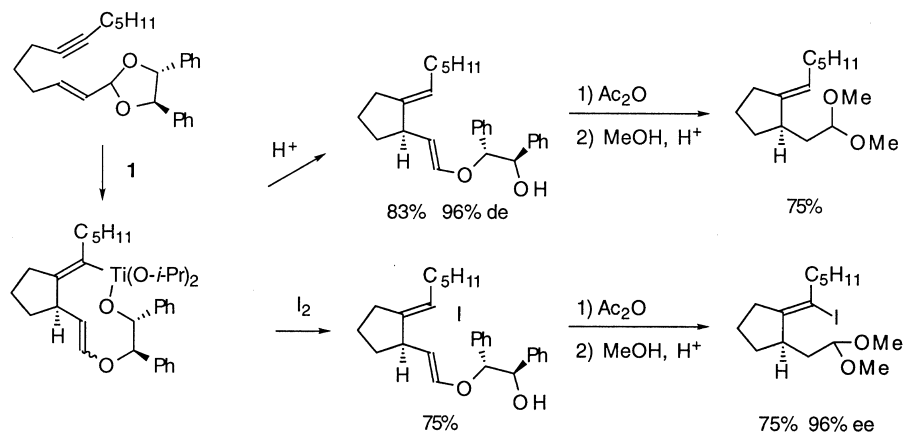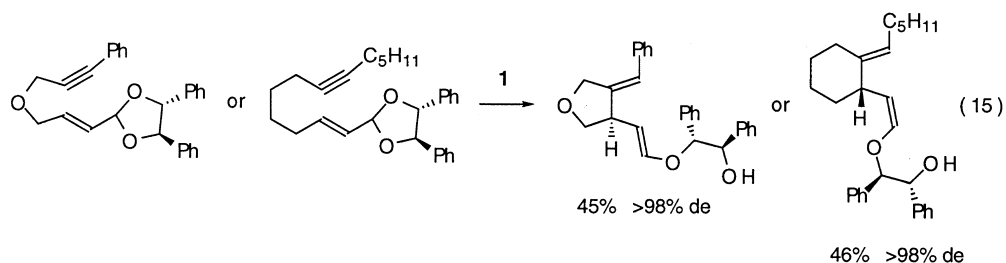
ASYMMETRIC CYCLIZATION OF OPTICALLY ACTIVE ENYNOATES

Although the cyclization of functionalized olefins or acetylenes such as 2-en-7-ynoates or 2-en-8-ynoates with group 4 metallocene-based reagents had not been reported, these substrates readily underwent the intramolecular cyclization with **1** [28,29]. For instance, *tert*-butyl 2-en-7-ynoates generated the titanacycle [30] which, in turn, reacts with carbonyl compounds exclusively at the carbon-titanium bond α to the ester moiety and with high diastereoselectivity to offer a potential method for the stereoselective construction of the side chain in addition to the cyclization (Eqn 16). The methyl or ethyl esters of the same structure generate the titanacycles as well, but this is followed by a second ring closure initiated by the reaction with an electrophile, giving eventually bicyclic ketones as shown in Eqn 17. The cyclization of 2,7-dienoates is also feasible in the same manner [28,29].

(16)

(17)

El+ = s-BuOH   El = H   80%
EtCHO   EtCH(OH)-   78%
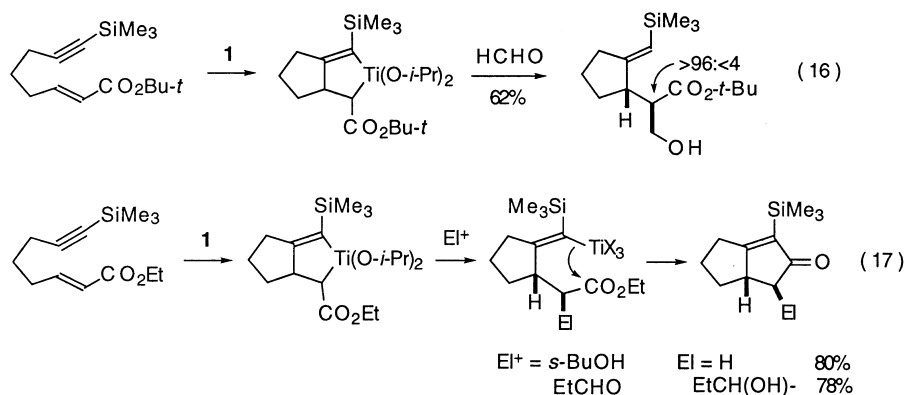
Incorporation of an optically active alcohol in the ester portion of the above substrates led to an asymmetric synthesis of bicyclic ketones, which have been a useful precursor for the synthesis of naturally occurring products. The cyclization of the 8-phenylmenthol-derived esters under the standard conditions showed the best result to afford the optically active ketones of high enantiomer excess values (Eqn 18) [31]. It is also noted that this cyclization permits a trisubstituted olefin as an acceptable cyclization partner, which is usually a sluggish functional group in group 4 metal-mediated cyclizations.


(18)

62%   91-93% ee
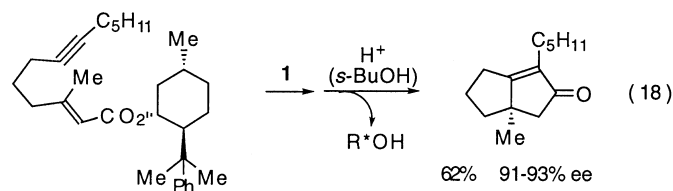
In contrast to the reactions of olefinic esters discussed above, the isomeric conjugated acetylenic esters, 7-en-2-ynoates, show other interesting behavior of cyclization (Scheme 5) [28,29], Deuterolysis

(3)   El = H   91%
       D   99%d2

(5)   El = H   74%
       D   78%, 99%d2

58%
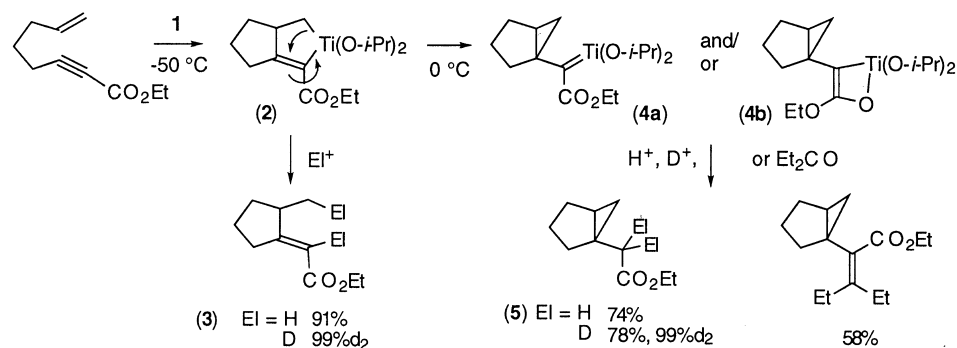
Scheme 5

of the intermediate titanacycle **2** at a low temperature gave bis-deuterated compound **3**. However, when the titanabicycle generated at –50 °C was allowed to warm to a higher temperature up to 0 °C, a new product **5** was obtained in good yield after aqueous workup. The titanium-carbene complex **4a** and/or bis-titanated species **4b** are the most likely species in the reaction as evidenced by their deuteriolysis and alkylidenation of diethyl ketone.

   Asymmetric construction of a cyclopropane moiety by the above transformation was readily performed by the chirality transfer from the allylic position of the substrate. Thus, the synthesis of *d*-sabinene, a monoterpene having an optically active bicyclo[3.1.0]hexane skeleton, was achieved starting from optically active enynoate as shown in Eqn 19 [29].

78%, ds >98-99%   *d*-sabinene

(19)
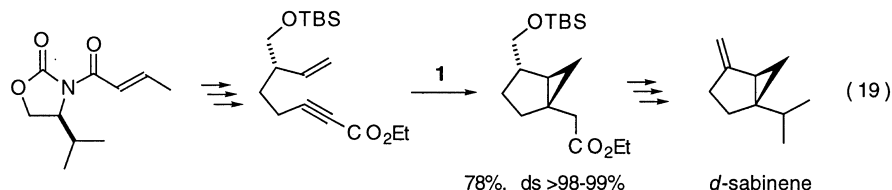
CONCLUSION

The bicyclization of dienes, enynes, and diynes mediated by the low-valent titanium complex **1** and a variety of subsequent reactions based on the resultant dialkoxytitanacycles have opened up a new area in group 4 metal-promoted reactions. The new reactions described herein have been readily applied to asymmetric synthesis to afford promising results. As the organotitanium intermediates are generated with very inexpensive $Ti(O\text{-}i\text{-}Pr)_4$ and a Grignard reagent, the transformations described herein should be also attractive from the economical point of view. Further study to disclose unique and efficient reactions based on **1** as well as the dialkoxytitanacyles is now in progress.

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