The Divalent Titanium Complex Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX as an Efficient and Practical Reagent for Fine Chemical Synthesis

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Abstract: This account describes synthetic transformations of unsaturated hydrocarbons, such as alkynes, alkenes, and dienes, mediated by the divalent titanium reagent Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX, which proceed *via* (η^2-alkene)- or (η^2-alkyne)-titanium intermediates. Many of these transformations are otherwise difficult or require multi-step reaction sequences. Since Ti(O-*i*-Pr)$_4$ and *i*-PrMgX are nontoxic and available in bulk at low price, the reagent satisfies the qualifications for use in large-scale synthesis.

Keywords: alkene complex; alkyne complex; allylation; divalent; metallacycles; titanium

1 Introduction

New efficient and sophisticated reagents and reactions for organic synthesis are being developed more and more rapidly each year. Owing to these developments, modern organic synthesis has reached such a level as to enable chemists to prepare any targeted complicated molecule. However, it is also true that when we want to synthesize fine chemicals such as pharmaceuticals and agricultural chemicals in quantity, such a synthesis often requires many steps even if the target compound has a rather simple structure. The lack of a practical and short access to the target compound sometimes has made researchers in industry give up attempts for its development in spite of its interesting properties. This is due to the fact that only a small portion of the reagents and reactions developed so far can be applied to large-scale production; the majority, unfortunately, suffer from at least one serious disadvantage in application to mass production such as lack of economical efficiency, dissatisfaction from the viewpoint of environmental impact and/or energy-saving, and operational difficulty. Further development of a highly efficient and practical synthetic methodology that is applicable to large-scale production of fine chemicals, therefore, remains as a most challenging research field for organic synthetic chemists.

In the development of new reagents and reactions for organic synthesis, much effort has been devoted to the use of organometallics in either a stoichiometric or a catalytic amount, because a synthetic method based on organometallics might allow a one-step access to the target compound which, otherwise, would require multi-step sequences, and eventually energy-saving and environmentally benign process can be achieved. The stoichiometric organometallics that have been used in a large-scale synthesis are mainly limited to lithium, magnesium, zinc, aluminum, boron, and copper compounds which, except

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Fumie Sato was born in 1942 in Tokyo. He obtained his B.Sc (1966) and Ph.D. (1971) degrees from Tokyo Institute of Technology. In 1971 he joined Tokyo Institute of Technology as Assistant Professor position, was promoted to Associate Professor in 1981 and to Professor in 1989. He was a postdoctoral fellow at Indiana University with Professor L. J. Todd from 1973 to 1974. He was the recipient of the Tejima Prize (1980) and the Ichimura Prize (1992). His research interests involve the development of new synthetic methodologies using organometallic compounds and their utilization for the synthesis of biologically active compounds. Some reactions and reagents developed by his group include titanium-catalyzed hydroalumination and hydromagnesiation reactions of carbon-carbon unsaturated organic compounds, stereocontrol of acyclic systems based on Cram's rule, and use of organocopper compounds as a reagent for stereocontrol. His group has developed the two-component coupling synthesis of prostaglandins as an industrially viable process, which is now in operation at Onoda factory of Nissan Chemical Industries, Ltd. A special area of emphasis of his group in the last six years has been the synthetic reactions mediated by the Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX reagent.

Sentaro Okamoto was born in 1961 in Hiroshima, Japan. He received his M.S. degree from Tokyo Institute of Technology in 1987 and became Assistant Professor at the same institute in 1989. He obtained his Ph.D. degree in 1993 from Tokyo Institute of Technology under the supervision of Professor Fumie Sato. He was also a visiting associate of Montana State University with Professor T. Livinghouse in 1998–1999. He received a Toray Award in Synthetic Organic Chemistry, Japan in 1997, and a Progress Award in Synthetic Organic Chemistry, Japan in 2000. He has been involved in the development of synthetic methodologies using organometallic compounds and their utilization for synthesis of biologically active compounds.

for copper, are representative elements. These complexes satisfy the following indispensable requirements for application to large-scale synthesis. First, these organometallics exhibit versatile reactivity, mainly as a carbanion source, and can be effectively used for functionalization and carbon-carbon-bond formation. Secondly, the compounds can be readily prepared starting from inexpensive and the corresponding non or less toxic metal or metal compound. And, thirdly, the work-up and isolation of the products, after the reaction, can be carried out readily and economically.

Many interesting and efficient synthetic transformations mediated by stoichiometric transition metal complexes in addition to organocopper reagents have been reported.[1] However, most of these reactions are difficult to apply to mass production. The following facts are obstacles to the use of a stoichiometric amount of transition metal compounds in mass production. Several transition metals are very expensive and/or toxic. There are metals, such as Fe, Mn, Ti, and Zr, or their salts, which are inexpensive and non or less toxic. However, transition metal reagents have been utilized, in most cases, with ligand(s) coordinated to the metal, such as carbon monoxide, triphenylphosphine, or the cyclopentadienyl group; thus, even in the case where the metal or its salt is inexpensive and non-toxic, with the ligand(s) it becomes expensive and sometimes shows toxicity. In such cases, recovery of the metal complex itself, or at least the ligand, is indispensable from an economical and environmental viewpoint, and this makes the process of work-up and isolation of the products laborious and costly.

Transition metal complexes, however, have a different character in their reactivity from that of representative metal complexes and thus allow synthetic transformations which are difficult to attain by using the latter. The development of synthetic reactions based on stoichiometric transition metal complexes applicable to large-scale production, therefore, has been strongly exploited.

Divalent group 4 metal complexes such as titanium(II) and zirconium(II) complexes or their equivalents, prepared as shown in Figure 1, have been widely accepted as useful synthetic reagents.[2] However, as these reagents contain a cyclopentadienyl group or a sterically hindered, special aromatic alkoxyl group, respectively, their application to large-scale production seems to be difficult. In 1989, Kulinkovich and coworkers reported the preparation of a Ti(O-*i*-Pr)$_2$-olefin complex by the reaction of Ti(O-*i*-Pr)$_4$ with 2 equivalents of an alkyl Grignard reagent and showed that the complex reacts with esters to afford cyclopropanols as shown in Equation 1.[3] In this reaction, the olefin attached to the titanium comes from the Grignard reagent and participates in the re-

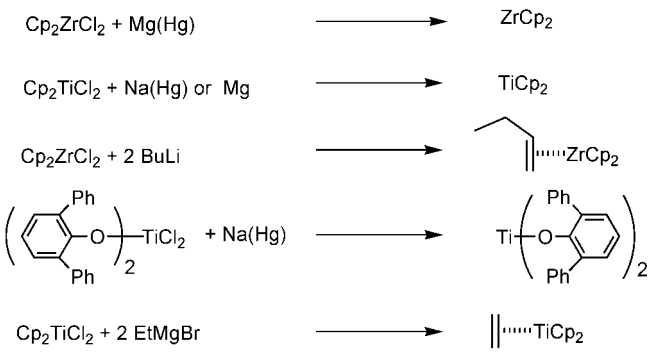
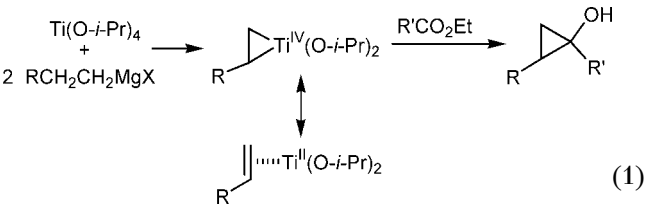


Figure 1.

action with the esters as a vicinal alkyl dianion, indicating that the complex works as a titanium(IV) complex, titanacyclopropane. This new type of synthetically useful reaction is potentially applicable to mass production, and has attracted much interest for its use in organic synthesis as well as for the development of further utility of the titanium-olefin complex as a Ti(IV) reagent.[4] As a titanium(IV)-cyclopropane complex can be represented as a hybrid with a (η^2-olefin)titanium(II) complex, the complex might serve as a titanium(II) reagent, as is the case for $Cp_2Zr(\eta^2$-butene) and $Cp_2Ti(\eta^2$-ethylene) shown in Figure 1. If the complex Ti(O-*i*-Pr)$_2$(η^2-olefin) derived from Ti(O-*i*-Pr)$_4$ and a readily available Grignard reagent works as a divalent titanium complex, it might become a practical divalent titanium reagent applicable to large-scale synthesis because Ti(O-*i*-Pr)$_4$ is non-toxic and is available in bulk at low price, and the reagent does not contain any special ligand except for the ligating olefin and the isopropoxy groups. However, initial efforts to utilize such complex as a divalent titanium reagent by the Kulinkovich group were not promising.[5]



(1)

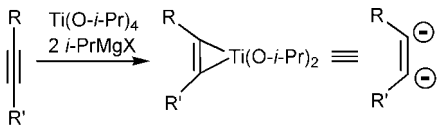
In the middle of 1994, we accidentally found that (η^2-propene)Ti(O-*i*-Pr)$_2$, derived from Ti(O-*i*-Pr)$_4$ and 2 equivalents of *i*-PrMgX (X = Cl or Br), reacts with an alkyne to afford a titanium-alkyne complex, (η^2-alkyne)Ti(O-*i*-Pr)$_2$, via the exchange of the ligating propene with the alkyne added, and that the latter works as a vicinal vinylic dianion. This finding that the propene coordinated to the titanium served as a Ti(O-*i*-Pr)$_2$-stabilizing ligand but did not participate in the following reaction strongly indicated that (η^2-propene)Ti(O-*i*-Pr)$_2$ behaved as an equivalent of divalent Ti(O-*i*-Pr)$_2$. Since the finding that a Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX reagent works as a Ti(O-*i*-Pr)$_2$ equivalent (Figure 2), we have been devoting our efforts to develop synthetic reactions mediated by the reagent with the expectation of developing new synthetic methodology applicable to mass production. The results so far obtained have shown that the reagent is unimaginably versatile, and opens up many new synthetic transformations including those which are otherwise not viable or require multi-step sequences.

Figure 2.

We have already reported in detail how we found the combination of Ti(O-*i*-Pr)$_4$ and 2 equivalents of *i*-PrMgX to be an efficient Ti(O-*i*-Pr)$_2$ equivalent, and the synthetic reactions mediated by the reagent revealed before early 1999 in an Account in *Synlett*.[6] We also reviewed comprehensively the synthetic transformations using the reagent in *Chemical Reviews*, this covers the reactions reported up to the latter half of 1999.[7] The present account, therefore, mainly discusses the most recent developments and examples appearing in the latest publications, while the reactions already reported in the above two reviews are limited to show one or two examples in the tables and/or equations, with a brief comment. First, we will give a general view of the reagent.

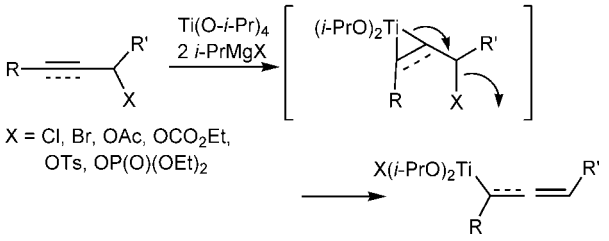
2 A General View of the Ti(O-*i*-Pr)$_4$/ 2 *i*-PrMgX Reagent

The synthetic reactions mediated by the Ti(O-*i*-Pr)$_4$/ 2 *i*-PrMgX reagent can be classified into four categories. One is the generation of titanium-alkyne complexes by the reaction with alkynes as shown in Equation 2 and their use as a vicinal vinylic dianion. The reaction opens up an easy, one-pot access to di-, tri-, or tetrasubstituted alkenes from alkynes.



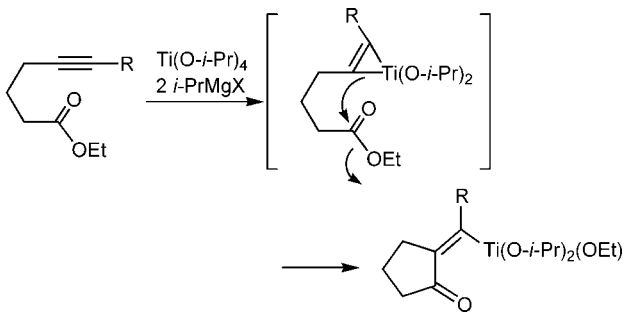
(2)

The second type of reaction is the generation of allyltitanium or allenyltitanium species from Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX and allylic alcohol or propargylic alcohol derivatives, respectively, and their use as an allylating or propargylating (sometimes allenylating) reagent. The reaction probably proceeds as shown in Equation 3 through a ligand exchange between the ligated propene in the intermediate (η^2-propene)Ti(O-*i*-Pr)$_2$ and an unsaturated carbon-carbon bond in the substrate, with a subsequent β-elimination reaction.



(3)

The third is the intramolecular nucleophilic acyl substitution reaction (INAS reaction) of unsaturated esters promoted by the Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX reagent. Representative examples are shown in Equations 4 and 5. The intermolecular nucleophilic acyl substitution reaction is a fundamental carbon-carbon bond forming reaction. In spite of its high synthetic potential, however, its intramolecular version, that is the INAS reaction, is rather rare because of the intrinsic difficulty entailed in carrying it out. One difficulty associated with the INAS reaction is that a reactive nucleophilic species must be generated in the presence of a carbonyl functionality, and at the same time this nucleophile is expected to react only with the carbonyl group in an intramolecular fashion, but not intermolecularly with the one present in the reaction product. Organometallic reagents such as zinc, copper, aluminum, and boron species lack the nucleophilicity to undergo the INAS reaction, while organolithium and -magnesium reagents are generally too reactive. The unprecedented type of INAS reaction mediated by the Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX reagent has wide generality and, in addition, the products obtained in these reactions are reactive organotitanium compounds as shown in Equations 4 and 5 which make further manipulations possible. It should be noted that, for the INAS reaction of olefinic esters, the resulting INAS products further undergo an intramolecular carbonyl addition reaction on warming up the reaction temperature, to afford bicyclic cyclopropanols as final product as shown in path b of Equation 5. This reaction is an intramolecular version of the aforementioned Kulinkovich reaction shown in Equation 1, and this type of INAS reaction was also reported, independently, by Cha.[50]



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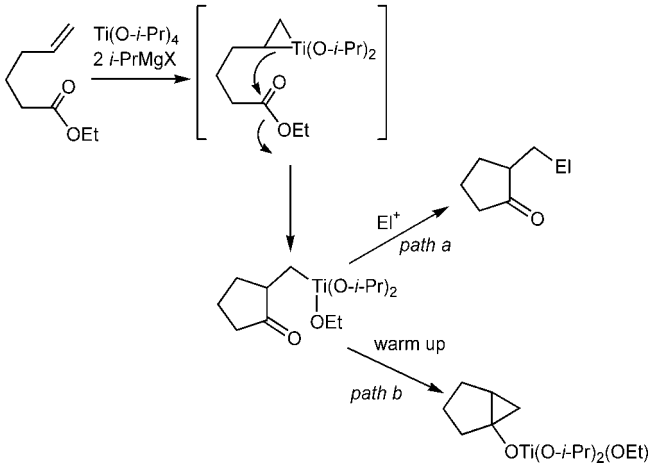
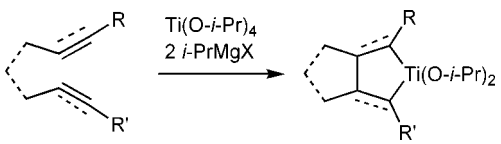


(5)

The fourth reaction is the inter- and intramolecular coupling of dienes, enynes, and diynes to afford titanacyclic compounds as shown in Equation 6, and their further manipulation. Inter- or intramolecular coupling reactions of olefins and acetylenes with a catalytic or stoichiometric amount of a metallic reagent represent a potential method for the construction of a carbon framework and have attracted much interest. When the reaction is performed with a stoichiometric amount of a metallic species, the primary product should be a metallacycle that could be used for further manipulations. The characteristic features of the titanium-mediated reaction are its excellent functional group compatibility and its easy manipulation by taking advantage of the high reactivity of the titanium-carbon bond.



(6)

These four types of reaction mediated by Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX involve, in common, the generation of alkene- or alkyne-titanium complexes through the coordination of the unsaturated carbon-carbon bond present in the substrates to the titanium, and their use as a carbanion source directly or after an accompanying conversion to new organotitanium complexes. The coordination of the carbon-carbon unsaturated bond to the titanium complex is based on a characteristic feature of titanium as a late transition metal, and the potential to utilize the resulting organotitaniums as a carbanion source is a characteristic behavior of titanium as a representative metal.[27] Thus, the Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX reagent utilizes fully the characteristic reactivities of titanium as an early transition metal element.

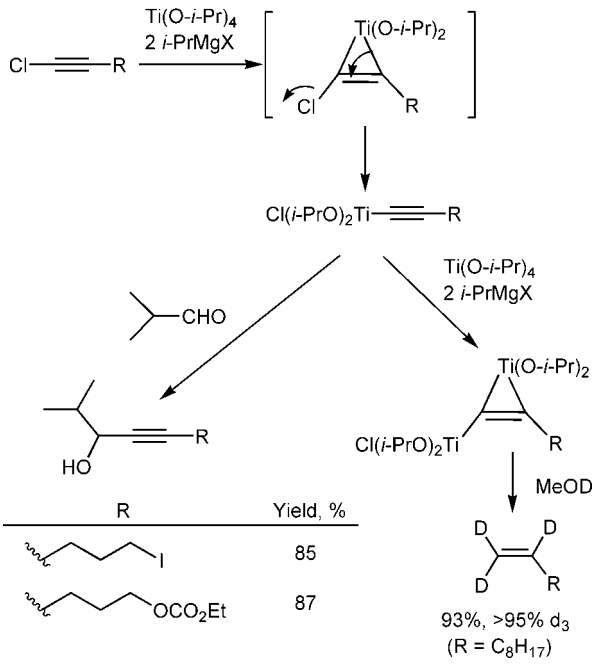
Before we describe these four types of reaction in more detail, we will mention a few aspects related to the experimental procedures. Regarding the isopro-

pyl Grignard reagents, both *i*-PrMgCl and *i*-PrMgBr can be used equally well. Other alkyl Grignard reagents including *n*-PrMgX rather than *i*-PrMgX might be used for some kinds of reactions; however, it should be noted that use of *i*-PrMgX is sometimes essential for the success of the reaction as was found for the generation of the titanium-acetylene complex,[8] and even in those cases where other Grignard reagents can be used, *i*-PrMgX frequently affords better yields. For the starting titanium compound, ClTi(O-*i*-Pr)$_3$ may be used instead of Ti(O-*i*-Pr)$_4$, and, at times, it affords better yield. The reaction is usually carried out by adding *i*-PrMgX to a mixture of Ti(O-*i*-Pr)$_4$ and the substrate; however, occasionally the reaction of the substrate with (η^2-propene) Ti(O-*i*-Pr)$_2$ prepared in advance from Ti(O-*i*-Pr)$_4$ and *i*-PrMgX affords better yield. Although most of the reactions are carried out in Et_2O, Bu_2O and *t*-BuOMe can equally be used as a solvent. THF can also be used for several kinds of reactions but sometimes gives capricious results. Since the reagents and the resulting organotitanium products are sensitive to moisture and air, all manipulations should be carried out in dry flasks under an atmosphere of an inert gas (argon or nitrogen), as is generally the case for Grignard or organolithium reagents. The work-up after the reaction can be carried out readily by either of the following two protocols. One is the addition of aqueous HCl to the reaction mixture and subsequent extractive work-up, while the other is the sequential addition of a limited amount of water [usually 8–16 equivalents to the amount of the starting Ti(O-*i*-Pr)$_4$], NaF, and Celite and subsequent filtration of the resulting mixture through a pad of Celite. In those cases where the products are sensitive to acid, such as amino and vinyl ether compounds, the latter protocol is better or essential. During the washing of the organic layers with water and evaporation of the organic solvents, the 2-propanol which comes from Ti(O-*i*-Pr)$_4$ can be easily removed, and the resulting crude residue does not involve the inorganic materials and 2-propanol. The isolation of the product(s), therefore, can be readily carried out by column chromatography or distillation.

3 Generation of an (η^2-Alkyne)-Ti(O-*i*-Pr)$_2$ and its Utilization as a Vicinal Vinylic Dianion

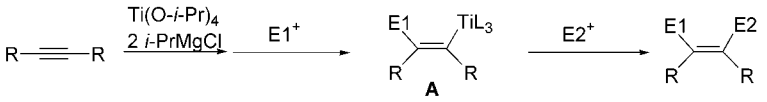
Treatment of an internal alkyne with the Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX reagent generates (η^2-alkyne)Ti(O-*i*-Pr)$_2$ via the exchange of the propene in the intermediate (η^2-propene)Ti(O-*i*-Pr)$_2$ with the alkyne added. The alkyne-titanium complex thus generated *in situ* reacts with a variety of electrophiles, including two different electrophiles in consecutive order as shown in the equation of Table 1. The reaction thus opens up a one-pot access to a variety of di-, tri-, or tetrasubstituted alkenes as summarized in Table 1. Reaction of a (η^2-unsymmetrical acetylene)-titanium complex with two different electrophiles may form two regioisomers. However, in the case of certain acetylenes, a high degree of regiocontrol has been attained, although the degree of the selectivity somewhat depends on the electrophiles applied. As can be seen from Table 1, phenylalkylacetylene (entry 5), silyl- or stannylacetylene (entries 6, 7, and 9–14), and propargyl alcohol derivatives (entry 8) belong to this class. The electrophiles applied to the reaction affect the regiochemistry; thus, while a (η^2-silylalkylacetylene)Ti(O-*i*-Pr)$_2$ complex reacts with aldehydes, ketones, and imines at the β-position to the silyl group (entries 6 and 9–11), the reaction with *s*-BuOH takes place exclusively at the α-silylcarbon-titanium bond to give the (β-silylalkenyl)titanium product (entries 13 and 14).

The following reactions which are not considered in our previous two reviews[6,7] mentioned above have been reported recently. Marek and his coworkers reported that the reaction of haloalkynes with one equivalent of Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX affords alkynyltitanium compounds by a β-elimination reaction from the (η^2-haloalkyne)Ti(O-*i*-Pr)$_2$ intermediate as shown in Equation 7, thus providing an easy access to functionalized alkynyltitanium species.[22] They also reported that when this reaction was carried out in the presence of one more equivalent of Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX, tris-titanated olefins of the type shown in Equation 7 were generated in excellent yield.[23]



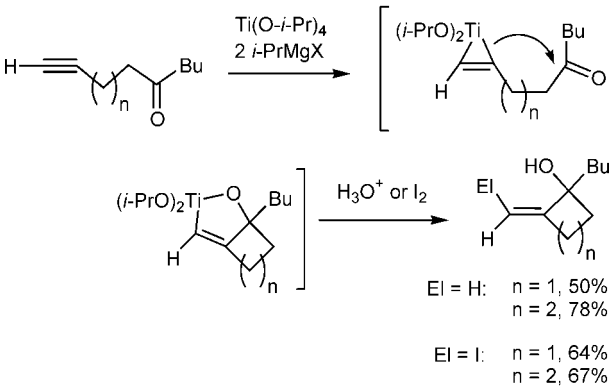
(7)

Table 1.



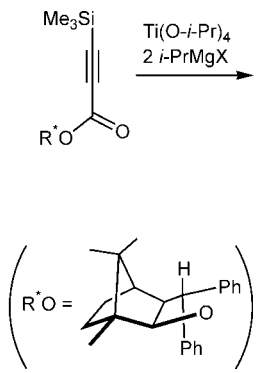
Entry	Alkyne	Electrophlie for $E1^+$	Ti-Intermediate (**A**)	Electrophlie for $E2^+$	Major Product	Regio-selectivity	Yield, %	Ref.
1	C_6H_{13}—≡—$SiMe_3$	H_2O (or D_2O)		H_2O (or D_2O)	(D) H, H (D); C_6H_{13}, $SiMe_3$ (96% d_2)	-	94	8,9
2	OTHP	D_2O		D_2O	D, D, OTHP, D, D	-	42	10
3	OH, N, S, $SiMe_3$	H_2O		H_2O	OH, N, S, $SiMe_3$	-	90	11
4	*t*-Bu—≡—Me	$PhPCl_2$		$PhPCl_2$	PPh, *t*-Bu, Me	-	72	12
5	Ph—≡—Me	*c*-$C_6H_{11}CHO$	*c*-C_6H_{11}, O, TiL_2, Ph, Me	H_2O	*c*-C_6H_{11}, OH, H, Ph, Me	86 : 14	90	9
6	C_6H_{13}—≡—$SiMe_3$	CHO	O, TiL_2, C_6H_{13}, $SiMe_3$	H_2O	OH, H, C_6H_{13}, $SiMe_3$	96 : 4	72	9
7	EtO, OEt, $SnBu_3$	CHO	O, TiL_2, EtO, EtO, $SnBu_3$	H_2O	OH, H, EtO, EtO, $SnBu_3$; d.r. 85 : 15	exclusively	60	13
8	THPO, $SiMe_3$	*n*-$C_5H_{11}CHO$	*n*-C_5H_{11}, O, TiL_2, THPO, $SiMe_3$	H_2O	*n*-C_5H_{11}, OH, H, THPO, $SiMe_3$	95 : 5	78	14,15
9	C_6H_{13}—≡—$SiMe_3$	N, Bn, Pr	Bn, N, Pr, TiL_2, C_6H_{13}, $SiMe_3$	I_2	Pr, NHBn, *I*, C_6H_{13}, $SiMe_3$	exclusively	76	16,21
10	〃	N, Bn, Et	Bn, N, Et, TiL_2, C_6H_{13}, $SiMe_3$	CO	Bn, N, Et, C_6H_{13}, $SiMe_3$	exclusively	74	17,21
11	〃	〃	〃	CO_2	Bn, N, Et, O, C_6H_{13}, $SiMe_3$	exclusively	67	18,21
12	N, Ph, $SiMe_3$			H_2O	H, H, N, Ph, H, Me_3Si; d.r. 91 : 9		94	19
13	C_6H_{13}—≡—$SiMe_3$	*s*-BuOH	L_3Ti, H, C_6H_{13}, $SiMe_3$	PhCHO	HO, H, Ph, Me_3Si, C_6H_{13}	98 : 2	84	20
14	〃	〃	〃	CO_2Et, CO_2Et	EtO_2C, EtO_2C, Me, H, C_6H_{13}, $SiMe_3$	98 : 2	84	20

Intramolecular addition reactions of the internal alkyne-titanium complex to imines (but not to aldehydes or ketones) are feasible as shown in entry 12 of Table 1. Although terminal acetylenes do not afford stable titanium-acetylene complexes upon reaction with Ti(O-*i*-Pr)$_4$/2 *i* -PrMgX, Marek reported that the reaction of Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX with terminal alkynes having a keto group at the γ- or δ-position induces an intramolecular cyclization via the titanium-acetylene intermediate to afford the 4- and 5-membered cycloalkanols as shown in Equation 8.[24]



(8)

The alkyne-titanium complexes derived from acetylenic esters and Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX react with aldehydes in excellent regioselectivity to afford, after hydrolysis, Baylis-Hillman-type allyl alcohols.[25] It is possible to carry out the reaction in an asymmetric way. As shown in Equation 9, the titanium-acetylene complex derived from silylpropynoate having a camphor-derived auxiliary reacts with aldehydes in excellent diastereoselectivity. Thus, the reaction affords a convenient entry to optically active Baylis-Hillman-type alcohols containing a substituent(s) β to the acrylate group, which are rather difficult to prepare by the Baylis-Hillman reaction.

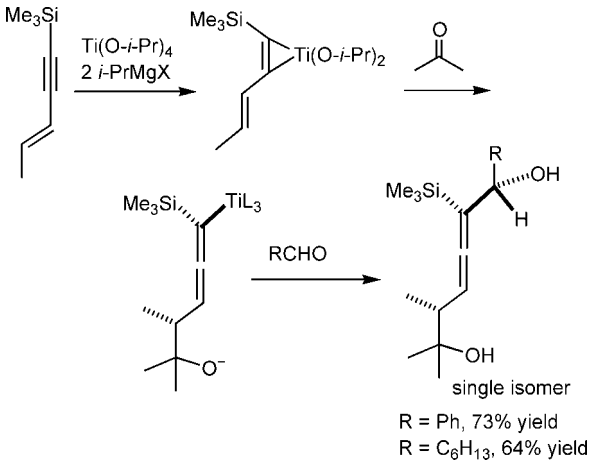


R	El	d.s.	Yield, %	
Et	H	97 : 3	95	
	D	97 : 3		(94% d)
	I	97 : 3	93	
c-C$_6$H$_{11}$	H	98 : 2	77	
Ph	H	99 : 1	97	

In all cases the regioselectivity was >97 : <3.

(9)

The acetylene-titanium complex generated from an enyne and Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX reacts with an aldehyde, ketone, or imine at the remote olefinic carbon in a regiospecific way to give the allenylic titanium compound. The resulting allenyltitanium reacts with a second electrophile, such as H_2O or an aldehyde, again with excellent regioselectivity. Both reactions with electrophiles are stereoselective as shown in Equations 10



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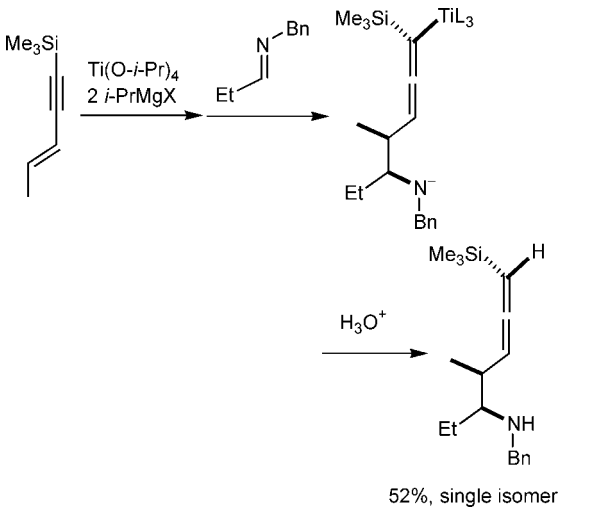
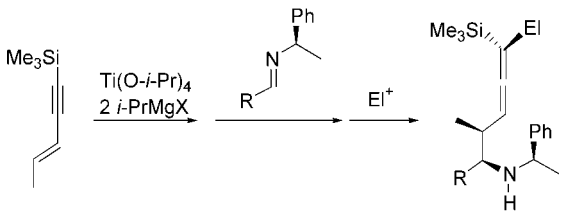


(11)

Table 2.



R	Electrophile	El	Yield, %	d.s. major : other
Et	H_2O	H	67	95 : 5
Et	Me_2C=O	Me_2C(OH)-	45	93 : 7
Me	H_2O	H	53	93 : 7
i-Bu	H_2O	H	53	97 : 3

and 11; thus, an expedient method for the construction of multiple stereogenic centers from readily available enynes has been opened up.[26] Table 2 summarizes the results for asymmetric construction of three stereogenic centers using optically active imines derived from phenylethylamine as the first electrophile.

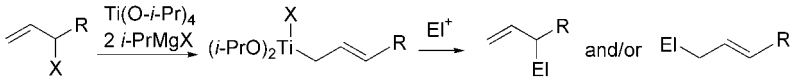
4 Preparation of Allyl- and Allenyltitanium Reagents and their Synthetic Utility

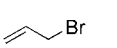
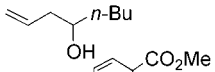
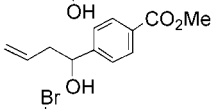
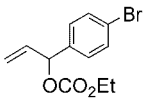
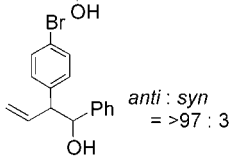
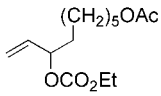
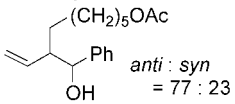
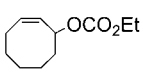
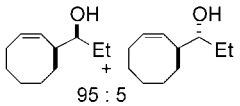
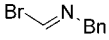
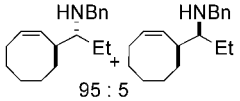
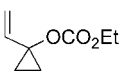
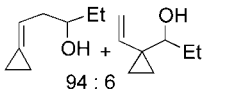
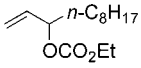
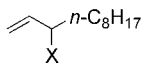
4.1 Allylic Titanium Reagents

Allyltitaniums of the type (η^1-allyl)Ti(O-*i*-Pr)$_3$, prepared from the corresponding allyllithium or magnesium compounds and ClTi(O-*i*-Pr)$_3$ via transmetallation reaction, have attracted considerable interest as useful allylating reagents.[27] The allyltitaniums thus produced have the potential to find utility for mass synthesis taking into account the ready and inexpensive availability of ClTi(O-*i*-Pr)$_3$ as well as their advantageous reactivity in comparison with other allylmetal complexes in terms of chemo-, regio-, and diastereoselectivity. The preparation of a variety of allyllithium or -magnesium complexes, however, is not necessarily an easy task, and this seems to limit the utility of the reagent. The direct preparation of allyltitaniums from the Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX reagent and readily available allylic compounds such as halides, acetates, carbonates, sulfonates, and phosphates as mentioned in the Section 2 (Equation 3) appears to surmount the foregoing limitation.

Table 3 summarizes the synthetic transformations starting from allylic compounds via allyltitaniums through their reaction with Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX. The following synthetically attractive features can be seen from this table. The reaction allows for the preparation of allyltitaniums having a variety of functional groups, thus opening up one-pot access to functionalized compounds (entries 3 and 4). Seven-, eight-, and nine-membered carbocyclic allyltitaniums can be readily generated from the corresponding cyclic allylic halides or carbonates and, in turn, react with aldehydes and imines stereoselectively, as exemplified by the eight-membered case shown in

Table 3.



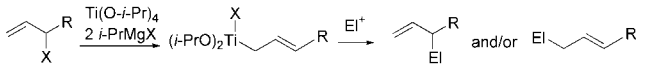
Entry	Allylic Compound	Electrophile	Product	Yield	Ref.
1		*n*-BuCHO		82%	28
2		*p*-MeO$_2$CC$_6$H$_4$CHO		77%	28
3		PhCHO	 *anti* : *syn* = >97 : 3	83%	28
4		PhCHO	 *anti* : *syn* = 77 : 23	76%	28
5		EtCHO	 95 : 5	83%	29
6			 95 : 5	72%	29
7		EtCHO	 94 : 6	76%	30
8		D_2O	 X = D (>95% d)	84%	31
9		NCS	X = Cl	77%	31

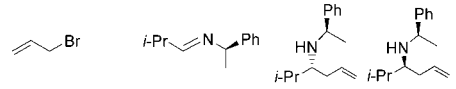
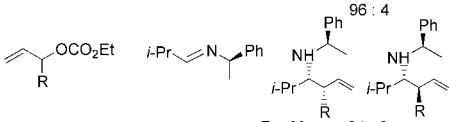
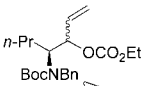
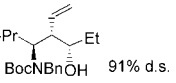
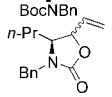
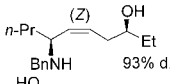
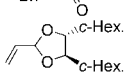
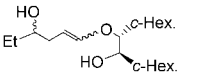
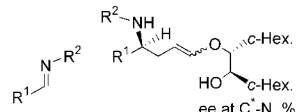
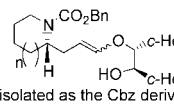
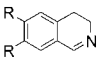
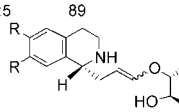
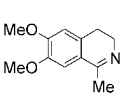
entries 5 and 6, thus affording an easy method for preparing medium-ring carbocycles having a stereodefined side-chain at the allylic position. Alkylidenecyclopropane derivatives can be readily prepared by the reaction of Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX with vinylcyclopropyl carbonates and subsequent trapping of the resulting allyltitaniums with aldehydes or ketones (entry 7). It should be noted that, in this case, the reaction occurs at the less substituted carbon but not at the more substituted carbon of the allyltitaniums, although the latter is the position usually observed for the addition reaction of substituted allyltitaniums. As shown in entries 8 and 9, the reaction of the allyltitaniums with D_2O and NCS proceeds with excellent regioselectivity and, thus, a new one-pot method for converting allyl alcohol derivatives to 1-alkenes having D and Cl at the allylic position is opened up.

The reaction also provides an efficient method for synthesizing optically active compounds as summarized in Table 4. The reaction of allyltitaniums with chiral imines prepared from aldehydes and optically active 1-phenylethylamine proceeds with excellent diastereoselectivity as shown in entries 1–3, thus furnishing a new method for synthesizing optically active homoallylic amines with and without a β-substituent. As shown in entries 4 and 5, chiral allyltitaniums having an amino substituent at the stereogenic center can be prepared from optically active 4-aminoalk-1-en-3-ol derivatives, and which, in turn, react with aldehydes at either the γ- or α-position of the allylic moiety by selecting ethyl carbonate or a cyclic carbamate, respectively, as the leaving group. The diastereoselectivity of both reactions is good; thus, the reaction provides a new entry to β-vinyl-γ-aminoalkanols and ε-aminoalkanols.

The allyltitanium compound derived from optically active acrolein 1,2-dicycloxylethylene acetal reacts with carbonyl compounds or imines in a regioselective way as shown in Equation 12. These results indicate that the allyltitanium complex serves as a propionaldehyde homoenolate equivalent. Although the degree of chirality transfer observed for the reaction with carbonyl compounds was low (entry 6 in Table 4), the reaction with imines proceeded with a high degree of chiral induction (see Equation 12). Thus, a chiral homoenolate equivalent which reacts with imines has been developed for the first time, and recent further study has revealed its wide generality.[36b] As summarized in entries 7–19 of Table 4, a variety of imines reacts with excellent stereoselectivity; these include methylimines (entry 7), primary and secondary alkylimines (entries 8 and 9), arylimines (entries 11–13), five-membered cyclic imines (entry 15), and six-membered cyclic imines including 3,4-dihydroisoquinolines (entries 16–19). However, tertiary alkylimines (entry 10) and acyclic ketimines (entry 14) did not afford the addition

Table 4.

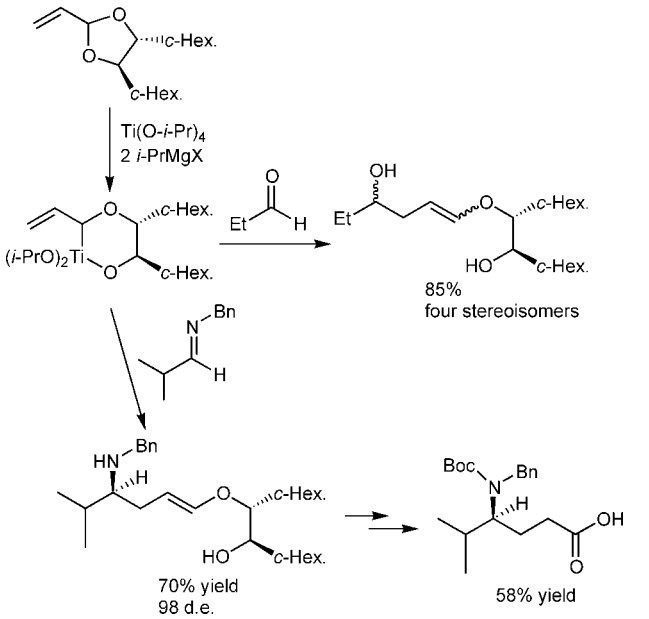


Entry	Allylic Compound	Electrophile	Product	Yield	Ref.
1			96 : 4	87%	32
2			R = Me 94 : 6	92%	32,33
3			R = Ph 92 : 8	83%	32
4		EtCHO	 91% d.s.	89%	34
5		EtCHO	 93% d.s.	79%	35
6		EtCHO	 four stereoisomers	85%	36
7		Me Bn	92 : 8 / 83		84%	36
8		*n*-Pr Bn	94 : 6 / 85		81%	
9		*i*-Pr Bn	94 : 6 / 88	98	85%	
10		*t*-Bu Bn			trace	
11		Ph Bn	93 : 7 / 86	96	82%	
12		Ph *n*-Pr	95 : 5 / 88		85%	
13		Ph Ph	95 : 5 / >85		71%	
14					trace	
15		n = 0	>95:5 / 78		63%	36b
16	 (isolated as the Cbz derivatives)	n = 1	>95:5 / 89		66%	36b
17		R = H	95:5 / 80	98	81%	36b
18		R = OMe	95:5 / 81		81%	36b
19			>95:5 / 94		75 %	36b

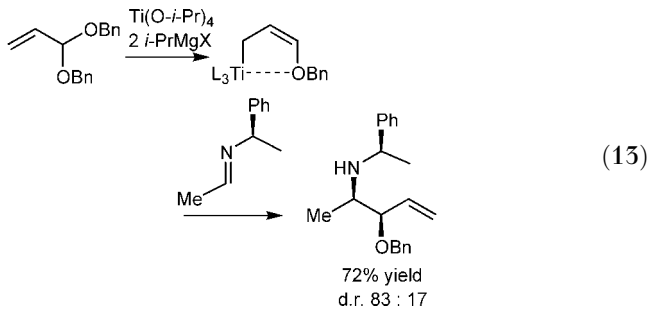
products, presumably due to their larger steric requirements. Meanwhile, cyclic ketimines such as shown in entry 19 have reacted smoothly with excellent stereoselectivity, probably owing to the strained dehydropiperidine structure.

Although the allyltitanium derived from an acrolein cyclic acetal reacts with aldehydes, ketones, and imines at the α-position, the one derived from an acrolein acyclic acetal reacts with them at the γ-position exclusively.[37,38] It is noteworthy that the reaction with chiral imines derived from optically active 1-phenylethylamine proceeds with a synthetically use-

ful diastereoselectivity. Thus, the reaction provides a new method for preparing optically active 1-vinyl-2-amino alcohol derivatives with *syn*-stereochemistry as shown in Equation 13.[37]



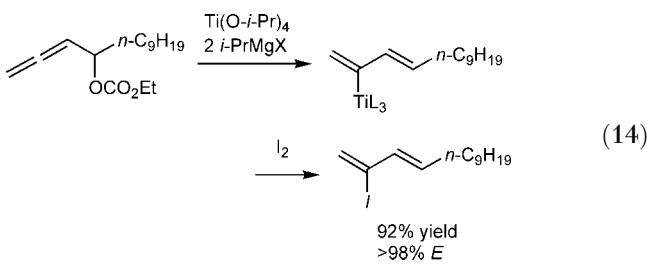
(12)



(13)

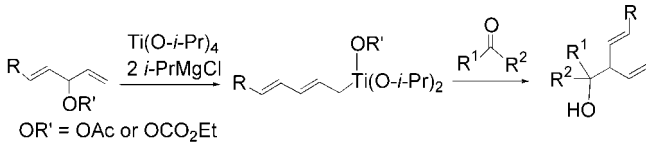
A variety of penta-1,4-dien-3-ylcarbinols including those having a functional group can be readily prepared from easily available penta-1,4-dien-3-yl carbonates and carbonyl compounds via the corresponding allylic titaniums.[39] Several representative results are shown in Table 5.

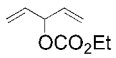
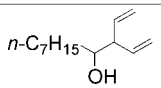
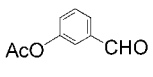
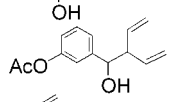
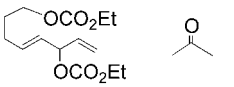
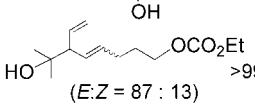
The reaction of alka-2,3-dien-1-yl carbonates with Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX resulted in a similar oxidative addition to afford 1,3-dien-2-yltitanium complexes as shown in Equation 14, thus providing a one-pot access to 2-iodo-1,3-dienes by a subsequent reaction with I_2, compounds that are otherwise tedious to prepare.[40]



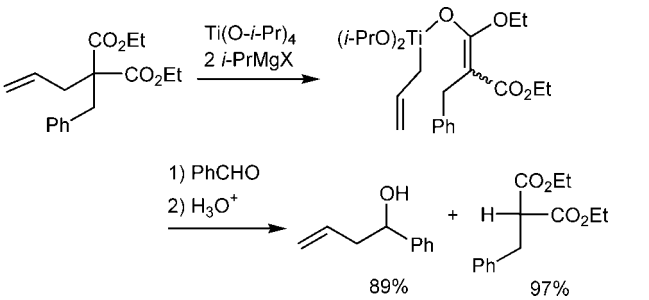
(14)

Table 5.



Allylic Compound	Carbonyl Compound	Product(s)	Regio-selectivity	Yield %
	*n*-C_7H_{15}CHO		93 : 7	89
			99 : 1	84
			>99 : 1	83
		(*E*:*Z* = 87 : 13)		

The reaction of Equation 15 showing the generation of CH_2=$CHCH_2$Ti(OR)$_3$ from the Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX reagent and (CH_2=$CHCH_2$)RC(CO_2Et)$_2$ indicates that the RC(CO_2Et)$_2$ anion can act as a good leaving group like halide, acetate, or carbonate.[41] By taking advantage of this reaction, we demonstrated that the allyl moiety can be used as a protecting group for the acidic hydrogen of malonic esters.



(15)

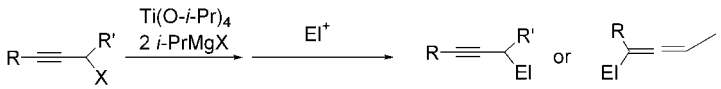
4.2 Allenylic Titanium Reagents

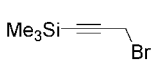
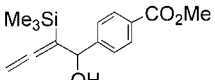
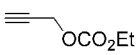
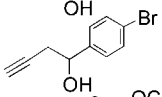
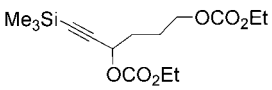
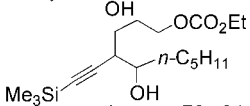
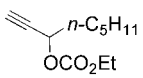
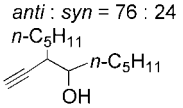
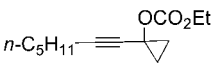
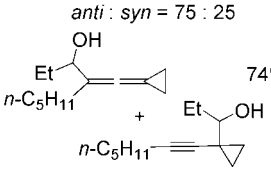
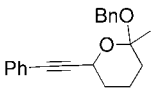
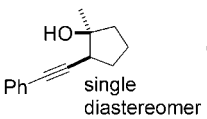
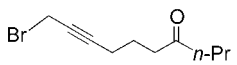
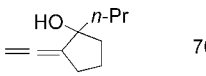
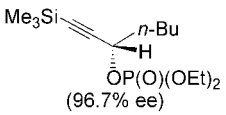
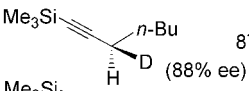
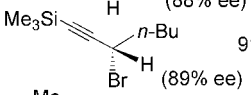
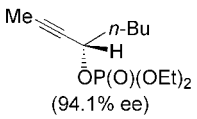
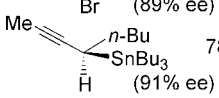
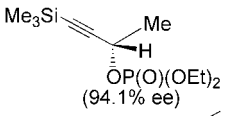
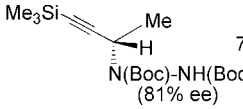
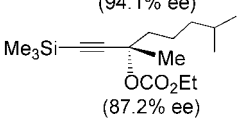
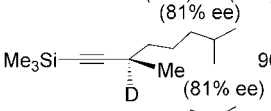
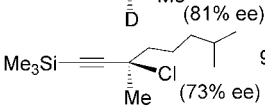
As a divalent titanium reagent Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX reacts with propargyl alcohol derivatives, such as acetates, carbonates, phosphates, sulfonates, and halides, to provide allenyltitanium complexes as described in Section 2 (Equation 3), thus opening an easy access to a variety of allenyltitaniums including those which are difficult to access by transmetallation reactions via the propargyllithium complexes, the only method available up to this time.[42] The allenyltitaniums synthesized for the first time by this method include optically active ones having axial chirality.[43] Thus, the reaction with optically active secondary propargyl phosphates proceeds with more than 97% chirality transfer via an *anti*-β-elimination pathway from the titanium-alkyne intermediate to afford opti-

cally active disubstituted allenyltitaniums (Equation 16). The reaction with tertiary propargyl carbonates also proceeds with more than 97% chirality transfer as shown in Equation 17; however, in this case, the β-elimination from the titanium-alkyne complex occurs in a *syn* fashion to provide optically active trisubstituted allenyltitaniums. The allenyltitaniums thus prepared are stable to racemization, at least up to room temperature.

The efficient entry to allenyltitaniums opens up a highly practical method for preparing a variety of homopropargyl or allenyl derivatives including opti-

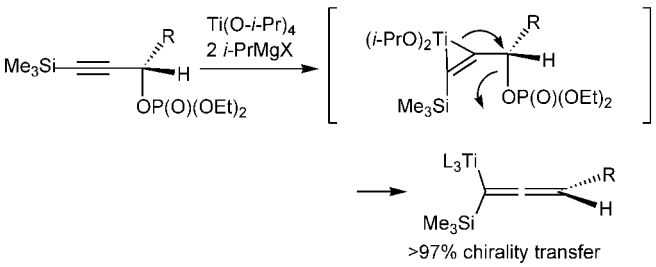
Table 6.



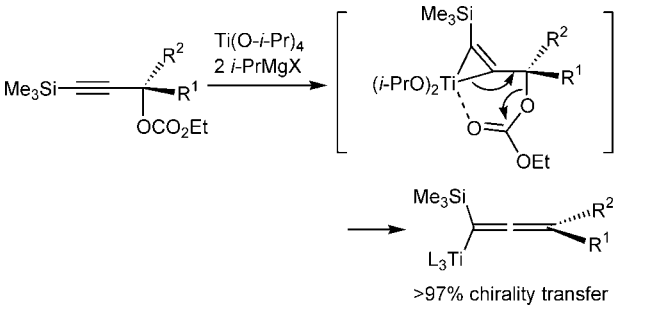
Entry	Propargyl Compound	Electrophile	Product(s)	Yield	Ref.
1		*p*-MeO$_2$CC$_6$H$_4$CHO		79%	44
2		*p*-BrC$_6$H$_4$CHO		91%	44
3		*n*-C$_5$H$_{11}$CHO	 *anti* : *syn* = 76 : 24	88%	44
4		*n*-C$_5$H$_{11}$CHO	 *anti* : *syn* = 75 : 25	89%	44
5		EtCHO	 >97 : 3	74%	30
6		— (intramolecular reaction)	 single diastereomer	62%	45
7[a]		— (intramolecular reaction)		70%	45
8	 (96.7% ee)	D_2O	 (88% ee)	87%	46
9		Br_2	 (89% ee)	91%	46
10	 (94.1% ee)	Bu_3SnCl	 (91% ee)	78%	47
11	 (94.1% ee)	BocN=NBoc	 (81% ee)	77%	48
12	 (87.2% ee)	D_2O	 (81% ee)	90%	46
13		NCS	 (73% ee)	94%	46

[a] ClTi(O-*i*-Pr)$_3$ was used instead of Ti(O-*i*-Pr)$_4$.

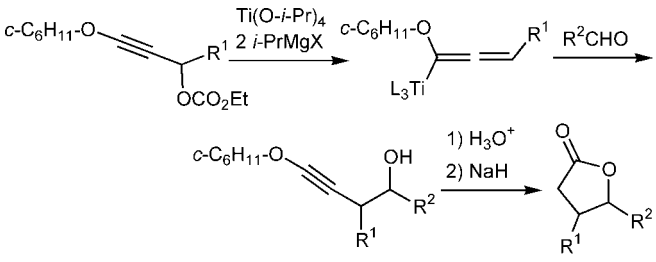
cally active ones because a variety of propargyl alcohols, including optically active ones, are readily available, and the reactions of allenyltitaniums with several electrophiles, such as aldehydes, ketones, R_3SnCl, dialkylazodicarboxylates, Br_2, or D_2O proceed with good to excellent selectivity. Representative results are shown in Table 6 which include the synthesis of racemic allenylic or propargylic alcohols (entries 1–5), and optically active compounds, such as propargylstannanes (entry 10), α-hydrazinoalkynes (entry 11), secondary and tertiary propargyl halides (entries 9 and 13), and acetylenes with D at the propargylic position (entries 8 and 12). Table 6 also illustrates the intramolecular reactions of cyclic propargyl acetals (entry 6) and propargyl halides having a keto group (entry 7) which afford the corresponding cycloalkanols.



(16)



(17)



R^1	R^2	Yield of the lactone, %
H	Ph	72
	n-$C_7H_{15}CHO$	70
	p-NCC_6H_4CHO	52
Me	PhCHO	67
		(d.r. = 5 : 3)

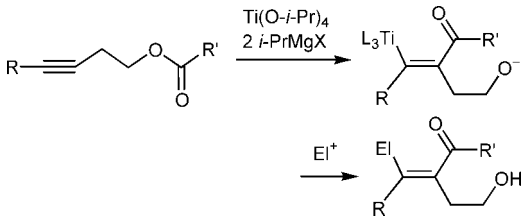
(18)

As shown in Equation 18, 3-alkoxy-2-propyn-1-yl carbonates were shown recently to react with Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX to afford titanated alkoxyallenes which, in turn, react with aldehydes regiospecifically to provide the corresponding γ-addition products, thus affording a convenient method for synthesizing γ-butyrolactones.[49]

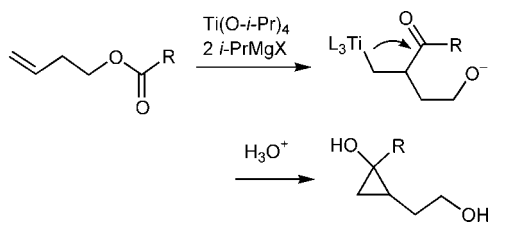
5 Intramolecular Nucleophilic Acyl Substitution (INAS) Reactions Mediated by Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX

5.1 Scope of the Reaction

It is well recognized that an organotitanium complex does not react with esters due to its low nucleophilicity. The INAS reaction of unsaturated esters mediated by the Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX reagent, however, proceeds smoothly as mentioned in Section 2 (Equations 4 and 5). The η^2-olefin- or -acetylene-titanium intermediate shown in Equation 4 or 5 has, respectively, a highly strained titanacyclopropane[3] or -propene structure, and the relief of the strain by the INAS reaction might work as a driving force. In addition to the substrates shown in Equations 4 and 5, unsaturated carbonates and esters of ω-unsaturated alcohols also undergo the INAS reaction as shown in Equations 19, 20,[50] and 21. As the primary products generated in these INAS reactions are organotitanium complexes, the subsequent reactions with electrophiles occur readily via an intramolecular way with the one present in the products, or intermolecularly with the one added. Several representative results of these INAS reactions are summarized in Table 7. As can be seen from this table, the reaction provides an efficient and practical method for synthesizing cyclopropanols, bicyclo[n.1.0]alkanols (n = 3, 4, 5), cyclic and acyclic α,β-unsaturated ketones and lactones, starting from readily available starting material(s).

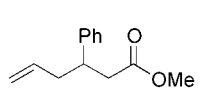
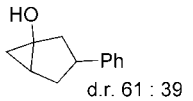
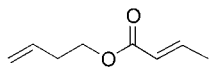
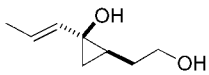
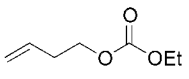
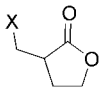
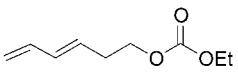
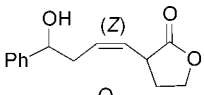
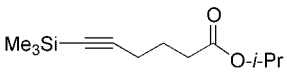
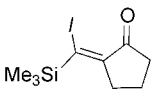
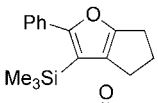
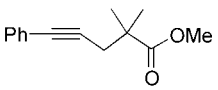
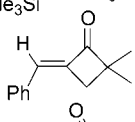
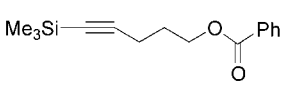
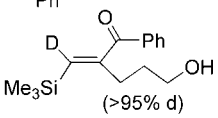
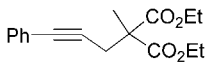
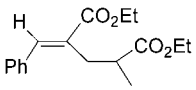
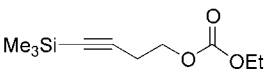
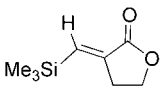
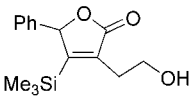


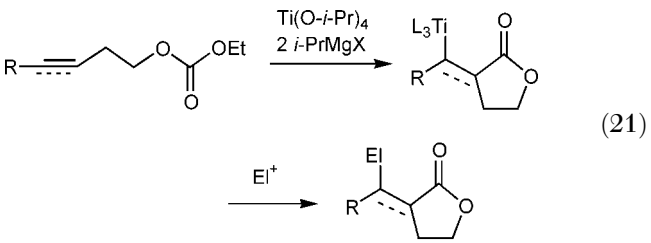
(19)



(20)

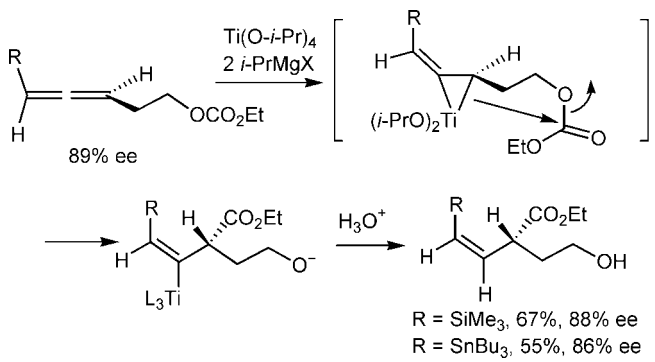
Table 7.

Entry	Substrate	Electrophlie	Product	Yield	Ref.
1		—	 d.r. 61 : 39	88%	51
2		—	 d.r. 93 : 7	78%	52,53
					
3		H_2O	X = H	92%	54b
4		I_2	X = I	90%	54b
5		PhCHO		89%	55
6		I_2		67%	54b
7		PhCHO		69%	54b
8		H_2O		77%	56
9		D_2O	 (>95% d)	77%	54b
10		H_2O		46%	57
11		H_2O		68%	54
12		PhCHO		65%	54



(21)

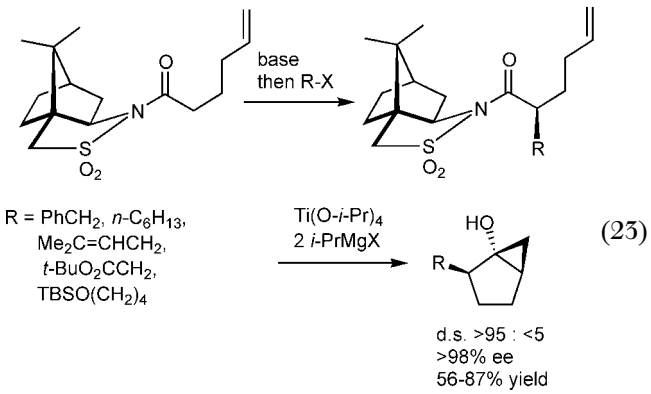
The INAS reaction of carbonates of 3,4- and 3,5-dienyl alcohols also proceeds smoothly to provide the corresponding β,γ-unsaturated esters.[58] The reaction of 4-silyl- or 4-stannyl-3,4-dienyl carbonates having axial chirality proceeds with excellent chirality transfer as exemplified in Equation 22, thus affording a new access to optically active α-substituted β,γ-unsaturated esters.



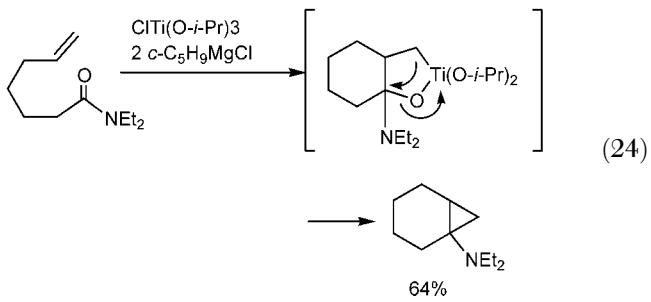
(22)

Olefinic acylsulfonamides act like olefinic esters; thus, their reaction with Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX affords the corresponding bicyclic cyclopropanols. As

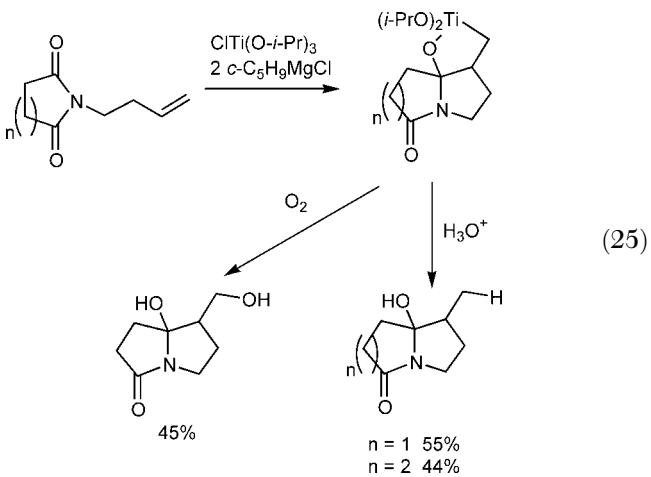
shown in Equation 23, the combination of the diastereoselective alkylation of a chiral acylsulfonamide and the following INAS reaction provides an efficient access to optically active bicyclic cyclopropanols. Thus, alkylation of Oppolzer's camphorsultam, which proceeds with excellent diastereoselectivity for a variety of alkyl halides, and the reaction of the resulting optically active unsaturated acylsulfonamides with Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX provide bicyclic cyclopropanols with the structure shown in the equation, exclusively.[59] The INAS reactions mediated by ClTi(O-*i*-Pr)$_3$/*c*-C$_5$H$_9$MgCl of ω-vinyl amides affording bicyclic cyclopropylamines shown in Equation 24, and of cyclic imides derived from ω-vinylamines furnishing acylaminal derivatives shown in Equation 25 were, respectively, reported by Cha.[60,61]



(23)



(24)



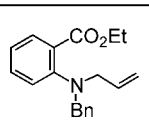
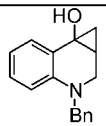
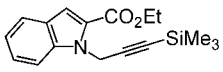
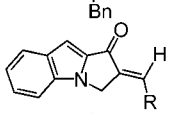
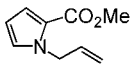
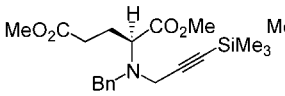
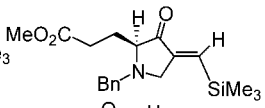
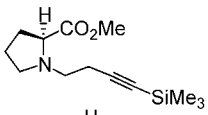
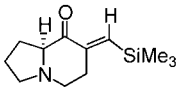
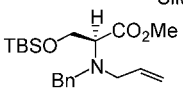
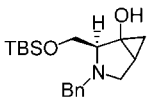
(25)

5.2 Synthetic Applications of the INAS Reaction

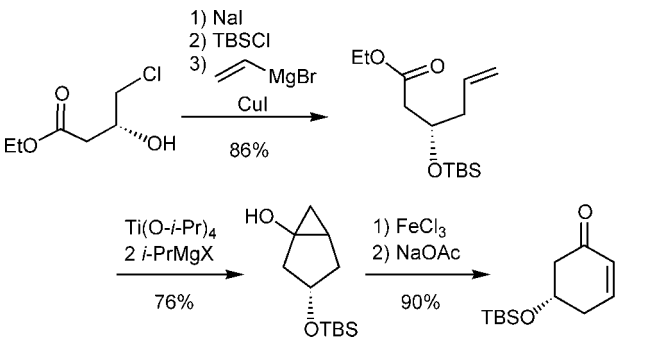
The newly developed INAS reaction makes it possible to connect the carbon-carbon bond intramolecularly at an almost unprecedented position and, moreover, the reaction products have a functional group enabling further manipulations, such as a ketone, enone, lactone, cyclopropanol or cyclopropylamine group. The reaction, therefore, allows for new synthetic designs in organic synthesis. The syntheses of *N*-heterocycles including optically active compounds starting from readily available starting materials exemplified in Table 8 strongly indicate the utility of the reaction.[62] Thus, the treatment of readily available *N*-allyl- or -propargyl-anthranilates, -indole-2-carboxylates, -pyrrole-2-carboxylates, and -α-amino esters with Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX reagent gave the corresponding pyrrolidines and piperidines. The synthetic utility of the reaction was further demonstrated by an efficient synthesis of azasugars[63] and allopumiliotoxin 267A,[62] which is one component of the toxic skin secretion of certain neotropical frogs and displays significant cardiotoxic activity.

Using the Ti(II)-mediated INAS reaction as a key step, optically active 5-[(*t*-butyl)dimethylsilyl]oxy-2-cyclohexenone was prepared efficiently from readily available 4-chloro-3-hydroxybutanoate or epichlorohydrin as shown in Equation 26.[64–66] While the enone thus synthesized reacted with R$_2$Cu(CN)Li$_2$ with excellent diastereoselectivity to afford an *anti*-1,4-addition product, the reaction with RCu(CN)Li gave a *syn*-1,4-addition product almost exclusively as shown in Equation 27. Both 1,4-addition products thus prepared can be converted readily into optically active 5-alkyl-2-cyclohexenones by treatment with a base. Thus, both enantiomers of 5-alkyl-2-cyclohexenones can be prepared starting from one enantiomer of 5-silyloxy-2-cyclohexenone (Equation 27).[67] The ready availability of optically active 5-[(*t*-butyl)dimethylsilyl]oxy-2-cyclohexenone in quantity and its versatile reactivity prompted us to utilize it for synthesizing biologically important compounds, which include penienone, penihydron, palitantin, carvone,[67b,68] and the A-ring precursor of 1α,25-dihydroxyvitamin D$_3$.[69–71] Among them, the synthetic procedure for the A-ring precursor of 19-nor-1α,25-dihydroxyvitamin D$_3$ is shown in Equation 28.[71] Thus, epoxidation of the enone with aqueous H$_2$O$_2$/base and the following Wittig reaction with (EtO)$_2$(O)PCH$_2$CO$_2$Et/NaH afforded the epoxy ester shown in Equation 28, from which the A-ring precursor was prepared by reductive epoxide ring-opening with HCOOH/cat. Pd(0) and subsequent silylation of the hydroxy group. 19-Nor-vitamin D$_3$ and its analogues have attracted much interest as potential therapeutic agents. Considerable efforts, therefore, have been made to develop a practical

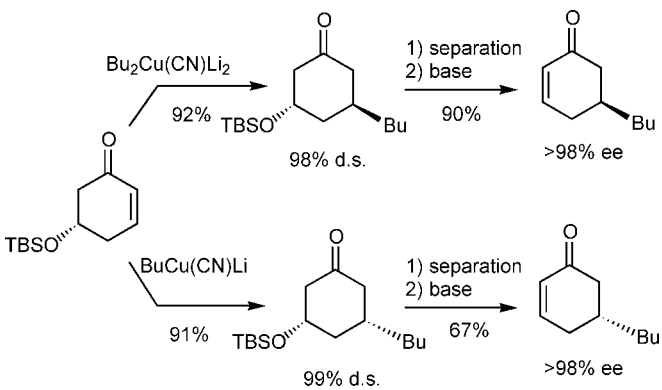
Table 8.

Entry	Starting Compound	Substrate for INAS Reaction	1) Ti(O-*i*-Pr)$_4$ 2 *i*-PrMgX 2) H_2O Product	Yield, %
1	anthranilic acid			94
2	indole-2-carboxylic acid			62
3	pyrrole-2-carboxylic acid			80
4	L-glutamic acid			78
5	L-proline			75
6	L-serine			86

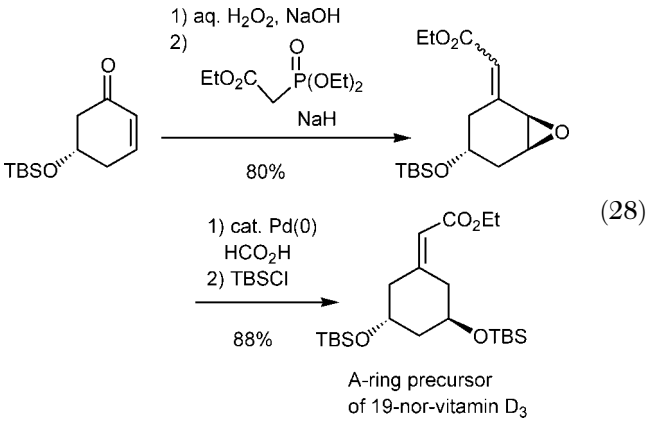
method for synthesizing the A-ring precursor shown in Equation 28 in quantity. We believe that the method we have developed is one of the most practical so far reported.



(26)



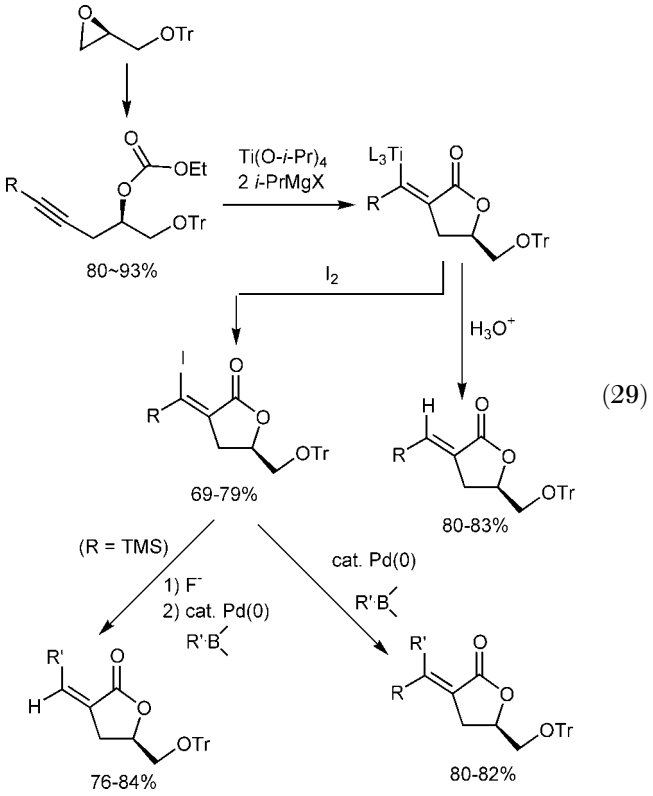
(27)



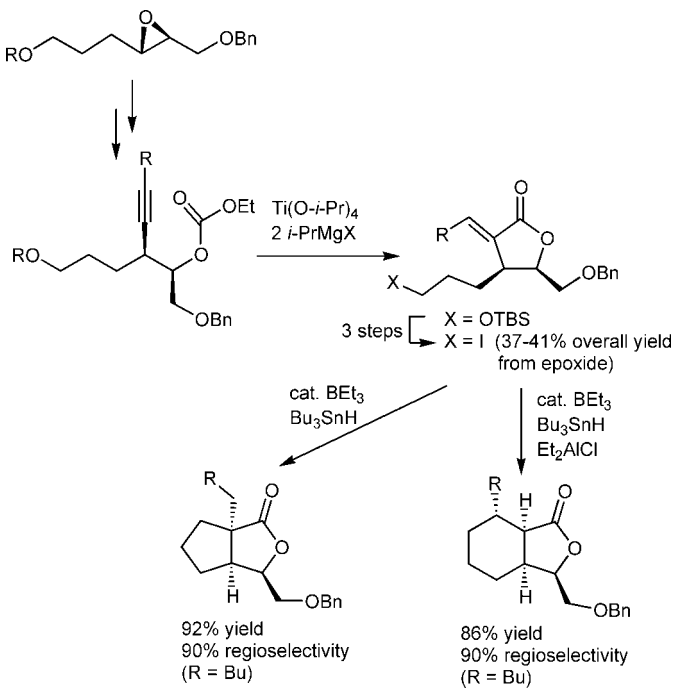
(28)

Modern organic synthesis allows easy access to a variety of optically active epoxides in quantity. The regioselective ring-opening of these epoxides with acetylenic anion, conversion of the newly generated hydroxy group in the product to carbonate and the following Ti(II)-mediated INAS reaction of the resulting carbonate can afford a conceptually practical method for preparing optically active α-alkylidene-γ-butyrolactones. This possibility was actually demonstrated by the synthesis of γ-[(trityloxy)methyl]-α-alkylidene-γ-butyrolactones having a stereodefined mono- and disubstituted alkylidene moiety starting from commercially available glycidyl trityl ether as shown in Equation 29.[72] These lactones have been utilized as versatile building blocks and intermediates for synthesizing chiral natural compounds. Similarly, we recently synthesized optically active α-alkylidenelactones having an alkyl iodide substituent as shown in

Equation 30 by starting with the corresponding optically active epoxy alcohols prepared by the Sharpless asymmetric epoxidation. From the lactones thus produced, optically active, functionalized cyclopentanes or cyclohexanes were synthesized selectively via radical cyclization in the absence or in the presence of Et_2AlCl, respectively, as shown in Equation 30.[73]



(29)

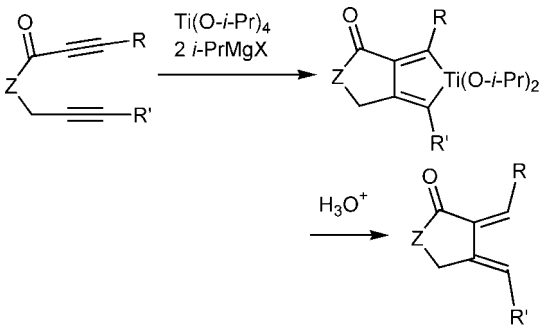


(30)

6 Intra- and Intermolecular Coupling of Olefins and Acetylenes.

6.1 Intramolecular Reactions

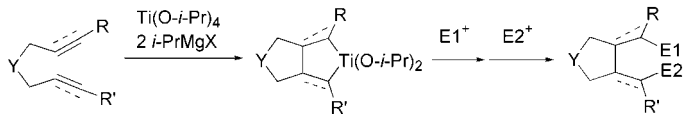
The intramolecular coupling reaction of bis-unsaturated compounds mediated by Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX proceeds smoothly with a variety of substrates. Thus, 1,6- or 1,7-dienes, enynes, and diynes, including those having a heteroatom at the tether portion, afford the corresponding titanabicyclic compounds. The resulting titanabicyclic compounds could be protonated, deuterated, and halogenated, and also could be used for carbon bond elongation through their reaction with an aldehyde and/or allyl bromide. The reaction with electrophiles frequently proceeds with excellent regio- and stereoselectivity, thus affording an attractive method for preparing five- and six-membered cyclic compounds. Several representative results are summarized in Table 9. Quite recently, we found that bis-acetylenic amides and esters are also good substrates; thus, a facile preparation of *exo*-cyclic conjugated dienes fused to lactams and lactones is possible as shown in Equation 31.[83] Cyclization of dienynes proceeds equally well as shown in Equation 32, and the resulting titanacycle intermediates reacted with aldehydes regiospecifically at the remote position of the allyltitanium system to permit the regioselective elongation of the side-chain with a *trans*-olefinic configuration.[84] The titanacyclopentadienes are sufficiently reactive even towards an ester group, provided that it is placed at a suitable position in the same molecule. Thus, the diyne having the structure shown in Equation 33 reacted with Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX via a domino pathway to afford the corresponding bicyclic cyclopentadienol.[85]

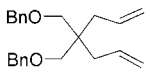
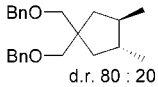
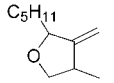
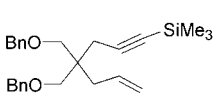
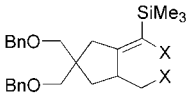
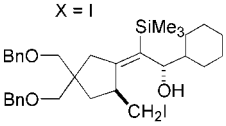
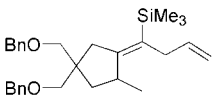
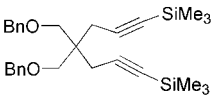
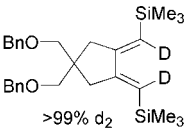
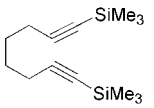
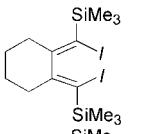
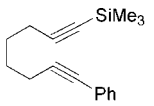
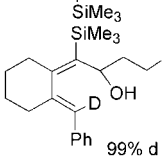
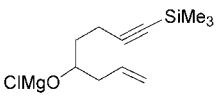
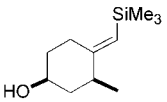
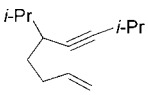
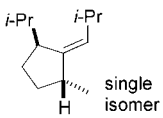
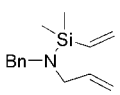
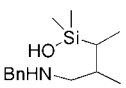


(31)

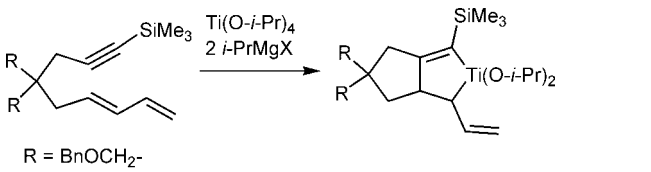
Z	R	R'	Yield, %
NBn	Me_3Si	Me_3Si	80
	n-C_6H_{13}	Me_3Si	51
	Me_3Si	Ph	67
Ph(Me)CHN	Me_3Si	Me_3Si	79
O	Me_3Si	Me_3Si	50

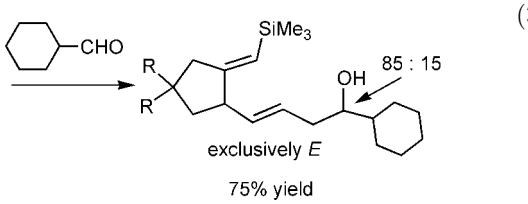
Table 9.



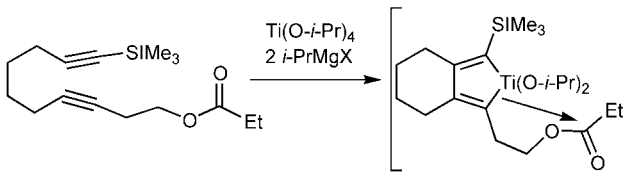
Entry	Substrate	Electrophile(s)	Product	Yield	Ref.
1		HCl	 d.r. 80 : 20	77%	74
2		HCl	 d.r. 73 : 27	65%	74
3		DCl	 X = D (>99% d_2)	90%	74
4		I_2	X = I	87%	74
5		1) *c*-$C_6H_{11}CHO$ with $TiCl_2(O\text{-}i\text{-}Pr)_2$ 2) I_2	 single isomer	58%	75
6		1)  with $L_2Cu(CN)Cl_2$ 2) H^+		90%	76
7		DCl	 >99% d_2	87%	74
8		I_2		89%	77,78, 79
9		1) $PhCH_2CH_2CHO$ with $TiCl_2(O\text{-}i\text{-}Pr)_2$ 2) D^+	 99% d	82%	76
10			 d.r. 90 : 10	70%	80
11		HCl	 single isomer	86%	81
12		H_2O	 d.r. 5 : 1	86%	82

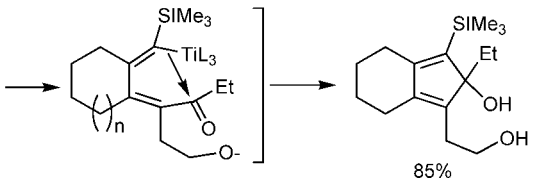
The intramolecular cyclization of 1,2-dien-7-ynes and 1,2-dien-6-ynes proceeded in a regiospecific way, respectively, to afford the corresponding titanabicyclo[3.3.0]octenes.[86] If the reactions started with optically active allenes, excellent chirality transfer was attained. As the reactions of the resulting titanacycles with electrophiles also proceeded with excellent chirality transfer, a new method for synthesizing optically active cyclopentane derivatives has been opened up as exemplified by Equations 34 and 35.



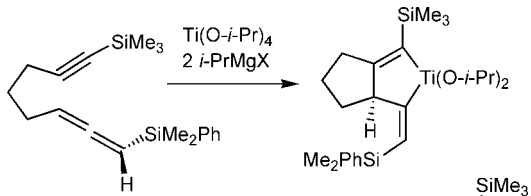


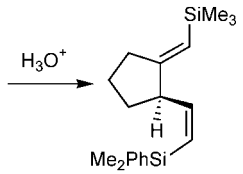
(32)



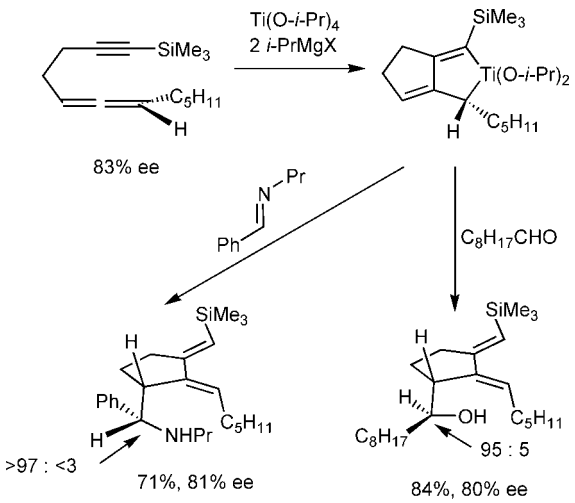


(33)



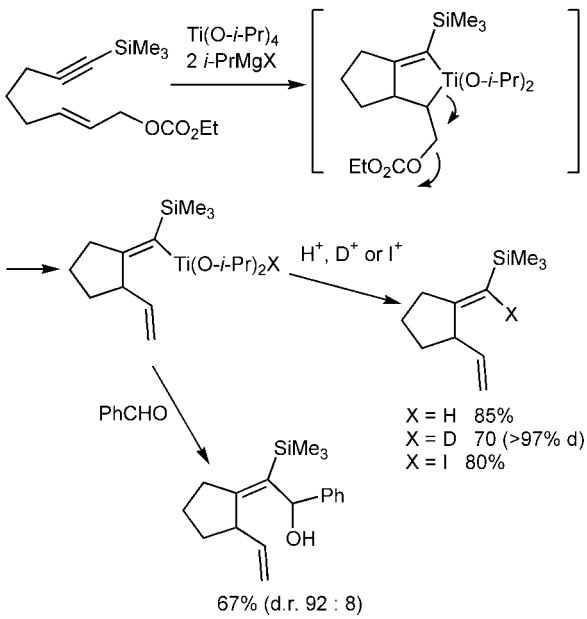


(34)



(35)

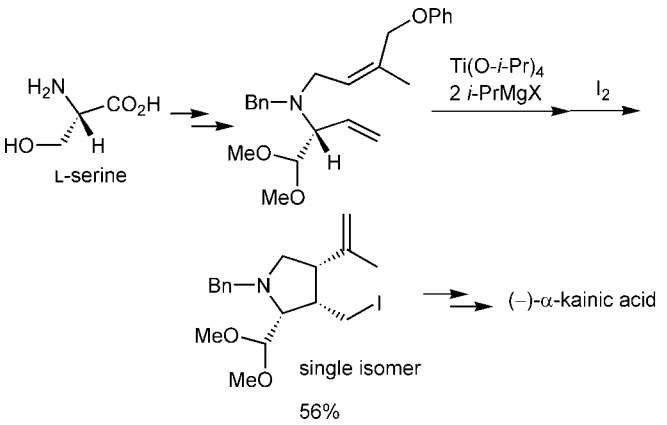
If the unsaturated compounds being subjected to the reaction mediated by the Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX reagent have a leaving group at the allylic or propargylic position, the resulting titanacycles experience the elimination of said group.[87] Equation 36 shows the reaction of 2,7-enynyl carbonate substrates as a representative case. Since the resulting vinyltitaniums can be intercepted with electrophiles including aldehydes, this reaction can be considered as an alternative of the stoichiometric intramolecular metallo-ene reaction via an allylic lithium, magnesium or zinc intermediate.[88] Based on this formal metallo-ene type reaction, optically active *N*-heterocycles[89] including the intermediate for synthesizing (−)-α-kainic acid (Equation 37)[90] were synthesized starting with naturally occurring amino acids. Cross-conjugated trienes useful for the diene-transmissive Diels–Alder reaction were also synthesized based on this method (Equation 38).[91] The utility of this metallo-ene-type reaction was highlighted by the reaction of 1,6- or 1,7-enynes carrying a chiral 1,2-diphenylethylene acetal moiety as the leaving group.[92] The reaction proceeded with excellent chiral induction to give optically active cyclopentane and –hexane derivatives, respectively, through the subsequent reaction of the resulting vinyltitaniums with electrophiles as exemplified in Equation 39.



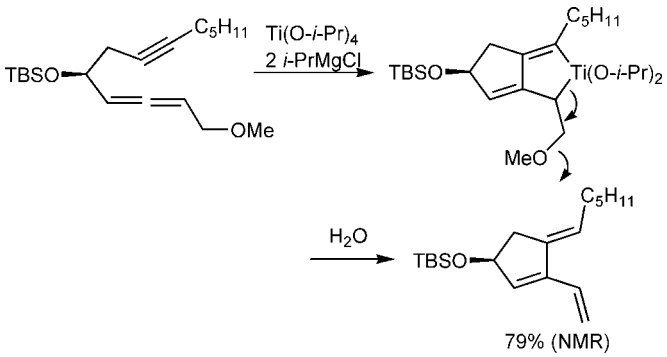
(36)

Cyclization of 2-en-7-ynoates or 2-en-8-ynoates proceeds readily regardless of the presence of an ester moiety.[93] Thus, the cyclization of a *tert*-butyl enynoate afforded the titanacycle which, in turn, reacted with electrophiles at the titanated ester portion regioselectively to afford cyclopentane or cyclohexane derivatives having a stereodefined alkylidene group and side-chain as exemplified by the reaction

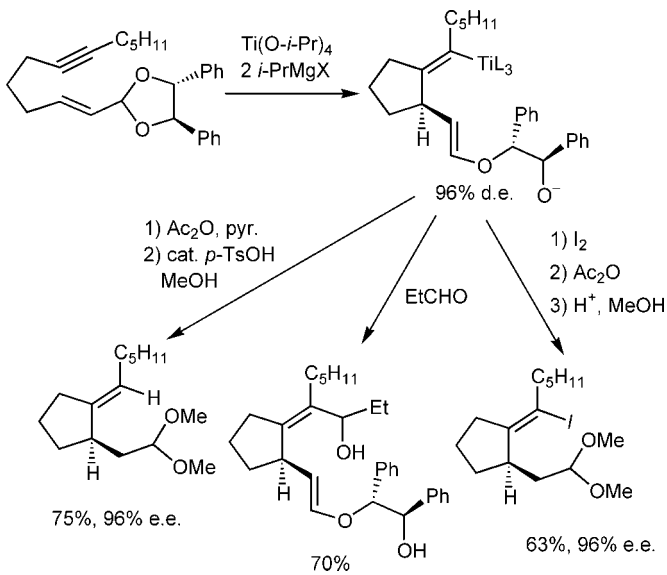
shown in Equation 40. The methyl or ethyl esters of the same structure generated the titanacycles as well, but this is followed by a second ring closure initiated by the reaction with an electrophile, eventually giving bicyclic ketones as shown in Equation 41.



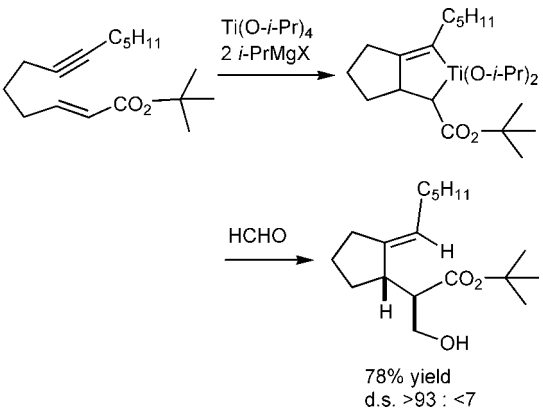
(37)



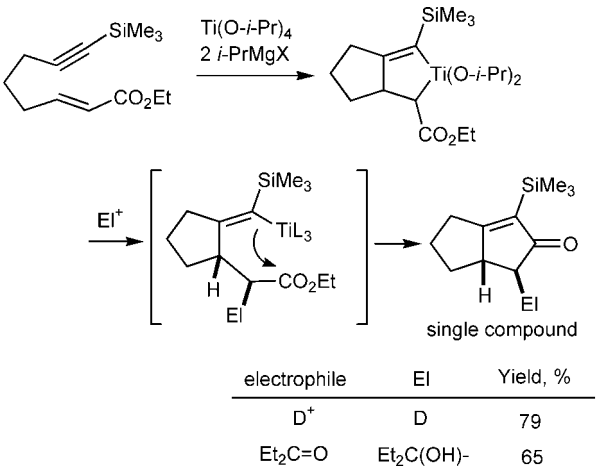
(38)



(39)



(40)



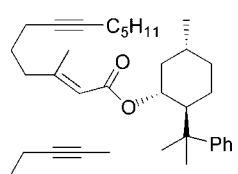
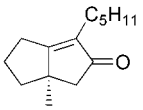
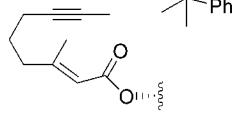
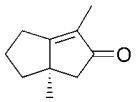
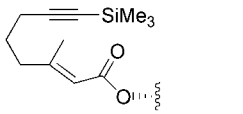
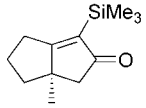
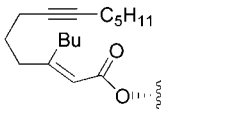
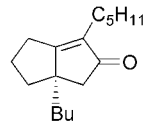
electrophile	El	Yield, %
D^+	D	79
$Et_2C{=}O$	$Et_2C(OH)$-	65

(41)

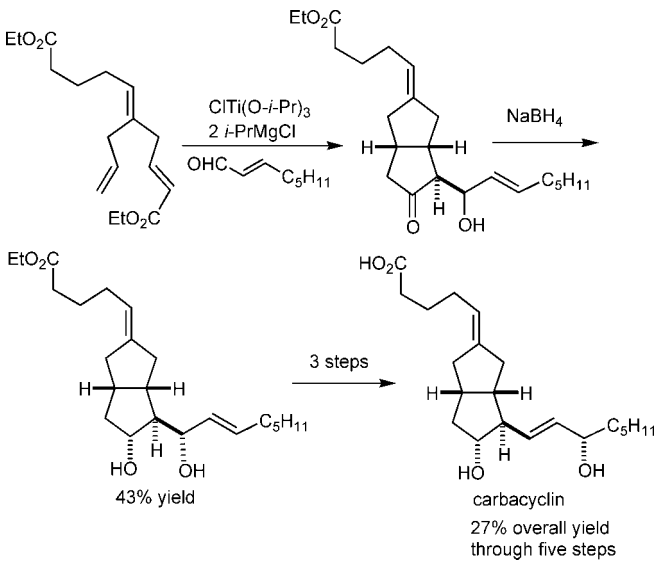
This tandem cyclization has recently been extended to substrates having a trisubstituted double bond and optically active esters, and it has been shown that the reaction opens up an efficient entry to angularly substituted, optically active bicyclic ketones which should be versatile for the preparation of cyclic compounds including naturally occurring compounds. Thus, as summarized in Table 10, a variety of bicyclo[3.3.0]octanes with a substituent at the angular position were obtained in excellent ee and in good yield starting from the corresponding 8-phenylmenthyl enynoates.[94] Transition metal-catalyzed or -mediated carbonylative cyclization of enynes provides an attractive method for preparing a variety of bicyclic ketones, including optically active ones. However, it should be noted that this process does not appear to be suitable for the preparation of the ketones shown in Table 10, because the cyclization of 1,1-disubstituted olefinic substrates, which are the precursors for the angularly substituted ketones, usually requires the presence of substituents to the tether portion to achieve good yields.

The tandem cyclization of 2,7-dienoates providing bicyclic ketones is also feasible, and recently, this reaction was effectively used for preparation of carbacyclin.[95] Thus, as shown in Equation 42, successive

Table 10.

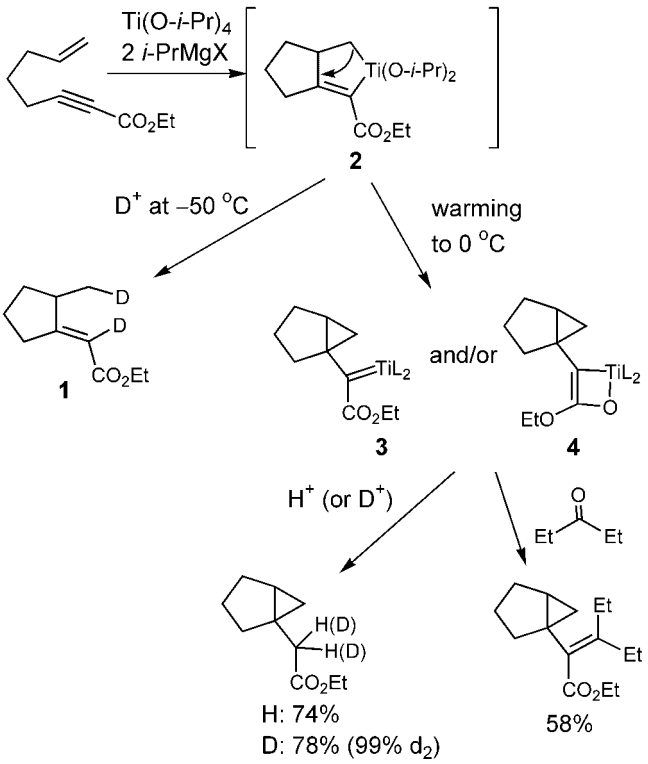
Substrate	Product	Yield, %	ee, %
		62	91-93
		66	93
		62	91
		49	94

treatment of the ethyl (*E*,*E*)-5-alkylidene-2,7-octadienoate (for the synthesis of which, see Equation 50 and Table 12 in Section 6.2) with the $ClTi(O\text{-}i\text{-}Pr)_3$/2 *i*-PrMgCl reagent and (*E*)-2-octenal afforded the corresponding bicyclic ketone with highly selectively and in high yield, from which racemic carbacyclin was easily obtained by conventional reactions which involve the stereospecific reduction of the ketone moiety with $NaBH_4$ and Pd-catalyzed allylic transposition reaction. Finally, separation of the enantiomers of the racemic product by HPLC using a chiral column provided optically active carbacyclin.



(42)

In contrast to the reactions of olefinic esters discussed above, 7-en-2-ynoates show another interesting behavior in cyclization as shown by Equation 43.[93] Deuteriolysis of the reaction mixture at low temperature gave the expected bis-deuterated compound, indicating the presence of a titanacycle intermediate. However, when the reaction mixture was simply allowed to warm to up to 0 °C, a product having a bicyclo[3.1.0]hexane skeleton was obtained in excellent yield. The conversion of the initially formed titanacycle intermediate to a titanium-carbene complex and/or α-titanated titanium-enolate compound might take place as evidenced by the deuteriolysis and smooth alkylidenation of diethyl ketone. The synthesis of *d*-sabinene was achieved by using this reaction as a key step.

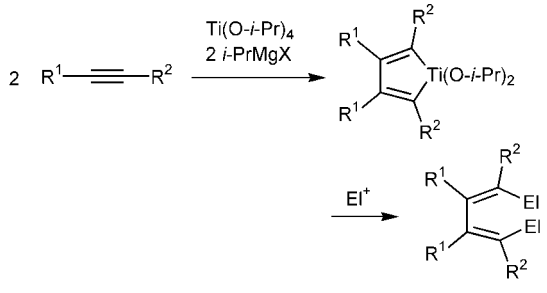


(43)

6.2 Intermolecular Reactions

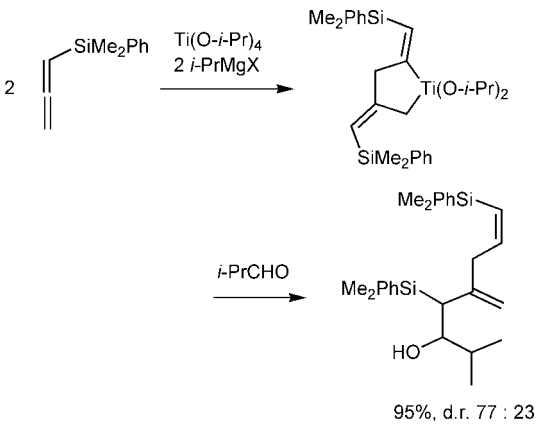
In comparison with the intramolecular reaction, an intermolecular reaction has intrinsically the problem of regiochemistry. The intermolecular coupling reactions mediated by $Ti(O\text{-}i\text{-}Pr)_4$/2 *i*-PrMgX, however, frequently show excellent regioselectivity which includes the homocoupling of acetylenes or allenes, coupling between internal acetylenes and terminal acetylenes, and cross-coupling of allenes and acetylenes. Representative results are summarized in Equations 44,[77,96] 45,[97] 46,[98] and 47,[96,97] respectively. Among these, the regioselective cross-coupling reaction between internal and terminal acetylenes exemplified in Equation 46 is especially noteworthy because it affords a highly practical method for

synthesizing a variety of conjugated dienes, including those having a functional group, which are frequently found as a partial structure of naturally occurring products and are also useful intermediates in organic synthesis.



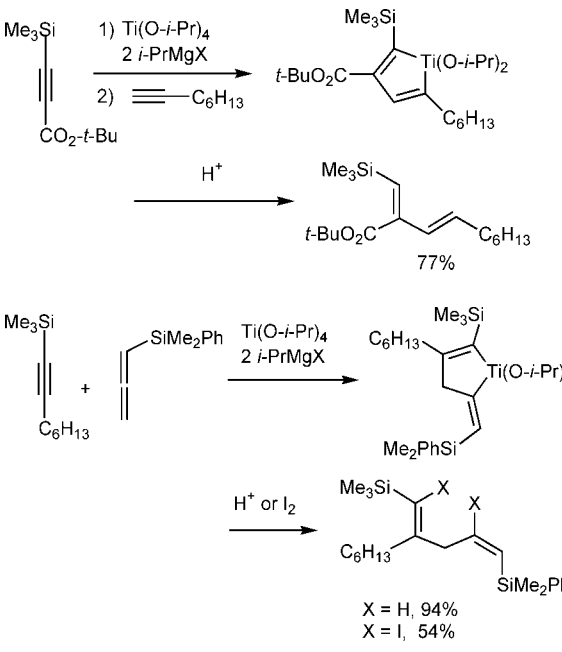
R^1	R^2	El (electrophile)	Yield, %	ref.
H	$SiMe_3$	I (I_2)	85	77,95
H	*t*-Bu	I (I_2)	93	95
H	$SiMe_3$	SCN ($(SCN)_2$)	56	95
Me	$SiMe_3$	I (I_2)	75	77

(44)



95%, d.r. 77 : 23

(45)



(46)

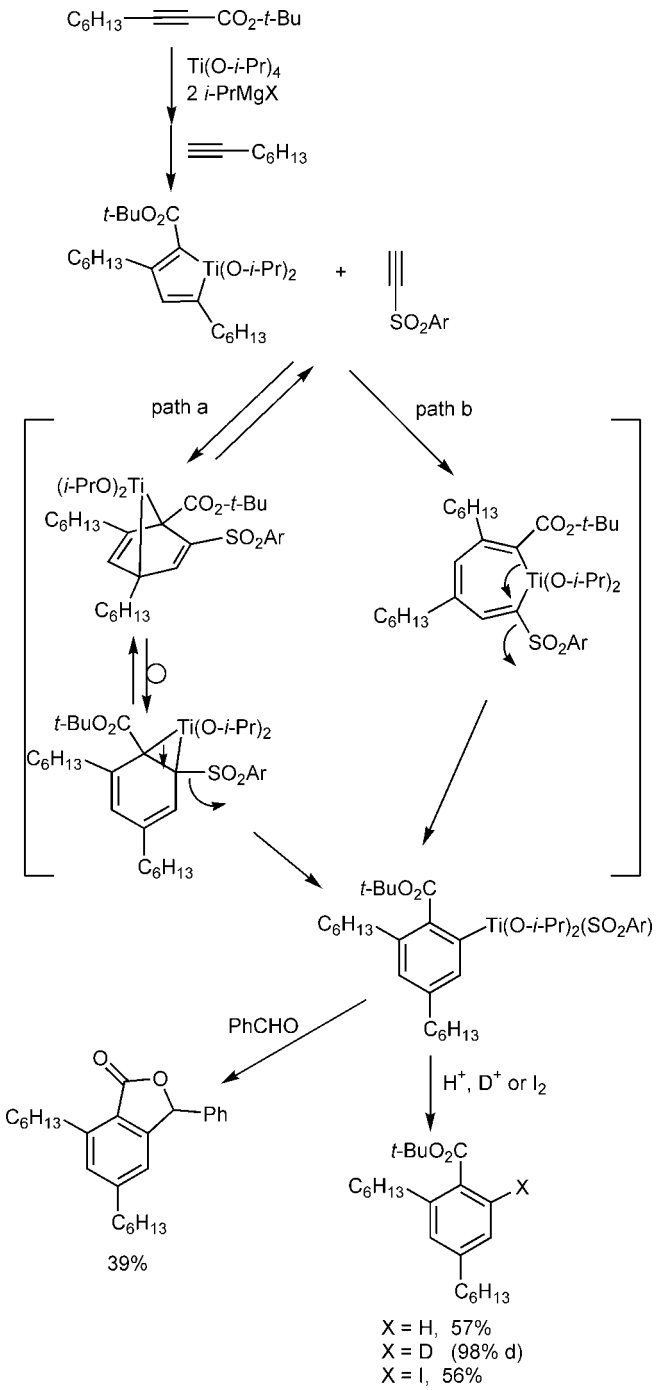
(47)

In the course of our study to explore the synthetic utility of the resulting titanacyclopentadiene intermediates thus generated, quite recently, we have found that their reaction with ethynyl *para*-tolyl sulfone provides aryltitanium compounds, thus affording a highly practical method for synthesizing polysubstituted benzene derivatives.[99] As exemplified in Equation 48, the reaction of the titanacyclopentadiene, derived from *t*-butyl 2-nonynoate and 1-octyne, with ethynyl *para*-tolyl sulfone afforded an aromatic titanium complex with the structure depicted exclusively which, in turn, reacted with electrophiles such as H^+, D^+, I^+ and carbonyl compounds to provide highly substituted benzene derivatives. We propose the following path a or b depicted in Equation 48 as being most likely to account for the transformation. Thus, in path a, the Diels–Alder reaction of the titanacyclopentadiene and the sufonylacetylene took place to furnish the bicyclic titanacycle, at least, in an equilibrium concentration. The regioselection as well as the high regioselectivity of this Diels–Alder reaction is the key to the later formation of the aryl-titanium bond at the defined position. Then, the carbon-titanium bond of the titanacycle rearranges to a suitable position where the 1,2-elimination of the sulfonyl group is feasible. Finally, the sulfonyl group is eliminated to shift the equilibrium to the formation of the aryltitanium compound. Alternatively, path b involves regioselective insertion of the sulfonylacetylene to the titanacyclopentadiene, followed by elimination of the sulfonyl group at the sp^2-carbon with inversion of configuration to give the aryltitanium. The reaction of a titanium-acetylene complex with two equivalents of ethynyl *para*-tolyl sulfone proceeded according to the reaction path shown in Equation 49,

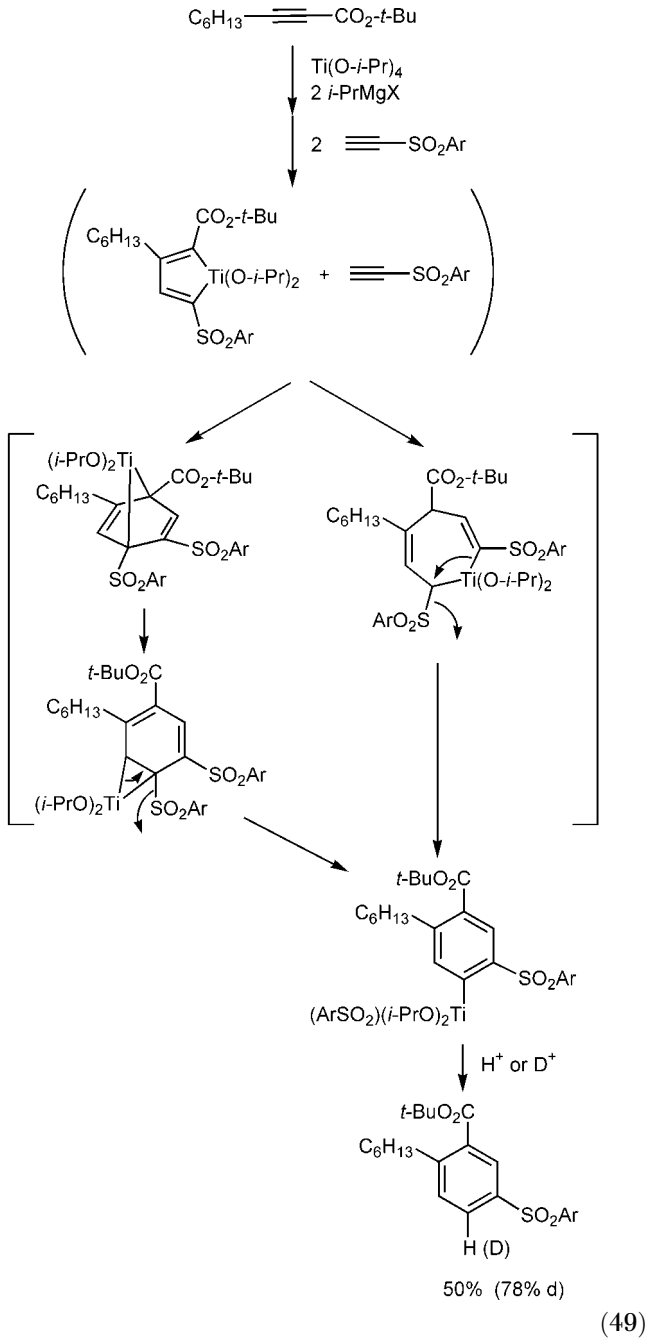
Table 11.

Alkynes 1st	Alkynes 2nd	Alkynes 3rd	Electrophile	Product(s)	Yield
Bu, Bu	OBn, SO_2Tol		H^+	Bu, Bu, BnO	59%
Bu, Bu	SO_2Tol (2 equiv)		H^+ (or D^+)	Bu, Bu, SO_2Tol, H (D) (80% d)	65%
t-BuO$_2$C, C$_6$H$_{13}$	Me_3Si	SO_2Tol	H^+	*t*-BuO$_2$C, C$_6$H$_{13}$, H (D), (94% d), Me_3Si	46%
	SO_2Tol		H^+	O, BnN, Si Me$_3$, Si Me$_3$, Si Me$_3$	88%

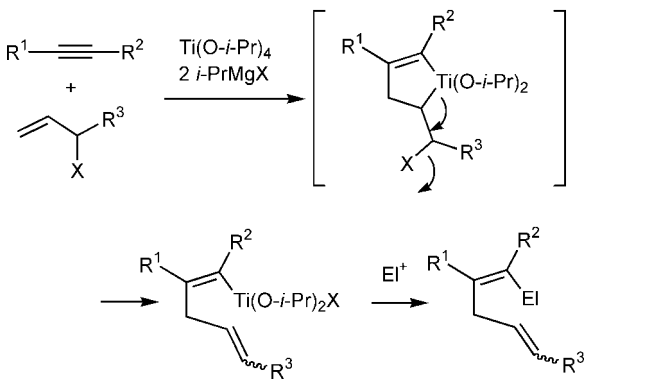
providing sulfonylbenzene derivatives. Table 11 summarizes several other examples for the synthesis of aromatic compounds including those prepared from diynes and the sulfone. It should be noted that this reaction is the first general method for synthesizing aromatics from three different kinds of unsymmetrical alkynes through chemoselective and regioselective trimerization. The reaction also opens up, for the first time, a direct method for synthesizing an aryltitanium complex.



(48)



(49)



(50)

Table 12.

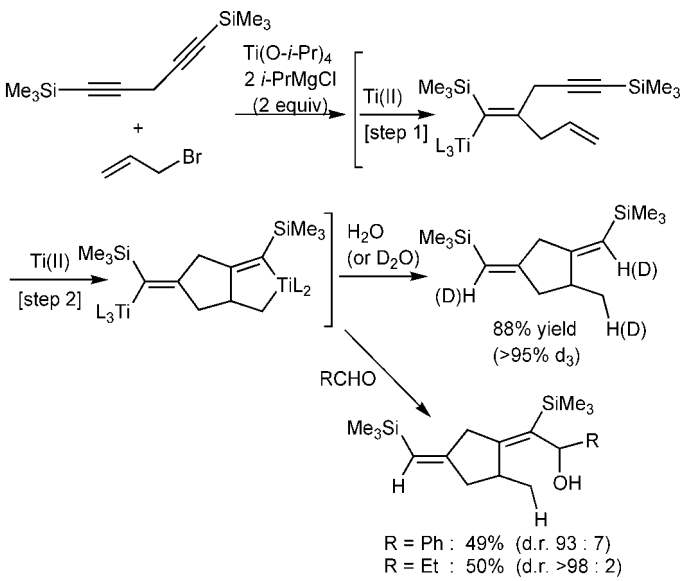
Alkyne	Allylic Compound	Electrophile	Product	Yield, % [*E* : *Z*]
Me_3Si—≡—*n*-Hex.	OCO_2Et	1N HCl	*n*-Hex., Me_3Si	70 [72 : 28]
Me_3Si—≡—OTBS	Br	I_2	Me_3Si, OTBS, I	73[a] [-]
n-Pr—≡—*n*-Pr	OEt, OEt	I_2	*n*-Pr, *n*-Pr, OEt, I	70 [85 : 15]
//	$CONEt_2$, OCO_2Et	PhCHO	*n*-Pr, *n*-Pr, $CONEt_2$, Ph, OH	75 [>95 : 5]
//	OAc	H_2O	*n*-Pr, *n*-Pr	68 [70 : 30]
//	OCO_2Et	I_2	*n*-Pr, *n*-Pr, I	51

[a] The product was used as a starting compound for carbacyclin synthesis, see Equation 42 and ref. 94.

Recently, it has been shown that cross-coupling of acetylenes with allylic compounds proceeds with excellent regioselectivity as shown in Equation 50, thus providing a convenient method for preparing 1,4-alkadienes including those having functional groups.[100] Similarly, 1,2,4-alkatrienes were synthesized from acetylenes and propargylic compounds. Representative results are summarized in Table 12.

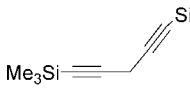
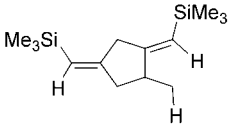
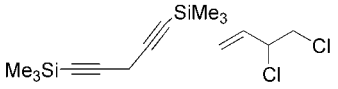
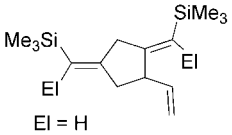
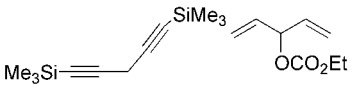
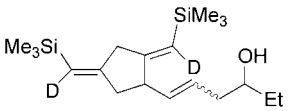
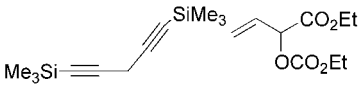
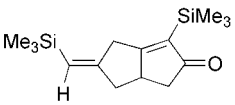
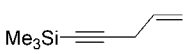
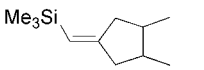
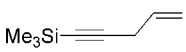
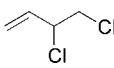
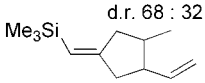
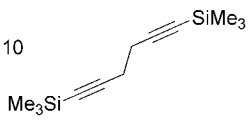
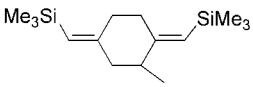
6.3 Tandem Inter- and Intramolecular Reactions

As mentioned in Section 2, inter- and intramolecular coupling reactions of olefins and/or acetylenes with a catalytic or a stoichiometric quantity of a metallic reagent have, respectively, received widespread acceptance as valuable methodology in organic synthesis. One metal species, frequently, can be used for both inter- and intramolecular reactions; however, there is no precedent to carry out the inter- and intramolecular coupling reaction successively in one pot in the presence of a single metal species, although such a reaction would allow advances in the design of new syntheses and also would minimize the use of chemicals and shorten the processing time. Quite recently, we have found that Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX can be used as a reagent to carry out successively inter- and intramolecular coupling reactions.[101] Thus, as shown in Equation 51, reaction of 2 equivalents of Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl with 1,5-bis(trimethylsilyl)-1,4-pentadiyne and allyl bromide gave, after the reaction with an electrophile including aldehydes, 1,4-bis(trimethylsilylmethylidene)-2-methylcyclopentane derivatives in good yield. The outcome of the reaction can be explained by assuming that a Ti(II)-mediated regiospecific intermolecular coupling reaction of the diyne and allyl bromide with a subsequent β-elimination reaction occur initially to afford an allyl-titanated intermediate *in situ* (step 1 in Equation 51) which, in turn, undergoes the Ti(II)-mediated intramolecular cyclization reaction to afford a titanabicyclic compound (step 2).



(51)

Table 13.

Entry	Alkyne	Allyic Compound	Electrophile(s)	Product(s)	Yield
1		X = OAc	H_2O		73%
2		X = OCO_2Et	H_2O		76%
3			H_2O	 El = H	85%
4			D_2O	El = D	(>95% d_2) 87%
5			I_2	El = I	64%
6			EtCHO then D_2O	 100% regioselectivity *E* : *Z* = 89 : 11 >95% D_2	68%
7			*sec*-BuOH then H_2O		44%
8			H_2O		77%
9			H_2O	d.r. 68 : 32 	85%
10			H_2O	d.r. 52 : 48 	73%

Other representative examples of the Ti(II)-mediated tandem reaction are summarized in Table 13. As can be seen from this table, the tandem reaction is not restricted to the reaction of 1,4-diynes; thus, 1-trimethylsilylpent-4-en-1-yne reacted with allyl bromide or 3,4-dichloro-1-butene to afford the corresponding tandem coupling/cyclization products (entries 8 and 9). The formation of cyclohexane derivatives is also possible by starting with 1,5-diynes (entry 10).

7 Summary and Outlook

When we found for the first time in the middle of 1994 that the Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX reagent worked as a divalent titanium equivalent, Ti(O-*i*-Pr)$_2$, to afford the titanium-acetylene complex by its reaction with an acetylene, it was easily recognized that the reagent met the qualifications for use in large-scale synthesis. By that time, divalent titanium and zirconium compounds such as Cp_2Ti and Cp_2Zr equivalents, respectively, had been shown to serve as useful and unique synthetic reagents starting from unsaturated hydrocarbons. We, therefore, were interested in extending the synthetic reactions mediated by Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX with great expectation of developing new synthetic methodology applicable to large-scale production. As time went by, it became more and more clear that the reagent is unimaginably versatile, thus allowing a variety of synthetic transformations starting from readily available alkenes and alkynes that are not viable or require multi-step sequences by conventional methods. As described herein, synthetic reactions based on the reagent are being elaborated and we are convinced that the future synthetic scope of the reagent will be further broadened. We hope that the reactions mediated by Ti(O-*i*-Pr)$_4$/2 *i* -PrMgX will be accepted as standard synthetic methodology and find wide utility in the laboratory and in industry.

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