Synthesis of Organotitanium Complexes from Alkenes and Alkynes and Their Synthetic Applications

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I. Introduction

Transformations using organometallic complexes have played a central role in modern organic synthesis. The types of reactions based on organometallic complexes can be divided broadly into two categories: one is utilization of the complex as a carbanion source which is mainly applied to reactions using elemental metal complexes, and the other is based on late transition metal behavior such as coordination of a carbon−carbon multiple bond, oxidative addition, reductive elimination, β-hydride elimination, or an addition reaction. Early transition metal complexes show both types of reactivity, and thus, in addition to their utility either as a carbanion source or as a synthetic reagent based on transition metal behavior, it is possible to utilize them for synthetic transformations based on the characteristic features of both types of reactivity. Group 4 early transition metal complexes are not exceptional, and their application in organic syntheses has continuously attracted much interest. Among them, reactions using organotitaniums and -zirconiums have been most extensively investigated.[1] This review surveys synthetic reactions starting from substrates having a carbon−carbon unsaturated bond such as olefins, conjugated dienes, or acetylenes where both characteristic reactivities of titanium mentioned above are used in tandem. The reaction involves, fundamentally, the generation of alkene− or alkyne−titanium complexes through the coordination of the carbon−carbon multiple bond to a titanium complex, which is a characteristic feature of transition metal behavior, and their use as a carbanion source directly or

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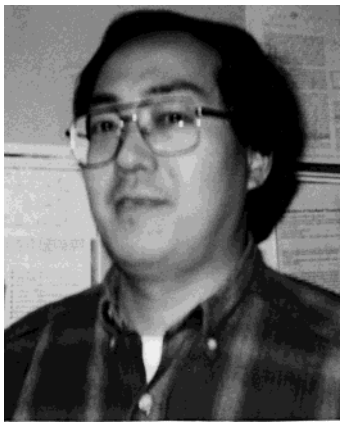
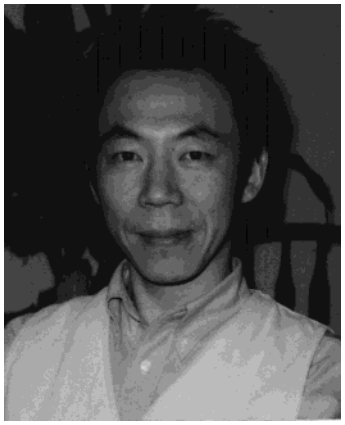
Fumie Sato was born in 1942 in Tokyo. He obtained his B.Sc. (1966) and Ph.D. (1971) degrees from Tokyo Institute of Technology. He got an Assistant Professor position in 1971 at Tokyo Institute of Technology, where he was promoted to Associate Professor in 1981 and Professor in 1989. He was a postdoctoral fellow at Indiana University with L. J. Todd from 1973 to 1974. His research interests involve the development of new synthetic methodologies using organometallic compounds and their utilization for 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, stereocontrole of acyclic systems based on Cram's rule, and use of organocopper compounds as a reagent for stereocontrole. His group has developed the two-component coupling synthesis of prostaglandins as 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 five years has been the synthetic reactions mediated by a Ti(O-*i*-Pr)$_4$/2*i*-PrMgX reagent.



Hirokazu Urabe was born in 1958 in Kanagawa, Japan. He received his Ph.D. degree in 1985 from Tokyo Institute of Technology under the direction of Professor Isao Kuwajima. He became Assistant Professor in 1985 and was appointed to Associate Professor in 2000 at Tokyo Institute of Technology. He was also a postdoctoral fellow at Stanford University with Professor Barry M. Trost for 1988–1990. He received a Progress Award in Synthetic Organic Chemistry, Japan, in 1998, and Sankyo Award in Synthetic Organic Chemistry, Japan, in 1999. His research interest has been focused on new synthetic methodologies and their application in efficient organic synthesis.

after accompanying conversion to new organotitanium complexes. Although the reactions of organotitaniums and -zirconiums have many characteristic features in common, they also display many differences. This review focuses on titanium complexes. The reviews relevant to zirconium complexes cited in the following individual sections will be helpful for understanding the common and different characteristic features of titanium and zirconium complexes.

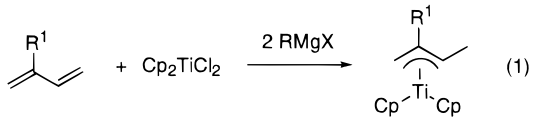


Sentaro Okamoto was born in 1961 in Hiroshima, Japan. He received his M.S. degree from Tokyo Institute of Technology in 1987 and became Assistant Professor at the same institute in 1989. He obtained his Ph.D. degree in 1993 from Tokyo Institute of Technology under the supervision of Professor Fumie Sato.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

II. Synthesis of Organotitanium Complexes as a Nucleophilic Reagent through Hydro-, Heteroatom-, and Carbotitanation of Olefins, Conjugated Dienes, and Acetylenes

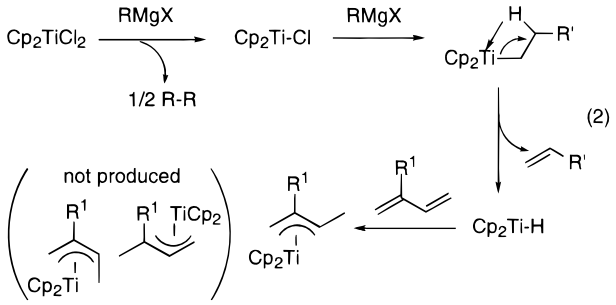
1. Synthesis of η^3-Allyltitanium Complexes, $Cp_2Ti(\eta^3$-allyl), from Conjugated Dienes via Hydrotitanation and Their Utilization as a Nucleophilic Allylating Reagent

In 1967, Martin and Jellinek reported that the reaction of Cp_2TiCl_2, conjugated dienes, and 2 equiv of an alkyl Grignard reagent having a β-hydrogen affords η^3-allyltitanium(III) complexes $Cp_2Ti(\eta^3$-allyl).[2] Thus, the reaction with 1,3-butadiene and 2-substituted butadienes proceeds smoothly under mild conditions to furnish the corresponding η^3-allyltitanium complexes with the structure depicted in eq 1 exclusively; however, with 1,3-butadienes having a substituent at the 1- and/or 4-position, the success of the reaction as well as the structure of the resultant η^3-allyltitanium complex is dependent on the substrate. Equation 2 illustrates a proposed



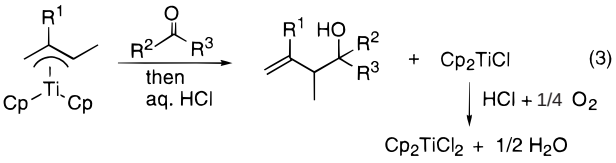
(1)

reaction mechanism for the reaction; 1 equiv of the RMgX is used for the reduction of Cp_2TiCl_2 to Cp_2TiCl, which reacts with another RMgX to afford Cp_2TiH through the formation of Cp_2TiR and the following β-hydrogen elimination, and then hydrotitanation of the conjugated dienes via a 1,4-addition pathway is followed, affording a sterically most favorable complex rather than other possible regio- and stereoisomers as shown in the equation. These allylic titaniums were shown later to serve as a nucleophilic



allylating reagent by Sato[3,4] and Teuben[5,6] independently. Thus, combination of these two findings provides an efficient method for elongation of the carbon chain of the conjugated dienes in a one-pot procedure.

Reaction of η^3-allyltitanocene complexes with aldehydes and ketones proceeds in a regiospecific way to afford, after hydrolysis, the corresponding β-methyl homoallyl alcohols in excellent yields (eq 3).[4−6] After



the reaction, Cp_2TiCl_2 can be recovered in good yield by quenching the reaction mixture with aqueous HCl, followed by stirring the solution under air, which resulted in an oxychlorination reaction as shown in eq 3; this result adds to the advantages of the reaction from a synthetic viewpoint. The results of one-pot preparation of homoallyl alcohols from conjugated dienes and aldehydes or ketones via allyltitaniums are summarized in Table 1. Thus, a variety of β-methyl homoallyl alcohols with and without a substituent including an alkoxy group[7,8] at the vinylic position can be prepared from butadiene or 2-substituted butadienes and carbonyl compounds, respectively. The reaction with aldehydes proceeds with good to excellent stereoselectivity to afford β-methyl homoallyl alcohols having an anti stereochemistry predominantly. The regio- and stereochemistry of the reaction with aldehydes can be explained by the formation of a σ-allyltitanium intermediate where the titanium is placed at the terminal position through the coordination of the aldehyde to the titanium and the addition reaction proceeds via a six-membered chairlike transition state as illustrated in Figure 1. The effect of a substituent on the cyclopentadienyl group in η^3-allyltitanocenes on the diastereochemistry of the addition reaction with aldehydes was investigated. In the case of a nonsubstituted crotyltitanocene species, an increase in anti diastereoselection with increasing the size of the substituent on the cyclopentadienyl group was observed (Table 1, entries 30−35);[9] however, in the case of (2-siloxycrotyl)titanocene, increasing the steric hindrance led to a progressive loss of anti stereoselectivity (entries 27−29).[7] η^3-Allyltitanocene complexes derived from five- and six-membered 1,3-cycloalkadienes, includ-

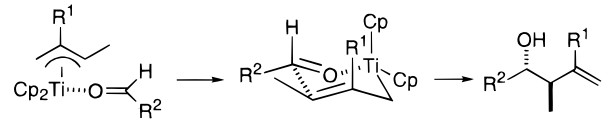
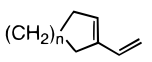
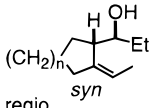
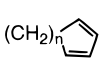
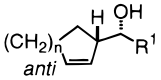
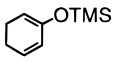
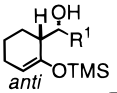
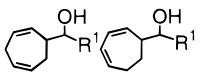
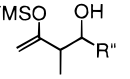
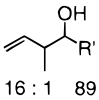
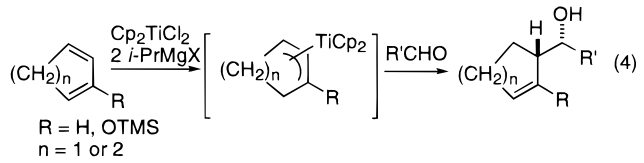


Figure 1.

Table 1. Preparation of η^3-Allyltitanocene Derivatives and Their Reaction with Aldehydes and Ketones

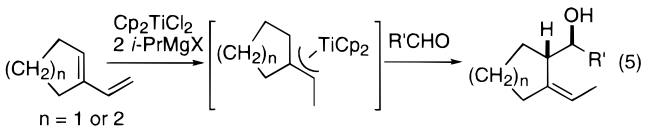
Entry	Diene	Carbonyl Compound	Product(s) *anti* :*syn*	yield %	Ref.
		Reaction using Cp_2TiCl_2 or Cp_2TiCl			
		$R^1C(O)R^2$			
		R^1 R^2			
1	R = H	Ph H	95:5	93	4
2		Et H	93:7	84	4
3		Me Me	-	88	4,5,6
4	Me	CH_2=CH Me	65:35	91	4
5		CH_2=CH H	90:10	90	4
6		$ClCH_2$ Me	n.d.	95	4
7		$MeO_2C(CH_2)_2$ Me (lactone)	n.d.	94	4
8	$(CH_2)_2CH$=CMe_2	Ph H	80:20	82	14
9		*n*-C_5H_{11} H	100:0	91	14
10		*t*-Bu H	100:0	90	14
11	TMSO	Ph H	70:30	63	7
12		*n*-C_5H_{11} H	100:0	57	7
13		*t*-Bu H	100:0	65	7
					
14		Et H	>98:2	64	8
15		CH_2=CH H	>90:10	58	8
					
			regio.		
16	n = 1	Et H	100:0 0:100	86	10
17	2	Et H	90:10 0:100	98	10
					
18	n = 1	Et H	100:0	86	10
19	n = 2	Ph H	100:0	79	10
20		Et H	80:20	-	10
					
21		Ph H	100:0	71	7
22		*n*-C_5H_{11} H	95:5	58	7
23		*t*-Bu H	100:0	70	7
		$R^1C(O)R^2$			
		R^1 R^2	(yield,d.e.(%))		
24		Ph H	59 (42,60) : 41		11
25		*n*-C_5H_{11} H	65 (48,60) : 35		11
26		*t*-Bu H	96 (73,56) : 4		11
	Reaction using $RCp(R'Cp)TiCl_2$				
					
	R R'	R"CHO R"			
27	Me Me	Ph	70 : 30	59	7
28	*t*-Bu H	Ph	57 : 43	62	7
29	*t*-Bu *t*-Bu	Ph	51 : 49	68	7
					
30	Me Me	$PhCH_2$	16 : 1	89	9
31	Me Me	*c*-C_6H_{11}	18 :1	95	9
32	Me Me	Ph	42 : 1	87	9
33	*i*-Pr *i*-Pr	$PhCH_2$	20 : 1	84	9
34	*i*-Pr *i*-Pr	*c*-C_6H_{11}	26 : 1	93	9
35	*i*-Pr *i*-Pr	Ph	52 : 1	89	9

ing those having a substituent at the 2-position, also react with aldehydes with excellent selectivity to provide cyclopentene and cyclohexene having a stereodefined side chain at the allylic position (eq 4, entries 18−23).[7,10] The allyltitanium complex derived



(4)

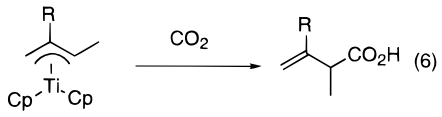
from 1-vinyl-1-cyclopentene or -cyclohexene reacts with aldehyde regiospecifically at the carbon on the cyclic framework as shown in eq 5 (entries 16 and 17). The addition reaction again occurs in a highly



(5)

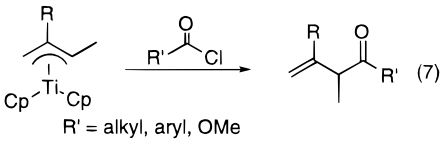
stereoselective way, and the olefin geometry of the resultant exocyclic double bond of the product is controlled as *Z*-geometry.[10] The reaction of a cycloheptenyl-η^3-allyltitanium species prepared from cycloheptatriene with aldehydes afforded a mixture of isomeric 1,3- and 1,4-cycloheptadienyl alkyl (aryl) carbinols (entries 24−26).[11]

$Cp_2Ti(\eta^3$-allyl) complexes also react with other electrophiles, in addition to aldehydes and ketones, such as carbon dioxide,[3,5,6,12,13] acid chlorides,[14,15] acetals,[16] isocyanides,[5,6] imines,[5,6] nitriles,[5,6] isonitriles[5,6] and organotin halides,[17] to afford the corresponding allylated products. Several representative results are summarized in Table 2. η^3-Allyltitanocenes react readily with carbon dioxide under ordinary pressure and at room temperature, thus affording one-pot access to 2-methyl-3-butenoic acid with and without a substituent at the C-3 position from butadiene or 2-substituted 1,3-butadiene, respectively, as shown in eq 6 (entries 1−5 in Table 2). The reaction



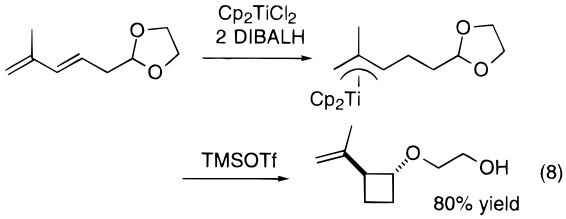
(6)

of $Cp_2Ti(\eta^3$-allyl) complexes with acid chlorides proceeds smoothly to give β,γ-unsaturated ketones having a substituent at the α-position as shown in eq 7 (entries 6−12 and 14−17). The reaction with steri-



(7)

cally less hindered acid chloride, however, produced the corresponding tertiary alcohol in a considerable amount (entries 8 and 9) or predominantly (entries 7 and 12). Similarly, β,γ-unsaturated esters were synthesized from 1,3-dienes and methyl chloroformate (eq 7, entries 13 and 18−20). The reaction of η^3-allyltitanium reagents with acetals proceeds in the presence of a Lewis acid to afford homoallylic ethers (entries 21−25). The reaction also proceeds in an intramolecular way as shown in eq 8.[16] The hydroti-



(8)

Table 2. Reaction of η^3-Allyltitanocenes with Electrophiles Other than Aldehydes and Ketones

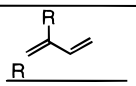
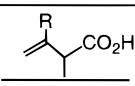
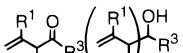
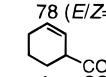
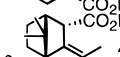
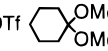
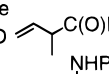
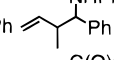
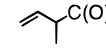
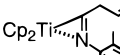
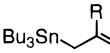
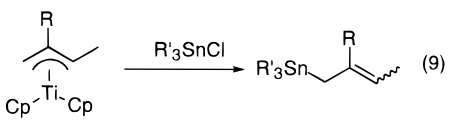
Entry	Diene	Electrophile	Product(s), Yield, %	Ref.
		CO_2		
1	H		82-85	3,5,6,12
2	Me		81-83	12
3	C_9H_{19}		66	12
4	$Me_2C{=}CHCH_2CH_2$		71	12
5			 58	12
				
	R^1 R^2	R^3		
6	H H	Ph	81	15
7	Me H	Me	0 48	15
8		$Me(CH_2)_4$	16 14	15
9		Ph	82 4	15
10		*i*-Pr	75	15
11		$MeO_2C(CH_2)_3$	76	15
12		*trans*-PhCH=CH	0 42	15
13		OMe	73	14
14				
15	CH_2Ph H	Ph	63	15
16	CH_2SiMe_3 H	$MeCH{=}CH_2$	64	15
	$SiEt_2Me$ H	Ph	70	15
17	H Me	Ph	51 (*E*/*Z*=1/1)	15
18	H OMe	OMe	78 (*E*/*Z*=4/6)	14
19		OMe	 77	14
20		OMe	 42	14
				
	L.A. R^1 R^2			
21	$TiCl_4$ Et Me		40	16
22	BF_3-OEt_2		65	16
23	TMSOTf		80	16
24	TMSOTf C_5H_{11} Me		64	16
25	TMSOTf 		60	16
26		PhN=C=O	 90	5,6
27		PhCH=NPh	 70	5,6
28		CH_3CN	 60	5,6
29			 quant.	5,6
		Bu_3SnCl		
30	R = H		70	17
31	Me		71	17
32	*n*-Bu		60	17
33	$PhCH_2$		72	17
34	$SiEt_2Me$		82	17

Table 3. Synthesis of Chiral η^3-Allyltitanocene Derivatives and Their Reaction with Aldehydes and Carbon Dioxide

Entry	Diene	Reagents	Product(s)	Yield %	Ref.
Reactions with CO_2					
1	R = H	+ 2 *i*-PrMgBr	(*S*),18.9% ee	70	3
2	Me		(*R*),11.3% ee	86	3
3	R = C_9H_{19}	+ 2 *i*-PrMgCl	(*S*),28% ee	61	13
4	R = C_9H_{19}	+ 2 *i*-PrMgCl	(*S*),44% ee	65	13
5	R = C_9H_{19}	+ 2 *i*-PrMgCl	(*S*),96% ee	57	13
6	$Me_2C{=}CHCH_2CH_2$		(*S*),94% ee	67	13
Reaction with Aldehydes					
7	C_9H_{19}	+ 2*i*-PrMgCl, then RCHO	R = Ph 71 (97) : 29 (23)	61-87	13
8			Et 76 (96) : 24 (46)	quant.	13
9			*i*-Pr 85 (94) : 15 (13)	quant.	13
10			*t*-Bu 95 (97) : 5 (n.d.)	91	13
11[a]		+ *t*-BuCHO	36 (56% ee):1	83	18

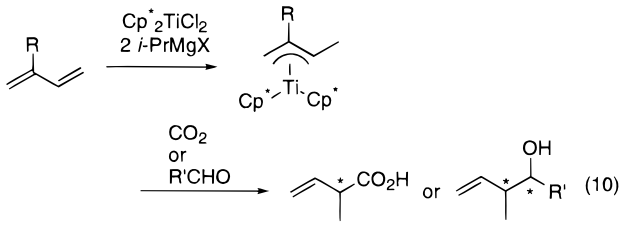
[a] The titanium compound was prepared from crotylMgCl and (EBTHI)Ti-Cl.

tanation of conjugated dienes followed by the reaction with R_3SnCl affords a new convenient method for synthesizing trialkylallylstannanes of the type $R_3SnCH_2C(R){=}CHMe$ as shown in eq 9 (entries 30−34).[17]



(9)

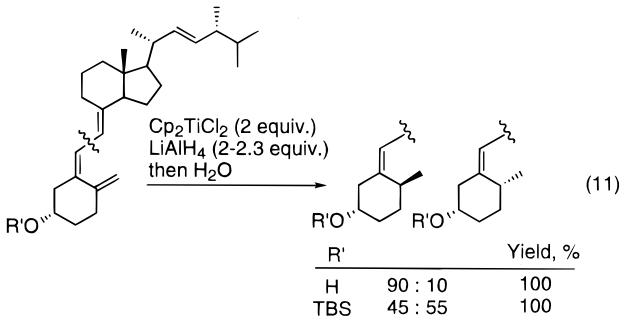
Asymmetric delivery of the allyl group by using optically active η^3-allyltitanocenes, $Cp^*_2Ti(\eta^3\text{-allyl})$, where Cp* stands for an optically active cyclopentadienyl group, has been realized (eq 10), and the results are summarized in Table 3. Thus, the reaction with CO_2 provides optically active 2-methyl-3-butenoic acid and its derivatives. The first report via $(neomenthyl\text{-}Cp)_2Ti(\eta^3\text{-crotyl})$ resulted in rather low



(10)

chiral induction of less than 20% ee (entries 1 and 2);[3] however, the ee reached 96% by using a chiral (*ansa*-bisindenyl)(η^3-allyl)titanium species (entry 5).[13] The (*ansa*-bisindenyl)(η^3-allyl)titanium complex also reacted with aldehydes highly selectively to give optically active homoallyl alcohols (entries 7−10).[12,13] While the major anti diastereomers showed very high ee values irrespective of the aldehydes used, minor syn isomers were always obtained with a low level of ee.

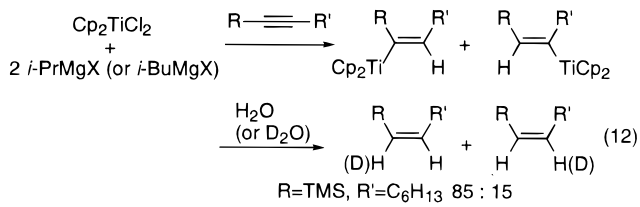
Hydrotitanation of the conjugated triene moiety of vitamin D_2 and its derivatives with the system $Cp_2TiCl_2/LiAlH_4$ or Cp_2TiCl_2/Red-Al and the following hydrolysis was reported to proceed in a regio- and stereoselective way, thus providing a method for synthesizing10,19-dihydrovitamins D_2 as represented by the reaction shown in eq 11.[19]



(11)

2. Synthesis of Organotitanium Complexes through Hydro-, Heteroatom-, and Carbotitanation of Olefins or Acetylenes and Their Reaction

Hydrotitanation of alkynes with Cp_2TiH, generated in situ from Cp_2TiCl_2 and 2 equiv of an alkyl Grignard reagent, afforded alkenyltitanium compounds in essentially quantitative yield, which was confirmed by the quantitative preparation of the corresponding *cis*-olefins after hydrolysis and deuteriolysis (eq 12).[20] It should be noted that the alkenyl

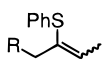
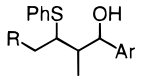
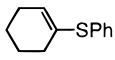
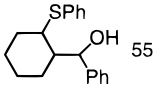
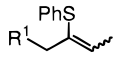
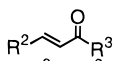
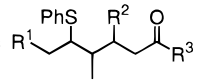


(12)

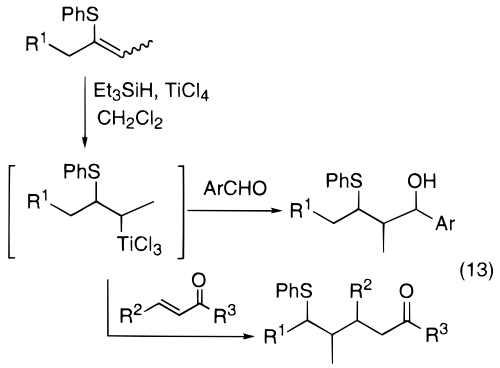
group in the alkenyltitanium compounds thus prepared could not be delivered to aldehydes; instead, their reaction with benzaldehyde gave hydrobenzoin.[21]

The reaction of alkenyl phenyl sulfide with triethylsilane in the presence of titanium tetrachloride gave β-phenylthioalkyltitanium compounds which, in

Table 4. Hydrotitanation of Alkenyl Phenyl Sulfides Using Et_3SiH and $TiCl_4$ and Reaction of the Resulting *β*-Thioalkyltitaniums with Aldehydes and α,*β*-Unsaturated Ketones (Ref 22)

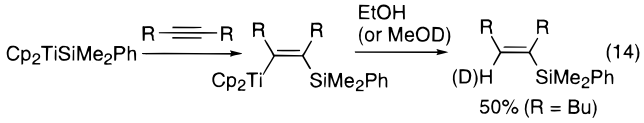
Alkenyl Sulfide	Electrophile	Product(s), Yield, %
		
R = H	PhCHO	77
	p-$MeO_2CC_6H_4CHO$	73
	p-ClC_6H_4CHO	72
R = Me	PhCHO	53
	PhCHO	 55
		
	R^2 R^3	
R^1 = H	Ph Me	76
	H Me	52
	-$(CH_2)_3$-	72
R^1 = Me	Ph Me	70

turn, reacted with aromatic aldehydes via 1,2-addition and with α,*β*-unsaturated ketone via a 1,4-addition pathway (eq 13). Representative results are



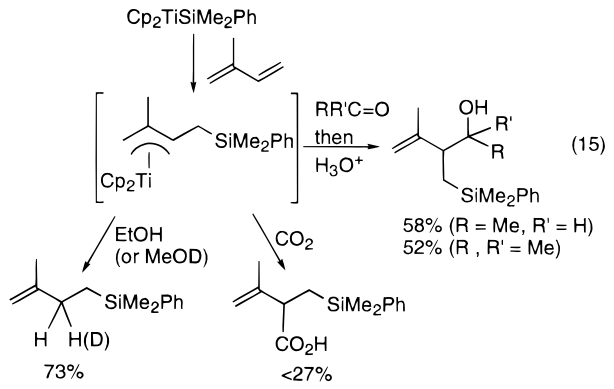
summarized in Table 4.[22] Synthesis of (2,6-diisopropylphenoxy)$_3$TiH−PMe_3 and hydrotitanation of alkynes by this species was reported.[23]

Silyl−titanation of acetylenes with $Cp_2Ti(SiMe_2Ph)$ generated from either Cp_2TiCl_2 and 2 equiv of $PhMe_2SiLi$ or from Cp_2TiCl and 1 equiv of $PhMe_2SiLi$ proceeded with good to excellent regio- and stereoselectivity as represented by the reaction shown in eq 14.[24] Highly selective silyltitanation of 1,3-dienes

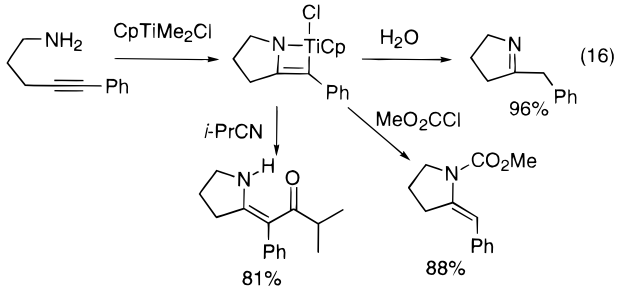


with $Cp_2Ti(SiMe_2Ph)$ and the following reaction of the resulting η^3-allyltitanium complex with electrophiles such as a proton source, carbonyl compounds, and CO_2 as shown in eq 15 has also been reported.[24]

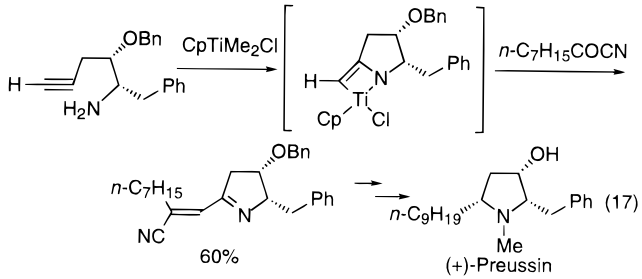
Reaction of pent-4-yn-1-ylamines with a mixture of $CpTiCl_3$ and *i*-Pr_2NEt or $CpTiMe_2Cl$ resulted in intramolecular imidotitanium−alkyne [2+2] cycloaddition to afford azatitanetines, which can be used in



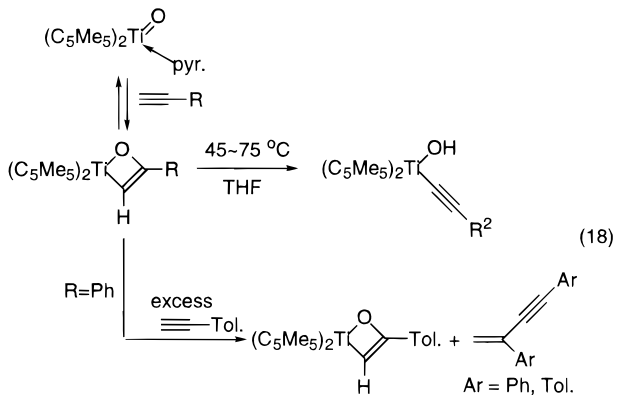
electrophilic reactions leading to selective C or N functionalization as illustrated in eq 16.[25−27] Table 5



summarizes the yield of Δ^1-pyrroline obtained by protonation of the reaction product with H_2O. Synthetic application of this reaction was demonstrated by synthesis of antifungal agent (+)-preussin (eq 17).[27]

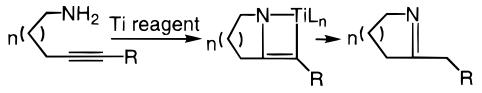


The reaction of a Ti(IV) oxo complex with alkynes shown in eq 18 was reported, but its synthetic utility has not been elucidated.[28]



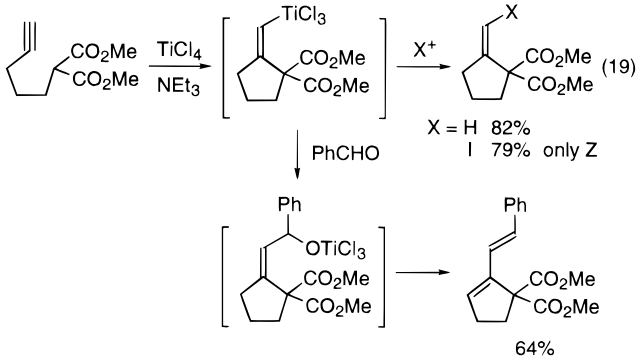
An intramolecular carbotitanation of acetylene with active methylene compounds in the presence of

Table 5. Synthesis of Δ¹-Pyrrolines and Δ¹-Piperidines by the Intramolecular Aza−Titanation Reaction of ω-Aminoalkynes (Ref 25)



Alkynylamine	Reagents	Product(s), Yield, %
R = Ph	cat. $CpTiCl_3$-*i*-Pr_2NEt	94
	$CpTiMe_2Cl$ then MeOH	96
R = *n*-Bu	cat. $CpTiCl_3$-*i*-Pr_2NEt	94
	$CpTiMe_2Cl$ then MeOH	92
R = Ph	cat. $CpTiCl_3$-$PhNMe_2$	88
R = *n*-Bu	cat. $CpTiCl_3$-$PhNMe_2$	89

$TiCl_4$ has been reported (eq 19).[29] The resultant

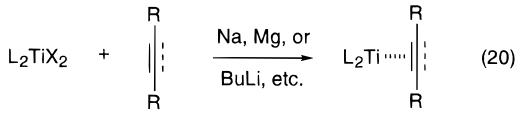


(19)

vinyltitanium species underwent iodinolysis and addition to an aldehyde, the stereochemistry of which revealed that the carbotitanation occurred in a cis fashion across the acetylenic bond.

III. Generation of η²-Alkene-, η²-Alkyne-, and η-Dienetitanium Complexes from These Unsaturated Compounds and Their Utilization as Vicinal Dianionic Species

Synthesis of alkene and alkyne complexes of titanium could be carried out by reduction of Ti(IV) complexes with a reducing agent such as sodium amalgam, magnesium metal, or an organometallic compound in the presence of these unsaturated compounds as shown in eq 20. Some other methods



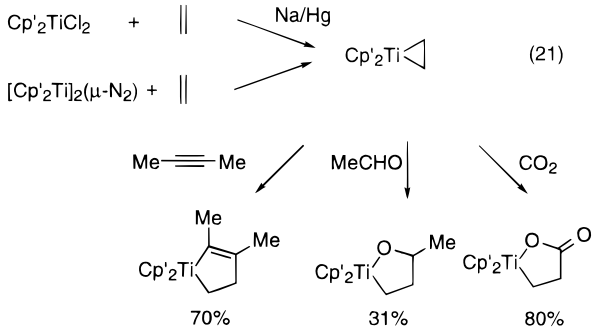
(20)

involving ligand exchange reaction, etc., which will be seen in the following discussion, are also available for the generation of the title titanium complexes.

A suitable choice of the aforementioned methods dependent upon the reactivity and availability of the precursors has enabled the generation of a variety of alkene− or alkyne−titanium complex as discussed in the following sections. Although the research has been pursued from the standpoint of both organometallic chemistry and synthetic organic chemistry, the latter aspect will be focused on in this review.

1. Alkene Complex

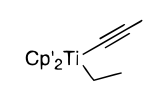
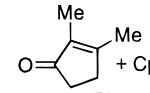
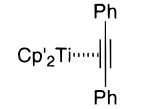
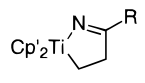
Bercaw et al. reported the preparation of a bis(pentamethylcyclopentadienyl)titanium−ethylene complex by the reduction of Cp'_2TiCl_2 (Cp′: pentamethylcyclopentadienyl) with sodium amalgam in the presence of ethylene or by the ligand exchange reaction of $[Cp'_2Ti]_2(\mu\text{-}N_2)$ with ethylene (eq 21).[30] The



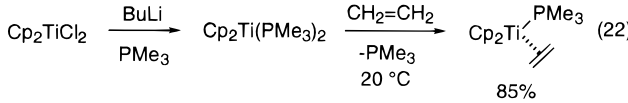
(21)

ethylene complex undergoes coupling reactions with a variety of unsaturated compounds to give the corresponding titanacycles (eq 21).[30−32] Other fundamental reactions of the ethylene complex are summarized in Table 6.[30−33]

Table 6. Reactions of $Cp'_2Ti(CH_2{=}CH_2)$ Complex (Refs 30 and 40)

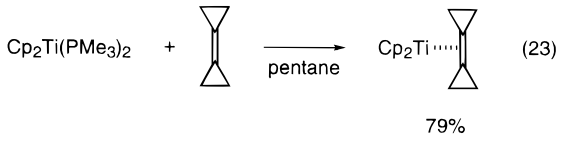
Substrate or Reagent	Product(s) and Yield	
2 H_2	Cp'_2TiH_2 + C_2H_6	
2 HCl	Cp'_2TiCl_2 + C_2H_6	
MeI	$Cp'_2TiI(Me)$ + C_2H_4 90%	
2 MeNC	$Cp'_2Ti(CNMe)_2$ + C_2H_4	quant.
2 CO	$Cp'_2Ti(CO)_2$ + C_2H_4	quant.
t-Bu—≡—H		quant.
Me—≡—Me and then CO	 + $Cp'_2Ti(CO)_2$	quant.
Ph—≡—Ph		
RCN		R = Me 62%; Et 86%; *t*-Bu 56%; *p*-tolyl 28%

Bis(cyclopentadienyl)titanium (Cp_2Ti) complex of ethylene was prepared by the ligand exchange of $Cp_2Ti(PMe_3)_2$ with ethylene (eq 22).[34] The generation of

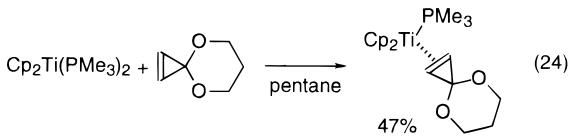


(22)

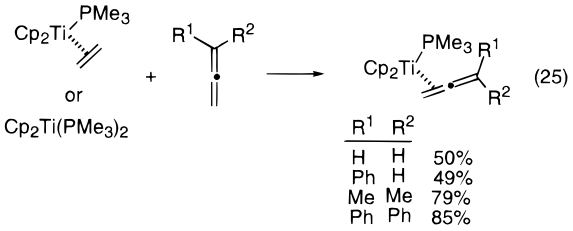
a bis(indenyl)titanium−ethylene complex was also mentioned.[35] It is interesting to note that a unique tetrasubstituted olefin−titanium complex has been generated from bicyclopropylidene (eq 23).[36] Some

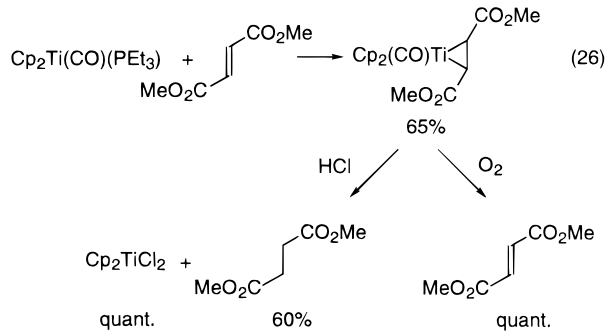


cyclopropene complexes were prepared by the same ligand exchange reaction (eq 24).[37−39]



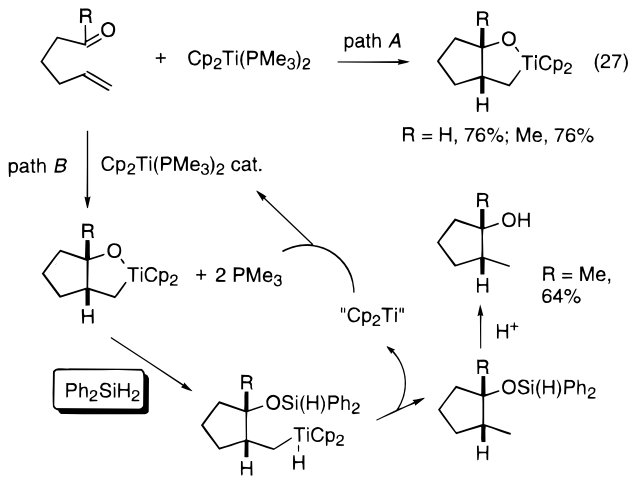
The above phosphine or ethylene complexes of titanium were found to be suitable starting materials for the preparation of some allene complexes as shown in eq 25.[34,40,41] Dimethyl fumarate and $Cp_2Ti(CO)(PEt_3)$ afforded the corresponding olefin complex, which, upon treatment with HCl or dry air, gives rise to the formation of dimethyl succinate or the starting olefin (eq 26).[42]



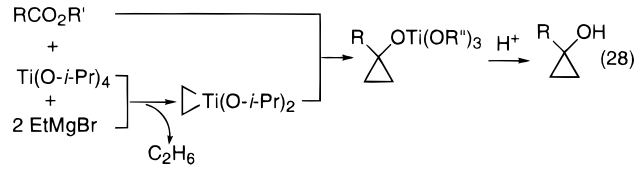


The generation of Cp_2Ti−olefin complex and its trap with a carbonyl compound could be performed in an intramolecular manner (cf. eq 21). Thus, unsaturated ketones and even aldehydes were treated with $Cp_2Ti(PMe_3)_2$ to give the cycloalkanols in good yields as shown in path *A*, eq 27.[43,44] The stoichiometric amount of the titanium reagent in path *A* was successfully decreased to a catalytic quantity by the use of a trialkylsilane as a stoichiometric reductant (path *B*).[45]

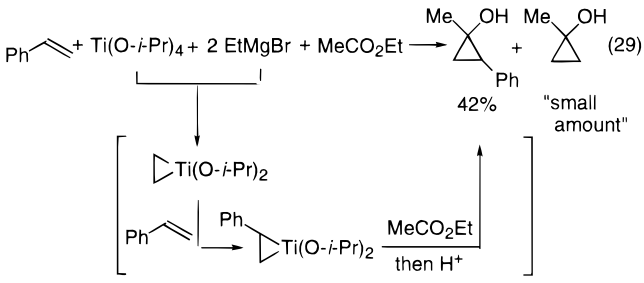
Preparation and reactions of titanium−olefin complexes with a nonmetallocene structure are also known. In 1989, Kulinkovich et al. reported a novel and useful preparation of cyclopropanols, starting



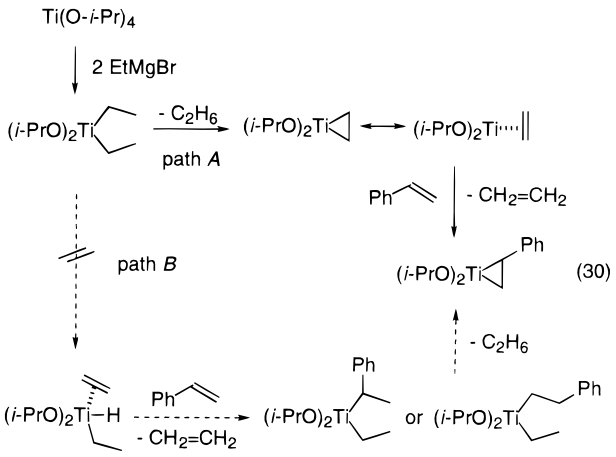
with an ester, $Ti(O\text{-}i\text{-}Pr)_4$, and an ethyl Grignard reagent (eq 28).[46] The reaction most likely involves



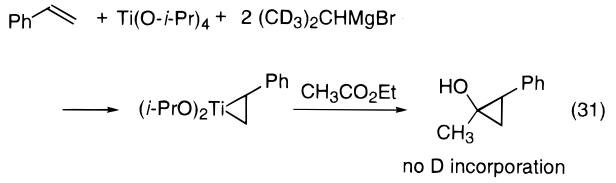
dialkoxytitanacyclopropane as an actual reagent effecting the above transformation. This reaction was soon extended to a catalytic version with respect to the titanium alkoxide[47] and even to an efficient catalytic asymmetric reaction by taking advantage of chiral titanium complexes involving tartarate-derived diols by Corey.[48] The ligand exchange of the titanacyclopropane primarily generated from ethyl Grignard reagent and $Ti(O\text{-}i\text{-}Pr)_4$ with an externally added olefin should provide a convenient way to prepare cyclopropanols from various olefins. This reaction was, in fact, realized by Kulinkovich, who reported that styrene and ethyl acetate in the presence of a catalytic amount of $Ti(O\text{-}i\text{-}Pr)_4$ and EtMgBr according to eq 29 afforded 2-phenyl-1-methylcyclopropanol rather than 1-methylcyclopropanol.[49]



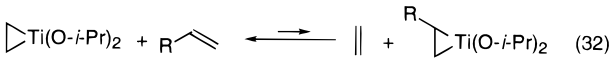
The mechanism of the above olefin exchange reaction most likely proceeds via the ligand displacement as shown in path *A* of eq 30, but another possibility, path *B*, which includes the β-hydride elimination followed by the hydrotitanation of the second olefin, may not be ruled out. However, quite recently, a Kulinkovich report firmly indicated excluding path



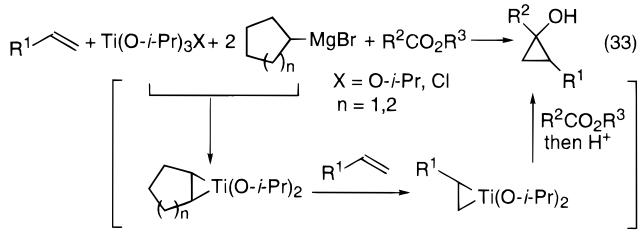
B, using a deuterium-labeled Grignard reagent (eq 31).[50] The D atom in the deuterated isopropyl Grignard reagent was not transferred to the final product, cyclopropanol, thus indicating a hydrotitanation path was definitely not involved.



Although this method established a convenient way to the generation of olefin−titanium alkoxide complexes in situ as shown above, other olefins such as 1-heptene, α-methylstyrene, and ethyl vinyl ether were mentioned as not participating in the reaction.[49] The failure of the reaction with 1-heptene may arise from the unfavorable equilibration to the desired alkene−titanium complex due to steric reasons under these reaction conditions (eq 32).

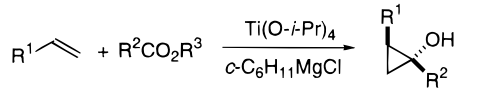


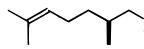
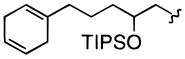
The issue, the selective generation of a terminal olefin−titanium complex, was ingeniously solved by Cha et al., who used a sterically demanding cyclopentyl or cyclohexyl Grignard reagent for this reaction.[51] Thus, an aliphatic terminal alkene is selectively titanated with Ti(O-*i*-Pr)$_4$ (or Ti(O-*i*-Pr)$_3$Cl) and the foregoing Grignard reagent, as the cyclopentene or cyclohexene in the primary olefin complex is easily expelled by the externally added terminal olefin (eq 33). Cyclopropanols prepared from terminal olefins

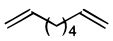
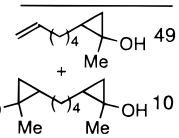
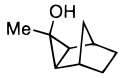
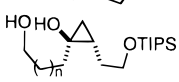


and esters by this method are shown in Table 7.[51]

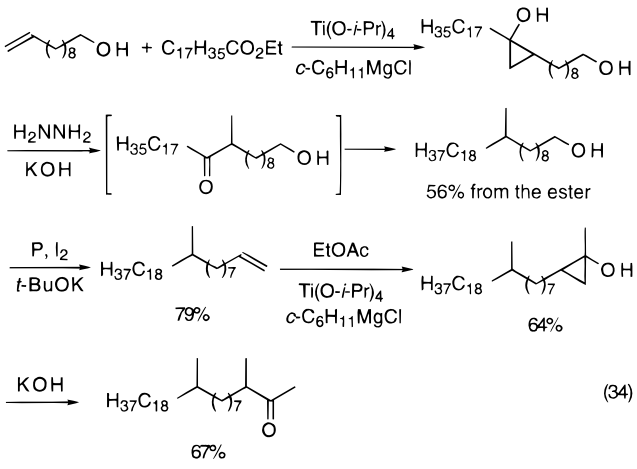
Table 7. Preparation of Cyclopropanols via Coupling Reaction of Alkene−Titanium Complex (Ref 51)



Alkene	Ester		Yield (%)
R^1	R^2	R^3	
Bu	Me	Et	95
Bu	Me_2C=CH-	Me	37
TIPSO$(CH_2)_2$-	$(CH_2)_3$-	Me	64
Br$(CH_2)_3$-	Me	Et	64
	Me	Et	87
	Me	Et	42

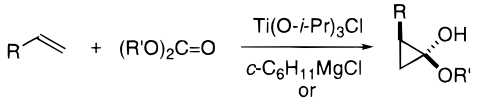
Alkene	Ester	Product(s)	Yield (%)
	$MeCO_2Et$		49
			10
	$MeCO_2Et$		37
TIPSO$(CH_2)_2$-CH=CH_2			n = 1 33 2 52

The repeated application of the above method achieved a synthesis of a sex pheromone of the German cockroach, 3,11-dimethylnonacosan-2-one, from readily available 10-undecen-1-ol as shown in eq 34.[52,53]



Carboxylic acid derivatives other than esters are also viable substrates, which include carbonates (Table 8)[54] and amides (Table 9).[55,56] The reaction of amides should deserve further comment; dialkylcyclopropylamines have previously been prepared from carboxylic acid dialkylamides and (alkene)Ti(O-*i*-Pr)$_2$ intermediates generated from Grignard reagents and Ti(O-*i*-Pr)$_4$ or MeTi(O-*i*-Pr)$_3$ by de Meijere et al.[57,58] The addition of an alkene−titanium complex to

Table 8. Coupling Reaction of Alkene−Titanium Complex with Carbonates (Ref 54)



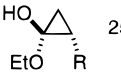
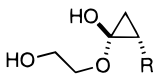
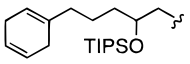
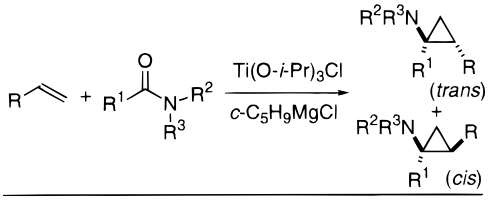
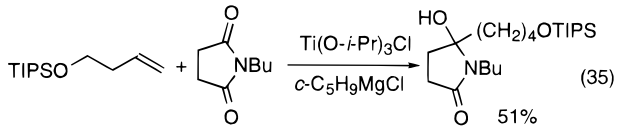
R	(R'O)$_2$C=O	Product	Yield (%)
TIPSO(CH$_2$)$_2$-	(EtO)$_2$C=O		25-30
TIPSO(CH$_2$)$_2$-	ClCO$_2$Et		37
TIPSO(CH$_2$)$_2$-			47
	"		37

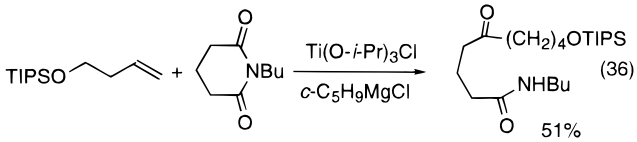
Table 9. Reaction of Olefin−Titanium Complex with Amides (Ref 55 and 56)

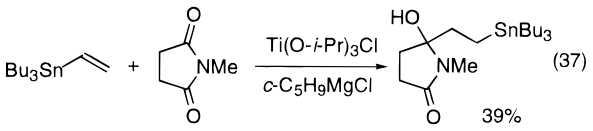


R	R^1	R^2	R^3	Yield (%) (*cis*/*trans*)
TIPSO-(CH$_2$)$_2$-	H	Me	Me	61 (1:2.2)
"	Me	Me	Me	68 (6.3:1)
"	Br(CH$_2$)$_7$	Et	Et	60 (7.6:1)
Me$_3$Si	α-furyl(CH$_2$)$_2$	Et	Et	68 (13:87)
Bu$_3$Sn	α-furyl(CH$_2$)$_2$	Et	Et	68 (*trans*)
"	H	Et	Et	57 (*trans*)
"	*i*-Pr	Et	Et	48 (*trans*)

imides stopped at the stage of single addition (eqs 35,[59] 36,[59] and 37[56]). The reactivity of a wide variety

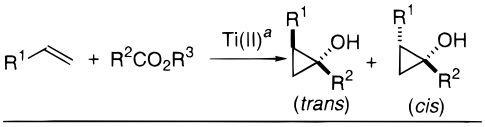






of carbonyl compounds toward the olefin−titanium complex has been compared.[59,60] The analogous ligand exchange between vinylsilane or vinylstannane and the alkene−titanium complex generated from a Grignard reagent and titanium alkoxide was applied to the preparation of silyl- or stannylcyclopropanols from various esters (Table 10).[56,61] The intramolecular version of these reactions, intramolecular nucleophilic acyl substitution (INAS) reaction, is the subject of a later section (section V).

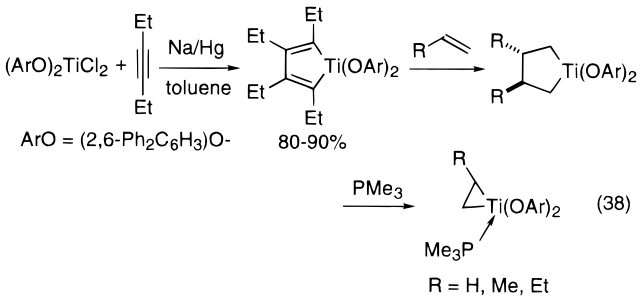
Table 10. Preparation of Silyl- or Stannylcyclopropanols (Ref 56 and 61)



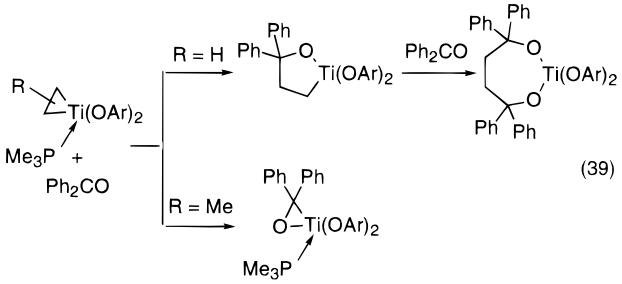
R^1	R^{2}CO$_2$R^3	Ti(II)[a]	Yield, % (*trans*:*cis*)
Me$_3$Si	PhCO$_2$Et	A	88 (93:7)
	Ph(CH$_2$)$_2$CO$_2$Et	A	76 (81:19)
	c-C$_6$H$_{11}$CO$_2$Me	A	62 (81:19)
	t-BuCO$_2$Me	A	82 (7:93)
	CH$_2$=CH(CH$_2$)$_4$CO$_2$Me	A	62 (88:12)
	CH$_2$=CH(CH$_2$)$_8$CO$_2$Me	A	81 (87:13)
	Br(CH$_2$)$_2$CO$_2$Et	A	42 (77:23)
	PhOCH$_2$CO$_2$Me	A	55 (88:12)
Me$_2$ClSi	PhCO$_2$Et	A	62[b] (85:15)
Bu$_3$Sn	α-furyl(CH$_2$)$_2$CO$_2$Me	B	51[c] (*cis*)

[a] A: Ti(O-*i*-Pr)$_4$ and *i*-PrMgCl; B: Ti(O-*i*-Pr)$_3$Cl and *c*-C$_5$H$_9$MgCl. [b] The silyl group in product is (Me$_2$(*i*-PrO)Si). [c] After silylation of hydroxy group.

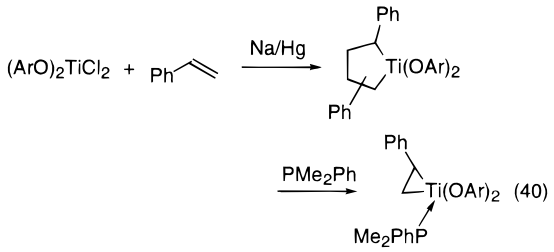
In 1990−91, Rothwell et al. reported that the reduction of (ArO)$_2$TiCl$_2$, where the aryl is a bulky aromatic group, with sodium amalgam in the presence of 3-hexyne afforded the titanacyclopentadiene,[62] which, in turn, gave the titanacyclopentane on treatment with an excess amount of olefin such as ethylene or 1-alkene.[63] The subsequent addition of PMe$_3$ induced the dissociation of the titanacycle to the olefin−titanium complex and the uncomplexed olefin (eq 38).[64,65] The reaction of benzophenone and



the alkene complex shows a different reaction course dependent on the kind of ligating olefin (eq 39).

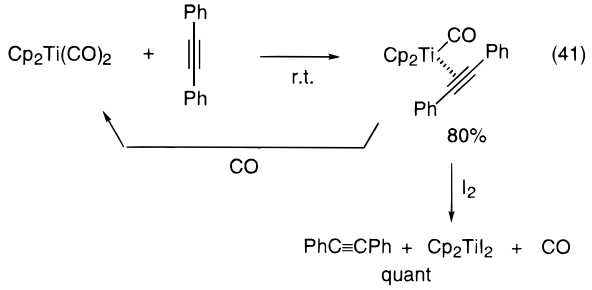


The styrene complex could be prepared in a more straightforward manner via the direct generation of the intermediate titanacyclopentane followed by the same treatment with a phosphine (eq 40).[65]

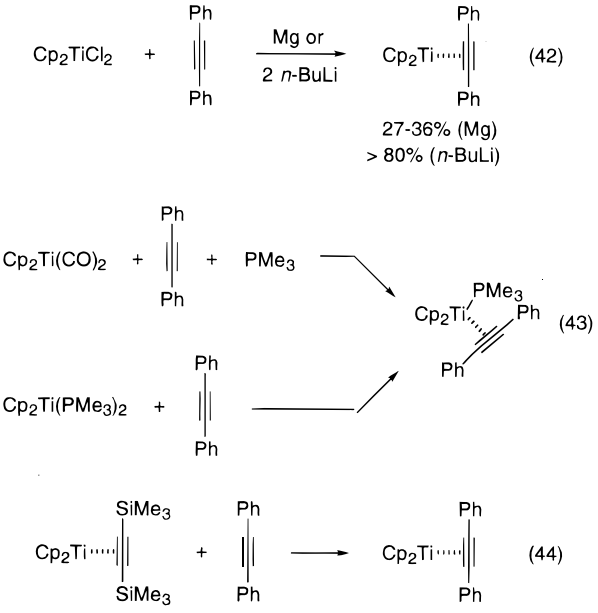


2. Alkyne Complex

In 1974, a Cp_2Ti complex of diphenylacetylene was obtained by the reaction of $Cp_2Ti(CO)_2$ and the acetylene (eq 41), and some of its chemical behavior was also reported.[66,67] Cp_2Ti−diphenylacetylene com-



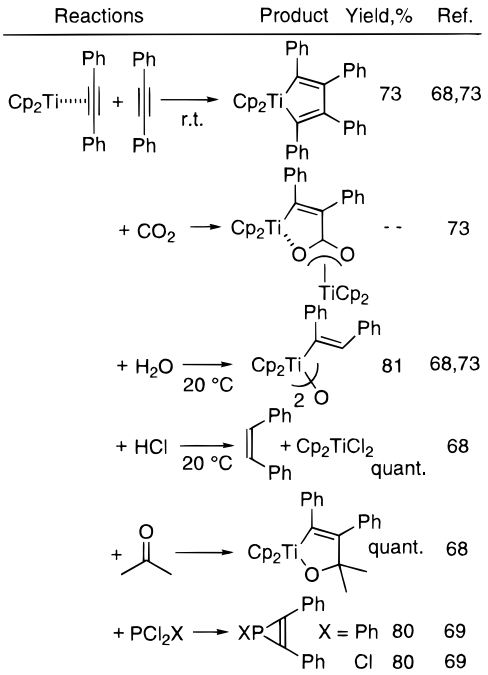
plex itself and the same complex having an additional ligand such as a phosphine were also prepared by several methods, which are summarized in eqs 42,[68,69] 43,[70−72] and 44.[73]



The diphenylacetylene complex undergoes a variety of reactions with electrophiles and unsaturated compounds (Table 11). In addition, preparation of other acetylene−titanocene complexes and their reactions are summarized in Table 12.

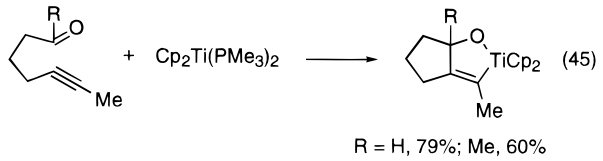
Intramolecular trap of the Cp_2Ti−acetylene complex with aldehyde or ketone, which is a useful method to prepare cyclic compounds and is similar

Table 11. Reaction of $Cp_2Ti(PhC{\equiv}CPh)$ Complex



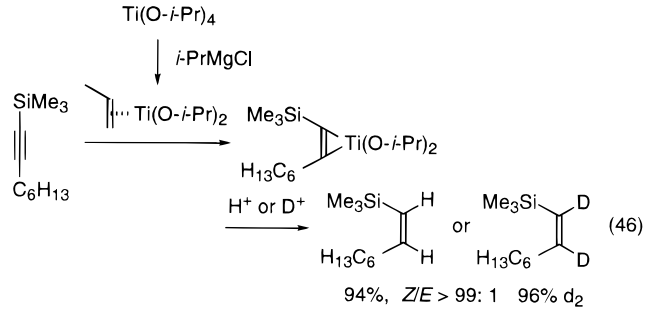
Reactions	Product	Yield,%	Ref.
$Cp_2Ti(PhC{\equiv}CPh)$ + PhC≡CPh, r.t.	Cp_2Ti(2,3,4,5-tetraphenylcyclopentadienyl)	73	68,73
+ CO_2	Cp_2Ti(O,O-carbonate)(TiCp$_2$)	- -	73
+ H_2O, 20 °C	Cp_2Ti(O)$_2$	81	68,73
+ HCl, 20 °C	+ Cp_2TiCl_2	quant.	68
+ acetone	Cp_2Ti(O,O-dimethylcyclopentadienyl)	quant.	68
+ PCl_2X	XP(Ph)(C=CPh)	X = Ph 80; Cl 80	69

to eq 27, is exemplified in eq 45.[43,44] The relevant



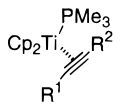
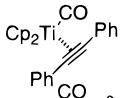
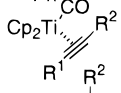
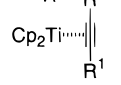
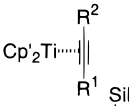
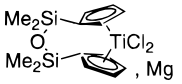
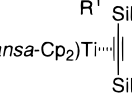
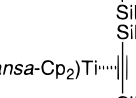
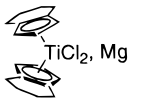
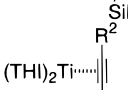
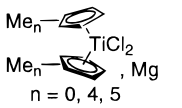
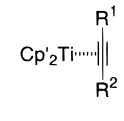
reactions starting with unsaturated esters will be presented in section V.

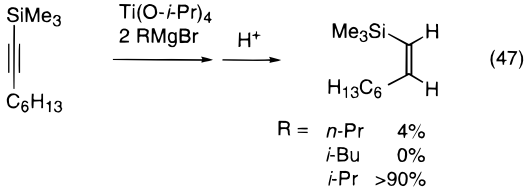
The generation of acetylene−titanium alkoxide complexes was recently reported.[84] The treatment of acetylene with (η^2-propene)Ti(O-*i*-Pr)$_2$ generated in situ from Ti(O-*i*-Pr)$_4$ and *i*-PrMgCl, which has been described above,[46] afforded the alkyne−titanium complex, the presence of which was verified by protonation (to give *cis*-olefin) and deuteriolysis (to give deuterated olefin with high deuterium content) according to eq 46. As far as the Grignard reagent is



concerned, *i*-PrMgCl is superior to other kinds of Grignard reagents (eq 47).[85] Applicability to many types of acetylenes is summarized in Table 13. The acetylenes may incorporate a functional group. Thus, conjugated acetylenic esters and amides afforded the corresponding acetylene complexes, which are shown in entries 11 and 12.[86]

Table 12. Preparation of Various Alkyne−Titanocene Complexes

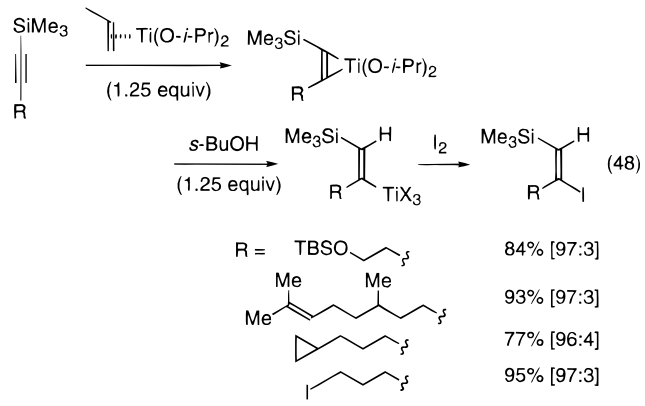
Precursor	Acetylene $R^1{\equiv}R^2$		Complex	Yield (%)	Subsequent reaction with	Ref.
	R^1	R^2				
$Cp_2Ti(PMe_3)_2$	H	H		- -		70,71
					CO_2, Me_2CO, MeCHO, $CH_2{=}CH_2$	75
					ROH, HCl, CF_3CO_2H	76
	Ph	H		- -		70,71
	Ph	Ph		- -		70,71
	Me	Me		85		75
					CO_2, Me_2CO, MeCHO, $CH_2{=}CH_2$	75
					ROH, CF_3CO_2H	76
$Cp_2Ti(CO)_2$	Ph	Ph		80		66,67
$Cp_2Ti(CO)(PEt_3)$	Ph	Ph		91		42
	C_6F_5	C_6F_5		- -		42
Cp_2TiCl_2, Mg	Ph	Ph		- -		68
					HCl, PhC≡CPh, Me_2CO	68
					H_2O	68,74
	Me_3Si	Ph		71		73,77
					PhC≡CSiMe_3, Me_2CO, ROH	74
					CO_2	73,76
	Me_3Si	Me_3Si		51		73
					$Ph_2C{=}NH$	78,79
					ROH	73,74
					PhC≡CPh, CO_2	73
					HC≡CH	80
	Me_3Si	*t*-Bu		53		74
					CO_2	74
	Me_3Si	*n*-Bu		71		74
					$Me_3SiC{\equiv}CBu$, Me_2CO	74
Cp'_2TiCl_2, Mg	Me_3Si	Me_3Si		73		73
	Me_3Si	Ph		75		73,77
 , Mg	Me_3Si	Me_3Si		40		81
 , Mg	Me_3Si	Me_3Si		41		82
 , Mg	Ph	Ph		64		82
					H_2O	82
	Me_3Si	Ph		75		82
	Me_3Si	Me_3Si		- -		82
 , Mg n = 0, 4, 5		$SiMe_3$ or Ph		77-92		83
Cp_2TiCl_2, 2 *n*-BuLi	Ph	Ph		> 95-65		69
	Ph	Me_3Si				
	Me_3Si	Me_3Si				
	Me_3Si	Bu				
	Ph	*t*-Bu				
	Me_3Si	Fc			$PhPCl_2$, PCl_3	69



(47)

R = *n*-Pr 4%
i-Bu 0%
i-Pr >90%

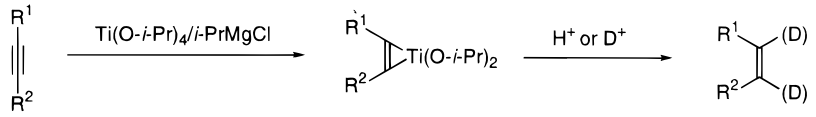
As the reagents necessary for this conversion are very inexpensive, this reaction should be a most convenient method for synthesis of *cis*-dideuterioalkenes from the corresponding alkynes. In addition to the exhaustive protonation, the monoprotonation of (1-silyl-1-alkyne)−titanium complexes proceeds with very high regioselectivity by treatment with a controlled amount of *sec*-BuOH (eq 48).[87] This reaction



(48)

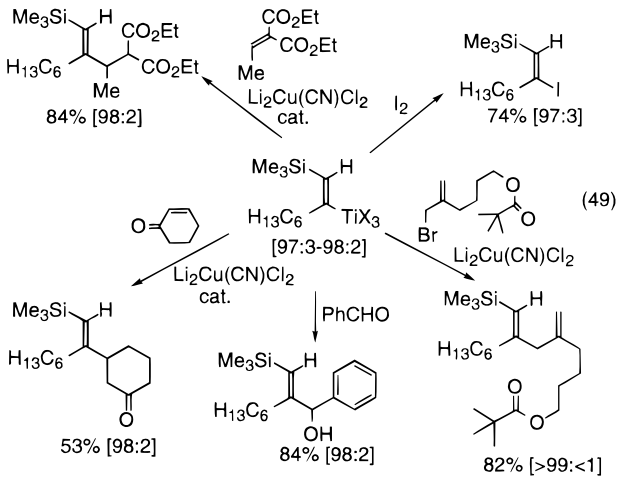
R = TBSO 84% [97:3]
93% [97:3]
77% [96:4]
95% [97:3]

Table 13. Generation and Deuteration of the Acetylene−Titanium Complex

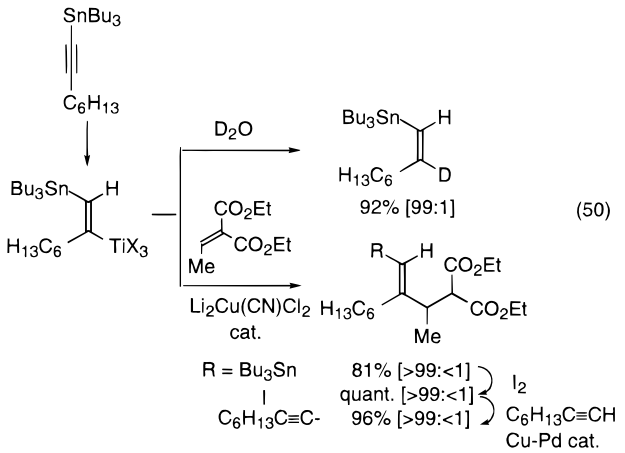


Entry	R^1	R^2	H^+/D^+	Yield, %	*Z*:*E*	Incorporation of D d_2 d_1 d_0	Ref.
1	C_5H_{11}	C_5H_{11}	D^+	81	>99: 1	96 3 1	84
2	C_6H_{13}	Me	D^+	100	>99: 1	100 0 0	84
3	$THPO(CH_2)_3$	$THPO(CH_2)_3$	D^+	81	pure *Z*	exclusively d_2	105,106
4	C_6H_{13}	CH_2OEE	D^+	96	>99: 1	94 6 0	84
5	Ph	Me	D^+	74	>99: 1	>86 - <14 -	84
6	Ph	Ph	D^+	96	99.4: 0.6	>91 - < 9 -	84
7	Me_3Si	C_6H_{13}	D^+	89	>99: 1	96 4 0	84
8	Me_3Si	Me_3Si	D^+	100	>99: 1	100 0 0	84
9	Bu_3Sn	$CH_2CH(OEt)_2$	H^+	70	pure *Z*		88
10	Bu_3Sn	$CH(OEt)_2$	H^+	70	pure *Z*		88
11	C_6H_{13}	CO_2Bu-*t*	D^+	77	pure *Z*	>98	86
12	Me_3Si	$CONEt_2$	D^+	89	pure *Z*	>90	86

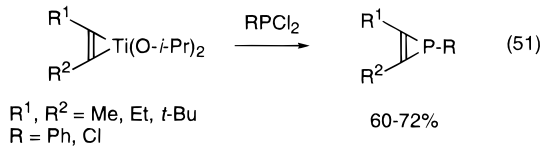
has been established as a convenient formal hydrotitanation of these acetylenes, as the regioselection observed herein is not attainable by the existing hydrometalation reactions, and the resulting alkenyltitanium species undergoes the reaction with a variety of carbon electrophiles shown in eq 49. The



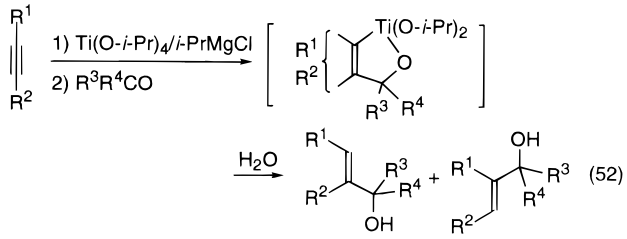
same reaction as well as its application proved possible for 1-stannyl-1-alkynes as shown in eq 50.



The alkyne−titanium alkoxide complex works as a vicinal dianionic species toward a heteroelectrophile. The reaction of the acetylene complex with chlorophosphines represents the synthetic utility of this type (eq 51).[69]



Addition of an (unsymmetrical acetylene)−titanium alkoxide complex to aldehydes or ketones may form two regioisomers (eq 52). However, in the case



of certain acetylenes, a high degree of regiocontrol has been attained. Thus, phenyl alkyl acetylene,[84] silyl-[84] or stannylacetylene,[88] and propargyl alcohol derivatives[89] belong to this class, which is summarized in Tables 14 and 15. The regiochemistry is also affected by the steric hindrance of carbonyl compounds. For example, the tendency that a sterically demanding carbonyl compound shows uniformly high regioselectivity as illustrated by the reaction with silylalkyne−titanium complex was observed

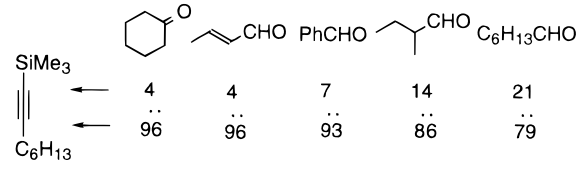
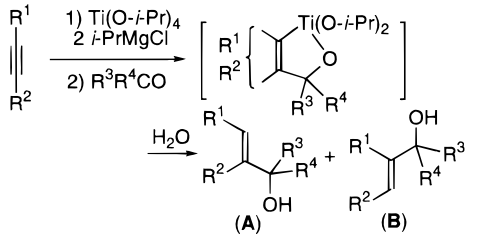


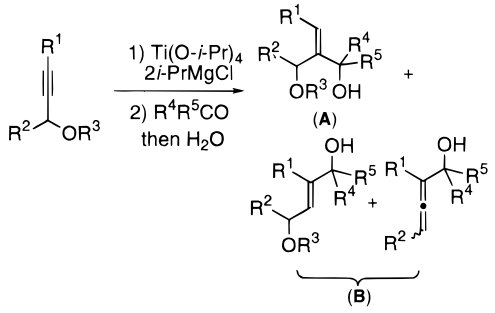
Figure 2.

Table 14. Reaction of Acetylene−Titanium Complex with Carbonyl Compounds (Refs 84 and 88)



R^1	R^2	R^3R^4CO	Yield %	Ratio **A**:**B**
C_5H_{11}	C_5H_{11}	*c*-$C_6H_{11}CHO$	70	- -
Ph	Me	"	90	14:86
Me_3Si	C_6H_{13}	$C_5H_{11}CHO$	79	79:21
		c-$C_6H_{11}CHO$	86	85:15
		MeCH=CH-CHO	72	96: 4
		PhCHO	47	93: 7
		cyclohexanone	84	96: 4
		$MeO_2C(CH_2)_3$-C(O)Me	83	exclusive-ly **A**
Me_3Si	Me_3Si	*c*-$C_6H_{11}CHO$	70	- -
Bu_3Sn	CH_2CH-$(OEt)_2$	PhCHO	40	exclusive-ly **A**
Bu_3Sn	CHMeCH-$(OEt)_2$	$EtC(=CH_2)$-CHO	60	exclusive-ly **A**

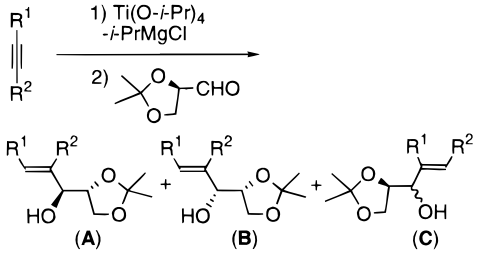
Table 15. Addition of Alkene−Titanium Complex Derived from Propargyl Alcohols to Carbonyl Compounds (Ref 89)



R^1	R^2	R^3	R^4R^5CO	Yield of **A** , %	Ratio **A**:**B**
$SiMe_3$	H	THP	$C_5H_{11}CHO$	78	96: 4
$SiMe_3$	H	THP	PhCHO	78	>98:<2
$SiMe_3$	H	THP	cyclohexanone	82	>98:<2
$SiMe_3$	H	EE	EtCHO	72	>98:<2
$SiMe_3$	H	TBS	EtCHO	71	>98:<2
Bu	H	THP	$C_5H_{11}CHO$	46	79:21
Ph	H	THP	EtCHO	63	80:20
$SiMe_3$	Bu	THP	EtCHO	71	90:10
$SiMe_3$	OEt	Et	EtCHO	64	>98:<2
Me_3SiCH_2	H	THP	$C_5H_{11}CHO$	78	95: 5

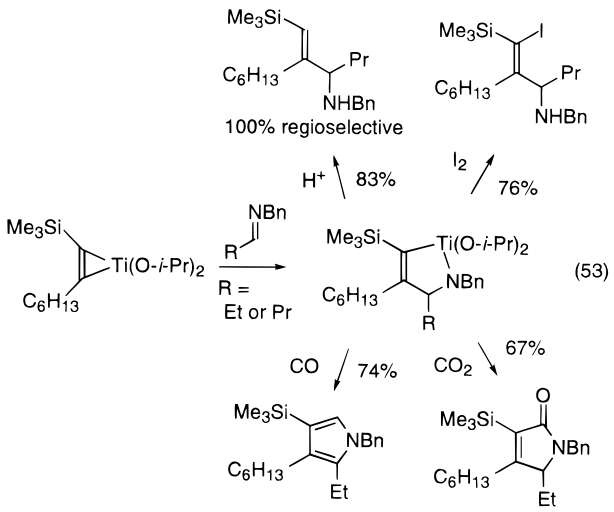
(Figure 2). The diastereoselective addition of the alkyne−titanium complexes to a chiral aldehyde was further investigated, the result of which is summarized in Table 16.[90] The TBS ether of (trimethylsilyl)propargyl alcohol and acetal of glyceraldehyde showed the marginally best result with respect to both regio- and stereoselectivities (entry 4, Table 16). Imines behave like aldehydes, but they showed uniformly higher regioselectivity as compared to

Table 16. Reactions of (η^2-Alkyne)titanium Complexes with (*R*)-2,3-*O*-Isopropylideneglyceraldehyde (Ref 90)



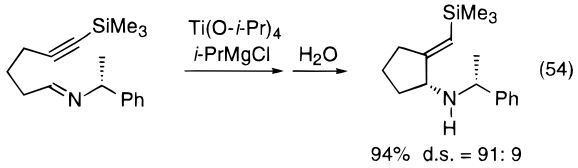
Entry	$R^1C{\equiv}CR^2$ R^1	R^2	Regio-selectivity (**A**+**B**):**C**	D.s. **A**:**B**	Isolated yield % **A**+**B**	**A**
1	C_3H_7	C_3H_7	--	75:25	85	
2	Me_3Si	C_6H_{13}	89:11	72:28	71	
3	"	$BnOCH_2$-	>98:<2	65:35	52	
4	"	$TBSOCH_2$-	>98:<2	94: 6	72	
5	Me_3SiCH_2	"	>98:<2	82:18	70	53
6	Ph	"	78:22	90:10	68	50
7	C_4H_9	"	85:15	80:20	63	48
8	$TBSOCH_2$	"	--	76:24	62	

aldehydes. In most cases, the selectivity reaches 100% as shown in Table 17.[91] The intermediate azatitanacyclopentene was successfully carbonylated[92] or carboxylated[93] to give pyrroles and unsaturated lactams (eq 53).



(53)

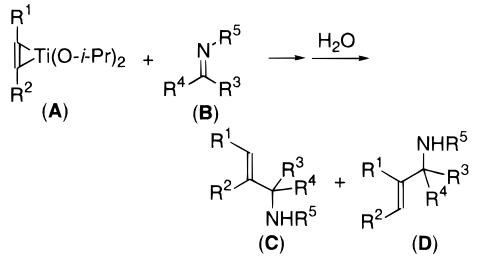
Asymmetric intramolecular addition of the acetylene−titanium complex to chiral imines proved to be feasible, which is represented by eq 54.[94]



(54)

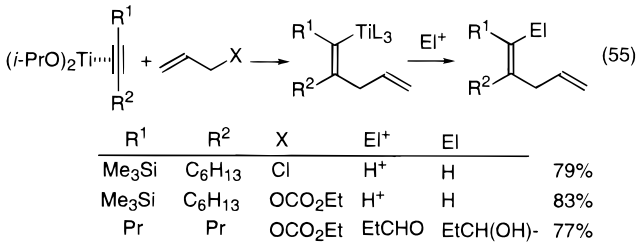
The acetylene complexes undergo coupling reaction

Table 17. Reaction of Titanium-Acetylene Complex with Imine (Ref 91)



A		B			Yield %	C:D
R^1	R^2	R^3	R^4	R^5		
Pr	Pr	Pr	H	CH_2Ph	75	--
Ph	Ph	"	"	"	82	--
Ph	Me	"	"	"	71	60:40
Me_3Si	Ph	"	"	"	72	100:0
Me_3Si	C_6H_{13}	"	"	"	83	"
Me_3Si	C_6H_{13}	"	"	Pr	90	"
"	"	c-C_6H_{11}	"	Ph	94	"
"	"	Ph	H	NMe_2	92	"
"	"	Et	Me	Li	75	"
"	"	Ph	"	"	68	"

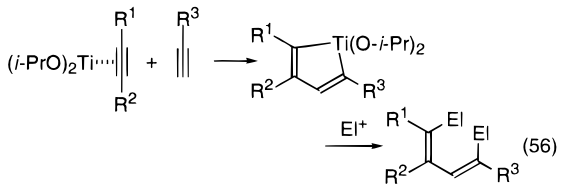
with olefins having an allylic leaving group as shown in eq 55.[95–97] Acetylenes are also an appropriate



R^1	R^2	X	El^+	El	
Me_3Si	C_6H_{13}	Cl	H^+	H	79%
Me_3Si	C_6H_{13}	OCO_2Et	H^+	H	83%
Pr	Pr	OCO_2Et	EtCHO	EtCH(OH)-	77%

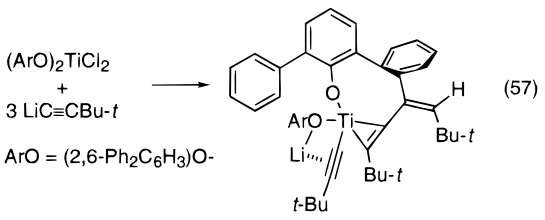
(55)

partner of the coupling reaction (eq 56),[86] which is the subject of section VI.



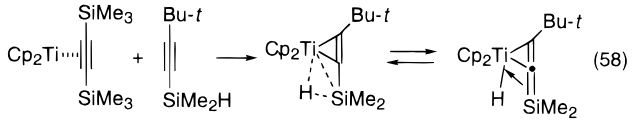
(56)

Some alkyne complexes of an unusual structure have been reported. Addition of a lithium acetylide to titanium aryloxide afforded the complex shown in eq 57 most likely via proximal C−H activation with the titanium center.[98] Activation of a Si−H bond was



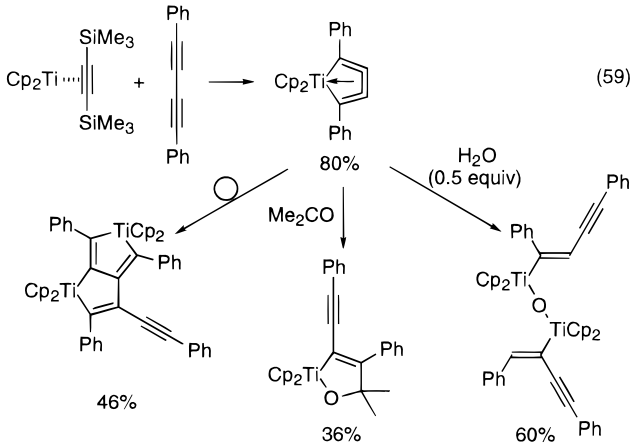
(57)

also reported as shown in eq 58.[99]



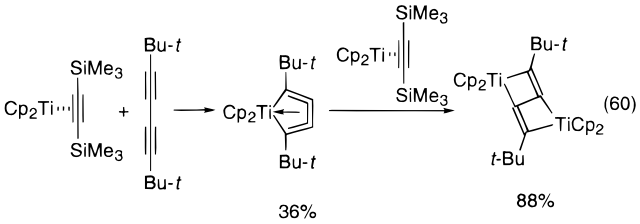
(58)

Diynes and poly-ynes are known to produce mono- to per-titanated compounds on treatment with disilylacetylene−titanium complex dependent on the molar ratio. Thus, the action of 1 equiv of disilylacetylene−titanium complex to diphenylbutadiyne produced the 1:1 complex, which undergoes the dimerization or the reaction with electrophiles as shown in eq 59.[100,101] When disilylacetylene−titanium



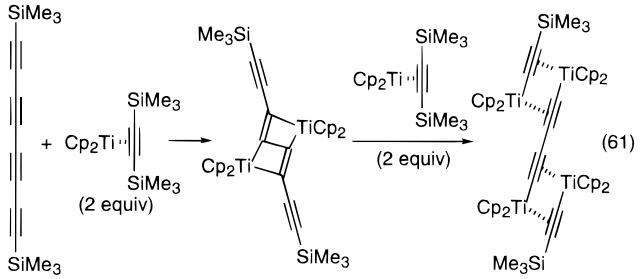
(59)

complex was added in double quantity to a diyne, the bis-titanated diyne was formed (eq 60).[102] It is



(60)

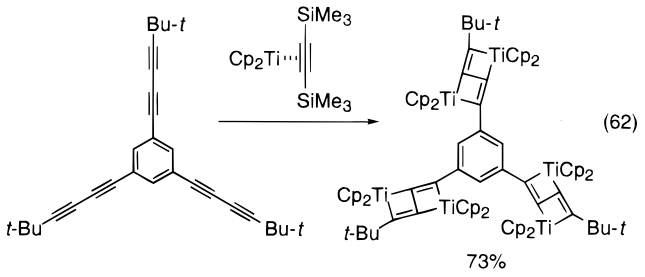
interesting to note that the tetrayne in eq 61 could be titanated with 2 or 4 equiv of the titanium reagent, and eventually, the terminal acetylene−acetylene bond was cleaved.[103] Analogous per-titanated hexayne



(61)

was reported as shown in eq 62.[104]

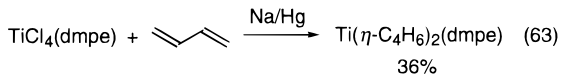
Similarly, the treatment of diynes with more than 2 equiv of (η^2-propene)Ti(O-i-Pr)$_2$ as shown in the reaction of eq 60 generated a bis-acetylene−titanium complex, which, upon hydrolysis or deuteriolysis,

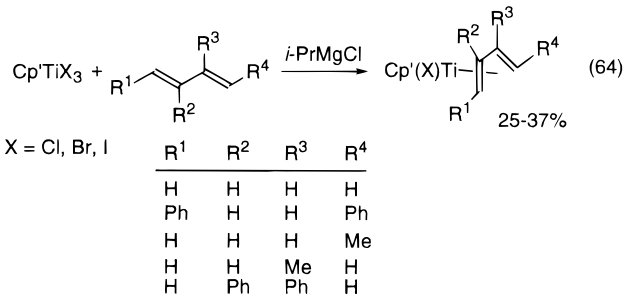


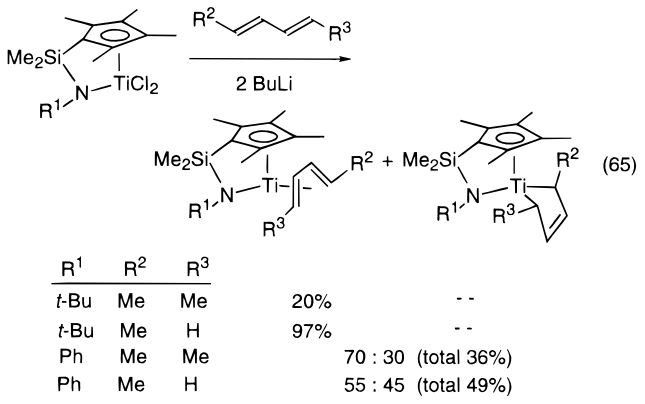
stereoselectively afforded the *cis,cis*-dienes (Table 18).[105,106] As the reaction is not restricted to conjugated acetylenes, some additional examples of the preparation of skip-type, nonconjugated poly-enes are also shown.[105,106]

3. Diene Complex

Diene complexes of titanium[1n] could be prepared according to the method of eq 20. Thus, the reduction of an appropriate titanium(IV) compound with sodium amalgam or an organometallic reagent in the presence of a butadiene afforded the titanium complex (eqs 63,[107] 64,[108] and 65[109]). Generation of a

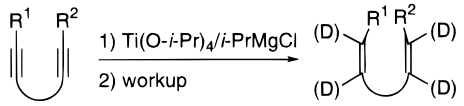






diene−titanium alkoxide complex in conjunction with diene polymerization by a titanium alkoxide was mentioned.[108] The synthetic utility of the diene−titanium alkoxide complex could be seen in the synthesis of (vinylcyclopropyl)amines from dienes and *N,N*-dibenzylformamide via the protocol described in eq 29. The overall transformation is shown

Table 18. *cis*-Hydrogenation of Dienes or Triynes via Its Titanium Complex (Refs 105 and 106)



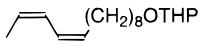
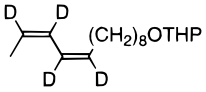
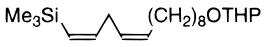
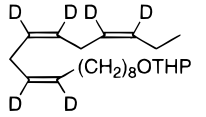
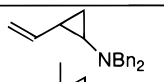
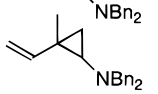
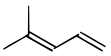
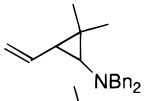
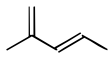
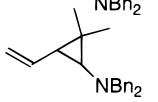
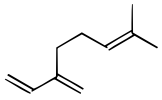
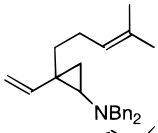
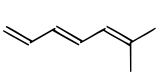
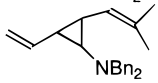
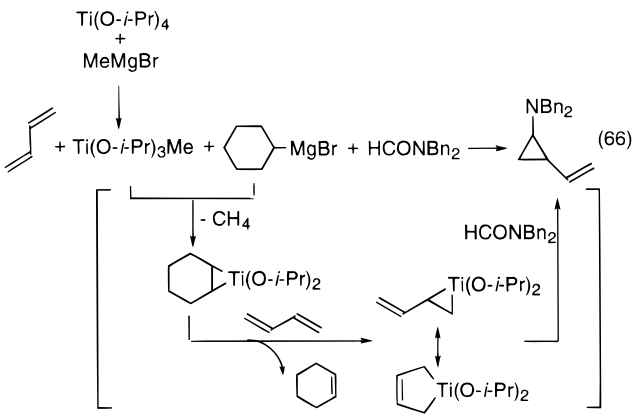
Workup	Product	Yield (%)
H^+		55-60
D^+		46
H^+		53
D^+		33

Table 19. Generation of Diene−Titanium Alkoxide Complex and Its Reaction with $HCONBn_2$ (Ref 110)

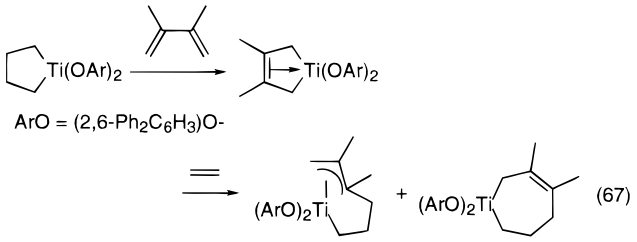
Diene	Product	Yield (%)	*Cis/trans*
		56	1:2.7
		59	>98:2
		56	1:5.3
		27	1:3
		51	>98:2
		54	1:1.5:1.5

in eq 66,[110] and the results are summarized in Table 19.

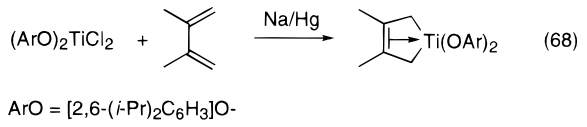


Rothwell reported that the treatment of titanacyclopentane having bulky aryloxy groups with a conjugated diene such as 2,3-dimethylbutadiene af-

fords a diene−titanium complex (eq 67).[111] Exposure



of this diene complex to ethylene generated new titanacycles having an η^3-allyl- or η^1-allyltitanium moiety.[111] Alternatively, a diene complex of the same kind was directly obtained by the sodium amalgam reduction of the dichlorotitanium aryloxide in the presence of a diene (eq 68).[112]



IV. Direct Synthesis of σ-Allyl-, Propargyl-, and Allenyltitanium(IV) Complexes from Carbon–Carbon Unsaturated Organic Compounds

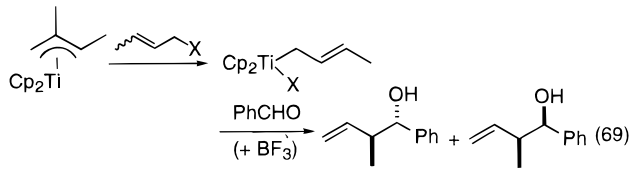
1. Synthesis of (σ-Allyl)titanium(IV) Complexes and Their Reaction with Electrophiles

Allyltitanium complexes have attracted considerable interest as allylating reagents because of their advantages in comparison to other allylmetal compounds in terms of chemo-, regio-, diastereo-, and enantioselectivity.[1p,r,u,v] As mentioned in section II.1, η^3-allyltitanium(III) complexes of the type $Cp_2Ti(\eta^3$-allyl) are synthesized directly from conjugated dienes via hydrotitanation reaction by Cp_2TiH and have been utilized in organic synthesis. η^1-Allyltitanium(IV) complexes (σ-allyltitanium complexes) have also received widespread acceptance as a selective allylating reagent owing to the extensive work done by the Reetz and Seebach groups.[113]

The σ-allyltitaniums can be prepared either by the transmetalation of the allyl moiety of allyl organometallics such as organo lithium, magnesium, and zinc reagents to titanium or directly by the reaction of titanium complexes with unsaturated organic molecules; this section focuses on the synthesis of σ-allyltitaniums according to the latter method and their synthetic applications.

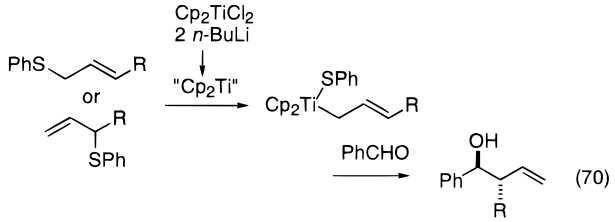
1.1. σ-Allyltitanium Complexes of the Type $Cp_2Ti(\eta^1$-Allyl)X

In 1981, Sato et al. reported the first preparation of σ-allyltitaniums through a method other than the transmetalation reaction. Thus, $Cp_2Ti(\eta^3$-allyl) prepared from 1,3-pentadiene or isoprene, Cp_2TiCl_2, and 2 equiv of *i*-PrMgBr was shown to react with but-2-enyl halides to provide $Cp_2TiX(CH_2CH{=}CHMe)$, where X represents a halogen atom, in essentially quantitative yield and which, in turn, reacts with aldehydes in a diastereoselective way (eq 69).[114] It should be noted that the kind of halogen atom (X) attached to the titanium strongly affects the diastereoselectivity, and complete anti selectivity is attained when X is Br (entry 2 in eq 69).[114] The diastereochemistry can be reversed from anti to syn by carrying out the reaction in the presence of $BF_3{-}OEt_2$ (entries 4−6).[115]



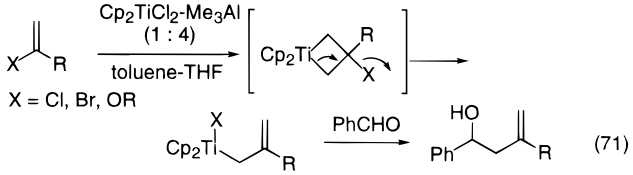
Entry	X	Additive	*anti* : *syn*	Yield, %
1	Cl	-	60 : 40	96
2	Br	-	100 : 0	92
3	I	-	94 : 6	96
4	Cl	BF_3	14 : 86	98
5	Br	BF_3	14 : 86	90
6	I	BF_3	24 : 76	90

Takeda and co-workers reported that the treatment of allyl sulfides with a low-valent organotitanium reagent, prepared by the reaction of Cp_2TiCl_2 and 2 equiv of *n*-BuLi, provides σ-allyltitanocenes of the type $Cp_2Ti(allyl)(SPh)$ which, in turn, react with aldehydes to give the homoallyl alcohols having an anti stereochemistry highly predominantly and in good yields (eq 70).[116]



R	*anti* : *syn*	Yield, %
Me	97:3	60-86
n-Bu	100:0	70
i-Bu	100:0	73
Bn	100:0	74

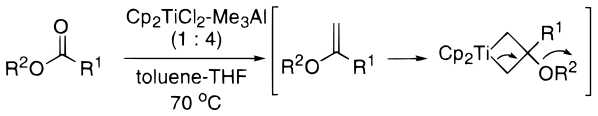
Hanzawa and Taguchi reported that the reagent prepared in advance by stirring a 1:4 mixture of Cp_2TiCl_2 and Me_3Al in toluene for 3 days reacts with vinyl halides or vinyl ethers to afford σ-allyltitanium complexes depicted in eq 71, which then react with aldehydes and ketones to give the corresponding homoallylic alcohols in moderate to good yields.[117,118]



R	X	yield, %
H	Br	47
Ph	Cl	50
Me	Cl	58
Me	Br	60
c-$C_6H_{11}CH_2$	Cl	60
Ph	OMe	41

The postulated mechanism for the preparation of the allyltitaniums involves the formation of a titanacy-

clobutane intermediate and the following β-elimination as shown in eq 71. A $Cp_2TiCl_2/4AlMe_3$ reagent also allows the direct conversion of carboxylic esters to allyl titanocenes (eq 72). Thus, the reaction of



(72)

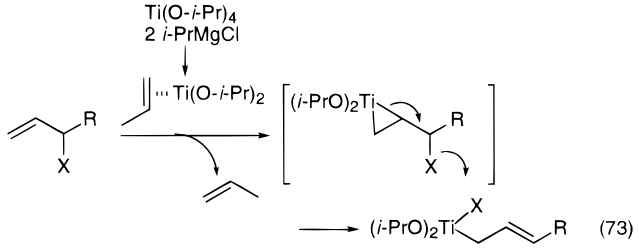
R^1	R^2	Yield, %
Ph	Ph	15
Ph	CH_2CF_3	34
Ph	Me	41
Me	Bn	36
$MeO(CH_2)_2$	Me	36

esters with 3 equiv of $Cp_2TiCl_2-AlMe_3$ (1:4) afforded vinyl ether compounds in situ by the Tebbe methylenation reaction and then followed by the reaction shown in eq 71.[118]

Although these direct preparations of σ-allyltitanium complexes are interesting from a mechanistic point of view, their feasibility for synthesizing a variety of allyltitaniums, including those having a functional group which are not accessible by the transmetalation method, is not clear, and in addition, the use of a titanium compound having cyclopentadienyl ligands, which is relatively expensive and often necessitates a tedious process for separation of the product, may be a disadvantage from a synthetic viewpoint.

1.2. σ-Allyltitanium Complexes of the Type (η^1-Allyl)TiX_3 from Allyl Alcohol Derivatives and a Ti(O-i-Pr)$_4$/2i-PrMgCl Reagent

In 1995, Sato and co-workers reported that a divalent titanium reagent (η^2-propene)Ti(O-*i*-Pr)$_2$, generated in situ from Ti(O-*i*-Pr)$_4$ and 2 equiv of *i*-PrMgCl (eq 46), reacts with allylic alcohol derivatives such as halide, acetate, carbonate, phosphate, sulfonate, and aryl ether through a ligand exchange reaction and the following β-elimination reaction to furnish allylic titanium compounds of the type (η^1-allyl)Ti(O-*i*-Pr)$_2$X[113] in excellent yields as shown in eq 73.[119,120] The reaction, thus, opens up a direct and

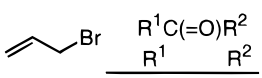
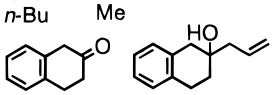
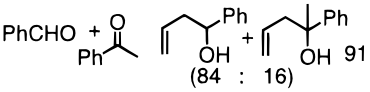
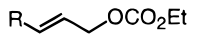
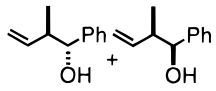
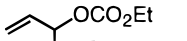
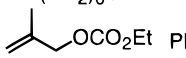
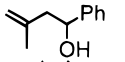
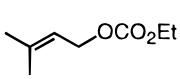
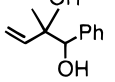
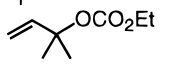
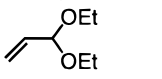
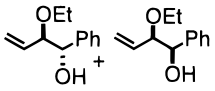
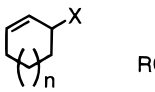
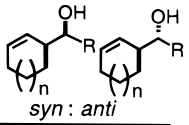
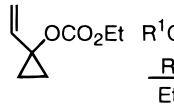
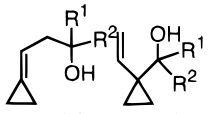
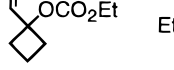
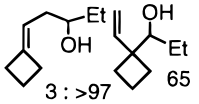


(73)

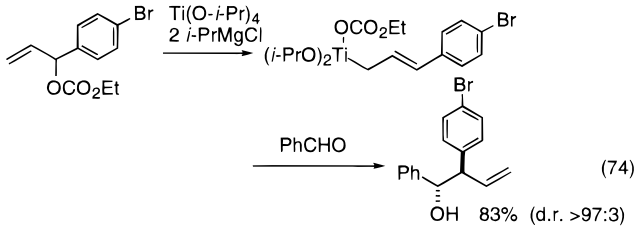
X = Cl, Br, OAc, OCO_2Et, $OP(O)(OEt)_2$, OTs, OPh

convenient entry to σ-allyltitanium compounds which do not contain a cyclopentadienyl ligand. The results of the reaction of allyltitaniums thus prepared with carbonyl compounds are summarized in Table 20.[119,121,122] This direct method for the preparation of allyltitanium compounds has the following advantages from a synthetic viewpoint. The synthesis can be carried

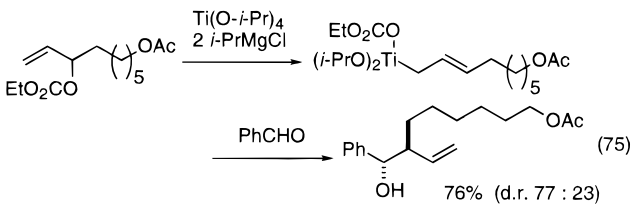
Table 20. Preparation of σ-Allyltitaniums from Allyl Alcohol Derivatives and a Ti(O-i-Pr)$_4$/2*i*-PrMgCl Reagent and Their Reaction with Carbonyl Compounds

Entry	Allylic Compound	Carbonyl Compound(s)	Product(s) Yield, %	Ref.
		$R^1C(=O)R^2$		
		R^1 R^2		
1		Ph H	94	119
2		*m*-Br-C_6H_4 H	80	119
3		*p*-$MeO_2CC_6H_4$ H	77	119
4		*n*-C_5H_{11} H	87	119
5		(*E*)-PhCH=CH H	88	119
6		Ph Me	85	119
7		*n*-Bu Me	82	119
8			92	119
9			91 (84 : 16)	119
				
10	R = Me	PhCHO	(75:25)	50 119
11	R = Ph	PhCHO	(>97:3)	23 119
				
12	R = Me	PhCHO	(75:25)	74 119
13	R = Ph	PhCHO	(>97: 3)	73 119
14	R = *p*-BrC_6H_4	PhCHO	(>97:3)	83 119
15	R = $(CH_2)_6OAc$	PhCHO	(77:23)	76 119
16		PhCHO		45 119
17				12 119
18				56 119
19			 (69 : 31)	93 127
		RCHO		
	n X		*syn* : *anti*	
20	1 Br	EtCHO	n.d.	3 121
21	1 OCO_2Et	EtCHO	64: 36	26 121
22	2 Br	EtCHO	84:16	14 121
23	2 OCO_2Et	EtCHO	80:20	71 121
24	3 Br	EtCHO	95:5	85 121
25	3 Br	PhCHO	97:3	93 121
26	3 OCO_2Et	EtCHO	95:5	83 121
27	4 OCO_2Et	EtCHO	90:10	98 121
28	7 OCO_2Et	EtCHO	stereo-mixture	70 121
		$R^1C(=O)R^2$		
		R^1 R^2		
29		Et H	94 : 6	76 122
30		Ph H	80 : 20	84 122
31		Me Me	>97 : 3	40 122
32		Et H	 3 : >97	65 122

out starting with readily available allylic alcohol derivatives and an inexpensive titanium alkoxide Ti(O-*i*-Pr)$_4$, and the method allows the preparation of σ-allyltitaniums having a functional group such as ester and halide as illustrated in eqs 74 and 75 (entries 14 and 15 in Table 20). The reaction with

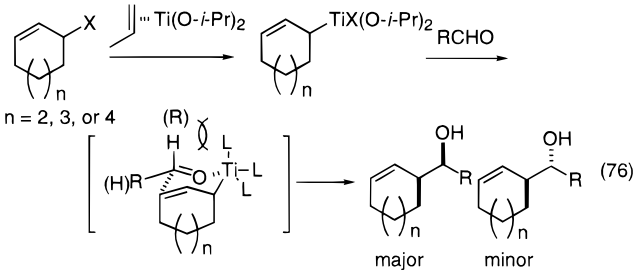


(74)



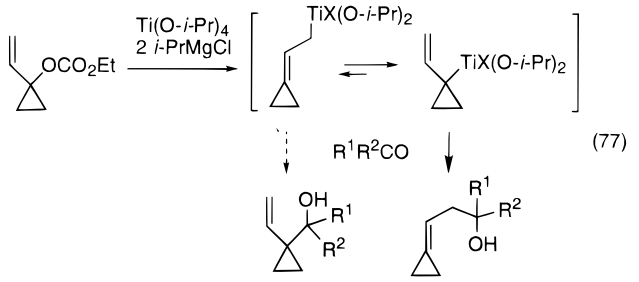
(75)

seven-, eight-, and nine-membered cyclic allylic halides or carbonates affords the corresponding cyclic allyltitaniums which, in turn, react with aldehydes selectively, thus providing a stereoselective method for synthesizing medium-ring carbocycles having a side chain at the allylic position (eq 76, entries 20−28).[121] The allylic titanium compound prepared from



(76)

(η^2-propene)Ti(O-*i*-Pr)$_2$ and 1-vinylcyclopropyl carbonate reacts with aldehydes or ketones highly selectively at the less substituted carbon but not at the more substituted one (eq 77, entries 29−31), the latter of which is the position usually observed for the addition reaction of substituted allyltitaniums.[122]



(77)

Thus, the reaction provides a convenient access to alkylidenecyclopropane derivatives from readily available 1-vinylcyclopropanol. This unusual regiochemistry might be explained by the assumption that the allyltitanium compound exists mostly as the tertiary

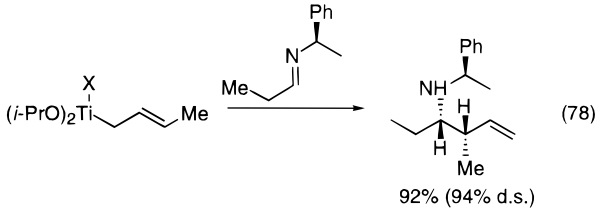
Table 21. Reaction of σ-Allyltitaniums of the Type $X_3Ti(\eta^1$-Allyl) with Imines (Ref 123)

Entry	Allylic Compound	Imine	Product(s) D.s.	Yield, %
1		Et	95 : 5	88
2		*i*-Pr	96 : 4	87
3		*i*-Pr	96 : 4	80
4		*i*-Pr	96 : 4	78
5		*i*-Pr	94 : 6	87
6			94 : 6	92
7		*i*-Pr	92 : 8	83
8[a]		Et	95 : 5	72

[a] See ref 121.

alkyl titanium species but not as the primary alkyl regioisomer in order to avoid the highly strained alkylidenecyclopropane structure as shown in eq 77.

The allyltitanium compounds thus obtained also react with imines to furnish homoallylic amines in good yield as summarized in Table 21. Especially noteworthy is the fact that the reaction of allyltitaniums with chiral imines prepared from aldehydes and optically active 1-phenylethylamine proceeds with excellent diastereoselectivity, thus furnishing a new method for synthesizing optically active homoallylic amines.[123] For example, as exemplified in eq 78, the crotyltitanium compound generated in situ from (η^2-propene)Ti(O-*i*-Pr)$_2$ and crotyl carbonate reacts with the chiral imines to provide the Cram−*syn* addition products highly predominantly. The

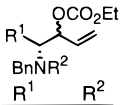
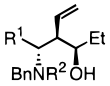
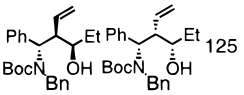
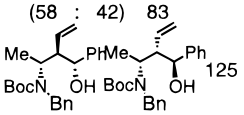
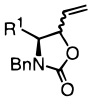
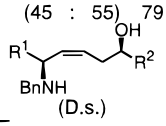
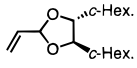
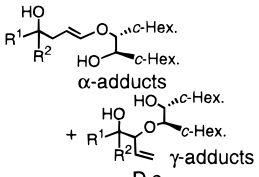
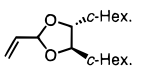
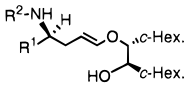


(78)

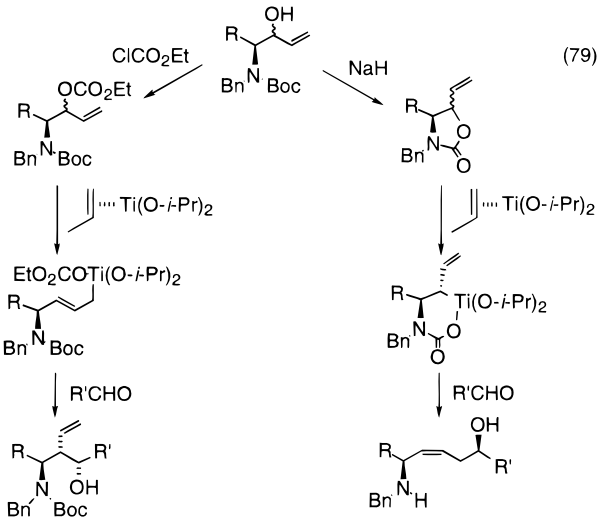
products thus obtained were used for the synthesis of optically active polysubstiuted pyrrolidines.[124]

The reaction also allows the synthesis of chiral allyltitaniums having a stereogenic center(s) in the allyl moiety. Table 22 summarizes the preparation of chiral allyltitanium compounds and their reaction with carbonyl compounds and imines. As shown in eq 79 and entries 1−11 in the table, chiral allyltitaniums having an amino substituent at the stereogenic center were prepared from optically active 4-aminoalk-1-en-3-ol derivatives, which were shown

Table 22. Generation of Chiral σ-Allyltitaniums and Their Reaction with Carbonyl Compounds and Imines

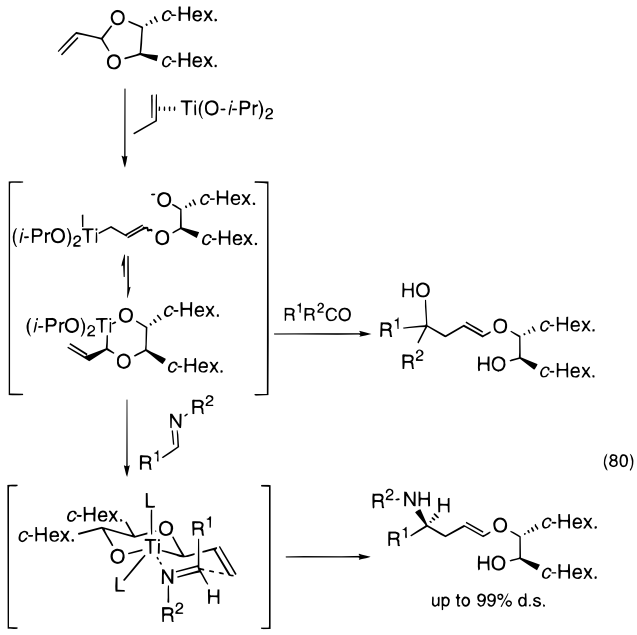
Entry	Allylic Compound	Electrophile	Product(s) (Selectivity) Yield, %		Ref.
					
	R^1 R^2		(D.s.)		
1	Me Bn	EtCHO	(92 : 8)	88	125
2	Me Boc	EtCHO	(91 : 9)	88	125
3	*n*-Pr Boc	EtCHO	(91 : 9)	89	125
4	Ph Boc	EtCHO	 (58 : 42)	83	125
5	Me Boc	PhCHO	 (45 : 55)	79	125
					
		R^2CHO	(D.s.)		
6	R^1 = Me	*n*-PrCHO	(5 : 1)	81	126
7	*n*-Pr	EtCHO	(14 : 1)	79	126
8	CH_2OTBS	MeCHO	(14 : 1)	83	126
9	CH_2OTBS	EtCHO	(18 : 1)	82	126
10	CH_2OTBS	PhCHO	(20 : 1)	79	126
11	CH_2OTBS	MeCH=CH-CHO	(11 : 1)	81	126
					
			α-adducts + γ-adducts		
			α (*E*/*Z*) : γ	D.s. (α-)	
12		PhCHO	90 (75/25):10	6:4 95	127
13		EtCHO	93 (66/34) : 7	6:4 85	127
14		EtC(=O)Et	>97 (87/13):<3	- 84	127
					
		R^1 R^2	*E*:*Z*	D.s. overall (pure *E*)	
15		Me Bn	92:8	83 84	127
16		*n*-Pr Bn	94:6	85 81	127
17		*i*-Pr Bn	94:6	88 (98) 85	127
18		Ph Bn	93:7	86 (96) 82	127
19		Ph *n*-Pr	95:5	88 85	127
20		Ph Ph	95:5	>85 71	127

to react with aldehydes with high diastereoselectivity.[125,126] Interestingly, the allyltitaniums derived from the corresponding carbonates react with aldehydes to afford β-vinyl-γ-aminoalkanols highly selectively (entries 1−5), presumably via a δ-amino allylic titanium intermediate,[125] while those prepared from the cyclic carbamates furnish another regioisomer, 1,5-amino alcohols, highly predominantly (entries 6−11) via a 2′-amino allylic titanium compound as shown in eq 79.[126] As shown in entries 12−20 of Table 22, the allyltitanium compound derived from acrolein (*R*,*R*)-1,2-dicyclohexylethylene acetal reacts with carbonyl compounds or imines in a regioselective



(79)

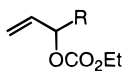
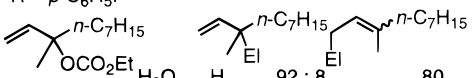
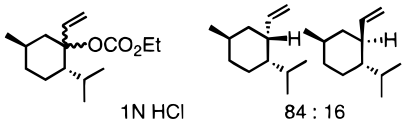
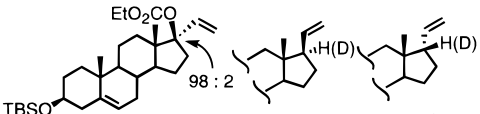
way to provide the corresponding addition product having the structure depicted in eq 80.[127] These



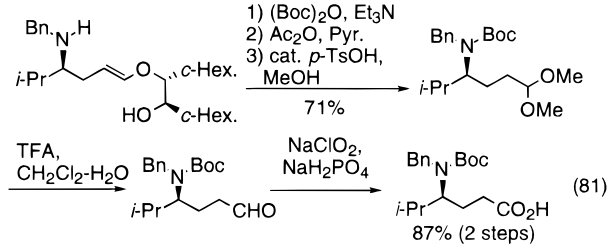
(80)

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 (entries 12−14 in Table 22), the reaction with imines proceeded with a high degree of chiral induction to give the corresponding optically active amines (entries 15−20). It should be noted that this allyltitanium compound is the first example of a chiral homoenolate equivalent which reacts with imines. The predominant production of the α-adduct can be explained by assuming that the generated allyltitanium would exist mostly as an internal titanium derivative, which can be stabilized by chelation, rather than the primary derivative (eq 80), and in the case of the reaction with imines, the reaction might proceed preferentially through the most stable transition state illustrated in eq 80, which has a *trans*-fused chair−chair conformation, to provide the product with the structure depicted in the equation.

Table 23. Selective Synthesis of 1-Alkenes and 3-Chloro-1-alkenes from Allyl Alcohol Derivatives by the Reaction with a Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl and the Following Hydrolysis or Halogenolysis (Ref 128)

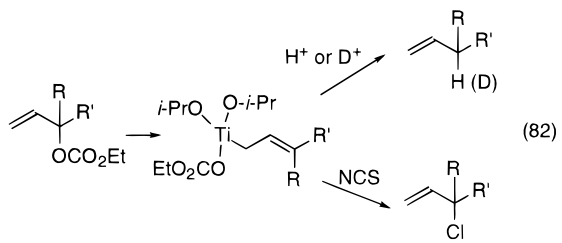
Substrate	Electrophile	Products: El	Selectivity	Yield, %
				
R = *n*-C_8H_{17}	H_2O	H	92 : 8	86
	D_2O	D	92 : 8	84
	NCS	Cl	95 : 5	77
R = Ph	H_2O	H	96 : 4	87
	D_2O	D	96 : 4	84
R = *p*-C_6H_5I	1N HCl	H	96 : 4	71
				
	H_2O	H	92 : 8	80
	NCS	Cl	95 : 5	81
				
	1N HCl		84 : 16	82
	t-BuOH		94 : 6	82
				
	t-BuOH		85 : 15	65
	D_2O		75 : 25	72

By taking advantage of the versatility of the enol ether functionality, the products could be readily transformed into a variety of γ-aminocarbonyl compounds as exemplified in eq 81.[127]



(81)

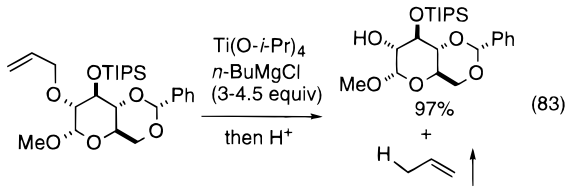
Easy access to a variety of allylic titanium compounds from readily available allylic alcohol derivatives prompted the Sato group to investigate their reactions with electrophiles other than carbonyl compounds and imines. As illustrated in eq 82, the hydrolysis and halogenolysis of allylic titanium compounds proceed with high regio- and stereoselectivities, thus affording a new protocol for converting allylic alcohol derivatives to 1-alkenes (by hydrolysis) or 3-chloro-1-alkenes (by reaction with NCS). The



(82)

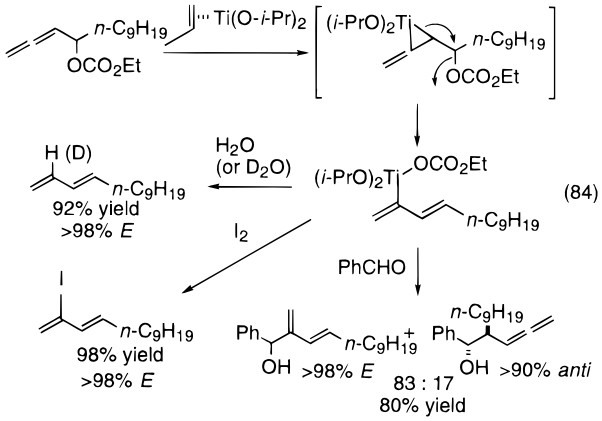
results are summarized in Table 23.[128]

The finding of the formation of allyltitaniums from a divalent titanium reagent and allylic alcohol derivatives was applied to a deallylation reaction of allylated organic compounds as exemplified by eq 83.[129]



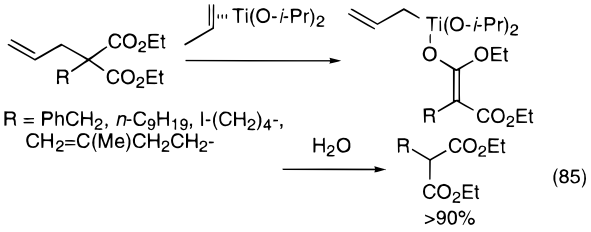
(83)

Treatment of carbonates of alka-2,3-dien-1-ols with (η^2-propene)Ti(O-*i*-Pr)$_2$ resulted in a similar oxidative addition to afford 1,3-dien-2-yltitanium complexes, which react with electrophiles such as H_2O, I_2, and aldehydes as shown in eq 84.[130] Especially noteworthy is the specific production of 2-iodo-1,3-dienes by the reaction with I_2, which are otherwise tedious to prepare.



(84)

The reaction of eq 85 showing the generation of an allyltitanium compound from (η^2-propene)Ti(O-*i*-Pr)$_2$ and $(CH_2{=}CHCH_2)RC(CO_2Et)_2$ indicates that the $RC(CO_2Et)_2$ anion can act as a good leaving group as halide, acetate, or carbonate.[131] By taking advantage



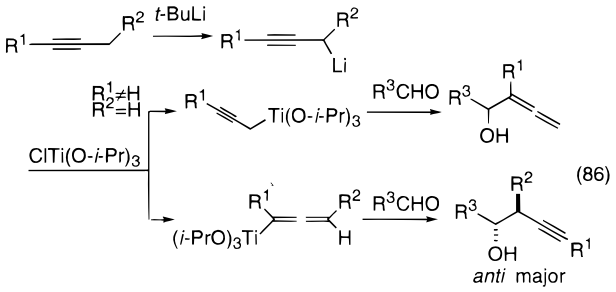
(85)

of this reaction, it has been shown that the allyl moiety can be used as a protecting group for the acidic hydrogen of the malonic ester.

2. Synthesis of Allenyl- and Propargyltitanium Compounds and Their Reaction with Electrophiles

Yamamoto and co-workers reported the synthesis of propargyl- and allenyltitanium reagents and their reaction with carbonyl compounds.[132,133] Thus, propargyl- and allenyltitanium reagents were prepared from 1-substituted and 1,3-disubstituted 1-propynes,

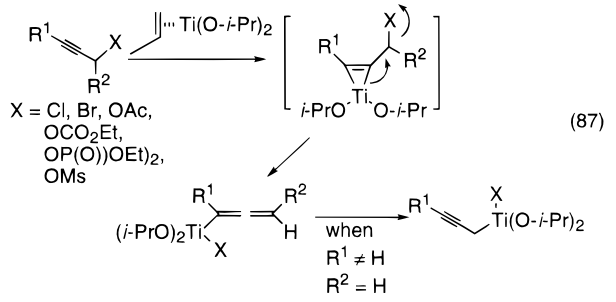
respectively, by lithiation with *t*-BuLi followed by the reaction with $Ti(O\text{-}i\text{-}Pr)_3X$ (X = O-*i*-Pr or Cl), and the reagents thus prepared were shown to react with aldehydes in a regio- and stereocontrolled manner to afford either α-allenyl or homopropargyl alcohols depending on the structure of the starting alkynes as shown in eq 86. However, the variety of allenyl-



(86)

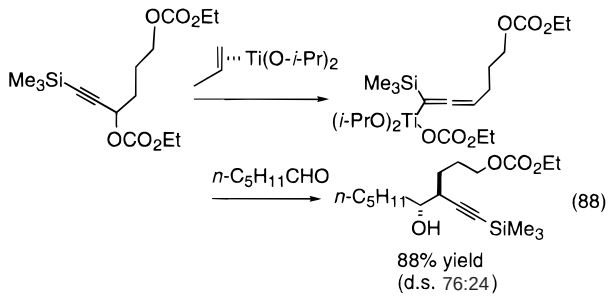
and/or propargyltitaniums available by this protocol is limited.

Sato et al. showed that a divalent titanium reagent (η^2-propene)$Ti(O\text{-}i\text{-}Pr)_2$ reacts with propargyl alcohol derivatives to provide propargyl- or allenyltitanium complexes in excellent yield (eq 87).[134,135] This direct



(87)

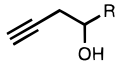
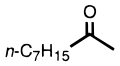
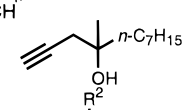
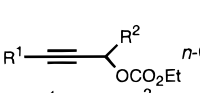
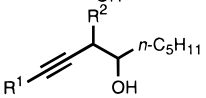
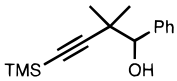
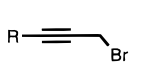
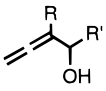
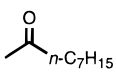
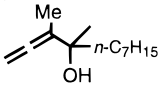
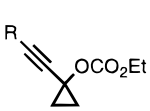
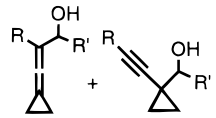
and efficient entry to a variety of allenyl- or propargyltitanium complexes, including those which cannot be prepared according to the reaction of eq 86, opens up a highly practical method for preparing a variety of homopropargyl and allenyl alcohol derivatives by their reaction with aldehydes and ketones as summarized in Table 24. The following characteristic features are noteworthy. It is possible to prepare the titanium reagents having a functional group as exemplified by eq 88, thus allowing an easy access to functionalized homopropargyl alcohols by their reaction with carbonyl compounds (entry 4). As



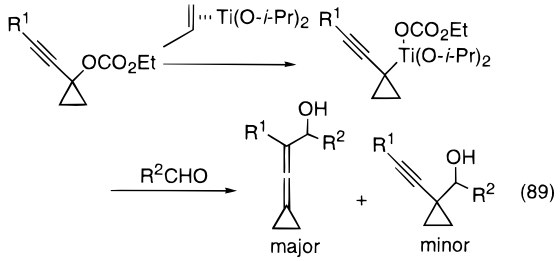
(88)

illustrated in eq 89, similarly to the reaction of the allyltitanium compound derived from 1-vinylcyclopropyl carbonate shown in eq 77, the titanium

Table 24. Preparation of Allenyl-/Propargytitaniums from Propargylic Alcohol Derivatives and a $Ti(O\text{-}i\text{-}Pr)_4/2i\text{-}PrMgCl$ Reagent and Their Reaction with Carbonyl Compounds

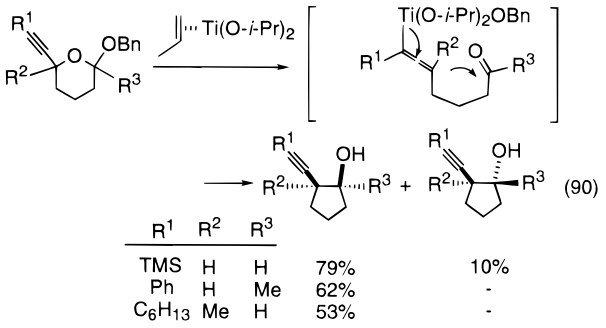
Entry	Propargyl Compound	Carbonyl Compound	Product(s) Yield, %	Ref.
1	 X = Cl, Br, OAc, OCO_2Et	RCHO R = Ph, *n*-C_8H_{17}, *p*-BrC_6H_4, *p*-$MeO_2CC_6H_4$, (*E*)-PhCH=CH		36 ~ 91	134
2	X = Br			85	134
		*n*-$C_5H_{11}CHO$			
	R^1 = TMS, R^2 = *n*-C_5H_{11}		*anti* : *syn* = 80 : 20	70	134
3	R^1 = TMS, R^2 = $(CH_2)_3OCO_2Et$		76 : 24	88	134
4	R^1 = H, R^2 = *n*-C_5H_{11}		75 : 25	89	134
5	R^1 = *n*-C_6H_{13}, R^2 = Et		72 : 28	89	134
6		PhCHO		78	134
7		R'CHO		79 ~ 89	134
8	R = Me, TMS, Ph	R' = Ph, *p*-$MeO_2CC_6H_4$			
9	R = Me			83	134
					
	R = Ph	R'CHO = PhCHO	Regioselectivity = 93 : 7	62	122
10	Ph	EtCHO	>97 : 3	65	122
11	Ph	EtCHO	>97 : 3	74	122
12	*n*-C_6H_{11}	H_2CO	>97 : 3	80	122
13	*n*-C_6H_{11}	EtCHO	74 : 26	45	122
14	TMS				

complexes derived from 1-alkynyl-1-cyclopropyl carbonates react with aldehydes at the less substituted carbon to afford the corresponding α-allenyl alcohol highly predominantly (entries 10−14 in Table 24).[122]



(89)

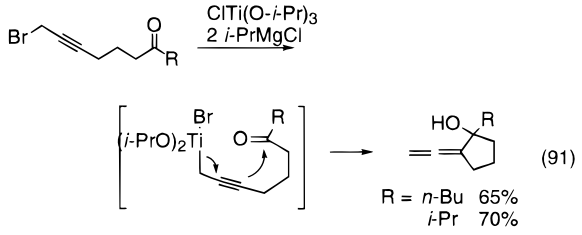
As shown in eq 90, the reaction of cyclic propargyl acetals results in generation of an allenyltitanium intermediate and the following intramolecular addition to the aldehyde moiety generated simultaneously in situ to furnish a cycloalkanol derivative having an acetylenic group at the β-position.[136] The reaction of propargyl halides having a keto group also proceeds through an intramolecular addition reaction pathway to afford cyclic allenyl alcohols, where the use of ClTi-



R^1	R^2	R^3		
TMS	H	H	79%	10%
Ph	H	Me	62%	-
C_6H_{13}	Me	H	53%	-

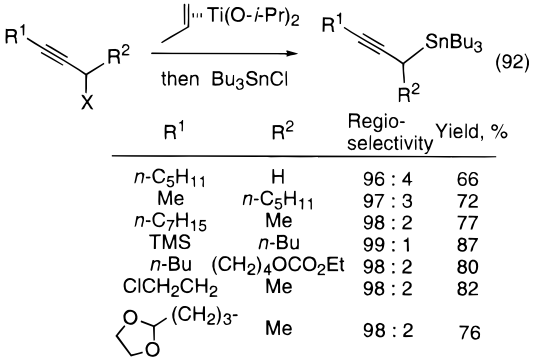
(90)

$(O\text{-}i\text{-}Pr)_3$ instead of $Ti(O\text{-}i\text{-}Pr)_4$ gave better yields (eq 91).[136]



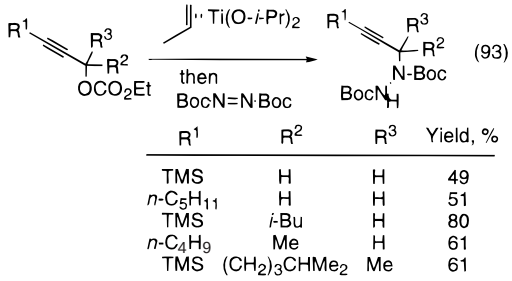
(91)

As shown in eq 92, the allenyltitanium compounds react with R_3SnCl in a regioselective way to afford the corresponding propargylstannanes highly predominantly;[137] thus, the reaction provides an easy one-pot access to a variety of propargylstannanes including those containing functional groups such as ester, chloride and acetal moieties. The allenyltitaniums also react smoothly with dialkyl azodicarboxylate to provide the corresponding α-hydrazinoalkynes in good yield (eq 93).[138]



R^1	R^2	Regioselectivity	Yield, %
$n\text{-}C_5H_{11}$	H	96 : 4	66
Me	$n\text{-}C_5H_{11}$	97 : 3	72
$n\text{-}C_7H_{15}$	Me	98 : 2	77
TMS	*n*-Bu	99 : 1	87
n-Bu	$(CH_2)_4OCO_2Et$	98 : 2	80
$ClCH_2CH_2$	Me	98 : 2	82
	Me	98 : 2	76

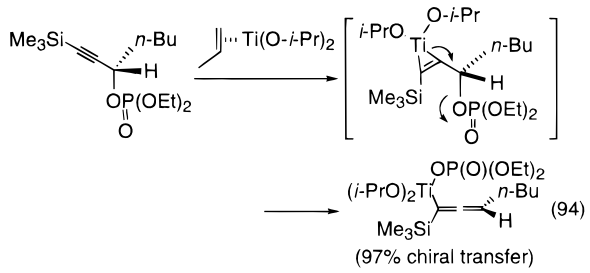
(92)



R^1	R^2	R^3	Yield, %
TMS	H	H	49
$n\text{-}C_5H_{11}$	H	H	51
TMS	*i*-Bu	H	80
$n\text{-}C_4H_9$	Me	H	61
TMS	$(CH_2)_3CHMe_2$	Me	61

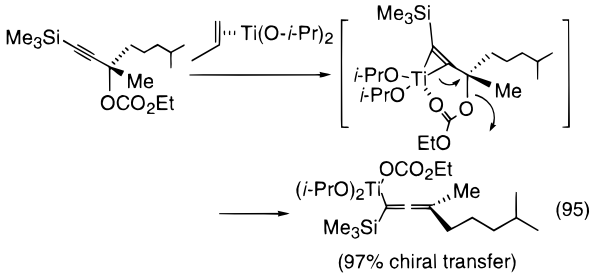
(93)

The synthetic method for preparation of allenyltitaniums from propargyl alcohol derivatives has allowed the synthesis of optically active compounds having axial chirality.[139] Thus, the reaction of a $Ti(O\text{-}i\text{-}Pr)_4/2i\text{-}PrMgCl$ reagent 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 optically active disubstituted allenyltitaniums (eq 94). The reaction with tertiary propargyl carbonate also proceeds with more than 97% chirality transfer to provide optically active trisubstituted allenyltitaniums as shown in eq 95; however, in this case, the reaction proceeds through a syn-elimination pathway. Since a variety of optically active propargyl alcohols are readily available, the reaction provides a highly efficient and general method for the preparation of di- and trisubstituted allenyltitaniums in a nonracemic form. The allenyltitaniums thus prepared are stable to racemization at least up to room temperature. As the reaction of allenytitaniums with carbonyl compounds[132−134] and imines[140] proceeds with high regio- and stereoselectivity, a new method for preparation of optically active homopropargyl alcohols and amines has been opened up. The reactions of optically active allenyltitaniums with several electrophiles other than carbonyl compounds and imines were also investigated by the Sato group, and the results are summarized in Table 25. The hydrolysis proceeds with an excellent degree of chiral transfer (94%) to afford optically active alkynes; thus, it provides an efficient asymmetric access to alkynes having a ^2H or alkyl group at the stereogenic propargylic center (entries 1, 3, and 4).[141] The halogenolysis also proceeds in a regiospecific way and with a high degree of chiral transfer to provide optically active propargyl halides (entries 2 and 5).[141] The reaction with azodicarboxylate shown in eq 93 proceeded with moderate to good chiral transfer to afford optically active α-hydrazinoalkynes (entries 6−8).[138] The stereochemical outcome observed in these reactions strongly indicates that the reaction with H_2O or D_2O proceeds through the coordination of the oxygen atom to the titanium and the following electrophilic cleavage via an S_E2'-type reaction as shown in Figure 3 (**A**). Meanwhile, the mechanism for halogenolysis can be explained by assuming that



(94)

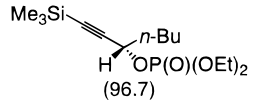
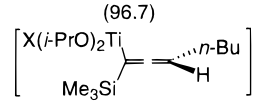
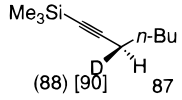
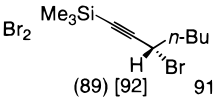
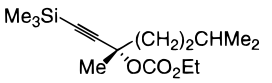
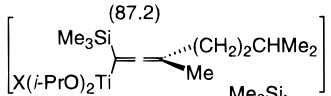
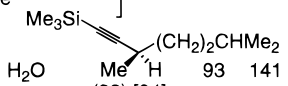
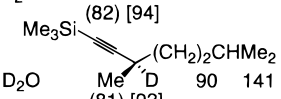
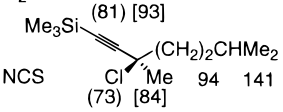
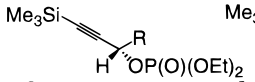
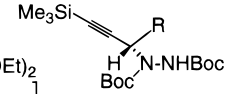
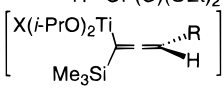
(97% chiral transfer)



(95)

(97% chiral transfer)

Table 25. Synthesis of Optically Active Allenyltitaniums Having Axial Chirality and Their Reaction with Electrophiles

Entry	Propargyl Compound (ee, %) [Allenyltitanium]	Electrophile	Product (Ee, %) [Chirality Transfer, %]	Yield, %	Ref.
					
					
1		D_2O	 (88) [90]	87	141
2		Br_2	 (89) [92]	91	141
					
					
3		H_2O	 (82) [94]	93	141
4		D_2O	 (81) [93]	90	141
5		NCS	 (73) [84]	94	141
					
					
6	R = Me (94)	BocN=NBoc	(81) [86]	77	138
7	*n*-Bu (96.7)	BocN=NBoc	(53) [55]	73	138
8	*i*-Bu (99)	BocN=NBoc	(27) [27]	74	138

the reaction involves the generation of a halogenium cation intermediate and the following S_E2'-anti halodemetalation reaction (Figure 3, **B**). In the case of the reaction with azo compounds, the reaction may proceed through an anti-periplanar transition state (Figure 3, **C**).

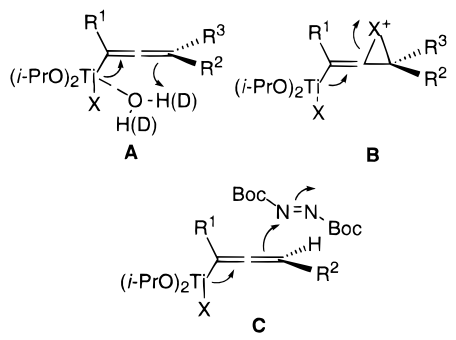


Figure 3.

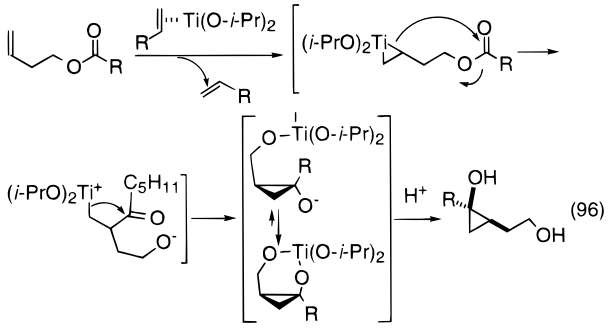
V. Titanium-Mediated Intramolecular Nucleophilic Acyl Substitution (INAS) Reaction through η^2-Alkene– and η^2-Alkyne–Titanium Complexes

The intermolecular nucleophilic acyl substitution reaction is a fundamental carbon−carbon bond-forming reaction. Despite its high synthetic potential, however, the intramolecular version, that is, intramolecular nucleophilic acyl substitution (INAS) reactions, are rather rare because of the intrinsic difficulty entailed in carrying them 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. Organometallics such as zinc and boron lack the nucleophilicity to undergo INAS reaction, while organolithiums and -magnesiums are generally too reactive. Recently, it has been discovered that a carbon−carbon unsaturated compound having an acyl moiety at the appropriate position reacts with a divalent titanium reagent to undergo an INAS reaction via an (η^2-alkene)- or (η^2-alkyne)titanium complex, and the reaction furnishes reactive organotitanium compounds as the product. This section describes this unprecedented type of highly useful INAS reaction.

1. INAS Reaction through η^2-Alkene Titanium Complexes

As described in section III, Kulinkovich and coworkers showed that (η^2-olefin)Ti(O-*i*-Pr)$_2$ derived from Ti(O-*i*-Pr)$_4$ and 2 equiv of an alkyl Grignard reagent reacts with esters to afford cyclopropanols (eq 28).[46] In this reaction, the ligating olefin in the titanium complex acts as a vicinal alkyl dianion and is incorporated in the products.

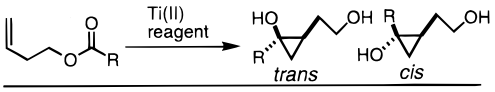
Recently, the Sato[142] and Cha[143] groups independently found that treatment of an ester of ω-alkenyl alcohols with an (η^2-alkene)titanium complex, generated in situ from XTi(O-*i*-Pr)$_3$ (X = O-*i*-Pr or Cl) and 2 equiv of a Grignard reagent, proceeds through the INAS reaction and the following intramolecular carbonyl addition reaction to afford disubstituted cyclopropanols in good to excellent yields as shown in eq 96. This reaction is an intramolecular version of the



(96)

Kulinkovich reaction and involves a step where the ligated olefin of the (η^2-alkene)titanium complex is exchanged by the olefin moiety of the substrate, thus

Table 26. Synthesis of 1,2-Disubstituted Cyclopropanols by the Intramolecular Kulinkovich Reaction of Esters of ω-Vinyl Alcohols

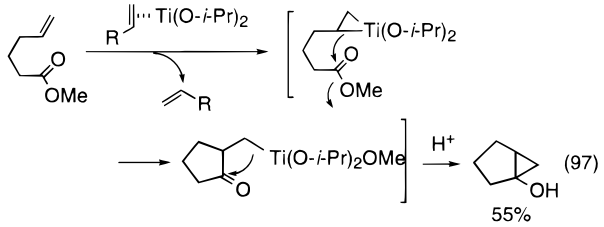


Entry	Substrate	Conditions[a]	Products trans :cis	Yield %	Ref.
1	R = Me	A	58 : 42	93	142
2	*n*-C_5H_{11}	A	88 : 12	95	142
3	(*E*)-CH=CHMe	A	93 : 7	78	142
4	*i*-Pr	A	88 : 12	88	142
5	Ph	A	>97 : 3	85	142
6	Ph	B	7 : 1	78	143
7		A	41 : 59	33	142
8		C	95 : 5	70	142
9		A	47 : 53	28	142
10		C	91 : 9	78	142
11		A	>97 : 3	74	142
12		A	n.d.	<5	142
13		C	45 : 55	61	142

[a] A: Ti(O-*i*-Pr)$_4$ / 2 *i*-PrMgCl (2 equiv), -45 °C to 0 °C, B: ClTi(O-*i*-Pr)$_3$ (0.5 equiv), *n*-BuMgBr (5 equiv), room temp., C: Ti(O-*i*-Pr)$_4$ / 2 *i*-PrMgCl (2 equiv), -45 °C to room temp.

indicating that the initially generated (η^2-alkene)-titanium complex serves as a divalent titanium species. The INAS reaction can be carried out by using the reagent prepared from 1 equiv of Ti(O-*i*-Pr)$_4$ and 2 equiv of *i*-PrMgCl at −50 °C to room temperature in ether[142] or alternatively by using 0.5−1 equiv of ClTi(O-*i*-Pr)$_3$ and 3−5 equiv of *n*-BuMgBr or *c*-C_5H_9MgCl at room temperature in THF or ether.[143] The results of the INAS reaction are summarized in Table 26. As revealed from the results shown in entries 7−10, the stereochemistry of the 1,2-disubstituted cyclopropanols was dependent on the reaction conditions, and the major isomers changed from cis to trans by increasing the reaction temperature. This thermodynamically controlled behavior can be rationalized by reversible dissociation of the Ti−OC(*tert*) bond in the final reaction product, which resulted in the more stable chelated compound (eq 96).

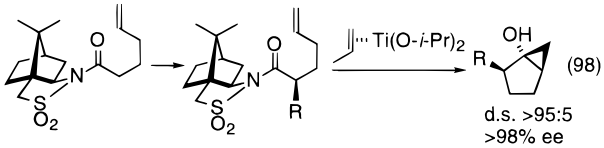
The reaction of ω-olefinic ester with an (η^2-alkene)-titanium complex also proceeds via the intramolecular Kulinkovich reaction to afford bicyclic cyclopropanols as shown in eq 97.[143−146] The results of the reaction are summarized in Table 27. As revealed from the table, a variety of bicyclic cyclopropanols, 1-hydroxybicyclo-[3.1.0]-alkanes and -[4.1.0]-alkanes, can be readily obtained in good to excellent yields, including tricyclic cyclopropanols (entries 14 and 22−28); however, bulky substituent(s) at the allylic position in the substrate causes a decrease of the yield (entry 12) or no production of the cyclized product (entry 20). The preparation of the bicyclo-



(97)

[5.1.0]octane derivatives is also possible from the corresponding ω-olefinic esters although it suffers from poorer yield due to the low efficiency of the seven-membered cyclization (entries 6 and 28).

Olefinic acylsulfonamides act like olefinic esters; thus, their reaction with (η^2-propene)Ti(O-*i*-Pr)$_2$ affords the corresponding bicyclic cyclopropanols.[147] As shown in eq 98, 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, alky-



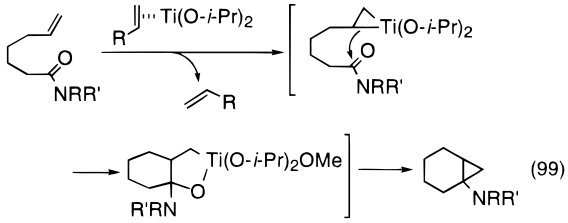
(98)

d.s. >95:5
>98% ee

R	Yield, %
$PhCH_2$	86
n-C_6H_{13}	58
$Me_2CHCH_2CH_2$	80
$Me_2C{=}CHCH_2$	87
$TBSO(CH_2)_4$	84
t-BuO_2CCH_2	56

lation of Oppolzer's camphorsultam, which proceeds with excellent diastereoselectivity for a variety of alkyl halides,[148,149] and the reaction of the resulting optically active unsaturated acylsulfoamides with (η^2-propene)Ti(O-*i*-Pr)$_2$ provides bicyclic cyclopropanols with the structure shown in the equation, exclusively.

As mentioned in section III, a *N*,*N*-dialkyl amide reacts with (η^2-olefin)titanium complexes to afford the corresponding cyclopropylamine.[56−60] The intramolecular version of this reaction, i.e., the INAS reaction of ω-vinyl amides, was reported by Cha (eq 99).[55,145,146]

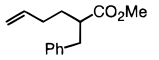
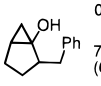
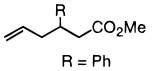
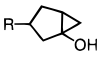
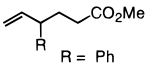
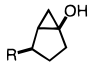
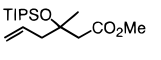
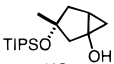
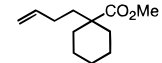
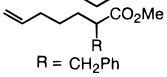
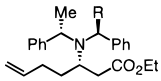
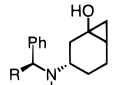
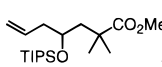
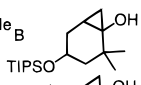
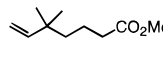
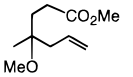
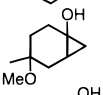
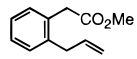
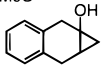
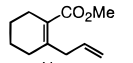
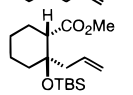
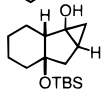
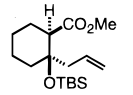
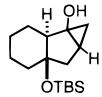
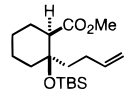
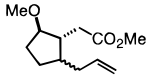
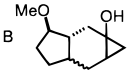
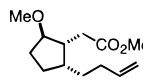
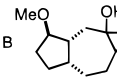


(99)

Thus, the ω-vinyl amide was treated with 0.5 equiv of ClTi(O-*i*-Pr)$_3$ and 3−4.5 equiv of *c*-C_5H_9MgCl in THF at room temperature to give the corresponding cyclopropylamine. The results are summarized in Table 28.

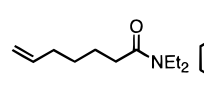
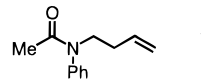
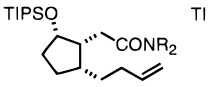
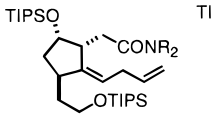
The carbonates of ω-vinyl alcohols underwent the INAS reaction, which was not followed by the consecutive intramolecular carbonyl addition reaction, thus affording the corresponding alkyltitanium complex having a lactone moiety (eq 100).[54,150] The titanium−carbon bond in the resulting β-titanacar-

Table 27. Synthesis of 1-Hydroxybicyclo[n.1.0]alkane by the Intramolecular Kulinkovich Reaction of *ω*-Alkenyl Esters

Entry	Substrate	Conditions[a]	Products	Yield,% (d.s.)	Ref.
1	n = 0, R = Me	B		0	143
2	n = 1, R = Me	B		55	143,145
3	n = 2, R = Me	A		57	144
4	R = Me	B		62	143,145
5	R = Et	A		52	144
6	n = 3, R = Me	B		11	143,145
7	n = 4, R = Me	B		0	143
8		A		77 (66:34)	144
9	 R = Ph	A		83 (61:39)	144
10	OTBS	A		76 (n.d.)	162
11	 R = Ph	A		76 (55:45)	144
12	OTIPS	B		14 (1:0)	143
13		B		58 (7:2)	143
14		A		88	144
15	 R = CH_2Ph	A		73 (89:11)	144
16	OTIPS	B		76 (2:1)	143
17	 R = H	A		76 (n.d.)	165
18	Me	A		63 (n.d.)	165
19		B		75 (1:1)	143
20		B		0	143
21		B		85 (1.2:1)	145
22		A		98	144
23		B		0	143
24		B		70 (2:1)	143 145
25		B		42 (3:2)	143 145
26		B		86 (9:1)	145
27		B		60 (1:1)	145
28		B		40 (1:1)	145

[a] A: Ti(O-*i*-Pr)$_4$ / 2 *i*-PrMgCl (2 equiv), -45 °C to room temp., B: ClTi(O-*i*-Pr)$_3$ (1 equiv), *n*-BuMgCl or *c*-C_5H_9MgCl (3-5 equiv), room temp.

Table 28. Intramolecular Cyclopropanation of *ω*-Vinylamides Mediated by a ClTi(O-*i*-Pr)$_3$/ *c*-C_5H_9MgCl Reagent

Entry	Substrate	Product	Yield,%	Ref.
1			64	55
2			93	55
3		R = Et	52	145
4		Bn	78	145
5		R = Et	71	145
6		Bn	83	145

bonyl compounds depicted in eq 100 can be trapped by electrophiles to give the corresponding lactone having a functionalized side chain at the α-position.

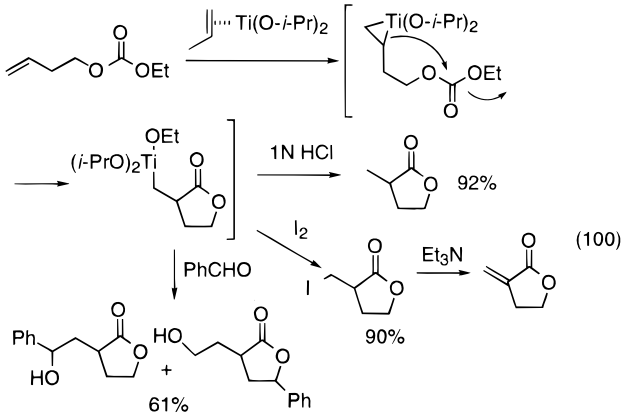
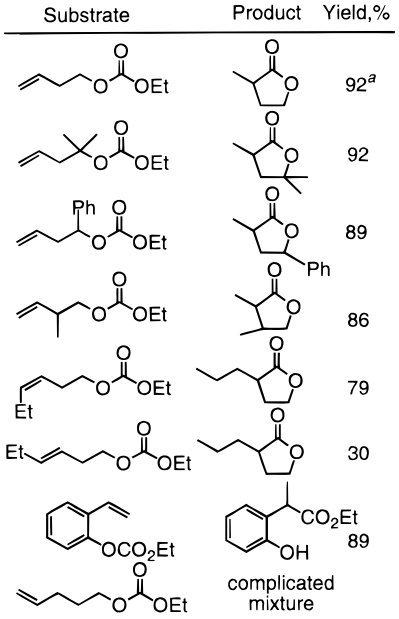


Table 29 summarizes the yields of lactones obtained by hydrolysis of the reaction products. As illustrated in eq 101, the carbonate of 3,5-dienyl alcohol also underwent the INAS reaction to furnish the corresponding allylic titanium complex having a lactone moiety, which, in turn, reacted with aldehydes regioselectively at the terminal position to give a homoallylic alcohol having *Z*-olefin geometry.[151] The

reaction can be explained by assuming that an

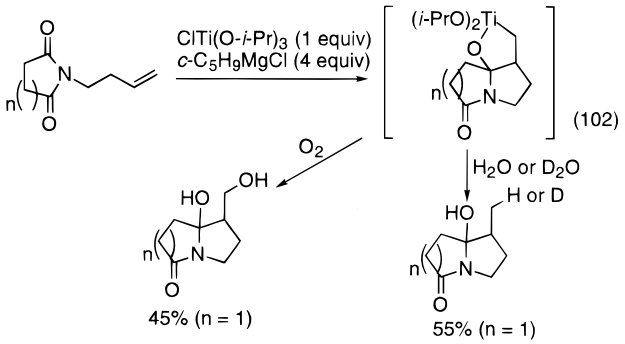
Table 29. INAS Reaction of Carbonates of ω-Alkenyl Alcohols Mediated by a Divalent Titanium Reagent (Ref 150)



[a]See also ref 54.

intermediate allyltitanium complex would exist as an internal titanium derivative, which may be stabilized by intramolecular coordination of carbonyl oxygen, and then reacts with aldehydes via a six-membered transition state.

The INAS reaction of cyclic imides derived from ω-vinylamines mediated by a divalent titanium reagent affords the respective acylaminals after hydrolysis (eq 102).[59] Thus, the reaction provides a new



route to synthesis of the functionalized pyrrolizidines and indolizidines. The oxidation of the titanium−carbon bond in the resulting titanium intermediate with O_2 provides the corresponding alcohols. Table 30 summarizes the results of this reaction. The products thus obtained were used as precursors of tertiary *N*-acyliminium ion.[152]

As shown in the equation of Table 31, the INAS reaction of carbonate of 3,4-alkadienol mediated by (η^2-propene)Ti(O-*i*-Pr)$_2$ generates the vinyltitanium compounds, which, in turn, react with electrophiles to give α-substituted β,γ-unsaturated esters.[153] It should be noted that the reaction of 4-silyl- or 4-stannyl-3,4-dienyl carbonate proceeds with excellent chirality transfer as exemplified in eq 103, thus

Table 30. INAS Reaction of Cyclic Imides of ω-Alkenyl Amines Mediated by a Divalent Titanium Reagent (Ref 59)

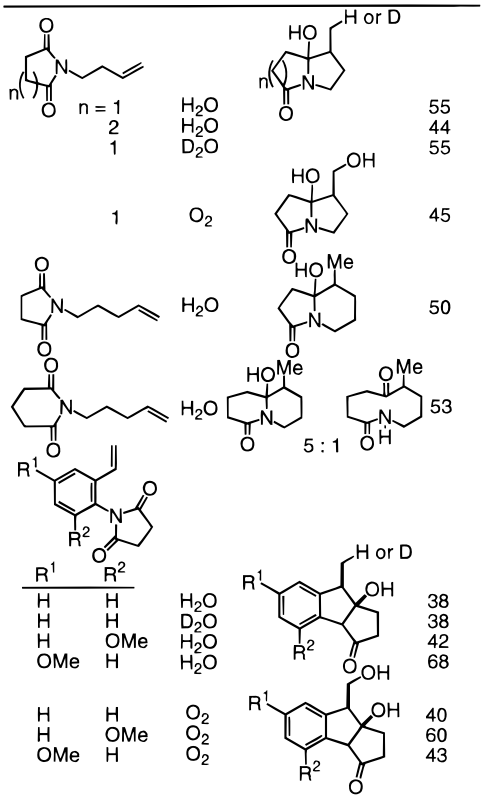
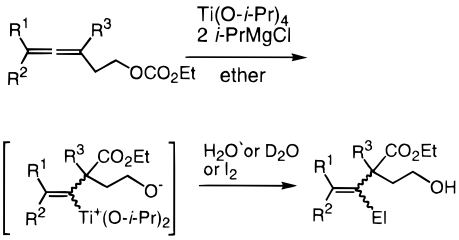
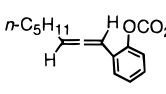
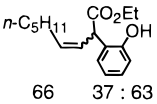
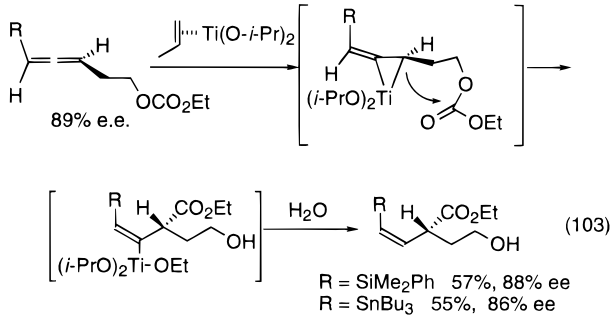


Table 31. Ti(II)-Mediated INAS Reactions of Allenic Carbonates (Ref 153)



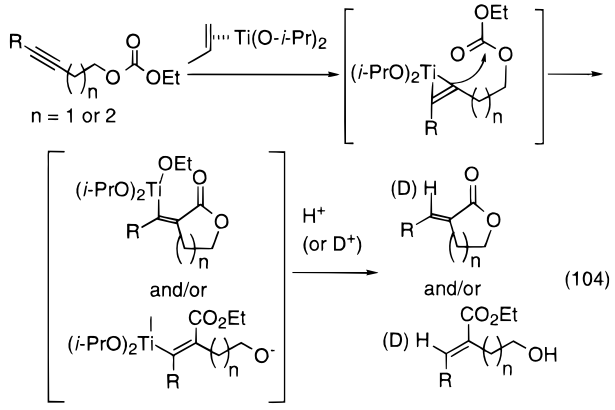
Entry	R^1	R^2	R^3	Product El	yield, %	*Z* : *E*
1	*n*-Bu	H	H	H	83	77 : 23
2	*i*-Pr	H	H	H	82	92 : 8
3	*t*-Bu	H	H	H	88	>98 : 2
4	Ph	H	H	H	77	65 : 35
5	Me_3Si	H	H	H	56	>98 : 2
				D	54	>98 : 2
				I	49	2 : >98
6	$PhMe_2Si$	H	H	H	57	>98 : 2
7	*n*-Bu_3Sn	H	H	H	55	>98 : 2
8				H		
					66	37 : 63

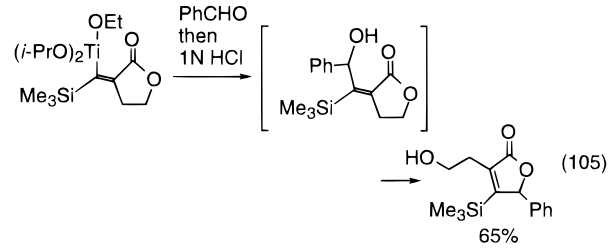
affording a new access to α-substituted β,γ-unsaturated esters in an optically active form.



2. INAS Reaction through η^2-Alkyne Titanium Complexes

The INAS reaction of acetylenic carbonates mediated by (η^2-propene)Ti(O-*i*-Pr)$_2$ also proceeds smoothly to afford lactones or α,β-unsaturated esters, after hydrolysis of the resulting vinyltitanium complexes, as illustrated in eq 104.[150,154] The resulting vinyltitanium intermediate can be trapped with an aldehyde. Thus, as shown in eq 105, treatment of the vinyltitanium complex thus generated with benzaldehyde affords the corresponding adduct which easily undergoes recyclization to give a substituted butenolide after acidic workup. The results of the reaction are summarized in Table 32.





In contrast to the reaction of alkynyl carbonates described above, the INAS reaction of esters of acetylenic acids, illustrated in eq 106, under the same reaction conditions gave poorer results, presumably due to problems associated with the enhanced reactivity to nucleophiles of the ketone moiety present in the resulting INAS product. It was revealed, however, that use of ClTi(O-*i*-Pr)$_3$ instead of Ti(O-*i*-Pr)$_4$ gives better yield, and also the yield is dependent on the nature of the ester group, and the isopropyl ester provides the highest and most synthetically useful yield. It can be seen from Table 33 that the INAS reaction of the isopropyl ester of acetylenic acids opens up an efficient entry to α-alkylidenecyclopentanones or -hexanones.[150] The reaction, however, could not be used for synthesizing cyclobutanone and cycloheptanone derivatives (entries 7 and 8). The vinyltitanium complex thus generated in situ

Table 32. Preparation of Alkenyltitanium Reagents Starting from Alkynyl Carbonates and Their Reactions with Electrophiles (Ref 150)

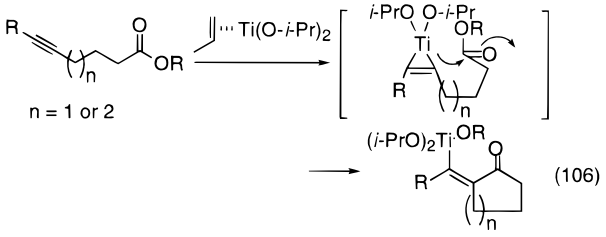
Entry	Substrate			Reaction Product with H_2O % yield	Reaction Product with PhCHO % yield
	R^1	R^2	n		
1	Me_3Si	H	1	68	65
2	Me_3Si	Et	1	58	50
3	Me_3Si	Ph	1	78	
4	n-C_6H_{13}	H	1	72	
5	Ph	H	1	81	40[a]
6	Me_3Si	H	2	76	70
7	Et	H	2	55	74
8	Me_3Si	H	3	66	38
9	R = H			74	78
10	R = Me			69	83

[a] Reaction with EtCHO instaed of PhCHO.

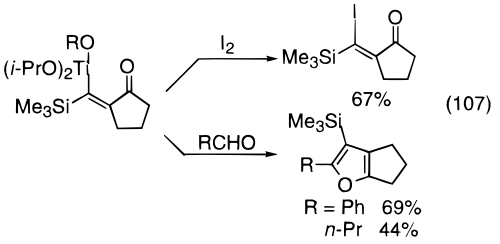
Table 33. INAS Reaction of Alkynyl Acid Esters Mediated by a Divalent Titanium Reagent (Ref 150)

Entry	Substrate			Product Isolated yield, %
	R^1	R^2	n	
1	Me_3Si	Me	2	30
2[b]	Me_3Si	Me	2	15
3	Me_3Si	Et	2	28
4	Me_3Si	*i*-Pr	2	73
5	Me_3Si	*t*-Bu	2	12
6	Me_3Si	*i*-Pr	3	79
7	Me_3Si	*i*-Pr	4	trace
8	Et	*i*-Pr	1	trace
9	*t*-Bu	*i*-Pr	3	60
10	Ph	*i*-Pr	3	83

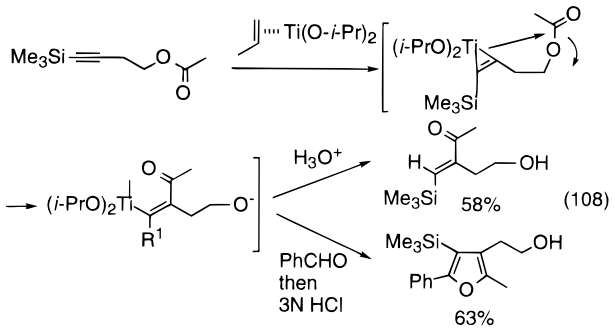
[a] 1.0 equiv of the substrate, 1.5 equiv of ClTi(O-*i*-Pr)$_3$ and 3.0 equiv of *i*-PrMgB r. [b] The reaction was carried out using Ti(O-*i*-Pr)$_4$ instead of ClTi(O-*i*-Pr)$_3$.



can readily be utilized for further transformation as exemplified in eq 107. In the case of the reaction with aldehydes, the adducts were transformed into the corresponding bicyclic furans during acidic workup.



As exemplified by eq 108, the reaction of esters of acetylenic alcohols with a $ClTi(O\text{-}i\text{-}Pr)_3/2i\text{-}PrMgCl$ reagent also proceeds through an INAS reaction pathway to afford α,β-unsaturated esters after hydrolysis; use of $Ti(O\text{-}i\text{-}Pr)_4$ instead of $ClTi(O\text{-}i\text{-}Pr)_3$ lowered the yield significantly.[150] The yields of hydrolysis or deuteriolysis of the reaction product are summarized in Table 34. The intermediate vinyltitanium complex reacts with aldehydes to produce the corresponding tetrasubstituted furans, as expected, after acidic workup (eq 108).



Treatment of alkynylmalonates or alkynetricarboxylates with $(\eta^2\text{-propene})Ti(O\text{-}i\text{-}Pr)_2$ resulted in an interesting C → C migration of an ester fragment (CO_2R) (eq 109).[155,156] The same type of reaction can be seen in the olefinic counterpart.

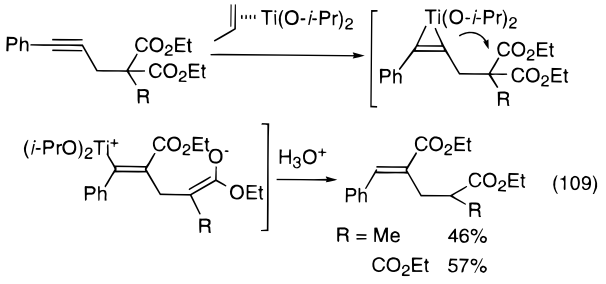


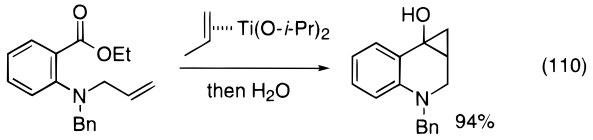
Table 34. INAS Reaction of Carbonates of Esters of Alkynyl Alcohols Mediated by a Divalent Titanium Reagent (Ref 150)

Entry	Substrate			Product Isolated Yield, %
	R^1	R^2	n	
1	Me_3Si	Me	2	58
2	Me_3Si	Me	3	47
3	Me_3Si	Ph	1	76
4	Me_3Si	Ph	2	77
5	Me_3Si	(*E*)-CH=CHMe	2	38
6	Ph	Ph	2	49
7	Me_3Si	*t*-Bu	2	40
8	Me_3Si	CF_3	2	48

3. Synthetic Applications of the Ti(II)-Mediated INAS Reactions

The INAS reactions mediated by a divalent titanium reagent mentioned above make it possible to connect the carbon−carbon bond intramolecularly at an almost unprecedented position, thus allowing a new synthetic design in organic synthesis. Moreover, the reaction products obtained in these reactions have a functional group such as an unsaturated carbonyl group or cyclopropanol moiety which allows further manipulation. The synthetic transformations mentioned below strongly indicate the versatility of the reaction which involves an efficient and practical synthesis of *N*-heterocycles (quinolines, pyrroles, and indoles) and several optically active compounds, including natural compounds.

As exemplified by eq 110, quinoline derivatives can be smoothly synthesized from readily available *N*-allylated anthranilic acid derivatives.[144,157] Similarly,



[1,2-*a*]indoles (annulated indoles) and [1,2-*a*]pyrroles can be synthesized starting from indole 2-carboxylate (eq 111) or pyrrole-2-carboxylate (eq 112). Table 35

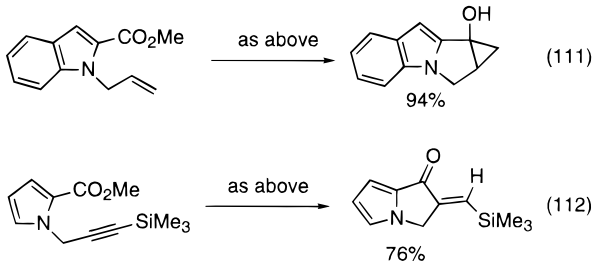
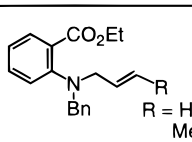
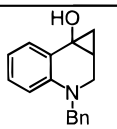
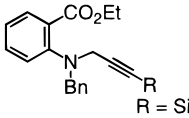
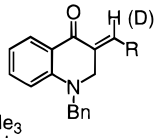
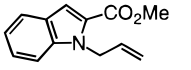
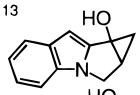
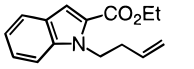
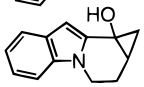
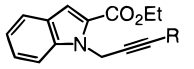
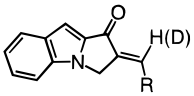
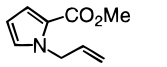
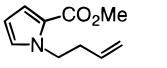
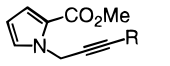
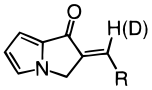
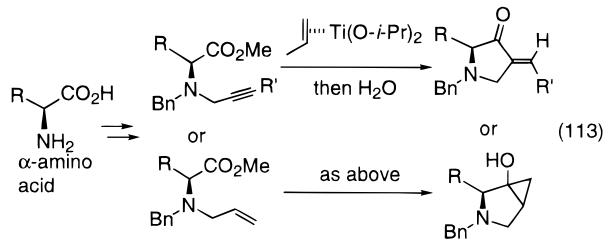


Table 35. Synthesis of Quinoline, [1,2-*a*]-Indole, and [1,2-*a*]-Pyrrole Derivatives by Ti(II)-Mediated INAS Reactions (Refs 144 and 157)

Entry	Substrate	Product	Yield,%
1	 R = H		94
2	Me		trace
3	 R = $SiMe_3$		63
4	nC_6H_{13}		50
5			94
6			74
7	 R = $SiMe_3$		62
8	n-C_6H_{13}		53
9			80
10			80
11	 R = $SiMe_3$		76
12	n-C_6H_{13}		65

summarizes the Ti(II)-mediated synthesis of quinolines, annulated indoles, and pyrroles.

Optically active *N*-heterocyclic compounds can also be synthesized conveniently from readily available amino acids or esters. Thus, as shown in eq 113, an α-amino acid was converted into the corresponding *N*-propargylated or *N*-allylated ester by conventional reaction sequences and then treated with (η^2-propene)Ti(O-*i*-Pr)$_2$ to afford the corresponding INAS product.[157] As summarized in Table 36, the reaction

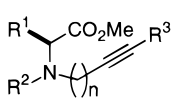
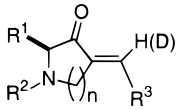
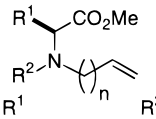
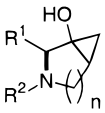


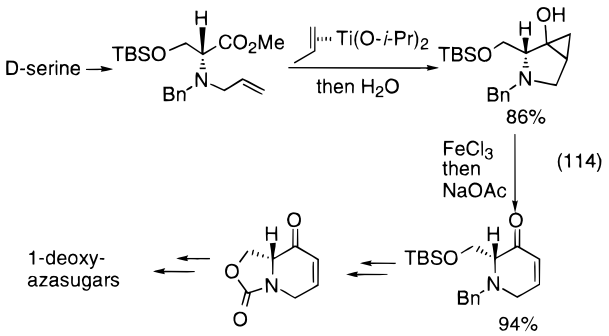
(113)

provides a convenient entry to optically active pyrrolidines which include those having a functionalized side chain (entries 3−5 and 10). The reaction also allows the preparation of piperidines from the corresponding *N*-homoallylated or *N*-homopropargylated esters (entries 2, 7, and 9).

The INAS product derived from D-serine was converted to oxazolidinylpiperidine,[158] which is a versatile intermediate for the synthesis of 1-deoxyazasugars, by the reaction with $FeCl_3$ and the following treatment with base[159] (eq 114).

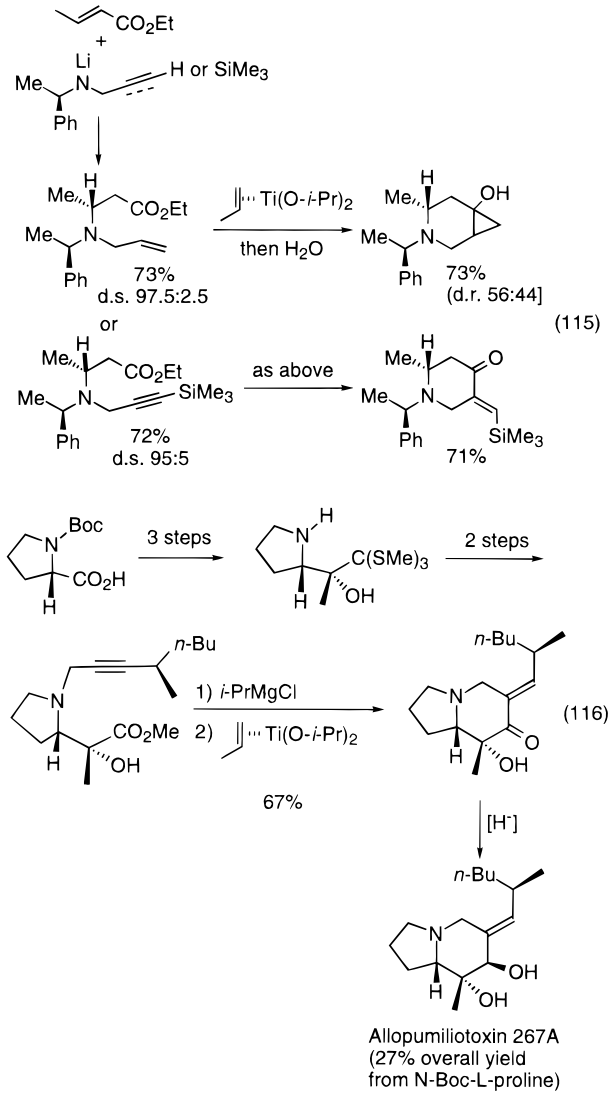
Table 36. Synthesis of Optically Active *N*-Heterocycles from *N*-Alkylated α-Amino Acid Esters and (η^2-Propene)Ti(O-*i*-Pr)$_2$ (Ref 157)

Entry	Substrate	Product, % Yield [d.r.]
		
	R^1 R^2 R^3 n	
1	Bn Bn $SiMe_3$ 1	74
2	Bn Bn $SiMe_3$ 2	75
3	CH_2OTBS Bn $SiMe_3$ 1	73
4	CH_2OTBS Bn C_5H_{11} 1	72
5	$(CH_2)_2CO_2Me$ Bn $SiMe_3$ 1	78
6	-$(CH_2)_3$- $SiMe_3$ 1	0
7	-$(CH_2)_3$- $SiMe_3$ 2	75
		
	R^1 R^2 n	
8	Bn Bn 1	75 [73 : 27]
9	Bn Bn 2	76 [92 : 8]
10	CH_2OTBS Bn 1	86 [75 : 25]
11	-$(CH_2)_3$- 1	0
12	-$(CH_2)_3$- 2	0



(114)

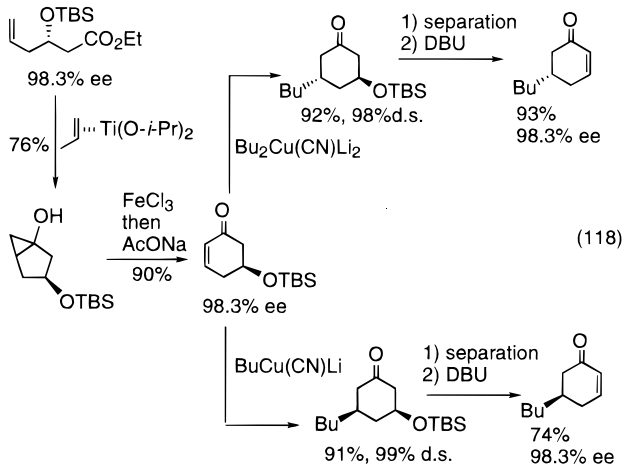
Another practical approach to optically active piperidines is shown in eq 115. Thus, diastereoselective Michael addition of optically active *N*-propargylated or *N*-allylated α-phenylethylamine to an α,β-unsaturated ester according to the Davies protocol,[160] which proceeded with excellent diastereoselectivity, followed by the reaction of the resulting product with (η^2-propene)Ti(O-*i*-Pr)$_2$ provides an optically active piperidine compound. This piperidine formation reaction has been applied for the total synthesis of allopumiliotoxin 267A.[157] Allopumiliotoxin 267A is one of the components of the toxic skin secretion of certain neotropical frogs and displays significant cardiotoxic activity. It was synthesized starting from L-proline, according to the reaction sequences summarized in eq 116, in which a Ti(II)-mediated INAS reaction of eq 115 is the key step. So far, total syntheses of allopumiliotoxin 267A have been ac-



complished by five groups, and all of them started with *N*-protected L-proline.[161] Among them, this synthesis is the shortest and gives the highest overall yield.

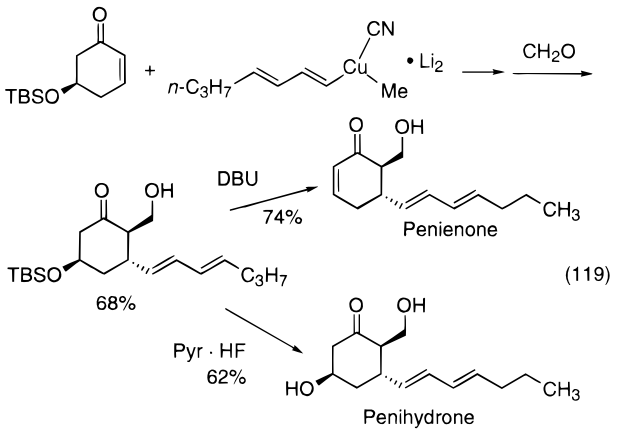
The synthesis of optically active 2-cyclohexenones having a substituent on the cyclohexyl ring has attracted much interest because this type of compound can be used as useful chiral building blocks or intermediates for synthesizing biologically important compounds. Optically active bicyclic cyclopropanols obtained by the reaction of the camphorsultam with (η^2-propene)Ti(O-*i*-Pr)$_2$ shown in eq 98 can be readily converted into 6-substituted 2-cyclohexenones without racemization by using the Ito−Saegusa method[159] as represented by eq 117; thus, a new efficient access to optically active 2-cyclohexenones having a substituent at the 6-position is now in hand.[147] The INAS reaction can also be used ef-

fectively for synthesizing optically active 2-cyclohexenones having a substituent at the 5-position. The synthetic method involves the preparation of optically active 5-[(*tert*-butyl)dimethylsilyl]oxy-2-cyclohexenone from readily preparable optically active 3-siloxy-5-hexenoate by using the INAS reaction of eq 97 as the key step and uses it as a chiral building block.[162] Thus, as shown in eq 118, the readily available ethyl 3-[(*t*-butyl)dimethylsilyl]oxy-5-hexenoate and (η^2-propene)Ti(O-*i*-Pr)$_2$ provided bicyclic cyclopropanol, which, in turn, was converted into 5-[(*tert*-butyl)dimethylsilyl]oxy-2-cyclohexenone by treatment with $FeCl_3$ and then NaOAc. The enone thus synthesized reacted

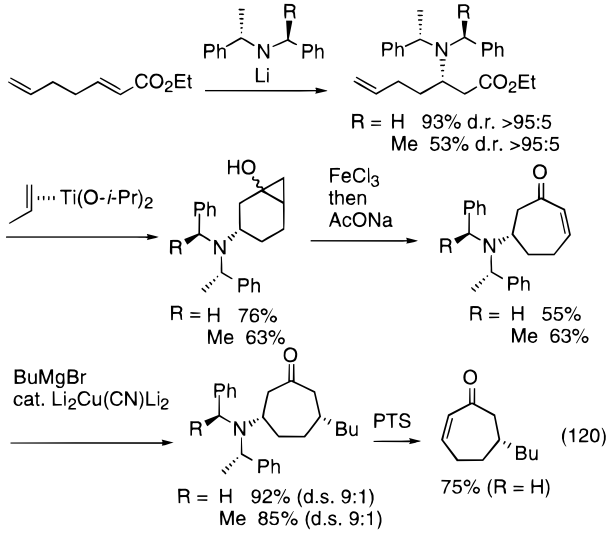


with a higher-order cyanoalkylcuprate prepared from CuCN and 2 equiv of alkyllithium with excellent diastereoselectivity to afford an anti-1,4-addition product.[162,164] Meanwhile, the reaction with a lower-order cyanoalkylcuprate derived from CuCN and 1 equiv of alkyllithium gave a syn-1,4-addition product almost exclusively (eq 118).[163,164] Both 1,4-addition products thus prepared can be converted readily into optically active 5-alkyl-2-cyclohexenones by treatment with a base (eq 118). Thus, both enantiomers of 5-alkyl-2-cyclohexenones can be prepared starting from one enantiomer of 5-siloxy-2-cyclohexenone.

The first total synthesis of penihydrone and penienone, both of which were isolated from the metabolite of fungus *Penicillium* sp. No 13 as new plant growth regulators, was readily accomplished by starting with the enone having (*R*)-configuration as illustrated in eq 119.[164]

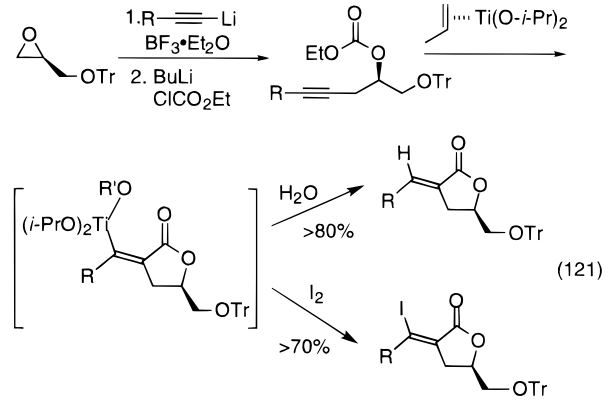


The tandem INAS−ring enlargement reaction described above was also applied for synthesizing chiral 6-amino-2-cycloheptenone, which can be used as a building block for preparation of optically active 6-alkyl-2-cycloheptenone (eq 120).[165]



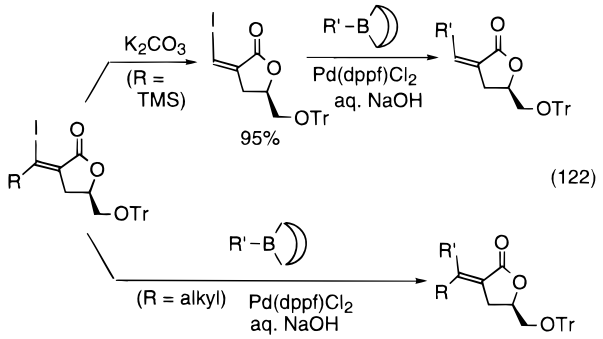
(120)

γ-(Alkoxymethyl)-α-alkylidene-γ-butyrolactones have been accepted as versatile building blocks and intermediates for synthesizing chiral natural compounds. The synthesis of these lactones having a stereodefined mono- or disubstituted exocyclic double bond can be readily carried out starting with optically active glycidyl ether by using the INAS reaction of eq 104 as the key step.[166] Thus, commercially available glycidyl trityl ether was converted into homopropargyl carbonates and was then treated with (η^2-propene)Ti(O-*i*-Pr)$_2$ to afford γ-[(trityloxy)methyl]-α-alkylidene-γ-butyrolactones having a trisubstituted exocyclic double bond with *E*-geometry after hydrolysis (eq 121). Meanwhile, those having *Z*-geometry as



(121)

well as those having a stereodefined tetrasubstituted exocyclic double bond were prepared by iodinolysis of the INAS reaction products and the following manipulation of the resulting iodolactones by using the Suzuki−Miyaura coupling reaction[167] as the key step as illustrated in eq 122.



(122)

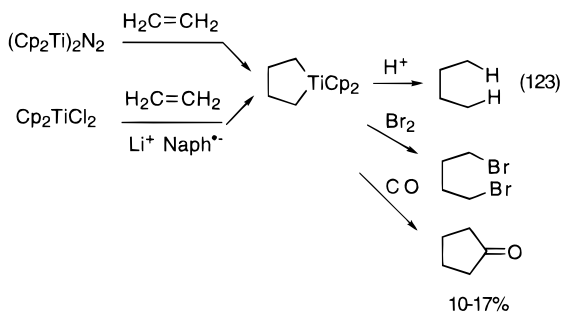
VI. Generation of Titanacycles via Inter- or Intramolecular Coupling of Alkenes and Alkynes and Their Synthetic Application

Inter- or intramolecular coupling reaction of olefins and acetylenes with a catalytic or a stoichiometric amount of a metallic reagent is a potential method for the construction of a carbon framework, especially ring systems. When the reaction is performed with a stoichiometric amount of a metallic species, the primary product should be a metallacycle, which is a quite useful intermediate for further functionalization or carbon−carbon bond formation. The reactions of this class mediated by a group 4 metal species such as titanium or zirconium, among which the metallocene reagents, i.e., Cp_2Ti or Cp_2Zr complexes, have been most frequently used, provide a variety of important synthetic methods.[1d,e,g,h−j,l−n,q,s] In addition to these fundamental reagents, some newer titanium species of a nonmetallocene structure have been introduced and, in fact, enabled characteristic transformations. In this section, the title reactions by conventional as well as new titanium reagents will be surveyed.

1.Titanacycles with Cyclopentadienyl Ligands

1.1. Intermolecular Reaction

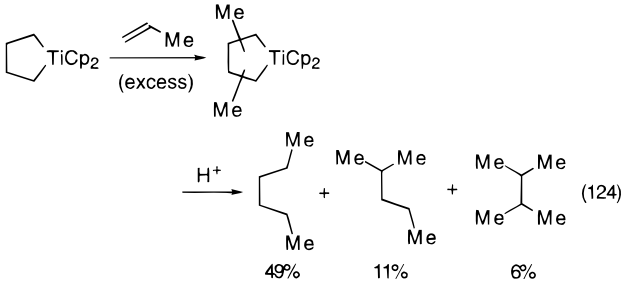
The formation of Cp_2-titanacyclopentanes was first carried out by a few methods analogous to eq 21. Thus, the nitrogen−titanium complex, an equivalent of titanocene, was allowed to react with ethylene to produce Cp_2-titanacyclopentane (eq 123).[168] More



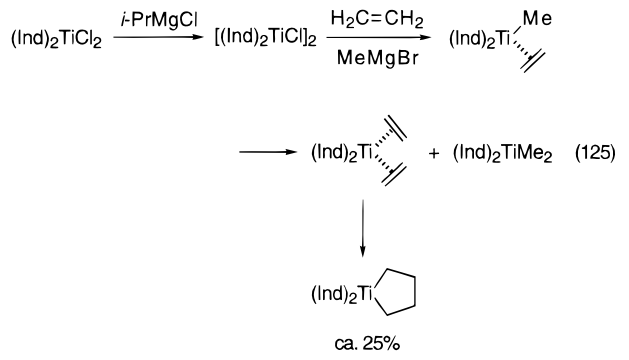
(123)

conveniently, the reaction of Cp_2TiCl_2 with lithium naphthalenide in the presence of ethylene afforded the same titanacycle. The presence of these titanacycles were evidenced by protonation, bromination,

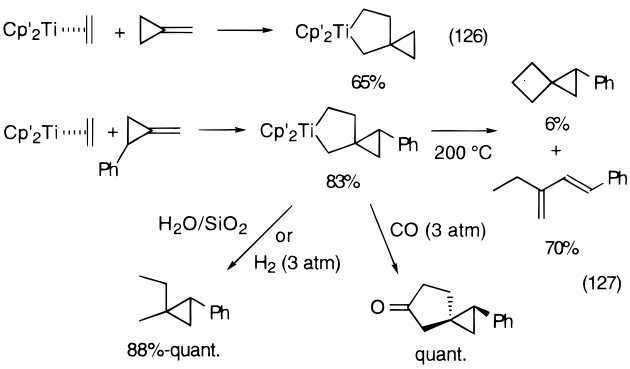
and carbonylation to give the corresponding products. The latter method was applied to several olefins to generate a variety of titanacyclopentanes.[168] A ligand exchange reaction between the titanacyclopentane and an externally added olefin is an alternative method to prepare new titanacyclopentanes (eq 124).[169]



A bisindenyltitanacyclopentane was generated via the successive reduction of $(Ind)_2TiCl_2$ with Grignard reagents in the presence of ethylene (eq 125).[35]

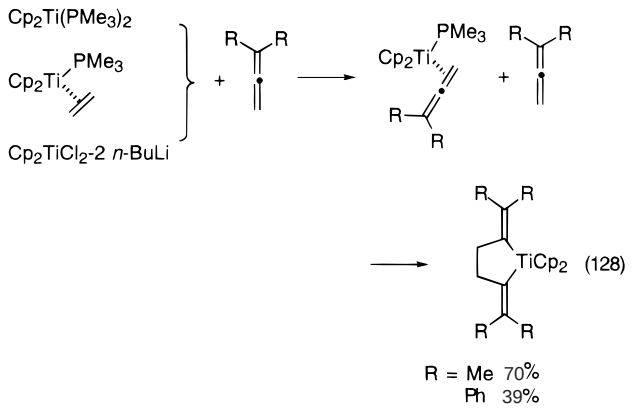


Cp'_2Ti(ethylene) complex already mentioned in eq 21 reacts with methylenecyclopropanes to give bicyclic titanacycles, a product of the cross-coupling reaction of ethylene and another olefin (eqs 126 and 127).[40,170] Some representative reactions of these titanacyclopentanes are shown in eq 127.

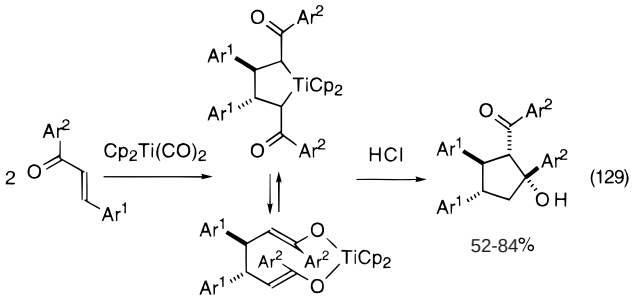


Homocoupling of allenes with a low-valent titanium complex such as $Cp_2Ti(PMe_3)_2$, $Cp_2Ti(PMe_3)$-$(CH_2{=}CH_2)$, or Cp_2TiCl_2-2*n*-BuLi afforded bis(alkylidene)titanacyclopentane via the intermediate allene–titanium complex (eq 128).[34]

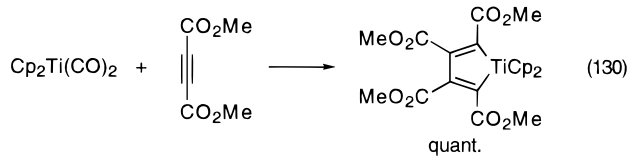
Dimerization of chalcones was achieved with $Cp_2Ti(CO)_2$ to give, after aqueous workup, cyclopentanols



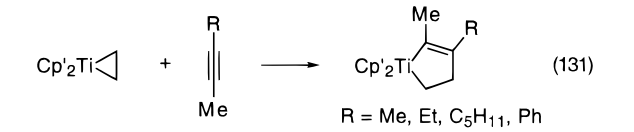
(eq 129).[171] The same complex is also effective for the



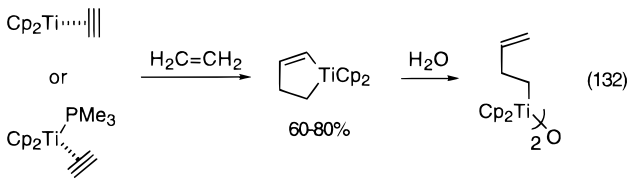
homocoupling of an acetylenedicarboxylate (eq 130).[72]



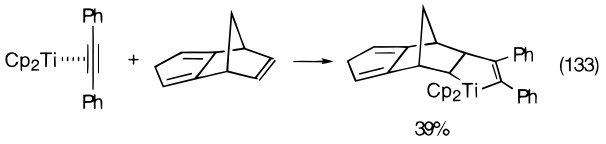
The coupling reaction of an olefin–titanium complex with a few acetylenes was documented (eq 131).[31] However, the intermolecular coupling of ole-



fins and acetylenes has mostly been achieved by the action of an olefin to an appropriate titanium–acetylene complex. Thus, when the acetylene complex of titanocene was treated with ethylene, the most simple Cp_2-titanacyclopentene was formed in good yield, which, upon hydrolysis with a limited amount of water, gives a μ-oxo complex (eq 132).[172] The

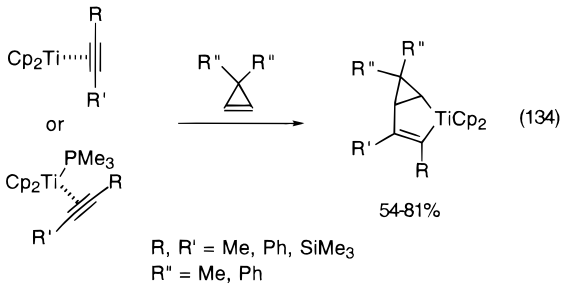


coupling product resulting from a norbornene derivative serves for the structural determination, because the titanacycle itself proved to be quite stable (eq 133).[173]

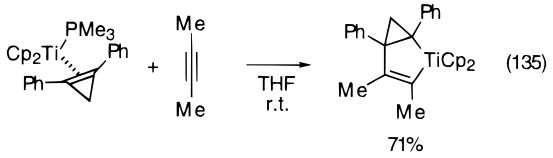


(133)

Cyclopropenes work as an olefinic component in the reaction with a Cp_2Ti−acetylene complex to yield the bicyclic titanacycles (eq 134).[38] Similarly, a cyclopropene−titanium complex reacts with an acetylene to give the same type of titanacycles (eq 135).[38] The



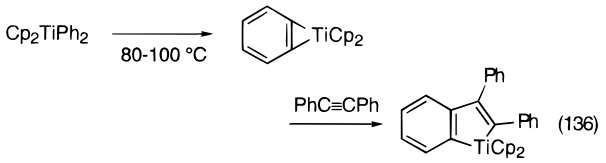
(134)



(135)

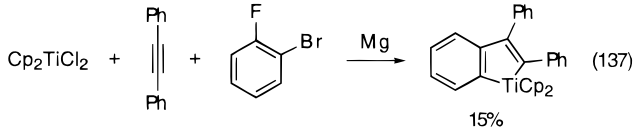
homocoupling of cyclopropenes with $Cp_2Ti(PMe_3)_2$ to give tricyclic titanacyclopentanes has also been reported.[39]

The addition of a benzyne−titanium complex to an unsaturated compound may be grouped together with the reactions of acetylene−titanium complexes. This reaction was initially carried out via thermolysis of diphenyltitanocene in the presence of diphenylacetylene (eq 136).[174] Alternatively, treatment of Cp_2TiCl_2



(136)

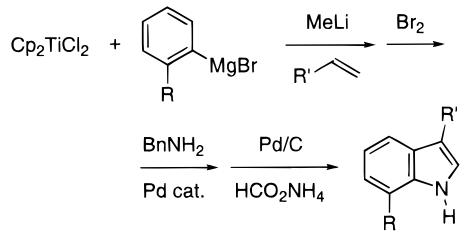
and PhC≡CPh with a benzyne precursor, fluorobromobenzene and Mg, afforded the same complex (eq 137).[175] However, the titanium−benzyne complex

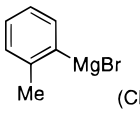
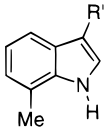
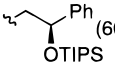
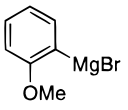
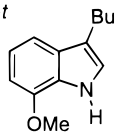
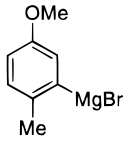
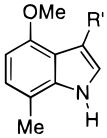


(137)

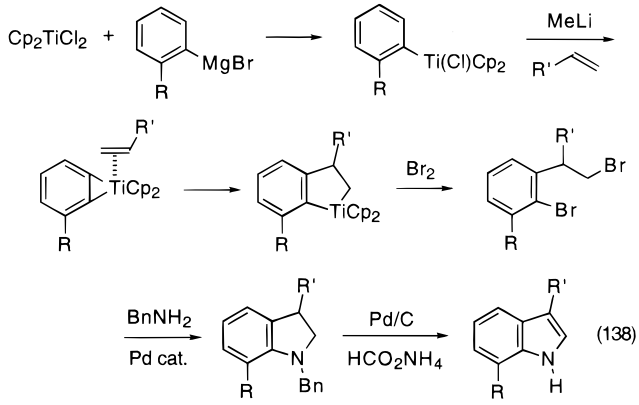
could be more conveniently generated and intercepted: Cp_2TiCl_2 is treated with an aryl Grignard reagent to give aryltitanocene chloride, which is further treated with MeLi in the presence of an olefin to give the corresponding benzotitanacyclopentane

Table 37. Synthesis of Indoles According to Eq 138 (Refs 176 and 177)



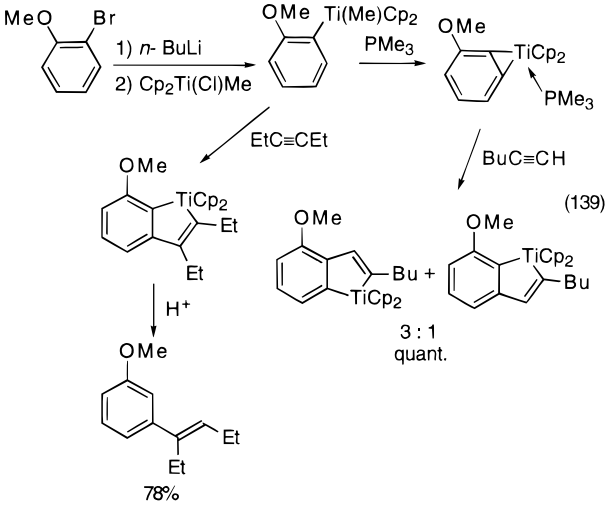
ArMgBr	R' in Olefin	Product	Yield (%)
	H		41
	Bu		54
	$(CH_2)_4OTIPS$		44
			44 (67% ee)
	$(CH_2)_8CO_2Bu$-*t*		33
	Bu		38
	H		30
	Bu		18

(eq 138). This titanacycle was utilized for the preparation of indoles via a few steps as shown in eq 138 and Table 37.[176,177] The interception of the benzyne−titanium complex with acetylene proved to be feasible as well, realizing the alkenylation of an aromatic ring (eq 139).[176] A terminal acetylene gave regioisomeric products with respect to the intermediate benzyne−titanium complex.

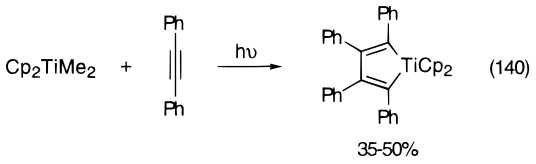


(138)

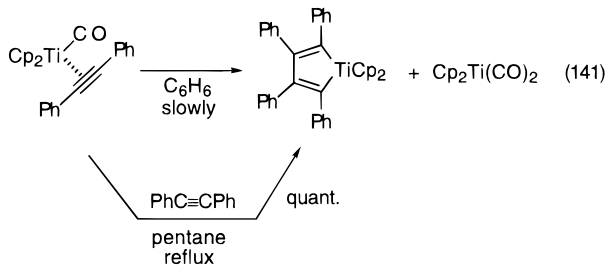
The alkyne−alkyne coupling reaction continues to be a potential method for the preparation of conjugated dienes after hydrolysis of the intermediate titanacyclopentadiene. The coupling of acetylenes with titanium reagents was first investigated in the mid-1970s. The earlier studies were centered on the generation and reaction of tetraphenyltitanacyclopentadienes. Photolysis of dimethyltitanocene pro-



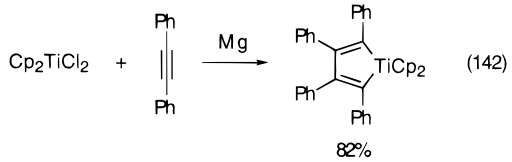
duced a titanium intermediate, which was trapped with diphenylacetylene to give the titanacycle (eq 140).[178,179] The reaction of $Cp_2Ti(CO)(PhC{\equiv}CPh)$ with



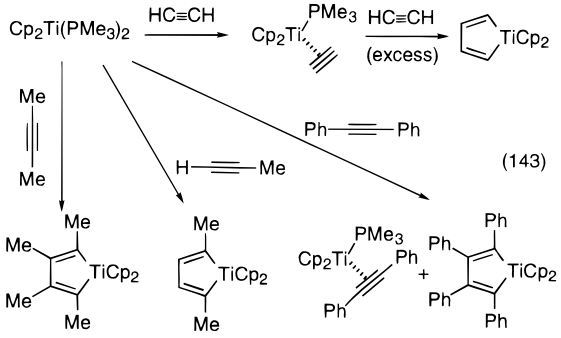
an additional diphenylacetylene generates the titanacycle as shown in eq 141.[66,67] The reaction of Cp_2-

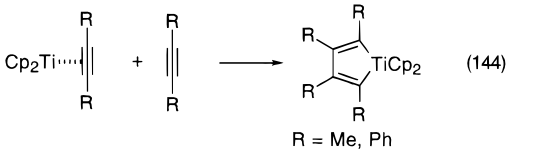


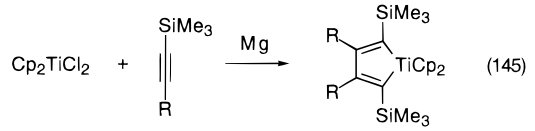
$TiCl_2$ with Mg in the presence of PhC≡CPh afforded the complex in a good yield (eq 142).[1e,175]

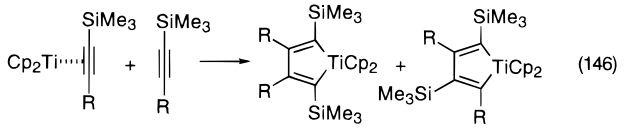


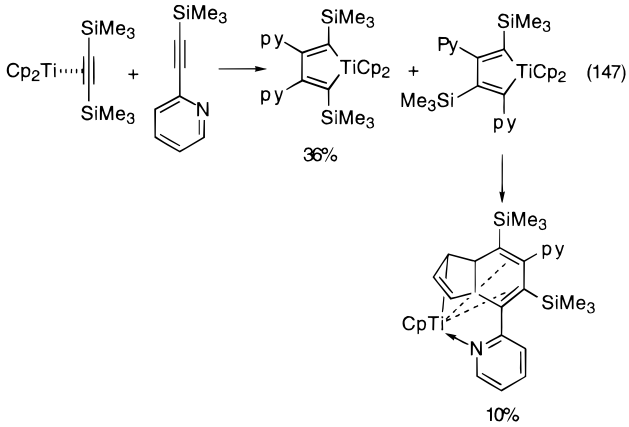
In addition to the above reactions, a broad range of acetylenes afford the desired titanacyclopentadienes as exemplified in eqs 143,[70,71] 144,[68,73,180] 145,[73,181] 146,[181−183] and 147.[182] In some instances (eq 147), an unusual coupling reaction involving the titanacycle and the cyclopentadienyl ligand was observed.[182−184] Homocoupling of a conjugated diyne proceeded to give the single titanacycle,[1e,102] which



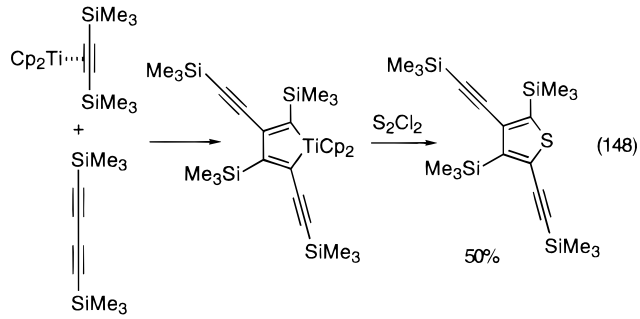






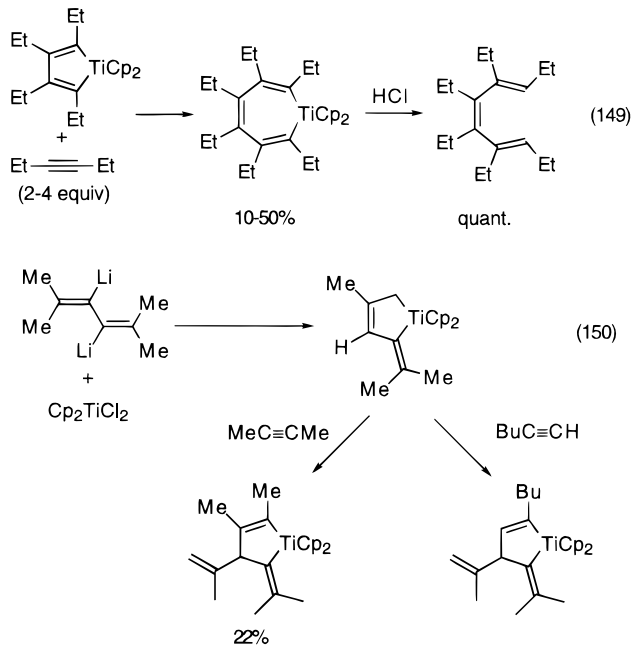


was utilized for the preparation of a heterocyclic compound (eq 148).[185]

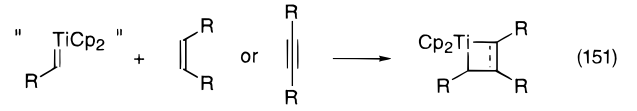


Cp_2-titanacycles could incorporate an additional unsaturated molecule to give a new titanacycle,

which is illustrated in eqs 149[186] and 150.[180]

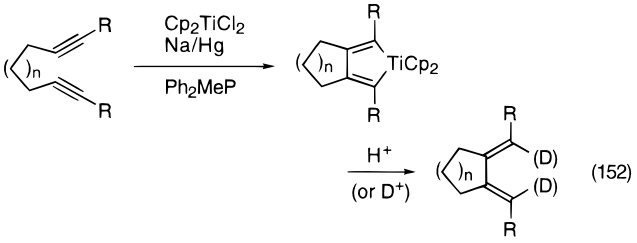


In addition to the five- and six-membered titanacycles, four-membered titanacycles, that is, titanacyclobutanes and -butenes, could be generated by the reaction with olefins or acetylenes with a titanium−carbene complex or its equivalents (eq 151), which has been reviewed.[187,188]



1.2. Intramolecular Reaction

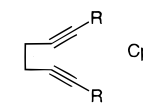
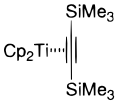
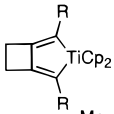
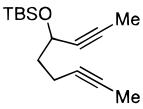
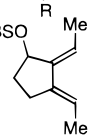
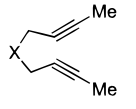
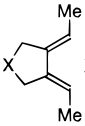
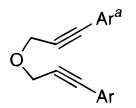
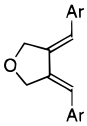
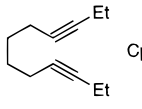
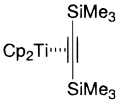
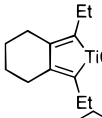
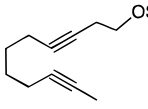
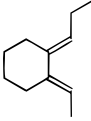
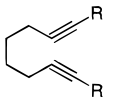
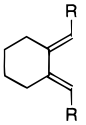
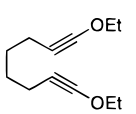
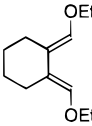
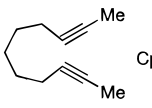
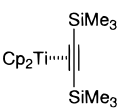
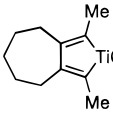
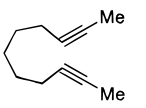
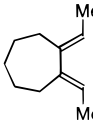
Intramolecular coupling of alkenes and alkynes, i.e., bicyclization of dienes, diynes, and enynes to give bicyclic titanacycles, is feasible as well.[1e,j,s] Although the bicyclization of a diene was reported earlier,[169] the synthetic utility of the intramolecular reaction was first demonstrated by Nugent et al. in his synthesis of *exo*-cyclic conjugated dienes, particularly useful for Diels−Alder reactions, from diynes (eq 152). The reaction was carried out with a low-valent



titanocene reagent generated from Cp_2TiCl_2, Na/Hg, and Ph_2MeP in the presence of diynes.[189,190] The various dienes produced after hydrolysis are summarized in Table 38. The subsequent Diels−Alder reaction of these dienes has indeed been demonstrated.[189] Other reagents such as an acetylene−titanium complex $Cp_2Ti(Me_3SiC{\equiv}CSiMe_3)$[184] are also effective for the same cyclization, the results of which are included in Table 38.

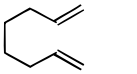
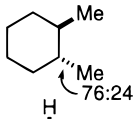
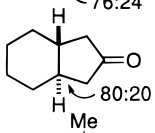
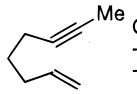
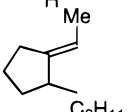
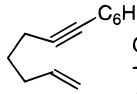
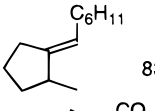
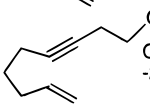
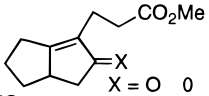
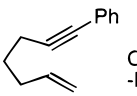
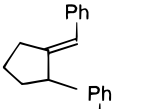
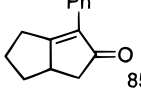
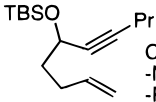
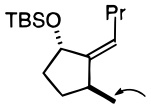
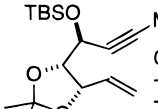
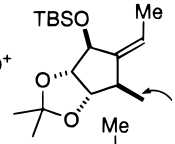
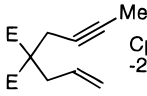
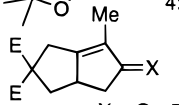
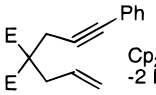
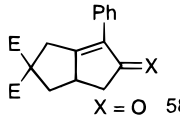
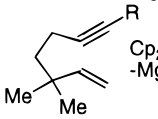
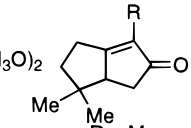
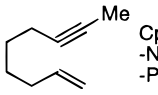
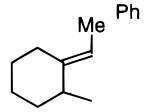
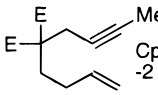
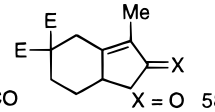
Intramolecular enyne cyclization provides versatile transformations in organic synthesis, because the resulting bicyclic titanacycles could be halogenated, carbonylated, etc., in addition to hydrolysis, to give mono- to polycyclic compounds. For example, the treatment of the enynes with Cp_2TiCl_2−Na/Hg−Ph_2-MeP reagent as above, followed by hydrolysis, car-

Table 38. Cyclization of Diynes with Titanocene Reagents

Enynes	Titanium reagent	Work-up	Product	Yield (%)	Ref.
		- -		R = Me 71, Bu 51	184
	Cp_2TiCl_2-Na/Hg-$PMePh_2$	H_3O^+		19	190
	Cp_2TiCl_2-Na/Hg-$PMePh_2$	H_3O^+		X = O 72, CH_2 60	190, 189
	Cp_2TiCl_2-Na/Hg-$PMePh_2$	H_3O^+		67	190
		- -		80	184
	Cp_2TiCl_2-Na/Hg-$PMePh_2$	H_3O^+		79	1m
	Cp_2TiCl_2-Na/Hg-$PMePh_2$	H_3O^+		R = $SiMe_3$ 0, Me 80, Et 68, Ph 35	190, 189, 189, 189
	Cp_2TiCl_2-Na/Hg-$PMePh_2$	H_3O^+		63	189
		- -		63	184
	Cp_2TiCl_2-Na/Hg-$PMePh_2$	H_3O^+		27	189

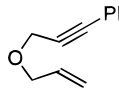
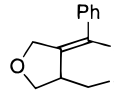
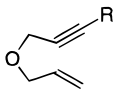
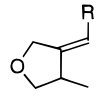
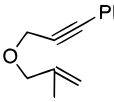
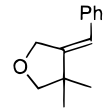
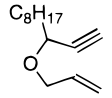
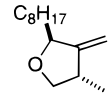
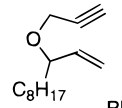
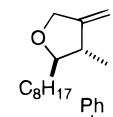
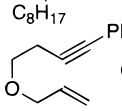
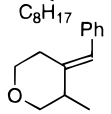
[a] Ar = 3,4-(methylenedioxy)phenyl.

Table 39. Preparation of Carbocyclic Compounds from Dienes and Enynes via the Titanacycle Formation[a]

Dienes or Enynes	Titanium reagent	Trapping reagent	Product	Yield %	Ref.
	$TiCp_2$	H_3O^+		94	169
	$TiCp_2$	CO		85	169
	Cp_2TiCl_2 -Na/Hg -$PMePh_2$	H_3O^+		80	191
	Cp_2TiCl_2 -Mg	H_2SO_4		83	193
	Cp_2TiCl_2 -2 EtMgBr	CO	 X = O	0	192
		t-BuNC	NBu-*t*	67	192
	Cp_2TiCl_2 -Mg	H_2SO_4		67	193
	Cp_2TiCl_2 -Mg-$P(OEt)_3$	$(CCl_3O)_2$ -CO		85	194, 195
	Cp_2TiCl_2 -Na/Hg -$PMePh_2$	H_3O^+		33	191
			7:1		
	Cp_2TiCl_2 -Na/Hg -$PMePh_2$	H_3O^+		32	191
			4:1-2:1		
 E = CO_2Et	Cp_2TiCl_2 -2 EtMgBr	CO	 X = O	58	192
		ArNC	N-Ar	81	192
	Cp_2TiCl_2 -Mg-$P(OEt)_3$	$(CCl_3O)_2$ -CO	X = O	82	194, 195
	Cp_2TiCl_2 -2 EtMgBr	CO	 X = O	58	192
		ArNC	N-Ar	65	192
	Cp_2TiCl_2 -Mg-$P(OEt)_3$	$(CCl_3O)_2$ -CO	X = O	65	194, 195
	Cp_2TiCl_2 -Mg-$P(OEt)_3$	$(CCl_3O)_2$ -CO	 R = Me	70	194, 195
			Ph	58	
	Cp_2TiCl_2 -Na/Hg -$PMePh_2$	H_3O^+		91	191
	Cp_2TiCl_2 -2 EtMgBr	CO	 X = O	58	192
		ArNC	N-Ar	86	192

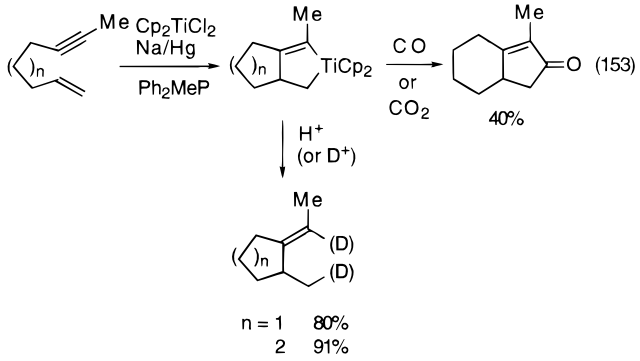
[a] ArNC = $(2,6\text{-}Me_2C_6H_3)NC$.

Table 40. Preparation of Heterocyclic Compounds from Enyne via the Titanacycle Formation (Ref 193)[a]

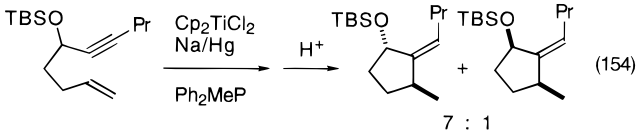
Enynes	Titanium reagent	Work-up	Product	Yield, % [D.s]
	Cp_2TiCl_2-Mg	$H(D)_2SO_4$		72
	Cp_2TiCl_2-Mg	H_2SO_4	 R = C_8H_{17}	49
			$SiMe_3$	40
	Cp_2TiCl_2-Mg	H_2SO_4		75
	Cp_2TiCl_2-Mg	H_2SO_4		46 [93:7]
	Cp_2TiCl_2-Mg	H_2SO_4		57 [>95:5]
	Cp_2TiCl_2-Mg	H_2SO_4		59

[a] ArNC = $(2,6\text{-}Me_2C_6H_3)NC$.

bonylation with CO, or the reaction with CO_2,[1m] gave the mono- or bicyclic products as shown in eq 153.



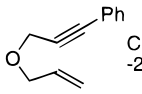
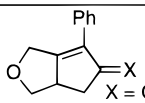
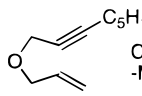
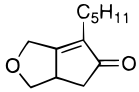
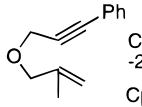
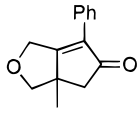
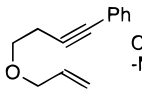
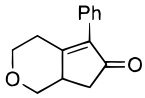
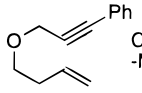
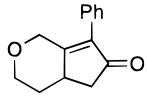
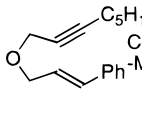
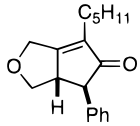
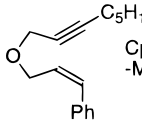
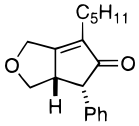
The diastereoselectivity of the cyclization was examined as illustrated by the reaction of eq 154.[191] Other



reagents including $Cp_2Ti(PMe_3)_2$,[192] Cp_2TiCl_2-2Et-MgBr,[192] Cp_2TiCl_2−Mg,[193−195] and Cp_2TiCl_2-2*n*-Bu-Li[195] promote the cyclization as well. The results of the diene and enyne cyclizations and the subsequent reactions are summarized in Tables 39−41.

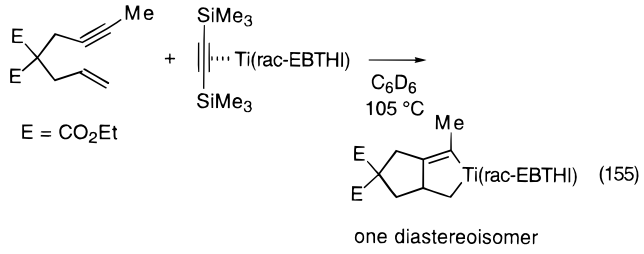
The enyne and a chiral titanium complex, (EBTHI)-Ti(disilylacetylene) [EBTHI = ethylenebis(tetrahydroindenyl)], furnished the corresponding titanacycle

Table 41. Preparation of Heterocyclic Ketones from Enynes via the Titanacycle Formation (Refs 192, 194, and 195)[a]

Enynes	Titanium reagent	Trapping reagent	Product	Yield, %
	Cp_2TiCl_2 -2 EtMgBr	CO	 X = O	49
		ArNC	N-Ar	63
	Cp_2TiCl_2 -Mg-$P(OEt)_3$	$(CCl_3O)_2CO$	X = O	82
	Cp_2TiCl_2 -Mg-$P(OEt)_3$	$(CCl_3O)_2CO$		77
	Cp_2TiCl_2 -2 *n*-BuLi	$(CCl_3O)_2CO$		60
	Cp_2TiCl_2 -Mg-$P(OEt)_3$	$(CCl_3O)_2CO$		84
	Cp_2TiCl_2 -Mg-$P(OEt)_3$	$(CCl_3O)_2CO$		63
	Cp_2TiCl_2 -Mg-$P(OEt)_3$	$(CCl_3O)_2CO$		30
	Cp_2TiCl_2 -Mg-$P(OEt)_3$	$(CCl_3O)_2CO$		61
	Cp_2TiCl_2 -Mg-$P(OEt)_3$	$(CCl_3O)_2CO$		74

[a] ArNC = 2,6-$Me_2C_6H_3NC$.

as a single diastereoisomer as shown in eq 155, demonstrating an efficient asymmetric cyclization.[196]

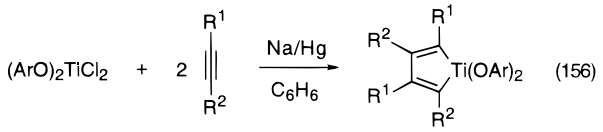


E = CO_2Et (155)

one diastereoisomer

2. Titanacycles Having a Non-Titanocene Structure

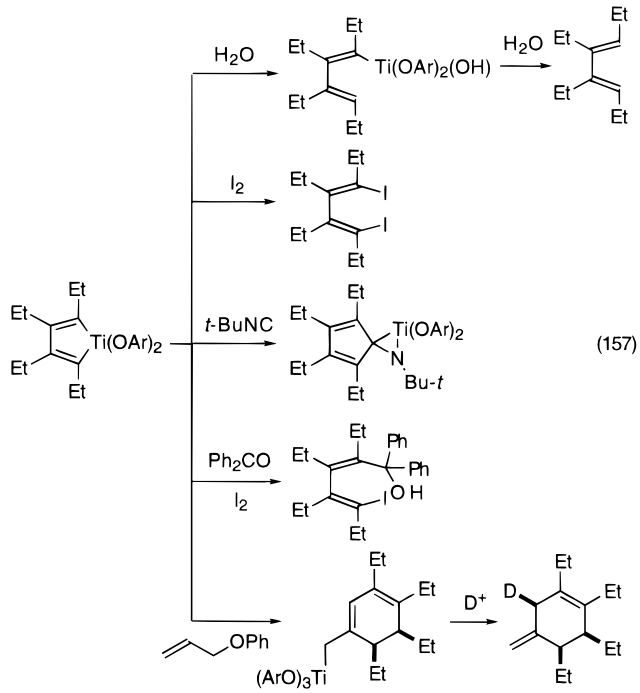
Titanacyclopentadienes having aryloxy ligands in place of cyclopentadienyl groups have been prepared by the reduction of dichlorotitanium aryloxide with sodium amalgam in the presence of acetylene as shown in eq 156.[197] The behavior of these titanacy-



(156)

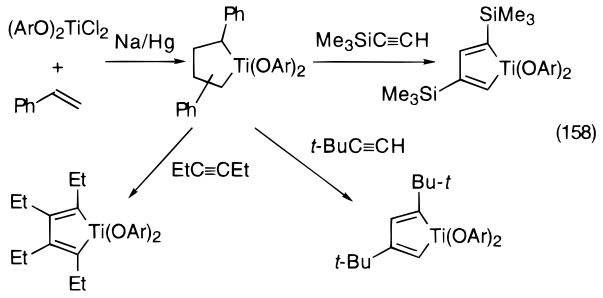
ArO = (2,6-$Ph_2C_6H_3$)O-
(R^1, R^2) = (Me, Me), (*t*-Bu, H), (Me, Ph), (Et, Et) 80-90%

clopentadienes toward several reagents is represented in eq 157.[197,198]



(157)

A diaryloxytitanacyclopentane could be generated from $(ArO)_2TiCl_2$ and styrene in the same manner as shown in eq 158.[199] When this diphenyltitanacy-

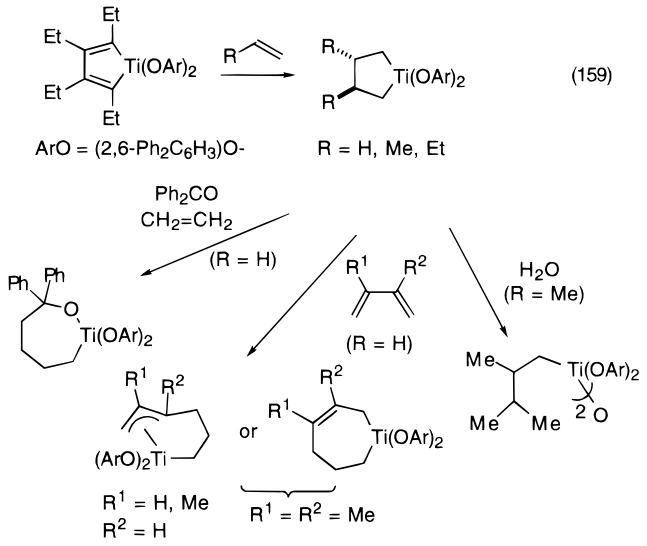


(158)

clopentane was treated with acetylenes, the conversion from the titanacyclopentane to titanacyclopentadienes took place.

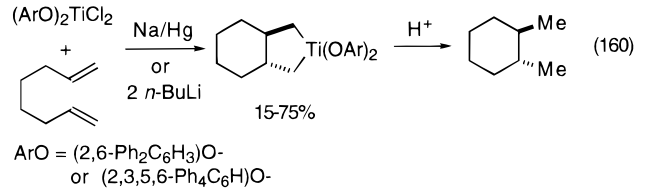
Alternatively, a few other titanacyclopentanes could be generated from the aforementioned tetraethyltitanacyclopentadiene (see eq 156) via the ligand exchange reaction with an appropriate olefin (eq

159).[62,63] The resulting titanacyclopentane undergoes

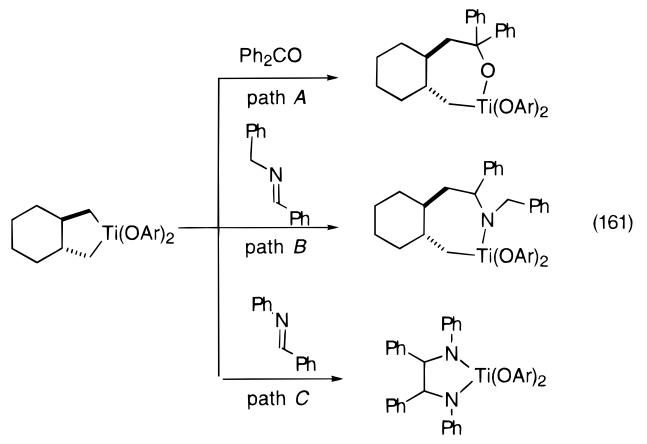


the coupling reaction with a variety of unsaturated compounds as shown in eq 159.[65] In addition, monoprotonation with water gave a (2,3-dimethylbutyl)titanium species.[65]

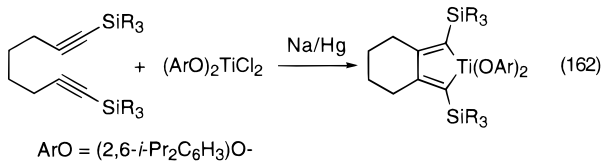
Treatment of 1,7-octadiene and $(ArO)_2TiCl_2$ with a reductant such as Na/Hg or, more conveniently, 2 equiv of *n*-BuLi afforded the bicyclic titanacyclopentane (eq 160).[65,200] The structure of the titanacycle



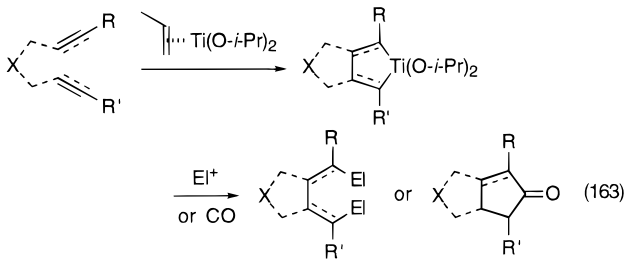
was confirmed by hydrolysis, which afforded *trans*-1,2-dimethylcyclohexane. In addition to the simple hydrolysis, the bicyclic titanacycle reacts with benzophenone or an imine to effect the carbon−carbon bond elongation (eq 161, paths *A* and *B*).[65] However,



the imine of an aromatic amine is an exceptional case that forms the homocoupling product of the imine with complete dissociation of the ligating alkyl group of the starting titanacycle (path *C*).[65] The intramolecular cyclization of diynes has also been documented to give bicyclic titanacyclopentadienes (eq 162).[201]

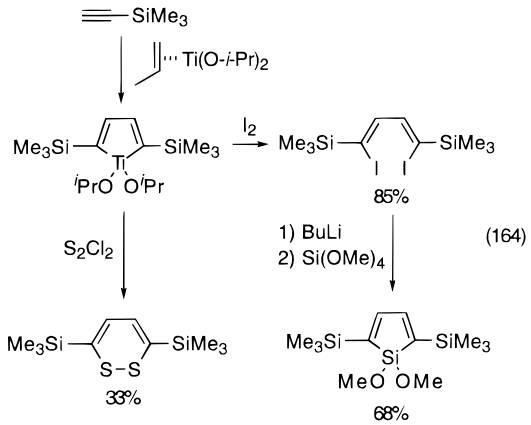


(η^2-Propene)Ti(O-*i*-Pr)$_2$ described in the foregoing sections was found to nicely effect the olefin or acetylene coupling reactions as shown in eq 163.[202]



As the titanium alkoxide is very inexpensive, the reactions in eq 163 are, to date, some of the most economical methods to achieve the formation of metallacycles of this type.[1d,e,g,j,q,s] Moreover, the titanium alkoxide-based method enables several new synthetic transformations that are not viable by the conventional titanocene-mediated methods.

Homocoupling reaction of several acetylenes with (η^2-propene)Ti(O-*i*-Pr)$_2$ has been reported.[88,203] Equation 164 shows a representative reaction, in which the titanacyclopentadiene thus generated was used for the synthesis of 1,2-dichalcogenins[204] and silacyclopentadienes.[203] Other results are summarized in Table 42.

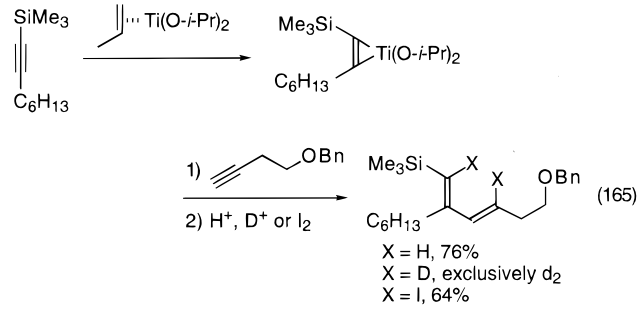


The cross-coupling reaction between internal and terminal acetylenes is also effected by (η^2-propene)-Ti(O-*i*-Pr)$_2$ to give the corresponding conjugated dienes after hydrolysis, deuteriolysis, and iodinolysis

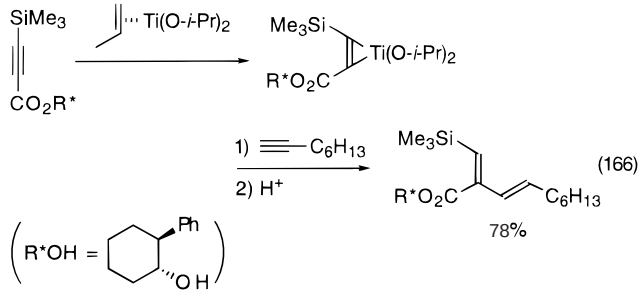
Table 42. (η^2-Propene)Ti(O-*i*-Pr)$_2$-Mediated Homocoupling of Acetylenes

Substrate	Work-up	Product	Yield (%)	Ref.
Bu-*t*	X_2	*t*-Bu, Bu-*t*, X X	X = I 93	204
			X = SCN 67	204
			X = SeCN 54	204
	S_2Cl_2	*t*-Bu, Bu-*t*, S–S	63	204
	$Se(SeCN)_2$	*t*-Bu, Bu-*t*, Se	74	204
$SiMe_3$	X_2	Me_3Si, $SiMe_3$, X X	X = Br 51	203
			X = I 68-85	203,204
			X = SCN 56	204
	S_2Cl_2	Me_3Si, $SiMe_3$, S–S	33	204
Ph	X_2	Ph, Ph, X X	X = Br 46	203
			X = I 47	203
$SiMe_3$, Me	I_2	Me, Me, Me_3Si, $SiMe_3$, I I	75	203

(eq 165).[86] It should be noted that functionalized



dienes can be prepared by this method from functionalized acetylenes, which appears to be difficult by other group 4 metal-mediated cyclizations (eq 166). Table 43 shows additional results of the synthesis of dienes via the cross-coupling reaction.



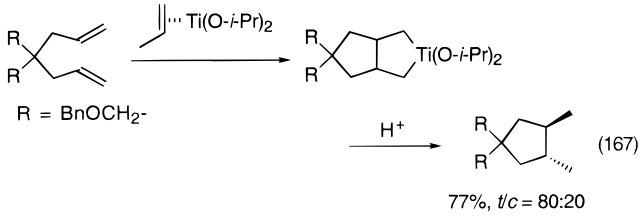
Intramolecular cyclization of dienes, enynes, and diynes proceeds smoothly to give cyclopentane or cyclohexane frameworks as formulated in eq 163.

Table 43. Preparation of Dienes via Cross-Coupling Reaction (Ref 86)

Internal Acetylene	Terminal Acetylene	Product	Yield (%)
$SiMe_3$, C_6H_{13}	OBn	$SiMe_3$, $H_{13}C_6$, OBn	76
$SiMe_3$, C_6H_{13}	OCO_2Et	$SiMe_3$, $H_{13}C_6$, OCO_2Et	67
$SiMe_3$, EtO, OEt	OTBS	EtO, $SiMe_3$, EtO, OTBS	88
CO_2Bu-*t*, C_6H_{13}	C_6H_{13}	CO_2Bu-*t*, $H_{13}C_6$, C_6H_{13}	60
$SiMe_3$, CO_2Bu-*t*	C_6H_{13}	$SiMe_3$, *t*-BuO_2C, C_6H_{13}	77
$SiMe_3$, CO_2R^*	C_6H_{13}	$SiMe_3$, R^*O_2C, C_6H_{13}	78
R^*OH = OH, Ph	$SiMe_3$	$SiMe_3$, R^*O_2C, $SiMe_3$	93
	CO_2Bu-*t*	$SiMe_3$, R^*O_2C, CO_2Bu-*t*	47
	R, R; R = $BnOCH_2$-	$SiMe_3$, R^*O_2C, R, R	78
CO_2NEt_2, C_6H_{13}	C_6H_{13}	CO_2NEt_2, $H_{13}C_6$, C_6H_{13}	65
CO_2NEt_2, C_6H_{13}	CO_2Bu-*t*	CO_2NEt_2, $H_{13}C_6$, CO_2Bu-*t*	59

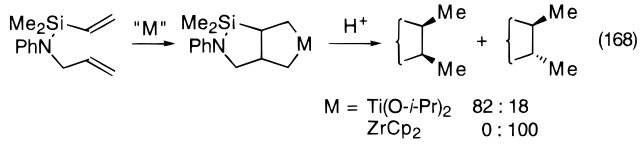
Cyclization of 1,6-diene with (η^2-propene)Ti(O-*i*-Pr)$_2$ afforded the bicyclic titanacyclopentane, which, upon

hydrolysis, gave a cyclopentane derivative (eq 167).[205]



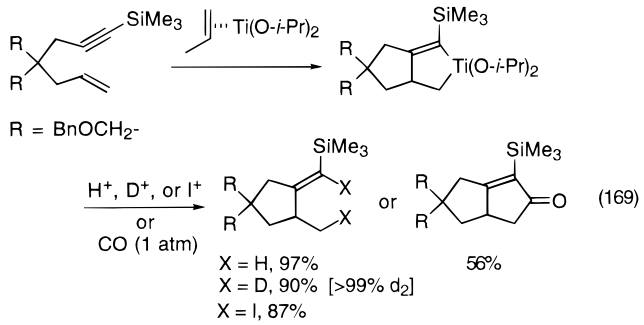
(167)

It has been reported that the stereoselections are opposite in the (η^2-propene)Ti(O-*i*-Pr)$_2$- and Cp_2Zr-mediated cyclizations (eq 168).[206] 1,6-Enynes or 1,7-



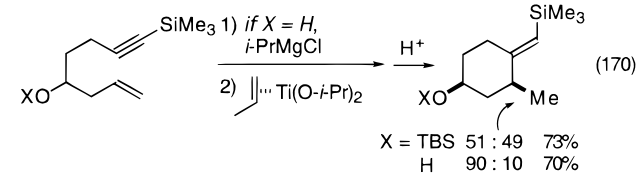
(168)

enynes underwent the cyclization to give the titanacyclopentenes, which show the routine reactivities to deuterium, iodine, or carbon monoxide to give the corresponding addition products as do other metallacycles of the group 4 transition metals (eq 169).[205]

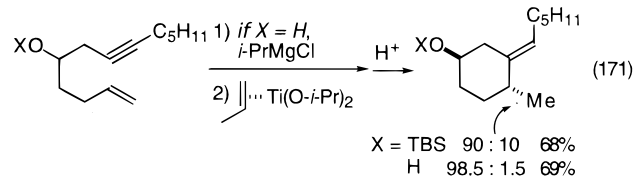


(169)

Substrate-controlled stereoselective cyclization is often required in the selective synthesis of naturally occurring products. In general, it is difficult to control the stereochemistry of the cyclization with a remote substituent to the reaction center. However, the (η^2-propene)Ti(O-*i*-Pr)$_2$-mediated cyclization of the substrates shown in eqs 170 and 171 proceeds in a highly stereoselective manner when the hydroxy group is converted to magnesium alkoxide prior to the cyclization.[207] The favorable effect of the alkoxide



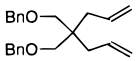
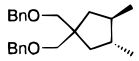
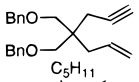
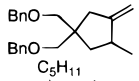
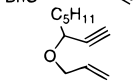
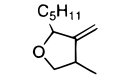
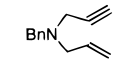
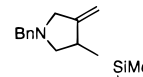
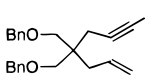
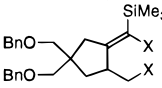
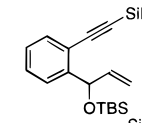
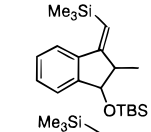
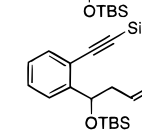
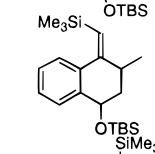
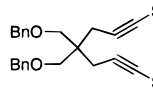
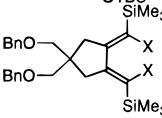
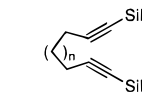
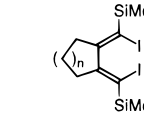
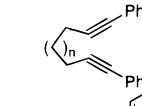
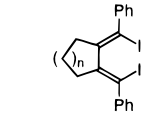
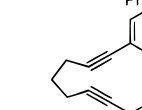
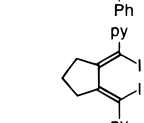
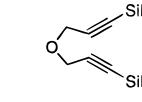
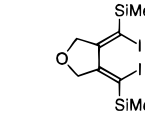
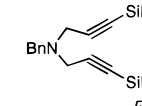
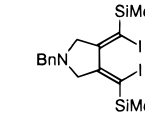
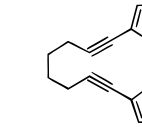
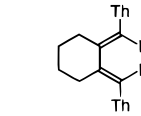
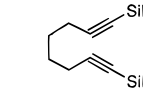
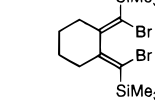
(170)



(171)

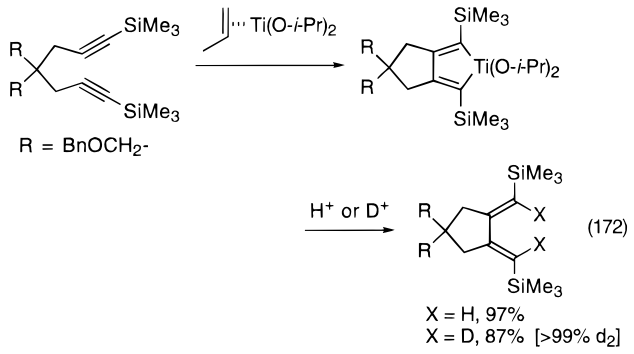
portion is obvious in comparison with the stereoselectivity observed for the corresponding TBS ethers.

Table 44. (η^2-Propene)Ti(O-*i*-Pr)$_2$-Mediated Cyclization of 1,6- or 1,7-Dienes, Enynes, and Diynes

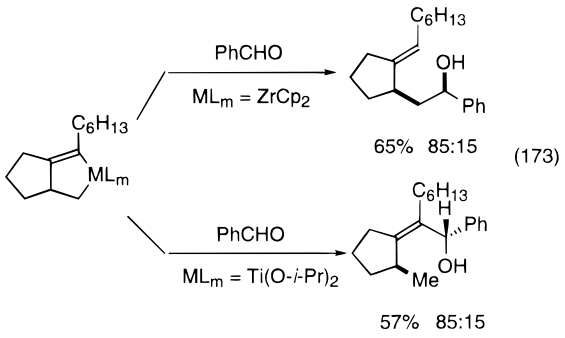
Substrate	Work-up	Product	Yield (%)	Ref.
	HCl		77 (*t*/*c* = 80:20)	205
	HCl		79	205
	HCl		65 (ds = 73:27)	205
	H_2O		53	205
	XCl		X = H, 97 X = D, 90 (>99% d_2)	205 205
	I_2		X = I, 87	205
	HCl		56	205
	HCl		47 (ds = 67:33)	205
	XCl		X = H, 97 X = D, 87 (>99% d_2)	205 205
	I_2		n = 1 83 n = 2 89	203,208, 209 203
	I_2		n = 0 63 n = 1 57 n = 2 40	203 203 203
	I_2		44	203
	I_2		--	209
	I_2		--	209
	I_2		56	203
	Br_2		78	203

The intramolecular cyclization of 1,6- or 1,7-diynes with (η^2-propene)Ti(O-*i*-Pr)$_2$ afforded the bicyclic titanacycles, which could be protonated, deuterated, and iodinated as illustrated in eq 172.[205] Other results of the cyclization of a variety of dienes, enynes, and diynes are summarized in Table 44.[205,208−211]

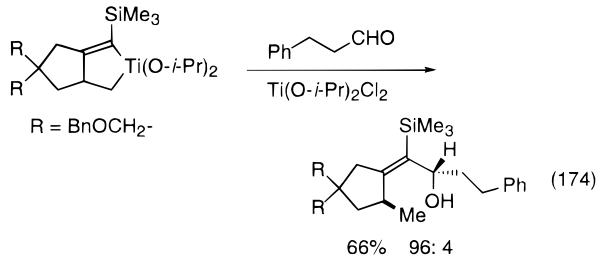
The addition of organometallic reagents to aldehydes is a fundamental synthetic transformation.



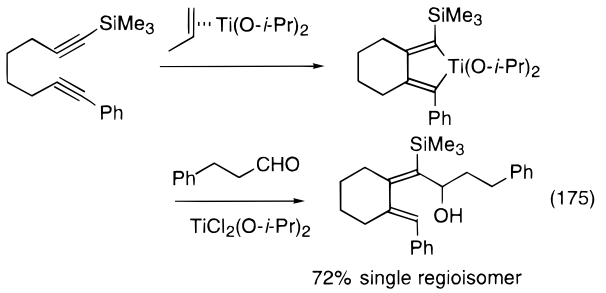
The dialkoxytitanacylcles shown above serve for this reaction. The titanacyclopentenes react with aldehydes selectively at the alkenyl−metal rather than alkyl−metal bond of the titanacycle,[210,211] which is in marked contrast to and complementary with the reaction of Cp_2-zirconacyclopentenes[1j,212] as shown in eq 173. The silylated dialkoxytitanacyclopentene,



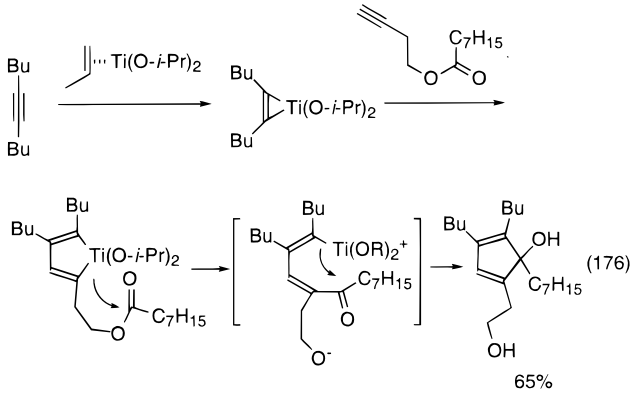
which requires an extra equivalent of $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ in the addition step to increase the product yields, showed a very high 1,4-diastereoselectivity as shown in eq 174. Similarly, dialkoxytitanacyclopentadienes



undergo the same addition to aldehydes again with very high regioselectivities (eq 175).[210,211] These reactions are surveyed in Tables 45 and 46.

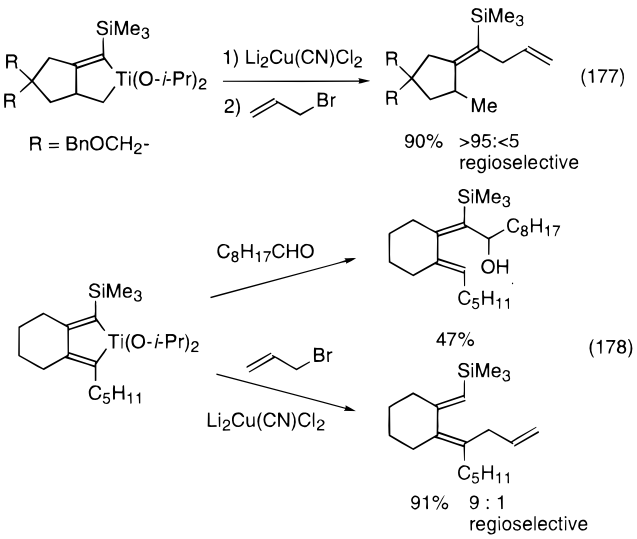


The above titanacyclopentadienes are reactive enough even toward an ester group, provided that it is placed at a suitable position in the same molecule. In such a case, both of the two carbon−titanium bonds of the titanacycle successively attacked the ester carbonyl group to give cyclopentadienols (eq 176).[213] This reaction can be applied to the prepara-



tion of mono- and bicyclic cyclopentadienols, which are shown in Table 47.

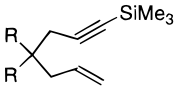
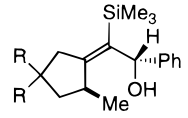
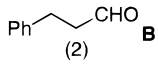
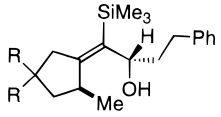
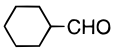
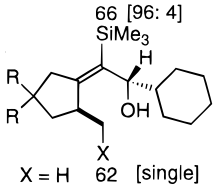
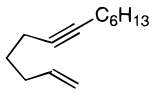
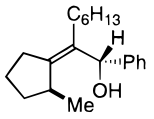
In addition to the reaction with carbonyl compounds, the alkylation of the titanacyclopentenes and -pentadienes with allyl bromide proceeds in the presence of 1 equiv of a copper salt at low temperature to give the products with high regioselectivity (eqs 177 and 178).[211] As transmetalation of titanium



compounds to other metallic species such as copper reagents has not been well studied, this would be an informative observation. The reaction stopped at the stage of monoallylation, and the other carbon−titanium bond could be identified by deuteration. The generality of this allylation reaction is shown in Table 48. The extension of a carbon chain at each carbon−titanium bond of the titanacyclopentadiene shown in eq 178 was possible by simply switching the kind of electrophiles.

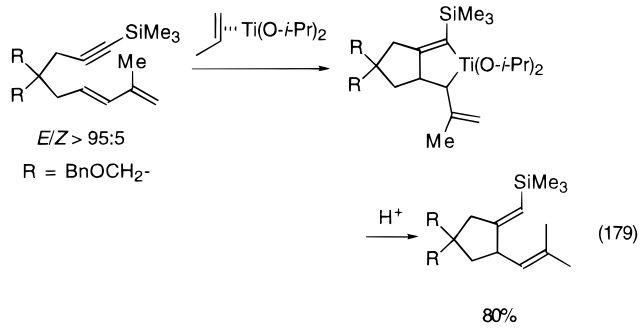
The cyclization of dienynes with (η^2-propene)Ti(O-*i*-Pr)$_2$ proceeded equally well.[214] Equation 179 shows

Table 45. Cyclization of Enynes and Subsequent Reaction with Aldehydes (Refs 210 and 211)

Enyne	Aldehyde (equiv)	Additive[a]	Work-up	Product Yield, % [Ds]
 R = BnOCH$_2$-	PhCHO (1.5)	**A**	H^+	 54 [>95:<5]
	 (2)	**B**	H^+	 66 [96: 4]
	 (0.6)	**B**	H^+	 X = H 62 [single]
	(2)	**B**	H^+	H 53-60 [single]
	"	**B**	D^+	D 60 [single] (98%d)
	"	**B**	I_2	I 58 [single]
	PhCHO (1.5)	None	H^+	 57 [85:15]

[a] **A**: Ti(O-*i*-Pr)$_3$Cl, **B**: Ti(O-*i*-Pr)$_2$Cl$_2$

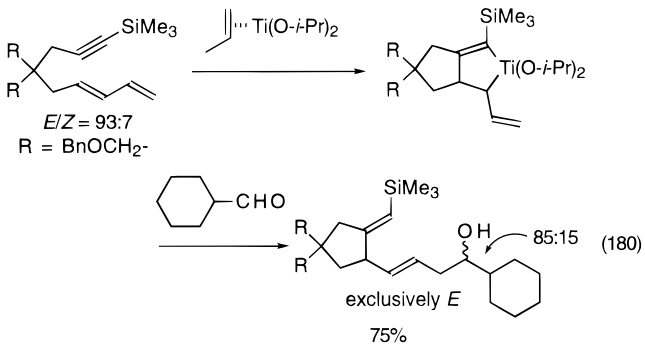
the protonation of the titanacycle, which produced a single regioisomer. The reaction of the intermediate



(179)

titanacycle and an aldehyde generally took place at the remote position of the allyltitanium system to permit the regioselective elongation of the side chain with *trans*-olefinic configuration (eq 180). Other results are summarized in Table 49.

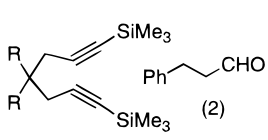
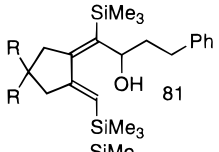
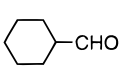
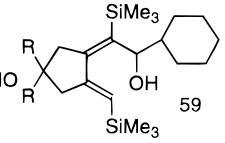
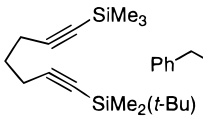
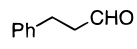
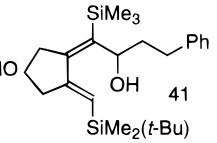
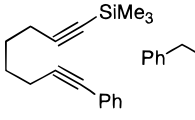
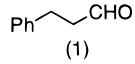
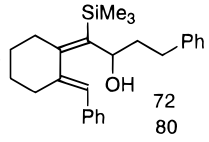
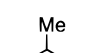
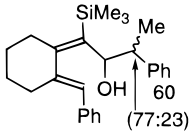
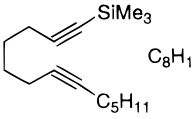
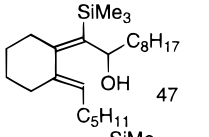
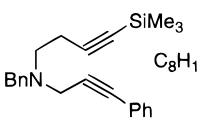
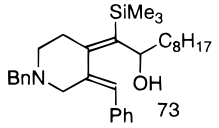
Homocoupling of allenes with (η^2-propene)Ti(O-*i*-Pr)$_2$ afforded two types of products dependent on the structure of the starting allenes.[215] A 1,1-disubstituted allene afforded a 1,5-diene after the hydrolysis or electrophilic substitution[204] of the carbon−titanium bonds of the titanacycle (eq 181), while a monosubstituted allene furnished a 1,4-diene after the reaction with an aldehyde (eq 182). The aldehyde adducts in eq 182 were converted to the stereodefined trienes via Peterson olefination.

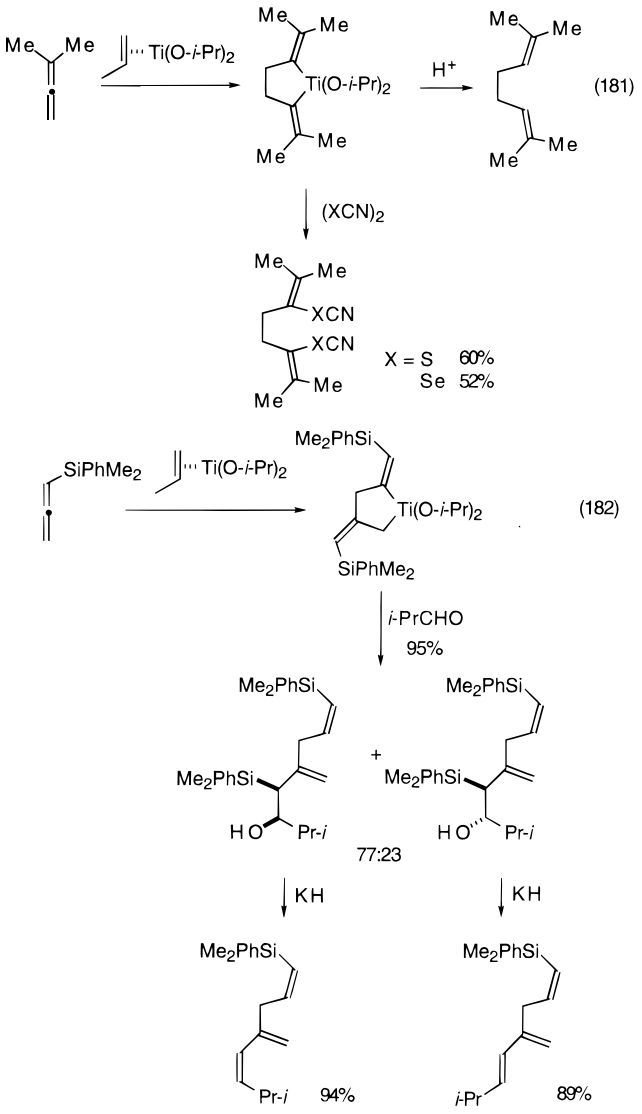


(180)

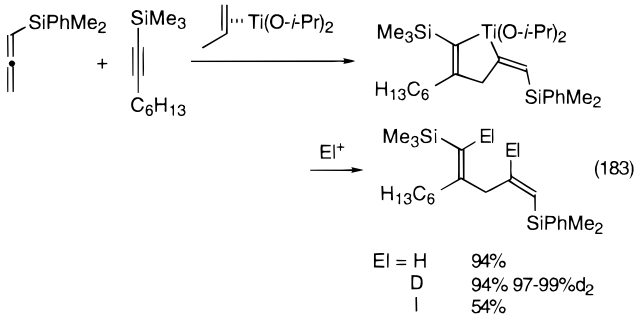
The intermolecular coupling of allene and acetylene[215] furnished the stereodefined 1,4-dienes as

Table 46. Cyclization of Diynes and Subsequent Reaction with Aldehydes (Refs 210 and 211)

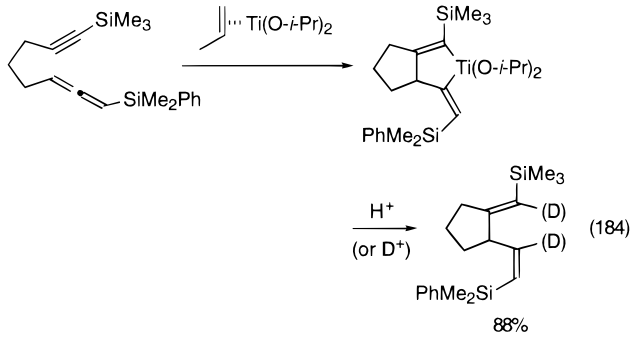
Diyne	Aldehyde (equiv)	Product Yield, %
 R = BnOCH$_2$-	(2)	 81
	 (2)	 59
	 (2)	 41
	 (1) (2)	 72 80
	 (1)	 60 (77:23)
	$C_8H_{17}CHO$ (1)	 47
	$C_8H_{17}CHO$ (1)	 73



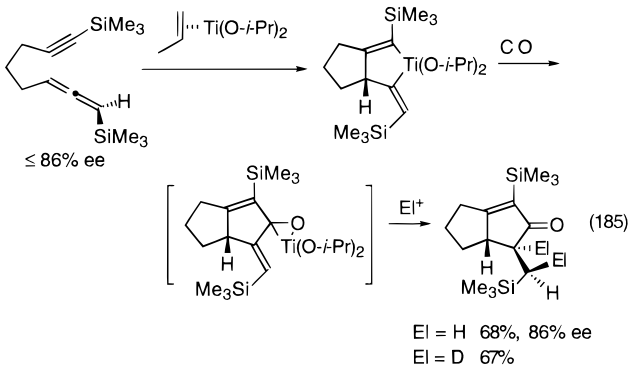
shown in eq 183.[204,215] The intramolecular cyclization



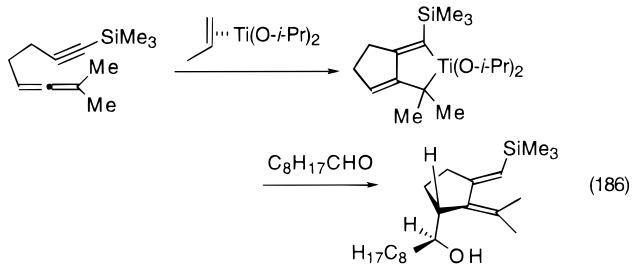
of the 1,2-dien-7-yne shown in eq 184 smoothly proceeds in the same manner as the intermolecular reaction (eq 183) to give the cyclopentane derivative as a single olefinic stereoisomer.[216] Other results are shown in Table 50. If the latter reaction starts with an optically active allene as shown in eq 185 and the carbonylation is applied in the subsequent step, a bicyclic ketone with a predictable stereochemistry

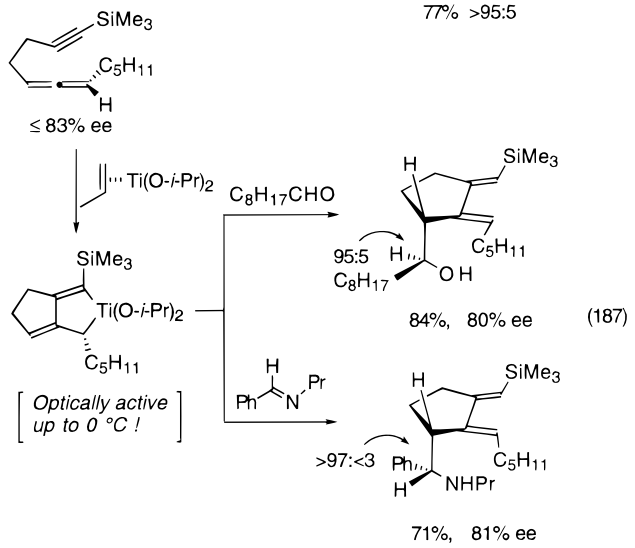


arising from virtually complete chirality transfer was obtained.[216]



Intramolecular cyclization of 1,2-dien-6-ynes shows a different mode of ring closure to give new titanacycles as shown in eqs 186 and 187.[216] The generality





of the cyclization as well as the subsequent reaction of the resultant titanacycles with electrophiles can

Table 47. Preparation of Cyclopentadienols via Titanacycle Formation (Ref 213)

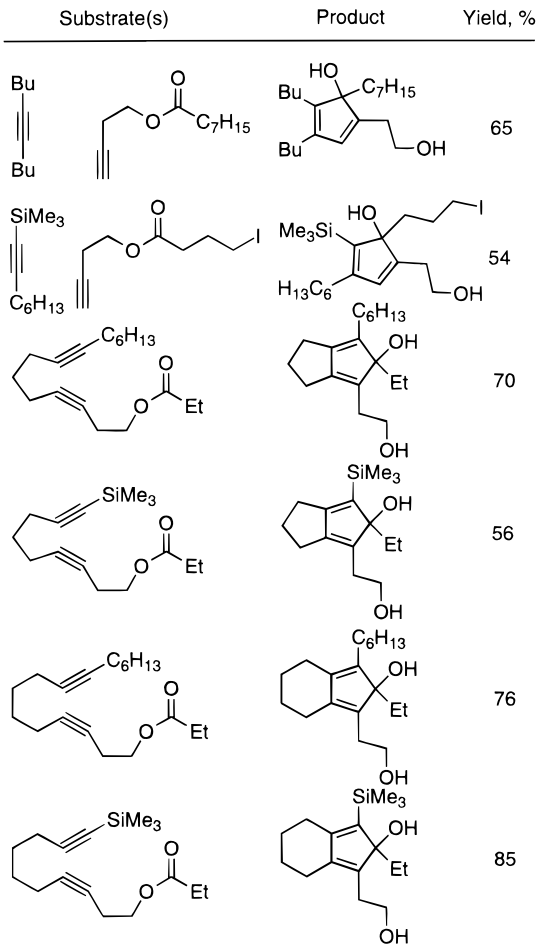
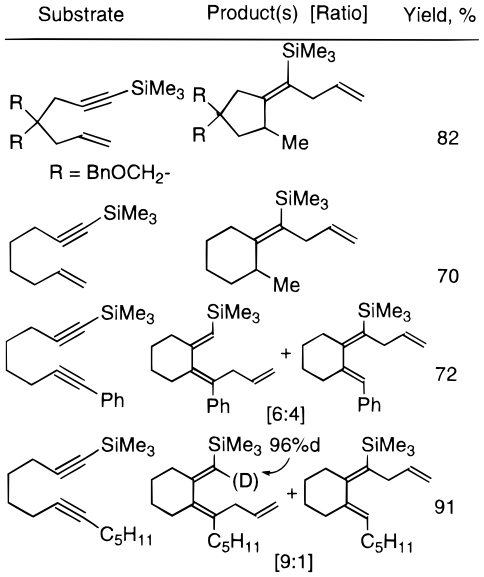


Table 48. Cyclization of Enynes or Diynes Followed by Copper-Mediated Alkylation with Allyl Bromide (Refs 210 and 211)



be seen in Table 51. It should be noted that a sterically demanding trisubstituted olefinic bond in the allene participated in the cyclization to form the titanacycle, which, upon reaction with an aldehyde, gave the exocyclic diene including an isopropylidene group (eq 186). More importantly, when the cyclization is initiated from an optically active allene, the optically active titanabicycle having no chiral auxiliary such as the one in eq 187, which belongs to a rare class of optically active allyltitanium species,[217] is generated. The titanacycle reacted with an aldehyde, ketone, or imine without loss of the enantiopurity of the starting allene to give an optically active cyclopentane skeleton (eq 187).

Table 49. (η^2-Propene)Ti(O-*i*-Pr)$_2$-Mediated Intramolecular Cyclization of Diene and Acetylene and Successive Reaction with Electrophiles (Ref 214)

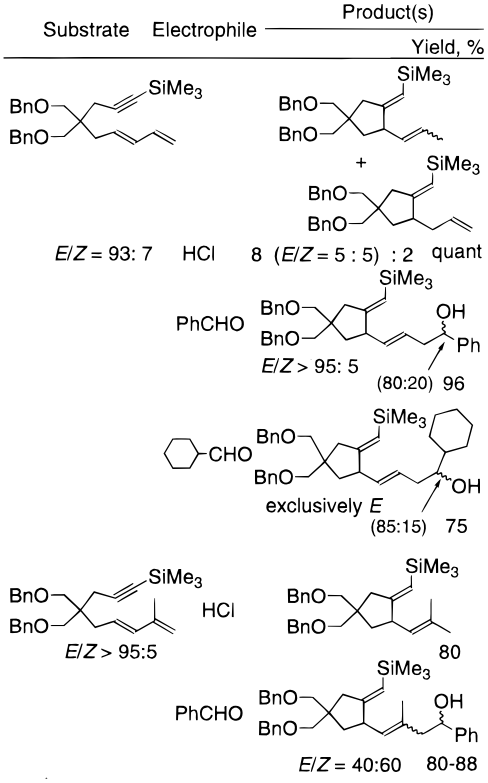


Table 50. Cyclization of 1,2-Dien-7-ynes (Ref 216)

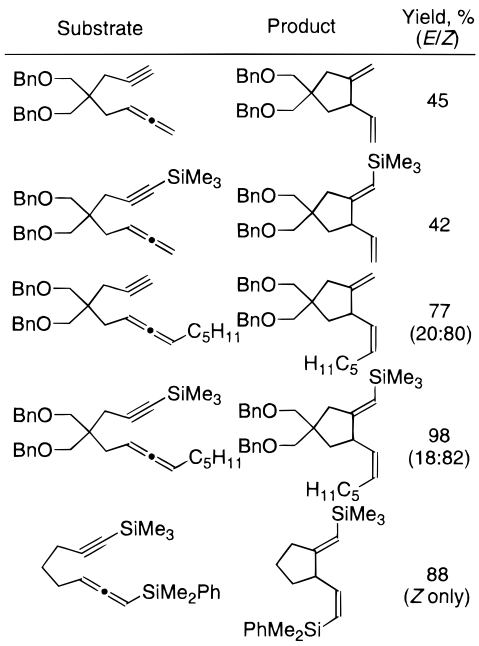
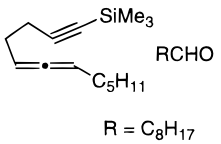
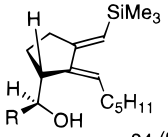
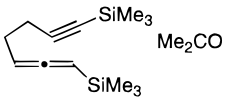
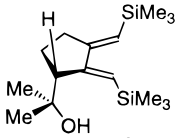
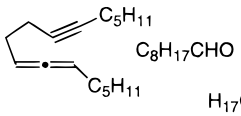
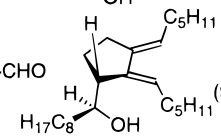
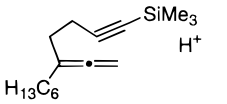
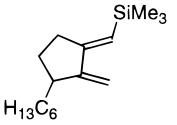
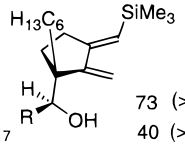
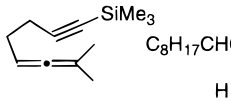
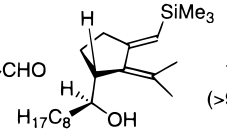
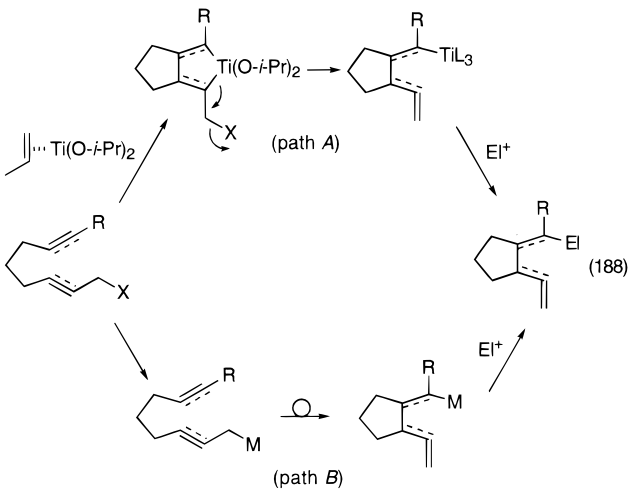


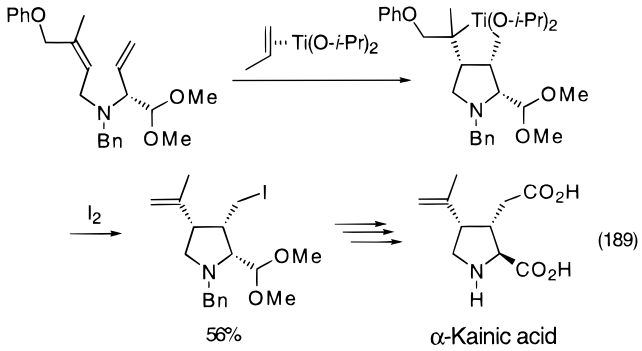
Table 51. Cyclization of 1,2-Dien-6-ynes and Subsequent Reaction with Electrophiles (Ref 216)

Substrate	Electrophile	Product	Yield, % (D.S.)
	RCHO		R = C_8H_{17} 84 (95: 5) $H_{13}C_6$ 68 (80:20) Ph 98 (74:26)
	Me_2CO		69
	$C_8H_{17}CHO$		62 (93: 7)
	H^+		75
	RCHO		R = Me 73 (>98:2) C_8H_{17} 40 (>98:2)
	$C_8H_{17}CHO$		77 (>95:5)

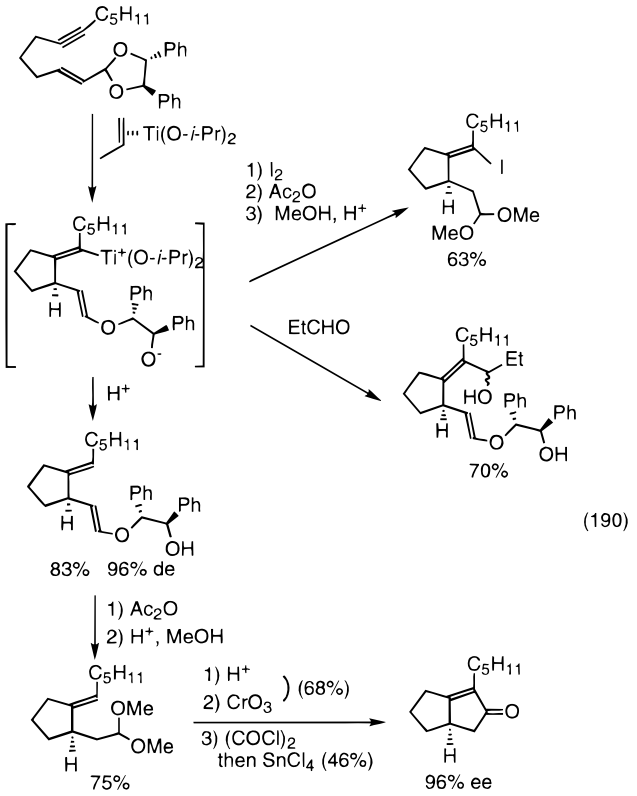
If the olefins and acetylenes that are being subjected to the intramolecular cyclization have a leaving group at an appropriate position, the resulting titanacycles experience the elimination of such group as shown in eq 188 (path *A*).[95−97] This reaction can



be considered as an alternative of the metalloene reaction (path *B*). The vinyltitanium species remaining in the product could be intercepted with electrophiles (El^+) including aldehydes. Table 52 shows the results of this transformation. Quite recently, (−)-α-kainic acid was prepared by taking advantage of the present method (eq 189).[218]



The above metalloene-type reaction of 1,6- or 1,7-enynes carrying a chiral ketal moiety such as 1,2-diphenylethylene ketal achieved an asymmetric cyclization to give optically active cyclopentane and -hexane derivatives, respectively. Equation 190 illustrates the preparation of optically active cyclopentane derivatives.[219] Some variations of the substrates are shown in Table 53. The utility of the product was further demonstrated in the synthesis of optically active bicyclic cyclopentenones.



As mentioned in the coupling reaction of functionalized acetylenes (eq 166), the intramolecular cyclization of a functionalized olefin and acetylene such as 2-en-7-ynoates or 2-en-8-ynoates readily proceeds.[220,221] Thus, the cyclization of *tert*-butyl enynoate afforded the titanacycle, the presence of which was confirmed

Table 52. Metallo-ene-Type Reactions Mediated by (η^2-Propene)Ti(O-*i*-Pr)$_2$

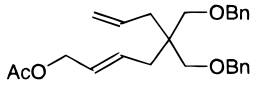
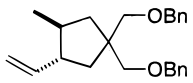
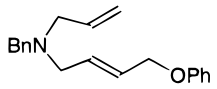
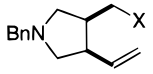
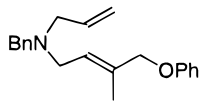
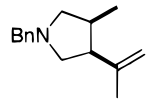
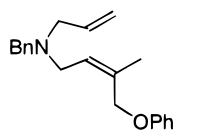
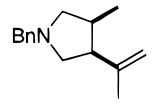
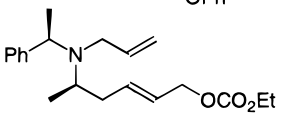
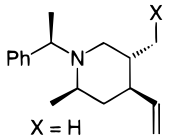
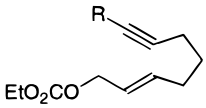
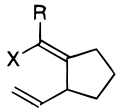
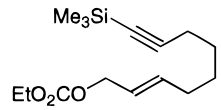
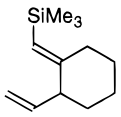
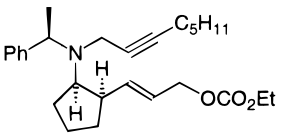
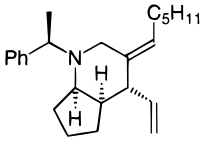
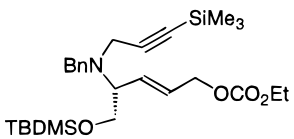
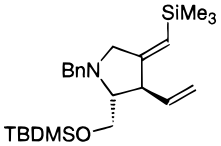
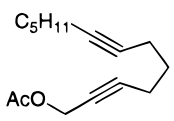
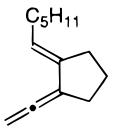
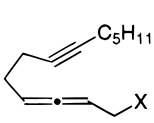
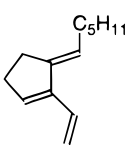
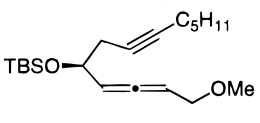
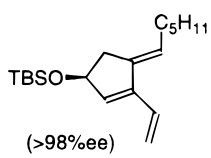
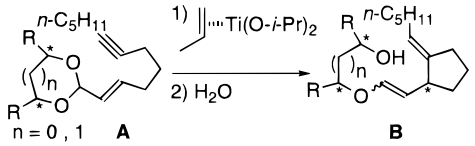
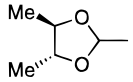
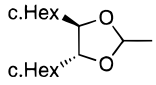
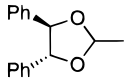
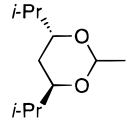
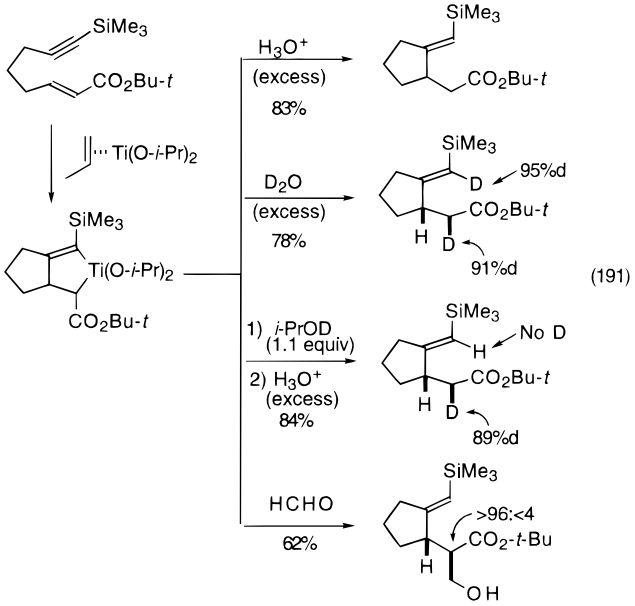
Substrate	Electrophile	Product	Yield, %	D.s. (main : other)	Ref.
	H_2O		70	90 : 10	95
	H^+	 X = H	85	6 : 1	218
	I_2	X = I	72	6 : 1	
	Br_2	X = Br	67	6 : 1	
	H^+		84	single	218
	H^+		86	single	218
	H_2O	 X = H	42	72 : 28	96
	I_2	X = I	37		
 R = Me_3Si	H_2O	 X = H	85		95
	D_2O	X = D	70 (> 97% d)		95
	I_2	X = I	80		95
	PhCHO	X = PhCH(OH)-	67	92 : 8	95
	H_2O		82		95
	H_2O		71	95 : 5	96
	H_2O		62	87 : 13	96
	H_2O		86		95
 X = OMgCl	H^+		34		97
OBn	H^+		57		97
OTBS	H^+		47		97
OAc	H^+		50		97
OCO_2Et	H^+		54		97
 (>98%ee)	H^+	 (>98%ee)	79		97

Table 53. Ti(II)-Mediated Intramolecular Cyclization of Chiral Acetals (Ref 219)



Acetal moiety in **A**	**B** Yield, %	*E/Z*	**C** *R* : *S*
	quant	66/34	66 : 34
	(93)	88/12	87 : 13
	77	pure *E*	97.5 : 2.5
	12	pure *Z*	20 : 80
	91	95/5	94 : 6
	83	pure *E*	98 : 2
	4	pure *Z*	5 : 95
	98	55/45	49 : 51
	31	pure *E*	4.3 : 95.7
	24	4/96	96.3 : 3.7

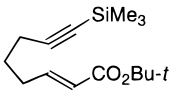
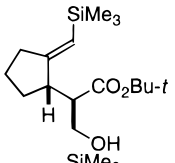
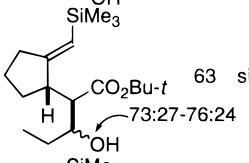
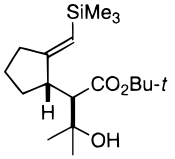
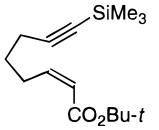
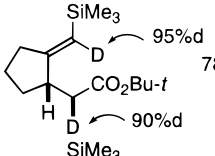
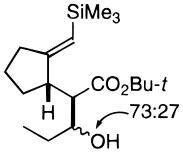
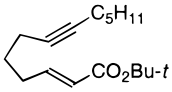
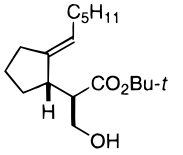
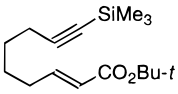
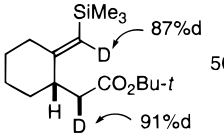
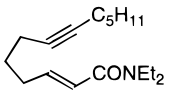
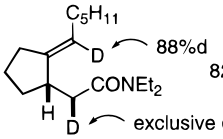
by protonolysis and deuteriolysis (eq 191). It should



(191)

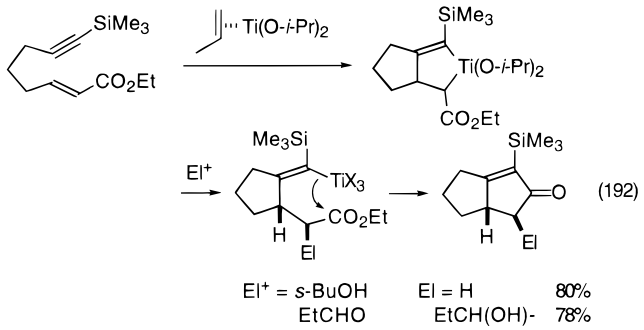
be noted that the carbon−titanium bond α to the ester group is the first position to be attacked by the proton (or D^+), as evidenced by the deuteriolysis with 1.1 equiv of *i*-PrOD. This is also true for other electrophiles such as carbonyl compounds that are exclusively introduced at this position and in a highly diastereoselective manner to offer a potential method

Table 54. Monocyclization of Bis-unsaturated Esters and Amides and Subsequent Reactions with Electrophiles (Refs 220 and 221)

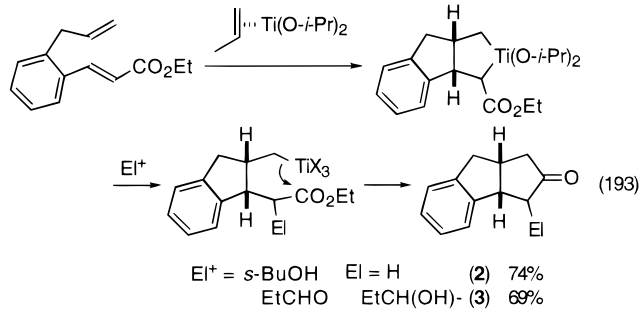
Unsaturated Ester	Electrophile	Product	Yield, %	D.S.
	HCHO		62	>96:<4
	EtCHO		63	single
	Me_2CO		34	single
	D_2O		78	single
	EtCHO		61	single
	HCHO		78	>93:<7
	D_2O		50	single
	D_2O		82	single

for the stereoselective construction of the side chain in addition to the cyclization (see the reaction with HCHO in eq 191). Other results are shown in Table 54, which shows that the same reaction proved to be possible with the corresponding amides as the substrate.

The methyl or ethyl esters of the same structure generate the titanacycles as well, but this is followed by a second ring closure initiated by the reaction with an electrophile, eventually giving bicyclic ketones as shown in eq 192.[220,221] This transformation to prepare bicyclic ketones avoids the use of toxic carbon monoxide gas as can be seen in eqs 169 and 185. The cyclization of 2,7-dienoates is also feasible to give the

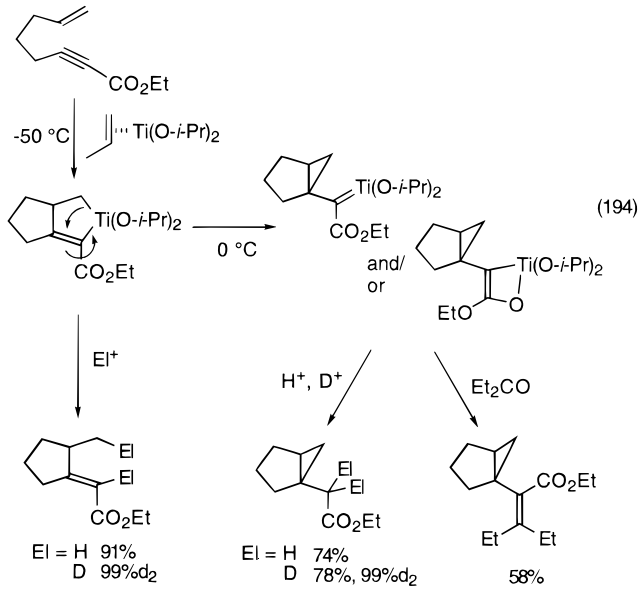


titanacycle. Its selective reaction with a proton or a carbonyl compound at the α-titanated ester moiety results in the same ring closure to give the polycyclic ketone in one step (eq 193). From a synthetic point



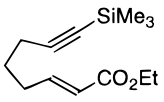
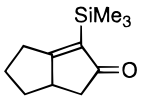
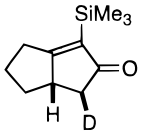
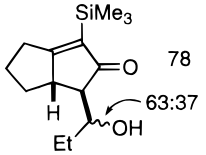
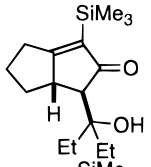
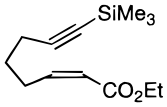
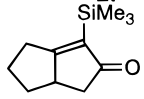
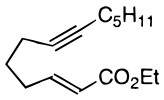
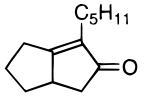
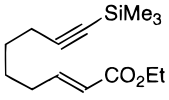
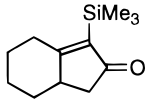
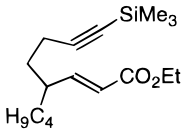
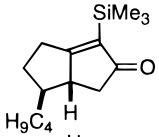
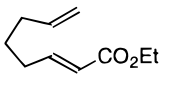
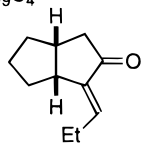
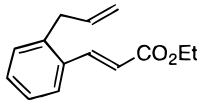
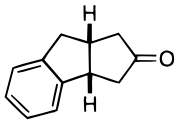
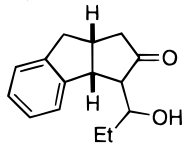
of view, the reaction of eq 193 serves as a one-pot preparation of an aldol with the defined regiochemistry, as the routine aldol reactions of the nearly symmetrical parent ketone with propionaldehyde will not show any good regioselectivity. The formation of bicyclic ketones by this method is shown in Table 55.

In contrast to the reactions of olefinic esters discussed above, 7-en-2-ynoates show another interesting behavior of cyclization (eq 194).[220,221] Deute-



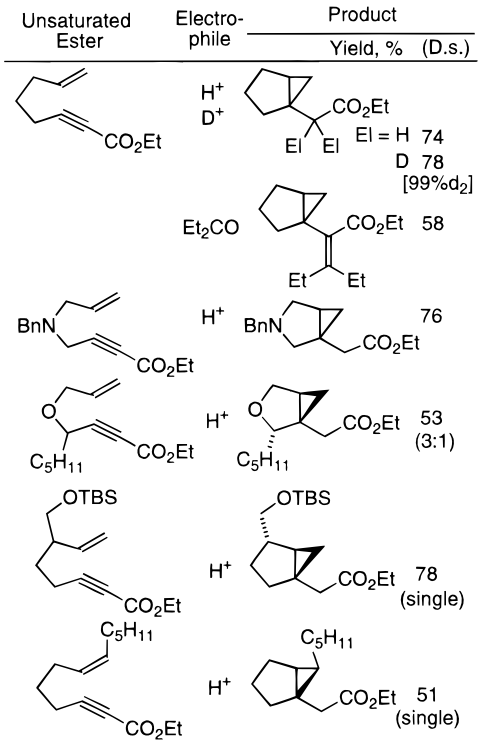
riolysis of the intermediate titanacycle at a low temperature gave a bis-deuterated cyclopentane derivative. However, when the titanabicycle generated

Table 55. Tandem Cyclization of Enynoates or Dienoates and Subsequent Reactions with Electrophiles (Refs 220 and 221)

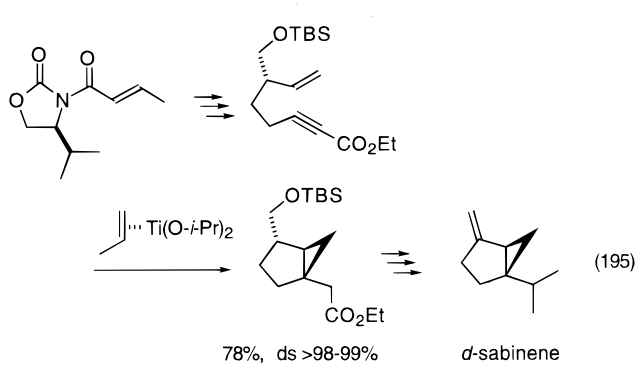
Unsaturated Ester	Electrophile	Product	Yield, %	D.S.
	H^+		80	--
	D^+		79	single
	EtCHO		78	single
	Et_2CO		65	single
	H^+		66	--
	H^+		73	--
	H^+		54	--
	H^+		89	97: 3
	EtCHO		53	--
	H^+		74	--
	EtCHO		69	single

at −50 °C was simply allowed to warm to a higher temperature up to 0 °C, a new product having a fused cyclopropane ring was obtained in good yield after aqueous workup. A titanium−carbene complex and/or a titanated ester enolate are the most likely species in the reaction at the higher temperature as evidenced by the results of their bis-deuteriolysis and smooth alkylidenation of diethyl ketone. Additional results of this cyclization are listed in Table 56. The

Table 56. Tandem Cyclization of 7-En-2-ynoates and Subsequent Reactions with Electrophiles (Refs 220 and 221)



stereochemistry of the cyclopropane formation was very effectively regulated by an alkyl substituent at the allylic position of the substrate, which was utilized in the synthesis of *d*-sabinene, a monoterpene having an optically active bicyclo[3.1.0]hexane skeleton, from optically active enynoate (eq 195).[221]



(195)

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