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Synthetic transformations mediated by the combination of titanium(IV) alkoxides and Grignard reagents: selectivity issues and recent applications. Part 2: Reactions of alkenes, allenes and alkynes

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Dedicated to Professor Oleg G. Kulinkovich

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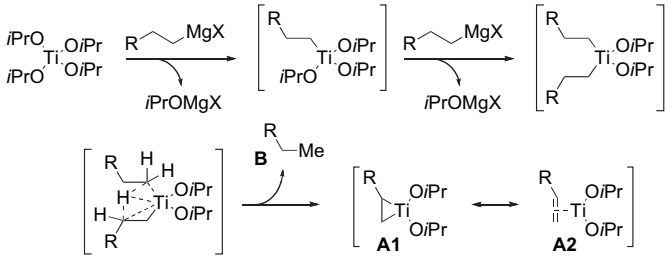
1. Introduction

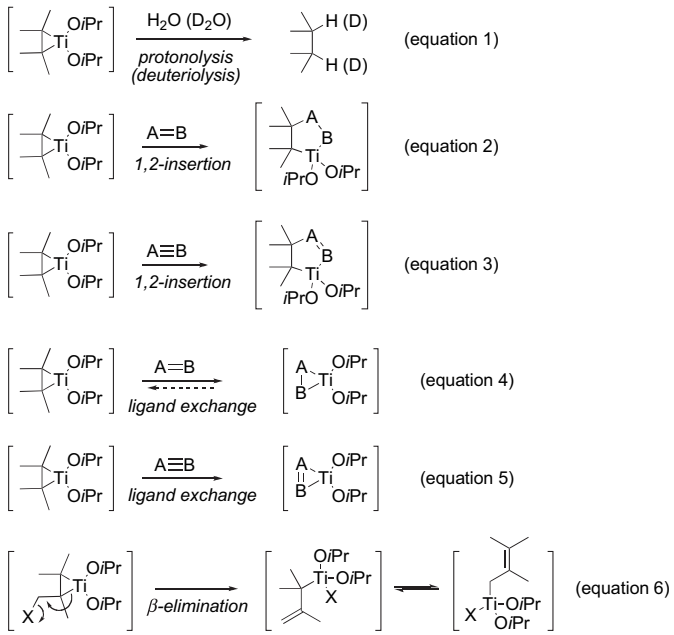
The discovery by the group of Kulinkovich from Minsk (Belarus), at the end of the 1980s, of an efficient and general titanium-mediated cyclopropanation reaction of carboxylic esters,[1] has opened a new area of organic chemistry, with a new family of reactions based on the use of Grignard reagents, in the presence of titanium alkoxides of the form $XTi(OR)_3$ (X=Me, Cl, OR; R=alkyl).[2–19]

These transformations use a cheap and non-toxic transition metal, which is a valuable advantage in today's context. As already discussed in some detail in Part 1 of this report, they involve the putative formation of titanium species **A** that can be viewed as the limiting structures, dialkoxytitanacyclopropane **A1** and dialkoxy(η^2-alkene)titanium complex **A2** (Scheme 1). These are presumably generated by two successive transmetallation reactions of the Grignard reagent, followed by a fast disproportionation process, with the simultaneous formation of an equimolar amount of the reduced compound **B**. Both representations **A1** or **A2** are commonly used when discussing reaction mechanisms operating in transformations based on this chemistry.



Scheme 1. Formation of dialkoxytitanacyclopropane/dialkoxy(η^2-alkene)titanium complexes in Kulinkovich-type reactions.

It is useful for the rest of the discussion to briefly recap the types of reactions that are usually observed with such complexes (Scheme 2), namely protonolysis or deuteriolysis reactions (Eq. 1), 1,2-insertion of unsaturated compounds (Eqs. 2 and 3), ligand exchange with unsaturated compounds (Eqs. 4 and 5), and leaving-group β-elimination reactions (Eq. 6). These processes are in full agreement with the transformations typically expected with dialkoxytitanacyclopropanes **A1** and/or dialkoxy(η^2-alkene)titanium complexes **A2**.



Scheme 2. Reactivity pattern of dialkoxytitanacyclopropanes.

Towards unsaturated compounds, the tendency of dialkoxytitanacyclopropanes to preferably undergo 1,2-insertion or ligand exchange has proved to be strongly dependent upon their structures, and a tentative ranking based on various literature results is represented in Figure 1. While all the dialkoxytitanacyclopropanes **1**–**5** may follow 1,2-insertion pathways, the bicyclic complex **5** usually performs rather poorly in such processes,[20,21] but is

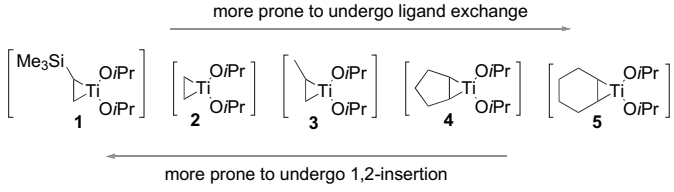


Figure 1. Behaviour of di*iso*-propyloxytitanacyclopropanes towards unsaturated compounds, depending upon their structures.

especially valuable in ligand exchange-based reactions.[20,22,23] In contrast, the silyl-substituted complex **1** exclusively undergoes 1,2-insertion.[24,25] The nature of the alkoxide ligands can also play an important role with regard to the properties of the titanacyclopropanes.[26]

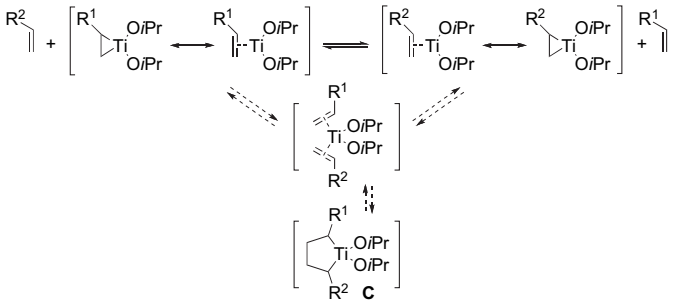
The relative rates of the reactions of dialkoxytitanacyclopropane species with unsaturated compounds have been the subject of several studies. Cha et al. have performed a study based on competition experiments involving several carbonyl derivatives,[27] and the group of Szymoniak has established that nitriles generally react faster than alkenes, 1,3-dienes or carboxylic esters.[22,28,29] Competition experiments executed with the preformed titanacyclopropane **4** have revealed the following order of reactivity for this complex: aldehydes>nitriles>ketones>alkynes>alkenes>carbonates.[30]

While Part 1 of this report was devoted to the transformations of carbonyl derivatives and nitriles, mainly represented by cyclopropanation reactions, the present report focuses on the reactions of alkenes, allenes and alkynes. We have tried to give as comprehensive as possible a view on the wide possibilities offered by these processes, with particular attention to selectivity issues and synthetic applications. Some additional transformations are described in the last section.

The present article covers the literature until 15 April 2009. Its scope does not include titanacyclopropane species where the titanium centre is attached to aryloxy or cyclopentadienyl ligands, although these are mentioned occasionally.

2. Transformation of alkenes

Alkene substrates may react with titanacyclopropane species generated from Grignard reagents and titanium alkoxides, and neat ligand exchange is most often observed (Scheme 3). This phenomenon, first disclosed by the group of Kulinkovich,[31] is unlike the pattern of reactivity observed with bis(cyclopentadienyl)zirconacyclopropanes, where metallacyclopentanes are usually formed by 1,2-insertion of the alkenes into one of the zirconium–carbon bonds.[32] From a mechanistic point of view,[33] the intermediary of a titanacyclopentane **C** is a distinct possibility, since (i) titanacyclopentanes are indeed formed if additional factors provide substantial enthalpic stabilisation (see for instance Section 2.4.2), and (ii) the reductive decoupling of the parent non-stabilised di*iso*-propyloxytitanacyclopentane into di*iso*-propyloxytitanacyclopropane **2** is a documented process.[34] Experimental evidence using a deuterium-labelled Grignard reagent rules out the possibility of a mechanism involving the formation of titanium hydride species.[35]



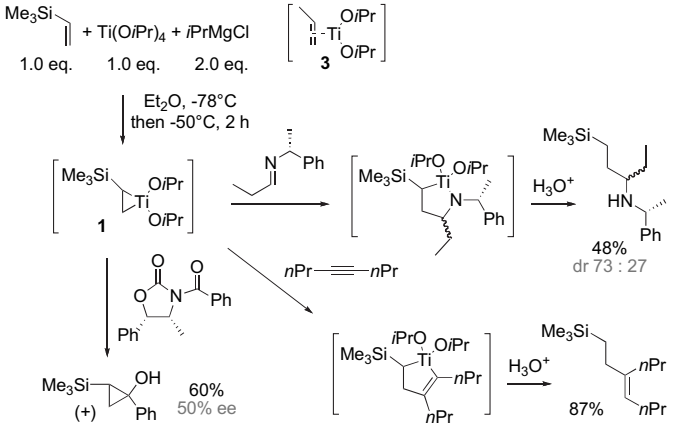
Scheme 3. Ligand exchange of titanacyclopropanes with alkenes.

The fact that the ligand-exchange process is fundamentally an equilibrium should be emphasised. The most popular ways to drive it towards the desired direction are the use of bicyclic titanacyclopropanes **4** and **5** prepared from *cyclo*-pentylmagnesium or *cyclo*-hexylmagnesium halides (see Fig. 1),[20,36] the choice of alkenes bearing substituents that can stabilise the newly formed titanacyclopropanes, and the use of alkenes bearing functional groups susceptible to irreversibly trigger further transformations of the newly formed titanacyclopropanes. Ligand exchange with alkenes bearing more than one substituent is generally a much disfavoured process,[20,26,37–42] although exceptions are known (vide infra).

2.1. Generation of stabilised titanacyclopropanes from alkenes by ligand exchange

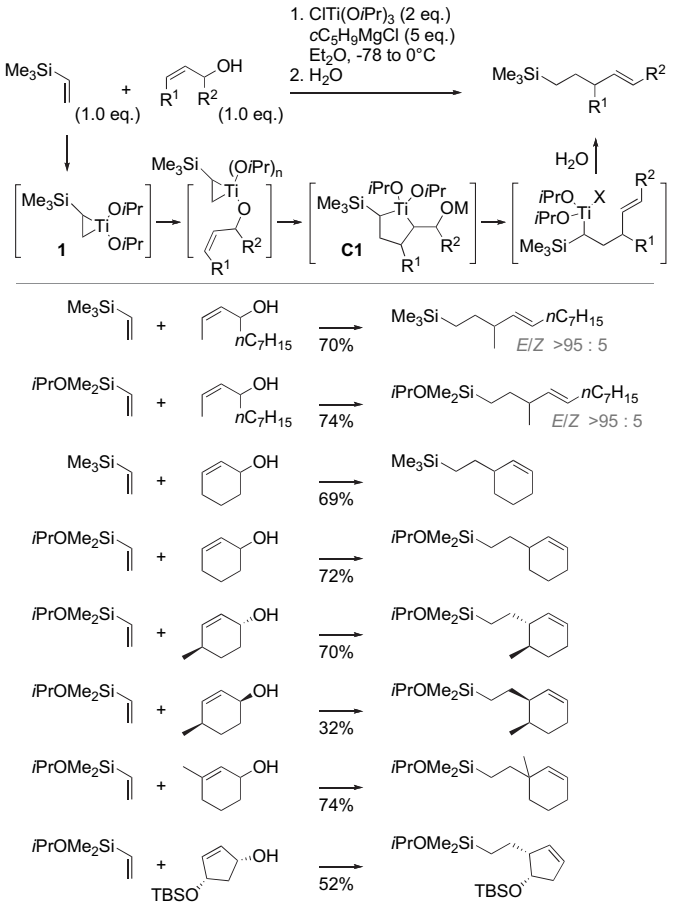
After ligand exchange with alkenes, the resulting dialkoxytitanacyclopropanes are usually unstable, and are typically generated as transient species that undergo subsequent processes (see Section 2.2). However, there are a few cases known where they are sufficiently stable to be prepared in the first place, and then transformed upon addition of other reagents.

For instance, ligand exchange of di*iso*-propyloxy(η^2-propene)-titanium **3** with trimethyl(vinyl)silane proceeds smoothly at −50 °C to deliver the silyl-substituted titanacyclopropane **1**. This complex exhibits unique properties: it can be trapped with a variety of unsaturated compounds, reacting according to a 1,2-insertion mode (Scheme 4),[25] even with aldehydes, imines and alkynes, that more typically follow ligand-exchange processes (see Part 1 and Section 4). Complex **1** reacts with esters to give silylcyclopropanols, the corresponding Kulinkovich reaction products. Remarkably, methyl 6-heptenoate also undergoes this transformation, even though an intramolecular Kulinkovich reaction triggered by olefin ligand exchange is normally observed with this substrate (see Part 1).[38] The critical influence of the silyl group, stabilising the titanacyclopropane complex and dramatically modulating its reactivity, is thus evidenced. It is worthy of note that the use of an amide derived from Evans oxazolidinone[43] in place of the ester partner delivers the corresponding silylcyclopropanol in 50% enantiomeric excess.[25]

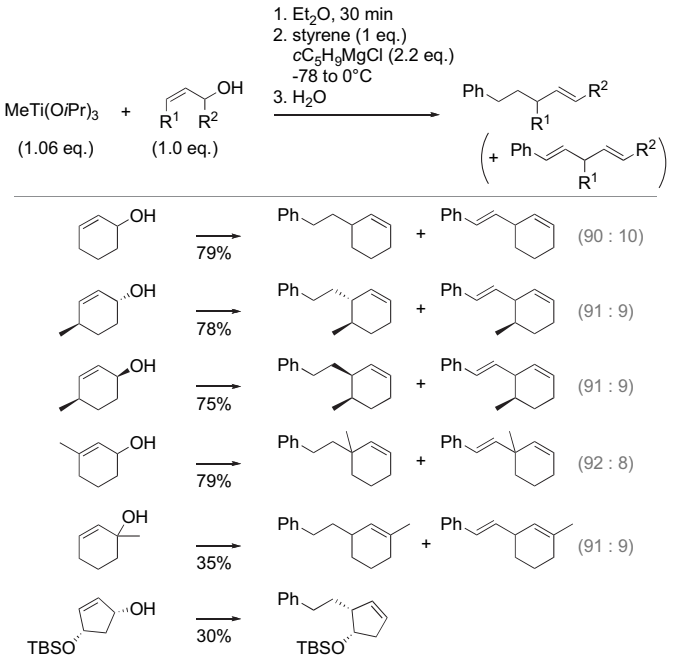


Scheme 4. Ligand exchange with trimethyl(vinyl)silane, followed by reaction with unsaturated compounds.[25]

Remarkably, complex **1** is formed sufficiently fast to be generated in the presence of an allylic alkoxide with a (*Z*)-di- or trisubstituted alkene function. Coordination of the alkoxide group to the titanium atom enables 1,2-insertion of the alkene moiety of the allylic alkoxide to occur, with high regio- and diastereo-selectivity, and the resulting titanacyclopentane intermediate **C1** finally undergoes a β-elimination process (Scheme 5). After hydrolysis, cross-coupled adducts are thus obtained. The diastereoselection can be rationalised similarly to the closely related ethylation reactions (see Section 2.3, Scheme 16). This method is not limited to trimethyl(vinyl)silane: vinylsiloxanes and styrene perform equally well in these reactions, although dienes are formed as minor products in the latter case (Scheme 6). 1-Methoxy-4-vinyl-benzene has been shown to be less reactive than styrene.[44]

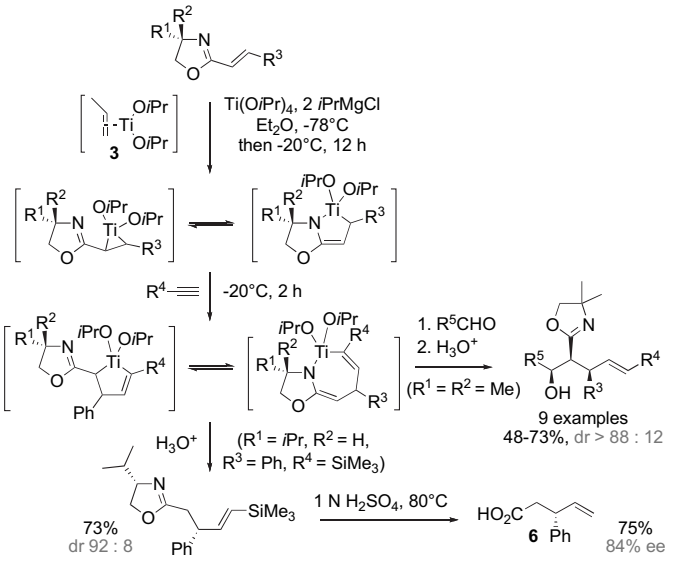


Scheme 5. Titanium-mediated cross-coupling of allylic alcohols with vinylsilanes.[44]



Scheme 6. Titanium-mediated cross-coupling of allylic alcohols with styrene.[44]

Ligand exchange of **3** with alkenyloxazolines also results in the formation of stable titanacycles that can be trapped with alkynes and aldehydes successively to afford highly substituted alcohols with high diastereoselectivity (Scheme 7).[45] This method was applied to the preparation of **6**, a plausible precursor of neurokinin receptor antagonists,[46] starting from an optically active chiral oxazoline.[45]

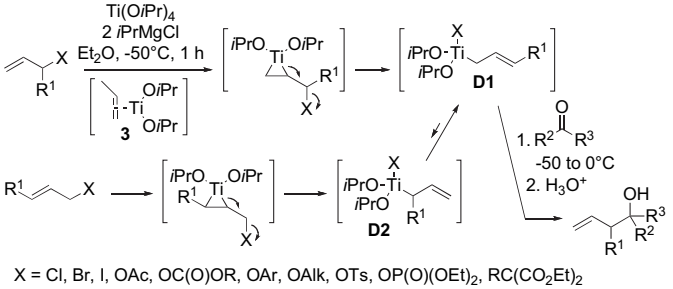


Scheme 7. Ligand exchange with alkenyloxazolines, followed by reaction with unsaturated compounds.[45]

As conjugated alkenes, 1,3-dienes can be regarding as belonging to the same category of substrates, and they also give rise to stable dialkoxytitanium complexes; their reactions are covered in Section 2.4.1.

2.2. Generation of transient titanacyclopropanes from alkenes by ligand exchange, and subsequent reactions

2.2.1. Elimination of a leaving group. Ligand exchange with an alkene bearing a suitable leaving group at the allylic position results in the formation of an η^1-allyltitanium complex[11] **D1** (Eq. 6, Scheme 2) that can then be trapped with an aldehyde or a ketone (Scheme 8).[37] Allyltitanium intermediates formed by this procedure react with imines as well, and high diastereoselectivities have been achieved using chiral imines derived from 1-phenylethylamine.[47–49] This method is an alternative to the formation of η^1-allyltitanium derivatives by the reaction of $ClTi(O\textit{i}\text{-}Pr)_3$ with allyl Grignard reagents,[50] and is reminiscent of a closely related zirconium-mediated process.[51] Valid leaving groups include halides, carbonates, phosphonates, acetals and alkoxides. A wide range of aldehydes and ketones can be used, including enolisable ketones and α,β-unsaturated substrates. In the latter case, 1,2 addition occurs.

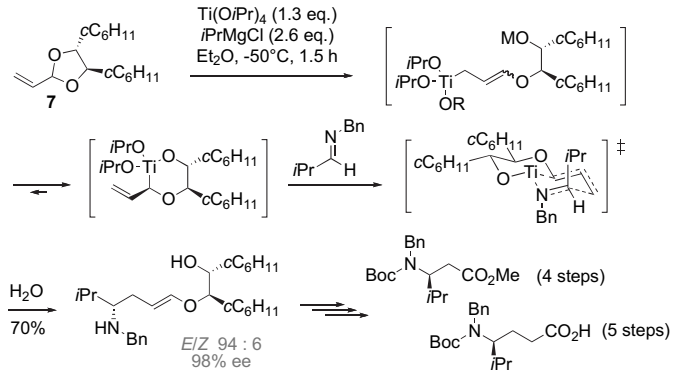


Scheme 8. Ligand exchange with alkenes bearing leaving groups in the allylic position.[37,39,66]

When the starting alkenes bear substituents at the α-position relative to the leaving groups, the homoallylic alcohol products are generally obtained with good regio- and diastereo-selectivities.[37,52–54] Isomeric alkenes bearing the same substituents at the γ vinylic

carbon give rise to the same allyltitanium intermediates **D1**, due to a [1,3] metallotropic rearrangement of the initially formed complexes **D2** (Scheme 8). Their use is not advantageous since, as disubstituted alkenes, they are usually poor substrates for ligand exchange and the yields are low.[37] Nonetheless, seven-, eight- and nine-membered cycloalkenes bearing a leaving group in the allylic position are suitable starting materials, and they provide a convenient access to cyclic allyltitanium species.[55] 1-Vinyl-alk-2-enyl or alka-2,4-dienyl carbonates are efficient substrates, and they lead to the formation of alka-2,4-dienyltitanium(IV) complexes, which constitute an interesting extension of the method described in this section.[56]

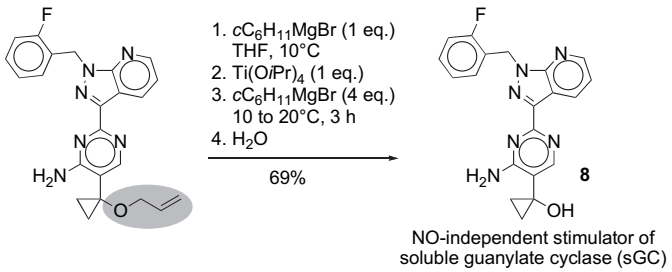
It is worthy of note that the equilibrium of the reversible [1,3] metallotropic rearrangement can be shifted towards the formation of the secondary titanium complexes **D2** by using cyclic carbamate starting materials derived from 4-aminoalk-1-en-3-ols. In this case, the elimination step releases a coordinating tether that efficiently stabilises the desired allyltitanium complexes,[57] and their reactions with aldehydes give the corresponding amino alcohols with good 1,5-asymmetric induction.[58] Similarly, the use of allylic cyclic acetals can also reverse the metallotropic equilibrium. In particular, good-to-excellent yields, regioselectivities and diastereoselectivities have been achieved in additions onto imines starting from the chiral di*cyclo*-hexylethylene acetal **7**, and this has been applied to the synthesis of β- and γ-amino acid derivatives with excellent enantiomeric purity (Scheme 9).[59,60] Conversely, non-cyclic acetals are converted into the usually observed 'branched' products after addition onto aldehydes, ketones or imines.[49,59] Another way to shift the metallotropic equilibrium in the unconventional direction is to introduce ring strain disfavouring the normally predominating primary allyltitanium complex. This has been achieved starting from a carbonate derived from 1-vinylcyclopropanol.[61]



Scheme 9. Ligand exchange with a chiral cyclic allylic acetal, and application to the synthesis of β- and γ-amino acid derivatives.[59,60]

Interestingly, direct hydrolysis or deuteriolysis of the allyltitanium intermediates generated by the process described above can proceed with good regioselectivity.[62,63] This is also the case for halogenolysis using NCS or NBS, and functionalised 3-halo-1-alkenes can thus be prepared efficiently.[62]

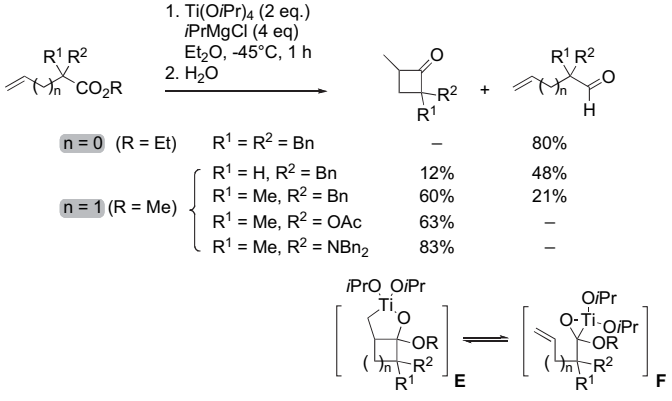
Cha et al. demonstrated that the method can also be used advantageously to cleave allyl ethers and carboxylates chemoselectively.[39,64] Benzylidene acetal, tri*iso*-propylsilyl ether, but-2-enyl ether and 2-methylallyl ether groups are not affected under these conditions. This method has been applied successfully by the group of de Meijere to the synthesis of a biologically active metabolite **8**, where the more conventional procedures had failed, due to the sensitivity of the cyclopropane ring (Scheme 10).[65] Similarly, Sato et al. showed that the allyl group is an efficient protecting group for the acidic hydrogen atoms of malonic esters, and can be readily cleaved using the Ti(O*i*-Pr)$_4$/*i*-PrMgCl reagent combination.[66]



Scheme 10. Titanium-mediated cleavage of an allyl group in the synthesis of a biologically active metabolite.[65]

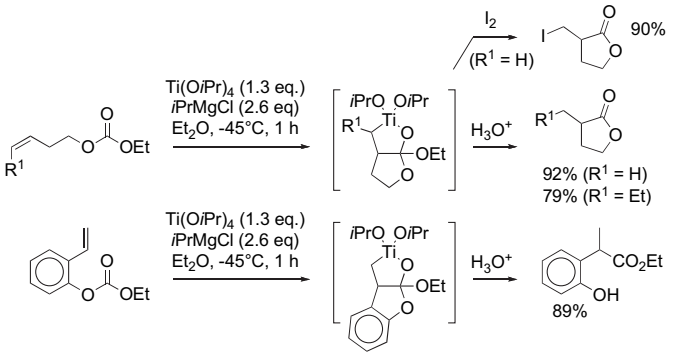
Finally, it is worth noting than an alkoxy group directly attached to an alkene moiety can also behave as a leaving group, triggering unusual transformations.[67]

2.2.2. Reaction with a carbonyl derivative or a nitrile. In principle, alkenes fitted with ester, amide or nitrile functions can undergo intramolecular cyclopropanation via Kulinkovich, Kulinkovich–de Meijere or Kulinkovich–Szymoniak reactions with ligand exchange, as described in Part 1. However, β,γ- and γ,δ-unsaturated esters are not converted into the corresponding strained [1.1.0] or [2.1.0] bicyclic cyclopropanols, but into aldehydes and/or cyclobutanones (Scheme 11).[68] This phenomenon can be interpreted on the basis of the generation of complex **E** by alkene–ligand exchange and 1,2-insertion of the carbonyl group into one of the two C–Ti bonds of the resulting titanacyclopropane. The normally expected cyclopropane formation is difficult because of high enthalpic and entropic cost, and an equilibrium between **E** and the oxatitanacyclopropane species **F** can take place, governed by the size of the smaller ring of **E** and Thorpe–Ingold effects. Hydrolysis of **E** (possibly preceded by the elimination of the alkoxide group OR) would result in the formation of the cyclobutanone products, while **F** would lead to the observed aldehydes. This is supported by a deuteriolysis experiment.[68]



Scheme 11. Reactions of β,γ- and γ,δ-unsaturated esters.[68]

Substituted but-3-enyl carbonate substrates lead to intramolecular nucleophilic acyl substitution (INAS), giving either lactones or carboxylic esters, depending upon which of the σ carbon–oxygen bonds is eventually cleaved (Scheme 12).[36,69] The final intermediates still contain a useful carbon–titanium bond, and the fact that disubstituted alkenes can be converted into the expected products in good yields is remarkable, although this seems to be true only in the case of the (*Z*) diastereoisomers.[69] Related Zr-mediated processes are known.[70–72]



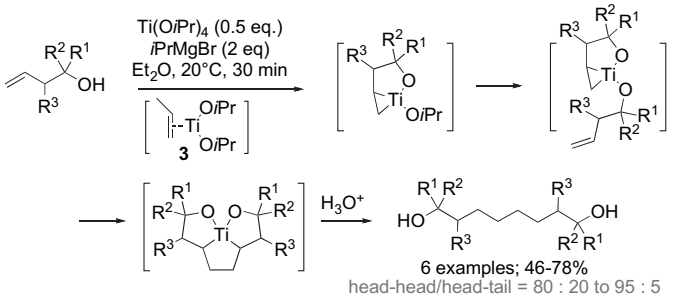
Scheme 12. INAS reactions of alkenyl carbonates.[69]

Finally, alkenes fitted with a ketone or an imine function at a suitable distance may undergo intramolecular coupling, as described in Part 1.

2.3. Miscellaneous reactions of alkenes

2.3.1. Reductive dimerisation processes. Although titanacyclopropanes usually react with alkenes according to a ligand-exchange pattern, cases of intermolecular 1,2-insertions have been marginally observed.[26,73–75] In particular, the cross-coupling of vinylsilanes or styrenes with allylic alkoxides is especially noteworthy (see Section 2.1, Schemes 5 and 6).[44]

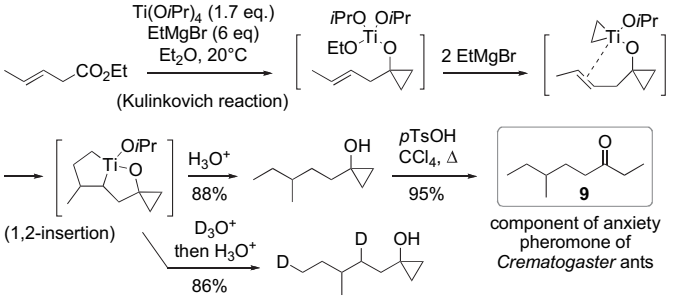
When the reagent **3** is generated in the presence of a homoallyl alkoxide with a monosubstituted carbon–carbon double bond, ligand exchange is followed by 1,2-insertion of a second molecule of substrate. This elementary step is facilitated in this situation because the alkoxide function plays the role of a tether, rendering the 1,2-insertion intramolecular. After hydrolysis, reductive dimerisation products are obtained in satisfactory yields with good head-to-head selectivity (Scheme 13). When the length of the chain spacer between the olefin and the alcohol functions is increased, head-to-tail and tail-to-tail selectivities gradually become more important, the latter being preponderant in the case of 10-undecen-1-ol.[76]



Scheme 13. Reductive dimerisation of homoallyl alcohols.[76]

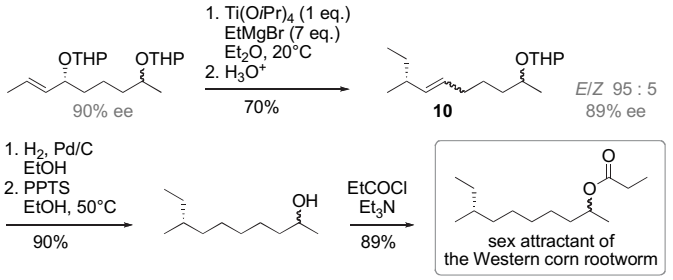
2.3.2. Alkylation processes. Starting from alkenyl alcohols with a disubstituted carbon–carbon double bond and with a large excess of ethylmagnesium bromide, the reaction follows a different course: the initially formed titanacyclopropane **2** directly undergoes 1,2-insertion of the substrate, again facilitated by the alkoxide tether. Clearly, the additional substituent substantially favours the resulting titanacyclopentane over the usual ligand-exchange product. After hydrolysis, the net result is regiospecific hydroethylation of the alkene moiety. This method can be preceded by a Kulinkovich reaction in a domino sequence, as in the synthesis of the ketone **9**, a constituent of the anxiety pheromone of *Crematogaster* ants (Scheme 14).[77]

Allyl alcohols with a disubstituted carbon–carbon double bond follow a similar mechanism, but in this case 1,2-insertion is followed by elimination.[78] Allyl ethers behave similarly,[78] and



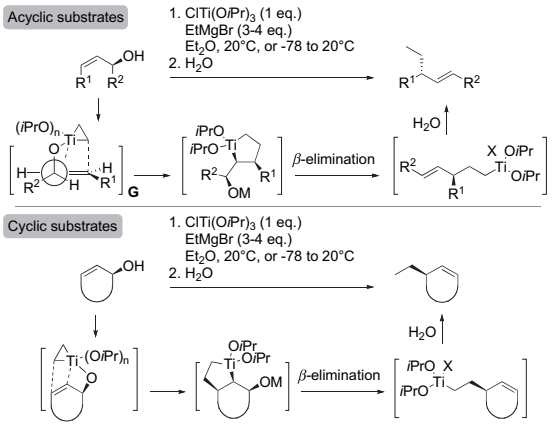
Scheme 14. Kulinkovich reaction–ethylation domino sequence.[77]

Kulinkovich et al. have applied this method to the total synthesis of (1*R*/*S*,7*R*)-1,7-dimethylnonyl propanoate, the sex attracting pheromone of the Western corn rootworm *Diabrotica virgifera virgifera* (Scheme 15). The isolated alkylated product **10** is obtained with no significant loss of enantiomeric excess, as a 95:5 mixture of (*E*) and (*Z*) diastereoisomers. This is inconsequential, since the double bond is hydrogenated in the next synthetic step.[79]

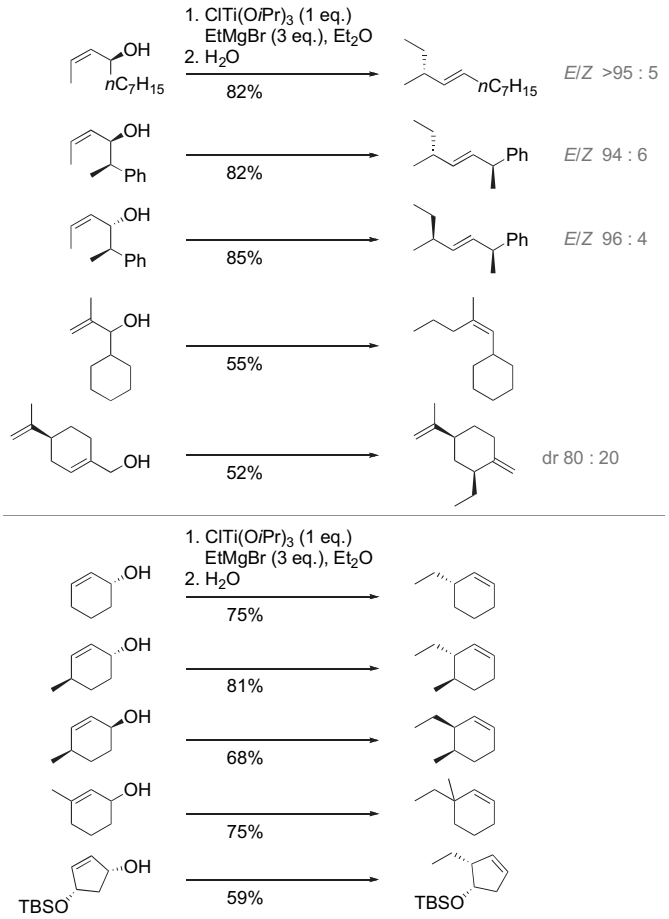


Scheme 15. Application of the titanium-mediated ethylation of an allyl ether to the synthesis of the sex attractant of the Western corn rootworm.[79]

Cha et al. have conducted a remarkable study on reactions of this type,[44] showing that allylic alcohol derivatives with the (*Z*) absolute configuration give better control of the configurations of the double bonds of the products. In every case, the (*E*) diastereoisomers are favoured, and the best selectivities are obtained using allylic alcohols, rather than the corresponding methyl or BOM ethers. Moreover, complete transfer of chirality has been evidenced. It is proposed that (*syn*) carbotitanation of the alkene group by the titanacyclopropane complex **2** is directed by the alkoxide group, and that the ensuing β-elimination step operates in a *syn* fashion. In the case of acyclic substrates, the stereochemical fate is rationalised by a directing effect of the alkoxide in such a way that the allylic strain is minimised (conformer **G**) (Scheme 16).[44] Examples are presented in Scheme 17,



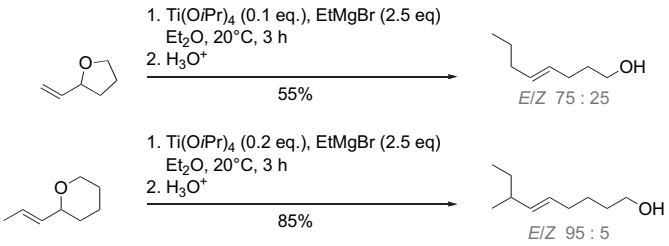
Scheme 16. Stereoselection of the titanium-mediated ethylation of (*Z*) allylic alcohols.[44]



Scheme 17. Examples of titanium-mediated ethylation of (*Z*) allylic alcohols.[44]

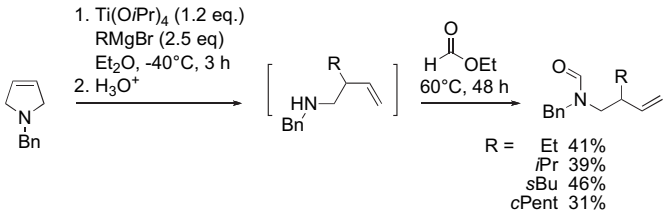
including reactions of allylic alcohols with a trisubstituted olefin moiety. This method has been extended to alkylations with 2-silylethyl or 2-phenylethyl groups by executing the reactions in the presence of vinylsilane or styrene derivatives, as already mentioned in Section 2.1 (Schemes 5 and 6).[44]

The case of 2-alkenyl-tetrahydrofurans and 2-alkenyl-tetrahydropyrans deserves special interest, since their reactions are catalytic in titanium. The alkenyl alcohol products are obtained with moderate-to-excellent *E* diastereoselectivity (Scheme 18).[80]



Scheme 18. Titanium-catalysed formal S_N2' substitution reactions of cyclic allyl ethers.[80]

N-Benzylpyrroline can also be subjected to a similar titanium-mediated S_N2' substitution reaction (Scheme 19).[81] In contrast, 2,5-dihydrofuran and *N*-sulfonyl-2,5-dihydropyrroles undergo dimerisation with concomitant ring opening to afford chiral *dl*-2,3-diethenylbutane-1,4-diol and *dl*-2,3-diethenyl-1,4-bis(sulfonylamino)butanes, respectively. Using titanium(IV)bis(4*R*,5*R*)-taddolate (albeit in a stoichiometric amount), *dl*-2,3-diethenylbutane-1,4-diol is obtained with 94% enantiomeric excess.[82]

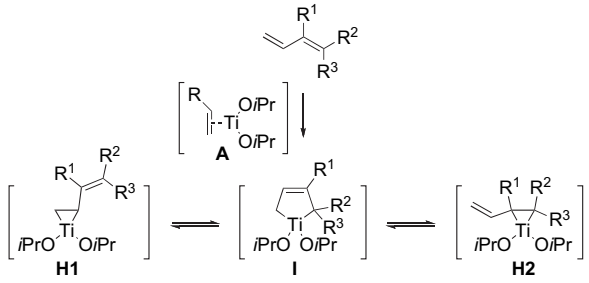


Scheme 19. Alkylative ring opening of *N*-benzylpyrroline.[81]

Finally, formal hydrogenation of the carbon–carbon double bond of some alkenes has been reported, and the experimental evidence suggests that hydrogen transfer occurs in part before the aqueous work-up.[83]

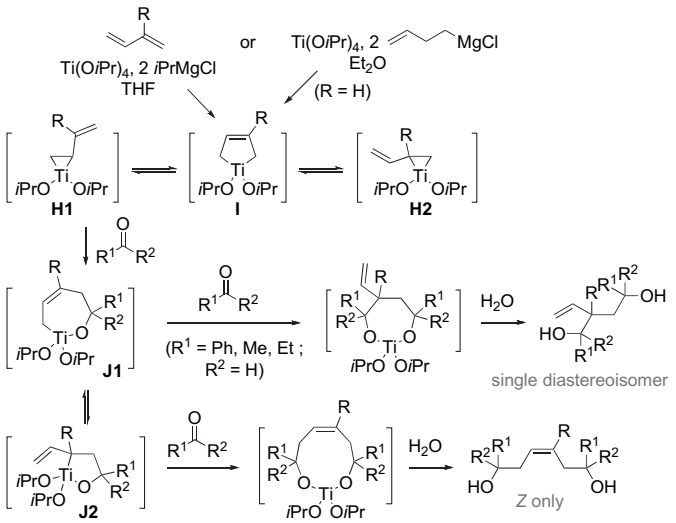
2.4. Transformation of dienes

2.4.1. 1,3-Dienes. 1,3-Dienes are interesting substrates that may react with titanacyclopropanes according to a ligand-exchange process. Two possible vinyltitanacyclopropanes **H1** or **H2** can be formed, depending upon which carbon–carbon double bond coordinates to the metal, as well as a titanacyclopentene **I**. All these species are thought to be in equilibrium via allylic rearrangement.[84] When one of the olefin functions is monosubstituted (as shown in Scheme 20), complex **H1** appears to be favoured over **H2** because of minimal steric bulk around the metal centre. Indeed, most of the reactions described in the literature may be explained by invoking an elementary step featuring **H1** reacting as an allyltitanium species (vide infra), although the intermediary nature of **I** has also been proposed.[85,86] When both carbon–carbon double bonds are at least disubstituted, ligand exchange usually becomes poorly efficient.



Scheme 20. Ligand exchange with 1,3-dienes.[84]

As already discussed in Part 1, vinyl aminocyclopropanes are obtained when intermediates **H1**, **I** and **H2** are generated in the presence of carboxylic amides.[84] It has been shown that the equilibrium mixture of **H1**, **I** and **H2** can be pre-formed by treating the starting diene with titanium(IV) *iso*-propyloxide and *iso*-propylmagnesium chloride at −70 °C, and then raising the temperature to at least −20 °C and up to 0 °C.[29,87–89] Alternatively, the same type of complex can be obtained by reacting Ti(O*i*-Pr)$_4$ with a homoallyl Grignard reagent.[86,87] Subsequent addition of aldehydes or ketones provides 1,6-diols as double addition products. 1,4-Diols may also be obtained when the reacting partner is either a reactive aldehyde (PhCHO, MeCHO or EtCHO) or a 1,4-diketone. This may be rationalised by invoking the initial formation of an allyltitanium complex **J1**, containing a trisubstituted carbon–carbon double bond, that can react only with the most reactive substrates or intramolecularly. **J1** is expected to be in equilibrium with complex **J2** more prone to add onto bulky substrates (Scheme 21).[86,89] Although double addition appears to be difficult to avoid,[86] mono addition has been reported

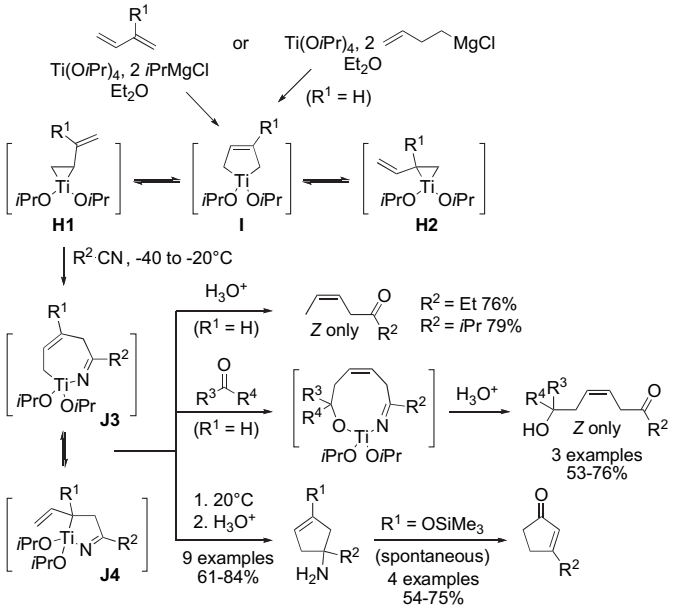


Scheme 21. Formation of complexes **H1**, **I** and **H2** followed by aldehyde or ketone addition.[86,89]

starting from 1,3-dienes bearing bulky trialkylsilyloxy groups in the 2-position, which may disfavour the formation of complex **J2**.[87]

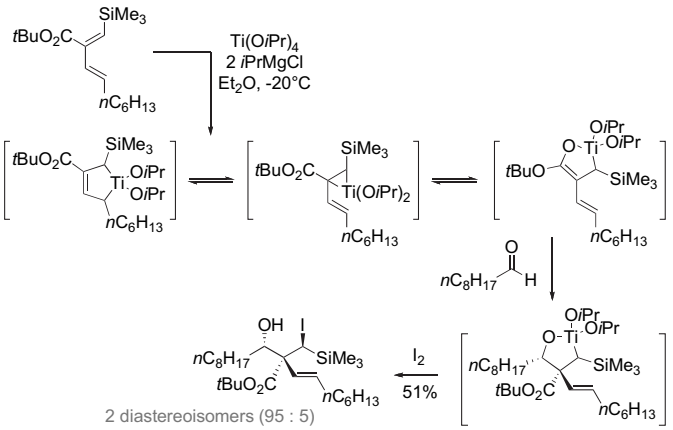
Addition reactions onto carboxylic esters produce intermediates that are similar to the complex **J1**. Upon warming to 20 °C, these undergo cyclisation and eventually furnish cyclopentenols.[87,89] Alternatively, they can be hydrolysed at low temperature (−40 to −30 °C) to yield allylic ketones with complete regioselectivity.[87,89] The use of very bulky substrates such as ethyl 2,2-dimethylpropionate results in a change of regioselectivity, possibly via the intermediary nature of complex **H2**, which is more constrained, but more reactive, than **H1**.[89]

The reactivity pattern of nitriles is similar to that of carboxylic esters: the initially formed iminotitanacyles **J3** and **J4** can be trapped at low temperature with electrophiles.[86,87] Alternatively, cyclisation may occur upon warming to deliver 3-cyclopentenyl amines that formally derive from [4+1] addition of the diene to the nitrile.[29,87] Cyclopentenones can also be prepared using 2-silyloxybutadienes as the starting dienes (Scheme 22).[29]



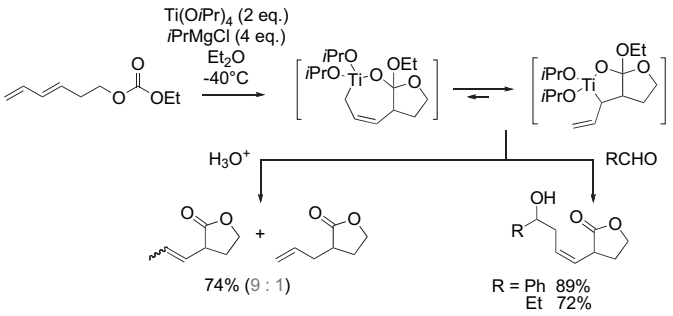
Scheme 22. Formation of complexes **H1**, **I** and **H2** followed by addition of a nitrile.[29,86]

Carboxylic ester-substituted 1,3-dienes constitute a special category of substrates: ligand exchange is probably much favoured by the presence of the ester group, and unusually highly substituted starting dienes are tolerated. Moreover, the ester group can exert a dominant influence on the regioselectivity of subsequent aldehyde addition, in contrast to the general situation previously depicted.[87] An example is shown in Scheme 23 that also highlights the high diastereoselectivity of such transformations.

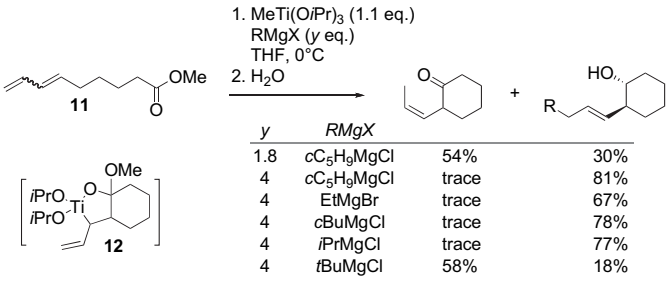


Scheme 23. Titanium-mediated reaction of an ester-substituted 1,3-diene.[87]

1,3-Dienes featuring a reactive group at a suitable position can lead, after ligand exchange, to transient titanium complexes that undergo further transformations. As already mentioned, alka-2,4-dienyl carbonates undergo elimination after ligand exchange, and alka-2,4-dienyltitanium species are generated (see Section 2.2.1).[56] With an additional methylene group separating the 1,3-diene and the carbonate functions, a process that can be viewed as a special case of the intramolecular nucleophilic acyl substitution (INAS) reactions described in Section 2.2.2 takes place. The final allyltitanium intermediates, stabilised by intramolecular coordination, can be trapped with aldehydes with complete regioselectivity to afford highly functionalised homoallyl alcohols (Scheme 24).[85] Octa-5,7-dienoate and nona-6,8-dienoate esters react in a similar fashion when treated with MeTi(O*i*-Pr)$_3$ and a Grignard reagent, rather than undergoing a plausible intramolecular Kulinkovich reaction. Moreover, when an excess of Grignard reagent is used starting from methyl nona-6,8-dienoate **11**, an interesting alkylation process occurs to deliver functionalised cyclohexanols as single (*trans*, *E*) diastereoisomers, presumably via intermediate **12** (Scheme 25).[90]



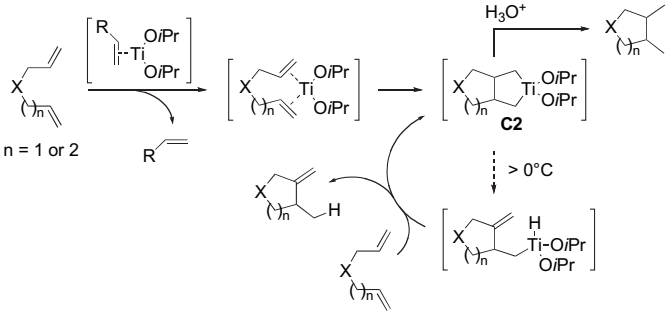
Scheme 24. INAS reaction of ethyl 3,5-hexadienyl carbonate.[85]



y	RMgX		
1.8	cC_5H_9MgCl	54%	30%
4	cC_5H_9MgCl	trace	81%
4	EtMgBr	trace	67%
4	*c*BuMgCl	trace	78%
4	*i*PrMgCl	trace	77%
4	*t*BuMgCl	58%	18%

Scheme 25. Titanium-mediated alkylative INAS reaction of methyl nona-6,8-dienoate.[90]

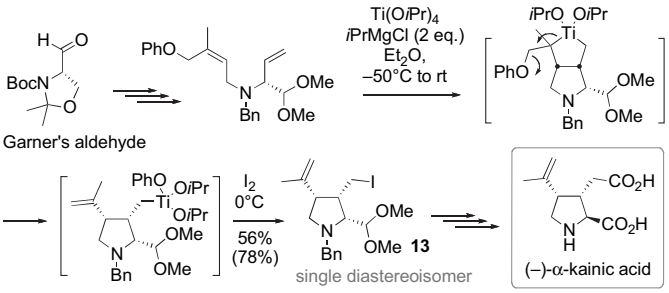
2.4.2. 1,n-Dienes (n>3). Dialkoxytitanacyclopropanes can react with 1,6- and 1,7-dienes to form titanacyclopentanes **C2**. This can be interpreted either as ligand exchange with one of the two olefin moieties, followed by coordination and intramolecular 1,2-insertion of the other alkene unit, or as direct ligand exchange with the diene, playing the role of a bidentate ligand, followed by oxidative coupling (Scheme 26).[91] Depending upon the reaction conditions and the substitution pattern of the intermediates **C2**, they may be stable and give 1,2-dialkylcyclopentanes or 1,2-dialkyl-cyclohexanes upon hydrolysis, or undergo subsequent transformations. For instance, in the presence of a suitable leaving group, elimination may occur to generate a new complex that can then be trapped with an electrophile such as H_2O, Br_2 or I_2 (vide infra).[92–94] Such reactions have been shown to proceed with consistently higher diastereoselectivity than the analogous 'Cp_2Zr'-mediated transformations.[95]



Scheme 26. Formation of fused bicyclic dialkoxytitanacyclopentanes from 1,6- or 1,7-dienes.

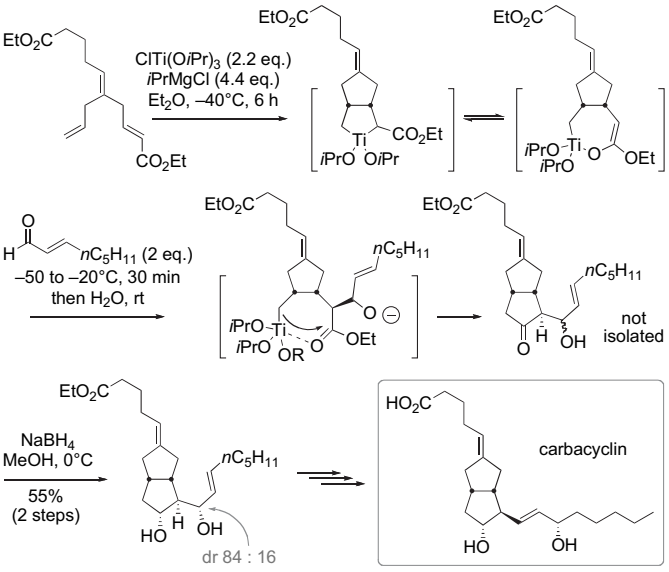
Very interestingly, Okamoto and Livinghouse have demonstrated that complexes of the type **C2** may slowly give rise, above 0 °C, to the formation of methylenecycloalkane compounds, presumably via β-hydrogen elimination followed by reductive elimination (Scheme 26). This process is catalytic in titanium and Grignard reagent, *cyclo*-hexylmagnesium chloride giving the best results among the reagents investigated. However, poor yields are obtained with Ti(O*i*-Pr)$_4$, and titanium(IV) aryloxide catalysts are much more useful for this cycloisomerisation reaction.[96]

The titanium-mediated diene cyclisation reaction has been applied to the total synthesis of (−)-α-kainic acid (Scheme 27).[94,95] The key pyrrolidine ring formation proceeds with excellent all-*syn* diastereoselectivity. Trapping the final intermediate with iodine furnishes **13**, a highly functionalised precursor of the target molecule. The latter is then obtained in a few steps that include the necessary epimerisation at C2.



Scheme 27. Synthesis of (−)-α-kainic acid.[94,95]

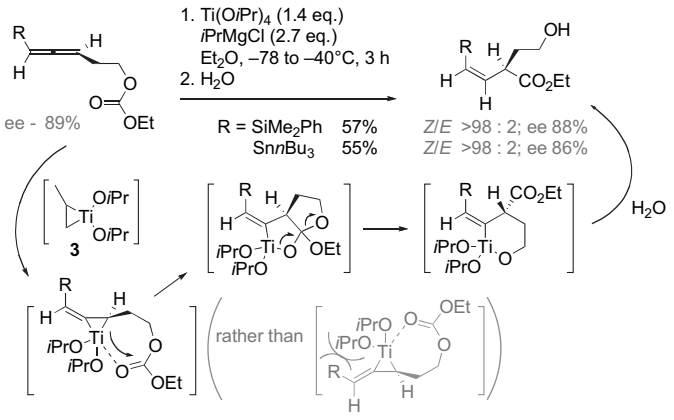
With substrates containing α,β-unsaturated ester moieties, dialkoxytitanacyclopentane species are generated as well, but the addition of an electrophile such as an aldehyde triggers intramolecular addition onto the carbonyl ester group, and bicyclic ketones are eventually obtained.[97,98] The group of Sato has applied this method to a remarkable total synthesis of carbacyclin, an analogue of prostaglandin I_2 (prostacyclin) (Scheme 28).[99] A $FeCl_2$/*t*-BuMgCl combination of reagents has recently been reported to mediate analogous transformations of dienedioate systems.[100]



Scheme 28. Synthesis of carbacyclin, a prostacyclin analogue.[99]

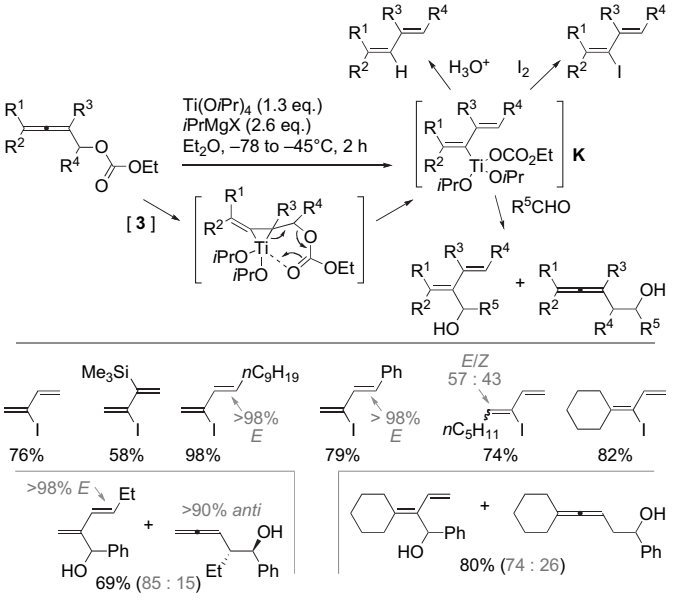
3. Transformation of allenes

Although several reactions involving allenes have been developed (see Section 4.2.3), the use of these compounds directly as the primary substrates, i.e., where they are treated with a titanium alkoxide and a Grignard reagent, is little documented. Nonetheless, Sato et al. have described the INAS reaction of alka-3,4-dienyl carbonates. Although it does not tolerate extra substitution at the 3-position, or the use of terminal allenes and compounds where the carbonate and allene moieties are separated by a longer chain spacer, this method provides a useful way to prepare α-substituted β,γ-unsaturated esters. Very good diastereoselectivities in favour of the (*Z*) products can be obtained in several cases. Moreover, transfer of chirality occurs with essentially no racemisation when the reaction is performed with enantiomerically enriched allenes (Scheme 29).[101]



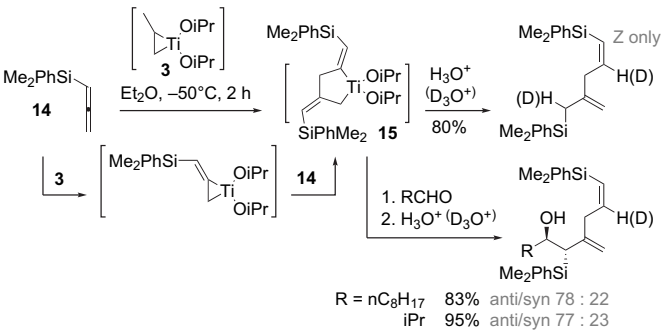
Scheme 29. INAS reactions of enantiomerically enriched allenyl carbonates.[101]

Alka-2,3-dienyl carbonates also undergo completely regioselective ligand exchange at the proximal Csp^2–Csp double bond relative to the carbonate function. However, this elementary step is followed by an elimination pathway, generating unique alka-1,3-dien-2-yl titanium species **K** that can be seen both as vinyltitanium and as allyltitanium complexes. When electrophiles such as iodine or the hydronium ion are added, **K** reacts completely regioselectively to deliver the corresponding conjugated dienes. With aldehyde electrophiles, the regioselectivity is highly dependent upon the nature of both the carbonate substrate and the aldehyde. Starting from monosubstituted allenes containing a substituent at the α-position relative to the carbonate and allene moieties, the conjugated diene products are produced with excellent (*E*) diastereoselectivity with respect to the absolute configuration of the 1,2-disubstituted double bond, and, in the case of aldehyde electrophiles, the β-hydroxy allene products are obtained with high *anti*-selectivity. In contrast, the control of the double bond geometries of conjugated diene products stemming from non-terminal allene substrates is much lower (Scheme 30).[102]



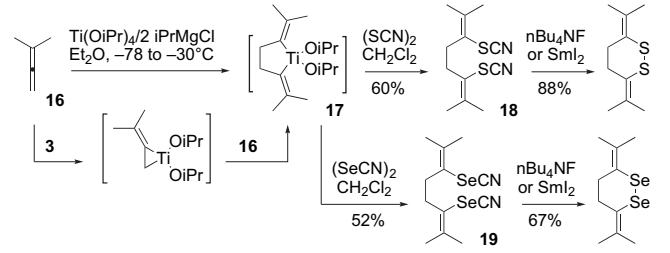
Scheme 30. Titanium-mediated transformation of alka-2,3-dienyl carbonates.[102]

Terminal allenes that are not susceptible to undertake intramolecular processes after ligand exchange in the presence of titanacyclopropane **3** undergo intermolecular 1,2-insertion of a second allene molecule. This parallels the fate of terminal alkynes under similar conditions (see Scheme 55). Both the ligand exchange and the insertion elementary steps occur at the terminal Csp^2–Csp double bond, either with head-to-head or head-to-tail regioselectivity, depending upon the substitution pattern. After hydrolysis, the net result is reductive dimerisation of the terminal allene starting materials. In the case of dimethylphenyl(propa-1,2-dienyl)silane **14**, the reaction is especially diastereoselective with respect to the geometries of the carbon–carbon double bonds of the titanacyclopentane intermediate **15** formed; the latter contains an allyltitanium moiety and reacts with aldehydes with high regioselectivity and moderate diastereoselectivity (Scheme 31).[103]



Scheme 31. Titanium-mediated reductive dimerisation of dimethylphenyl(propa-1,2-dienyl)silane.[103]

Starting from 3-methyl-1,2-butadiene **16**, titanacyclopentane **17** is generated highly regioselectively as well. As demonstrated by Block et al., this complex reacts with $(SCN)_2$ or $(SeCN)_2$ to give compounds **18** and **19**, that can be readily converted into cyclic disulfides or diselenides (Scheme 32).[104]



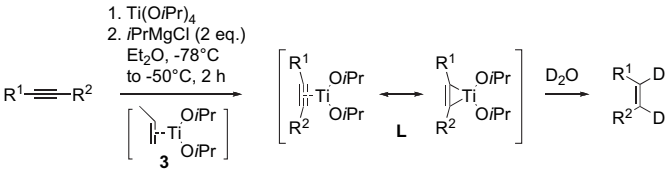
Scheme 32. Titanium-mediated reductive dimerisation of 3-methyl-1,2-butadiene, with subsequent reaction with $(SCN)_2$ or $(SeCN)_2$.

4. Transformation of alkynes

4.1. Titanacyclopropene putative species

In 1995, the group of Sato reported that di*iso*-propyloxy(η^2-alkyne)titanium complexes **L** are produced when internal alkynes are treated with the Ti(O*i*-Pr)$_4$/*i*-PrMgCl combination of reagents.[105] In this transformation, di*iso*-propyloxy(η^2-propene)titanium **3** is probably generated first, and ligand exchange with the alkyne then operates to give **L**.[106] The formation of these complexes that can be seen as titanacyclopropenes has been evidenced by trapping with deuterium oxide, giving bis-deuteriated alkenes with pure (*Z*) configuration (Scheme 33). To the best of our knowledge, however, there is no direct proof at present that the structure **L** is a correct representation of the reactive organometallic species involved. Nonetheless, the latter clearly has a *cis*-1,2-bismetallated alkene character and the structure **L** accounts for the reactions observed in a reliable and convenient way. Moreover, the structures of related titanocene complexes of the type, $Cp_2Ti(\eta^2$-alkyne) or

$Cp^*_2Ti(\eta^2$-alkyne), have been studied by spectroscopic techniques and X-ray crystallography.[107–112] They are in full agreement with this kind of representation, with a dominant contribution of the titanacyclopropene form, and therefore it will be used in the rest of the discussion for the corresponding dialkyloxy complexes.



Scheme 33. Ligand exchange with alkynes, followed by deuteriolysis.[105]

Dialkoxytitanacyclopropenes **L** are generally prepared at low temperature, with a wide range of substituents being tolerated on the starting alkynes (vide infra). Using Ti(O*i*-Pr)$_4$ and *i*-PrMgCl in diethyl ether, alkyne ligand exchange is usually complete within 2 h at −50 °C.[105] It has been shown that the conversion of 4-octyne is only partial after 15 min at −30 °C using Ti(O*i*-Pr)$_4$ and *c*-C_5H_9MgCl in diethyl ether, and a reaction time of 30 min is necessary under these conditions. Ligand exchange with bulkier substrates can take a longer time.[113]

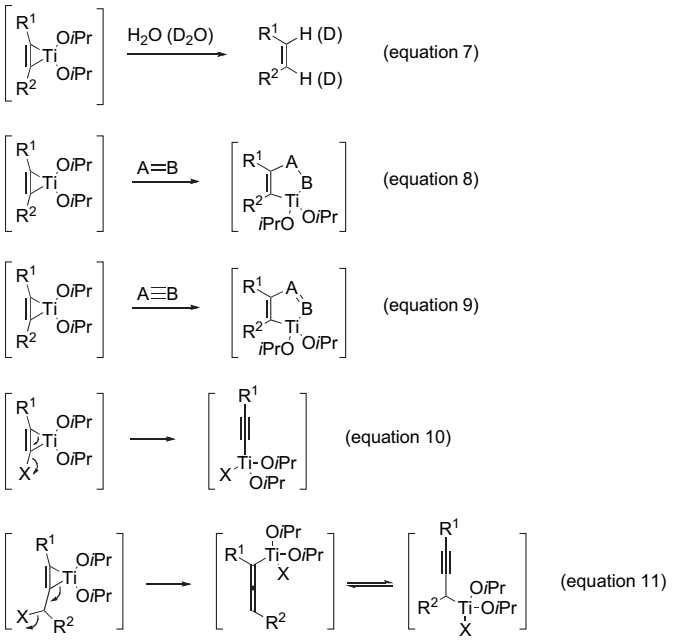
In contrast to dialkoxytitanacyclopropanes **A**, dialkoxytitanacyclopropenes **L** are usually fairly stable, at least below −30 °C in diethyl ether.[6] Above that temperature, they may decompose to yield titanacyclopentadiene complexes, and, at least formally, Ti(O*i*-Pr)$_2$.[114,115] Their recombination has been proposed to account for unexpected results observed at +25 °C starting from 1-alkynylphosphonates.[115] Some substituents can exercise a significant stabilising effect: the dialkoxytitanacyclopropenes generated from (3,3-dimethylbut-1-ynyl)phosphonic acid diethyl ester[115] and 1-benzyloxyhex-2-yne[116] are stable at least up to +25 and 0 °C, respectively.

4.1.1. Influence of reagents. Ti(OEt)$_4$ and Ti(O*t*-Bu)$_4$ give poor results, compared with Ti(O*i*-Pr)$_4$,[117] but ClTi(O*i*-Pr)$_3$ and chlorotris[(−)-menthoxy]titanium are suitable titanium alkoxides.[37,117] In the latter case, enantiomerically pure chiral titanacyclopropenes are generated.[117] With respect to the Grignard reagent, *iso*-propylmagnesium chloride has been shown to be generally superior to ethylmagnesium bromide, *n*-propylmagnesium bromide and *iso*-butylmagnesium chloride.[117] *cyclo*-Pentylmagnesium chloride gives good results.[113,118] Organolithium reagents such as *n*-BuLi or *s*-BuLi can be used as well.[119,120] Remarkably, the di*iso*-propyloxytitanacyclopropenes thus formed are thermally stable,[119] and they can even withstand a temperature of +50 °C.[120]

4.1.2. Reactions of dialkoxytitanacyclopropenes. The manifold reactivity of dialkoxytitanacyclopropenes (Scheme 34) consists mainly of protonolysis or deuteriolysis reactions (Eq. 7), 1,2-insertion reactions of unsaturated compounds (Eqs. 8 and 9), and leaving-group elimination processes (Eqs. 10 and 11). To the best of our knowledge, ligand exchange from dialkoxytitanacyclopropenes is not documented, in contrast to the behaviour of the analogous bis(*cyclo*-pentadienyl)titanium complexes such as $Cp_2Ti[\eta^2$-bis(trimethylsilyl)acetylene],[108] and of dialkoxytitanacyclopropanes **A** (Eqs. 4 and 5, Scheme 2).

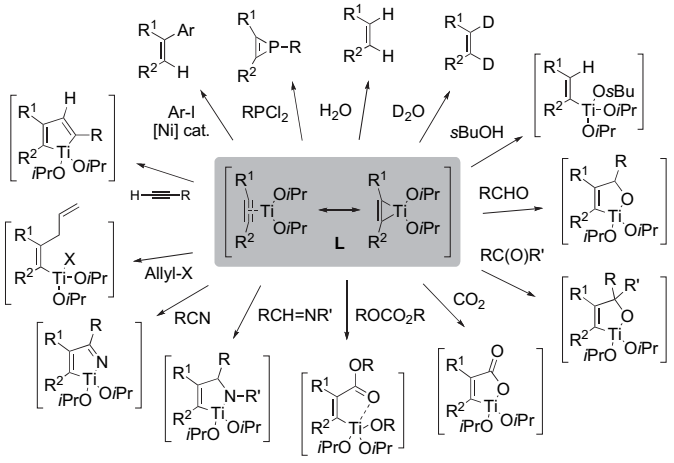
4.2. Generation of titanacyclopropenes from alkynes, followed by intermolecular trapping

Because of the reasonable stability of dialkoxytitanacyclopropenes, stepwise sequences can be performed, where they are generated in the first place, and then made to react with reagents added subsequently. The present section deals with such



Scheme 34. Reactivity pattern of di*iso*-propyloxytitanacyclopropenes.

transformations. After the addition of a first reagent, a vinyltitanium intermediate is generally formed that can then react with a second reagent. The spectrum of possibilities offered by this chemistry is very wide, but we have attempted to summarise it in Scheme 35.



Scheme 35. Reagents used against pre-formed titanacyclopropenes.

4.2.1. Functional group tolerance. A large variety of substituents are tolerated on the starting alkyne, including alkyl, phenyl,[105] pyridinyl,[121] alkynyl,[122] trimethylsilyl,[105] tri-*n*-butylstannyl,[114,123] *tert*-butyloxycarbonyl, diethylaminocarbonyl,[124] diethylphosphono[125,126] and alkylsulfonylamino groups.[127–129] The following functions are in principle compatible with the reaction: acetals, alkyl ethers, alcohols protected with THP, 1-ethoxyethyl or silyl groups, di- or trisubstituted alkenes (depending upon the distance from the alkyne moiety)[130] and cyclopropyl and halide functions.[123]

4.2.2. Regioselectivity issues. In most applications, unsymmetrical disubstituted alkynes are used, and therefore a regioselectivity issue is raised. In our own rudimentary view of this problem, two main factors have to be considered: (i) the structure of the

dialkoxytitanacyclopropene intermediate, and (ii) the nature of the reagent with which it is intended to react.

(i) The dialkoxytitanacyclopropene complex generated from an alkyne bearing two different substituents has a dissymmetrical structure, with different lengths for the two carbon–titanium bonds and different partial negative charges located at the two carbon atoms bound to the titanium centre (Fig. 2). This asymmetry can be caused by a combination of electronic or geometric effects that are tentatively discussed as follows:

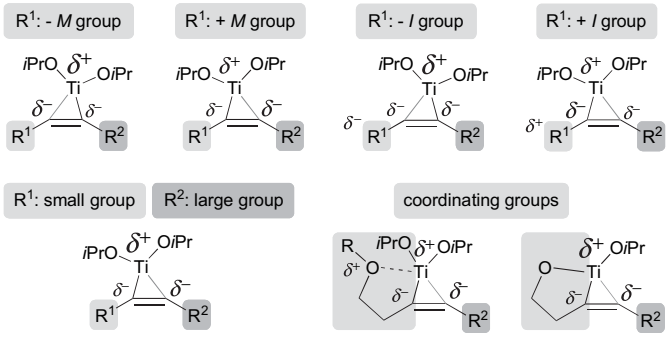


Figure 2. Intrinsic relative reactivities of the two carbon–titanium bonds of dialkoxytitanacyclopropenes.

- $-M$ groups can stabilise a partial negative charge at the adjacent carbon, and as such should favour greater polarisation of the adjacent carbon–titanium bond. In addition, these groups should decrease the electron density at the β-carbon via the mesomeric effect; they are expected to behave as α-directing groups.
- On the contrary, $+M$ groups increase electronic density at the β carbon and behave as β-directing groups.
- The effect of $-I$ groups is more difficult to predict: they can stabilise a partial negative charge at the α carbon, which should elongate the adjacent carbon–titanium bond, but at the same time they are expected to somewhat reduce the electron density at the α carbon. The selectivity can thus depend on the hard or soft nature of the reagent involved.
- Conversely, $+I$ groups should disfavour a large polarisation of the adjacent carbon–titanium bond, which should tend to shorten the α carbon–titanium bond. However, they should increase the electron density at the α carbon. Here again, the selectivity can vary, depending upon the nature of the other reagent.
- As usual, resonance effects can be assumed to predominate over field effects. For instance, $+M$, $-I$ groups are expected to be β-directing groups.
- Because of steric repulsion with the di*iso*-propyloxytitanium moiety, the carbon–titanium bond adjacent to large substituents of the titanacyclopropene should tend to be elongated. This can reinforce the electronic effects exposed above, or, on the contrary, exercise an opposite effect.
- Finally, groups with the ability to coordinate to the titanium atom in an intramolecular fashion can lead to the formation of a strained bicyclic system, which should result in elongation of the β carbon–titanium bond and increase its reactivity.[131] The formation of dimeric or oligomeric species assembled by intermolecular coordination is also a distinct possibility, depending upon the length of the tether, with a similar β-directing effect.[132] Moreover, this effect is reinforced by the fact that 1,2-insertion of an unsaturated compound into the α carbon–titanium bond would lead to the formation of a bridged bicyclic system with an sp^2 carbon atom at the bridgehead, which is disfavoured according to Bredt's rule.

(ii) The nature of the reagent with which the titanacyclopropene is made to react often plays a critical role. For instance, the trimethylsilyl group, a large substituent with a positive field effect (+I), displays strong α-directing properties in protonation reactions with *s*-BuOH,[123] a small, hard electrophile, moderate α-directing properties in reactions with carbon dioxide,[113] and marked β-directing properties in reactions with aldehydes and ketones, which are larger and softer electrophiles. The steric requirement of the reagents plays an important role: in the latter case, the β-selectivity increases with the size of the carbonyl compound,[105] which can be explained by the increasing steric repulsion with the bulky trimethylsilyl group.

Finally, it should be noted that the choice of solvent may somewhat modulate regioselectivity as well.[133]

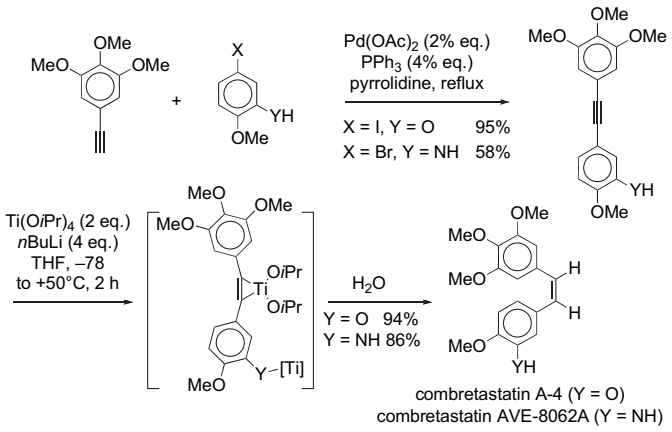
In summary, regioselectivity results from a complex combination of additive or conflicting factors, the analysis of which can help understanding and predicting results. The directing effects of some common groups are summarised in Table 1. Nonetheless, the regioselectivity is detailed in each of the following relevant sections, given the variations caused by the nature of the reagents used.

Table 1
Known directing effects of some functional groups substituting dialkoxytitanacyclopropenes

Substituent	Directing properties
CO_2t-Bu	Moderately α-directing vis-à-vis aldehydes; β-directing vis-à-vis alkynes
$C(O)NEt_2$	Strongly β-directing vis-à-vis alkynes
$P(O)(OEt)_2$	Strongly β-directing vis-à-vis aldehydes and imines
$NR^1SO_2R^2$	Strongly β-directing vis-à-vis aldehydes
$SiMe_3$	Strongly α-directing vis-à-vis *s*-BuOH; moderately α-directing vis-à-vis CO_2; β-directing vis-à-vis aldehydes and ketones; strongly β-directing vis-à-vis imines, nitriles, alkenes, allenes and alkynes
$SnBu_3$	Strongly α-directing vis-à-vis *s*-BuOH; strongly β-directing vis-à-vis aldehydes
Ph	Moderately α-directing vis-à-vis aldehydes; moderately β-directing vis-à-vis imines; β-directing vis-à-vis CO_2
CH_2OTBS	Strongly α-directing vis-à-vis aldehydes; moderately α-directing vis-à-vis CO_2
CH_2OTHP, CH_2OCH_2OEt, $CH(OEt)_2$	Strongly α-directing vis-à-vis aldehydes
Alkyl-OLi or coordinating alkyl chain (2- to 4-carbon tether)	β-Directing vis-à-vis aldehydes, carbonates, imines, alkenes, allenes and alkynes

4.2.3. Reduction of alkynes to alkenes. One of the simplest uses of titanacyclopropene complexes consists of hydrolysing them. This is sometimes exercised in order to prepare (*Z*) olefins in a diastereospecific fashion,[130,134–137] as an alternative to other methods such as catalytic hydrogenation,[138–140] DIBAL reduction,[141] or zinc–copper couple reduction.[142] In particular, some 1-tri-*n*-butylstannyl-1-alkynes have been converted into the corresponding (*Z*)-vinyltin derivatives.[114] This method has also been recently applied to a synthesis of combretastatins A-4 and AVE-8062A, potent anticancer agents disrupting the aggregation of tubulin. Thus, generation of thermally stable titanacyclopropenes[120] from the corresponding alkynes followed by hydrolysis delivers the target compounds with great efficiency and high purity (Scheme 36). Indeed, purification of the synthetic combretastatin A-4 allowed the acquisition of its X-ray crystal structure.[135]

Another interesting and recent application has been reported, where poly(phenylene ethynylene) polymers (PPEs) are efficiently converted into all-*cis*-poly(phenylene vinylene) polymers (PPVs). All-*cis*-PPV/PPE co-polymers can also be accessed by a Sonogashira polymerisation of diynes with all-*cis*-PPV oligomers prepared by the same method (Scheme 37).[143]

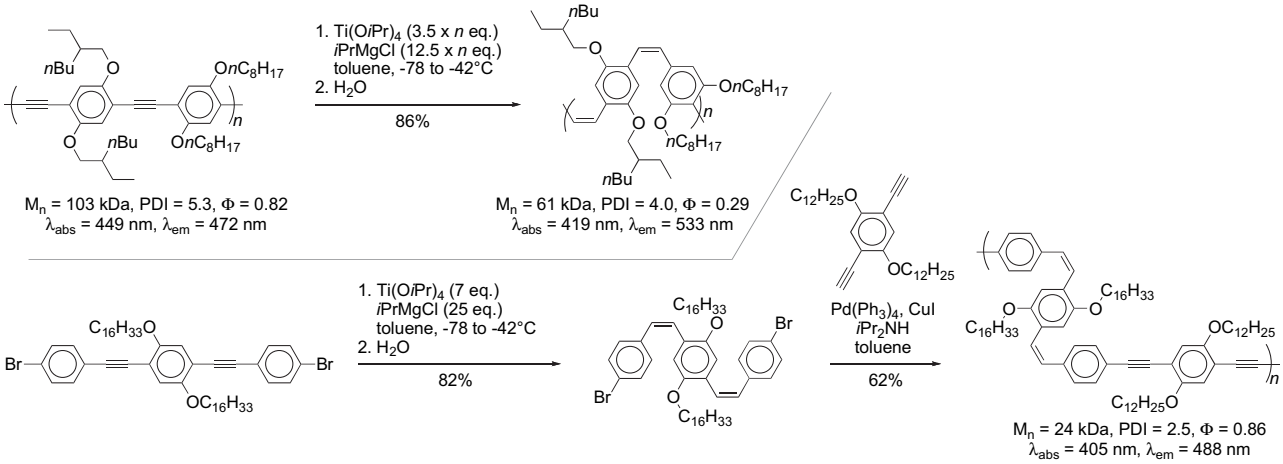


Scheme 36. Synthesis of combretastatins A-4 and AVE-8062A.[135]

carbon atom 1 with virtually complete regioselectivity. The vinyltitanium species thus generated can then be submitted to further transformation to prepare substituted olefin compounds with defined configurations (Scheme 39).[123] With other alkynes such as 5,5-diethoxy-pent-2-yne, the regioselectivity of the protonation step is lower: after the addition of iodine, various ratios of regioisomeric vinyl iodides are produced, depending upon the proton source.[145]

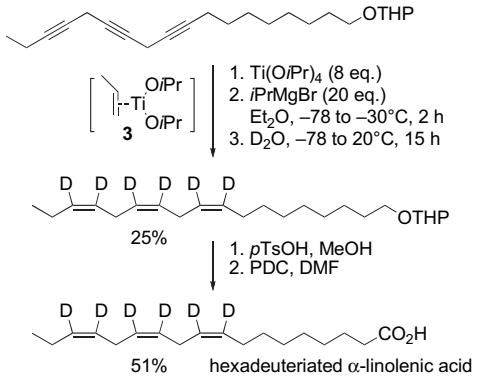
4.2.4. *Reaction of titanacyclopropenes with carbonyl derivatives, imines and nitriles*

4.2.4.1. Aldehydes and ketones. Dialkyloxytitanacyclopropenes react at low temperature with aldehydes and ketones according to Eq. 8 (Scheme 34). The resulting oxadialkyloxytitanacyclopentene intermediates **M1** retain one carbon–titanium bond, the reactivity of which can be taken advantage of by adding a second reagent. Highly functionalised allylic alcohols can thus be prepared in one synthetic step with full control of the geometry of the carbon–carbon double bond (Scheme 40).[105]



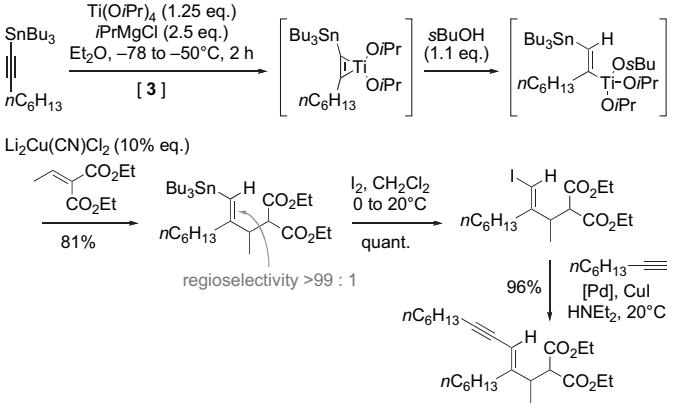
Scheme 37. Synthesis of conjugated polymers containing *cis*-phenylene vinylene moieties.[143]

The conversion of alkynes into titanacyclopropenes is a method of choice when bis-deuteriated (*Z*) olefins are desired. Deuteriolysis results in net *cis* di-deuterium addition, providing the wanted compounds in a diastereospecific, convenient and inexpensive way, the source of deuterium being deuterium oxide.[105,144] This reaction has been applied to the preparation of deuterium-labelled α-linolenic acid needed for biosynthetic studies (Scheme 38).[130,134]

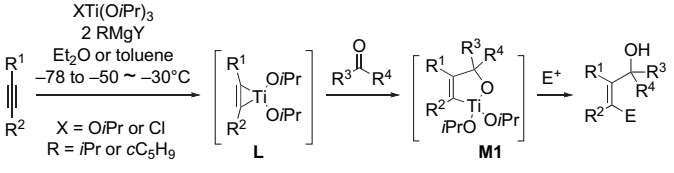


Scheme 38. Synthesis of deuterium-labelled α-linolenic acid.[130,134]

Very interestingly, partial protonolysis of dialkoxytitanacyclopropenes can be executed by the addition of 1 equiv of *sec*-butanol. With complexes generated from 1-trimethylsilyl-1-alkynes or 1-tri-*n*-butylstannyl-1-alkynes, protonation occurs at



Scheme 39. Regioselective partial protonolysis of a di*iso*-propyloxytitanacyclopropene, and further transformations.[123]

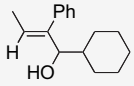
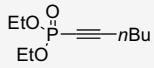
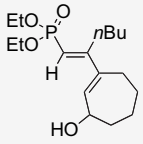
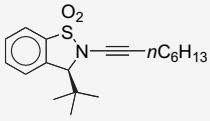
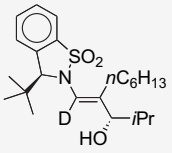
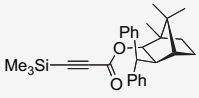
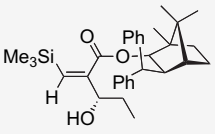
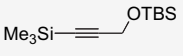
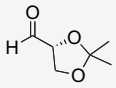
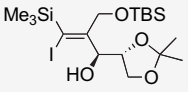
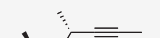
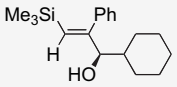
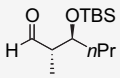
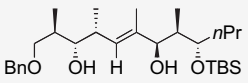
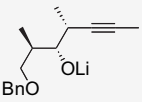
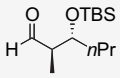
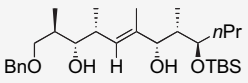


Scheme 40. Titanium-mediated one-pot conversion of alkynes into highly substituted allylic alcohols.[105]

A wide variety of substrates and reagents can be used; a selection of examples is presented in Table 2. Alkyl, aryl and α,β-unsaturated aldehydes and ketones participate in these reactions, although some α,β-unsaturated ketones have been reported to give rearranged products (Table 2, entry 2).[126] As far as the regioselectivity is concerned, α- and β-directing groups can be identified from the results reported in the literature; these are displayed in Table 3. The conversion of 1-sulfonylamino-1-alkynes is especially interesting, since it provides access to functionalised enamides in a highly regio- and diastereo-selective fashion.[127] Moreover, starting from enantiomerically pure chiral benzosultame substrates, efficient remote 1,5-asymmetric induction operates, and the products are obtained with good-to-excellent optical purity (Table 2, entry 3).[128,129] Conjugated acetylenic esters are suitable alkyne partners as well, and eventual aldehyde addition provides interesting Baylis–Hillman-type allylic alcohols. In particular, esters carrying a D-camphor-derived chiral auxiliary give the products with excellent regio- and diastereo-selectivities, and cleavage of the auxiliary by a saponification reaction delivers the corresponding functionalised chiral acids with high enantiomeric excess (Table 2, entry 4).[133]

Using non-chiral alkynes and (*R*)-2,3-*O*-isopropylideneglyceraldehyde as the aldehyde partner, the resulting chiral allylic alcohols are obtained with medium-to-good *anti*-diastereoselectivities (Table 2, entry 5).[146] This is in contrast to the very poor diastereocontrol and lower yield that have been reported for a similar reaction mediated by zirconium with the same aldehyde.[147] Excellent *anti*-diastereoselectivities have been reported with Garner's aldehyde as well.[53] Remarkably, the group of Sato has shown that optically active allylic alcohols can be obtained in up to 38% ee from non-chiral alkyne and aldehyde educts by using chlorotris[(−)-menthoxy]titanium in place of Ti(O*i*-Pr)$_4$ (Table 2, entry 6).[117] Double diastereocontrol is observed when both the alkyne and the aldehyde are enantiomerically enriched chiral molecules, and mismatch/match effects can be evidenced (Table 2, entries 7 and 8).[148] These examples by Micalizio et al. show that the titanium-mediated alkyne–aldehyde coupling reaction can be a valuable method for the synthesis of highly functionalised fragments of polyketide natural products. Indeed,

Table 2
Functionalised allylic alcohols obtained by reaction shown in Scheme 40

Entry	Starting alkyne	Conditions for formation of L[a]	Aldehyde or ketone	E^+	Product (major isomer)	Yield (regioselectivity)
1[105]		A		H_3O^+		90% (86:14)
2[126]		B		H_3O^+		54% (100:0) *rearranged product only*
3[128]		A		D_2O		88% (>96:4) dr 93:7
4[133]		A		H_3O^+		95% (97:3) dr 97:3
5[146]		A		I_2		62% (>98:2) dr 94:6
6[117]		C		H_3O^+		63% (95:5) ee 25%
7[148]		D		H_3O^+		66% (95:5) dr 60:40
8[148]		D		H_3O^+		65% (93:7) dr 80:20

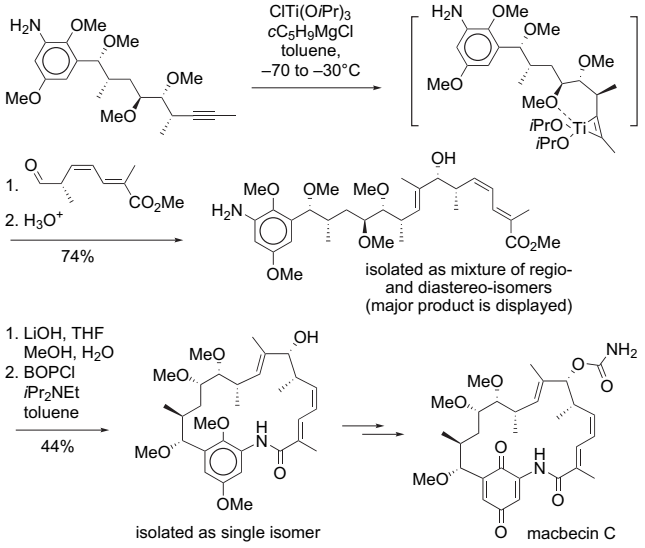
[a] Conditions A: alkyne, Ti(O*i*-Pr)$_4$ then 2 *i*-PrMgCl, Et_2O, −78 to −50 °C. Conditions B: Ti(O*i*-Pr)$_4$, 2 *i*-PrMgCl, then alkyne, Et_2O, −78 to 5 °C. Conditions C: alkyne, ClTi[(−)-menthoxy]$_3$ then 2 *i*-PrMgCl, Et_2O, −78 to −35 °C. Conditions D: lithiated alkyne, ClTi(O*i*-Pr)$_3$ then 2 *c*-C_5H_9MgCl, toluene, −78 to −30 °C.

Table 3
Directing properties of starting alkyne substituents in reactions of dialkoxytitanacyclopropenes with aldehydes and ketones, ranked approximately from top to bottom by decreasing order of magnitude

α-Directing groups	β-Directing groups
$CH(OEt)_2$, CH_2OBn, CH_2OTHP, CH_2OTBS	$N(R)SO_2R'$
Ph	$P(O)(OEt)_2$
CO_2t-Bu	$SiMe_3$, CH_2SiMe_3, $SnBu_3$
Alkyl	Alkyl–OLi (4-carbon tether)
	Alkyl–OLi or alkyl–OMe (2-carbon tether)
	Alkyl

starting from alkynes bearing a polyoxygenated substituent, good regiocontrol can be achieved, owing to the coordinating effect presented in Section 4.2 (Fig. 2). A δ-alkoxide function relative to the alkyne ensures better regioselectivity than a β-alkoxide function, but good regiocontrol can also be achieved with methyloxy or benzyloxy functions. The regioselectivity is also modulated by the relative configurations of the chiral centres of the polyoxygenated alkyne and of the aldehyde.[131,132,148]

This method has been recently applied to a synthesis of macbecin C, a benzoquinone ansamycin antibiotic.[149] Although the regio- and diastereo-selectivity of the key insertion of the aldehyde into the titanacyclopropene intermediate could not be measured accurately in this case, the authors report that a similar reaction performed with the same starting alkyne and a closely related aldehyde lacking the ester function proceeds with 7:1 regio- and 3:1 diastereo-selectivity. After saponification of the methyl ester function and subjecting to macrolactamisation reaction conditions, only the desired isomer undergoes cyclisation. The target molecule is then obtained in two steps following an already described sequence (Scheme 41).[150]

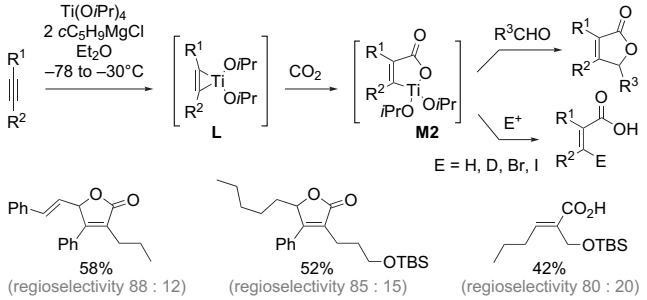


Scheme 41. Total synthesis of macbecin C.[149]

4.2.4.2. Carboxyl derivatives. Dialkoxytitanacyclopropenes **L** react with carbon dioxide according to a 1,2-insertion pathway. The pattern of regioselectivity (Table 4) is quite different from that observed with aldehydes. For instance, whereas the trimethylsilyl group acts as a strong β-directing group in the latter reactions, it exercises a moderate α-directing effect in the case of carbon dioxide insertion. In fact, this process is analogous to closely related reactions involving titanacyclopropenes with *cyclo*-pentadienyl-type ligands. In those examples described by the groups of Vol'pin, Shur, Dixneuf, and Rosenthal, titanafuranones are formed, which have been characterised by X-ray crystallography or by analytical and spectroscopic methods.[151–157] Similarly, although the intermediates generated in the dialkoxytitanium series have not been characterised, they react in a way that is consistent with the titanafuranone structure **M2**. Thus, the reactivity of the remaining carbon–titanium bond can be used advantageously to generate highly substituted acrylic acids in a one-pot operation. Moreover, the addition of an aldehyde after the carbon dioxide-insertion step provides access to substituted furanones (Scheme 42).[113,118]

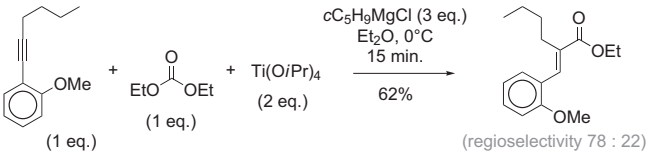
Table 4
Directing properties of starting alkyne substituents in reactions of dialkoxytitanacyclopropenes with carbon dioxide, ranked approximately from top to bottom by decreasing order of magnitude

α-Directing groups	β-Directing groups
CH_2OTBS	Ph
$SiMe_3$	Alkyl chain longer than Me
Me	



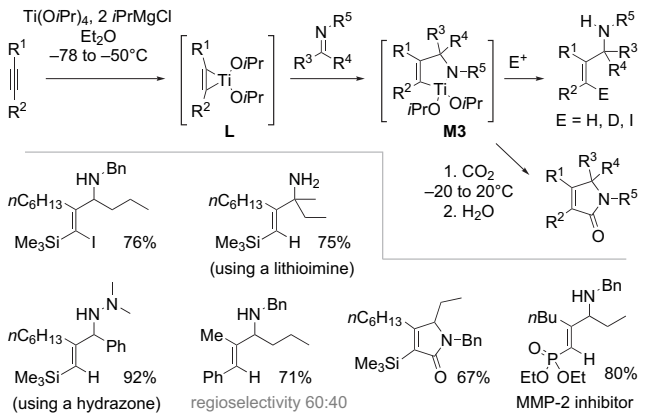
Scheme 42. Reaction of dialkoxytitanacyclopropenes with carbon dioxide.[113,118]

The complexes **L** may also react with carbonates in an intermolecular fashion. This reaction can be executed according to a very simple experimental procedure where a diethyl ether solution of the chosen educts and Ti(O*i*-Pr)$_4$ is treated with *cyclo*-pentylmagnesium chloride at 0 °C (Scheme 43).[116,158]



Scheme 43. Titanium-mediated intermolecular alkyne–carbonate coupling.[116,158]

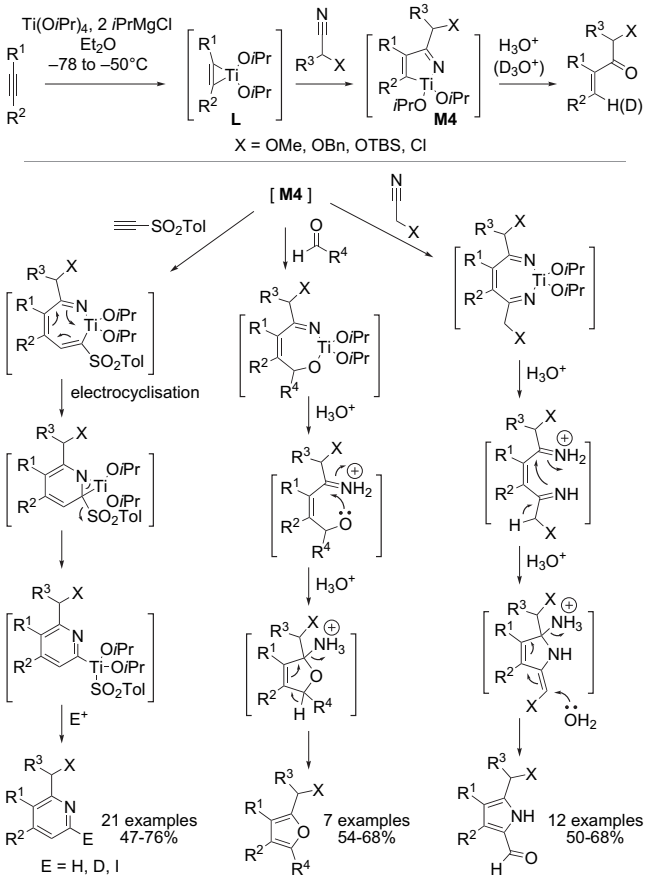
4.2.4.3. Imine derivatives. The reaction of di*iso*-propyloxytitanacyclopropenes with imine derivatives has been first described by the group of Sato.[159] The scope of this process includes the use of ketimines, hydrazones and lithioimines, but oxime derivatives do not appear to participate in the reaction. Similarly to the situation encountered with the 1,2-insertion of aldehydes and ketones, the vinyltitanium intermediate **M3** can eventually react with H_2O, D_2O or I_2 (Scheme 44). Highly functionalised allylic amines are thus obtained very quickly and efficiently. Moreover, treating **M3** with carbon dioxide provides access to 1,5-dihydro-2*H*-pyrrol-2-ones.[160]



Scheme 44. Titanium-mediated, one-pot, alkyne-imine derivative coupling reaction.[159–162]

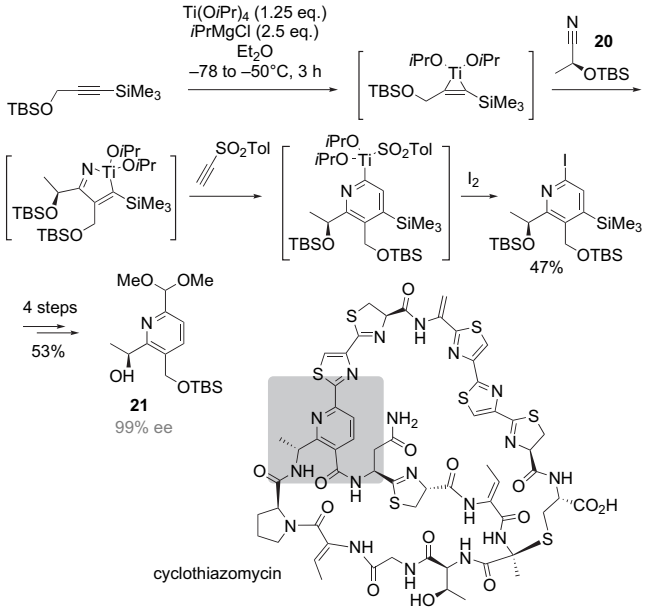
The regioselectivity of these reactions seems to be governed by steric factors to a larger extent than the related reactions with aldehydes. For instance, whereas the phenyl group is an α-directing group in the latter processes, it acts as a moderate β-directing group in the reactions with imines. Moreover, trimethylsilyl and diethylphosphono groups display a strong β-directing effect, and the regioselectivity is complete when the other substituent of the alkyne is an alkyl or even a phenyl group.[159,161] A few 3-aminovinylphosphonates prepared by the application of this method exhibit moderate-to-interesting inhibitory activity towards matrix metalloproteinase MMP-2.[162]

4.2.4.4. Nitriles. Dialkoxytitanacyclopropenes may react with nitriles according to a 1,2-insertion pathway to provide highly interesting azatitanacyclopentadiene intermediates **M4** (Scheme 45).[163] The presence of a heteroatom-substituted moiety in the nitrile seems to be important for this process to operate in good yield.[131,163] The regioselectivity follows a similar pattern to that of the corresponding reaction with imines, with 1,2-insertion occurring at carbon 2 starting from 1-trimethylsilylalkynes. The versatility and synthetic potential of this reaction are remarkable: complexes **M4** are reactive enough to undergo further regioselective 1,2-insertions of *p*-toluenesulfonylacetylene, aldehydes or α-alkyloxynitriles, eventually yielding highly functionalised pyridines, furans and pyrroles, respectively.



Scheme 45. Applications of the reactions of dialkoxytitanacyclopropenes with nitriles.[163]

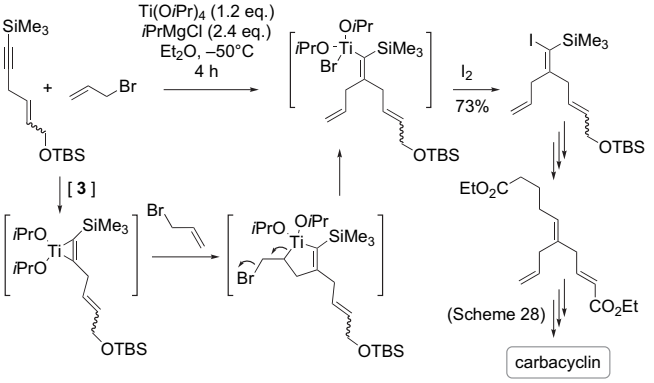
In particular, no racemisation occurs during the preparation of pyridines with the chiral nitrile **20** (99% ee). This was applied to the expedient synthesis of the functionalised pyridine **21**,[163] a plausible synthetic fragment towards the macrobicyclic antibiotic, cyclothiazomycin (Scheme 46).[164,165]



Scheme 46. Preparation of a cyclothiazomycin fragment.[163]

4.2.5. Reaction of titanacyclopropenes with alkenes, allenes and alkynes

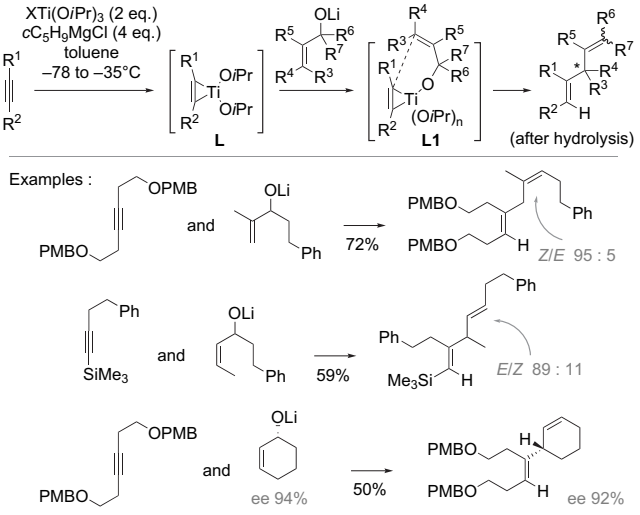
4.2.5.1. Alkenes. The *intermolecular* 1,2-insertion of alkenes into dialkoxytitanacyclopropenes **L** is generally a poorly efficient process.[166] However, the group of Sato has demonstrated that complexes **L** react with alkenes bearing a Lewis-basic leaving group in the allylic position to give 1,4-dienyltitanium complexes. The reaction probably proceeds by coordination of the leaving group to the titanium centre followed by 1,2-insertion of the carbon–carbon double bond into one of the two C–Ti bonds (Eq. 8, Scheme 34), and then by β-elimination of the leaving group, which can be a halide, acetate, carbonate or epoxide. As usual, the remaining carbon–titanium bond can be simply hydrolysed or functionalised upon addition of a suitable electrophile such as iodine or an aldehyde.[92,167] This alkyne–allyl coupling reaction was applied to the synthesis of carbacyclin (Scheme 47).[99] From a practical point of view, it is worthy of note that this process does not have to be executed in a stepwise manner: *iso*-propylmagnesium chloride can be simply added to a diethyl ether solution of the alkyne, the allyl compound and Ti(O*i*-Pr)$_4$. Intramolecular reactions are possible as well (see Section 4.3.4).



Scheme 47. Beginning of the synthesis of carbacyclin.[99]

It is worthy of note that, in the case of reactions of 1,4-enyne substrates with allylic compounds, as shown in Scheme 47, the intermolecular coupling process may be followed by cyclisation of the resulting 1,6-diene moiety when excess amounts of Ti(O*i*-Pr)$_4$ and Grignard reagents are used.[168]

Micalizio et al. have shown that allylic lithium alkoxides can also be used as allylating agents, thereby extending the known scope of the reaction to a variety of functionalised substrates such as secondary or tertiary alkoxides and di- or even trisubstituted olefins.[169] Indeed, coordination of the alkoxide function to the titanium centre of the intermediate **L1** facilitates the 1,2-insertion (carbometallation) elementary step and ensures excellent regiocontrol from the point of view of the alkene partner, with the new C–C bond being formed at the distal olefinic carbon atom relative to the alkoxide function. Importantly, starting from secondary alcohols, the formation of the new carbon–carbon double bond operates with excellent stereocontrol using alkoxides bearing 1,1-disubstituted olefins or (*Z*)-disubstituted olefins,[44,169] presumably because of a boat-like geometry of the transition state.[169] Moreover, the transfer of chirality can be very high if a new chiral carbon centre is created (Scheme 48).[169]

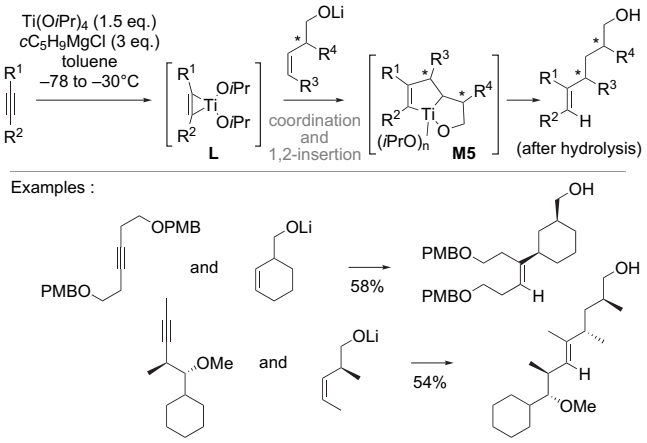


Scheme 48. Reactions of dialkoxytitanacyclopropenes with allylic lithium alkoxides.[169]

The behaviour of homoallylic lithium alkoxides towards dialkoxytitanacyclopropenes **L** is analogous to that of allylic lithium alkoxides, except that the titanacyclopentene intermediates **M5** are stable in this case, since β-elimination can no longer take place. The result is a net alkyne–alkene reductive coupling. Here, again, the intramolecular nature of the olefin 1,2-insertion step into the titanacyclopropene lowers the energy barrier and ensures excellent regiocontrol with C–C bond formation taking place at the distal carbon of the alkene moiety. Moreover, high diastereocontrol can be achieved starting from chiral homoallylic alkoxides with a (*Z*) disubstituted double bond, which validates the utility of this method for the assembly of complex fragments without functional group manipulation (Scheme 49).[131,166]

With respect to the starting alkyne partners, the regioselectivities of the reactions of this type have been relatively little studied, but trimethylsilyl, 2-methoxyalkyl and lithium 4-alkoxide groups have a strong β-directing effect in comparison to non-functionalised alkyl groups, as can be seen in the examples shown in Schemes 48 and 49. Finally, and interestingly, when thermally stable dialkoxytitanacyclopropenes are treated with allyl bromides at 50 °C, both carbon–titanium bonds can participate in the allylation process, which then seems to operate by direct S_N2 displacement.[120] It should be noted, however, that the products are obtained as mixtures of *Z* and *E* diastereoisomers.

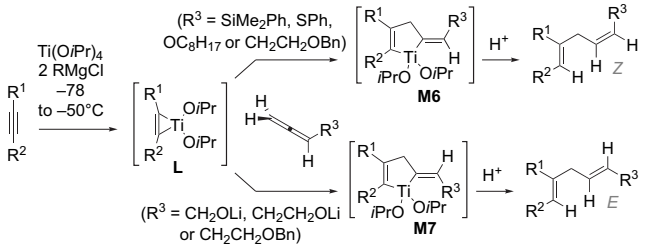
4.2.5.2. Allenes. Although only a few reports describe the 1,2-insertion of allenes into dialkoxytitanacyclopropenes, this chemistry is quite rich, since the allene substitution pattern can strongly



Scheme 49. Reactions of dialkoxytitanacyclopropenes with homoallylic lithium alkoxides.[166]

influence the regio- and diastereo-selectivity of these processes, and possibly command spontaneous further transformations. With respect to the alkyne moiety, the regioselectivity is similar to that observed with alkene 1,2-insertion (see previous section), but it has been shown that its magnitude may be influenced significantly by the nature of the allene partner.[170]

As a general rule, monosubstituted allenes undergo carbometallation at the terminal double bond, with carbon–carbon bond formation occurring at the Csp^2 centre. Since the approach of the titanacyclopropene usually occurs preferentially at the less-hindered face of the allene, the intermediate alkylidenetitanacyclopentene **M6** is normally formed, with the substituent of the allene and the titanium centre in a trans relative configuration. The (*Z*) diastereoisomer is obtained as the major product after hydrolysis (Scheme 50). However, the group of Sato has shown that larger amounts of the (*E*) diastereoisomer are produced with a 2-benzyloxy-substituted allene. This can be explained by the formation of the intermediate **M7**, now stabilised by intramolecular coordination to the titanium atom.[103] This effect can be favoured even further using lithium alkoxide tethers, and very high (*E*) diastereoselectivity can thus be reached (Scheme 50).[171] In this case, however, carbometallation at the internal Csp–Csp^2 bond becomes more facile and mixtures of products may be obtained. This problem can be overcome by adding a substituent on the allene at the proximal carbon, or, on the contrary, this process can be favoured by adding substituents at the distal carbon (Fig. 3).[171,172] Both site selectivities are valuable and can be taken advantage in interesting applications.



Scheme 50. 1,2-Insertion of allenes into dialkoxytitanacyclopropenes.

With carbometallation occurring at the remote position from the alkoxide, the method is well suited for the rapid diastereoselective assembly of complex fragments containing a skipped dienyl system (Scheme 51).[131,171] In the cases where carbometallation takes place near the alkoxide, elimination can happen in

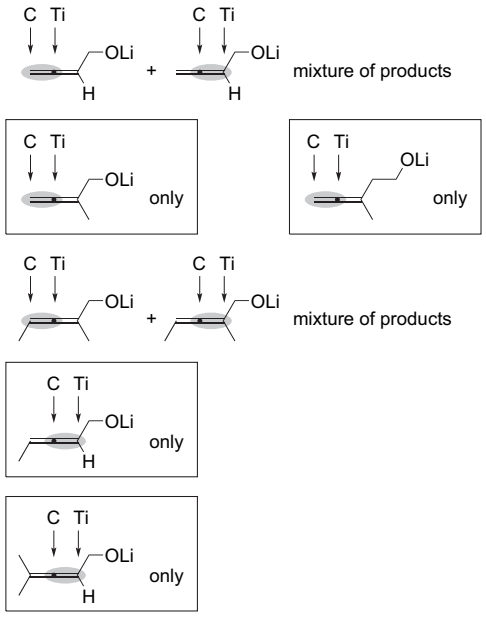
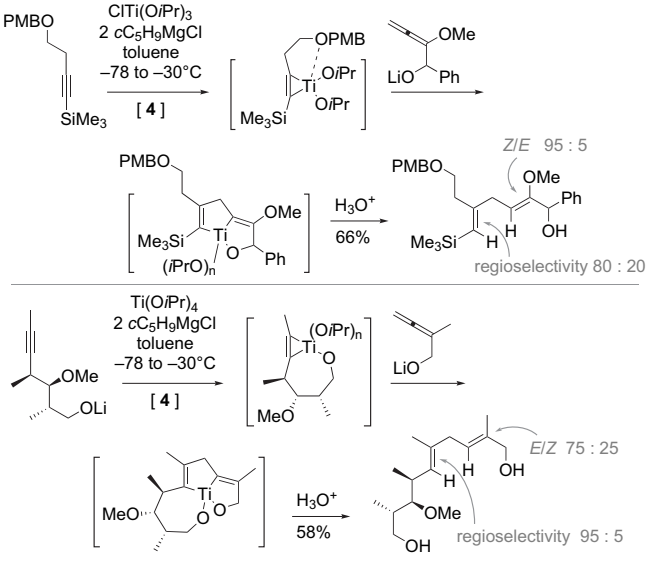
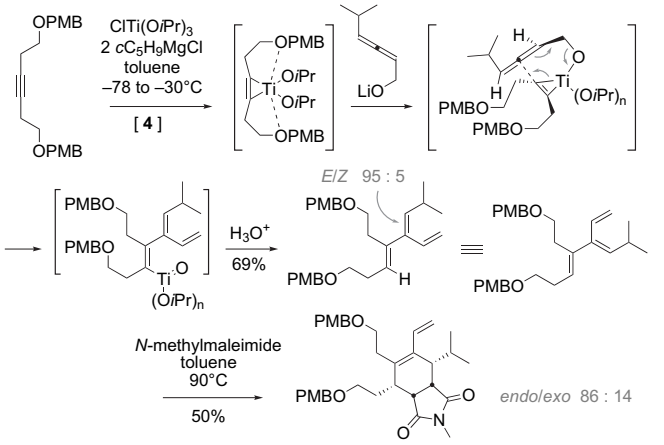


Figure 3. Regioselectivity of the carbometallation of allenes bearing a lithium alkoxide function by titanacyclopropenes.[171,172]



Scheme 51. Synthesis of skipped dienes by titanium-mediated coupling of alkynes with allenes bearing a lithium alkoxide function.[131,171]

a process that can be viewed as a special case of the reaction of allylic lithium alkoxides shown in Scheme 48. Substituted cross-conjugated trienes are then obtained with excellent diastereoselectivity, and can be used in Diels–Alder cycloadditions to build complex molecules (Scheme 52).[172]

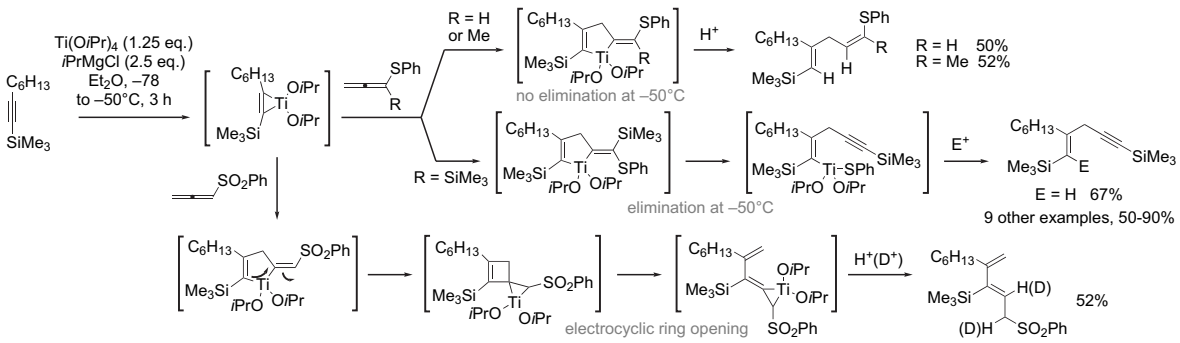


Scheme 52. Synthesis of cross-conjugated trienes by titanium-mediated coupling of alkynes with allenes bearing a lithium alkoxide function.[172]

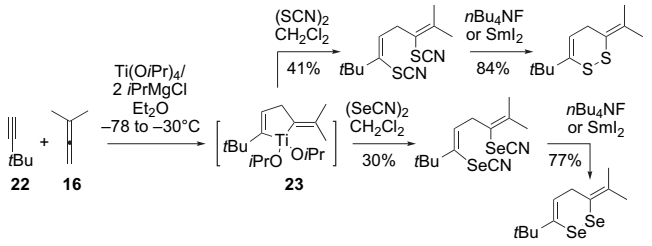
Bromo- or thiophenyl-substituted terminal allenes may undergo elimination after the carbometallation elementary step if the leaving group is located cis to the titanium atom in the resulting intermediate, which in practice is attainable starting from substrates with a bulky trimethylsilyl group in the α--position. The net transformation is then a fully diastereoselective propargyltitanation of the starting alkyne that may then be followed by trapping with electrophiles such as iodine or aldehydes (Scheme 53).[170] Using phenylsulfonyl-substituted terminal allenes, rearrangement takes place and 1,3-diene derivatives are obtained.[170]

Finally, an interesting example of alkyne–allene coupling is the direct formation of titanacyclopentene **23** upon treatment of a mixture of 3,3-dimethylbutyne **22** and allene **16** with the Ti(O*i*-Pr)$_4$/2*i*-PrMgCl combination of reagents, although subsequent trapping with (SCN)$_2$ or (SeCN)$_2$ delivers the corresponding products in rather low yields (Scheme 54).[104]

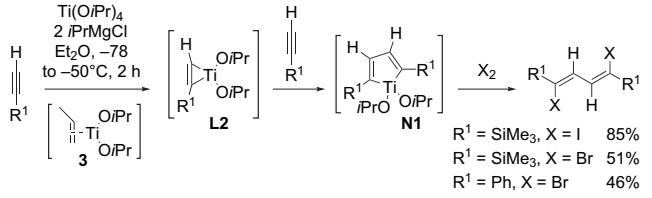
4.2.5.3. Alkynes. The preparation of dialkoxytitanacyclopropenes **L2** from terminal alkynes is elusive, because as soon as they are generated, these species undergo fast insertion of the alkyne starting material (Eq. 9, Scheme 34), and dialkoxytitanacyclopentadienes **N1** are formed with a high head-to-head regioselectivity (Scheme 55).[173] The reaction of the bulky alkyne **22** (Scheme 54) is a notable exception. Presumably, insertion of another molecule of **22** into the putative



Scheme 53. Reactions of dialkoxytitanacyclopropenes with functional allenes.[170]



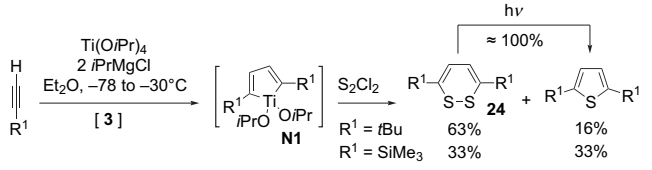
Scheme 54. Direct alkyne–allene coupling followed by trapping with $(SCN)_2$ or $(SeCN)_2$.[104]



Scheme 55. Titanium-mediated homocoupling of terminal alkynes and trapping of the titanacyclopentadiene intermediate with bromine or iodine.[173]

titanacyclopropene intermediate **L2** is sufficiently slow to allow insertion of the allene reactant **16** also present in the reaction medium, although the possibility that the initially formed titanacyclopropane **3** reacts with the allene **16** first cannot be excluded in this case.[104]

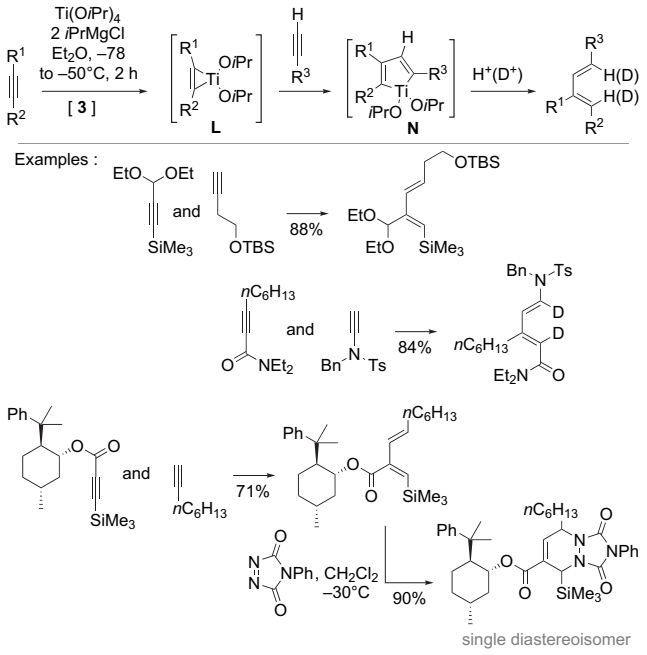
Titanacyclopentadiene complexes **N1** can be trapped with bromine or iodine[174] to deliver (*Z*,*Z*)-1,4-dihalobuta-1,3-dienes (Scheme 55),[173] or with chalcogenising reagents such as selenocyanogen $(SeCN)_2$, thiocyanogen $(SCN)_2$, $Se(SeCN)_2$ or disulfur dichloride S_2Cl_2. In the latter case, 1,2-dithiins **24** are obtained, along with thiophenes (Scheme 56).[104]



Scheme 56. Titanium-mediated synthesis of 1,2-dithiins from terminal alkynes.[104]

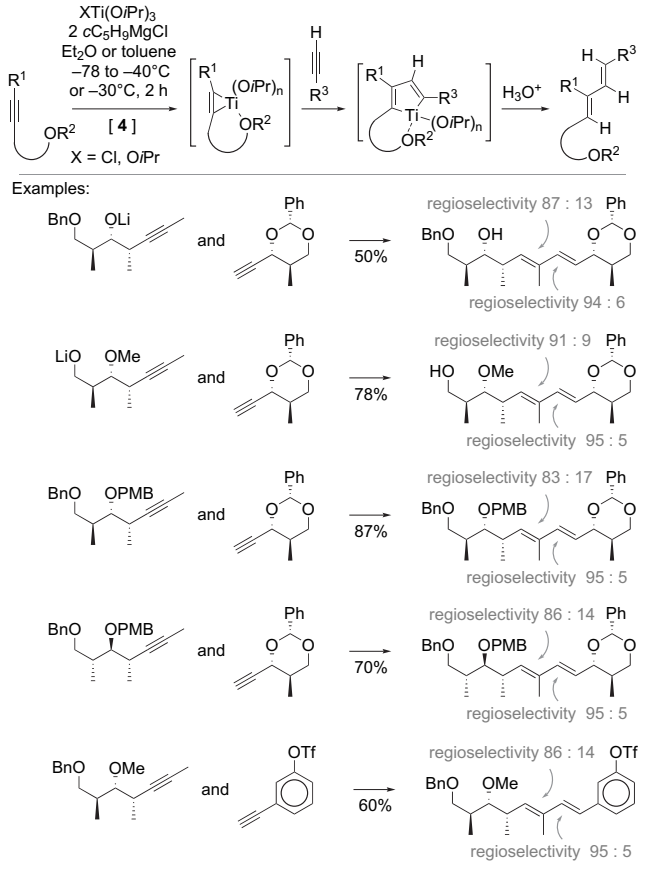
More generally, titanacyclopentadienes **N** can be generated by reacting dialkoxytitanacyclopropenes **L**, pre-formed from *internal* alkynes, with *terminal* alkynes. In the 1,2-insertion process, carbon–carbon bond formation takes place at the terminal sp carbon atom. A variety of chemical functions are tolerated on the terminal alkyne partner, such as carboxylic ester, carbonate, alkyl ether, silyl ether or alkene groups, and terminal alkynes such as trimethylsilylacetylene, *tert*-butyl propynoate, *N*-alkyl-*N*-ethynyltosylamides, *N*-alkyl-*N*-ethynylbenzamides, alkynylaryl triflates and alkynylaryl bromides can be used. Hydrolysis of the intermediate dialkoxytitanacyclopentadienes **N** gives access to a variety of stereodefined substituted unsymmetrical dienes,[124,127,129] including optically active chiral dienes that can be used in diastereoselective Diels–Alder reactions (Scheme 57).[124] Very few reports of reactions of **N** with aldehydes can be found, but examples are known where the nucleophilicity of the titanacycle partner is enhanced by the presence of a nitrogen substituent.[127]

Micalizio et al. showed recently that this titanium-mediated intermolecular alkyne-to-alkyne cross-coupling is a powerful method for the expedient synthesis of complex polyketide fragments. Indeed, a high regioselectivity can be achieved using titanacyclopropenes generated from elaborated alkynes with



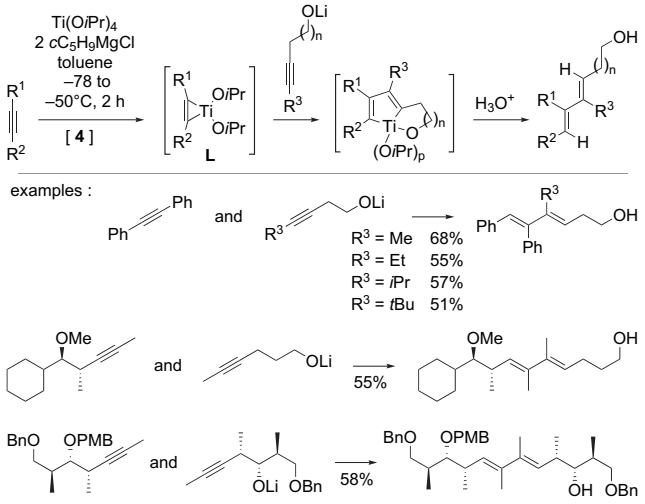
Scheme 57. Titanium-mediated intermolecular alkyne–alkyne cross-coupling.[124,127]

oxygen-based substituents. In these reactions, both the relative configurations of the chiral centres and the presence of alkoxide tethers play a role in the reaction efficiency and the level of regioselection (Scheme 58).[131,175] Moreover, while very few examples can be found where an internal alkyne is inserted into a dialkoxytitanacyclopropene in an intermolecular fashion,[173,184] the



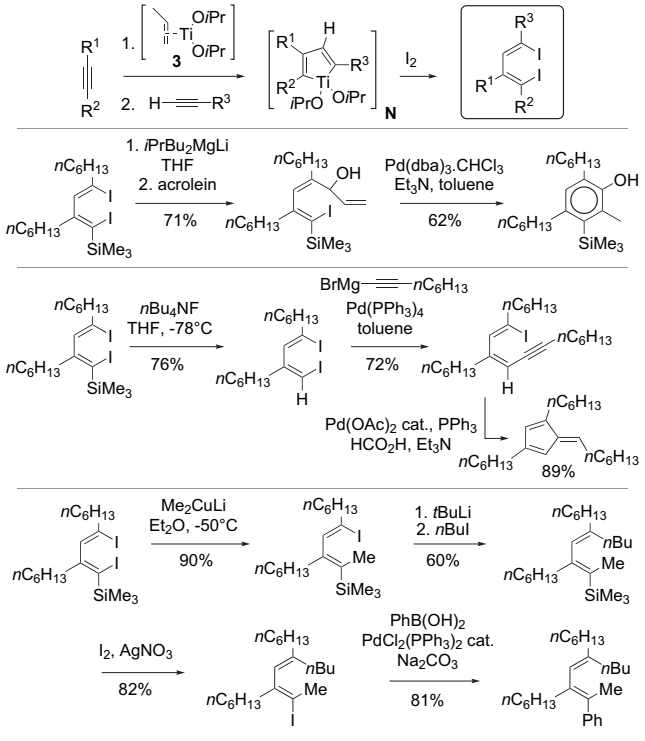
Scheme 58. Synthesis of polyketide fragments by titanium-mediated alkyne–alkyne cross-coupling.[131,175]

group of Micalizio has demonstrated that internal alkynes bearing a lithium alkoxide function at the β or γ positions are suitable substrates. Importantly, the alkoxide tether ensures virtually complete regioselectivity with respect to the alkyne containing this function, and carbon–carbon bond formation occurs at the distal Csp centre (Scheme 59).[176]



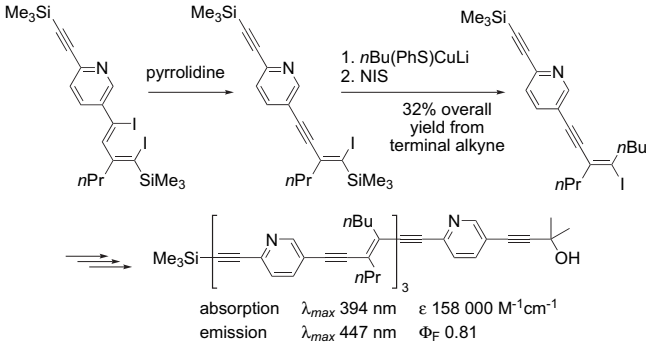
Scheme 59. Carbometallation of lithium alkoxide-substituted internal alkynes.[176]

When halogenolysis is performed as described above, unsymmetrical (*Z*,*Z*)-1,4-dihaloalka-1,3-dienes are obtained. In particular, the diiodo compounds are useful building blocks for a number of interesting applications, such as the synthesis of silole derivatives.[173] Site-selective iodine–magnesium exchange at the least crowded carbon–iodine bond is possible and has been applied to the preparation of highly substituted styrenes and phenols (Scheme 60).[177] Palladium-catalysed mono-coupling with Grignard reagents can be performed as well, with good-to-high selectivity, providing access to variously substituted 1-iodoalka-1,3-dienes, some of which can be converted into fulvene derivatives (Scheme 60).[178] Upon addition of lithium dialkyl(or diaryl)cuprates, 1,4-diiodo-1-trimethylsilylalka-1,3-dienes selectively undergo alkylation (or arylation) at the α-position relative to the silyl group. The remaining carbon–iodine bond may then be functionalised by iodine–lithium exchange followed by the addition of an electrophile, or by Pd-catalysed coupling processes such as Suzuki or Sonogashira reactions. Further functionalisation is then possible by converting the silyl group into an iodo group (Scheme 60).[179]



Scheme 60. Applications of 1,4-diodo-1,3-dienes prepared by titanium-mediated intermolecular alkyne–alkyne cross-coupling followed by iodonolysis.[177–179]

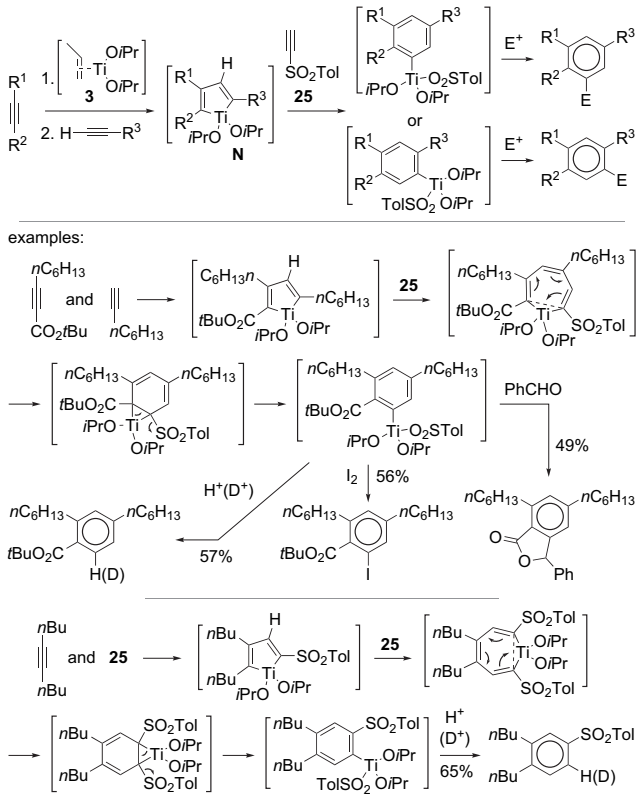
When treated with pyrrolidine, 1,4-diiodo-1-trimethylsilylalka-1,3-dienes give 4-iodo-1-trimethylsilylalka-1-yn-3-enes. These have been used in iterative approaches relying on the Sonogashira coupling reaction to prepare monodisperse linear π-conjugated oligoenynes and oligoenediynes,[180–182] and a similar process was used to synthesise monodisperse linear π-conjugated oligo(arylene enediyne)s that show intense fluorescence emission (Scheme 61).[183]



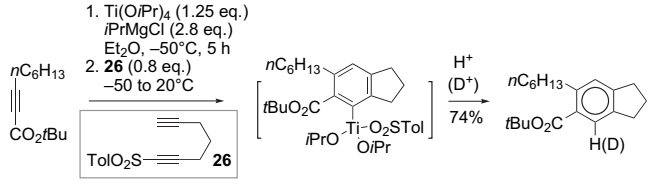
Scheme 61. Synthesis of a fluorescent monodisperse linear π-conjugated oligo(arylene enediyne).[183]

The high potential of the insertion of alkynes into dialkoxytitanacyclopropenes is illustrated by the possibility of reacting the resulting titanacyclopentadienes **N** with *para*-toluenesulfonylacetylene **25**. Aryltitanium complexes are generated, the formation of which can be accounted for either by invoking a 1,2-insertion process and a titanacycloheptatriene intermediate, or by a [4+2] cycloaddition between **N** and **25**. The whole transformation can be seen as a metallative Reppe [2+2+2] alkyne cyclisation, with very high control of the selectivity of the aryl formation. The remaining Csp^2–Ti bond may be used in several ways to access variously substituted compounds, namely by terminating the reaction either with water, deuterium oxide, iodine or an aldehyde (Scheme 62).[184] Interestingly, the second alkyne and the *para*-toluenesulfonyl-substituted alkyne can be part of the same molecule, as in **26**, which provides access to bicyclic products (Scheme 63).[184]

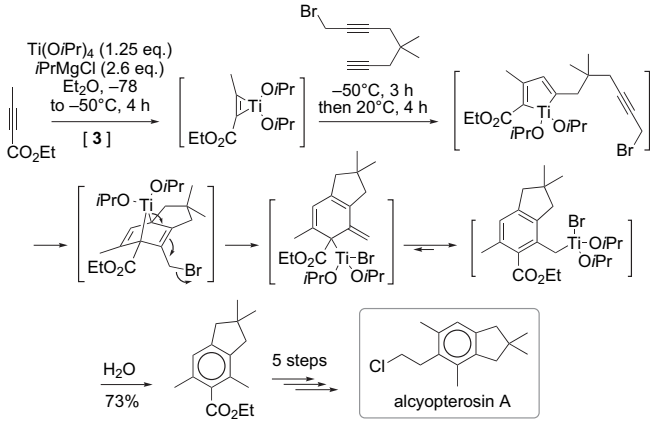
In a similar vein, highly substituted benzyltitanium species are generated selectively by the sequential insertions of terminal alkynes and propargyl bromides into dialkoxytitanacyclopropenes **L**. Again, the insertion of the propargyl bromide partner could proceed via the formation of an intermediate titanacycloheptatriene, or via a [4+2] cycloaddition. The final benzyltitanium complex eventually formed can be trapped with a variety of reagents, including water, deuterium oxide, iodine, oxygen, and allyl bromide in the presence of $Li_2Cu(CN)Cl_2$. The terminal alkyne and the propargyl bromide reaction partners can be part of the same molecule, in which case bicyclic products are obtained. This was applied to the total synthesis of the natural product, alcyopterosin A (Scheme 64).[185]



Scheme 62. Titanium-mediated metallative Reppe [2+2+2] alkyne cyclisation.[184]

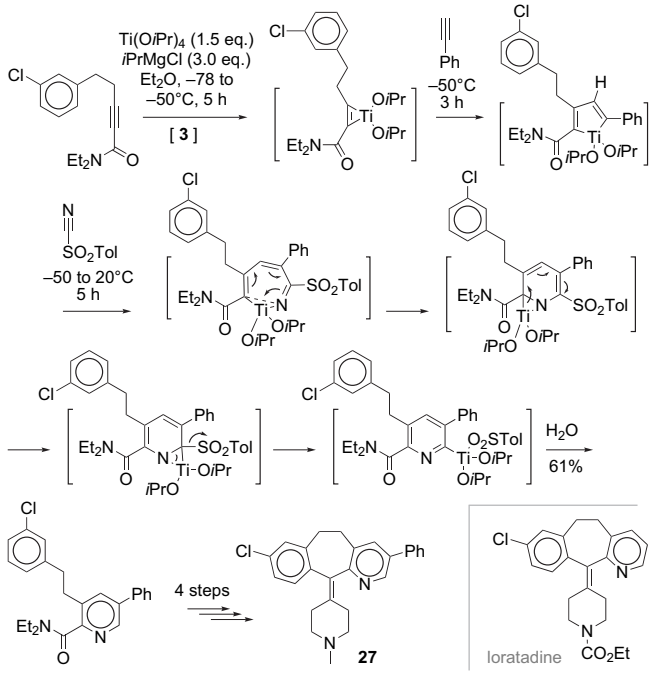


Scheme 63. Titanium-mediated metallative Reppe [2+2+2] alkyne cyclisation involving a *p*-toluenesulfonyl-substituted diyne.[184]



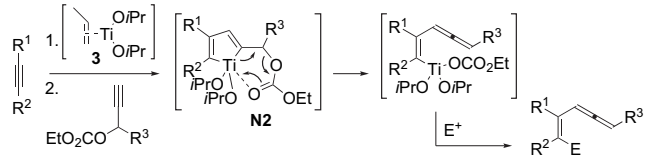
Scheme 64. Total synthesis of alcyopterosin A, involving a titanium-mediated metallative Reppe-type reaction.[185]

Metallated pyridines can also be generated by the stepwise reactions of a dialkoxytitanacyclopropene with a terminal alkyne and a nitrile.[186] This is conceptually related to the method depicted in Section 4.2.2 that involves the insertion of a nitrile into a titanacyclopropene followed by the addition of *para*-toluenesulfonylacetylene (Scheme 45). In the present approach, several types of products are possible, depending upon the substitution pattern of the starting alkynes and the nitrile involved, with the presence of leaving groups modulating the mechanistic pathway. These aspects have been described in detail by Sato et al. a few years ago.[187] This method was applied to the synthesis of the molecule **27**,[188] a derivative of loratadine, which is an antihistamine drug commercially distributed under the trade name Claritin (Scheme 65).[187]



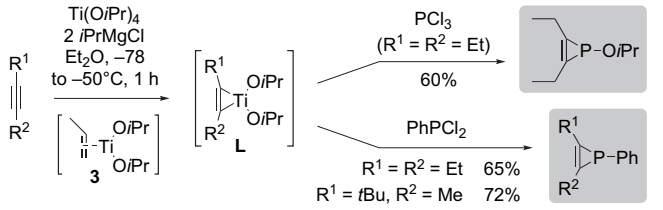
Scheme 65. Application of a titanium-mediated pyridine synthesis to the preparation of a loratadine derivative.[187]

The insertion into titanacyclopropenes **L** of terminal alkynes bearing a leaving group at the α-position results in an interesting process. In this case, the di*iso*-propyloxytitanacyclopentene intermediate **N2** undergoes elimination of the leaving group to produce an alka-1,3,4-dienyltitanium complex that may then react with an electrophile to deliver a functionalised alka-1,2,4-triene derivative (Scheme 66).[167]



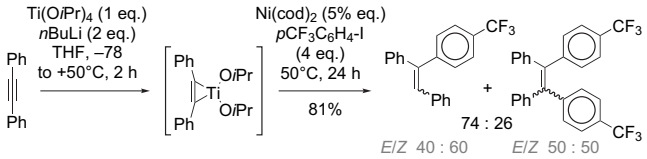
Scheme 66. Insertion of propargyl carbonates into di*iso*-propyloxytitanacyclopropenes.[167]

4.2.6. Other reactions of titanacyclopropenes. More than ten years ago, the group of Mathey and Le Floch disclosed interesting reactions of di*iso*-propyloxytitanacyclopropenes **L**—and bis(cyclopentadienyl)titanacyclopropenes—with phosphorus trichloride and phenylphosphorus dichloride. These processes deliver phosphirenes in a very direct and efficient way (Scheme 67).[189]



Scheme 67. Synthesis of phosphirenes by the reaction of titanacyclopropenes with PCl_3 or $PhPCl_2$.[189]

Additionally worthy of note is the pioneering work of Tsuji et al., who reported a Ni(cod)$_2$ cross-coupling reaction of thermally stable dialkoxytitanacyclopropenes with aryl iodides. This transformation proceeds with good selectivity in favour of the mono-coupling products, but mixtures of (*E*) and (*Z*) diastereoisomers are usually obtained (Scheme 68). Only symmetrical titanacyclopropenes appear to have been studied.[120]



Scheme 68. Nickel-catalysed cross-coupling reaction of dialkoxytitanacyclopropenes with aryl iodides.[120]

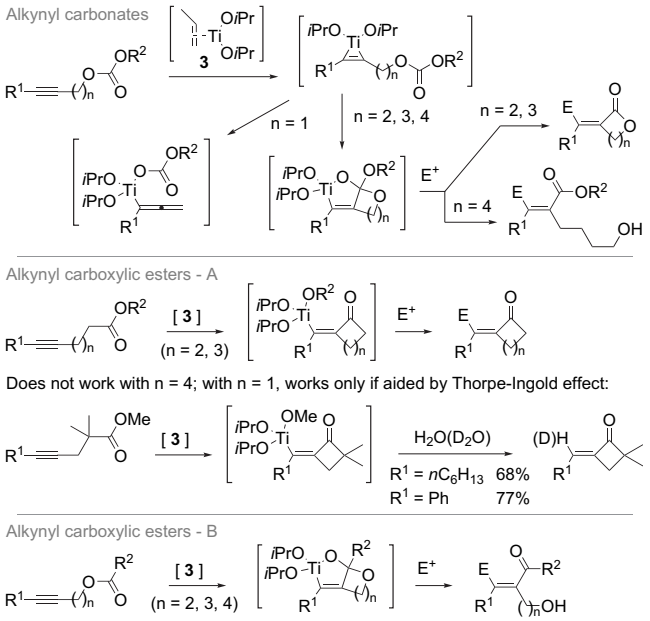
Dialkoxytitanacyclopropenes generated from diethyl 1-alkynylphosphonates react with Grignard reagents with alkylation at the remote Csp centre in a net cis diastereoselective carbometallation of the alkyne starting materials, with the possibility of further reactions with electrophiles.[125] However, this method is perhaps not particularly advantageous, compared to the direct carbocupration of 1-alkynylphosphonates developed by Cristau et al., which is highly cis diastereoselective as well.[190]

4.3. Intramolecular reactions of alkynes bearing reactive functions

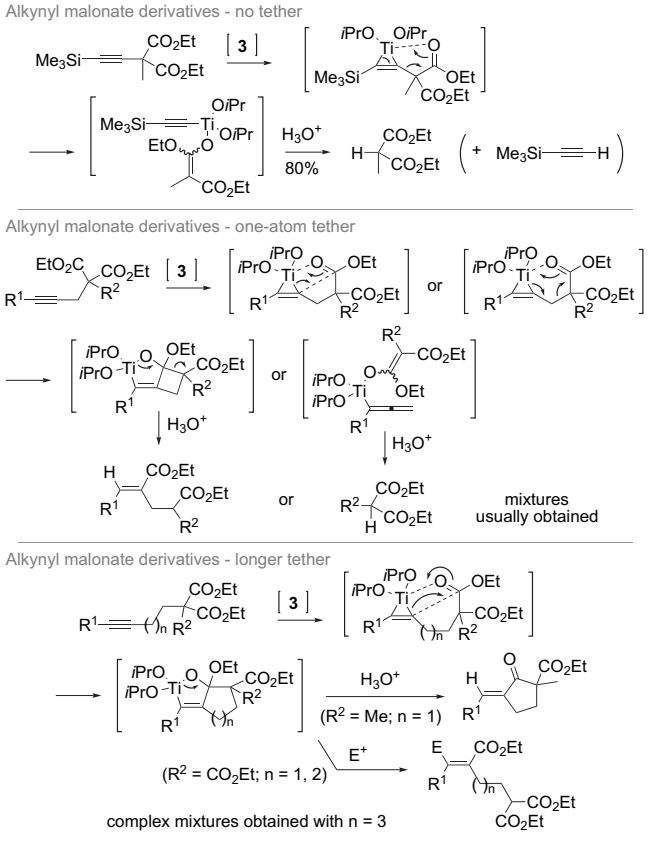
4.3.1. Alkynyl carboxylic derivatives. When treated with the Ti(O*i*-Pr)$_4$/*i*-PrMgCl combination of reagents, propargylic carbonates undergo elimination of the carbonate group consecutively with the formation of the intermediate titanacyclopropene complex (Eq. 11, Scheme 34). This is a particular case of the processes described in Section 4.4. Under the same conditions, homopropargylic carbonates follow an INAS reaction pathway, with the initially formed titanacyclopropene undergoing 1,2-insertion of the carbonyl group. Two types of products can be obtained, depending upon which of the σ carbon–oxygen bonds gets broken in the subsequent elimination process. This is dependent upon the length of the tether separating the alkyne and carbonate functions, as well as the degree of ramification of this chain, the presence of additional substituents favouring the formation of cyclic compounds because of the Thorpe–Ingold effect.[69,191] In all cases, vinyltitanium species are eventually produced. The remaining Csp^2–Ti bond can be used in reactions with electrophiles such as water, deuterium oxide and aldehydes. In the latter case, cyclisation delivering substituted butenolides is usually observed.[69,191]

Alkynes bearing a carboxylic ester function may also undergo INAS-type reactions. These processes are more challenging, for a sensitive ketone function is generated. In general, good results can nonetheless be obtained, provided that ClTi(O*i*-Pr)$_3$ is used in place of Ti(O*i*-Pr)$_4$. Choosing *iso*-propyl esters as the substrates, rather than methyl or ethyl esters, is also a key to the success of these transformations, and cyclic α-methylene ketones can thus be prepared in satisfactory yields.[68,69] Reactions carried out with carboxylic esters derived from alkynols are also possible using excess amounts (>2 equiv) of the ClTi(O*i*-Pr)$_3$/2*i*-PrMgBr combination of reagents. As in the case of alkynyl carbonates, a variety of electrophiles can be used at the end of the reactions, including water, deuterium oxide, iodine and aldehydes.[69] Malonate and methanetricarboxylate derivatives are special substrates that display a borderline behaviour, with transformations recalling either carbonate-like reactivity, with elimination or acyl-substitution processes, or ester-like reactivity, affording cyclic α-methylene ketones.[68,192]

All these reactions have been reviewed in detail,[5–7,9] and a short simplified summary of the various possibilities offered by this chemistry is presented in Schemes 69 and 70.

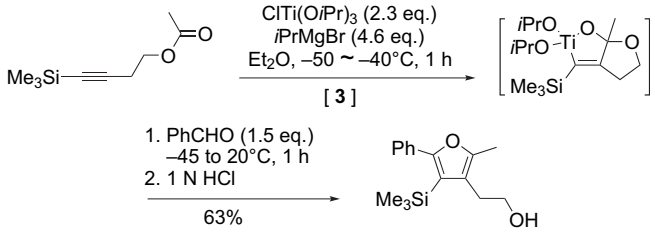


Scheme 69. INAS reactions of alkynyl carbonates and carboxylic esters.[68,69,191]

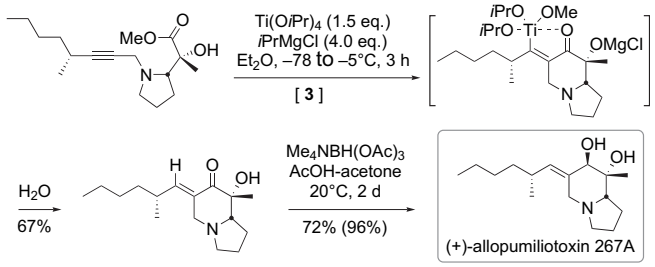


Scheme 70. Transformation of alkynyl malonate derivatives.[68,192]

Interesting applications have been reported in the literature, such as the preparation of substituted furans (Scheme 71),[69] and the total synthesis of (+)-allopumiliotoxin 267A, a Dendrobatidæ alkaloid displaying significant cardiotoxic activity (Scheme 72).[193]

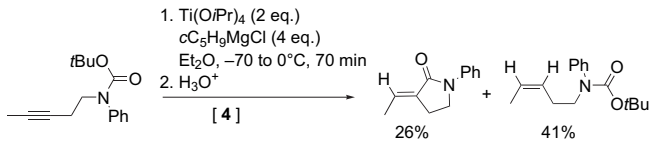


Scheme 71. Synthesis of substituted furans based on the INAS reaction of alkynyl esters.[69]



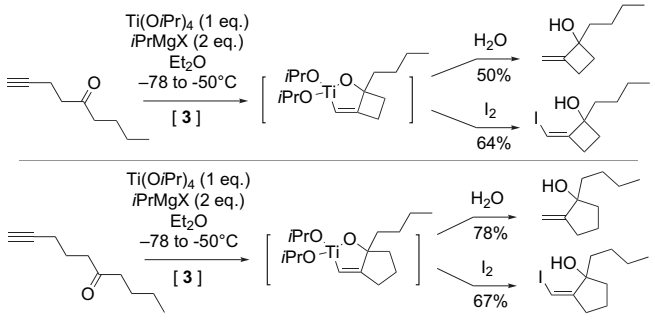
Scheme 72. INAS reaction of an alkynyl ester applied to the synthesis of allopumiliotoxin 267A.

INAS reactions can also occur starting from *N*-alk-3-ynyl carbamates, yielding 3-methylenepyrrolidine-2-ones, again with complete diastereoselectivity. However, the cyclisation step is poorly efficient, which hampers the synthetic utility of this transformation (Scheme 73).[194]



Scheme 73. Titanium-mediated cyclisation of a *N*-alk-3-ynyl carbamate.[194]

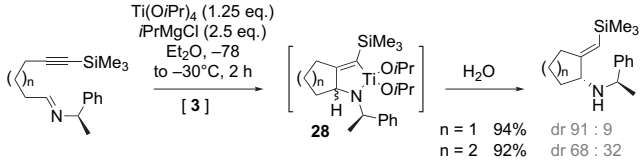
4.3.2. Alkynyl aldehydes and ketones. The group of Marek has shown that alk-1-yn-5-ones and alk-1-yn-6-ones undergo intramolecular coupling to yield cyclobutanols or cyclopentanols (Scheme 74).[195] The proposed mechanism involves ligand exchange with the alkyne function followed by 1,2-insertion of the carbonyl group into the intermediate titanacyclopropene, eventually leading to an oxatitanacyclopentene complex. This is in contrast with the analogous transformations mediated by $Cp_2Ti(PMe_3)_2$, where the corresponding final intermediates are thought to arise from alkyne insertion into initially formed metallaoxiranes. The results obtained using the Ti(O*i*-Pr)$_4$/*i*-PrMgX combination of reagents are especially remarkable, since terminal alkynes are generally rather poor substrates in reactions of this type.[196,197]



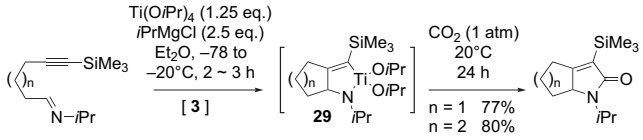
Scheme 74. Cyclisation of alkynyl ketones.[195]

The cyclisation of alkynes containing both a ketone group and a leaving group at the propargylic position is documented as well (see Section 4.4).[198]

4.3.3. Alkynyl imines. It has been found that 6- or 7-imino-1-trimethylsilylalk-1-ynes cyclise efficiently to form azatitanacyclopentene species (e.g., **28** and **29**) that deliver cyclic allylic amines upon hydrolysis. The use of chiral imines leads to moderate-to-satisfactory chiral induction (Scheme 75).[199] Since the titanacycle intermediates are similar to the complexes **M3** obtained by stepwise intermolecular reactions, as displayed in Scheme 44, their reactions with carbon dioxide are possible too, and furnish interesting bicyclic lactams (Scheme 76).[160]

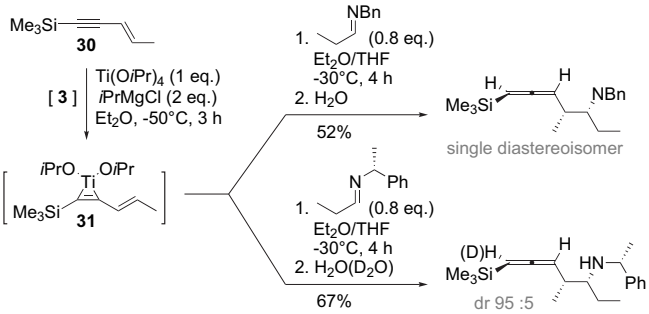


Scheme 75. Titanium-promoted cyclisation of alkynyl imines.[199]



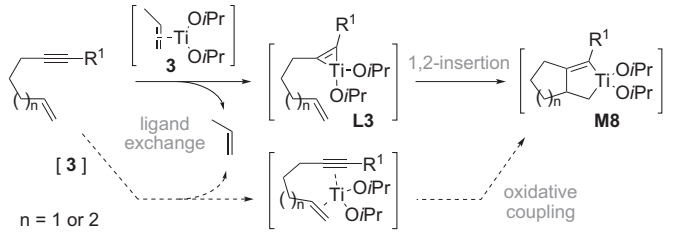
Scheme 76. Synthesis of lactams by titanium-promoted cyclisation of alkynyl imines.[160]

4.3.4. Enynes. In agreement with the relative reactivities of alkyne and alkene functions (see Section 1), enynes react with titanacyclopropanes **A** preferentially at the alkyne moiety, following a ligand-exchange pathway (Eq. 5, Scheme 2). In some cases, the titanacyclopropenes thus formed may be quite stable, with the olefin function being preserved. Such situations have been observed with substrates containing di- or tri-substituted alkene moieties, conjugated or not with the alkyne carbon–carbon triple bond.[123,200] Starting from conjugated alk-1-en-3-ynes such as **30**, the resulting dialkoxytitanacyclopropene intermediates (e.g., **31**) are also allyltitanium species, and they react accordingly with aldehydes, ketones and imines at the distal olefinic carbon atom, rather than at one of the Csp^2–Ti bonds. Very high diastereoselectivities have been achieved with respect to the relative configurations of the newly created Csp^3 chiral centres and allene functions, especially in reactions with imines (Scheme 77).[200]



Scheme 77. Titanium-promoted coupling of a conjugated enyne with imines.[200]

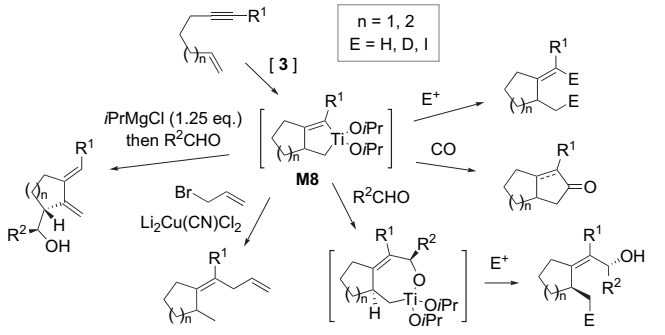
In contrast, starting from suitable alk-1-en-6-ynes or alk-1-en-7-ynes, the olefinic carbon–carbon double bond may undergo intramolecular 1,2-insertion into the titanacyclopropene intermediate **L3** (Eq. 8, Scheme 34). As in the conceptually related reactions of 1,6- or 1,7-dienes (Section 2.4.2), an alternative mechanism involving the direct formation of the resulting bicyclic dialkoxytitanacyclopentene complexes **M8** by coordination of both unsaturated carbon–carbon bonds to the metal followed by oxidative coupling cannot be ruled out (Scheme 78).[91]



Scheme 78. Formation of fused bicyclic dialkoxytitanacyclopentenes from enynes.[91]

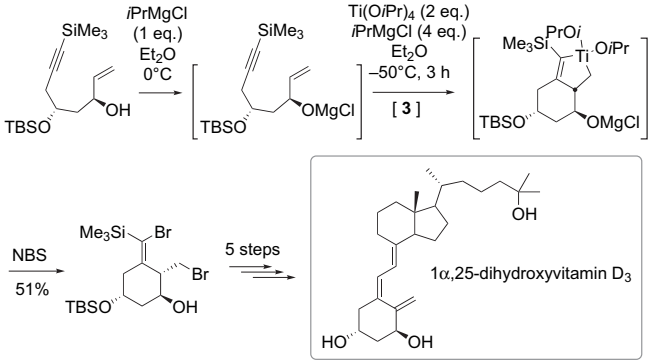
Most of these transformations can be seen as special cases of the reactions of dialkoxytitanacyclopropenes with alkenes covered in Section 4.2.3, but their intramolecular character induces important differences, namely (i) non-activated alkenes, i.e., those that are not substituted with a coordinating group, can participate in the alkyne–alkene coupling, and (ii) the regioselectivity pattern is imposed by geometrical factors, rather than substituent effects. Moreover, the known scope of the transformations that may be undergone by the titanacyclopentene intermediates **M8** is much wider. Since these processes have been reviewed quite extensively in 1999–2002,[2,3,5–7,9] our discussion will concentrate on the most recent developments described in the literature. It is worthy of note that closely related transformations have been developed as well, starting from 1,3-dien-8-ynes, 1,2-dien-6-ynes and 1,2-dien-7-ynes.[201–204]

Complexes **M8** may be hydrolysed or deuteriolysed in a similar manner to the species formed by related intermolecular reactions (see, for instance, Scheme 49).[91,203] Remarkably, enynes containing a terminal alkyne moiety are suitable substrates,[91] in contrast to what has been observed with bis(*cyclo*-pentadienyl)titanium- and zirconium-mediated related reactions.[205,206] Enynes containing an *N*-(1-alkynyl)-sulfonamide moiety can be used as well, providing access to cyclic enamine derivatives.[129] In addition, titanacycles **M8** can react with carbon monoxide at atmospheric pressure to give a mixture of cyclopentenone and cyclopentanone derivatives,[91] and with aldehydes to provide allylic alcohol derivatives. In the latter transformation, addition occurs at the Csp^2–Ti bond exclusively, and with high 1,4-diastereoselectivity. The remaining Csp^3–Ti bond can then undergo hydrolysis, deuteriolysis or iodonolysis.[207,208] Starting from substrates where the alkyne is substituted with a trimethylsilyl group, $ClTi(O\textit{i}\text{-}Pr)_3$ or $Cl_2Ti(O\textit{i}\text{-}Pr)_2$ must be added for the carbonyl insertion to proceed.[207,208] Copper-mediated allylation with allyl bromide also proceeds regioselectively at the alkenyl–titanium bond.[208] An unusual coupling reaction with aldehydes has been reported that occurs when a slight excess of *iso*-propylmagnesium chloride is added prior to the aldehyde. It proceeds with formal dehydrogenation and with a peculiar carbonyl addition taking place in a virtually completely diastereoselective fashion at the carbon atom initially located at the allylic position of the chain separating the alkene and the alkyne moieties of the starting material.[208] A summary of these various processes is displayed in Scheme 79.

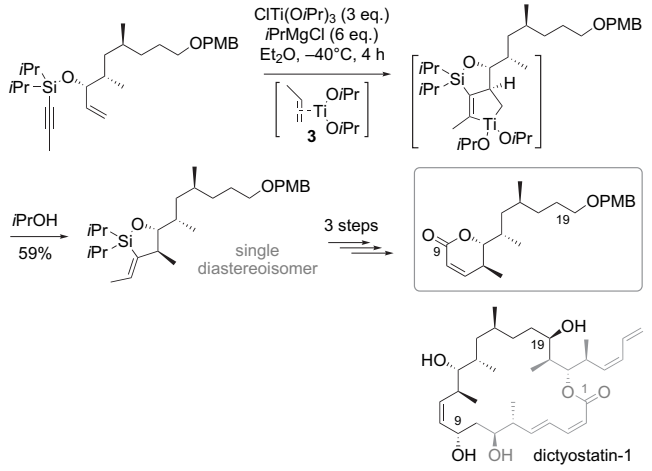


Scheme 79. Transformations of dialkoxytitanacyclopentenes generated from enynes.[91,208]

The value of this method has been illustrated by several synthetic applications. For instance, Sato et al. used it in convergent syntheses of vitamin D_3, retiferol and 1α,25-dihydroxyvitamin D_3 (Scheme 80).[209,210] The group of Phillips has developed an interesting variation of the reaction, where the alkyne and the alkene moieties are linked by a silicon tether. The diastereoselectivities of these cyclisations are virtually total.[211] The net result, after cleavage of the silicon–carbon bond, is equivalent to a completely regio- and diastereo-selective intermolecular reductive coupling of a terminal alkyne with an alkene. This method was applied successfully to the synthesis of the C9–C19 subunit of dictyostatin-1 (Scheme 81),[211] and to a total synthesis of (−)-7-demethylpiericidin A_1 (Scheme 82).[212] In this last example, the survival of the three disubstituted double bonds of the starting material, including that conjugated with the alkyne group, is especially worthy of note.

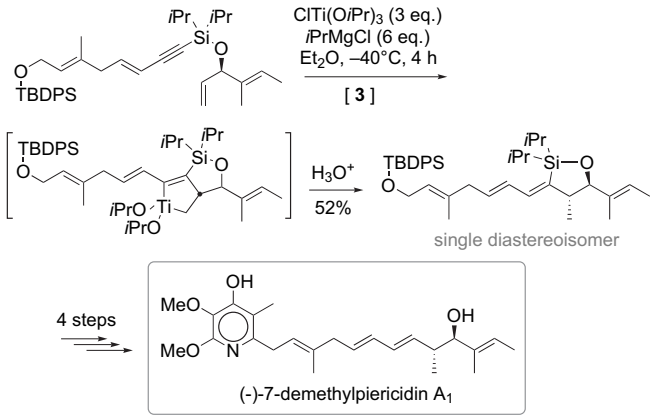


Scheme 80. Total synthesis of 1α,25-dihydroxyvitamin D_3 involving a titanium-mediated enyne cyclisation.[209,210]



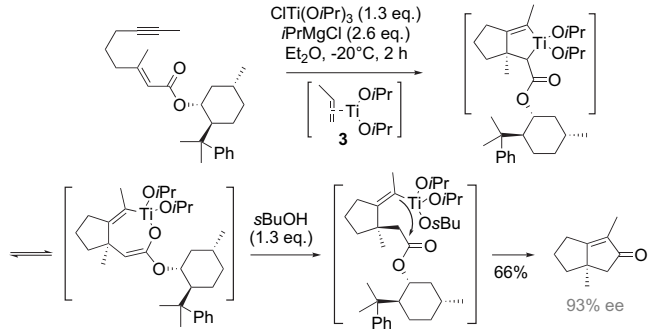
Scheme 81. Synthesis of the C9–C19 subunit of dictyostatin, based on the titanium-mediated cyclisation of a silicon-tethered enyne.[211]

Substrates where the alkene function is part of an α,β-unsaturated ester moiety give particular results.[97,98] Indeed, in these cases, aldehyde or ketone addition onto the titanacyclopentene intermediate proceeds at the Csp^3–Ti bond, in the α-position relative to the ester group, rather than at the Csp^2–Ti bond. Other electrophiles such as *s*-BuOH or *i*-PrOD used in stoichiometric amounts react with the same regioselectivity. The facial selectivity is high in all cases, but (*E*) and (*Z*) substrates give identical results. The ultimate fate of the reaction is the formation of a cyclopentenone, which is analogous to the transformation of dienes substituted with a conjugated ester (Scheme 28). Indeed, the addition of the electrophile triggers ring opening of the titanacycle, and an intramolecular addition of the remaining carbon–titanium bond onto the ester group follows. It should be noted, however, that



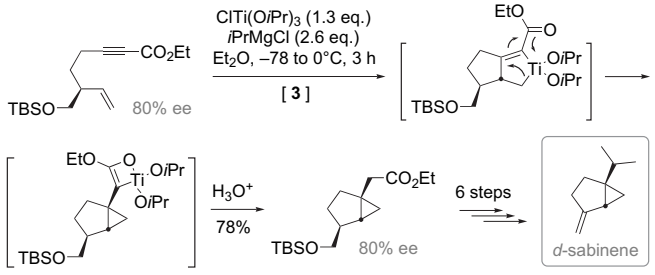
Scheme 82. Total synthesis of (−)-7-demethylpiericidin A_1, based on the titanium-mediated cyclisation of a silicon-tethered enyne.[212]

this last elementary step does not occur when hindered esters such as *tert*-butyl esters are employed, or when the ester function is replaced with an *N*,*N*-dialkylamide group.[98] Starting from substrates containing a chiral carbon atom on the chain separating the alkene and alkyne functions, the bicyclic cyclopentenone products can be obtained with good diastereoselectivities, especially when the chiral centre is located at the allylic position.[98,213] Remarkably, educts featuring a trisubstituted or even a tetrasubstituted olefin function can be used, which highlights the activating effect of the conjugated carboxylic ester function. In these cases, very good asymmetric induction is observed with 8-phenylmenthyl esters, as illustrated in Scheme 83.[214]



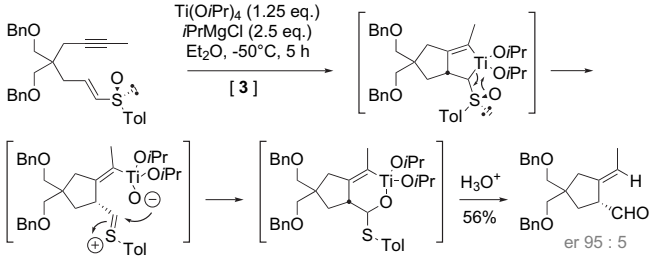
Scheme 83. Titanium-mediated cyclisation of an enyne with a conjugated carboxylic ester group containing a chiral auxiliary.[214]

Enynes bearing a carboxylic ester group conjugated with the alkyne function behave completely differently. When the usually formed dialkoxytitanacyclopentene intermediates are allowed to warm to 0 °C, they undergo a cyclopropanation process to deliver a titanium complex with carbene character, that can be trapped with electrophiles such as H_3O^+, D_3O^+ or carbonyl compounds.[97,98] This process was applied to a total synthesis of enantiomerically enriched (+)-*d*-sabinene (Scheme 84).[98]

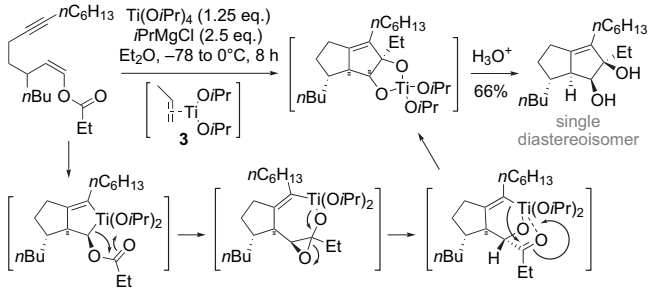


Scheme 84. Synthesis of *d*-sabinene using the titanium-mediated cyclisation of an enantiomerically enriched chiral enyne.[98]

Dialkoxytitanacyclopentene complexes generated from enynes substituted with a sulfinyl or an acyloxy group at the olefin part undergo spontaneous transformations. In the first case, a Pummerer-type rearrangement operates and functionalised cycloalkane carboxaldehydes are eventually obtained. Importantly, good chiral induction occurs when enantiomerically enriched sulfoxide substrates are used (Scheme 85).[215] In the second case, a remarkable rearrangement takes place, providing bicyclic 1,2-diols in the cis relative configuration exclusively. Only (*Z*) substrates appear to be suitable for this transformation (Scheme 86).[216]



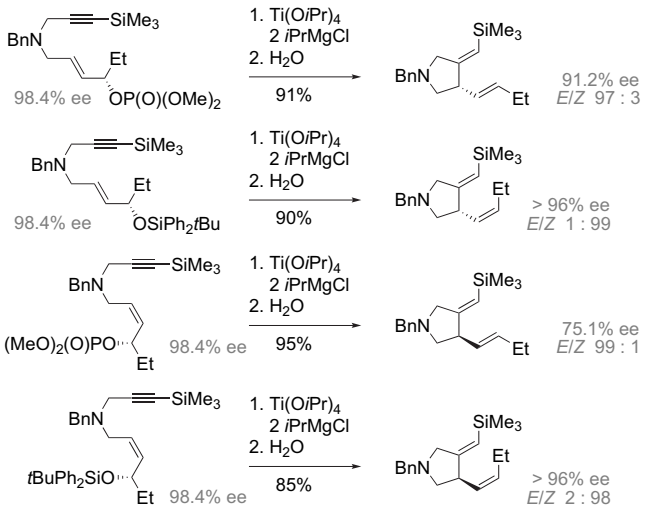
Scheme 85. Titanium-mediated cyclisation of an enyne substituted with a sulfoxide group at the olefin moiety.[215]



Scheme 86. Titanium-mediated cyclisation of an enyne substituted with a carboxy group at the olefin moiety.[216]

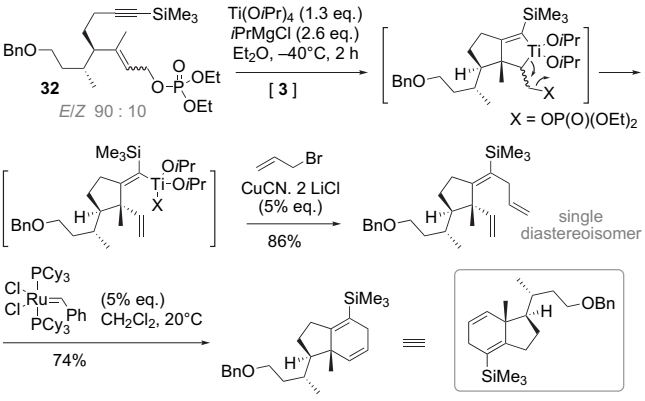
Another interesting process occurring from intermediates of the type **M8** is the β-elimination of a suitable leaving group (acetate, dialkyl phosphate, ethyl carbonate, chloro, silyloxy, or methoxy),[92,93,217–219] in a similar manner to the related intermolecular reactions (see Scheme 47). The alkene moiety may be part of a ring and this delivers bicyclic systems with moderate-to-excellent diastereoselectivity.[218]

In order to prepare enantiomerically enriched chiral cyclised products, the use of enantiomerically pure chiral leaving groups has been investigated. Among the functions put under study, chiral alkoxides give low chiral induction. However, better results are obtained with acetals derived from chiral diols with C_2 symmetry. Indeed, the (*E*) and (*Z*) diastereoisomers of the cyclised products may be obtained with good enantiomeric excesses. However, the (*E*) to (*Z*) diastereoisomeric ratios are often moderate.[220] More generally, and very interestingly, high stereocontrol can be achieved using substrates where dimethyl phosphate or *tert*-butyldiphenylsilyloxy leaving groups are attached to an asymmetric centre. Remarkably, the choice of leaving group dictates the absolute configuration of the newly formed alkene function, with dimethyl phosphate-substituted molecules giving (*E*) products and *tert*-butyldiphenylsilyloxy-substituted molecules giving (*Z*) products. Moreover, with the absolute configuration of the chiral centre bearing the leaving group being fixed, both the (*R*) and (*S*) products are accessible with good chirality transfer, depending upon the (*E*) or (*Z*) configuration of the starting alkene moiety (Scheme 87).[219]

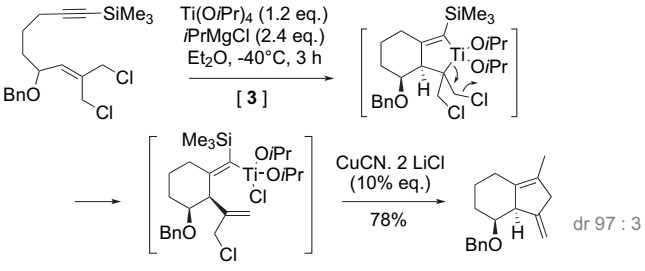


Scheme 87. Highly stereoselective titanium-mediated cyclisations of enynes bearing a leaving group at the allylic position.[219]

Reactions of this type have found an interesting application in the synthesis of 3a-methylhydrindane compounds, where highly *syn* diastereoselective cyclisations are combined with further functionalisation. This is achieved by copper-catalysed allylation of the vinyltitanium reactive moiety, followed by Ru-catalysed ring-closing metathesis (Scheme 88).[221] Starting from substrates featuring an additional allylic halide group, the allylation step can operate in an intramolecular fashion (Scheme 89).[222] Similarly, bicyclic systems can be generated, starting from enynes bearing a leaving group and a methyl carboxylic ester function. In this case, the elimination step is followed by an intramolecular addition of the remaining Csp^2–Ti bond onto the carbonyl group.[222]



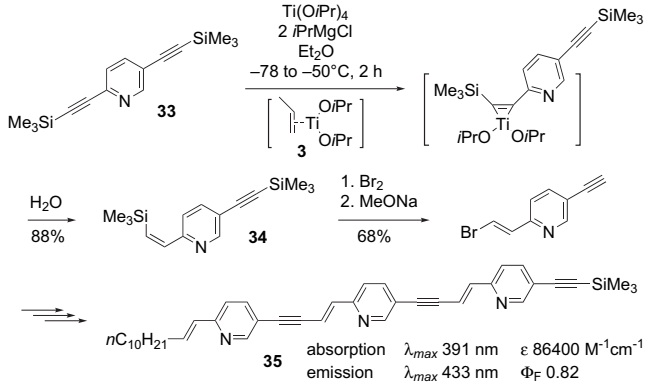
Scheme 88. Preparation of a 3a-methylhydrindane from an enyne bearing a phosphate leaving group.[221]



Scheme 89. Tandem cyclisation of an enyne bearing two allylic leaving groups.[222]

4.3.5. Diynes. Like the transformations of enynes (Section 4.3.4), the reactions of diynes have been covered in reviews published in 1999–2002,[2,3,5–7,9] and therefore we have tried to focus our discussion on the most recent developments described in the literature. Similarly to enynes, diynes can either react at an alkyne moiety with the formation of a titanacyclopropene **L** independently from the other unsaturated function, or undergo cyclisation by alkyne–alkyne intramolecular coupling.

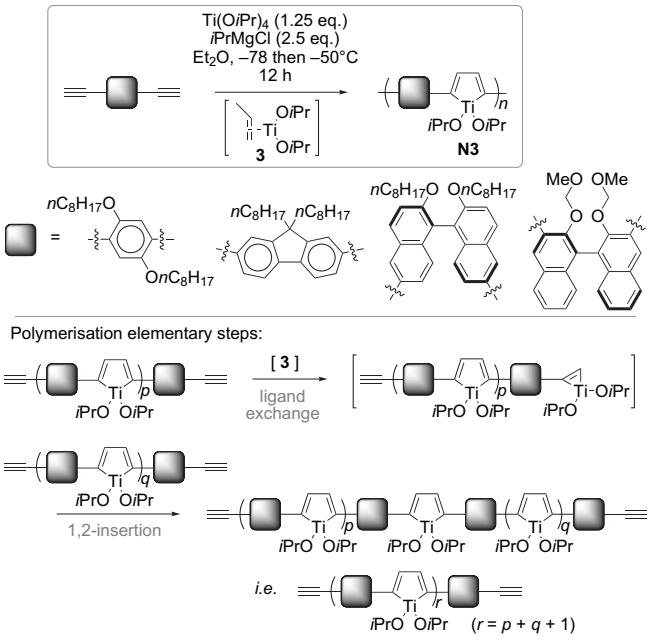
4.3.5.1. Mono-titanation of dialkynylpyridines. An example of the first situation is found in the syntheses of π-conjugated monodisperse oligomeric molecules with fluorescence properties, starting from various dialkynylpyridines. In almost every case, dominant electronic effects ensure efficient site-selective mono-titanation in favour of the carbon–carbon triple bonds located at the 2-position and at the 4-position of the pyridine rings. Thus, hydrolysis of the titanacyclopropene intermediate generated from 2,5-bis(trimethylsilylethynyl)pyridine **33** cleanly delivers the corresponding alkenylpyridine **34** in 88% yield, which can then be converted into the fluorescent molecule **35** in a few steps following an iterative palladium-mediated coupling sequence (Scheme 90).[121]



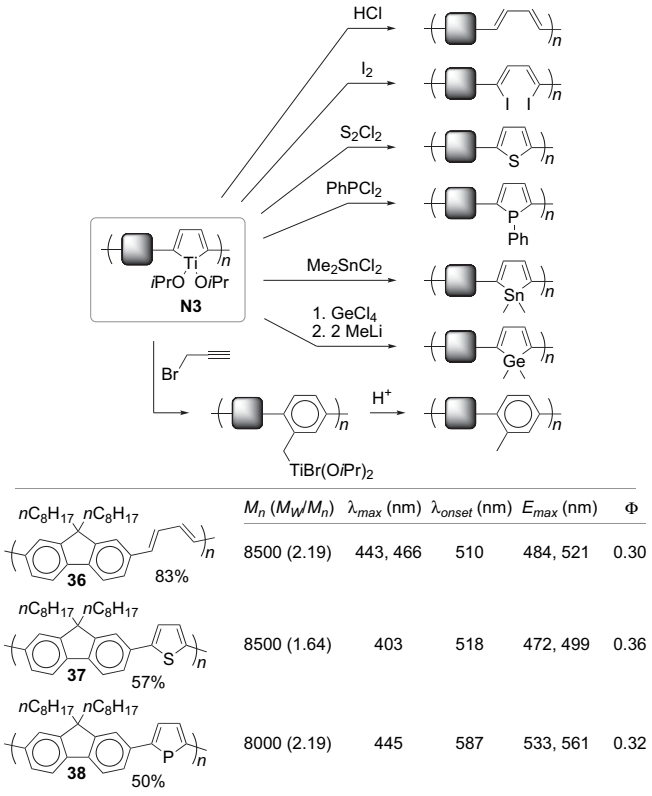
Scheme 90. Synthesis of a fluorescent π-conjugated molecule.[121]

4.3.5.2. Polymerisation of terminal diynes. The group of Tomita has developed a fascinating application, whereby terminal diynes are used as precursors for the expedient preparation of conjugated linear polymers. The elementary steps of the polymerisation process are special cases of the titanium-mediated dimerisation of terminal alkynes presented in Section 4.2.3 (see Schemes 55 and 56). Thus, ligand exchange with the initially formed complex **3** generates reactive monosubstituted titanacyclopropene moieties, that undergo fast *intermolecular* reaction with terminal alkyne functions, and a poly(aryl-substituted dialkoxytitanacyclopentadiene) chain **N3** is obtained (Scheme 91).[223,224] This method is especially powerful, since such metallated polymers may then undergo various further transformations, giving access to a diversity of conjugated linear polymers (Scheme 92).[223–225] In particular, the hydrolysis and iodonolysis reactions presented in Scheme 55 are applicable. Polymers with thiophene (similarly to Scheme 56), phosphole, stannole or germole units can also be prepared, as well as polymers containing benzyltitanium moieties using the reaction of **N3** with propargyl bromide (see Scheme 64 for an analogous process). Several polymers synthesised by this method exhibit interesting photoluminescent properties that can be tuned by the choice of the reaction of **N3**. For instance, the fluorene-containing polymers **36**, **37** and **38** display green, blue and orange luminescence, respectively (Scheme 92).[225]

4.3.5.3. Reaction of 1,3-, 1,4- and 1,5-diynes. The feasibility of the mono-titanation of conjugated diynes has been studied, showing that, using 1.25 equiv of Ti(Oi-Pr)$_4$ and 2.5 equiv of *iso*-propylmagnesium

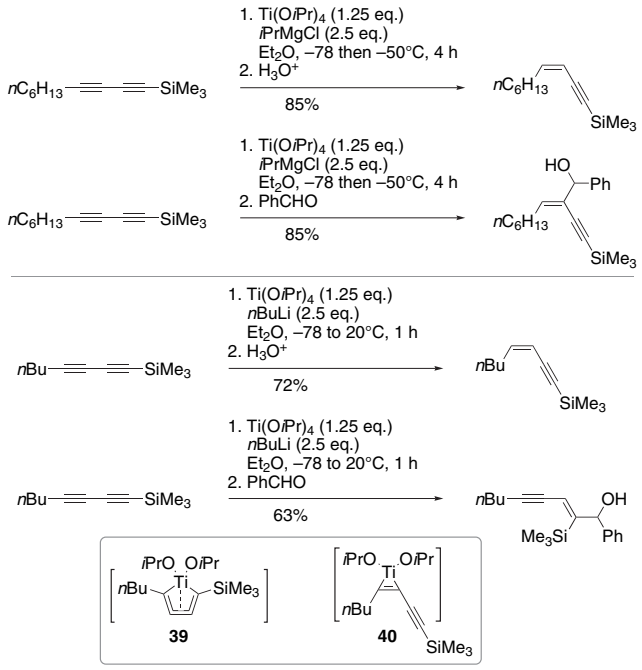


Scheme 91. Synthesis of polymers containing titanacyclopentadiene moieties.[223–225]



Scheme 92. Transformations of metallated polymers generated from terminal diynes.[223–225]

chloride, these compounds can be efficiently converted into the corresponding mono-di*iso*-propyloxytitanacyclopropene complexes. The regioselectivity is highly dependent upon the substituents, ranging from very poor to virtually complete. In particular, alka-1,3-diynes substituted with a *tert*-butyloxycarbonyl group in the 1-position or a trimethylsilyl group in the 4-position undergo titanacyclopropene formation exclusively at the C1–C2 triple bond, providing an efficient access to functionalised conjugated enyne derivatives (Scheme 93).[122]



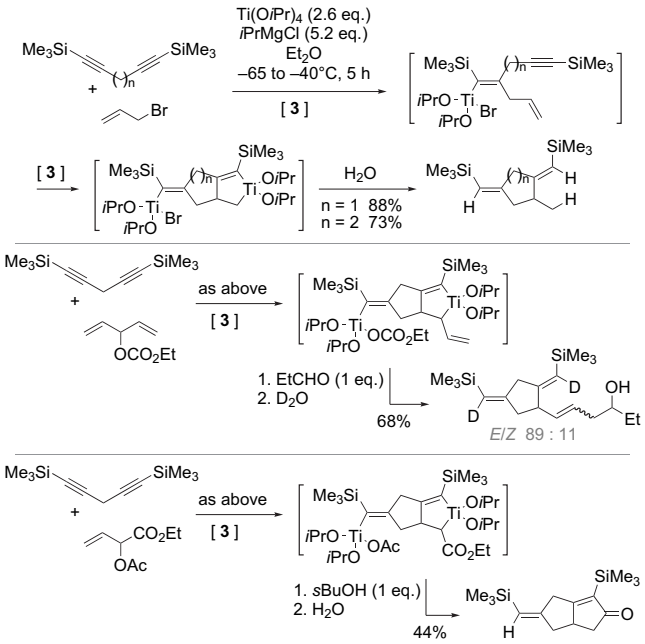
Scheme 93. Titanium-mediated synthesis of enynes and enynols from 1,3-diynes.[122,226]

These reactions have been recently revisited by Liu et al. using the Ti(O*i*-Pr)$_4$/*n*-BuLi system introduced by the group of Eisch.[119] In this case, the mono-titanated species obtained are thermally stable, and the regioselectivity pattern is somewhat different from that observed with the Ti(O*i*-Pr)$_4$/*i*-PrMgCl system. Moreover, and interestingly, the regioselectivity also varies, depending whether simple hydrolysis or aldehyde addition is performed (Scheme 93).[226] In the latter case, the nature of the quenching reagent may also affect the product distribution. Under these reaction conditions, the formation of a titanacyclopenta-2,3,4-triene species **39**,[227] rather than a well-defined titanacyclopropene, is a distinct possibility. Alternatively, a titanacyclopropene intermediate **40** substituted with an alkyne group might react with aldehydes at ambient temperature as a propargyl–titanium species exclusively, i.e., with transposition.

As demonstrated by the synthesis of deuterium-labelled α-linolenic acid displayed in Scheme 38, the exhaustive conversion of each of the C–C triple bonds of a polyyne system using excess amounts of reagents can sometimes be achieved.[130,134]

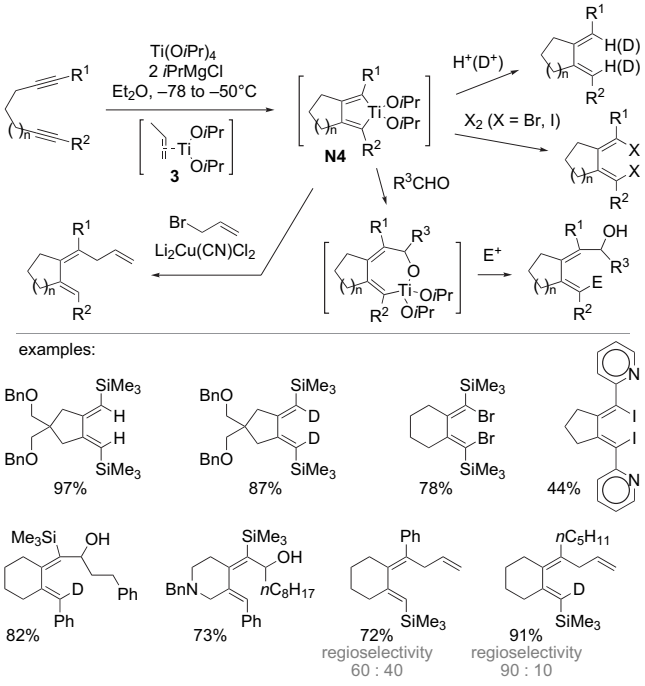
An elegant tandem reaction has been developed, starting from alka-1,4-diynes or alka-1,5-diynes with equimolar amounts of alkenes containing a leaving group at the allylic position. Using excess amounts of Ti(O*i*-Pr)$_4$ and *i*-PrMgCl, the initially formed mono-di*iso*-propyloxytitanacyclopropene intermediate undergoes 1,2-insertion of the allylic compound (Eq. 8, Scheme 34; see also Section 4.2.3). The subsequent β-elimination of the leaving group generates a 1,6- or 1,7-enyne moiety that undergoes cyclisation upon reaction with an additional equivalent of titanacyclopropane (see Section 4.3.4). The final intermediate complex contains three carbon–titanium bonds that can participate in reactions with electrophiles (Scheme 94).[168]

4.3.5.4. Cyclisation of 1,6- and 1,7-diynes. In the special cases mentioned above, cyclisation to dialkoxytitanacyclopentadiene systems is either forbidden or prohibitively difficult for geometrical and/or thermodynamical reasons. However, 1,6- and 1,7-diynes may undergo intramolecular alkyne–alkyne coupling, leading to the generation of dialkoxytitanacyclopentadienes **N4** (Scheme 95). As with dienes and enynes, a mechanistic possibility consists of the direct ligand exchange from **3** by the diynes as bifunctional ligands followed by oxidative coupling. Perhaps more likely is that these



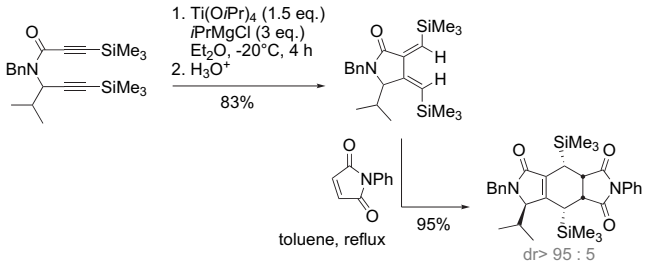
Scheme 94. Titanium-mediated coupling and cyclisation of allylic compounds with alka-1,4- or alka-1,5-diynes.[168]

reactions can be seen as intramolecular versions of the 1,2-insertion of alkynes into dialkoxytitanacyclopropenes already met in Section 4.2.2 (Schemes 55–66). Whatever the elementary pathways leading to their formation, the generated bicyclic complexes **N4** exhibit similar reactivities to the dialkoxytitanacyclopentadienes already described. In particular, hydrolysis, deuteriolysis and halogenolysis can be performed,[91,173] as well as aldehyde addition.[207,208] As in the case of the transformation of enynes (Section 4.3.4), $Cl_2Ti(O\textit{i}\text{-}Pr)_2$ must be added for carbonyl insertion to proceed efficiently. Functionalisation of **N4** by copper-mediated allylation is also feasible, with a quite different regioselectivity pattern (Scheme 95).[208] For geometrical reasons, the *exo*,*exo*-cyclic conjugated dienes obtained



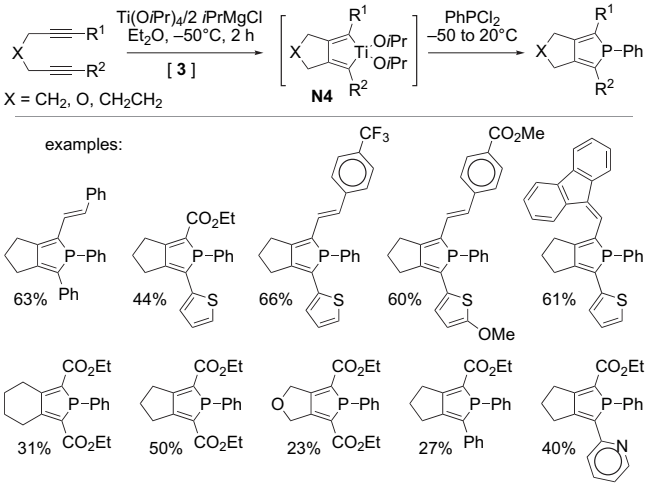
Scheme 95. Titanium-mediated alkyne–alkyne intramolecular coupling starting from 1,6- and 1,7-diynes.[91,173,207,208]

from **N4** upon hydrolytic work-up can only exist as the *s-cis* conformers, and this makes them especially suited for subsequent Diels–Alder cycloadditions. Heteropolycyclic systems can thus be expeditiously assembled in a selective manner (Scheme 96).[228]

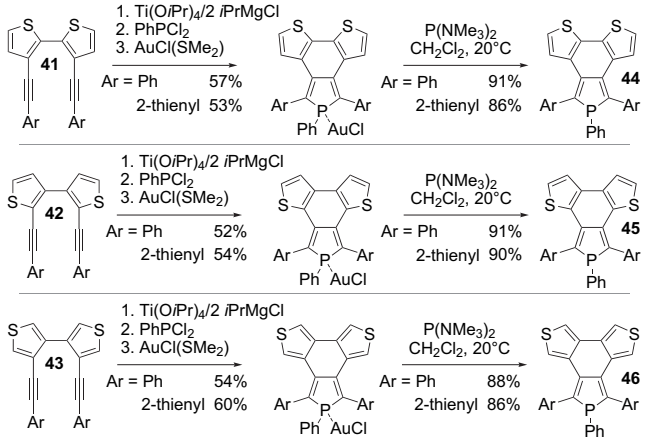


Scheme 96. Diels–Alder reaction of a diene prepared by the titanium-mediated cyclisation of a 1,6-enyne.[228]

4.3.5.5. Preparation of polycyclic phosphole and thiophene systems. Another interesting use of the cyclisation of 1,6- and 1,7-diynes is the preparation of phosphole-containing systems.[229] Indeed, intermediates **N4** react with dichloro(phenyl)phosphine $PhPCl_2$ to produce phosphole rings (Scheme 97; see also Scheme 92).[230,231] In particular, this method has been applied to the synthesis of phosphole-cored dendrimers that display intense blue-green photoluminescence.[232] Using di-alkynylated bithiophene substrates **41**–**43**, bithiophene-fused benzo[*c*]phospholes **44**–**46** could be prepared efficiently (Scheme 98).[233,234] In these examples,



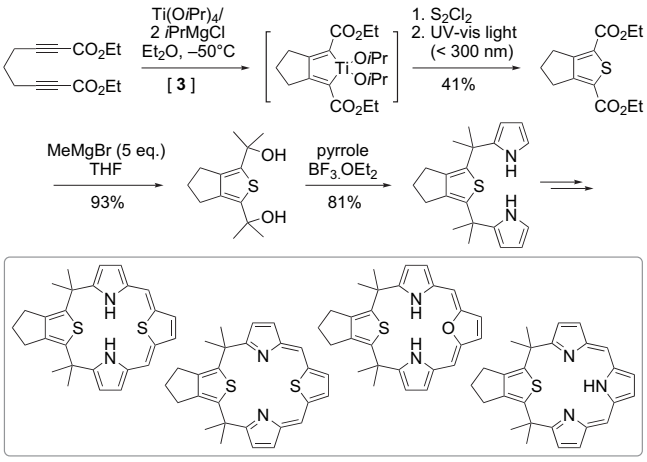
Scheme 97. Preparation of bicyclic phospholes from enynes.[230,231]



Scheme 98. Preparation of bithiophene-fused benzo[*c*]phospholes.[233,234]

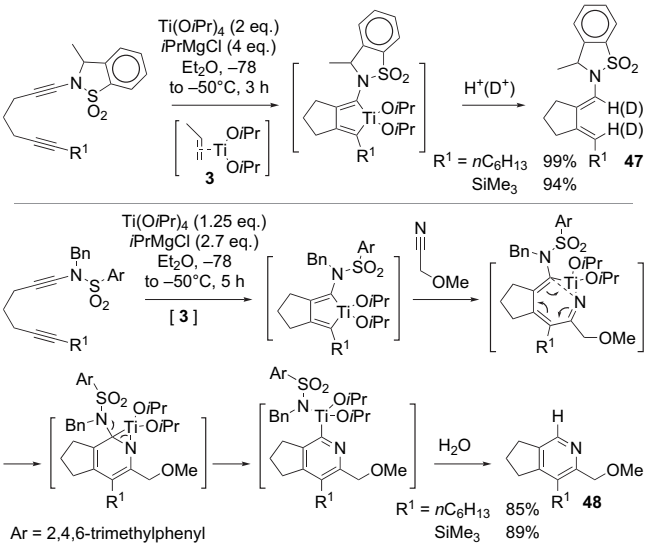
the products are contaminated with unreacted diyne starting materials, but treatment with $AuCl(SMe_2)$ delivers the corresponding Gold(I)–phosphole complexes that can be purified by column chromatography. Decomplexation is then performed by treatment with $P(NMe_2)_3$ in toluene at 20 °C. Compounds **44**–**46** emit fluorescence in the orange-red regions and such systems are considered as a promising platform for the construction of phosphole-containing optoelectronic materials.

Similarly, treatment of bicyclic titanacyclopentadiene complexes of the type **N4** with S_2Cl_2 yields 1,2-dithiin derivatives that are eventually converted into thiophenes upon exposure to light. This has been applied to the synthesis of thiophene-containing hybrid calixphyrins (Scheme 99).[235]



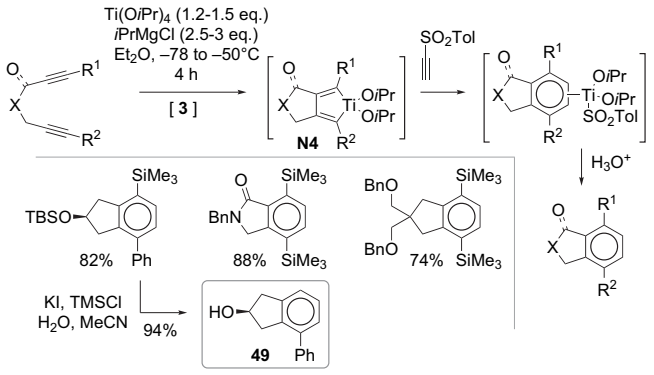
Scheme 99. Synthesis of thiophene-containing hybrid calixphyrins.[235]

4.3.5.6. Titanium-mediated [2+2+2] reactions involving diynes. Alka-1,6-diynes substituted with an *N*-sulfonylamino group at one of the two alkyne functions can participate in reactions of this type, providing access to cyclic dienamine derivatives **47** after hydrolysis or deuteriolysis.[129] Alternatively, bicyclic pyridines **48** can be synthesised upon addition of nitriles, following a mechanistic pathway related to that shown in Scheme 65, and where the *N*-sulfonylamino group plays the role of a leaving group (Scheme 100).[187]

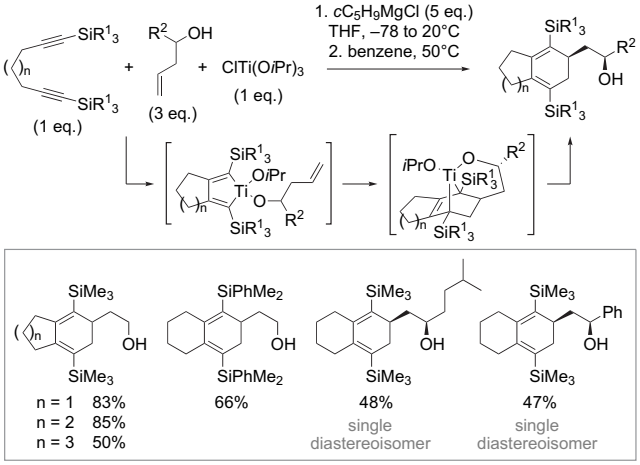


Scheme 100. Reactions of alka-1,6-diynes bearing *N*-sulfonylamino groups.[129,187]

Similarly, the metallative [2+2+2] Reppe-type reactions described earlier as sequential, intermolecular processes (Scheme 62) are readily amenable to the preparation of bicyclic indane derivatives, starting from 1,6-diynes.[184,185,236] For instance, (*S*)-4-phenyl-indan-2-ol **49**, the indanol moiety of a highly effective pyrethroid derivative, was synthesised in more than 99% ee by application of this method (Scheme 101).[236] Very interestingly, bicyclic titanacyclopentadiene complexes **N4** generated from 1,6-, 1,7- or 1,8-diynes can couple with alkenes as well, provided the latter bear an alcohol function in the homoallylic position. After deprotonation, the resulting alkoxide coordinates to the titanium centre, which considerably facilitates the [4+2] cycloaddition process by giving it an intramolecular nature. The best yields are obtained with $ClTi(OiPr)_3$ associated with *cyclo*-pentylmagnesium chloride, and heating at 50 °C for several hours is necessary. Importantly, when secondary homoallyl alcohols are used, the bicyclic cyclohexadiene products are obtained with excellent 1,3 diastereoselectivity (Scheme 102).[237]



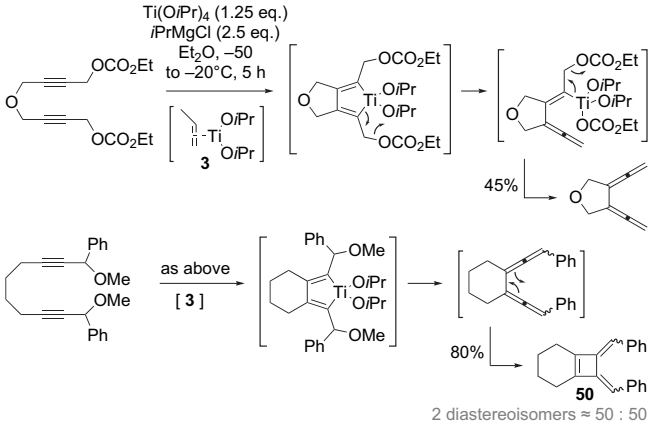
Scheme 101. Metallative [2+2+2] Reppe-type reactions starting from diynes.[184,236]



Scheme 102. [2+2+2] Coupling of diynes with homoallylic alcohols.[237]

4.3.5.7. Diynes with leaving groups. Starting from diynes fitted with leaving groups in the propargylic position relative to one or both of the alkyne functions, the titanacyclopentadiene intermediates may undergo β-elimination to produce *exo*-cyclic allene derivatives.[92,217] The ethyl carbonate function is a valid leaving group, except when 1,7-diyne substrates are used, in which case β-elimination from the initially formed titanacyclopropene complex (Eq. 11, Scheme 34) is a faster process than six-membered ring closure. This problem can be avoided using methoxy groups. In contrast to the corresponding four- and five-membered ring

products, the six- and seven-membered bis-conjugated allenes formed from tethered bis(propargylic) alcohol derivatives are not isolated, since they undergo electrocyclisation to give bicyclic cyclobutene compounds **50** (Scheme 103).[217]

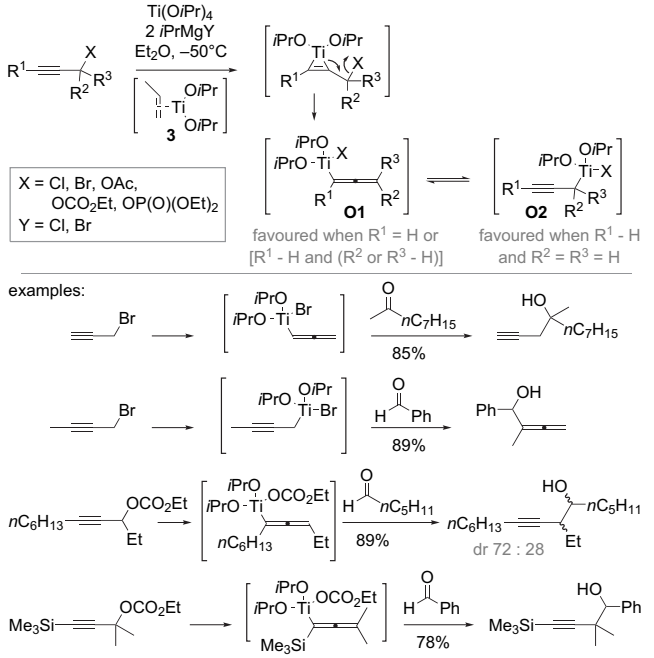


Scheme 103. Reactions of tethered bis(propargylic) alcohol derivatives.[217]

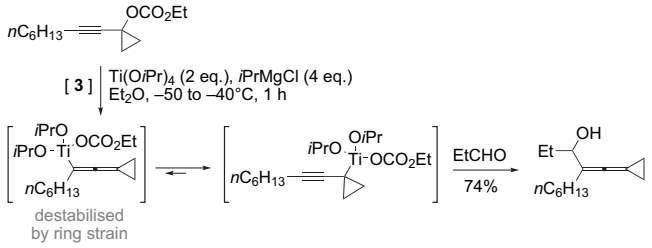
Finally, and as already mentioned, related intramolecular alkyne–allene coupling reactions starting from allenynes (1,2-dien-6-ynes and 1,2-dien-7-ynes) have been described as well.[202–204]

4.4. Reactions of alkynes bearing a leaving group at a suitable position

Titanacyclopropanes generated from Ti(O*i*-Pr)$_4$ and a Grignard reagent react with alkynes with a suitable leaving group at the propargylic position to give allenyltitanium complexes **O1** that are in equilibrium with the corresponding propargyl–titanium complexes **O2** via a metallotropic shift (Scheme 104).[238] The formation of these species can be explained by β-elimination of the leaving group from a titanacyclopropene intermediate produced by ligand exchange (Eq. 5, Scheme 2, followed by Eq. 11, Scheme 34).[238] Various leaving groups can be used, including chloro, bromo, acetate, carbonate and phosphate. Malonate groups may also act as leaving groups (see Section 4.3.1). The equilibrium between species **O1** and **O2** is dependent upon the substitution pattern of the starting propargylic derivatives, and is shifted in such a direction that the steric bulk around the titanium moiety is minimised (Scheme 104).[238] This effect can be overcome by making use of ring strain disfavouring the normally predicted complex. For instance, Sato et al. showed that carbonates derived from 1-alkynylcyclopropanols preferentially give rise to propargylic titanium species (Scheme 105).[61]

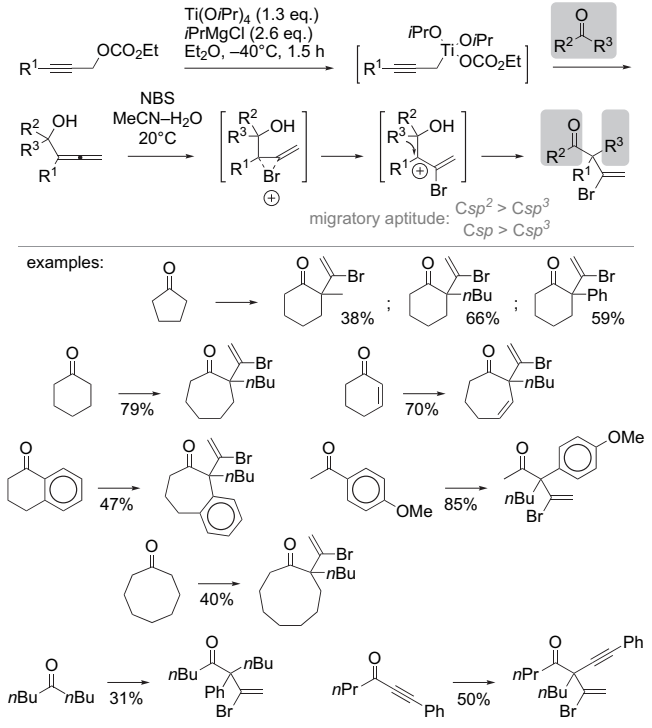


Scheme 104. Formation of allenyl–titanium and/or propargylic–titanium complexes from alkynes bearing a leaving group at the propargylic position.[238]



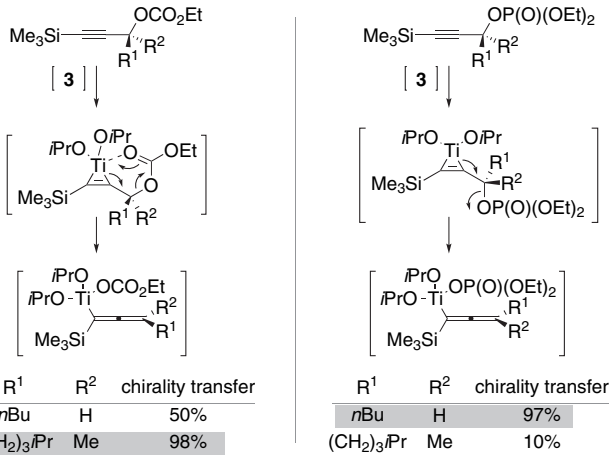
Scheme 105. Reaction of carbonates derived from 1-alkynylcyclopropanols.[61]

Allenyl–titanium and propargyl–titanium complexes **O1** and **O2** react with aldehydes and ketones with allylic transposition, delivering homopropargyl and α-allenyl alcohols, respectively.[238] Okamoto et al. have recently reported an interesting application of this reaction, whereby ketones are allenylated, and then treated with NBS in wet acetonitrile. A pinacol-type rearrangement takes place, and the net result of the sequence is an insertion of a quaternary allylic carbon centre between the ketone group and a carbon atom at the α position. Moderate-to-good yields are obtained, and good regioselectivities are observed, starting from aryl alkyl ketones (Scheme 106).[239]

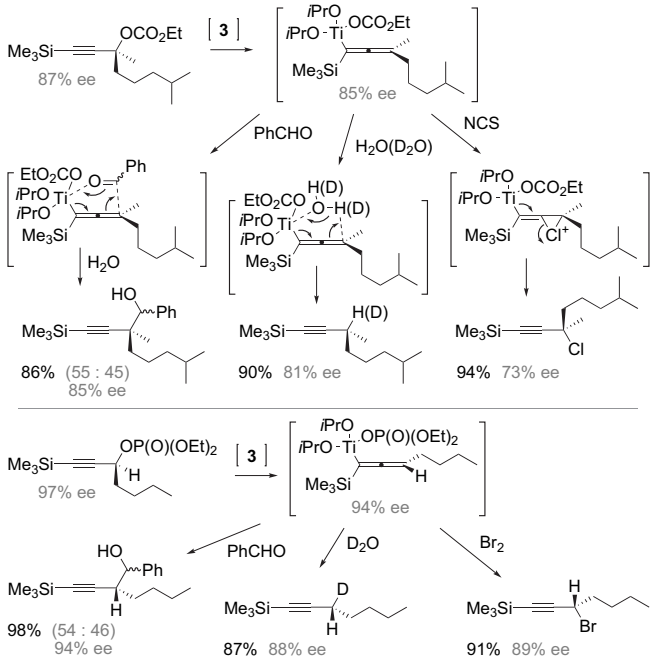


Scheme 106. Insertion of quaternary allylic carbon centres into ketones.[239]

Importantly, when optically active chiral substrates derived from secondary or tertiary propargyl alcohols are used, the corresponding allenyltitanium complexes are generated with moderate-to-excellent chiral transfer. Moreover, both absolute configurations can be accessed, depending upon the nature of the leaving group. Indeed, carbonate and phosphate groups follow different elimination pathways: *syn*-elimination via a cyclic transition state in the case of carbonate groups, and elimination according to an *anti*-coplanar transition state in the case of phosphate groups (Scheme 107).[240] Optically active homopropargyl alcohols can thus be obtained upon reaction with aldehydes, albeit with low diastereoselectivity. Optically active chiral alkynes and propargyl halides can also be prepared by hydrolysis or halogenolysis, respectively, and these transformations operate in a highly regioselective fashion with good chiral transfer (Scheme 108).[240,241] Another kind of stereocontrol is observed when Garner's aldehyde is employed in reactions of this type, with good-to-excellent facial selectivity operating with respect to the addition of the intermediate organotitanium species onto the carbonyl group, leading predominantly to the *anti*-products.[53]

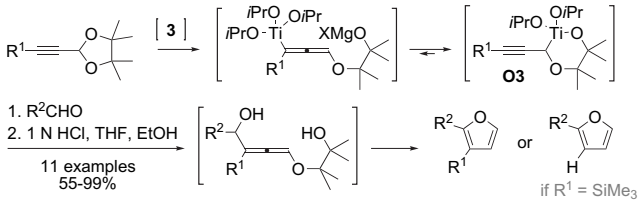


Scheme 107. Formation of non-racemic chiral allenyltitanium complexes.[240]



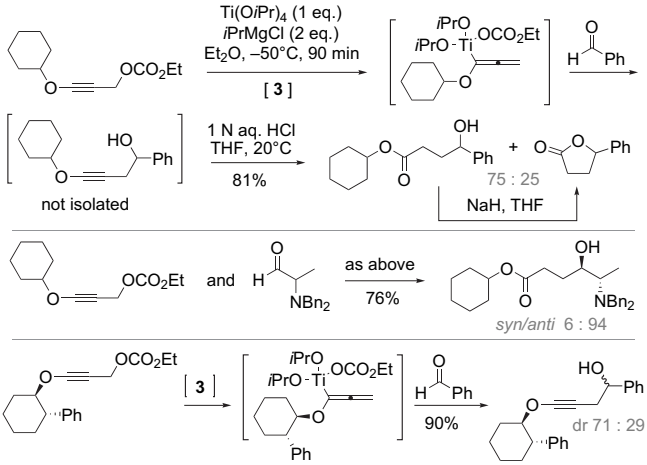
Scheme 108. Stereospecific transformations performed on non-racemic chiral allenyltitanium complexes.[240,241]

Although dialkoxytitanacyclopropanes generated from THP-protected propargylic alcohols and other acetals do not readily undergo β-elimination and can generally be trapped with aldehydes at −50 °C,[242] β-elimination does occur, starting from acetals derived from alk-2-ynals, if the reaction temperature is raised to 0 °C. In particular, starting from pinacol-derived cyclic acetal substrates, propargyl–titanium complexes **O3** are generated highly selectively because of intramolecular coordination of the alkoxide function liberated. α-Allenyl alcohols are thus readily obtained upon addition of aldehydes. Subsequent acidic treatment provides a general and efficient access to 2-substituted and 2,3-disubstituted furans (Scheme 109).[243] Another interesting application has been developed, starting from another type of cyclic acetal **51** designed so that the initial β-elimination step generates an alkoxide with a benzyloxy group in the α-position. A second elimination elementary step occurs, revealing a carbonyl group that reacts intramolecularly with the allenyltitanium species (see Scheme 111).[198]



Scheme 109. Synthesis of furans from 2-alkynal tetramethylethylene acetals.[243]

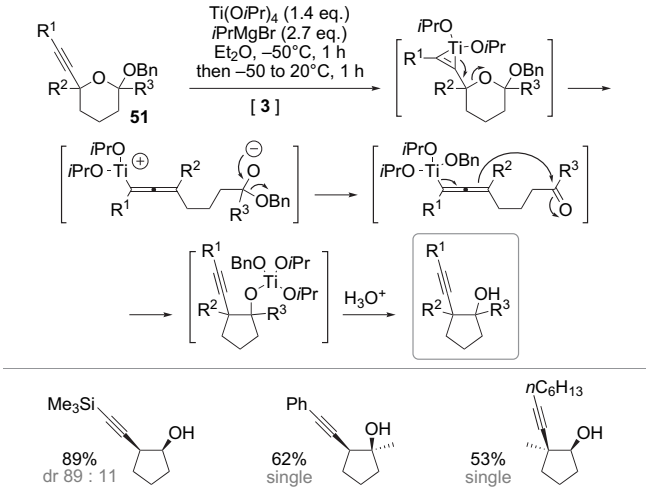
The reaction was also extended by the group of Sato to 3-alkoxy-2-propyn-1-yl carbonate substrates. High regioselectivity is observed in aldehyde addition reactions when the alkoxyl substituent is an *n*-butyl or a *cyclo*-hexyl group. Final acidic treatment delivers γ-hydroxyesters and/or γ-lactones. The titanium intermediates involved in these transformations can thus be viewed as homoenolate equivalents. High *anti*-diastereoselectivity can be achieved from chiral α-aminoaldehydes, and encouraging 1,6-chiral induction is observed, starting from chiral alkynes derived from *trans*-2-phenylcyclohexanol (Scheme 110).[244]



Scheme 110. Homoaldol-type reactions using 3-alkoxy-2-propyn-1-yl carbonates.[244]

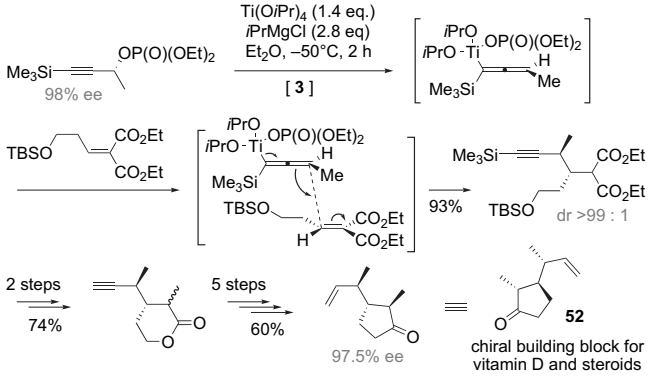
Interestingly, the carbonyl electrophile and the starting propargylic system can be parts of the same molecule. In this case, the substrate may undergo the following sequence of elementary steps: ligand exchange with the dialkoxytitanacyclopropane initially formed, β-elimination of the leaving group from the titanacyclopropene intermediate, and intramolecular addition onto the

carbonyl compound. However, this process suffers from the limitations caused by the high reactivity of carbonyl compounds towards titanacyclopropanes (see Part 1), and poor results are occasionally obtained. In particular, the expected cyclised products are not obtained with aldehyde substrates. An ingenious solution to this problem consists of starting from cyclic acetal derivatives **51**, designed in such a way that the β-elimination step triggers the generation of the carbonyl group by the departure of an alkoxide group. Fair-to-good yields and high-to-excellent diastereoselectivities have been obtained in the preparation of cyclopentanol derivatives (Scheme 111).[198]

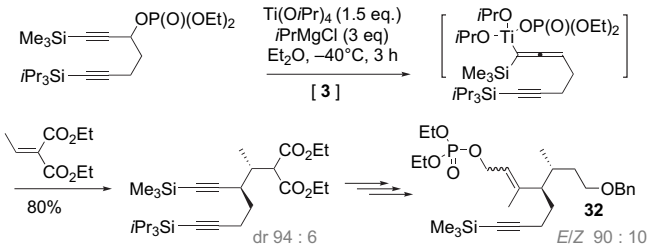


Scheme 111. Titanium-mediated transformation of cyclic propargylic acetal derivatives.[198]

The allenyltitanium complexes generated by the method described in this section can react with Michael acceptors. Excellent *anti*/*syn* diastereoselectivity can be observed with trisubstituted alkylidene malonates. As a result, in cases where chiral allenyltitanium intermediates are generated from enantiomerically pure chiral alkyne substrates with high chiral transfer (see Scheme 107), chiral products can be obtained with high enantiospecificity, and essentially as single diastereoisomers.[245] This method was applied to the asymmetric synthesis of cyclopentanone **52**, a plausible precursor for the synthesis of vitamin D and steroid derivatives (Scheme 112).[246] This reaction was also applied to the preparation of the racemic starting material **32** shown in Scheme 88 (Scheme 113).[221] In this example, the fact that β-elimination of the phosphate leaving group is faster than five-membered ring cyclisation (see Section 4.3.5) is of special interest. The use of the bulky tri*iso*-propylsilyl substituent is likely to play an important role in this chemoselectivity.

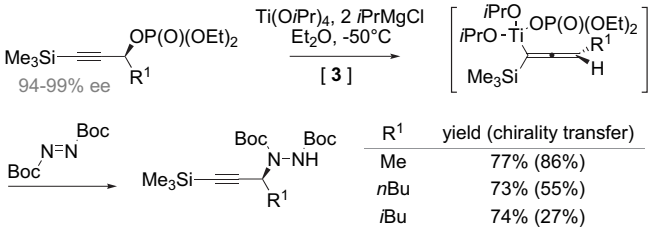


Scheme 112. Application of the reaction of an allenyltitanium complex with an alkylidene malonate to the synthesis of a cyclopentanone building block.[246]



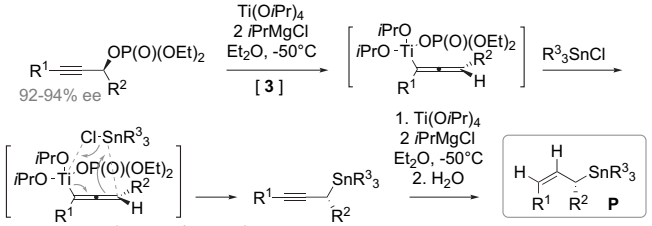
Scheme 113. Preparation of a highly functionalised enyne by the reaction of an allenyltitanium complex with an alkylidene malonate.[221]

These transformations have been further extended to the use of other electrophilic unsaturated compounds: dialkyl azodicarboxylates,[247] trialkylstannyl chlorides[248] and imines[249] can be used. Their reactions deliver α-hydrazinoalkynes, propargylstannanes and homopropargylic amines, respectively, including optically active chiral products with usually excellent chiral transfer, starting from optically active secondary propargyl phosphates (Schemes 114–116),[135,249] although azodicarboxylates perform less efficiently.[247]



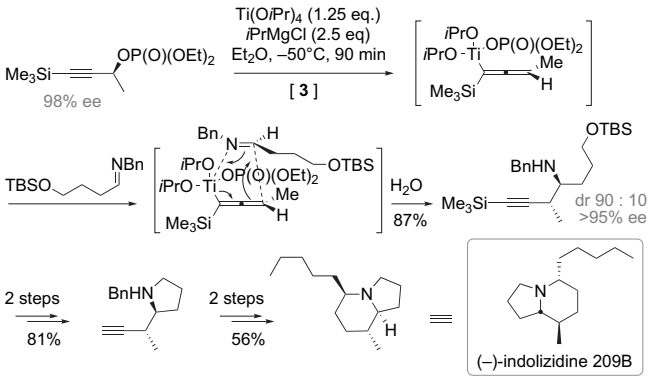
R^1	yield (chirality transfer)
Me	77% (86%)
*n*Bu	73% (55%)
*i*Bu	74% (27%)

Scheme 114. Reaction of chiral allenyltitanium complexes with di-*tert*-butyl azodicarboxylate.[247]



R^1	R^2	R^3	yield	yield (chirality transfer)
Me	*n*Bu	*n*Bu	78%	91% (> 97%)
*n*Bu	Me	*n*Bu	79%	91% (> 97%)
*n*Bu	Me	Me	77%	88% (> 97%)
$SiMe_3$	*n*Bu	*n*Bu	80%	85% (> 93%)

Scheme 115. Reaction of chiral allenyltitanium complexes with trialkylstannyl chlorides.[135]

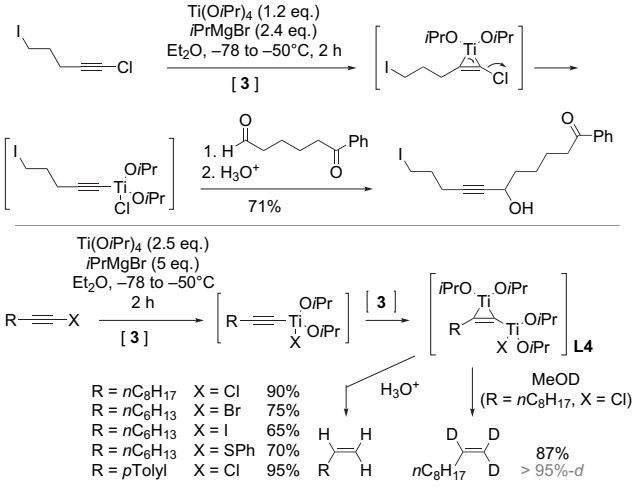


Scheme 116. Application of the reaction of allenyltitanium complexes with imines to the total synthesis of (−)-indolizidine 209B.[249]

While the propargylstannanes synthesised by this method provide a valuable entry to chiral allyltin derivatives **P** by their conversions into di*iso*-propyloxytitanacyclopropene species followed by hydrolysis (see Section 4.2.1),[135] the power of the stereoselective addition of non-racemic chiral allenyltitanium complexes onto imines has been illustrated by a total synthesis of the amphibian alkaloid, (−)-indolizidine 209B (Scheme 116).[249]

It is worthy of note that a related titanium-mediated transformation of propargylic acetates and carbonates has been reported, leading to homocoupling products, 1,5-diynes and 1,2-dien-5-ynes. The reaction conditions involve stirring of diethyl ether solutions of $Ti(Oi\text{-}Pr)_2Cl_2$ with activated Mg powder, followed by the addition of the substrates. It is proposed that the low-valent '$Ti(Oi\text{-}Pr)_2$' is initially formed, that coordinates to the alkyne function to give a di*iso*-propyloxytitanacyclopropene. β-Elimination follows to give an allenyltitanium species that would then undergo reduction to a propargyl radical on the Mg surface. Dimerisation of this radical intermediate could account for the formation of the products.[250]

Substrates bearing a leaving group directly attached to the alkyne function may also follow an elimination pathway when subjected to standard conditions ($Ti(Oi\text{-}Pr)_4$ and Grignard reagent). This provides a convenient access to alkynyltitanium species (Eq. 10, Scheme 34).[73,192,251] These complexes react chemoselectively with a variety of functional aldehydes. Remote sensitive functions are tolerated under the reaction conditions, including halo, tosylate, carbonate, acetate and ketone groups.[251] Very interestingly, Marek et al. showed that, using an excess of reagents, a ligand exchange/β-elimination/ligand exchange sequence may proceed to generate metallated dialkoxytitanacyclopropenes **L4**. Deuteriolysis with MeOD has provided convincing evidence for the formation of these complexes that are equivalent to vinylic 1,1,2-trianions (Scheme 117).[73]



Scheme 117. Generation of alkynyltitanium complexes from halo- and thioalkynes.[73,251]

5. Other transformations

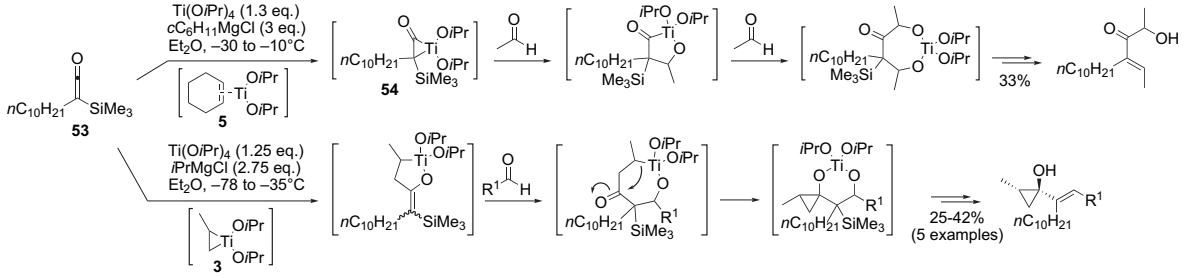
Ketenes are particular substrates, the transformations of which under Kulinkovich-type conditions have been little studied. Nonetheless, Pons et al. reported interesting results obtained with decyl(trimethylsilyl)ketene **53**. Using *cyclo*-hexylmagnesium chloride as the Grignard reagent, the initially formed titanacyclopropane **5** undergoes ligand exchange with **53**, generating a titanacyclopropanone species **54** that can be trapped with acetaldehyde. With *iso*-propylmagnesium chloride, a titanacyclopropane intermediate complex **3** is formed, that rather undergoes 1,2-insertion of the carbonyl moiety of **53**. Eventual addition of an aldehyde triggers the production of a vinylcyclopropanol (Scheme 118).[252]

Under similar conditions to those employed in the Kulinkovich reaction, 1,1-dichlorocyclopropanes and 1,1-dibromocyclopropanes undergo efficient and selective mono-hydrodehalogenation. Typical conditions involve the slow addition, at 20 °C, of an excess amount (1.3 to 3 equiv) of ethylmagnesium bromide to a solution of the substrate and a catalytic amount of $Ti(Oi\text{-}Pr)_4$ (20% equiv). The diastereoselectivity of this reaction is usually quite low, which is not a problem in cases where the products are prepared in order to be subjected to a dehydrohalogenation process (Scheme 119).[253–255] Although CBr_2 fragments are clearly more reactive than CHBr moieties, complete reduction of the 1,1-dibromocyclopropane **55** has been reported using 0.1 equiv of $Ti(Oi\text{-}Pr)_4$ and 3 equiv of EtMgBr.[253]

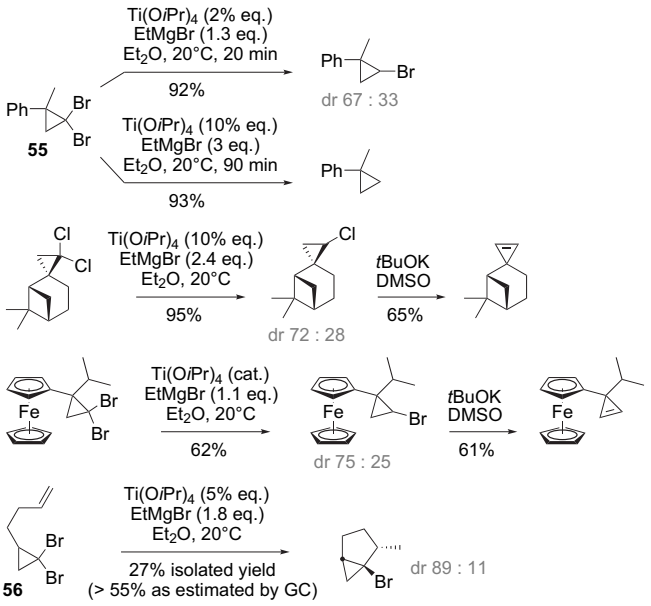
The scope of the reaction includes ferrocenyl-substituted cyclopropanes,[256,257] and substrates bearing an ester group. In the latter case, hydrodehalogenation is accompanied by a Kulinkovich reaction converting the ester group into a cyclopropanol.[254]

The mechanism involved in this reaction is not clear, but it is accepted that a 1-halocyclopropyltitanium(IV) intermediate is formed.[254,255,258] Deuterium-labelling experiments suggest that the Grignard reagent is not the source of the hydrogen atom replacing the halogen atom initially present on the substrate.[254] However, a distinct possibility is the eventual production of a cyclopropyl radical that would abstract a hydrogen atom from the diethyl ether solvent. This proposal is in agreement with the reaction of compound **56** (Scheme 119), since the bicyclic molecule observed could stem from 5-*exo*-*trig* attack of a 1-bromocyclopropyl radical onto the alkene function, followed by hydrogen abstraction of the resulting methyl radical from the solvent.[255]

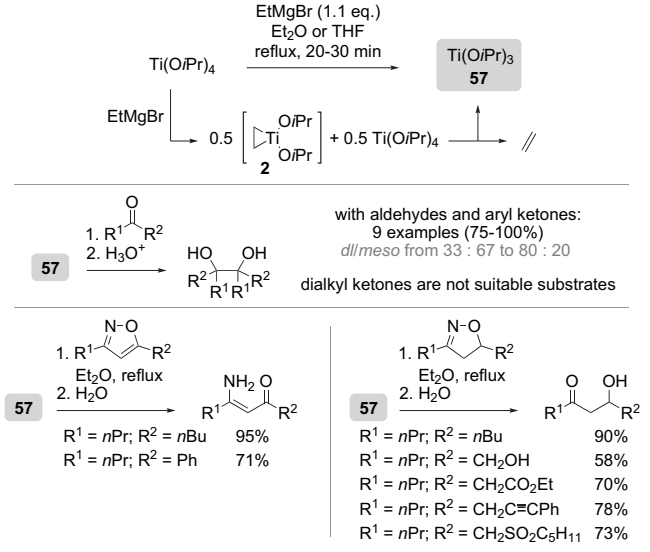
Another interesting extension of the chemistry of Grignard reagents associated with $Ti(Oi\text{-}Pr)_4$ has been reported by Kulinkovich et al., who showed that Ti(III) species are generated when THF or diethyl ether solutions of $Ti(Oi\text{-}Pr)_4$ are treated with equimolar amounts of EtMgBr and then heated at reflux under argon. This is rationalised by the comproportionation of $Ti(Oi\text{-}Pr)_4$ with titanacyclopropane **2** gradually formed, giving the putative complex $Ti(Oi\text{-}Pr)_3$ **57** with the evolution of ethylene (Scheme 120).[259] This Ti(III) species mediates the pinacol coupling of aldehydes and aryl ketones efficiently,[259] as well as the reductive cleavage of isoxazoles and isoxazolines.[260,261] The latter process is particularly chemoselective and can be executed in the presence of alkyne, ketone, ester and hydroxyl functions (Scheme 120).



Scheme 118. Titanium-mediated transformations of decyl(trimethylsilyl)ketene.[252]



Scheme 119. Titanium-mediated dehalogenation reactions of 1,1-dihalocyclopropanes.[253,255,257]



Scheme 120. Generation of a Ti(III) reagent by the reaction of Ti(O*i*-Pr)$_4$ with EtMgBr.[259,260]

6. Conclusions

The organometallic species generated by the reaction of excess amounts of Grignard reagents with Ti(O*i*-Pr)$_4$ or related titanium(IV) alkoxides can mediate an impressive number of reactions, starting from a wide variety of substrates, and these are not limited to the cyclopropanation processes reviewed in Part 1 of this report. Many of these transformations are analogous to reactions catalysed or promoted by other organometallic reagents, especially Group IVb transition-metal complexes such as titanocene- or zirconocene-based complexes. However, the functional-group tolerance and the selectivity patterns of these processes frequently differ sharply, and the behaviour of the reactive intermediates depicted in this report is often complementary to that of the complexes mentioned above. Moreover, a number of the reactions mediated by titanium alkoxide/organomagnesium combinations of reagents have, to this day, no equivalent, which highlights the unique properties of the intermediate complexes involved.

Perhaps one negative aspect of these transformations is the often-met necessity of having to use more than 1 equiv of titanium(IV) alkoxide, but this drawback is actually associated with the majority of the reagents commonly employed in synthetic organic chemistry. Besides, this is counterbalanced by several major advantages. Titanium(IV) *iso*-propoxide, typically used as the titanium source, is inexpensive and non-toxic (although it should be remembered that it is flammable and irritating to the eyes). Moreover, as several examples have shown, the protection of alcohol functions is not always necessary, which results in attractive step economy, and these groups may sometimes participate in regioselection or facilitate transformations that would otherwise be difficult to perform.

Many of the methods presented in this report have been thoroughly investigated and have become powerful and highly selective tools. They are illustrated by a great deal of impressive applications, which also reflect their increasing popularity and recognition. Examples cover large areas of chemistry, ranging from natural product total synthesis and the expedient preparation of complex building blocks, up to polymer synthesis and the preparation of novel organic materials with interesting physical properties. It is, nonetheless, our feeling that a number of potentially interesting ideas remain unexplored, and that the scope of this chemistry may be extended further. Moreover, new molecular-modelling studies could bring a useful and significant contribution to a more detailed knowledge of the fundamental aspects coming into play with this type of chemistry. New processes and attractive applications can be expected to be unveiled in the coming years, which is an exciting prospect.

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Yvan Six was born in Sète (France) in 1970. He graduated from the *Ecole Polytechnique* (Palaiseau), and then completed his PhD at the same institution, where he worked under the supervision of Professor Jean-Yves Lallemand on a synthetic approach towards clerodin, an insect antifeedant. In 1997, he joined the group of Professor William B. Motherwell at University College London (UK) as a post-doctoral fellow to work on the design of polymer catalysis using the molecular imprinting technique. He then returned to France in 1999 to complete another post-doctoral period with Professor Samir Z. Zard at the *Institut de Chimie des Substances Naturelles* in Gif-sur-Yvette, where he worked mainly on tandem reactions using the radical chemistry of dithiocarbonates. He was appointed chargé de recherche at the *Centre National de la Recherche Scientifique* (CNRS) in 2000. His current research interests focus on the design of novel methods based on the chemistry of organotitanium compounds, as well as the synthesis of biologically active molecules.