Synthetic Methods

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Ti-Catalyzed Straightforward Synthesis of Exocyclic Allenes

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((Dedication----optional))

Allenes were considered highly unstable compounds or simple chemical curiosities during many years. Nowadays, however, more than 150 natural products containing the allene motif are known and many of them, such as grasshopper ketone (**1**) or the carotenoid mimulaxanthin (**2**), have the allene function in exocyclic position.[1] Furthermore, allenes have proved themselves to be useful building blocks in organic synthesis, especially in addition, cyclization, cycloaddition and cycloisomerization reactions.[2] In this way, exocyclic allene **3** has been recently reported as the key intermediate in the bioinspired synthesis of the alkaloid stemoamide.[3]

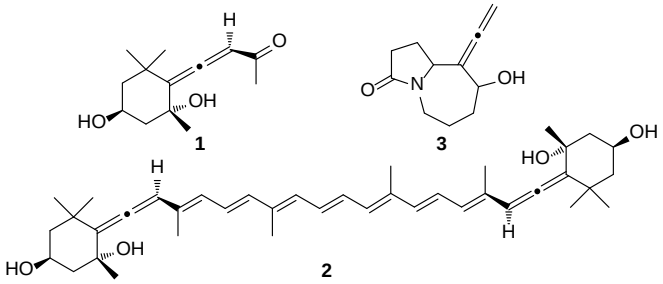
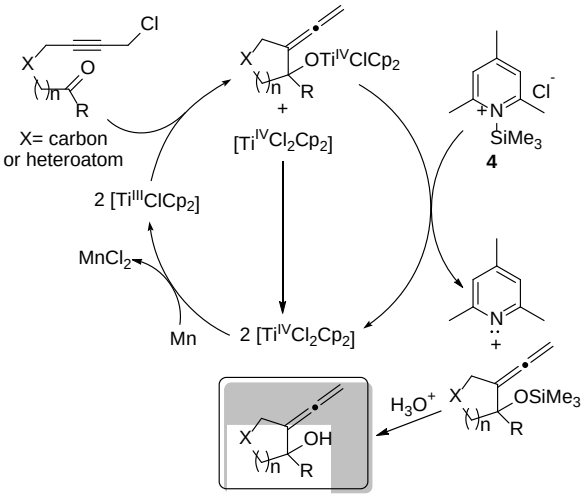


Figure 1. Chemical structure of exocyclic allenes **1**-**3**.

Owing to the growing interest of allenes in pharmacy and contemporary chemistry, several procedures for allene synthesis have been developed in recent years, including alkyne isomerizations, diene rearrangements, electrocyclic ring openings, Pd-catalyzed reactions of propargyl alcohol derivatives, 1,4-additions to conjugated enynes, Zn-promoted condensations between terminal alkynes and aldehydes, and others.[4] Nevertheless, there is still a lack of a general procedure to provide exocyclic allenes in a straightforward manner.[5] Here we describe the Barbier-type cyclization of propargyl halides catalyzed by [Cp_2TiCl] (Nugent's reagent).[6] This novel C-C bond forming reaction directly give five-, six- and seven-membered carbocycles and heterocycles bearing an exocyclic allene group. Moreover, this procedure can be carried out in an enantioselective manner.

Titanium is the seventh most-abundant metal on Earth (the second among transition-metals) and many titanium compounds are non-toxic and environmentally friendly.[7] Very recently, we observed the formation of allenyl alcohols by condensation between aldehydes and internal propargyl halides catalyzed by [Cp_2TiCl].[8] This observation prompted us to conceive the possibility of developing a sustainable Ti-catalyzed cyclization to exocyclic allenes, using the titanocene-regenerating agent **4** to close the catalytic cycle (Scheme 1).[9]



Scheme 1. Anticipated catalytic cycle for the Ti-catalyzed synthesis of exocyclic allenes.

To check this hypothesis, aldehyde **5** was treated with a substoichiometric quantity of commercial [$TiCl_2Cp_2$] (0.2 equiv), relatively cheap Mn dust, and a combination of Me_3SiCl and 2,4,6-collidine to form **4**.[10] As expected, an acceptable 74% yield of exocyclic allene **19** was obtained (Table 1, entry 1).[11]

Subsequent treatment of ketone **6** under the same conditions provided a good 85% yield of allenyl tertiary alcohol **20** (Table 1, entry 2). This was a gratifying but unexpected result because [Cp_2TiCl]-catalyzed intermolecular condensations between propargyl halides and ketones always led to homopropargylic

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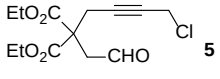
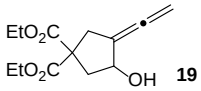
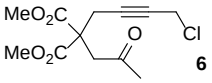
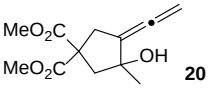
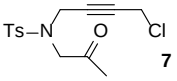
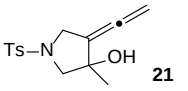
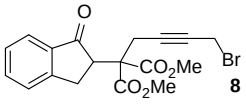
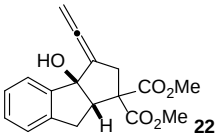
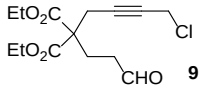
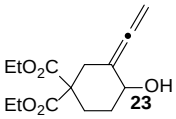
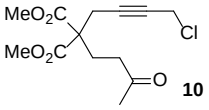
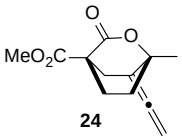
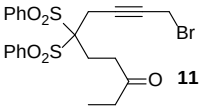
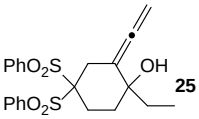
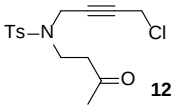
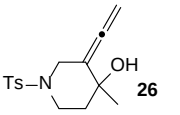
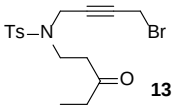
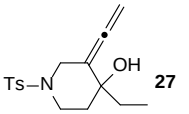
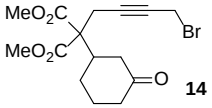
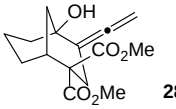
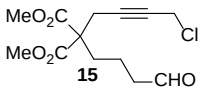
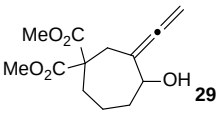
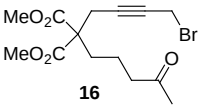
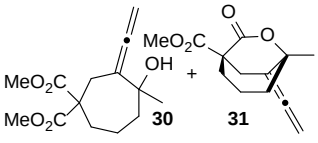
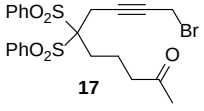
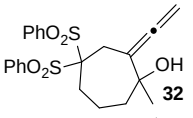
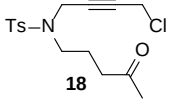
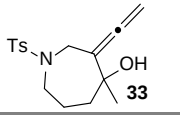
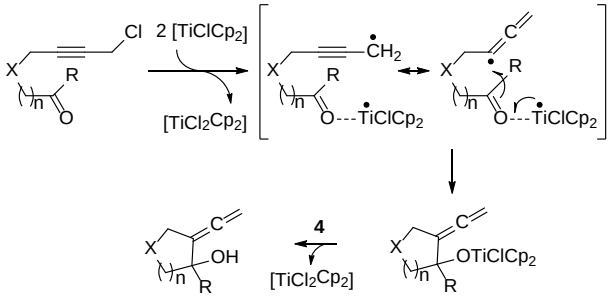
Table 1. Cp_2TiCl-catalyzed Barbier-type cyclization of propargyl halides **5**-**18**.

Entry	Substrate	Product[a]	Yield
1	 **5**	 **19**	74
2	 **6**	 **20**	85
3	 **7**	 **21**	78
4	 **8**	 **22**	87[b]
5	 **9**	 **23**	77
6	 **10**	 **24**	76
7	 **11**	 **25**	88
8	 **12**	 **26**	80
9	 **13**	 **27**	71
10	 **14**	 **28**	81
11	 **15**	 **29**	75
12	 **16**	 **30** **31**	48[c] 24[d]
13	 **17**	 **32**	90
14	 **18**	 **33**	74

[a] The alcohol was sometimes accompanied by a minor quantity of the corresponding trimethylsilyl ether, which was easily transformed into the alcohol. [b] Only the *cis* diastereomer is formed. [c] isolated yield of **30**. [d] isolated yield of **31**.

alcohols.[8,12] This intermolecular reaction presumably proceeds via allenyl-Ti(IV) organometallic species, which attack ketones to form homopropargylic alcohols.[8] In contrast, it seems that the intramolecular reaction (cyclization) might proceed via propargyl radicals, facilitated by coordination between the carbonyl group and $[Cp_2TiCl]$ (Scheme 2). In this way, Ti-catalyzed cyclization of ketone **7** also gave the exocyclic allene present in pyrrolidine **21** (Table 1, entry 3).



Scheme 2. Presumable free-radical character of $[Cp_2TiCl]$-catalyzed Barbier-type cyclization of propargyl halides.

$[Cp_2TiCl]$-catalyzed cyclization of indanone **8** provided stereoselectively the tricyclic vinylidene **22** in a good 87% yield (Table 1, entry 4). It should be noted that only the *cis* stereoisomer was formed. Moreover, the newly formed OH group, which occupies a benzylic, tertiary and homoallenic position, remained in the cyclization product **22** and no dehydration products were detected, underlying the experimental mildness of this method. Moreover, the good yield obtained confirms the compatibility of allenyl radicals with aromatic rings.

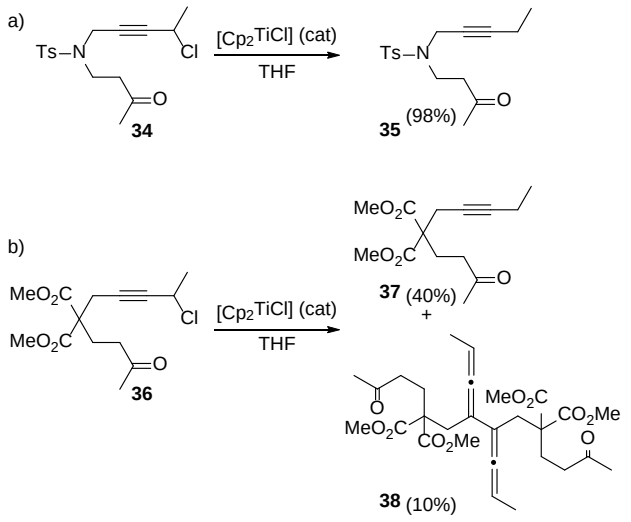
Once we were confident about the ability of $[Cp_2TiCl]$ to catalyze 5-*exo* cyclizations to exocyclic allenes, we decided to essay 6-*exo* ones, because these processes might facilitate the access to interesting terpenoids and carotenoids scarce in nature which possess one or two vinylidencyclohexane units in their molecules.[1] In this way, treatment of aldehyde **9** with a substoichiometric quantity of $[Cp_2TiCl]$ gave the expected vinylidencyclohexanol **23** (Table 1, entry 5).[11] When ketone **10** was treated under the same conditions, however, bicyclic lactone **24** was obtained (Table 1, entry 6). The lactonization process leading to **24** might be possibly provoked by the tendency of the methyl group to occupy an equatorial disposition, thus pushing the tertiary alcohol towards the spatial proximity of the corresponding *cis* methyl-ester group.[13] On the other hand, $[Cp_2TiCl]$-catalyzed cyclization of phenylsulfone **11** cleanly provided an 88% yield of cycloalkanol **25** (Table 1, entry 7). Additionally, Ti-catalyzed cyclization of tosylamides **12** and **13** afforded 80% and 71% yields of vinylidenpiperidines **26** and **27** respectively (Table 1, entries 8 and 9). In this way, this reaction might provide a novel method for piperidine synthesis.

The capacity for efficiently increasing molecular complexity is one of the most valuable properties of new methods in organic synthesis.[14] In this context, $[Cp_2TiCl]$-catalyzed cyclization of cyclohexanone **14** gave an 81% yield of bicycloalcanol **28** bearing the expected exocyciclic allene (Table 1, entry 10) and thus confirming the utility of the method to prepare bridged carbocycles. As can be seen, molecular complexity was considerably increased in only one step, underlying the synthetic potential of the method.

Seven-membered rings are often classified as “common rings” owing to their relatively low ring strain.[15] It is not surprising

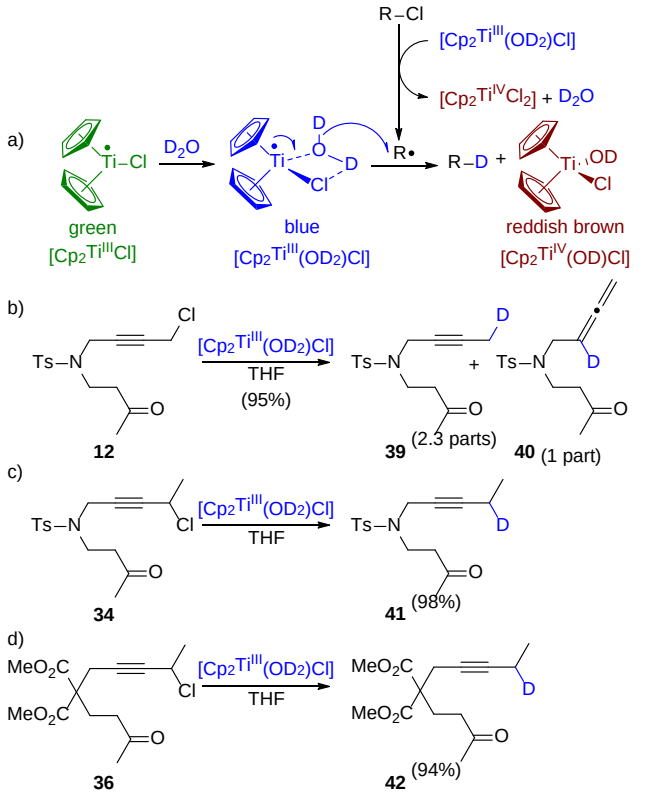
therefore that they are quite widespread in nature, where they can be found in the carbon skeleton of different alkaloids and terpenoids.[16] Nevertheless, compared to five- and six-membered rings, methods for the synthesis of seven-membered ones are still notoriously scarce.[17] In this scenario, [Cp_2TiCl]-catalyzed cyclization of aldehyde **15** afforded a 75% yield of cycloheptanol **29** (Table 1, entry 11). Moreover, cyclization of ketone **16** gave tertiary alcohol **30** accompanied by a minor amount of bicyclic lactone **31** (72% total yield) (Table 1, entry 12).[18] Thus, it seems that the (pseudo)equatorial methyl group of **30** has lesser power to promote lactonization than the equatorial methyl group of the six-membered alcohol precursor of lactone **24** (see Table 1, entry 6). Once again, replacement of ester groups by sulfones in **17** avoided lactonization and cycloheptanol **32** was obtained in an excellent 90% yield (Table 1, entry 13). Moreover, cyclization of tosylamide **18** afforded azepane **33** (Table 1, entry 14), providing a new method for the synthesis of this kind of heterocycles which are present in the structure of numerous pharmacologically active alkaloids, such as the anti Alzheimer's disease drug galantamine,[19] the *Stemona* alkaloids,[20] and others.[21]

Once primary propargyl halides demonstrated to be suitable substrates for the synthesis of exocyclic allenes, we checked secondary ones. Nevertheless, treatment of secondary propargyl chloride **34** with a substoichiometric quantity of [Cp_2TiCl] gave dehalogenated alkyne **35** (98% yield) and none cyclization product was detected. Moreover, similar treatment of secondary chloride **36** gave alkyne **37** accompanied by a minor amount of dimeric allene **38** (Scheme 3).



Scheme 3. [Cp_2TiCl]-catalyzed reductive dehalogenation of secondary propargyl halides **34** (a) and **36** (b).

The unexpected behaviour shown by secondary propargyl halides was intriguing and, consequently, we tackled the study of radicals involved in these processes. It is well known that free radicals are reduced by H-atom transfer (HAT) from water via the aqua-complex [$Cp_2Ti(OH_2)Cl$].[22] This phenomenon can be exploited to study the reactivity of radicals using the aqua-complex [$Cp_2Ti(OD_2)Cl$] as deuterium labeller.[8] In this way, propargyl halides **12**, **34** and **36** were treated with blue [$Cp_2Ti(OD_2)Cl$], generated *in situ* by adding D_2O to green [Cp_2TiCl] (Scheme 4). In all products obtained, deuterium incorporation (DI) was higher than 95%. These DI values are significant because high DI percentages are characteristic for radical reductions by D-atom transfer (DAT) from [$Cp_2Ti(OD_2)Cl$] but not for the hydrolysis of alkyl-Ti(IV) complexes with D_2O (0-60% DI).[8]

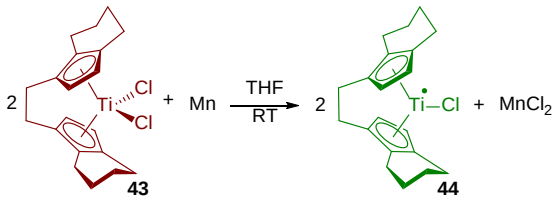


Scheme 4. a) *In situ* generation of [$Cp_2Ti(OD_2)Cl$] and DAT to free radicals; b) deuterium labelling of the primary propargyl radical derived from **12**; c) and d) deuterium labelling of secondary propargyl radicals derived from **34** and **36** respectively.

In spite of the great advances in free-radical chemistry achieved in the last decades,[23] the structure and chemical behaviour of secondary propargyl radicals is still poorly understood. In contrast, both spectroscopic techniques and theoretical calculations have shown that primary propargyl radicals are bidentate, with unequal distribution of spin densities between the sp^2 carbon (65%) and the *sp* one (35%),[24] which is consistent with the 2.3/1 mixture of alkyne **39** and allene **40** obtained in the deuterium labelling experiment depicted in Scheme 4b.[25] To the best of our knowledge, however, no theoretical calculations on secondary propargyl radicals have been reported so far. Thus, although a relative increase in the spin density on the sp^2 carbon has been suggested, there are no conclusive data for these secondary radicals.[26] In this scenario, results depicted in Schemes 3, 4c and 4d suggest that on the *sp* carbon of secondary propargyl radical might be a low spin density (lower than 35%) capable of providing some stabilization degree and even allowing reactions with very low activation energy, such as the radical-radical coupling leading to dimer **38**.[27] Nevertheless, this spin density is not enough to pull out a deuterium atom from [$Cp_2Ti(OD_2)Cl$] or to attack the carbonyl groups of ketones **34** and **36**, reactions which involve higher activation energies. Thus, from a practical point of view, it seems that in front of mild single-electron donors, such as titanocene(III) complexes, secondary propargyl radicals behave as monodentate ones, with their reactivity concentrated at the sp^2 carbon.[28] Consequently, Ti(III)-catalyzed synthesis of exocyclic

allenes is limited to primary propargyl halides due to the inherent reactivity of secondary propargyl radicals.

Asymmetric catalysis plays a crucial role in contemporary organic synthesis.[29] Therefore, we decided to assay an enantiomerically pure titanium catalyst to check the possibility of achieving an unprecedented Ti(III)-catalyzed procedure for the enantioselective synthesis of exocyclic allenes. To this end we chose commercially available Brintzinger's complex (+)-dichloro(*R*, *R*)-ethylenebis(4, 5, 6, 7-tetrahydro-1-indenyl)titanium(IV) (**43**) as pre-catalyst. *In situ* generation of the corresponding Ti(III) enantiopure catalyst (**44**) was carried by simple stirring of **43** with Mn dust (Scheme 5).



Scheme 5. Easy *in situ* generation of enantiopure titanocene(III) catalyst **44** from commercially available **43**.

For our delight, cyclization of ketone **6**, catalyzed by titanocene(III) complex **44**, gave optically active cycloalkanol (-)-**20** (Table 2, entry 1). Chiral HPLC analysis indicated a moderate 15% enantiomeric excess (ee). This is the first metal-catalyzed enantioselective synthesis of an exocyclic allene reported to date.

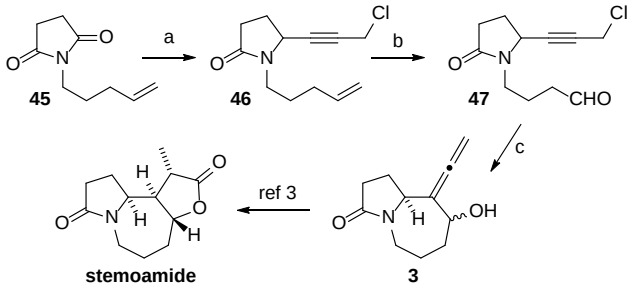
Table 2. Enantioselective synthesis of exocyclic allenes catalyzed by titanocene(III) complex **44**.

Entry	Substrate	Product	Yield	ee[a]
1	**6**	**(–)-20**	70%	15%
2	**7**	**(+)-21**	71%	29%
3	**9**	**(+)-23**	71%	36%
4	**10**	**(–)-24**	78%	39%
5	**12**	**(+)-26**	75%	17%
6	**15**	**(–)-29**	72%	43%

[a] Determined by chiral HPLC analysis

Subsequent cyclization of substrates **7**, **9**, **10**, **12** and **15** catalyzed by **44** gave optically active allenes (+)-**21**, (+)-**23**, (-)-**24**, (+)-**26** and (–)-**29** in yields ranging from 70 to 78% and ees from 15 to 43% (Table 2, entries 2-6). Despite of the moderate ee values obtained, these results confirm that the titanocene(III) catalyst participates in the key C-C bond forming step and, consequently, paves the way for the development of more efficient catalysts.

The synthesis of natural products constitutes one of the most demanding tests of the viability of a new method in organic synthesis. Therefore we decided to try out the Ti-catalyzed synthesis of exocyclic allenes for preparing natural products. To this end we chose the alkaloid stemoamide as target molecule. Due to its biological properties, stemoamide, isolated from the Chinese folk medicine plant *Stemona tuberosa*, has been the subject of several synthetic efforts. Among them, Hong and co-workers have recently reported a bioinspired synthesis via the key intermediate **3**. We have prepared this advanced intermediate following Scheme 6. The required starting product was obtained by alkylation of the sodium salt of commercial succinimide with 5-bromo-1-pentene, which afforded **45** in near quantitative yield as previously described.[30] Selective monopropargylation was achieved in a quite straightforward way. Thus, treatment of propargyl chloride with *n*-BuLi and addition to **45** gave a hydroxy derivative which was immediately reduced with $NaBH_3CN$ to give the desymmetrized succinimide derivative **46.** After chemo-selective oxidative cleavage of the terminal olefin of **46**, the aldehyde **47** was obtained. Finally, [Cp_2TiCl]-catalyzed cyclization of **47** gave exocyclic allene **3** as a 2.7/1 mixture of diasteromers.[31] This mixture can be used to give a single isomer of stemoamide as it has been previously reported.[3] In this way, the formal synthesis of stemoamide is achieved in a considerably shorter way for the preparation of key intermediate **3**, thus proving the synthetic utility of our method.



Scheme 6. Synthesis of exocyclic allene **3**, key intermediate in the synthesis of (±) stemoamide. a) i: propargyl chloride, *n*-BuLi, THF, –50º C; ii: $NaBH_3CN$, MeOH, AcOEt, –78º C, 50%; b) OsO_4 cat., KIO_4, THF/H_2O, 0º C to 5º C, 59%; c) Cp_2TiCl_2, Mn, 2,4,6-collidine, TMSCl, THF, reflux, 76%.

In conclusion, here we present a general procedure for the straightforward synthesis of exocyclic allenes catalyzed by titanocene(III) complexes. The reaction proceeds under mild conditions compatible with different functional groups and provides good yields of five-, six- and seven-membered carbocycles and nitrogen-containing heterocycles bearing an exocyclic allene group. Therefore, this method affords a new retrosynthetic disconnection in the α-position of an exocyclic allene. Additionally, this procedure can be carried out in an enantioselective manner by using chiral titanocene(III) complexes. The utility of this method has been proved in the synthesis of the natural alkaloid stemoamide. At the moment we are engaged in a more-in-depth study of the reaction mechanism, the design and synthesis of more efficient chiral titanocene(III) catalysts and the total synthesis of terpenoid **1** and carotenoid **2**.

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