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Diene–Titanium Complexes as Synthetic Intermediates for the Construction of Three- or Five-Membered Carbocycles

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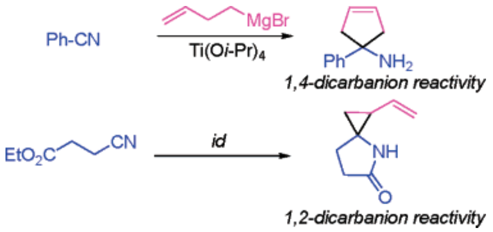
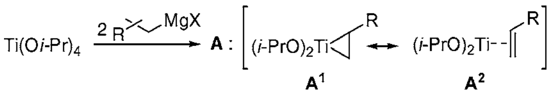
ABSTRACT



It has been shown that diene–titanium complexes exhibit substrate-dependent 1,2- or 1,4-dicarbanion reactivity. On this basis, 3-cyclopentenylamines and spiro-vinylcyclopropane lactams were easily prepared by using homoallylic Grignard reagents, Ti(O-*i*-Pr)$_4$, and nitriles or cyanoesters, respectively.

Titanacyclopropanes ($\mathbf{A^1}$), which can also be considered as π-complexes ($\mathbf{A^2}$), are typically formed by transmetalation and a successive β-fragmentation (Scheme 1).[1] These putative intermediates are involved in the Kulinkovich hydroxycyclopropanation of esters[2] as well as in the related syntheses of tertiary[3] and primary[4] cyclopropylamines from amides and nitriles, respectively.

Scheme 1



Following the discovery of the Kulinkovich reaction, Ti(II) chemistry has been widely developed,[1] particularly due to the 1,2-dicarbanion pattern of titanacyclopropanes. In addition, exchange of alkenes, imines, or alkynes starting from the initial Ti(II)−alkene complex has broadened the scope of the cyclopropanation and other reactions.[5]

In contrast to **A**, reactions of diene−titanium complexes **B** have been less investigated.[6−10] This species can be

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(1) (a) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789. (b) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835.

(2) (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevsky, D. A. *Synthesis* **1991**, 234. (b) Kulinkovich, O. G. *Eur. J. Org. Chem.* **2004**, 4517.

(3) (a) Chaplinski, V.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 413. (b) de Meijere, A.; Kozhushkov, S. I.; Savchenko, A. I. *J. Organomet. Chem.* **2004**, *689*, 2033.

(4) (a) Bertus, P.; Szymoniak, J. *Chem. Commun.* **2001**, 1792. (b) Bertus, P.; Szymoniak, J. *Synlett* **2007**, 1346.

(5) Some recent examples: Alkenes: (a) Keaton, K. A.; Phillips, A. J. *Org. Lett.* **2007**, *9*, 2717. (b) Quan, L. G.; Kim, S.-H.; Lee, J. C.; Cha, J. K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2160. Imines: (c) Takahashi, M.; Micalizio, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 7514. (d) Fukuhara, K.; Okamoto, S.; Sato, F. *Org. Lett.* **2003**, *5*, 2145. Alkynes: (e) Bahadoor, A. B.; Flyer, A.; Micalizio, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 3694. (f) Suzuki, D.; Nobe, Y.; Watai, Y.; Tanaka, R.; Takayama, Y.; Sato, F.; Urabe, H. *J. Am. Chem. Soc.* **2005**, *127*, 7474.

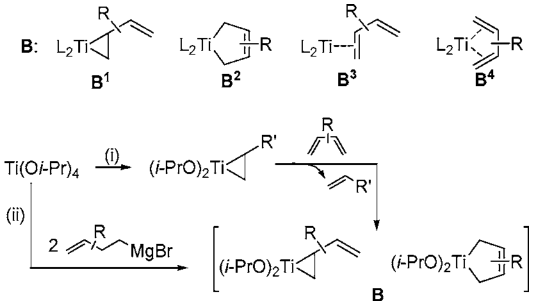
(6) (a) Williams, C. M.; Chaplinski, V.; Schreiner, P. R.; de Meijere, A. *Tetrahedron Lett.* **1998**, *39*, 7695. (b) de Meijere, A.; Williams, C. M.; Kourdioukov, A.; Sviridov, S. V.; Chaplinski, V.; Kordes, M.; Savchenko, A. I.; Stratmann, C.; Noltenmeyer, M. *Chem. Eur. J.* **2002**, *8*, 3789.

(7) (a) Urabe, H.; Kasatkin, A.; Sato, F. *Chem. Commun.* **1996**, 197. (b) Urabe, H.; Takeda, T.; Sato, F. *Tetrahedron Lett.* **1996**, *37*, 1253. (c) Urabe, H.; Mitsui, K.; Ohta, S.; Sato, F. *J. Am. Chem. Soc.* **2003**, *125*, 6074.

(8) Laroche, C.; Bertus, P.; Szymoniak, J. *Chem. Commun.* **2005**, 3030.

10.1021/ol702917c CCC: $40.75

Scheme 2

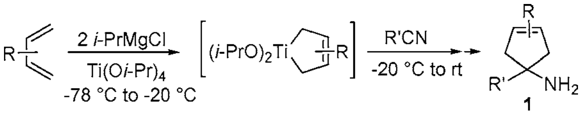


described by several canonical forms, η^2 or η^4, including metalacycles ($\mathbf{B}^1$ or $\mathbf{B}^2$) or π-complexes ($\mathbf{B}^3$ or $\mathbf{B}^4$) (Scheme 2).

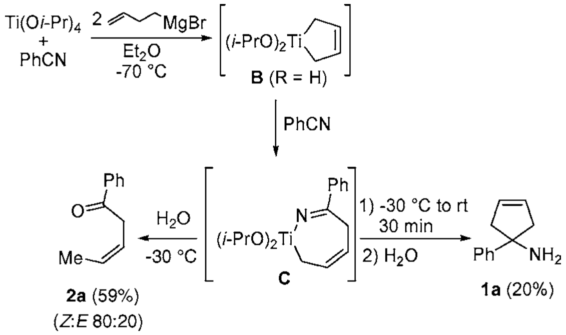
Two approaches for generating diene−titanium complexes are known. The ligand exchange between (η^2-alkene)Ti(O*i*-Pr)$_2$ and 1,3-dienes (Scheme 2, path i) is a convenient procedure.[6−9] More recently, the low temperature addition of homoallylic Grignard reagents to titanium isopropoxide (path ii) has been reported.[10] In some cases, 1,4-dicarbanion reactivity has been revealed. Thus, the addition of electrophiles such as aldehydes, ketones, or nitriles led to the corresponding open-chain products.[7,10] In contrast, 1,2-dicarbanion reactivity has been observed when using *N*,*N*-dialkylamides as starting materials.[6] In these reactions, performed under ligand-exchange conditions, 2-vinylcyclopropylamines were exclusively formed. Based on the dichotomous 1,4- vs 1,2-dicarbanion pattern of diene−titanium complexes, we describe herein simple synthetic approaches to three- and five-membered carbocyclic compounds which use nitriles or cyanoesters and homoallylic Grignard reagents as starting materials.

As a part of our work on the titanium-mediated synthesis of cyclopropylamines from nitriles,[4] we studied the feasibility of preparing 2-vinylcyclopropylamines. The ligand-exchange procedure with the initial propene−titanium complex and isoprene was applied. To make the exchange efficient, the temperature was allowed to slowly increase from −78 to 20 °C and during this period a nitrile was added. When the nitrile addition took place at about −20 °C, 3-cyclopentenylamines **1** were formed in good yields (Scheme 3).

Scheme 3



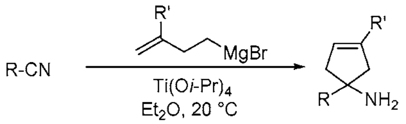
Scheme 4



To gain a better insight into this [4 + 1] assembly reaction, the diene-titanium intermediate of type **B** was then generated from Ti(O-*i*-Pr)$_4$ and a homoallylic Grignard reagent according to Goeke et al. (Scheme 4).[10] When 3-butenylmagnesium bromide (2 equiv) was added at −70 °C to benzonitrile and Ti(O-*i*-Pr)$_4$ in Et$_2$O and the mixture allowed to warm to −30 °C during 1 h, the ketone **2a** was obtained in 59% yield after hydrolysis at −30 °C, in agreement with Goeke's results. Interestingly, when the reaction mixture was warmed to room temperature the cyclopentenylamine **1a** was obtained after hydrolysis, albeit in low yield (20%), and no trace of **2a** was detected. This result clearly indicated that the contraction of the azatitanacycle intermediate **C**, leading to a five-membered carbocycle, occurred only at temperatures higher than −30 °C.

It should be noted that the simultaneous use of homoallylic Grignard reagent and a nitrile is possible. This is in contrast to the ligand-exchange method in which the nitrile must be added only after the Grignard reagent-promoted transmetalation−fragmentation and ligand-exchange processes occur.[8] As a consequence, an efficient room-temperature procedure for directly preparing cyclopentenylamines could be envisioned. The feasibility of such reactions was checked by simply adding the homoallylic Grignard reagent to a mixture of the nitrile and Ti(O-*i*-Pr)$_4$ at room temperature. The reactions were carried out for about 1 h, followed by a hydrolytic workup. Some results obtained by employing aromatic and aliphatic nitriles as well as unsubstituted and substituted Grignard reagents are presented in Scheme 5.

Scheme 5



R = Ph	R' = H	**1a** (56%)
R = *n*-C_9H_{19}	R' = H	**1b** (42%)
R = Ph	R' = Me	**1c** (79%)
R = *n*-C_9H_{19}	R' = Me	**1d** (66%)
R = Bn	R' = Me	**1e** (55%)

With this room-temperature-based protocol, the corresponding cyclopentenylamines were obtained in moderate to good yields. The unsubstituted cyclopentenylamines **1a**

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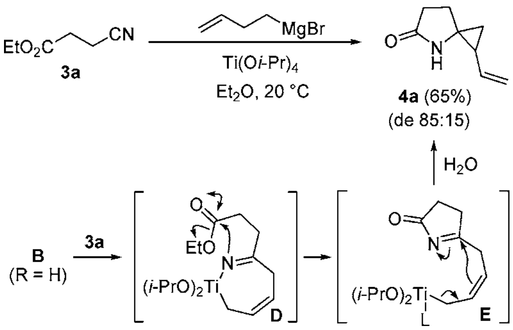
(9) Baraut, J.; Perrier, A.; Comte, V.; Richard, P.; Le Gendre, P.; Moise, C. *Tetrahedron Lett.* **2006**, *47*, 8319.

(10) Goeke, A.; Mertl, D.; Jork, S. *Chem. Commun*. **2004**, 166.

and **1b** were formed by using 3-butenylmagnesium bromide, which amounts to the ligand-exchange-based protocol involving the gaseous 1,3-butadiene. This straightforward method uses readily available and simple starting materials.

Starting from nitriles, no trace of the vinylcyclopropylamine derivative was observed. This contrasted sharply with the exclusive formation of 2-vinylcyclopropylamines from *N*,*N*-dialkylamides.[6] In the case of cyanoesters, a 1,2-dicarbanion pattern was observed which was similar to amides and different from nitriles. Thus, **4a** was the only product formed from ethyl 3-cyanopropionate (**3a**) under the conditions employed for nitriles (Scheme 6).

Scheme 6

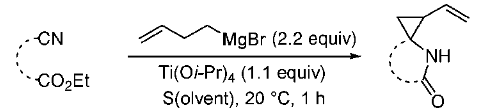


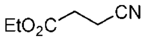
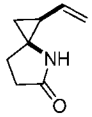
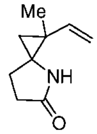
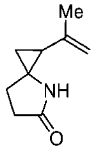
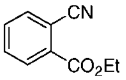
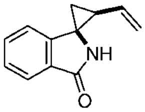
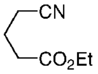
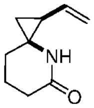
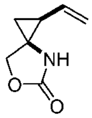
The formation of the azaspirocyclic compound **4a** can be explained as depicted in Scheme 6. The chemoselective insertion of the CN group into **B** produces the intermediate **D**. The carboxylate-induced ring opening of **D** affords the allyltitanium intermediate **E**, which in turn reacts intramolecularly with the *N*-acylimine moiety to give the spirovinylcyclopropane lactam **4a** after hydrolysis.[11,12]

As depicted in Table 1, the titanium-mediated reaction of cyanoesters or cyanocarbonates with homoallylic Grignard reagents led to 1-azaspirocyclic compounds **4a**−**f**, having a vinylcyclopropylamine (and not a cyclopentenylamine) moiety.

When using THF instead of Et_2O as solvent, **4a** was obtained in higher yield and in almost pure diastereomeric form (entry 1).[13] With a substituted Grignard reagent, i.e., 3-methyl-3-butenylmagnesium bromide, the regioisomers **4b** and **4c** were obtained in a 2:1 ratio regardless of the solvent used (entry 2). The presence of both **4b** and **4c** supported the intermediacy of complex **B**, followed by a nonselective insertion of the CN group.[14] Mixtures of diastereomeric spirocyclic lactams **4d** and **4e** (entries 3 and 4) could be separated by flash chromatography.[15] Finally, the oxazolidinone **4f**, prepared from Boc-protected glycononitrile (**3d**), was obtained as a unique stereoisomer in THF (entry 5).

Table 1. Ti-Mediated Synthesis of Spirocyclic Lactams from Cyanoesters and Homoallylic Grignard Reagents



entry	nitrile	product, solvent, yield[a,b]
1	 **3a**	 **4a** S = Et_2O: 65% (85:15) S = THF: 72% (98:2)
2[c]	**3a**	 **4b**  **4c** S = Et_2O: **4b** (40%, 90:10) + **4c** (21%, 74:26) S = THF: **4b** (44%, >98:2) + **4c** (24%, 97:3)
3	 **3b**	 **4d** S = Et_2O: 85% (70:30) S = THF: 81% (70:30)
4	 **3c**	 **4e** S = Et_2O: 75% (70:30) S = THF: 77% (63:37)
5	 **3d**	 **4f** S = THF: 57% (>98:2)

[a] Isolated yields. [b] Only the major diastereomer is depicted. Diastereoisomeric ratio is given in parentheses. [c] 3-Methyl-3-butenylmagnesium bromide was used.

In summary, diene−titanium complexes, generated from homoallylic Grignard reagents and Ti(O-*i*-Pr)$_4$, exhibit substrate-dependent 1,2- or 1,4-dicarbanion reactivity. On this basis, a straighforward access to 3-cyclopentenylamines from nitriles and spiro-vinylcyclopropane lactams from cyanoesters has been developed. The simultaneous presence of aminocyclopropane[16] and vinylcyclopropane[17] moieties would make the latter compounds versatile synthetic inter-

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(11) An analogous allyltitanium intermediate has been postulated for the cyclopropanation of *N*,*N*-dialkylamides with 1,3-dienes; see ref 6.

(12) An alternative mechanism, similar to the vinylcyclopropane−cyclopentene rearrangement can also be considered; see, for example: (a) Danheiser, R. L.; Bronson, J. J.; Okano, K. *J. Am. Chem. Soc.* **1985**, *107*, 4579. (b) Rieke, R. D.; Sell, M. S.; Xiong, H. *J. Am. Chem. Soc.* **1995**, *117*, 5429.

(13) The relative stereochemistry of **4a** was elucidated by NOE.

(14) Similar results were obtained by applying the ligand-exchange procedure.

(15) See the Supporting Information.

(16) For some synthetic uses of cyclopropylamines, see: (a) Madelaine, C.; Six, Y.; Buriez, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 8046. (b) Osipova, A.; Yufit, D. S.; de Meijere, A. *Synthesis* **2007**, 131. (c) Tanguy, C.; Bertus, P.; Szymoniak, J.; Larionov, O. V.; de Meijere, A. *Synlett* **2006**, 2339. (d) Laroche, C.; Behr, J.-B.; Szymoniak, J.; Bertus, P.; Schütz, C.; Vogel, P.; Plantier-Royon, R. *Bioorg. Med. Chem.* **2006**, *14*, 4047.

(17) Vinylcyclopropanes are involved in a number of ring expansion and cycloaddition reactions; see, for example: (a) Wender, P. A.; Gamber, G. G.; Williams, T. J. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; Chapter 13. (b) Trost, B. M.; Shen, H. C.; Horne, D. B.; Toste, F. D.; Steinmetz, B. G.; Koradim, C. *Chem. Eur. J.* **2005**, *11*, 2577. (c) Baldwin, J. E. *Chem. Rev.* **2003**, *103*, 1197.

mediates. Mechanistic investigations and synthetic applications are underway in our laboratory.

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Supporting Information Available: Experimental procedures and characterization data and NMR spectra of compounds **1a**−**e** and **4a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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