Ti(II)-Mediated Tandem Inter- and Intramolecular Coupling Reaction of Unsaturated Hydrocarbons: One-Pot Preparation of Cyclopentanes and Cyclohexanes from Readily Available Acyclic Starting Materials

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Inter- and intramolecular coupling reactions of olefins and/or acetylenes with a catalytic or a stoichiometric quantity of a metallic reagent have, respectively, received widespread acceptance as valuable methods in organic synthesis. One metal species is frequently effective for both inter- and intramolecular coupling reactions; however, there is no precedent to carry out the inter- and intramolecular coupling reactions successively in one pot in the presence of a single metal species although such reaction would allow advances in the design of new synthesis and also would minimize the use of chemicals and shorten the processing time.[1] Recently, we have developed the inter-[2,3] and intramolecular[4−7] coupling reactions in the presence of a stoichiometric amount of a divalent titanium reagent, Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX (**1**).[8] The titanacycles thus produced can be effectively used for further functionalization or carbon−carbon bond formation. Herein we report that **1** can be used as a reagent to carry out successively the inter- and intramolecular coupling reactions, which methodology opens up one-pot access to cyclopentanes and -hexanes from readily available acyclic diynes or enynes and allylic compounds.

Scheme 1

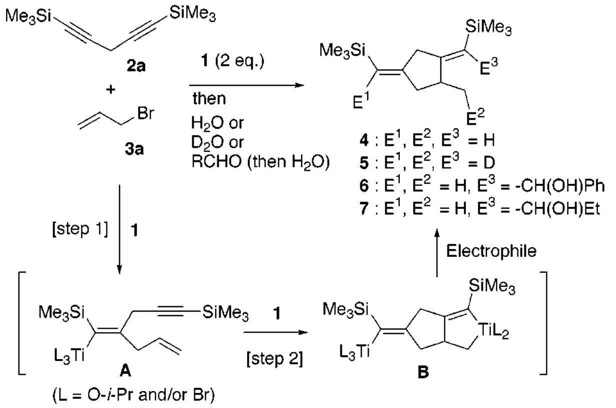
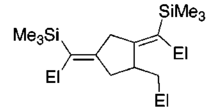
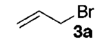
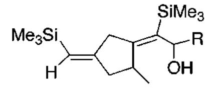
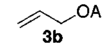
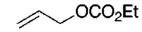
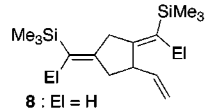
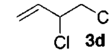
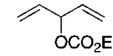
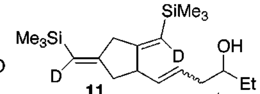
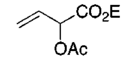
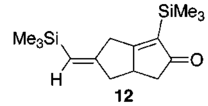


Table 1. T(II)-Mediated Tandem Inter-/Intramolecular Coupling Reaction of Diyne **2a** with Allylic Compounds **3**[a]

Entry	Allylic Compound	Electrophile(s)[b]	Product(s)	Yield, %[c]
				
1	 **3a**	H_2O	**4** : El = H	88
2	**3a**	D_2O	**5** : El =D (>95% D_3)[d]	87
				
3	**3a**	PhCHO[e]	**6** : R = Ph (d.r. 93 : 7)[d,f]	49
4	**3a**	EtCHO[e]	**7** : R = Et (d.r. >98 : 2)[d,f]	50
5	 **3b**	H_2O	**4**	73
6	 **3c**	H_2O	**4**	76
				
7	 **3d**	H_2O	**8** : El = H	85
8	**3d**	D_2O	**9** : El = D (>95% D_2)[d]	87
9	**3d**	I_2	**10** : El = I	64
10	 **3e**	EtCHO[e] then D_2O	 **11** (100% regioselectivity *E* : *Z* = 89 : 11 >95% D_2)[d,g]	68
11	 **3f**	*s*-BuOH[e]	 **12**	44

[a] All reactions were carried out using **2** (1.0 equiv), **3** (1.0 equiv), Ti(O-*i*-Pr)$_4$ (2.6 equiv) and *i*-PrMgCl (5.2 equiv). [b] An excess amount was used unless otherwise stated. [c] Isolated yield. [d] Determined by ^{1}H NMR and GC/MS analyses. [e] 1.0 equiv. [f] Stereochemistry was not determined. [g] A mixture of four stereoisomers.

Reaction of 2 equiv of **1** with 1,5-bis(trimethylsilyl)-1,4-pentadiyne (**2a**) and allyl bromide (**3a**) in ether at −65 to −40 °C over 5 h gave, after hydrolysis, 1,4-bis(trimethylsilylmethylidene)-2-methylcyclopentane (**4**) in 88% yield as shown in Scheme 1 and entry 1 in Table 1. The outcome of the reaction can be explained by assuming that the **1**-mediated regiospecific intermolecular coupling reaction of **2a** with **3a** and the following β-elimination reaction occurs initially to afford titanated complex **A**[2] in situ (step 1 in Scheme 1), which in turn undergoes **1**-mediated intramolecular cyclization reaction to afford titanabicyclic compound **B** (step 2).[5] Production of the product **B** was confirmed by deuteriolysis of the reaction product that provided trideuterated product **5** with excellent deuterium incorporation (entry 2 in Table 1). In situ generation of the intermediate **A** was supported by a high-yield production of its hydrolysis product 1-trimethylsilyl-4-(trimethylsilylmethylidene)hept-6-en-1-yne when the reaction of **2a** and **3a** was carried out in the presence of 1 equiv of **1**.[9] Although complex **B** has three different titanium−

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[1] Most recent examples for a tandem inter-/intramolecular reaction: Smulik, J. A.; Diver, S. T. *Tetrahedron Lett.* **2001**, *42*, 171. Wei, X.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 409. Trost, B. M.; Frontier, A. J. *J. Am. Chem. Soc*. **2000**, *122*, 11727. Jeong, N.; Seo, S. D.; Shin, J. Y. *J. Am. Chem. Soc.* **2000**, *122*, 10220. Suffert, J.; Raeppel, S.; Raeppel, F.; Didier, B. *Synlett* **2000**, 874.

[2] Okamoto, S.; Takayama, Y.; Gao, Y.; Sato, F. *Synthesis* **2000**, 975.

[3] Yamaguchi, S.; Jin, R.-Z.; Tamao, K.; Sato, F. *J. Org. Chem.* **1998**, *63*, 10060. Hamada, T.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 7342. Urabe, H.; Narita, M.; Sato, F. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3516.

[4] (a) Takayama, Y.; Gao, Y.; Sato, F. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 851. (b) Takayama, Y.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1997**, *38*, 8351 (c) Yamazaki, T.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 7333. (d) Takayama, Y.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 3559.

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[6] Urabe, H.; Takeda, T.; Sato, F. *Tetrahedron Lett.* **1996**, *37*, 1253.

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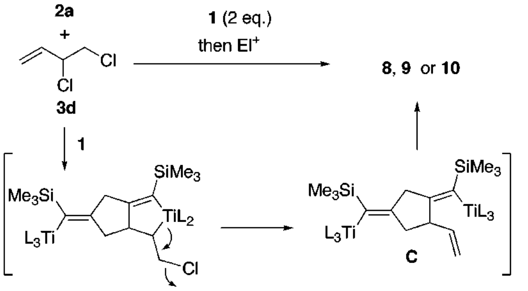
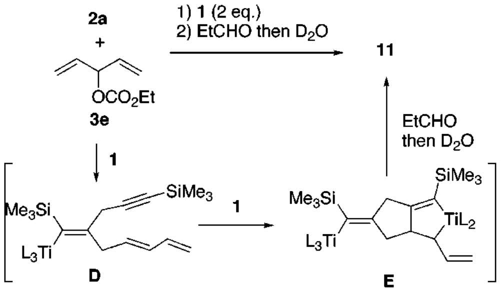
[8] Reviews for synthetic reactions mediated by the titanium(II) reagent: Sato, F.; Urabe, H.; Okamoto, S. *Pure Appl. Chem.* **1999**, *71*, 1511. Sato, F.; Urabe, H.; Okamoto, S. *Synlett* **2000**, 753. Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835.

10.1021/ja0155837 CCC: $20.00

Scheme 2



Scheme 3

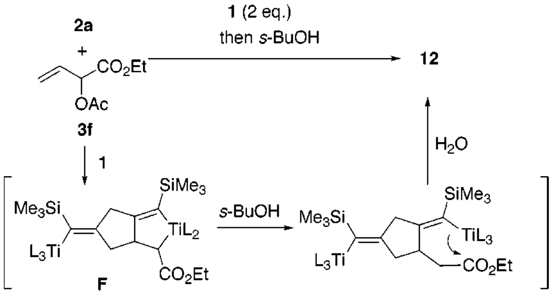


carbon bonds, i.e., two Ti−C(sp^2) bonds, one of which comprises a titanacyclopentene portion, and one Ti−C(sp^3) bond, interestingly, the reaction with aldehydes such as benzaldehyde and propanal proceeded regioselectively at the titanated sp^2-carbon present in the titanacyclopentene to afford the addition products **6** and **7**, respectively (entries 3 and 4 in Table 1).

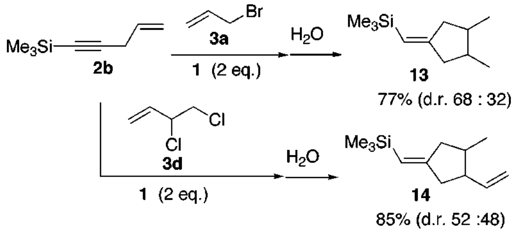
The respective reactions of steps 1 and 2 in Scheme 1 are well established;[2,5] however, it is rather surprising, and fortunate, that the reaction proceeded in good order, and afforded little, if any, other conceivable byproducts such as homo-coupling products of the starting compounds or the cross-coupling products between **A** and **2a** or **3a**. The production of compound **B** is also noteworthy, since the synthesis and reactivity of polymetalated organic compounds have attracted considerable interest.[10,11]

Other representative examples of the **1**-mediated tandem reaction are summarized in entries 5−11 in Table 1. In regard to the starting allyl compound, allyl acetate **3b** and allyl carbonate **3c** can be used equally as well as allyl halide **3a** (entries 5 and 6). The tandem coupling reaction of **2a** and 3,4-dichloro-1-butene (**3d**) proceeded smoothly; however, in this case, further elimination reaction from the resulting titanabicyclic intermediate[4] followed to afford bistitanated compound **C** nearly exclusively as shown in Scheme 2, thus furnishing products **8**, **9**, and **10**, after hydrolysis, deuteriolysis, and iodinolysis, respectively, as shown in entries 7, 8, and 9 in Table 1. The reaction of **2a** with 1,4-pentadien-3-yl carbonate (**3e**) afforded the titanacyclized product **E** via **D** as shown in Scheme 3, which has a reactive allylic titanium bond, and thus, as expected, its reaction with an aldehyde occurs at the allylic position in a regioselective way[6] to afford, after deuteriolysis, **11** as shown in entry 10 in Table 1. The result given in entry 11 in Table 1, showing the production of bicyclic ketone **12** from **2a** and ethyl 2-acetoxy-3-butenoate (**3f**) (after treatment of the reaction mixture with *sec*-BuOH), can be explained by the reaction mechanism illustrated in Scheme 4.

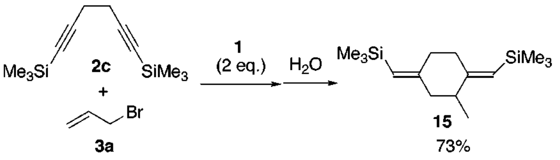
Scheme 4



Scheme 5



Scheme 6



Thus, **1**-mediated reaction of **2a** and **3f** afforded organotitanium compound **F**, which on treatment with *sec*-BuOH resulted in regioselective protonation and the following intramolecular acyl substitution.[7]

The present tandem reaction is not restricted to the reaction with diyne **2a**. Thus, as shown in Scheme 5, the reaction of 1-(trimethylsilyl)pent-4-en-1-yne (**2b**) with allyl compounds such as **3a** and **3d** in the presence of 2 equiv of **1** afforded, after hydrolysis, tandem coupling products **13** and **14**,[12] respectively. The formation of cyclohexane derivatives is also possible by starting with 1,6-bis(trimethylsilyl)-1,5-hexadiyne (**2c**): thus, **2c** and **3a** reacted smoothly with **1** in a tandem fashion to afford **15**[12] (Scheme 6).

In summary, a divalent titanium reagent Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX (**1**) has been demonstrated to mediate tandem inter- and intramolecular reactions of diynes or enynes **2** and allylic compounds **3**, providing a variety of functionalized cyclopentanes and cyclohexanes. Further investigation on the scope of the present reaction is under way in our laboratory.

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Supporting Information Available: Experimental procedures and spectral data for **4**−**15** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) See Supporting Information.

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(11) Marek, I. *Chem. Rev.* **2000**, *100*, 2887−2900. Averbuj, C.; Kaftanov, J.; Marek, I. *Synlett* **1999**, 1939.

(12) The olefinic geometry of **14** and **15** is presumed based on the expected organometallic intermediate.