Tetrahedron Letters 49 (2008) 6655–6658

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Dialkyltitanium-mediated titanation of conjugated 1,3-butadiynes and its coupling reactions with aldehydes: a facile synthesis of stereodefined enynes and *trans*-enynols

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ARTICLE INFO

Article history:
Received 25 July 2008
Revised 1 September 2008
Accepted 9 September 2008
Available online 11 September 2008

Keywords:
Dialkyltitanium complex
Titanium–butadiyne complex
Coupling
Oxatitanacyclopentene
trans-Enynol

ABSTRACT

A highly efficient and convenient method for the selective titanation of 1,3-butadiynes using $Ti(O^iPr)_4/{}^nBuLi$ reagent has been developed. The method provided a facile synthesis of enynes and *trans*-enynols in a well-stereodefined manner.

The organometallic chemistry of group 4 metal complexes with 1,3-butadiynes $R(C{\equiv}C)_2R$ and polyynes $R(C{\equiv}C)_nR$ has attracted considerable attention owing to their fascinating structural features, their unique M–C bonding, and their unusual capacity to induce highly selective transformation reactions.[1–4] Recently, we have investigated the intermolecular cross-coupling of α-alkynylated zirconacyclopentenes[5] prepared by the reaction of zirconocene-ethylene complex with 1,3-butadiynes with unsaturated compounds, which afforded a regio- and stereocontrollable synthesis of *trans*-enediynes.[5a] We have also shown that zirconium-mediated coupling of 1,3-butadiynes with aldehydes or ketones provides efficient access to *cis*-[3]cumulenols.[5b] These unusual and interesting results prompted us to study the formation and the reactivities of other group 4 metal complexes such as titanium–butadiyne complexes. Sato et al. had reported that a site-selective mono-titanation of coujugated 1,3-butadiynes has been achieved through a Ti(II) alkoxide reagent ($Ti(O^iPr)_4/2^iPrMgCl$).[6] However, the thus formed Ti(II)–butadiyne complexes are thermally unstable and can only be used below −30 °C, and the subsequent coupling with aldehydes also need to proceed at low temperature of −50 °C. On the other hand, Eisch and Gitua reported[7a] that thermally stable Ti(II)–alkyne (only mono alkynes have been used) complexes could be generated through a $Ti(O^iPr)_4/2^nBuLi$ (or $Bu_2Ti(O^iPr)_2$) reagent.[7] These works prompted us to develop an efficient and convenient method for the regioselective titanation of 1,3-butadiynes. In this Letter, we demonstrated that Ti(II)–butadiyne complex could be readily formed and thermally stable at room temperature using $Bu_2Ti(O^iPr)_2$, and the subsequent coupling with aldehydes could also be performed conveniently at room temperature.

As shown in the Scheme of Table 1, the alkoxytitanium–butadiyne complexes **2** and/or **3** could be successfully generated by $Ti(O^iPr)_4/2^nBuLi$ system (Table 1). The procedure is operationally convenient and practical: to a solution containing 1,3-butadiyne **1** and 1.25 equiv $Ti(O^iPr)_4$ in THF at −78 °C was added 2.5 equiv *n*-BuLi, the mixture was then warmed up to room temperature and stirred at the same temperature for 1 h. After quenching the mixture by 3 N HCl, *cis*-enynes **4** and/or **5** were formed in good yields and in high purity. The results also indicated a selective mono-titanation that occurred under these conditions. As proposed by Eisch and Gitua in Ti(II)–monoalkyne complex formation reactions, the highly efficient titanation in this case might be due to the strong coordination ability of the butadiynes, which facilitates a reductive elimination of an octahedral-like transition state,[7a] leading to the Ti(II)–butadiyne complex or titanacyclopropene intermediates like **2** and **3**. A wide range of 1,3-butadiynes, including TMS-, TBS-(*tert*-butyldimethylsilyl), alkyl-, and aryl-substituted ones, participated in this titanation reaction, furnishing the corresponding enynes in 53–90% yields (Table 1). Moreover, in the case of unsymmetrically substituted butadiyne **1f**, titanation selectively occurred at the acetylenic moiety substituted with an

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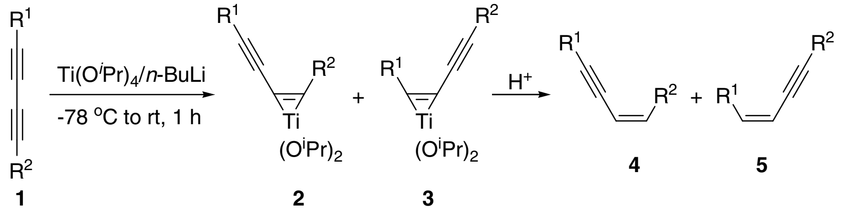
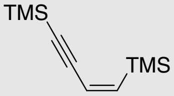
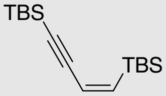
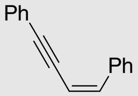
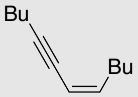
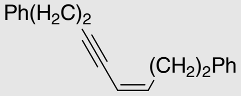
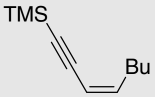
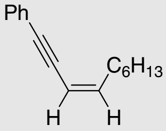
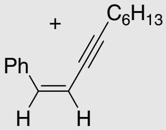
doi:10.1016/j.tetlet.2008.09.042

Table 1

Regioselective mono-titanation of conjugate butadiynes



Entry	R^1—≡—≡—R^2	Product		Yield[a] (%)
1	TMS—≡—≡—TMS **1a**		**4a**	56
2	TBS—≡—≡—TBS **1b**		**4b**	90
3	Ph—≡—≡—Ph **1c**		**4c**	77
4	Bu—≡—≡—Bu **1d**		**4d**	53
5	Ph(CH$_2$)$_2$—≡—≡—(CH$_2$)$_2$Ph **1e**		**4e**	68
6	TMS—≡—≡—Bu **1f**		**4f**	72[b]
7	Ph—≡—≡—C$_6$H$_{13}$ **1g**	 + 	**4g** **5g**	9 55

[a] Isolated yields.

[b] The product was concomitant with small amount of byproduct.

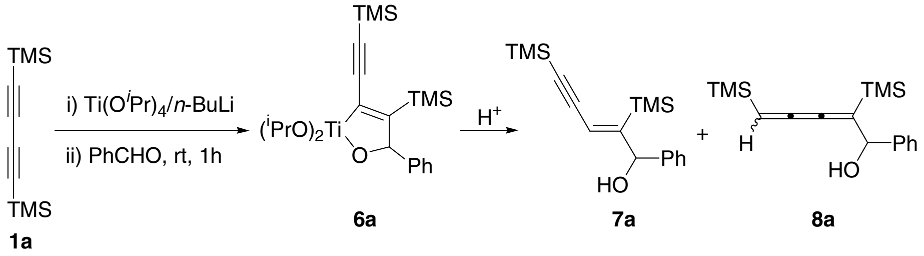
alkyl group due to the less steric effect caused by alkyl group compared with a trimethylsilyl group (Table 1, entry 6). However, when phenyl, hexyl-substituted butadiyne **1g** was employed, the major product was enyne **5g** derived from the coordination of phenyl acetylenic moiety to titanium (Table 1, entry 7). This may be due to the ability of the aryl group for the stabilization of a Ti–Csp^2 bond in the Ti(II)–butadiyne complex **3**.

The Ti(II)–butadiyne complexes **2** and **3** formed in situ are valuable intermediates for further transformations. To demonstrate the utility of these complexes, we first carried out the coupling reaction of **1a** with benzaldehyde. Thus, addition of 1 equiv of benzaldehyde to the reaction mixture containing titanacyclopropene intermediate afforded oxatitanacyclopentene[8,9] **6a**, which was hydrolyzed to give a mixture of *trans*-enynol **7a** and cumulenol **8a** (Table 2). The structure of enynol **7** has been confirmed by 2D NOESY spectrum of **7a** and several products listed in Table 3, and also by X-ray crystallographic analysis of the ester derivative of compound **7g**.[10] It is interesting to note that the product distribution can be influenced by the quenching reagent. While 3 N HCl afforded **7a** and **8a** in a ratio of 83:17, the use of H$_2$O and saturated NaHCO$_3$ produced **7a** in a high selectivity ($\geqslant$94:6).[11]

The coupling reaction could be applied to a variety of aldehydes. As shown in Table 3, by quenching the reaction mixture with saturated NaHCO$_3$, the *trans*-enynol **7** was selectively generated in

Table 2

Optimization studies for the selective coupling of conjugated butadiyne **1a** with aldehyde



Entry	Quenching reagent	Yield (%) of **7a** and **8a**[a]	**7a:8a**[b]
1	3 N HCl	64	83:17
2	H_2O	69	96:4
3	Satd $NaHCO_3$	68[c]	94:6

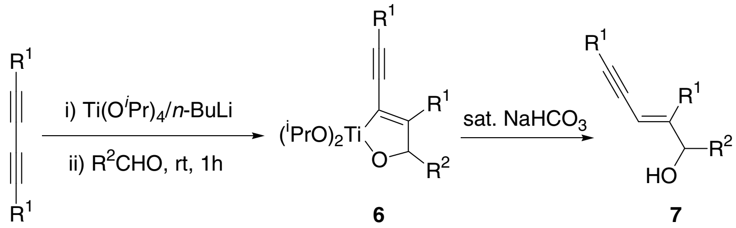
[a] Combined NMR yields.

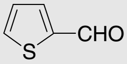
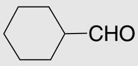
[b] Determined by ^{1}H NMR. Compound **8a** was obtained as a single stereoisomer, the *E* or *Z* configuration of this compound has not been assigned.

[c] Compound **7a** was isolated in 52% yield.

Table 3

Selective coupling of conjugated 1,3-butadiynes with aldehydes



Entry	R^1		R^{2}CHO	Product	Yield[a] (%)
1	TMS	**1a**	PhCHO	**7a**	52
2	TBS	**1b**	PhCHO	**7b**	85
3	TBS	**1b**	p-MeOC$_6$H$_4$CHO	**7c**	85
4	TBS	**1b**	p-ClC$_6$H$_4$CHO	**7d**	74
5	TBS	**1b**		**7e**	81
6	TBS	**1b**		**7f**	81[b]
7	Ph	**1c**	PhCHO	**7g**	67
8	Bu	**1d**	PhCHO	**7h**	55
9	Ph(CH$_2$)$_2$	**1e**	PhCHO	**7i**	68

[a] Isolated yields.

[b] Containing two regioisomers in a ratio of 92:8 after column chromatography. Pure **7f** could be obtained in 69% yield after recrystallization.

good to high yields. The aryl aldehydes bearing electron-donating or electron-withdrawing substituent were all compatible with this reaction, furnishing **7c** and **7d** in 85% and 74% yields, respectively, (Table 3, entries 3 and 4). A heterocyclic group could also be incorporated into the final product, and the desired enynol **7e** was obtained in 81% yield (Table 3, entry 5).

When unsymmetrically substituted butadiynes **1f** and **1g** were employed, regioselective coupling reactions have been observed. Silylated butadiyne **1f** afforded **7j** as a sole product in 63% yield. The regioselectivity in this case is in sharp contrast with Sato's result, in which C–C bond formed at the olefinic carbon having the alkynyl group.[6] The phenylated butadiyne **1g** afforded **7k** as a major isomer (Fig. 1).

The oxatitanacycle **6** could be further confirmed by deuteriolysis or iodinolysis of the metal intermediate, which provided a deuterated compound **7b–d** in 86% yield with excellent deuterium incorporation ($D = 97\%$) and an iodinated product **10** in 66% yield, respectively (Scheme 1). Interestingly, iodination of the oxatitanacycle derived from a silyl-butadiyne **1b** did not afford the desired iodinated enynol, instead, a butadiyne derivative **11** was formed in good yields, presumably via a Brook rearrangement mechanism (Scheme 2).[12]

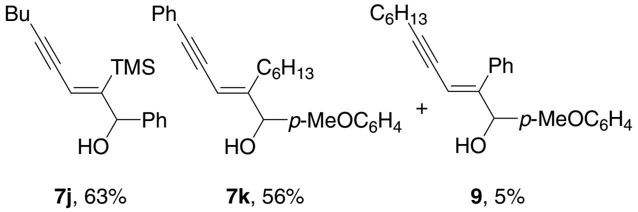
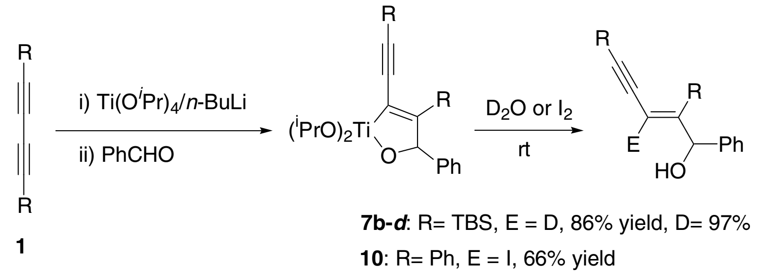
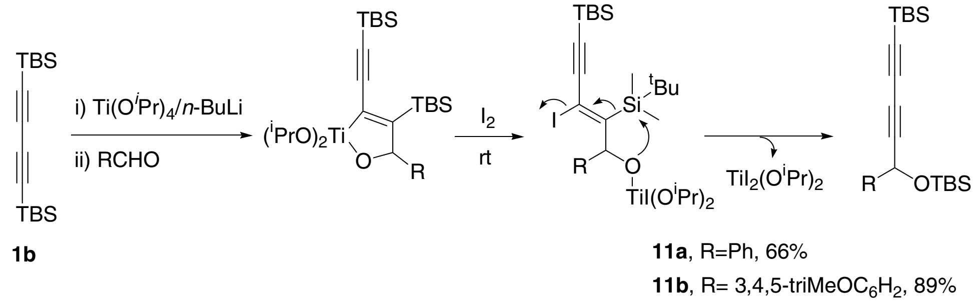


Figure 1.

In summary, we have developed an efficient and convenient method for the selective titanation of 1,3-butadiynes using Ti(O^{i}Pr)$_4$/^{n}BuLi reagent. The method provided a facile synthesis of



Scheme 1.



Scheme 2.

enynes and enynols in a well-stereodefined manner. Further research to explore the new synthetic utility of these titanacycle intermediates is currently underway.

Acknowledgments

We thank the National Natural Science Foundation of China (Grant Nos. 20672133 and 20732008), Chinese Academy of Science, Science and Technology Commission of Shanghai Municipality (Grant Nos. 08QH14030 and 07JC14063), and the Major State Basic Research Development Program (Grant No. 2006CB806105) for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.042.

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