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Site-selective mono-titanation of conjugated diynes with a Ti(II) alkoxide reagent. Concise preparation of stereo-defined enynes and dienynes

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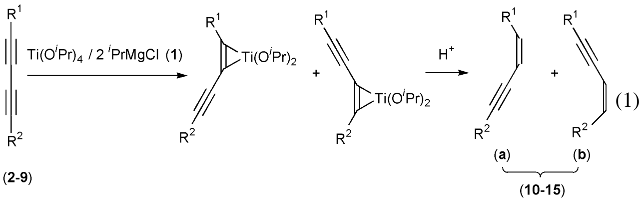
Conjugated diynes underwent selective mono-titanation with a Ti(II) reagent to give 1:1 diyne–titanium alkoxide complexes, which reacted with proton, aldehyde, and another acetylene to give stereo-defined enynes, enynols, and dienynes.

Conjugated enynes, dienynes, and their derivatives are useful intermediates and/or important structural constituents in organic synthesis, natural product chemistry, and materials science.[1–3] There are already many methods available for the synthesis of enynes. However, methods that permit the stereoselective construction of the enyne structure and, at the same time, facile introduction of a necessary substituent(s) to the enyne system in correct array and in one step are notably limited.[1] We report herein such a method by taking advantage of acetylene–titanium alkoxide complexes prepared from acetylenes and $Ti(O^iPr)_4$/2 ^{i}PrMgCl reagent (**1**),[4] which are versatile and economical intermediates for the preparation of various olefins.[5] Thus, we theorized that, if site-selective† mono-titanation of unsymmetrical conjugated diynes is a viable process as well, it should serve for a concise construction of the aforementioned enyne systems as shown in the equations and Tables below. Although several 1:1 *symmetrical* diyne-group 4 metallocene complexes are known,[6] their versatility in organic synthesis has not been amply highlighted. Moreover, site-selective generation of mono-metalated *unsymmetrical* diynes, which is described below, has not been pursued.[7]

First, representative unsymmetrical diynes **2–7**, which are readily available by coupling of two acetylenes,[8] were chosen as the starting material. The feasibility and site-selection of the mono-titanation were investigated [Eqn. (1) in Table 1)].‡ The titanation of a couple of symmetrical diynes **8** and **9** was also carried out for comparison. The site-selection for diynes **2–9**, which was estimated after hydrolysis of the resultant acetylene–titanium complexes, is summarized in Table 1. All cases, except entries 4 and 6, cleanly afforded enynes uncontaminated by the corresponding dienes arising from exhaustive titanation, which means that mono-titanation is an exclusive path under these reaction conditions.[9] More importantly, the complexation occurs with excellent site-selectivity for a few unsymmetrical diynes. Thus, diyne **2** having silyl and alkyl substituents generated the titanium complex, in which the titanium is placed at the alkylacetylene moiety, to give a single enyne **10** after hydrolysis (entry 1). Another case is of 2,4-diynoate **6**, for which the triple bond bearing an ester group was selectively titanated to give enyne **13** (entry 5). The origin of these site-selections appears to be mainly steric in the former case, while, in the latter case, it seems to be an electronic effect, as the electron-deficient acetylenic bond (conjugated to ester group) is more reactive to the electron-rich low-valent titanium complex. Contrarily, almost no preference was observed for the reactions with diynes **3** and **4** (entries 2 and 3), both of which involve a phenylacetylene structure. A couple of diynes such as **5** and **7** (entries 4 and 6) did not generate the expected acetylene–titanium complex and gave a mixture of messy products after aqueous workup.

Table 1 Generation of mono-titanated diynes estimated by their hydrolysis to enynes1

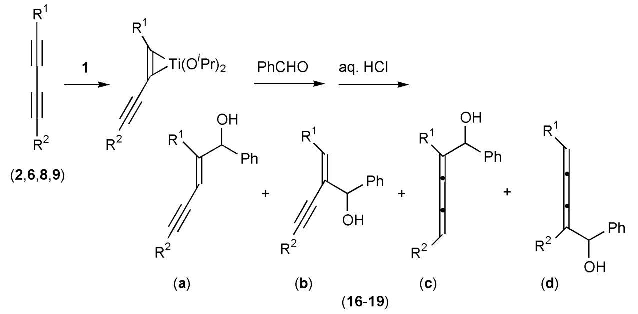


	Diyne			Product (Enynes)		
Entry	R^1	R^2		Yield (%)		**a**:**b**
1	C_6H_{13}	Me_3Si	**2**	85	**10**	100:0
2	Ph	Me_3Si	**3**	81	**11**	57:43
3	Ph	C_6H_{13}	**4**	65	**12**	50:50
4	Ph	$CO_2{}^tBu$	**5**	^{a}		
5	$CO_2{}^tBu$	C_6H_{13}	**6**	81	**13**	100:0
6	$CO_2{}^tBu$	Me_3Si	**7**	^{a}		
7	Me_3Si	Me_3Si	**8**	85	**14**	—
8	C_4H_9	C_4H_9	**9**	66	**15**	—

[a] Intractable mixture, in which the desired enyne is a minor constituent, was recovered.

Having chosen diynes **2**, **6**, **8**, and **9**, which generate a single acetylene–titanium complex, we then focused our attention on the introduction of a substituent(s) to the enyne system based on the electrophilic reaction to the carbon–titanium bonds.[4] Thus,

Table 2 Results of the addition of diyne–titanium complexes to aldehydes



	Diyne			Product		
Entry	R^1	R^2		Yield (%)		**a**:**b**:**c**:**d**
1	C_6H_{13}	Me_3Si	**2**	85	**16**	0:100:0:0
2	$CO_2{}^tBu$	C_6H_{13}	**6**	57	**17**	55:0:0:45^a
3	Me_3Si	Me_3Si	**8**	79	**18**	79:0:21^a:—
4	C_4H_9	C_4H_9	**9**	61	**19**	100:0:0:—

[a] Obtained as a single stereoisomer, to which the structure (i.e., *E* or *Z*) has not been assigned.

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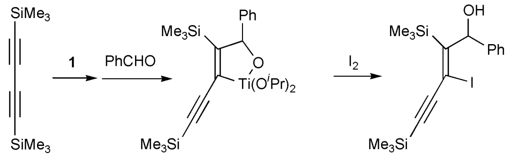
the acetylene complexes derived from the above diynes were allowed to react with an aldehyde, the results of which are summarized in Table 2. Titanium complexes derived from **2** and **9** afforded single enynols **16b** and **19a** (entries 1 and 4, Table 2). It is interesting to note that the position of the reacting carbon center was completely reversed dependent on the remote substituents (alkyl *vs.* silyl) in these cases, which demonstrate a facile, selective synthesis of stereo-defined enynols. A functionalized diyne **6** afforded a mixture of enynol **17a** and cumulenol **17d** (entry 2, Table 2), the latter of which should come from S_E2'-type addition of the aldehyde to the intermediate acetylene–titanium complex. Even the complex from symmetrical diyne **8** afforded a mixture of two isomeric products, enynol **18a**§ and cumulenol **18c**, upon aqueous workup with dilute hydrochloric acid (entry 3). In order to obtain a single product, we looked for a suitable method of workup; and, eventually, we found that iodinolysis of the same reaction mixture cleanly afforded single iodo-enynol **20** as shown in Eqn. (2), which demonstrates the successful double introduction of substituents to the stereo-defined enyne structure.



(2)

(**8**) (**20**) 65% single isomer

Coupling reaction of the acetylene complexes generated from unsymmetrical diynes **2** and **6** with an acetylene[10] successfully afforded the single dienynes **21** and **22** virtually with complete regio- and stereoselectivities (entries 1 and 2 in Table 3). Thus, this transformation provides one of the easiest and most dependable methods for the concise construction of stereo-defined dienynes. It is also noteworthy that the ester group in diyne **6** survived the reaction conditions to allow the preparation of a functionalized dienyne. While symmetrical diyne **9** having alkyl substituents at both termini did not participate in the clean coupling reaction (entry 4), bis-silylated counterpart **8** afforded the dienyne **23**§ in good yield (entry 4).

In summary, the viability and site-selectivity of mono-titanation of diynes as well as the regiochemistry of their coupling reactions with an aldehyde or acetylene have been disclosed. The observation described herein is informative for further manipulation of acetylene–titanium alkoxide complexes and provides a useful method for the construction of regio- and stereo-defined enynes, dienynes, and their substituted or functionalized derivatives from readily available conjugated diynes.

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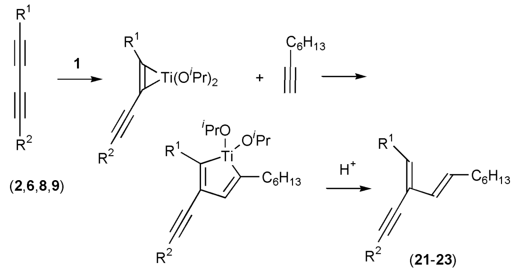
Table 3 Coupling of diyne–titanium complexes with 1-octyne



	Diyne			Product (Dienynes)	
Entry	R¹	R²		Yield (%)	
1	C_6H_{13}	Me_3Si	**2**	70	**21**
2	$CO_2{}^iBu$	C_6H_{13}	**6**	75	**22**
3	Me_3Si	Me_3Si	**8**	70	**23**
4	C_4H_9	C_4H_9	**9**	*a*	

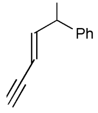
[a] Intractable mixture, in which the desired enyne is a minor constituent, was recovered.

Notes and references

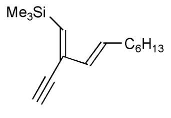
† Site-selectivity refers to the discrimination between the two acetylenic bonds of a diyne.

‡ General procedure. To a stirred solution of a conjugated diyne (0.579 mmol) and $Ti(O^iPr)_4$ (0.723 mmol) in 3 mL of Et_2O was added ^iPrMgCl (solution in Et_2O, 1.45 mmol) at −78 °C under argon to give a yellow homogeneous solution. The solution was warmed to −50 °C over 1 h. After stirring at −50 °C for an additional 4 h, the reaction mixture was quenched with dilute HCl to give crude enynes. Alternatively, in place of the simple hydrolysis, the reaction mixture was again cooled to −70 °C and benzaldehyde or 1-octyne was added. The solution was stirred at −50 °C for an additional 30 min. Then, aqueous workup as above and standard purification gave the products.

§ Exhaustive or selective desilylation of products **18a** and **23** with Bu_4NF in THF afforded new enyne units **24** and **25** in 87 and 100% yields, respectively.



(**24**)



(**25**)

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