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An Alkoxide-Directed Carbometalation of Internal Alkynes

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The discovery and development of regio- and stereoselective carbon−carbon and carbon−heteroatom bond-forming reactions is an ongoing challenge in organic chemistry. A common strategy for the design of such transformations targets preassociation of a reagent with a substrate as a means to render a reaction intramolecular.[1] Reactions that proceed by such preorganization often provide products with exquisite levels of regio- and stereoselection as a function of the highly ordered transition-state geometries through which they proceed. Directed carbon−carbon bond construction represents a growing class of substrate-directable reactions with great potential to enable the efficient construction of complex organic architecture.[1−4] Of these, directed carbometalation reactions have the potential to be among the most powerful, as regio- and/or stereoselective carbon−carbon bond construction is accompanied by the formation of a new organometallic species with a diverse reactivity profile. However, only a few examples of directed carbometalation reactions have been described, and many of these proceed under vigorous reaction conditions.[1,4] We herein present an approach to the control of site selectivity in intermolecular C−C bond formation between two differentially functionalized internal alkynes that defines the utility of alkoxide tethering as a means to control regioselection in group 4 metal-mediated bond construction.

Intermolecular carbometalation reactions of terminal alkynes with preformed metallacyclopropenes are known.[5] However, substrate scope in these reactions is limited based on factors influencing regioselection and reactivity. For example, regioselection across the internal alkyne is typically controlled by the relative steric environment about each side of the metallacyclopropene (Figure 1), with only a few substituents known that provide high levels of selectivity.[5] Additionally, to have sufficient reactivity with the preformed metallacyclopropene, the structure of the second π-component is generally limited to terminal alkynes.[5a]

Given the challenges associated with accomplishing site-selective C−C bond formation across internal alkynes, we sought an alternative means to control regioselection in such functionalization reactions. We speculated that the participation of a tethered alkoxide[6] on the second π-electrophile in a group 4 metal alkoxide-mediated coupling reaction could provide a unique means to control regioselection in carbometalation processes across internal alkynes. As depicted in Figure 2, preformation of a titanacyclopropene **2** via exposure of the corresponding symmetrical alkyne to the combination of a titanium(IV) alkoxide and Grignard reagent[7] followed by exposure to an unsaturated alkoxide **1** was anticipated to result in rapid transesterification and transiently provide the mixed titanate ester **3**. Ensuing intramolecular carbometalation would then furnish the stereodefined bicyclic titanacyclopentadiene **4**, which on protonation would deliver the stereodefined 1,3-diene **5** as a single regioisomer.

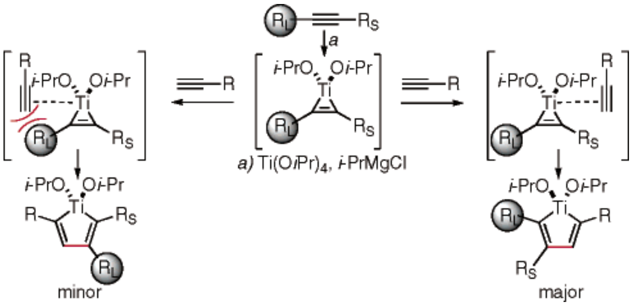

Figure 1. Background to the control of regioselection in group 4 metal-mediated coupling reactions of internal alkynes with terminal alkynes.

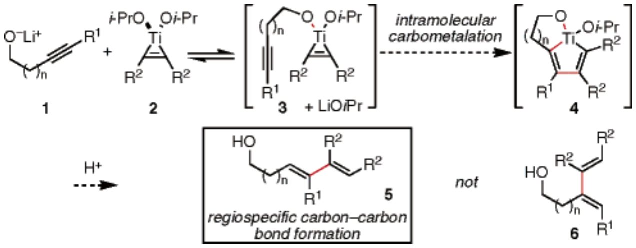

Figure 2. Directed carbometalation reaction for 1,3-diene synthesis.

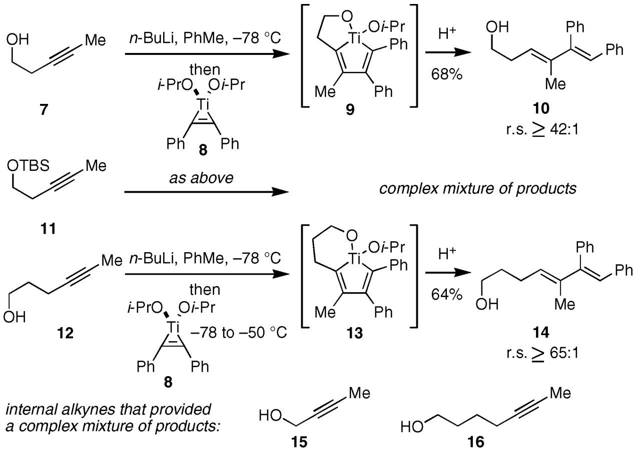

Figure 3. Presence of the tethered alkoxide and the length of the tether influence reactivity as well as regioselectivity.

On the basis of this proposal, we examined unsaturated alcohols of general structure **1** in coupling reactions with symmetric titanacyclopropenes **2**. As illustrated in Figure 3, deprotonation of the unsaturated alcohol **7**, followed by exposure to the preformed metallacyclopropene **8** (formed by treatment of diphenylacetylene with Ti(Oi-Pr)$_4$ and C_5H_9MgCl, PhMe −78 to −50 °C) and aqueous workup, provided the stereodefined diene **10** with high regioselection (rs ≥ 42:1).[8] Interestingly, in a related experiment, exposure of an internal alkyne lacking a free hydroxyl (**11**) to the preformed titanium alkyne complex **8** led only to a complex mixture of products. As such, the tethered alkoxide plays a central role in determining regioselection, as well as in realizing a productive mode of reactivity, in these C−C bond-forming reactions.

The significance of tether length was then explored. Whereas the bis-homopropargylic alcohol **12** provided similarly high levels

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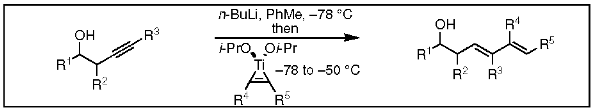
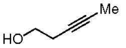
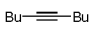
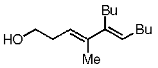
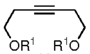
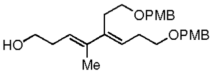
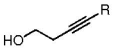
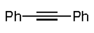
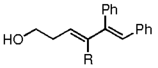
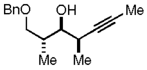
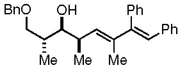
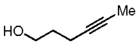
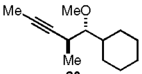
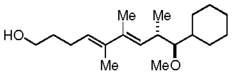
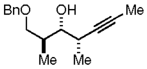
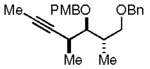
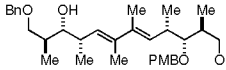
Table 1



entry	alkynyl alcohol	first š-electrophile[a]	yield	product[b]
1	 **7**	 **17**	52	 **18**
2	**7**	 **19** R¹= PMB	52	 **20**
3	 R = Et; **21**		55	 R = Et; **23**
4	R = *i*-Pr; **24**	**22**	57	R = *i*-Pr; **25**
5	R = *t*-Bu; **26**		51	R = *t*-Bu; **27**
6	 **28**	**22**	54	 **29**
7	 **12**	 **30**	55	 **31**
8	 ***ent*-28**	 **32**	58	 **33**

[a] These internal alkynes serve as the substrates for the formation of the reactive titanacyclopropene. [b] ^{1}H NMR spectra of these coupling reactions provided no evidence for the production of a second regioisomer.

of regioselection in coupling reactions with the titanacyclopropene **8** (rs ≥ 65:1),[8] alkynes **15** and **16** were not suitable substrates for this reaction, each leading to a complex mixture of products.

The generality of this directed carbometalation reaction was then investigated (Table 1). Symmetrical metallacyclopropenes derived from **17** and **19** (Ti(O*i*-Pr)$_4$, C$_5$H$_9$MgCl, PhMe, −78 to −50 °C) were found to be similarly effective coupling partners with the homopropargylic alcohol **7** and provided the stereodefined 1,3-dienes **18** and **20** (entries 1 and 2). The substitution of the unsaturated alcohol did not significantly influence the effectiveness of this site-selective bond construction. As depicted in entries 3−5, the ethyl-, isopropyl-, and *t*-Bu-substituted alkynes **21**, **24**, and **26** were all viable substrates for this reaction and provided the stereodefined tetrasubstituted 1,3-dienes **23**, **25**, and **27** in coupling reactions with diphenylacetylene. In all cases, the new carbon−carbon bond is formed at the site distal to the free hydroxyl, independent of substitution on the alkyne.

The role of substitution along the chain bearing the homopropargylic alkoxide was then explored. Coupling of the syn−anti homopropargylic alcohol **28**[5b] with the symmetrical metallacycle derived from diphenylacetylene **22** provided diene **29** in 54% yield, again as the only observable regioisomer (entry 6).

Finally, this directed carbometalation was extended to the coupling of two different unsymmetrical internal alkynes. As illustrated in entry 7, directed carbometalation of bis-homopropargylic alcohol **12** with internal alkyne **30** provided diene **31** in 55% yield. Similarly, the syn−anti homopropargylic alcohol ***ent*-28** was coupled to internal alkyne **32**[5b] to provide the complex tetrasubstituted 1,3-diene **33** in 58% yield (entry 8).

Overall, we have defined an approach to control regioselection in intermolecular group 4 metal-mediated C−C bond formation based on alkoxide tethering. Our preliminary studies in this area have resulted in a mild method for the stereoselective synthesis of tetrasubstituted 1,3-dienes via a new regiospecific directed carbometalation reaction. We further speculate that this general control element, defined by transient preorganization of organic architecture around a group 4 metal center, can provide a unique means for the control of *reactivity* and *selectivity* in new carbon−carbon bond-forming reactions. Studies aimed at the discovery and development of such processes are currently underway, and progress made along these lines will be reported in due course.

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Supporting Information Available: Experimental procedures and tabulated spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The other regioisomer possible was prepared independently and compared to the product mixture obtained from this reaction. The regioselectivity was then determined based on the signal-to-noise ratio of the spectrum. See Supporting Information for details.

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