Synthetic Methods

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A Site- and Stereoselective Intermolecular Alkene–Alkyne Coupling Process**

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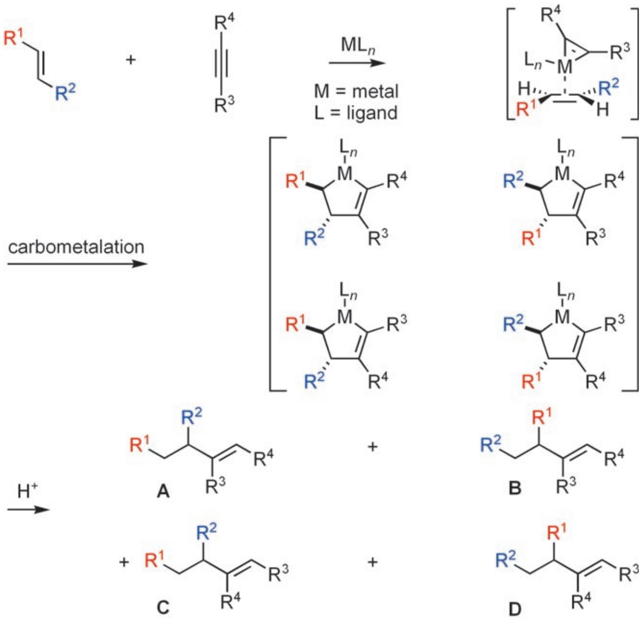
Intermolecular coupling reactions that proceed through carbon–carbon (C−C) bond formation are central to modern organic chemistry.[1] The subset of these reactions that proceed through site- and stereoselective coupling of substituted π bonds (C=C, C≡C) typically require the unsaturated unit(s) to be electronically activated or sterically differentiated. In our efforts to identify highly selective metal-mediated pathways for coupling *unactivated* and differentially functionalized π systems, we recently defined a regioselective and stereospecific intermolecular coupling reaction of differentially functionalized internal alkynes that proceeds via Group 4 metallacyclopentadienes.[2] The corresponding intermolecular coupling reaction between an unactivated polysubstituted alkene and an internal alkyne represents a potentially more significant and correspondingly more difficult problem.[3,4] This mode of coupling is complicated by: 1) the lower reactivity of the C=C bond in reactions with metal–carbon σ bonds, 2) the stability of the intermediate metallacyclopentenes, and 3) the potential of generating numerous regio- and stereoisomeric products **A**–**D** (Scheme 1).[5,6] In fact, aside from the classical cycloaddition reactions, intermolecular C−C bond formation through site- and stereoselective functionalization of unactivated, polysubstituted olefins has eluded organic chemists.[3] A general means to accomplish this transformation with high regio- and stereocontrol would define a versatile new bond construction for organic synthesis (Scheme 1).

Carbometalation, the process by which an organometallic reagent adds across a π system and generates one C−C bond and one carbon–metal bond, represents a powerful means to accomplish complex fragment-union processes; C−C bond formation is accompanied by the formation of a new complex organometallic species possessing a diverse reactivity profile. However, to date, this type of functionalization reaction has been of limited utility in *bimolecular* olefin functionalization because of both the low reactivity of polysubstituted olefins in reactions with metal–carbon σ bonds, and difficulties in controlling regio- and stereoselection in the intermolecular carbometalation event (Scheme 1; **A**–**D**).[4] Here, we describe a new class of bimolecular coupling reactions that exploit the unique reactivity of titanium alkoxide–alkyne complexes,[5,6] and provides a general means for coupling complex organometallic reagents and unactivated disubstituted olefins (*E*, *Z*, and 1,1-disubstituted) with high levels of regio- and stereocontrol.



Scheme 1. Coupling of disubstituted olefins with internal alkynes through intermolecular carbometalation. M = metal, L = ligand.

A common strategy to lower the energy barrier for intermolecular reactions is to preassociate the reactive partners and hence render the bimolecular reaction intramolecular. With this notion, we speculated that exposure of an unsaturated alkoxide **1** to a preformed ($(i\text{PrO})_2$Ti)–alkyne complex **2** could result in rapid transesterification to afford a transient mixed titanate ester **3** (Scheme 2).[2] This mode of association was further anticipated to facilitate carbometalation across the substituted olefin en route to a functionalized metallacyclopentene.[3a–d] Such intramolecular carbometalation may proceed to provide either a fused or bridged bicyclic metallacycle **4** or **5**, protonation of which would deliver the regioisomeric product **6** or **7**, respectively.

Based on this proposal, the reactivity of unsaturated alkoxides **1** in coupling reactions with symmetric titanacyclopropenes (generated in situ by treatment of the corresponding alkyne with $Ti(OiPr)_4$ and cyclopentylmagnesium chloride, toluene, −78 to −30 °C) was examined. As depicted in Scheme 3, reaction of the homoallylic alkoxide derived from **8**

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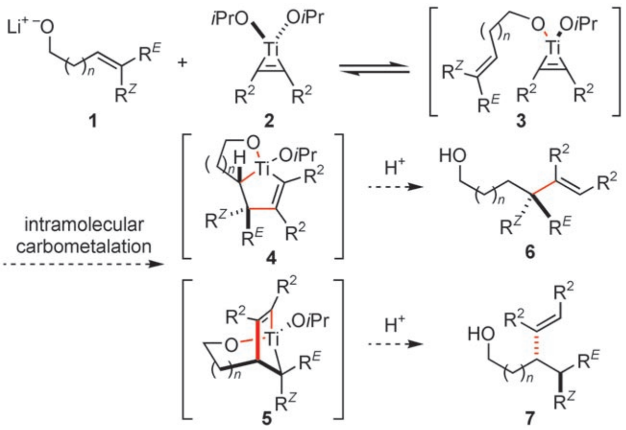
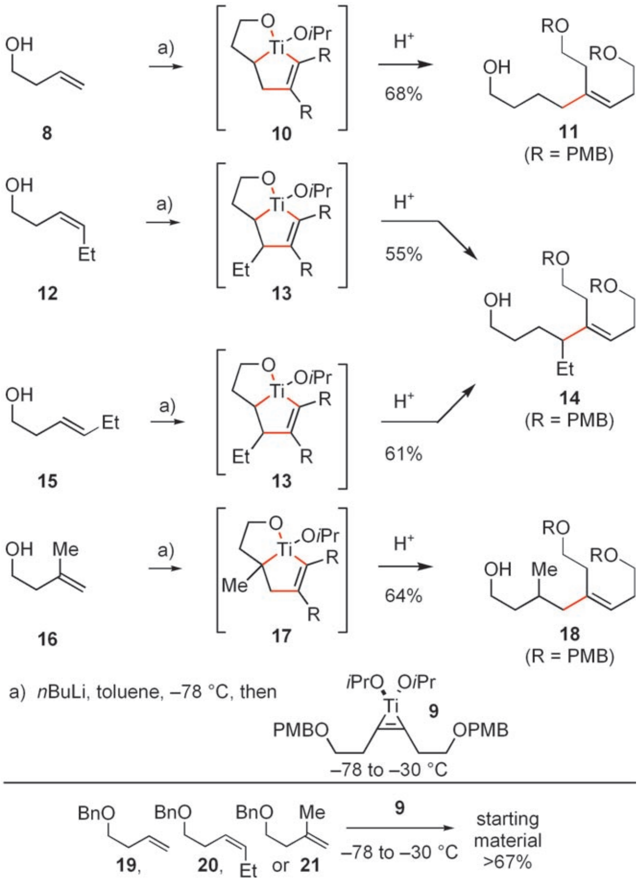


Scheme 2. A directed coupling of polysubstituted olefins and internal alkynes.



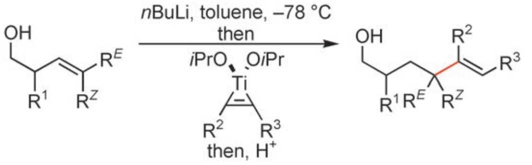
Scheme 3. Intermolecular alkoxide-directed coupling of substituted olefins and alkynes. PMB = *para*-methoxybenzyl.

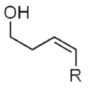
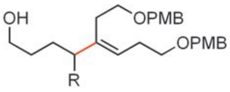
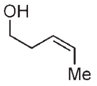
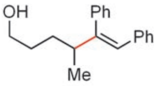
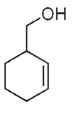
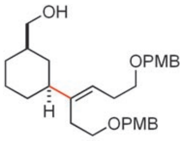
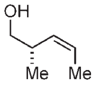
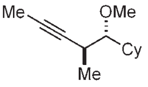
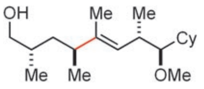
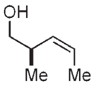
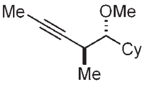
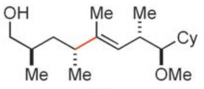
with the metallacyclopropene **9** provided the coupled product **11** as the only observable regioisomer—consistent with the formation of an intermediate fused bicyclic metallacyclopentene **10** in preference to a bridged bicyclic isomer (that is, **5**; Scheme 2). This preference was observed in the coupling of the two internal olefins **12** and **15**, which indicates that substitution at the terminus of the double bond does not override the directing effect of the homoallylic alkoxide. The 1,1-disubstituted olefin **16** was also shown to be a viable coupling partner in this directed carbometalation and furnished the branched product **18** as a single regioisomer.

Interestingly, attempted coupling of the unsaturated benzyl ethers **19–21** with the titanium–alkyne complex **9** did not lead to efficient C–C bond formation. In each case, starting material was recovered in greater than 67% yield. These control experiments confirm the significance of the tethered alkoxide in enabling reactivity, while also providing a means to control regioselectivity in the alkene–alkyne coupling reactions.

Regioselective carbometalation reactions were also effective with differentially functionalized homoallylic alcohols. The methyl-, benzyl-, and trimethylsilyl-substituted olefins **22**, **23**, and **24** were all compatible substrates for reaction with the titanium–alkyne complex derived from **25**, and each provided regioselective access to the corresponding functionalized trisubstituted olefins **26**, **27**, and **28** (entries 1–3, Table 1).

Table 1: Examples of the regioselective carbometalation reactions.



Entry	Unsaturated alcohol	First π electrophile[a]	Yield [%]	Major regioisomer[b]
				
1	R = Me, **22**	R = PMB, **25**	56	R = Me, **26**
2	R = Bn, **23**		50	R = Bn, **27**
3	R = TMS, **24**		63	R = TMS, **28**
4	 **22**	Ph—≡—Ph **29**	58	 **30**
5	 **31**	**25**	58	 **32**
6[c]	 **33**	 **34**	54	 **35**
7[c]	 **36**	 **34**	51	 **37**

[a] These internal alkynes serve as substrates for the formation of the reactive titanacyclopropene (2 equiv of alkyne: 1 equiv of olefin). Bn = benzyl, Cy = cyclohexyl, TMS = trimethylsilyl. [b] ^{1}H NMR spectra of these reaction mixtures provided no evidence for the production of a second regioisomer. [c] Stereochemistry of the coupled product was assigned by analogy with entry 5, and consideration of allylic 1,3-strain.[8]

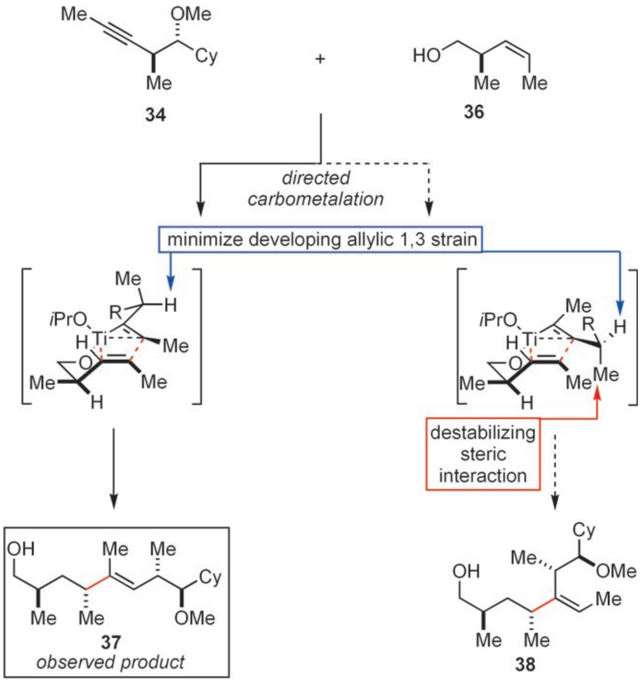
Notably, the coupling process depicted in entry 3 provides a novel convergent route to the synthesis of functionalized allylic silanes **28**.[7] As described in entry 4, directed carbometalation was similarly effective with the titanium–alkyne complex of an aryl-substituted alkyne **29**.

Carbocyclic olefins also serve as substrates for this bimolecular carbometalation reaction. As depicted in entry 5 (Table 1), coupling of homoallylic alcohol **31** with the titanium–alkyne complex derived from **25** furnished the 1,3-*syn*-functionalized carbocycle **32** in 58 % yield. As in previous examples, no evidence was found for the production of regio- or stereoisomeric products.

Entries 6 and 7 (Table 1) further demonstrate the potential of this new carbometalation in stereoselective synthesis. Coupling of homoallylic alcohols **33** or **36** with the titanium–alkyne complex derived from the unsymmetrical internal alkyne **34** proceeded effectively to afford the deoxypropionate products **35** and **37** in 54 and 51 % yield, respectively. In both cases, no evidence was found for the production of a regioisomeric product with respect to either reaction component. Whereas regioselection with respect to the internal olefin **33** or **36** is controlled by the presence of the homoallylic alcohol, regioselective carbometalation of the alkyne component is presumably dictated by the steric difference in the pendent alkyl chains (Scheme 4).

Some limitations were observed in this alkene–alkyne coupling process: 1) bishomoallylic alcohols gave varied yields in coupling reactions with the titanium–alkyne complex of **25**, and 2) allylic and trishomoallylic alcohols gave complex product mixtures in the coupling reactions attempted with the titanacyclopropene derived from **25**.

Overall, we have described a general solution to the problem of bimolecular carbometalation of unactivated disubstituted olefins. Regioselection is high in all cases, with C−C bond formation occurring distal to a pendent hydroxy group. We have demonstrated the potential of this reaction for the development of new complex fragment-union processes through simultaneously addressing site- and stereoselective C−C bond formation (entries 5–7, Table 1). Future work will focus on exploring the potential of this new olefin-functionalization process for defining novel fragment-coupling reactions, and the use of these convergent C−C bond-forming reactions in target- and diversity-oriented synthesis.



Scheme 4. A model for regioselection in the alkoxide-directed coupling of internal olefins and differentially substituted internal alkynes.

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