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Cyclopropenes in Metallacycle-Mediated Cross-Coupling with Alkynes: Convergent Synthesis of Highly Substituted Vinylcyclopropanes

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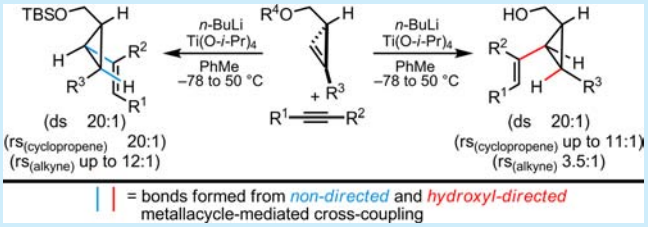
Supporting Information

ABSTRACT: Stereodivergent metallacycle-mediated cross-coupling reactions are described for the synthesis of densely functionalized vinylcyclopropanes from the union of alkynes with cyclopropenes. Strategies explored include hydroxyl-directed and nondirected processes, with the latter of these delivering vinylcyclopropanes with exquisite levels of regio- and stereoselectivity. Challenges inherent to these coupling reactions include diastereoselectivity (with respect to the cyclopropene) and regioselectivity (with respect to both coupling partners).



Convergent coupling by way of site and stereoselective C–C bond formation is arguably among the most powerful strategies for enhancing efficiency in complex molecule synthesis, particularly in the context of natural product synthesis.[1] While this significance is widely appreciated, few classes of reactivity have proven to be of broad utility for such bond construction (i.e., nucleophilic addition to polarized π-bonds, cycloaddition, and metal-catalyzed cross-coupling).[2] With the goal of establishing a class of reactions capable of realizing complementary bond-forming processes to these well-established strategies, we have focused on controlling the course of metallacycle-mediated cross-coupling (Scheme 1A).[2] To date, alkoxide-directed strategies for the union of internal alkynes with a range of other π-systems have been quite successful, with examples including a variety of alkenes, enynes, terminal and internal alkynes, allenes, and carbonyl systems (Scheme 1B).[3] Our recent studies have been focused on expanding substrate scope within this class of reactivity to further develop its broad utility in stereoselective synthesis. Here, we target the development of coupling chemistry capable of delivering highly substituted and stereodefined vinylcyclopropanes—structural motifs that are of great value in stereoselective synthesis (Scheme 1C).[4] Our efforts have resulted in the realization of stereodivergent strategies for alkyne–cyclopropene coupling that deliver vinylcyclopropanes containing a 1,2,3-trisubstituted cyclopropane motif.

Investigations began by contemplating the course of alkoxide-directed coupling between internal alkynes **1** and hydroxymethyl-substituted cyclopropenes **2** (Scheme 2A).[5] While confident that the stereoselectivity of this process would be quite high, with C–C bond formation occurring *syn* to the hydroxymethyl substituent, the regioselectivity with which such a process would functionalize the cyclopropene was less clear. Alternatively, given the high reactivity of the cyclopropene double bond, we expected that it may be possible to conduct the coupling reaction in the absence of a directing group.[6] As illustrated in Scheme 2B, it was expected that the coupling reaction would proceed under steric control, with C–C bond formation occurring *anti* to R^4. While stereoselectivity was thought to be readily controlled, regioselectivity would remain a concern for this non hydroxyl-directed reaction.

Our studies began by exploring the feasibility of hydroxyl-directed metallacycle-mediated coupling between hydroxymethyl-substituted cyclopropenes and internal alkynes. As depicted at the top of Scheme 3, the general reaction process was designed to proceed by initial formation of the Ti–alkyne complex **12** and subsequent addition of the Li–alkoxide of cyclopropene **13**. Rapid and reversible ligand exchange would then ensue to provide a transient mixed titanate ester capable of undergoing intramolecular carbometalation en route to **14**. Finally, protonation of the organometallic intermediate would generate the substituted vinylcyclopropane **15**, a process that was anticipated to proceed with retention of configuration.

Treatment of symmetrical alkyne **16** with the combination of $Ti(O\text{-}i\text{-}Pr)_4$ and *n*-BuLi,[7] followed by addition of the lithium alkoxide of **17** and protonation, led to vinylcyclopropane products in 89% yield and with very high levels of stereoselection; all coupled products had the vinyl and hydroxymethyl substitutents *syn* about the cyclopropane core (eq 1). Interestingly, this coupling reaction proceeded with 3:1 regioselectivity in favor of the 1,2,3-trisubstituted cyclopropane **18**, *a product that is typically the minor isomer in related carbometalation chemistry of cyclopropenes*.[8] As illustrated in eq 2, use of diphenylacetylene led to vinylcyclopropenes with similar stereoselection, in this case with much higher levels of

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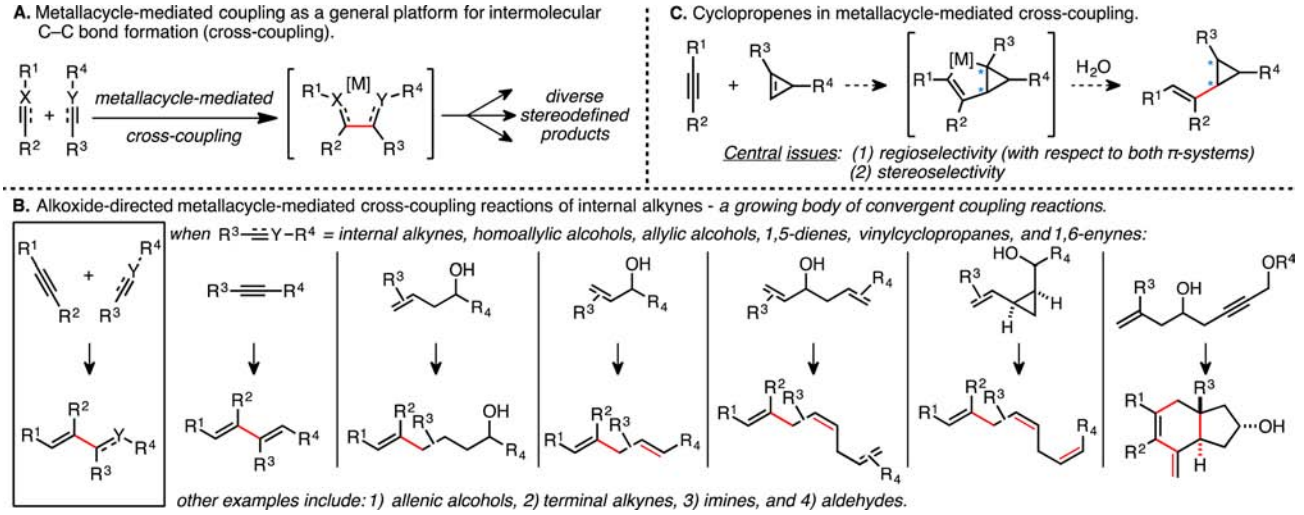
Scheme 1. Introduction to Metallacycle-Mediated Cross-Coupling and Its Potential Utility for the Convergent Synthesis of Vinylcyclopropanes



regioselectivity (11:1), again in favor of the 1,2,3-trisubstituted cyclopropane **21**.

While we were excited to observe regio- and stereocontrol in this new alkoxide-directed metallacycle-mediated cross-coupling, the use of an unsymmetrical alkyne (**23**) in a coupling reaction with cyclopropene **17** led to dampened levels of enthusiasm (eq 3). Here, while stereoselection remained high, the vinylcyclopropane products were produced with low levels of regioselectivity (**24**/**25**/**26** = 6:2:1). Regioselectivity with respect to cyclopropene functionalization was reasonable (**24** + **25**/**26** = 8:1), but regioselectivity with respect to alkyne functionalization was only 3.5:1 (**24** + **26**/**25**).[9]

Moving on, we wondered whether the high reactivity of the cyclopropene π-system would be sufficient to enable non-directed alkyne–"alkene" coupling; *it is well appreciated that in the absence of a directing group substituted alkenes are sluggish to react in metallacycle-mediated coupling chemistry.*[6] As depicted in Scheme 4 (eq 4), non-alkoxide-directed coupling of alkyne **16** with cyclopropene **30** proceeds in 75% yield and delivers the 1,2,3-trisubsituted cyclopropene **31** as the only observed regio- and stereoisomer. Similar success was seen in the coupling of diphenylacetylene **20** with **30**, delivering **32** in 58% yield (eq 5).

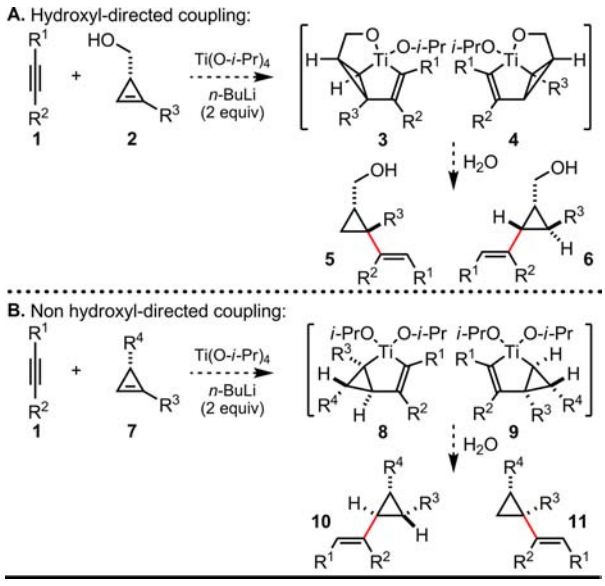
Distinct from earlier attempts to employ unsymmetrical alkynes in coupling reactions with cyclopropenes (eq 3, Scheme 3), union of TMS-propyne **23** with **30** proceeded in 82% yield and delivered an 11:1 mixture of isomeric vinylcyclopropanes (eq 6). Here, regioselectivity with respect to the cyclopropene remained very high (no regioisomer was observed), with the minor product being derived from C–C bond formation occurring at the TMS-containing carbon of the alkyne **34**. To explore the potential role of the PMB ether of **30** in the regiochemical course of cyclopropene functionalization,[10] we explored a substrate lacking this motif. As illustrated in eq 7 of Scheme 4, reaction of TMS-propyne **23** with cyclopropene **35** delivered the vinylcyclopropane product **36** in 96% yield; *no evidence was found for the production of regio- or stereoisomeric products in this coupling reaction.*

Moving on to explore substrate scope, TMS-phenylacetylene **37** and the α-branched alkyne **40** could be coupled to **30** in high yield (eqs 8 and 9). Here, regioselectivity with respect to alkyne functionalization varied from 12:1 in the case of **37** to 5:1 with the α-branched coupling partner **40**.

The observation that this coupling reaction proceeds in the absence of an alkoxide directing group led us to further consider the unique reactivity of cyclopropenes in metallacycle-mediated cross-coupling. While unstrained 1,2-disubstituted alkenes have not proven to be exceptionally useful for the formation of titanacyclopropanes, we thought that the strained π-unsaturation resident in the cyclopropene could offer distinct character of potential utility in metallacycle-mediated cross-coupling.[11]

As illustrated in the top portion of Scheme 5, we expected that treatment of a cyclopropene with Ti(O-*i*-Pr)$_4$ and *n*-BuLi could result in the formation of an unusually stable saturated metallacyclopentane **43**, this stability being thought to derive from the expected difficulty of either regenerating the cyclopropene (accompanied by formation of a Ti–butene complex) or accessing the strained Ti–cyclopropene complex (with loss of butene).[12] We suspected that heating **43** in the presence of a terminal alkyne may result in ligand exchange,

Scheme 2. Strategies for Cyclopropene–Alkyne Coupling



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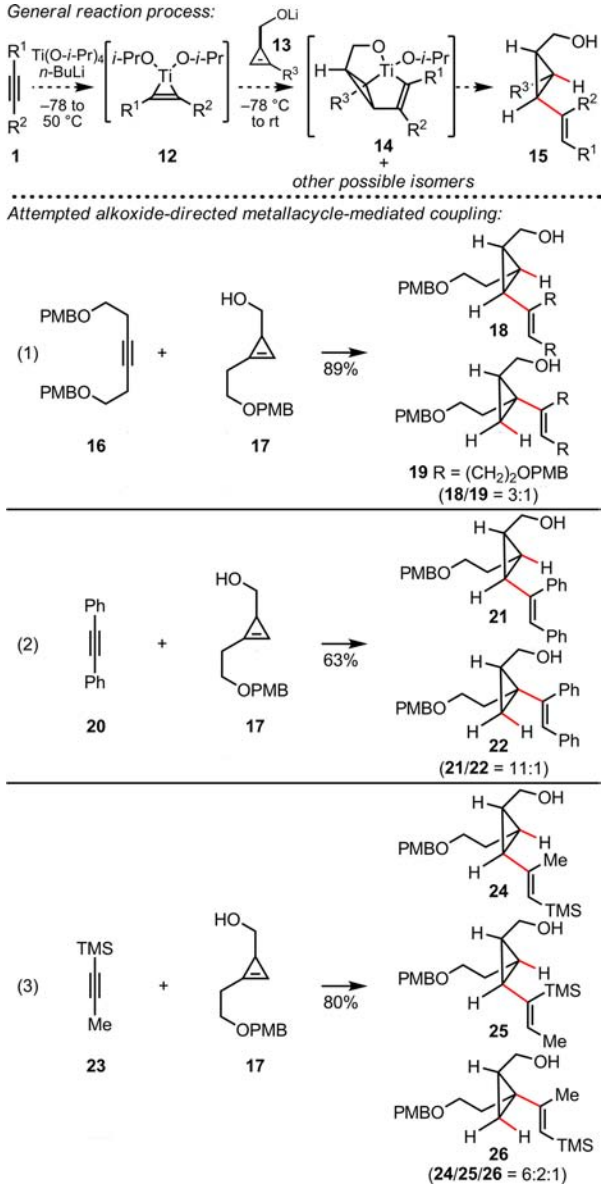
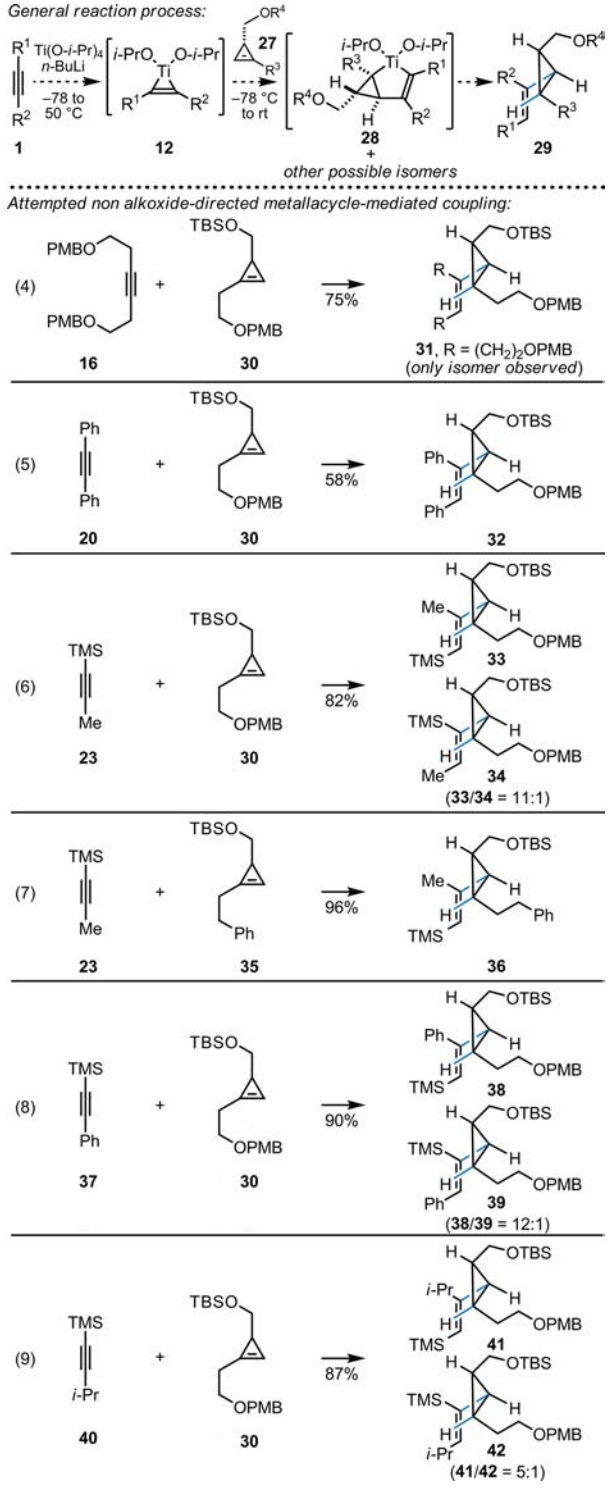
Scheme 3. Alkoxide-Directed Cyclopropene−Alkyne Coupling



Scheme 4. Non-alkoxide-Directed Cyclopropene−Alkyne Coupling



with loss of butene and formation of a fused bicyclic titanacyclopentene **45**.[13] Protonation would then deliver the vinylcyclopropane product possessing a disubstituted alkene **46**. Unfortunately, attempted union of cyclopropene **30** with alkyne **47** was not successful (eq 10, Scheme 5). Efforts to explore this lack of desired reactivity led to the experiment depicted in eq 11 (Scheme 5). Here, treatment of cyclopropene **30** with $Ti(O\text{-}i\text{-}Pr)_4$ and EtMgCl was directly followed by quenching with a proton source. As illustrated, quenching with 1 N HCl led to a 2:1 mixture of the ethylated cyclopropanes **51** and **52** in 65% yield. To confirm that this alkylative process was proceeding through the intermediacy of fused bicyclic metallacyclopentane intermediates **49** and **50**, the reaction was also quenched with D_2O. In this latter process, the dideuterated products (**51** and **52**; X = D) were generated.

While we were not successful in realizing a coupling reaction of a cyclopropene with a terminal alkyne, we speculate that such a process may be successful by initial formation of a Cp_2Zr-alkyne complex by Buchwald's method,[14] followed by exposure to the cyclopropene coupling partner.

Overall, we report the use of unsymmetrically substituted cyclopropenes in metallacycle-mediated cross-coupling and define concise and convergent paths to the synthesis of stereodefined vinylcyclopropanes. We demonstrate that both alkoxide-directed and nondirected metallacycle-mediated cross-coupling reactions of cyclopropenes with alkynes proceed with exquisite levels of diastereoselection and generally favor the

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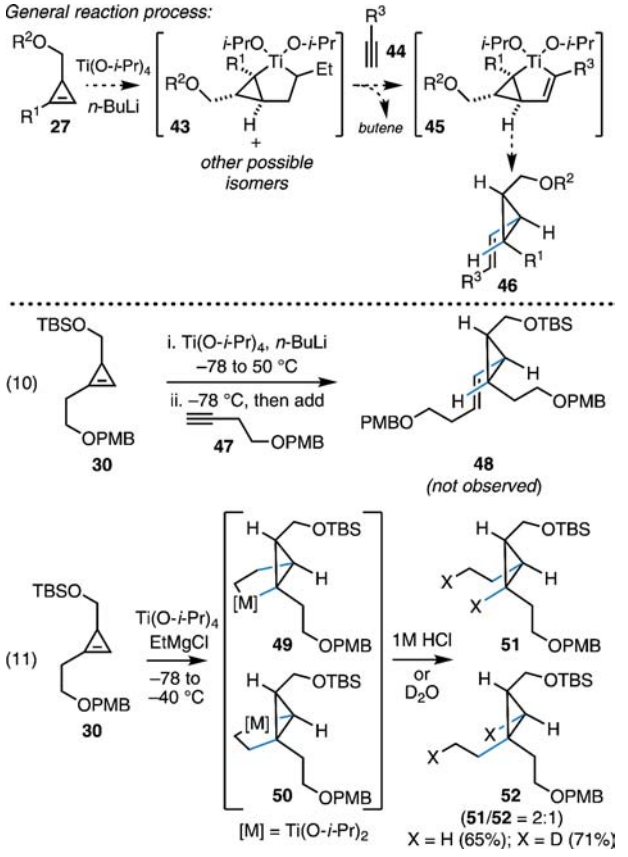
Scheme 5. Attempted Cyclopropene−Terminal Alkyne Coupling



formation of 1,2,3-trisubsituted cyclopropane products, *an isomer not typically observed in carbometalation* reactions *of cyclopropenes*. In addition, we have observed unusual stability of titanacyclopentanes formed by exposure of cyclopropenes to $Ti(O\text{-}i\text{-}Pr)_4/2RMgCl$.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00072.

Procedures and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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