



Generation of quaternary centers by reductive cross-coupling: shifting of regioselectivity in a subset of allylic alcohol-based coupling reactions

Dexi Yang^a, Justin K. Belardi^b, Glenn C. Micalizio^{a,*}

^a Department of Chemistry, The Scripps Research Institute, Scripps Florida, Jupiter, FL 33458, United States

^b Department of Chemistry, Yale University, New Haven, CT 06520, United States

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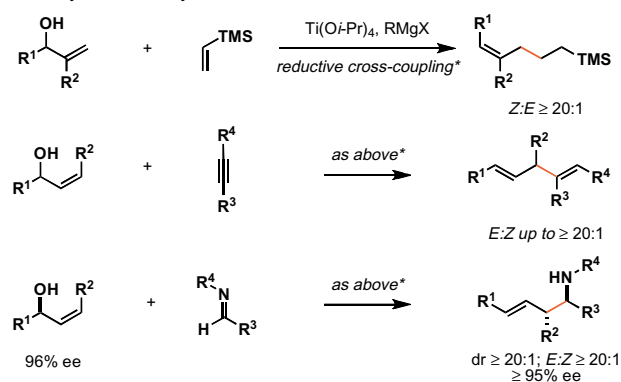
ABSTRACT

Regioselective titanium alkoxide-mediated reductive cross-coupling reactions of allylic alcohols with vinylsilanes and imines have previously been demonstrated to proceed with allylic transposition by formal metallo-[3,3]-rearrangement [thought to proceed by a sequence of: (1) directed carbometallation, and (2) *syn*-elimination]. While many examples have been described that support this reaction path, a collection of substrates have recently been identified that react by way of an alternative pathway, delivering a concise convergent route to coupled products bearing a quaternary center.

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Reductive cross-coupling is emerging as a powerful strategy for bimolecular C–C bond formation.¹ Within this broad class of chemical reactions, metallacycle-mediated union of allylic alcohols with alkynes, vinylsilanes, and imines, defines a suite of transformations that provide convergent stereoselective access to a variety of structural motifs not readily achieved by other convergent methods in organic/organometallic chemistry.² As depicted in Figure 1A, intermolecular C–C bond formation is accomplished in concert with the stereoselective generation of isolated (*Z*)-trisubstituted alkenes, stereodefined 1,4-dienes, and complex homoallylic amines through processes that afford C–C bond formation at the *sp*² carbon located distal to the allylic alcohol. Overall, these coupling reactions proceed with allylic transposition, deliver products containing stereo-defined di- or trisubstituted alkenes, and can be performed in an enantioselective manner with transfer of stereochemical information from the allylic alcohol starting material to the functionalized product.³ Herein, we describe recent observations in a subset of these coupling reactions where subtle changes in substrate structure result in a change in the regiochemical course of carbometallation. In short, these observations have culminated in the identification of reductive cross-coupling reactions of utility for

A. Previously reported: Reductive cross-coupling of allylic alcohols with vinylsilanes, alkynes and imines:



B. Described here: Reductive cross-coupling for the generation of quaternary centers:

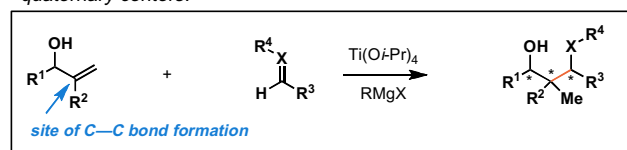
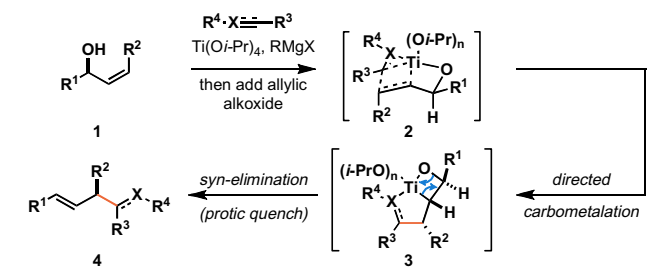


Figure 1. Reductive cross-coupling reactions of allylic alcohols.

* Corresponding author.

E-mail address: micalizio@scripps.edu (G.C. Micalizio).

A. Reductive cross-coupling by directed carbometalation—syn-elimination:



B. Hoveyda's carbomagnesiation:

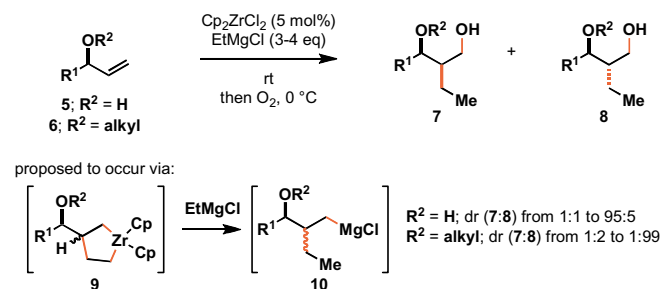


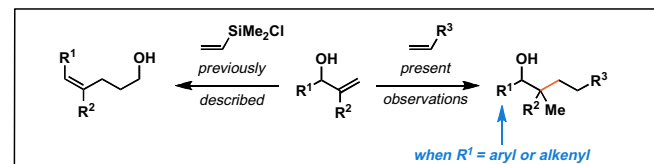
Figure 2. Reductive cross-coupling of allylic alcohols/ethers: regioselection.

the generation of quaternary carbon centers (Fig. 1B). Due to the relative scarcity of intermolecular reactions suitable for the establishment of quaternary centers, and the well-accepted difficulties associated with their synthesis,⁴ these initial findings are of considerable interest, pointing to a new bimolecular class of reactions capable of forging these highly congested C–C bonds.

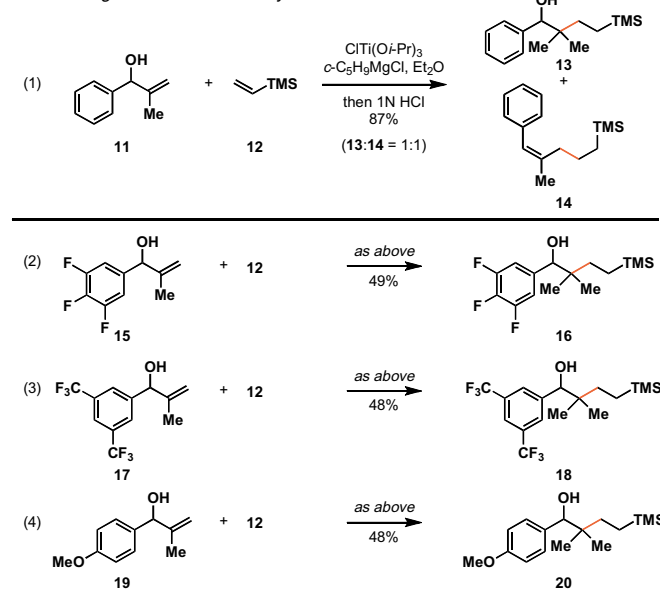
Our study of metallacycle-mediated reductive cross-coupling reactions of substituted allylic alcohols with alkynes,^{2a} vinylsilanes,^{2b} and imines^{2c–f} has defined a collection of novel stereoselective synthetic methods. Initial observations in this area pointed to a general and reproducible pattern of reactivity, where C–C bond formation occurs with allylic transposition. These observations were consistent with the proposition of a reaction pathway composed of: (1) directed carbometalation, and (2) syn-elimination (Fig. 2A). While regioselective reactions of this ilk had previously been described, they were uniformly of limited synthetic utility, as bimolecular C–C bond formation was demonstrated to result in mixtures of alkene isomers.⁵ Our studies, focused on the use of a titanium alkoxide as the central metal component and an allylic alkoxide as the reactive allylic system, led to highly stereoselective coupling reactions that likely derive from a distinct and highly organized boat-like transition state for regioselective directed carbometalation ($2 \rightarrow 3$), and a conserved mechanistic pathway for syn-elimination ($3 \rightarrow 4$). Our early investigations have led to the identification of stereoselective reactions for the preparation of products bearing either an (*E*)-disubstituted, or (*Z*)-trisubstituted alkene, whereby C–C bond formation occurs distal to the allylic alcohol.

Interestingly, related studies in Zr-catalyzed carbomagnesiation by Hoveyda, define coupling processes that proceed by a unique regioselective path, where C–C bond formation occurs α - to the allylic alcohol, and delivers saturated products (7 and 8) by way of metallacycle 9 (Fig. 2B).⁶ While being described over 15 years ago, this regio- and stereoselective intermolecular carbomagnesiation has, to our knowledge, not been demonstrated to be useful for the establishment of quaternary centers.⁷

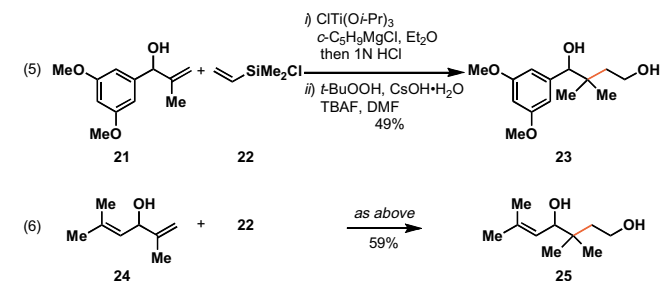
Initial study of allylic alcohol–vinylsilane reductive cross-coupling resulted in the elucidation of a useful reaction for the preparation of (*Z*)-trisubstituted olefins. In fact, the substitution



A shift in regioselection with benzylic alcohols:



Access to 1,4-diols containing a quaternary carbon:



Regioselection appears sensitive to substrate substitution

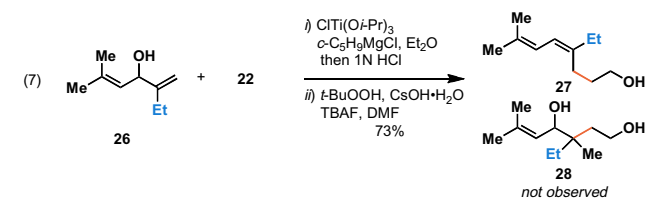


Figure 3. Access to quaternary centers by allylic alcohol–vinylsilane reductive cross-coupling

pattern of the products from this process were similar to those anticipated from Claisen rearrangement, but possessed a stereochemistry not easily attained with this classic sigmatropic rearrangement.^{2b} In subsequent studies of this transformation, we observed an unprecedented shift in regioselection, and accompanying mechanistic course of this subset of metallacycle-mediated cross-coupling reaction.

As depicted in Eq. 1 of Figure 3, reductive cross-coupling of allylic alcohol 11 with vinyltrimethylsilane proceeds in 87% yield, but delivers a mixture of regioisomeric products 13 and 14. While this cross-coupling reaction did not proceed in a regioselective manner, the differences in polarity associated with these two products made purification of product 13 trivial. As illustrated in

Eqs. 2–4, related substrates **15**, **17**, and **19** could also be converted to products containing a quaternary center (**16**, **18**, **20**) in ca. 50% yield. Aiming to define a synthetically more useful coupling reaction, 1,4-diols could be prepared from a related reaction of allylic alcohol **21** with chlorodimethylvinyl silane **22**. Here, reductive cross-coupling was followed by oxidation of the C–Si bond to deliver diol **23** in 49% yield (over two-steps).

While these observations marked a dramatic shift in regioselection for reductive cross-coupling reactions of benzylic alcohols, similar results were obtained for the coupling of the 1,4-diene-3-ol substrate **24** with **22**. After the two-step process of cross-coupling and oxidation, the 1,4-diol **25** was isolated in 59% yield.

Next, we aimed to realize a version of this coupling reaction that would be suitable for generating a stereodefined quaternary center. As depicted in Eq. 7 of Figure 3, these efforts targeted the coupling of substrate **26** with **22**. While the only difference in substrate structure of **26** with respect to substrate **24** was the substitution of a Me- group for an Et-substituent, this coupling reaction of **26** with **22** delivered diene **27** in 73% yield; no evidence was found for the production of **28**. Overall, this result indicated that the regioselection associated with coupling reactions of benzylic- and allylic- alcohols is quite sensitive to subtle perturbation of substrate structure.

In the related coupling reactions of allylic alcohols with imines, a similar change in regioselection was not observed. As shown in Eq. 8 of Figure 4, coupling of the benzylic alcohol **11** with imine **29** proceeds in 87% yield, and delivers the homoallylic amine product **30**. Unlike the coupling reaction of **11** with a vinylsilane, no evidence could be found for the formation of a product containing a quaternary center. Similarly, the coupling of allylic alcohol **26** with **29** also delivered homoallylic amine products (Eq. 9).

Interestingly, in this subset of reductive cross-coupling, if the starting material is a primary allylic alcohol, substantial quantities of isomeric products result. For example, coupling of **32a** with **29** resulted in a 2:1 mixture of products **33a** and **34a** in 90% combined yield (Eq. 10). While the product containing a quaternary center was the minor product of this transformation, a subtle change in the structure of **32a** resulted in a significant perturbation of the reaction course. As depicted in Eq. 11, coupling of **32b** with imine **29** resulted in the preferential formation of the 1,3-aminoalcohol product **34b** over the homoallylic amine **33b** (selectivity = 4:1).^{2f} The stereochemistry of the major product formed was addressed as illustrated in Eq. 12. Here, coupling of **32b** with imine **35** was followed by formation of the rigid bicyclic heterocycle **37**. Subsequent NOE analysis indicated that the major product of this coupling reaction is as depicted in **36**.

While the reaction of **32b** with imines is selective for the formation of products containing a quaternary center, simple substitution of this starting material results in a shift of regioselection back to the preferential formation of homoallylic amine products. As depicted in Eq. 13, coupling of the secondary allylic alcohol **38** with imine **29** results in the formation of **39** in 70% yield, as a single olefin isomer. Here, no evidence was found for the production of a 1,3-aminoalcohol-containing product.^{2f}

These studies have identified structural features that lead to a change in the regiochemical course of $\text{Ti}(\text{O}i\text{-Pr})_4$ -mediated reductive cross-coupling reactions between allylic alcohols and vinylsilanes or imines. The factors that influence each of these cross-coupling reactions are distinct. With vinylsilane-based coupling reactions, additional unsaturation (in the form of a benzylic alcohol or a 1,4-diene-3-ol system) shifts the regiochemical course of coupling. In these cases, substantial quantities of products containing a quaternary carbon are formed. With imine-allylic alcohol coupling, such additional unsaturation does not affect the regiochemical course of reductive cross-coupling. However, a different structural feature shifts regioselection in these reactions. Specifi-

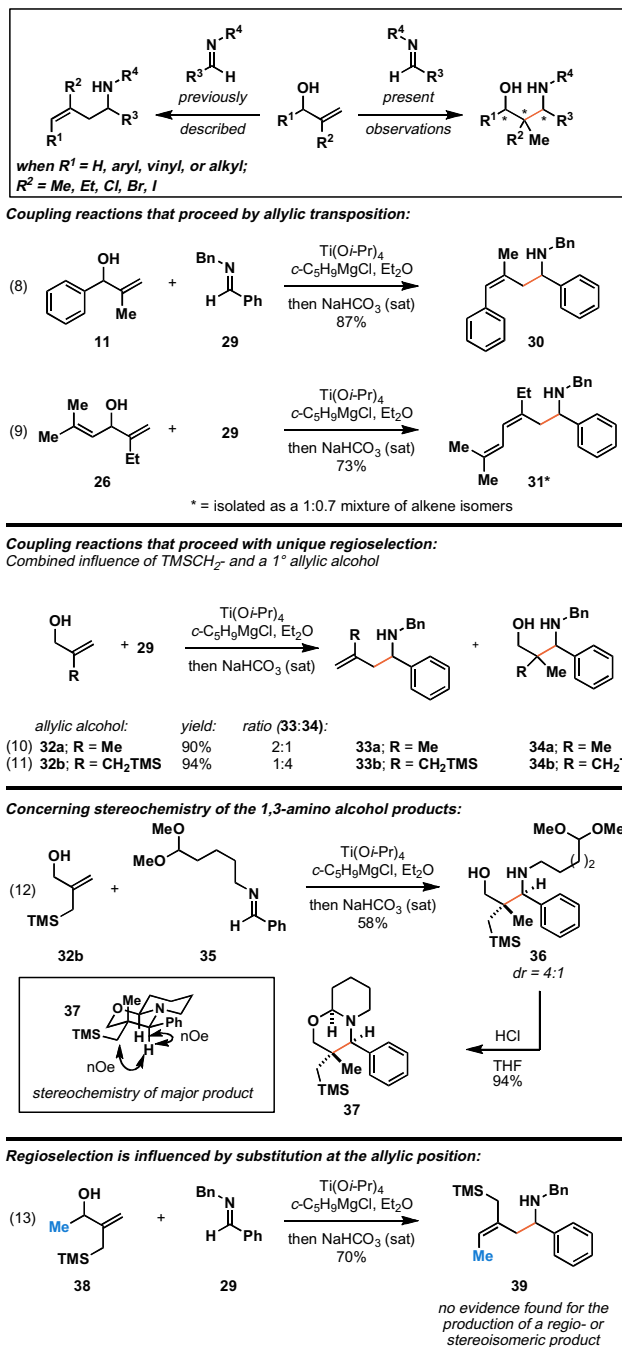


Figure 4. Access to quaternary centers by allylic alcohol-imine reductive cross-coupling.

cally, coupling of primary allylic alcohols with imines results in a substantial quantity of product containing a 1,3-aminoalcohol and accompanying quaternary center. This tendency is further enhanced with a substrate that contains a TMSCH_2 -substituent (**32b**), indicating a potential role of electronic factors in changing the regiochemical course of this coupling reaction. A mechanistic rationale in support of these subtle changes in regioselection as a function of substrate structure remains to be defined.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, compound characterization, copies of spectral data) associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2010.11.059](https://doi.org/10.1016/j.tetlet.2010.11.059).

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