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Catalytic Anti-Markovnikov Hydroallylation of Terminal and Functionalized Internal Alkynes: Synthesis of Skipped Dienes and Trisubstituted Alkenes

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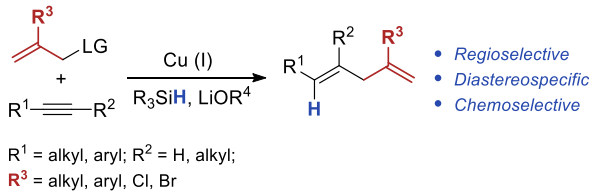
Catalytic Anti-Markovnikov Hydroallylation of Terminal and Functionalized Internal Alkynes: Synthesis of Skipped Dienes and Trisubstituted Alkenes

Melrose Mailig,† Avijit Hazra,† Megan K. Armstrong, and Gojko Lalic*

Department of Chemistry, University of Washington, Seattle, Washington 98195

ABSTRACT: We have developed catalytic anti-Markovnikov hydroallylation of terminal and functionalized internal alkynes. In this article, we describe the development of the reaction, exploration of the substrate scope, and a study of the reaction mechanism. Synthesis of skipped dienes through the hydroallylation of terminal alkyl and aryl alkynes with simple allyl phosphates and 2-substituted allyl phosphates is described. The hydroallylation of functionalized internal alkynes leads to the formation of skipped dienes containing trisubstituted alkenes. We demonstrate that the hydroallylation of internal alkynes can be used in the regio- and diastereoselective synthesis of complex trisubstituted alkenes. A mechanism of the hydroallylation reaction is proposed, and experimental evidence is provided for the key steps of the catalytic cycle. Stoichiometric experiments demonstrate an unexpected role of lithium alkoxide in the carbon-carbon bond-forming step of the reaction. A study of the hydrocupration of internal alkynes provides new insight into the structure, stability, and reactivity of alkenyl copper intermediates, as well as insight into the source of the regioselectivity in reactions of internal alkynes.



Introduction

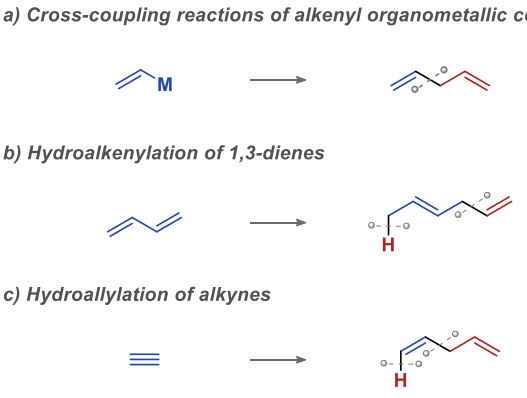
Skipped or 1,4-dienes are found in a number of natural products.[1] The importance of this class of compounds and the challenges associated with their preparation[2] have spurred the development of numerous methods for their synthesis. Some rely on reactions commonly used in preparation of simple alkenes.[3] Others have been specifically designed for the synthesis of skipped dienes. One example of such a method, and at the same time one of the best stoichiometric methods for the synthesis of skipped dienes, is titanium-mediated coupling of allylic alcohols with alkynes, developed by Micalizio et al.[4]

Over the last ten years, the focus has mostly been on the development of new catalytic reactions that yield skipped dienes. These catalytic reactions generally belong to one of the three major classes: 1) Cross-coupling reactions of alkenyl organometallic reagents with electrophiles, 2) hydroalkenylation of 1,3-dienes, and 3) hydroallylation of alkynes (Scheme 1).

Transition metal catalyzed cross-coupling reactions of various organometallic reagents with a variety of electrophiles have been used to access skipped dienes.[5] The most notable examples of this approach are catalytic enantioselective reactions of alkenylboron[6] and alkenylaluminum[7] compounds with allylic electrophiles. Another excellent method, developed by Sigman et al., is based on a variation of the cross-coupling approach, and involves palladium-catalyzed reaction of 1,3-butadiene with enol triflates and alkenylboron compounds.[2,5n]

Hydroalkenylation of 1,3-dienes also provides skipped dienes and can be accomplished using Co,[8] Ni,[9] or Fe[10] catalysts. A major advantage of hydroalkenylation methods over cross-coupling reactions is that substrates do not need to be pre-functionalized. Furthermore, this approach allows the preparation of highly substituted skipped dienes, which may be difficult to prepare using other methods. One drawback of the hydroalkenylation approach is that a mixture of diastereoisomers is often obtained,[8b] although high diastereoselectivity can be achieved.[10]

Scheme 1. Catalytic reactions for the synthesis of skipped dienes.

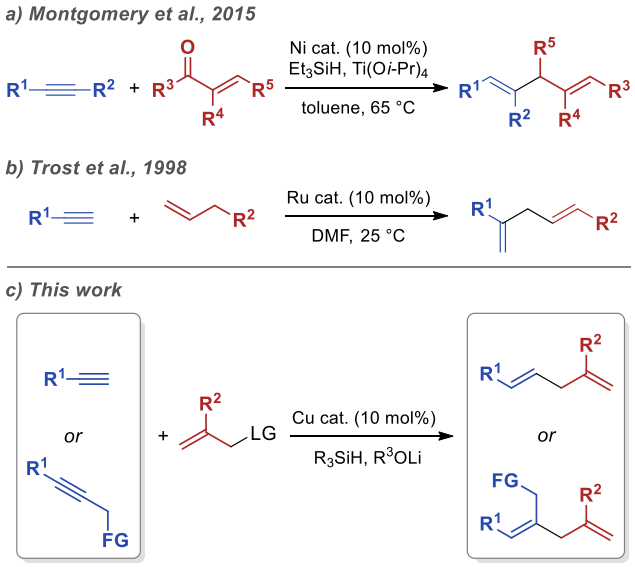


Finally, skipped dienes can also be prepared by hydroallylation of alkynes.[11] While less common than cross-coupling and hydroalkenylation reactions, hydroallylation methods have proven to be highly effective. Recently, Montgomery et al. reported an excellent method for the synthesis of skipped dienes shown in Scheme 2a.[11d] In this formal hydroallylation reaction, alkynes are reductively coupled with enones in the presence of a nickel catalyst, a silane, and a stoichiometric

amount of Ti(O*i*-Pr)$_4$. Excellent regio- and diastereoselectivity was observed with a wide range of substrates, together with a good functional group compatibility. The reaction works particularly well with symmetrical internal alkynes and alkyl aryl alkynes.

Several methods for Markovnikov hydroallylation of alkynes are known.[12] The most general is the ruthenium-catalyzed hydroallylation of terminal alkynes reported by Trost et al. in 1998 (Scheme 2b).[11a,11b] The reaction proceeds with excellent Markovnikov selectivity (with respect to the alkyne) and has exceptional substrate scope and functional group compatibility. This method has been successfully used with complex substrates and as a key step in the synthesis of natural products.[5o,11a,13] Lee and Trost have later shown that good regioselectivity can also be obtained using boro-,[14] silyl-,[15] and alkynyl-substituted[16] internal alkynes. Overall, this reaction is one of the most well-developed and broadly applicable methods for the synthesis of skipped dienes.[17]

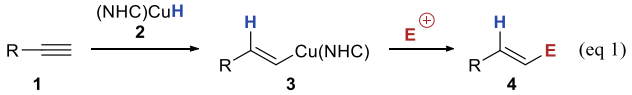
Scheme 2. Alkynes in the synthesis of skipped dienes.



In this article, we describe the development of a direct hydroallylation of terminal alkynes (Scheme 2c) with regioselectivity opposite from the Markovnikov selectivity of Trost's method. We also demonstrate that nonsymmetrical dialkyl-substituted alkynes can be used as substrates to provide trisubstituted alkene products with excellent regioselectivity. This class of substrates has not been previously used in the synthesis of skipped dienes, or in any other copper-catalyzed hydrofunctionalization reaction. We demonstrate that hydroallylation can be used in synthesis of complex trisubstituted alkenes. Finally, we also describe our investigation of the reaction mechanism, which suggests a new role of the alkoxy turnover reagent and provides a new insight into the structure, stability, and reactivity of the β-functionalized alkenyl copper complexes.

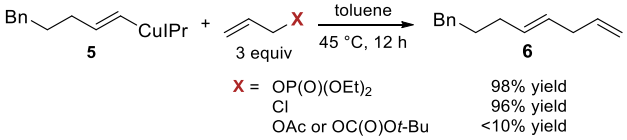
Results and Discussion

Reaction development. In the last several years, our group has focused on the development of a general approach to the hydrofunctionalization of alkynes. Several groups, including ours, have shown that syn-diastereospecific hydrocupration of alkynes, followed by electrophilic functionalization of the alkenyl copper intermediate can be used to accomplish a range of hydrofunctionalization reactions with excellent anti-Markovnikov regioselectivity and *E* diastereoselectivity (eq 1). Using this approach, Tsuji et al. developed a catalytic hydrocarboxylation of alkynes,[18] while our group developed catalytic methods for the hydrobromination[19] and hydroalkylation of alkynes.[20] We anticipated that the same approach could be used to accomplish an anti-Markovnikov hydroallylation of alkynes.



Stoichiometric experiments shown in Scheme 3 demonstrate that both allyl chloride and allyl phosphate are competent electrophiles in a reaction with isolated alkenyl copper complex **5**.[21] The less reactive electrophiles, such as allyl acetate and allyl carbonate provide the desired product in less than 10% yield. Using these results as a starting point we were able to develop a method for the catalytic hydroallylation of terminal alkynes, shown in Table 1. The best results were obtained using IPrCuO*t*-Bu as a catalyst, polymethylhydrosiloxane (PMHS) as a hydride source, and LiO*t*-Bu as a turnover reagent. The reaction is performed in toluene and is completed after 16 h at 45 °C. During our efforts to identify the best conditions for the hydroallylation reaction, we made several observations summarized in Table 1.

Scheme 3. Stoichiometric allylation of an alkenyl copper complex



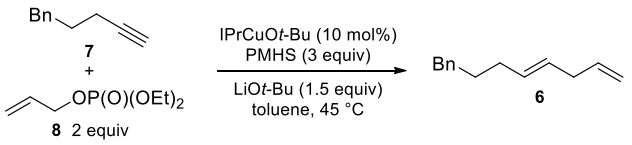
Even though both allyl chloride and allyl phosphate gave high yields in the stoichiometric reaction with the alkenyl copper complex, in the catalytic reaction, allyl phosphate provided a significantly higher yield of the desired product (entries 1 and 2). NHC copper(I) *tert*-butoxide performed better than NHC copper(I) chloride as a catalyst precursor (entries 1 and 3). As in other catalytic transformations that involve hydrocupration of alkynes,[19-20,22] we found that copper complexes supported by IPr or SIPr ligands are the most effective catalysts. Closely related ligands shown in entries 5, 6, and 7 gave significantly lower yields of the desired product. Although the exact reason for the superior performance of these two ligands is not clear, we suspect that it is related to the lower aggregation and higher stability of copper hydride complexes supported by these sterically hindered ligands.[23] Finally, a wide range of copper complexes supported by phosphine ligands were completely ineffective as catalysts in the hydroallylation reaction (see SI for details). Surprisingly, the catalytic system commonly used in hydrofunctionalization of styrenes, including hydroallylation, was also completely ineffective.[24] This observation further supports our observations that the NHC-copper complexes are uniquely effective in hydrofunctionalization of alkynes.

High yields in the hydroallylation reaction were obtained in both aromatic hydrocarbon solvents, such as toluene and chlorobenzene, and in ethereal solvents such as THF and 1,4-dioxane (entries 8, 9, and 10). Surprisingly, isooctane was also an effective solvent (entry 11). Silane choice proved to be essential for the success of the reaction. PMHS and $(Me_2HSi)_2O$ both performed well (entries 1 and 12). However,

highly reactive $(EtO)_3SiH$ (entry 14) gave significantly lower yield of the desired product, while a variety of other di and trialkyl substituted silanes also provided very little of the desired hydroallylation product (entries 13 and 15).

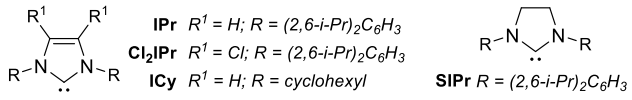
Hydroallylation of terminal alkynes. Hydroallylation of a wide range of terminal alkynes can be accomplished using the optimized reaction conditions (Table 2). In all cases, a single regioisomer and *E*-diastereoisomer of the desired product is obtained. The observed selectivity is in line with the results of the stoichiometric hydrocupration of terminal alkynes, which is syn-diastereospecific and selective for the anti-Markovnikov product.[22] Furthermore, the reaction can be performed in the presence of a wide range of functional groups. Electrophilic carboxylic acid derivatives, such as esters and nitriles, are compatible with the reaction conditions (compounds **11** and **12**). Surprisingly, ketones are also tolerated, despite reports of rapid reduction of ketones under similar reaction conditions (compound **13**).[25] Alkyl electrophiles such as alkyl chlorides, bromides, and tosylates (compounds **14**, **15**, **23**), as well as aryl fluoride and aryl iodide (compounds **9** and **10**), are also compatible with the reaction conditions and provide functionalized skipped dienes.

Table 1. Reaction development



entry	change from standard conditions	yield[a]
1.	none	89% [b]
2.	allyl chloride as an electrophile	44%
3.	IPrCuCl as catalyst	69%
4.	SIPrCuCl as catalyst	59%
5.	Cl_2IPrCuCl as catalyst	31%
6.	ICyCuCl as catalyst	42%
7.	IPr*CuCl as catalyst	36%
8.	chlorobenzene	88%
9.	THF	76%
10.	dioxane	72%
11.	isooctane	88%
12.	$(Me_2HSi)_2O$ instead of PMHS	86%
13.	*t*-Bu_2SiH_2 instead of PMHS	28%
14.	$(EtO)_3SiH$ instead of PMHS	16%
15.	Et_3SiH instead of PMHS	0%

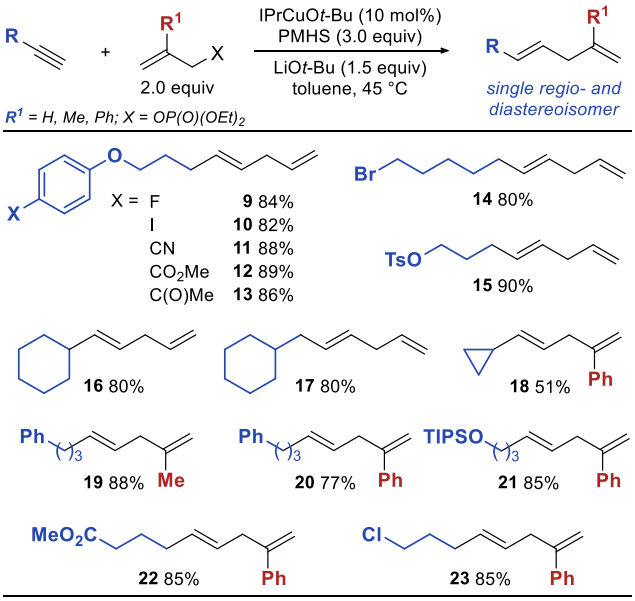
[a] GC yields are reported. All reactions performed on 0.1 mmol scale.
[b] Yield of the pure isolated product is reported.



Variation of the electrophilic components of the hydroallylation reaction proved to be significantly more challenging. Substitution at the central carbon of the allylic electrophile led to a dramatic decrease in reactivity. In fact, from a range of 2-substituted allylic electrophiles we explored, only phenyl- and methyl-substituted substrates provided the desired products in significant yields under the standard reaction conditions described in Table 1. These two electrophiles reacted with a variety of alkynes, as shown in Table 2 (entries **18**-**23**).

With electrophiles containing other substituents at the 2 position, we observed significantly lower yields. For example, with benzyl substituted electrophile **24**, we observed a complete conversion of the starting alkyne within 16 h (Table 3). However, the desired hydroallylation product was a minor product of the reaction (Table 3, entry 1). Furthermore, all other identifiable products (desired hydroallylation product, reduced alkyne, and reductive homo-coupling of the alkyne) accounted for less than half of the starting material consumed.

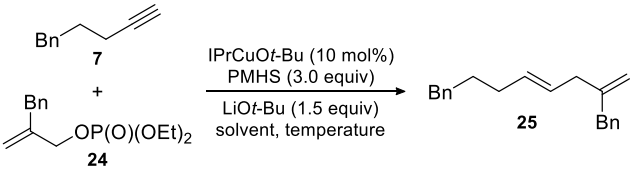
Table 2. Hydroallylation of terminal alkynes[a]



[a] All reactions performed on 0.5 mmol scale. Yields of pure isolated products are reported.

The failure to obtain the desired product with substituted phosphates led us to explore conditions that in our preliminary reaction optimization provided promising results. We found that isooctane gave results superior to those obtained in toluene (Table 3, entry 1 vs. 3). Surprisingly, while increasing the reaction temperature to 60 °C marginally effected the yield of the desired product, a further increase to 90 °C resulted in the formation of the desired product in 90% yield (entries 4 and 5).[26] A similar increase in temperature with toluene as the solvent was not productive (entry 2).

Table 3. Solvent and temperature effects in reactions with 2-substituted allylic electrophiles[a]



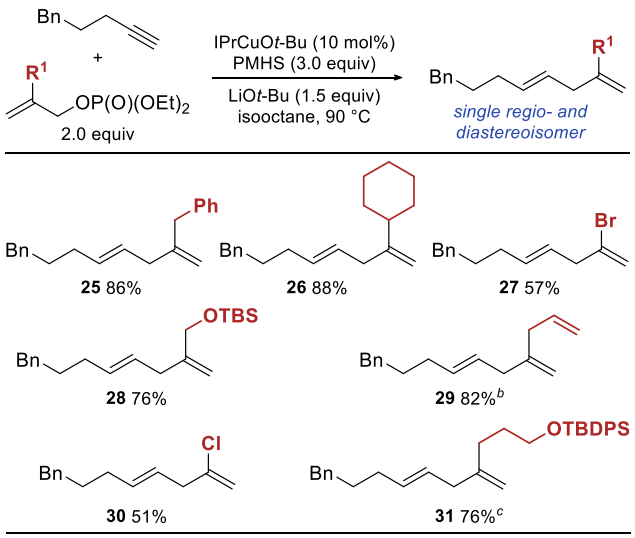
entry	solvent	temperature	yield[a]
1.	toluene	45 °C	15%
2.	toluene	90 °C	22%
3.	isooctane	45 °C	68%
4.	isooctane	60 °C	63%
5.	isooctane	90 °C	90%

[a] GC yields at the full conversion of **7** are reported.

Using the reaction conditions shown in entry 5 of Table 3, we were able to perform hydroallylation reaction with various substituted allylic phosphates (Table 4). Sterically hindered substituents and functionalized alkyl substituents are well-

tolerated (compounds **26**, **28**, and **31**). Chloro- and bromo-substituted electrophiles provide functionalized products which can be further derivatize (compounds **27** and **30**).

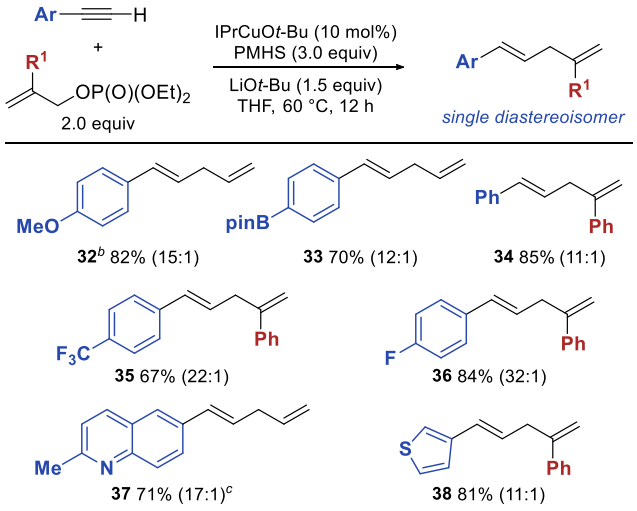
Table 4. Reactions of 2-substituted allylic electrophiles[a]



[a] Unless otherwise noted, all reactions performed on 0.5 mmol scale. Yields of pure isolated products are reported. [b] Reaction performed on 0.15 mmol scale. [c] Reaction performed on 0.25 mmol scale.

Hydroallylation of aryl alkynes. Aryl alkynes are often poor substrates for reactions catalyzed by late transition metal complexes. The increased acidity of the alkynes makes the formation of the metal acetylide difficult to avoid, especially in the presence of a strong base such as LiO*t*-Bu. Furthermore, the presence of the aryl substituent can influence the regioselectivity of the hydrometallation step.

Table 5. Reactions of aryl alkynes[a]

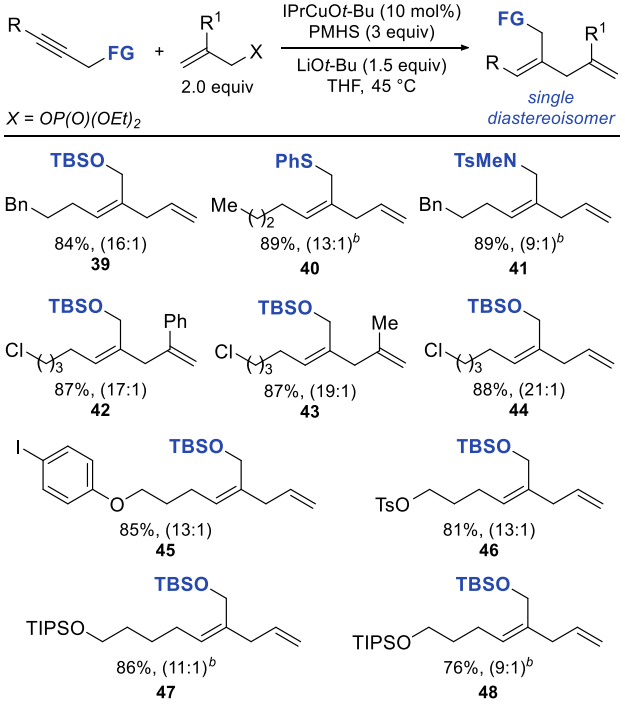


[a] All reactions performed on 0.5 mmol scale. Yields of pure isolated major regioisomer of the products are reported. Regioselectivity reported in parenthesis was determined by GC analysis of the crude reaction mixture. [b] 3.0 Equivalents of phosphate were used. [c] Reaction performed on 0.25 mmol scale.

Our initial attempts to achieve hydroallylation of aryl alkynes using the standard reaction conditions were not successful. However, the change of the solvent to THF and the increase of the reaction temperature to 60 °C allowed hydroallylation of several aryl and heteroaryl alkynes (Table 5). Both electron-withdrawing and electron-donating substituents on the arene were tolerated (**32** and **35**). However, somewhat lower yield of **35** suggests that the with highly acidic aryl alkynes the formation of the acetylide may be a problem. Finally, in all reactions only one diastereoisomer is formed and good anti-Markovnikov regioselectivity is observed (>10:1).

Hydroallylation of internal alkynes. One of the major challenges in the hydroallylation of alkynes is the reactivity of nonsymmetrical internal alkynes. To achieve good regioselectivity with this class of substrates, the existing methods require significant electronic or steric differentiation of the alkyne substituents. As a result, the use of internal alkynes in the synthesis of skipped dienes has been generally limited to reactions of aryl-,[11d] alkynyl-,[16] and silyl-substituted[17b] alkyl acetylenes. In the light of these constraints, we were interested in exploring the reactivity of differentially functionalized dialkyl alkynes. We found that good regioselectivity (~10:1) can be obtained with substrates containing a polar functional group in the propargylic position. With minor changes in the standard reaction conditions, we were able to accomplish the regio- and diastereoselective synthesis of skipped dienes that contain a trisubstituted alkene (Table 6).

Table 6. Hydroallylation of internal alkynes[a]



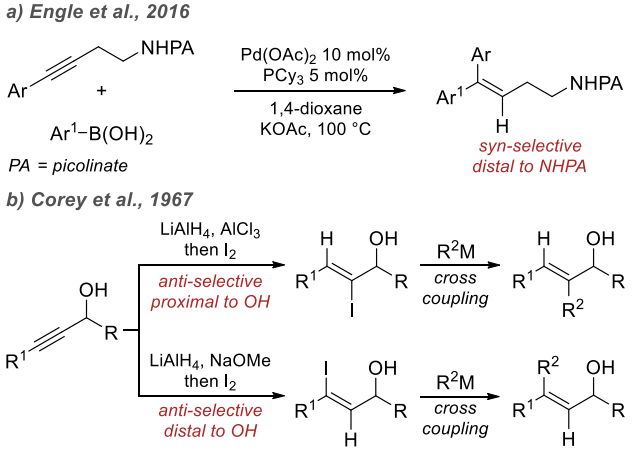
[a] Yields of the isolated pure major regioisomer are reported. Regioselectivities reported in parenthesis were obtained by GC analysis of the crude reaction mixtures prior to purification. Reactions performed on 0.5 mmol scale. [b] Reaction performed in isooctane at 60 °C.

Derivatives of propargylic alcohols, amines, and thiols were all effective in controlling the regioselectivity of the hydroallylation (compounds **39**-**41**). In all cases, the allylation occurred at the position closer to the functional group (FG, in Table 6). With substrates in which both sides of the alkyne contain a polar functional group, the one closer to the alkyne had a dominant effect and controlled the selectivity (compounds **45**-**48**). As the examples of hydroallylation reaction shown in Table 6 demonstrate, the overall scope of the reaction with internal alkynes generally mimics the scope observed

with terminal alkynes. *It is worth noting that the trisubstituted alkene products shown in Table 6 are isolated as a single regio- and diastereoisomer after purification by silica gel column chromatography.*

Hydroallylation of internal alkynes in the synthesis of complex trisubstituted alkenes. The hydroallylation of internal alkynes is also interesting in the context of the synthesis of trisubstituted alkenes. Selective synthesis of this class of alkenes is still a major challenge, as detailed in reviews and recent publications by Negishi et al.[27] The transformation of internal alkynes into trisubstituted alkenes is a potentially efficient and appealing synthetic strategy. However, it is difficult to achieve transformations of internal alkynes to trisubstituted alkenes with high regio- and diastereoselectivity. Recently, Engle et al. reported a breakthrough in this area, using homopropargylic picolinamide directing group to achieve selective hydroarylation of internal alkynes (Scheme 4a).[28] The best method for the hydroalkylation of internal alkynes relies on the cross coupling of alkenyl iodides prepared by Corey's selective hydroalumination of propargylic alcohols (Scheme 4b).[29]

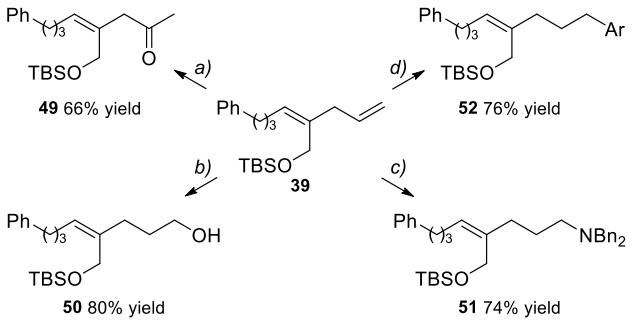
Scheme 4. Synthesis of trisubstituted alkenes from internal alkynes.



The hydroallylation of internal alkynes described in Table 6 allows the regio- and diastereoselective synthesis of trisubstituted alkenes from internal alkynes. Considering that the reaction is syn-selective and the allylation occurs proximal to the directing group, our method provides an excellent complement to the existing methods shown in Scheme 4. The terminal alkene of the hydroallylation products is a versatile synthetic handle that can be used to access a variety of more complex trisubstituted alkenes. We demonstrated that the terminal alkene of the hydroallylation products can be selectively elaborated through oxidation, hydration, hydroamination, and hydroarylation (Scheme 5).

Mechanism of the hydroallylation reaction. Previous work on copper-catalyzed hydrofunctionalization reactions makes the general mechanism shown in Scheme 6 plausible. Elementary steps I, II, and III have strong precedent in the literature in the form of stoichiometric experiments that demonstrate their feasibility.[18,22-23,30] Stoichiometric reactions shown in Scheme 3 also demonstrate the feasibility of the elementary step IV (Scheme 6).

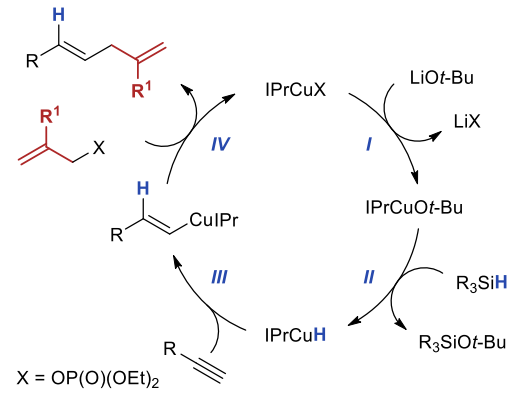
Scheme 5. Elaboration of trisubstituted alkenes prepared by hydroallylation.



Conditions: ***a)*** $PdCl_2$ (15 mol%), CuCl (1.4 equiv) O_2, DMF:H_2O (7:1), 24 h; ***b)*** 9-BBN (1.1 equiv), 1,4-dioxane, 60 °C, 12 h; then $NaBO_3$ (3.3 equiv), THF, 25 °C, 4 h; ***c)*** 9-BBN (1.0 equiv), 1,4-dioxane, 60 °C, then ICyCuCl (5 mol%, LiO*t*-Bu (1.1 equiv), Bn_2NOBz (1.0 equiv), toluene, 60 °C; ***d)*** 9-BBN (1.0 equiv), 1,4-dioxane, 2. $Pd(OAc)_2$ (1 mol%), PCy_3 (2 mol%), Cs_2CO_3 (3.0 equiv), 1,4-dioxane, 100 °C, 24 h.

However, one observation called into question the proposed mechanism. We noticed that the stoichiometric reaction of alkenyl copper complex **5** with 1 equiv of allyl phosphate takes more than 24 h to complete (see SI for details), while under the same reaction conditions the catalytic reaction is completed in 16 h. This observation indicates that the proposed allylation of the alkenyl copper complex is kinetically incompatible with the proposed mechanism of the hydroallylation reaction.

Scheme 6. Proposed mechanism of hydroallylation

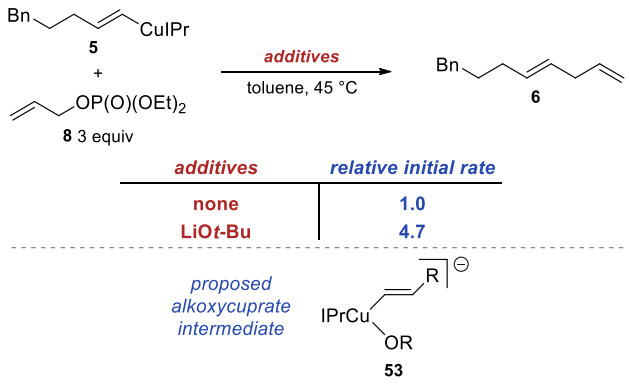


To resolve this apparent paradox, we explored the effect of individual components of the catalytic reaction on the rate of allylation of the alkenyl copper complex (Scheme 7). In the presence of LiO*t*-Bu, the initial rate of the stoichiometric allylation of alkenyl copper complex **5** was 4.7 times higher than in its absence (see SI for details). To separate the effect of lithium ions and of the alkoxide we measured the rate of the reactions in the presence of both 12-crown-4 and LiO*t*-Bu. The crown ether has only a minor effect on the initial rate (see SI for details), indicating that the alkoxide is likely responsible for the observed rate increase. We also found that the effect is solvent dependent, and was much smaller in THF (1.6-fold acceleration with LiO*t*-Bu vs 4.7 in benzene) (see SI for details).

In related catalytic transformations, it has been shown that the identity of the metal alkoxide turnover reagent can have a significant effect on the overall rate of the reaction.[24a,31] In instances in which the NHC ligand used to support the copper catalyst contains a sulfonate group, the identity of the sulfonate counterion derived from the metal alkoxide has been shown to effect the selectivity of the reaction between the organocopper intermediate and the electrophile.[32] However, the

results shown in Scheme 7 provide the first direct evidence for participation of the alkoxide anion in the electrophilic functionalization of the organocopper intermediate.

Scheme 7. Effect of base on the allylation of an alkenyl copper complex

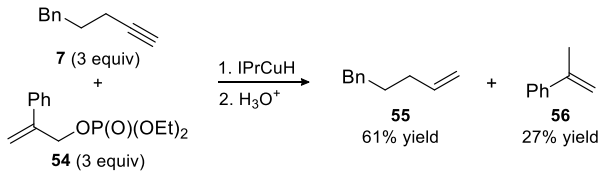


One plausible explanation for the rate increase in the presence of the alkoxide is the formation of alkoxycuprate (**53**) (Scheme 7), which acts as the reactive nucleophile in the reaction with allyl phosphates. Alkoxycuprates have been postulated as reactive intermediates in asymmetric reactions of alkyl lithium reagents performed in the presence of a stoichiometric amount of copper and chiral alkoxide.[33] There are also examples of isolated and characterized alkoxycuprates.[34] Recently, Sawamura et al, have proposed a related phenoxycuprate as a reactive species in several copper-catalyzed reactions.[35] The proposed phenoxycuprate is formed by an intramolecular addition of the phenoxide, which is a part of the NHC ligand that supports the copper catalyst.

We investigated the interaction of the alkenyl copper **5** with LiO*t*-Bu using in situ ^{1}H and ^{13}C NMR and found no evidence for the cuprate formation. Nevertheless, if the reversible formation of the alkoxycuprate is unfavorable under the reaction conditions, we would not observe the cuprate by NMR. In that case, the cuprate could still contribute to the increased rate of the allylation in a typical Curtin-Hammett scenario (low equilibrium concentration and high reactivity).

The third step of the proposed catalytic cycle also required additional verification, as it was not consistent with our previous work on copper-catalyzed hydrofunctionalizations of alkynes. One of the key features of (NHC)CuH complexes is that they quickly reduce a range of organic electrophiles including alkyl iodides,[36] alkyl triflates,[36] propargylic epoxides,[37] and carbonates.[38] As a result, in both hydroalkylation and hydrobromination of alkynes selective hydrocupration in the presence of the electrophile was not possible. Instead, hydroalkylation was shown to proceed through a different mechanism that involves a series of dinuclear analogues of the intermediates proposed in Scheme 6. In the hydrobromination reaction, on the other hand, slow addition of the electrophile was necessary in order to avoid its reduction. In contrast to these two hydrofunctionalization reactions, the mechanism of the hydroallylation (Scheme 6) requires selective hydrocupration of alkynes by IPrCuH in the presence of the allyl phosphate.

Scheme 8. Hydrocupration of alkynes in the presence of allyl phosphate

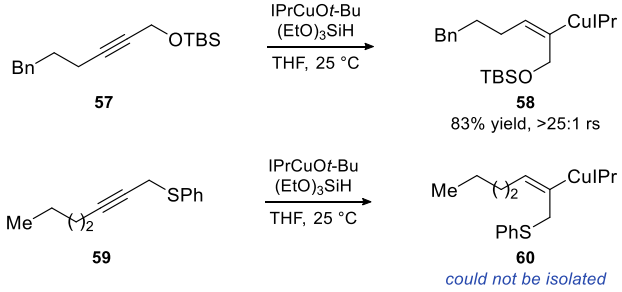


The result of the competition experiment shown in Scheme 8 provides evidence that selective hydrocupration of the alkyne is feasible. The alkene product **55**, which is obtained by the protonation of the alkenyl copper complex, is formed about two times faster than **56**, which is formed by phosphate reduction. The competitive reduction of the phosphate is consistent with the fact that more than one equivalent of an allylic phosphate is generally required for the complete consumption of an alkyne in the hydroallylation reaction.

Hydrocupration of internal alkynes. Nonsymmetrical internal alkynes have not previously been used as substrates in copper-catalyzed hydrofunctionalization reactions. As a result, we were interested in the inherent regioselectivity of the hydrocupration of these substrates, as well as in the source of the regioselectivity. We were also curious about the apparent resistance of the resulting alkenyl copper complexes to β-elimination of the polar functional groups. Such β-elimination reactions from alkenyl copper intermediates are well-documented in catalytic reductions of propargylic electrophiles[37-39] and in copper-catalyzed alkylation and arylation of propargylic phosphates.[31d,40]

To explore the regioselectivity of the hydrocupration and the stability of the alkenyl copper complex, we performed the stoichiometric hydrocupration of OTBS-substituted alkyne **57** (Scheme 9). ^{1}H NMR analysis of the crude reaction mixture indicated that hydrocupration proceeds with excellent regioselectivity (rs >25:1). We were able to obtain an X-ray crystal structure of hydrocupration product **58**, and thus unambiguously establish the regioselectivity of the hydrocupration (see Fig. 1).

Scheme 9. Stoichiometric hydrocupration of internal alkynes



Alkenyl copper complex **58** proved to be quite stable in C_6D_6 solution at 45 °C: after 1 h, 99% of material remained intact, while after 24 h, 79% of the material was still present in solution (see SI for details). On the other hand, the hydrocupration product obtained from thioether substituted alkyne **59** was significantly more prone to elimination. We could identify a small amount of the expected alkenyl copper complex **60** by ^{1}H NMR analysis of the reaction mixture. However, attempts to isolate **60** yielded only IPrCuSPh, the expected product of the β-thiolate elimination. The formation of the hydroallylation product **40** (Table 6) suggests that the allylation of the

alkenyl copper intermediate can outcompete the β-thiolate elimination.

The stoichiometric hydrocupration of OTBS-substituted alkyne **57**, also provides important information about the source of the regioselectivity in the hydrocupration. The oxygen atom in ROTBS moiety is significantly less basic than oxygen atom in dialkyl ethers,[41] and has been shown not to coordinate even highly electrophilic metal complexes, such as $TiCl_4$.[42] Furthermore, the X-ray structure of the alkenyl copper complex **58** (Figure 1) reveals no interaction between the OTBS and copper (Cu-O distance is 3.22 Å). Based on these considerations, we conclude that the regioselectivity is not a result of a direct interaction between OTBS and the catalyst. Instead, the likely explanation is that the inductive effect of the OTBS substituent causes polarization of the alkyne and results in the observed regioselectivity. Similar electronic effects were recently invoked by Hartwig et al.[43] to rationalize regioselectivity in the hydroamination of alkenes containing homoallylic directing groups.

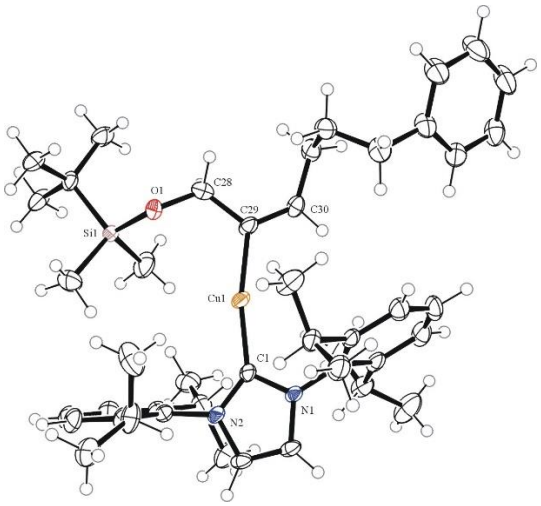
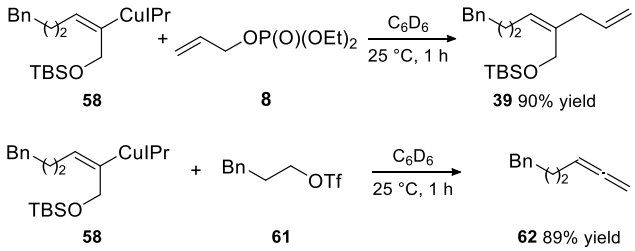


Figure 1. ORTEP presentation of the crystal structure of alkenyl copper complex **58**, with thermal ellipsoids at the 50% probability level. Disorder omitted for clarity (see SI for details).

Allylation vs. alkylation of alkenyl copper complexes 58. After exploring the structure and stability of **58**, we examined its reactivity. We performed stoichiometric reactions with two carbon based electrophiles that can produce trisubstituted alkenes (Scheme 10). In the reaction with allyl phosphate (**8**), we observed the formation of the desired product in 90% yield within 1 h at 25 °C. It is interesting to note that this allylation reaction is significantly faster than the reaction of terminal alkenyl copper complex (**5**) with the same electrophile (Scheme 3).

The alkylation of alkenyl copper complexes with alkyl triflates is the key step in the catalytic hydroalkylation of alkynes previously developed in our lab.[20] With terminal alkenyl copper complexes, the stoichiometric alkylation reaction proceeds quickly to produce the alkylation product in 50% yield, together with the formation of half an equivalent of the dinuclear alkenyl copper complex.[20] In the reaction of the alkenyl copper complex **58** with alkyl triflate **61**, we observed elimination product **62** in 89% yield. The unexpected elimination reaction shows the dramatic effect the electrophile has on the reactivity of alkenyl copper complexes derived from internal alkynes and may explain why internal alkynes, such as **57**, are not viable substrates in the catalytic hydroalkylation reaction. These results also emphasize the unique potential of the hydroallylation reaction as a method for the regio- and diastereoselective synthesis of trisubstituted alkenes from internal alkynes.

Scheme 10. Allylation and alkylation of alkenyl copper complex 58



Conclusion

We have developed a new method for the anti-Markovnikov hydroallylation of alkynes. The hydroallylation is *syn*-stereospecific and highly regioselective, which in most cases leads to the formation of a single product. The reaction can be performed in the presence of a wide range of functional groups, including esters, nitriles, ketones, sulfonate esters, alkyl halides, aryl halides, sulfonamides, thioethers, and silyl ethers. The new method provides stereoselective access to a range of skipped dienes from readily available starting materials. The method also allows regio- and stereoselective synthesis of trisubstituted alkenes from functionalized internal alkynes. This is a major advantage of the hydroallylation reaction over the recently reported copper-catalyzed hydroalkylation reaction, which was limited to transformations of terminal alkynes. Our studies of the key steps of the proposed catalytic cycle suggest that divergent reactivity of the alkenyl copper intermediate with alkyl triflates and allyl phosphates is responsible for this major difference in scope of the two reactions. These studies also suggest an unexpected role of LiO*t*-Bu in allylation step of the catalytic cycle. We have also uncovered unexpected resistance of alkenyl copper complexes to β-elimination of polar functional groups and interesting differences in the reactivity of alkenyl copper complexes derived from internal alkynes toward allylic and alkyl electrophiles.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization of new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI:

AUTHOR INFORMATION

Corresponding Author

*lalic@chem.washington.edu

Author Contributions

† These authors contributed equally. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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ABBREVIATIONS

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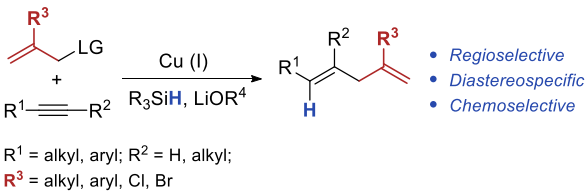
TOC artwork



R^1 = alkyl, aryl; R^2 = H, alkyl;
R^3 = alkyl, aryl, Cl, Br