Allylic Compounds

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Rhodium-Catalyzed Enantioselective Intermolecular Hydroalkoxylation of Allenes and Alkynes with Alcohols: Synthesis of Branched Allylic Ethers

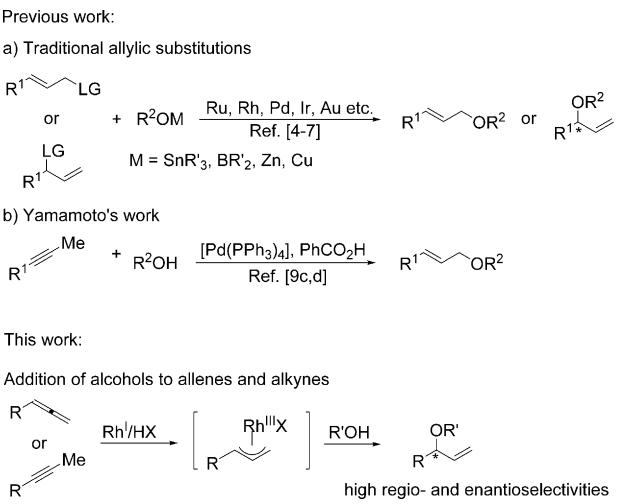
*Zi Liu and Bernhard Breit**

Abstract: *Regio- and enantioselective additions of alcohols to either terminal allenes or internal alkynes provides access to allylic ethers by using a Rh^{I}/diphenyl phosphate catalytic system. This method provides an atom-economic way to obtain chiral aliphatic and aryl allylic ethers in moderate to good yield with good to excellent enantioselectivities.*

Allylic ethers are key components of bioactive molecules and natural products and serve as versatile synthetic intermediates for further construction of numerous structures[1] through a wide variety of reactions such as [2,3] and [3,3] sigmatropic rearrangements and olefin metathesis reactions, among many others.[1b,2,3] Significant progress towards their synthesis has been achieved recently by employing transition metal catalyzed allylic substitution. In most cases, allyl acetates[4] or carbonates[5] have been used as electrophiles. However, recent studies show that even allylic alcohols can serve as allyl precursors.[6] To date, premetalated alkoxides have been used as nucleophiles along with metals to soften the hard nucleophilic character of an alkoxide (such as tin,[4a] boron,[7] zinc,[4b,c,5f] and copper[5a,c–e]).

Following on the initial work with palladium catalysts of the groups of Trost[8] and Yamamoto,[9] we recently reported on a series of rhodium-catalyzed pronucleophile addition reactions to allenes and alkynes, reactions that can be regarded as atom-economic alternatives to allylic substitution chemistry displaying complementary branch regioselectivity (Scheme 1).[10] Thus, hydroamination,[11] hydroesterification,[12] hydroacylation,[13] and hydrothiolation[14] have been achieved to afford versatile enantioenriched branched allylic products. In this context, it would be highly interesting if simple and non-deprotonated alcohols could be added atom economically to allenes or even to alkynes, thus giving valuable branched allylic ether products.

We herein report on the implementation of such a transformation allowing the highly regio- and enantioselective addition of simple and functionalized alcohols, including methanol and ethanol, to terminal allenes and internal alkynes to give a wide range of valuable building blocks for synthetic organic chemistry.



Scheme 1. Intermolecular allylic hydroalkoxylation. LG = leaving group.

Initial reactions were conducted with 3-phenylpropyl allene (**1a**) and ethanol (**2b**) as model substrates. First reactivity assays indicated that the presence of an acidic cocatalyst was necessary. The reaction proved to work using a rhodium(I)/DPEphos/diphenyl phosphate catalyst in dichloromethane (DCM) at 40 °C for 18 hours and furnished the desired allylic ether in 34% yield (Table 1, entry 1).[15] Inspired by this result, various chiral bidentate diphosphine ligands with different backbones were subjected to this model reaction. While many standard privileged chiral ligands failed to catalyze this reaction,[16] the chiral ferrocene-type ligand **L4** proved to be the best (entries 5 and 6). To our delight, switching the solvent from DCM to 1,2-dichloroethane (DCE) gave the desired allylic ether in 76% yield with a remarkable 92% *ee* (entry 6).

With these optimized reaction conditions in hand, we first explored the scope of this reaction with regard to different alcohols and **1a** as the privileged allene (Table 2). A variety of allylic ethers could be prepared in moderate to good yields with excellent enantioselectivities. Not only common primary alcohols but also alcohols possessing functional groups such as chloro, unprotected hydroxy, TMS, and alkenyl moieties (**3e**–**h**) behaved well in this reaction. Notably, upon employing propane-1,3-diol as the reaction partner, only the monoallylated product **3f** was obtained in 71% yield with 92% *ee*. In addition to this, secondary alcohols were also successfully allylated to furnish the corresponding products (**3k**,**l**) with high enantioselectivities, but with slightly lower yields.

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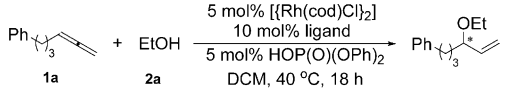
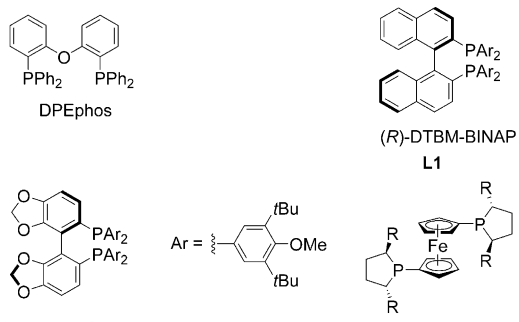
Table 1: Optimization of the reaction conditions.[a]





Entry	Ligand	Yield [%][b]	*ee* [%][c]
1	DPEphos	34	*rac*
2	**L1**	34	49
3	**L2**	19	56
4	**L3**	28	59
5	**L4**	30	75
6[d]	**L4**	76	92

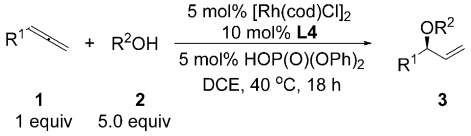
[a] Reaction conditions: **1a** (0.375 mmol), **2b** (5.0 equiv), [{Rh(cod)Cl}$_2$] (5 mol%), ligand (10 mol%) and diphenyl phosphate (5 mol%) in 0.75 mL DCM at 40°C for 18 h. [b] Yield of isolated product. [c] The *ee* values were determined by chiral GC. [d] 0.75 mL DCE was used as solvent. cod = 1,5-cyclooctadiene, DCE = 1,2-dichloroethane, DCM = dichloromethane.

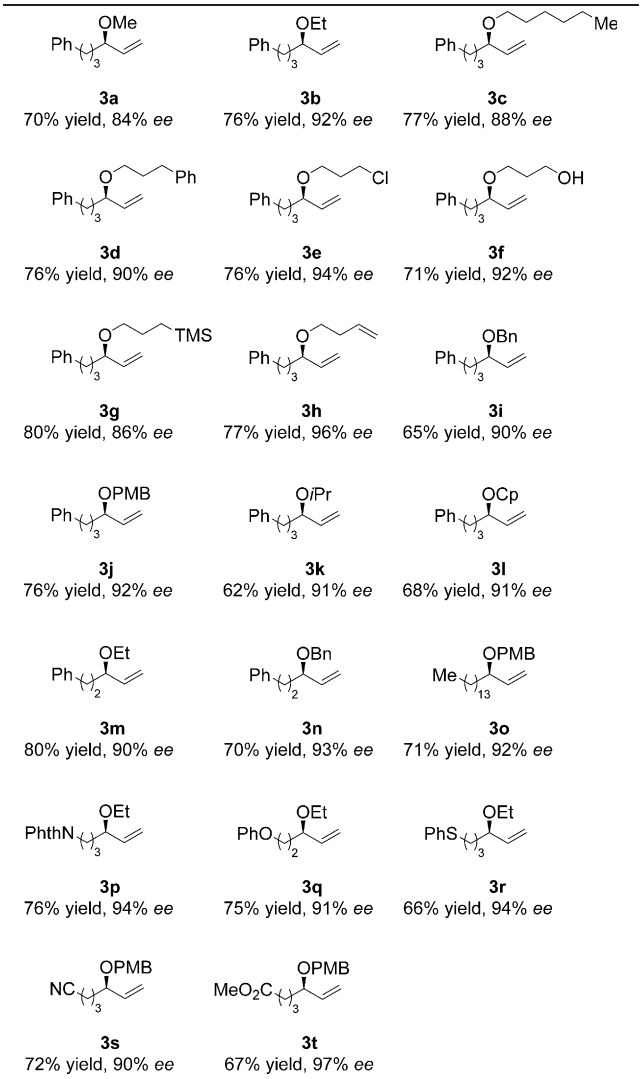
Next, the reactivity of different allenes as suitable reaction partners was explored (Table 2). A linear aliphatic terminal allene devoid of any functional group was compatible (**3o**). Allenes containing a number of different functional groups, such as a phthalimide (**3p**), an ether (**3q**), a thioether (**3r**), a nitrile (**3s**), and an ester (**3t**), smoothly underwent allylic hydroalkoxylation to afford the corresponding products in good yields and excellent enantioselectivities.

To our delight, only a slight change of our initial reaction conditions in terms of the ligand and reaction temperature paved the way to alkynes as suitable reaction partners.[9,17,18] Applying the commercially available (*R*)-DTBM-Garphos as a privileged ligand, a clean allylic etherification of phenylmethyl alkyne could be observed, thus furnishing the allylic ether **5a** in 63% yield and with 89% *ee* (Table 3). At this point, the absolute configuration of **5a** could be assigned upon comparison of the optical rotation with known data.[4d] Aromatic substituents in the vicinity of the alkyne, either being electron-donating or electron-withdrawing, were tolerated well (Table 3, **5b–d**). To our delight, even a cyclopropyl-substituted internal alkyne reacted with benzyl alcohol to provide the desired allylic ether **5e** with an astoundingly high *ee* value (92%). Moreover, functionalized alcohols were still suitable coupling partners for asymmetric alkyne allylation to form branched allylic ethers (**5f–i**).

To illustrate the use of the furnished products and to generate a small synthetic toolbox, some assorted transformations of the allylic ether products featured their utility

Table 2: Asymmetric hydroalkoxylation of allenes.[a,b]

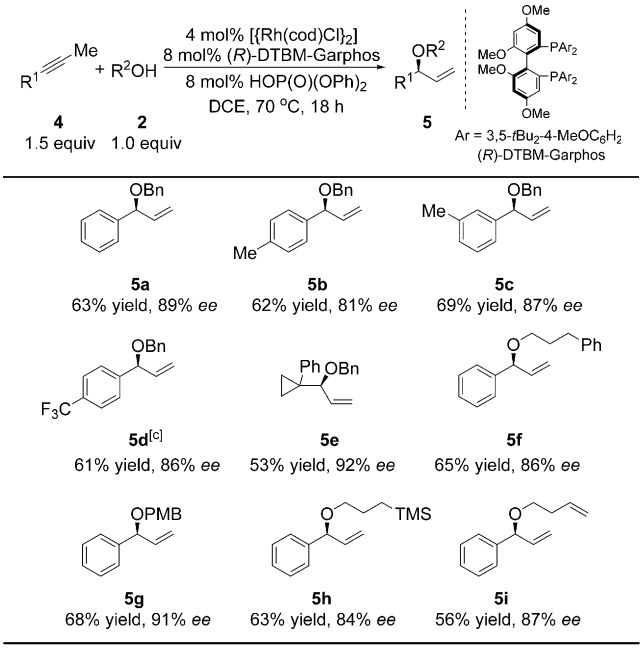




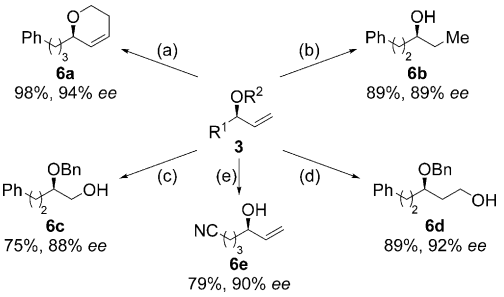
[a] Yield of isolated product. [b] The *ee* values were determined by chiral-phase GC or HPLC. Cp = cyclopentyl, Phth = phthaloyl, PMB = 4-methoxybenzyl, TMS = trimethylsilyl.

as synthetic building blocks (Scheme 2). **3h** was subjected to the reaction conditions of a ring-closing metathesis (RCM) to furnish the 3,6-dihydro-2*H*-pyran derivative **6a** in 98% yield and 94% *ee*. Hydrogenation of **3n** with Pd/C under H_2 (1 atm) at ambient temperature generated the secondary alcohol **6b** through concomitant reduction of the alkene function and cleavage of the benzyl ether. Moreover, the C=C bond was readily modified by ozonolysis and hydroboration to give the 1,2- and 1,3-orthogonally dioxygen-functionalized products **6c** and **6d**, respectively. The PMB ether of **3s** could be cleaved under mild reaction conditions, thus providing an efficient procedure to synthesize the chiral allylic alcohol **6e**.

Table 3: Asymmetric hydroalkoxylation of alkynes.[a,b]



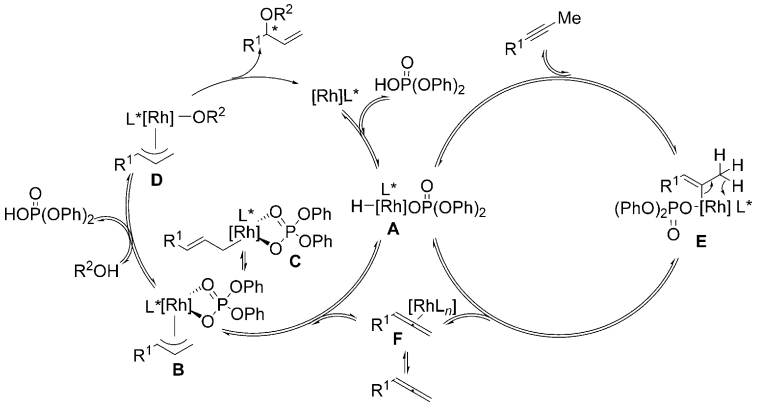
[a] Yield of isolated product. [b] The *ee* values were determined by chiral-phase GC or HPLC. [c] *R*-DTBM-Binap instead of *R*-DTBM-Garphos.



Scheme 2. Transformations of branched allylic ethers. a) Hoveyda–Grubbs second generation catalyst (2 mol%), CH_2Cl_2, 40°C, overnight; **6a** (product of **3h**), 98% yield, 94% *ee*. b) Pd/C (10 mol%), H_2 (1 atm), MeOH, RT, 18 h; **6b** (product of **3n**), 89% yield, 89% *ee*. c) O_3, CH_2Cl_2, −78°C; then MeOH, $NaBH_4$, 0°C, 2 h; **6c** (product of **3n**), 75% yield, 88% *ee*. d) 9-BBN (2.0 equiv), THF, −78°C to RT, overnight; then H_2O_2, NaOH, EtOH, 0°C to RT, 3 h; **6d** (product of **3n**), 89% yield, 92% *ee*. e) DDQ (1.2 equiv), DCM, H_2O, 0°C to RT, 3 h; **6e** (product of **3s**), 79% yield, 90% *ee*. 9-BBN = 9-borabicyclo-[3.3.1]nonane, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, THF = tetrahydrofuran.

On the basis of our previous investigations,[11–14,19] the reaction mechanism is proposed in Scheme 3. For the reaction starting from allenes, we suggest that the rhodium catalyst undergoes oxidative addition with diphenyl phosphate to yield the rhodium(III) hydride (**A**). Hydrometallation of the allene furnishes the σ- or π-rhodium-allyl species (**B** or **C**). Anion exchange with the alcohol followed by a reductive elimination of **D** generates the allylic ether product and regenerates the rhodium(I) catalyst. However, at this stage, a direct external attack of the alcohol on the rhodium allyl species (**B**) cannot be ruled out. For the alkyne reaction, the formation of the rhodium vinyl species **E** is followed by β-hydride elimination to generate either a rhodium/allene complex **F** and/or the free allene (right side of Scheme 3).[20] From here on, the reaction mechanism follows the allene cycle (left side of Scheme 3). Detailed mechanistic studies of this rhodium-catalyzed enantioselective allylic alkoxylation of allenes and alkynes are currently underway.

To conclude, we have developed a mild and efficient protocol for the regio- and enantioselective addition of simple and functionalized alcohols to terminal allenes and internal alkynes. The use of a catalytic amount of diphenyl phosphate as an acid in combination with an appropriate rhodium(I)/chiral diphosphine was crucial for success in realizing this atom-economic allylic etherification. This protocol was found to be applicable to a wide range of substrates, including primary and secondary alcohols and various substituted allenes or alkynes. Further exploration of the rhodium(I)/diphenyl phosphate catalytic system is currently underway in our laboratories.



Scheme 3. Possible mechanism.

Acknowledgments

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Keywords: alkynes · allenes · allylic compounds · rhodium · synthetic methods

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[15] Diphenyl phosphate proved to be a unique acidic cocatalyst since other Brønsted acids failed to catalyze these reactions for reasons which are unknown to date. For screening of other potential acidic cocatalysts see the Supporting Information.

[16] For a comprehensive ligand screening see the Supporting Information.

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[20] The rhodium(I)/Garphos/diphenyl phosphate catalyst reacted with phenylallene and benzyl alcohol to give the corresponding allylic ether in low yield (7%) in addition to a complex mixture of side products. However, the reaction starting from the corresponding internal alkyne is much cleaner (Table 3, entry 1). This difference indicates that for the alkyne reaction, a high concentration of allene is never reached. Instead, the reaction may proceed more smoothly through the allene rhodium complex **F** indicated in Scheme 3.

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Communications

Allylic Compounds

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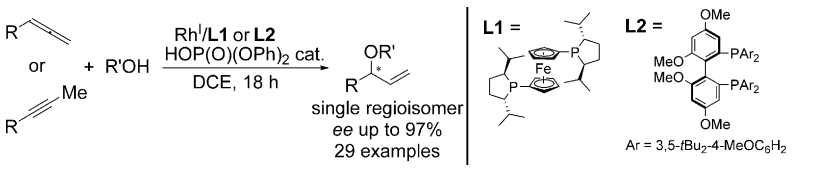
Rhodium-Catalyzed Enantioselective Intermolecular Hydroalkoxylation of Allenes and Alkynes with Alcohols: Synthesis of Branched Allylic Ethers



Allenes, alkynes, and alcohols: The rhodium-catalyzed atom-economic coupling of simple and functionalized alcohols with functionalized terminal allenes and internal alkynes proceeds with chiral bidentate diphosphine ligands and rhodium. The reaction furnishes branched allylic ethers with high regio- and enantioselectivity.