Hydrogenation

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C-Propargylation Overrides *O*-Propargylation in Reactions of Propargyl Chloride with Primary Alcohols: Rhodium-Catalyzed Transfer Hydrogenation

*Tao Liang, Sang Kook Woo, and Michael J. Krische**

Abstract: *The canonical S_N2 behavior displayed by alcohols and activated alkyl halides in basic media (O-alkylation) is superseded by a pathway leading to carbinol C-alkylation under the conditions of rhodium-catalyzed transfer hydrogenation. Racemic and asymmetric propargylations are described.*

The merger of carbonyl addition and transfer hydrogenation has enabled a new class of metal-catalyzed C–C couplings wherein lower alcohols are converted directly into higher alcohols.[1] Three mechanistic pathways are corroborated, in which alcohol dehydrogenation mediates a) C–C π-bond hydrometalation (Ir^I, Ru^{II}), b) metalacycle transfer hydrogenolysis (Ru^0, Os^0), or c) reductive cleavage of a C–X bond (Ir^I).[1] In the latter context, iridium-based catalysts operate exclusively, promoting the coupling of primary alcohols with a diverse array of allylic carboxylates[2a–d] and related pronucleophiles, such as vinyl epoxides[2e] and vinyl aziridines.[2f] The identification of metal catalysts, beyond iridium, that promote alcohol C–H functionalization by C–X bond reductive cleavage pathways should enable further expansion of substrate scope. Rhodium-based catalysts, being isostructural with respect to iridium, were viewed as promising candidates. However, rhodium is used less frequently than iridium in transfer hydrogenation,[3] with the vast majority of examples involving analogues of the classic ruthenium-based system [RuCl(Tsdpen)(η^6-arene)].[4,5b–e] Indeed, rhodium analogues of the broadly utilized cyclometalated π-allyliridium *ortho-C,O*-benzoate complexes developed in our laboratory have not yet proven effective (Figure 1).

As the pronucleophile serves as oxidant in all transfer hydrogenative couplings, we reasoned that more easily reduced pronucleophiles might be accommodated by rhodium, which is a weaker reductant than iridium.[6] Accordingly, we turned our attention to the redox-triggered coupling of primary alcohols and propargyl chloride, with the goal of developing methods for enantioselective carbonyl propargylation (Figure 2).[7–15] In earlier work from our laboratory,[16] an iridium-catalyzed transfer hydrogenative carbonyl propargylation was developed [Eq. (1)],[16c] but suffered from two severe limitations in scope: a) trialkylsilyl substitution was required at the acetylenic terminus of the propargyl chloride,

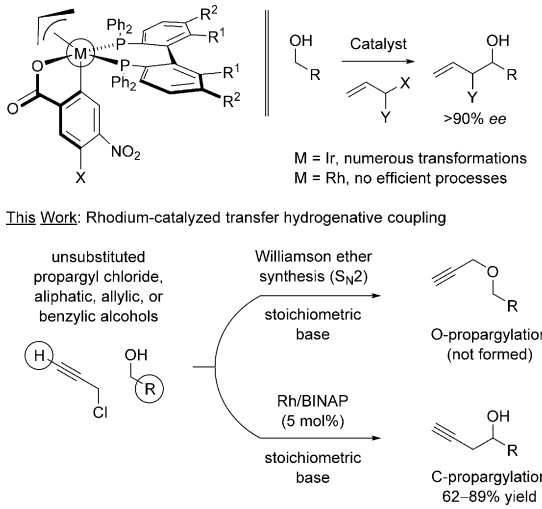

Figure 1. Rhodium versus iridium catalysts for redox-triggered carbonyl addition.

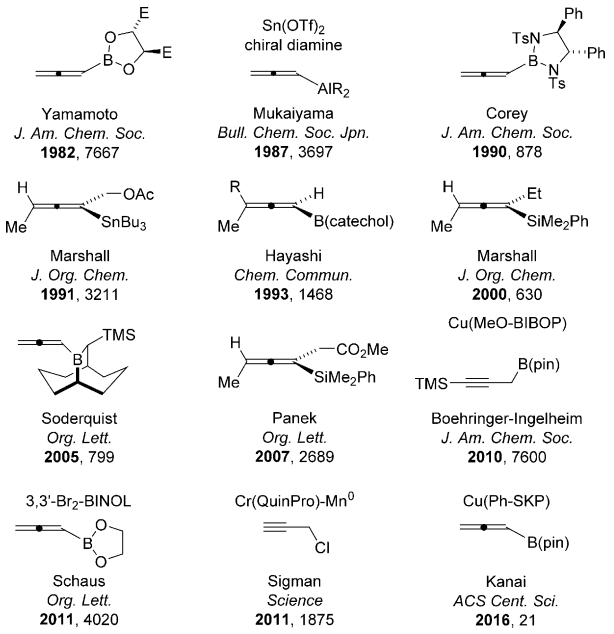

Figure 2. Selected methods for enantioselective carbonyl propargylation.[15–17]

and b) only benzylic alcohols would participate in C–C coupling. To determine whether rhodium catalysts could overcome these restrictions, a series of experiments were performed. The rhodium analogue of the optimal iridium

[*] Dr. T. Liang, Dr. S. K. Woo, Prof. M. J. Krische
University of Texas at Austin, Department of Chemistry
105 E 24th St. (A5300), Austin, TX 78712-1167 (USA)
E-mail: mkrische@mail.utexas.edu

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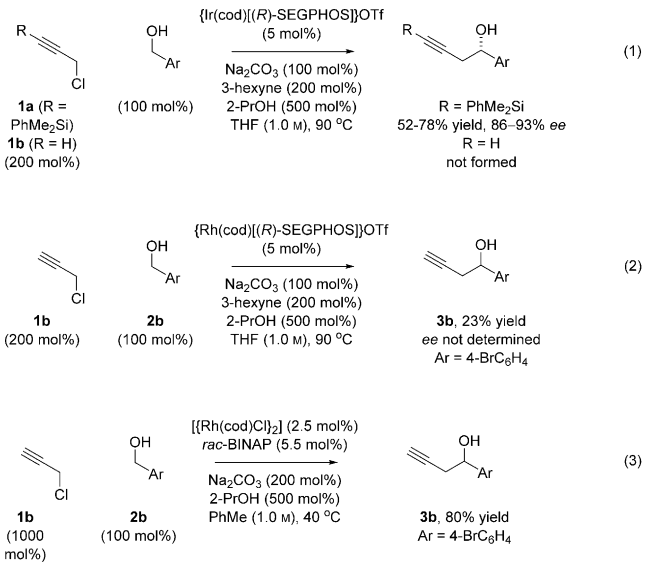
catalyst, identified for the coupling of the silyl-terminated propargyl chloride **1a** with benzyl alcohols, was prepared and evaluated in the coupling of the benzylic alcohol **2b** with the unsubstituted propargyl chloride **1b** [Eq. (2)]. The desired product, homopropargyl alcohol **3b**, was obtained in 23% yield. Further improvements in the yield of **3b** were obtained by conducting the reaction at 40 °C in toluene, a remarkably low temperature for alcohol dehydrogenation, using a neutral rhodium/BINAP catalyst and increasing the loading of **1b** (1000 mol%). Applied in concert, these changes enabled formation of **3b** in 80% yield [Eq. (3)]. Reactions conducted at a lower loading of **1b** (500 mol%) under otherwise identical reaction conditions led to a modest but significant decrease in the yield of **3b** (10–15% lower). A comparable decrease in the yield of **3b** is observed upon omission of 2-propanol. Remarkably, products of *O*-propargylation by S_N2 substitution were not observed.[17]



To establish the generality of these reaction conditions, in particular, the ability to engage aliphatic alcohols in *C*-propargylation, these reaction conditions were applied to the primary alcohols **2a–o** (Table 1). The benzylic alcohols **2a–h**, including the *ortho*-substituted benzylic alcohol **2f** and heteroaromatic benzylic alcohol **2h**, were converted into the corresponding homopropargylic alcohols **3a–h** in good to excellent yield. Remarkably, the allylic alcohols **2i** and **2j** were converted into the homopropargyl alcohols **3i** and **3j**, respectively, without competing internal redox isomerization.[18] Most importantly, the aliphatic alcohols **2k–o** were converted into the homopropargylic alcohols **3k–o**, respectively, in good yield. Finally, as illustrated in the conversion of *dehydro*-**2b** to **3b**, these reaction conditions are applicable to the 2-propanol-mediated reductive coupling of **1b** with aldehydes [Eq. (4)].

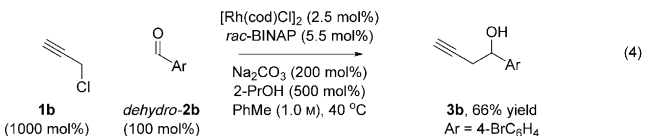
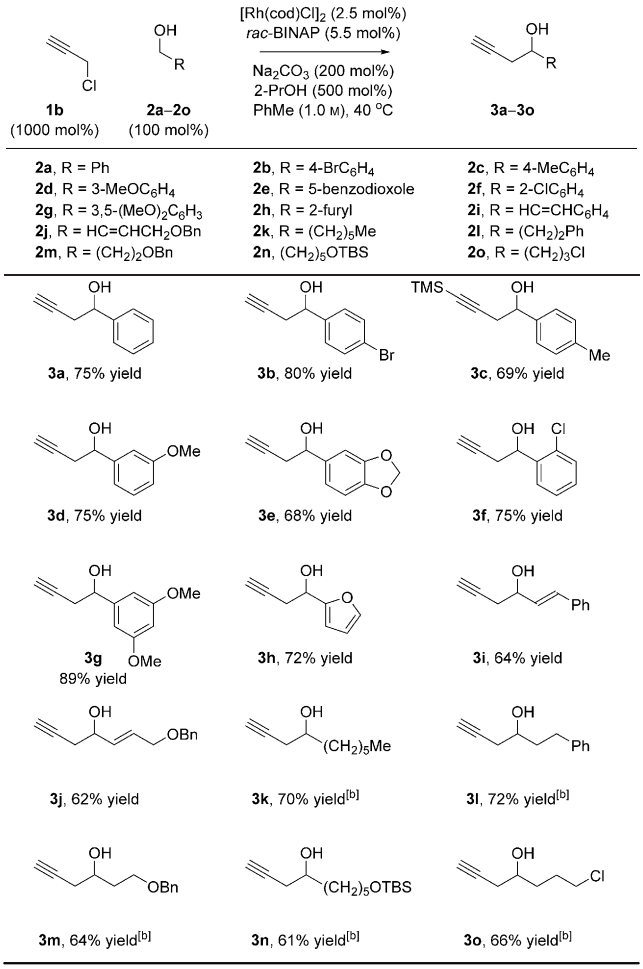
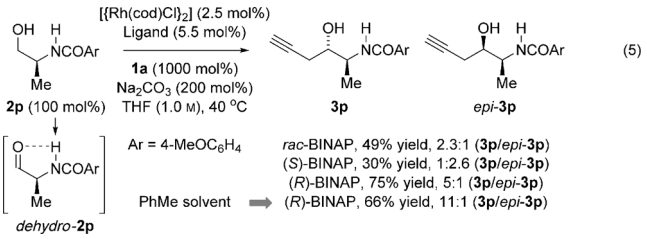


Table 1: Rhodium-catalyzed C–C coupling of **1b** with the alcohols **2a–o** to form homopropargyl alcohols **3a–o**.[a]



[a] Yields are of material isolated by silica gel chromatography. See the Supporting Information for further experimental details. [b] 2-PrOH was omitted. TBS = *tert*-butyldimethylsilyl.

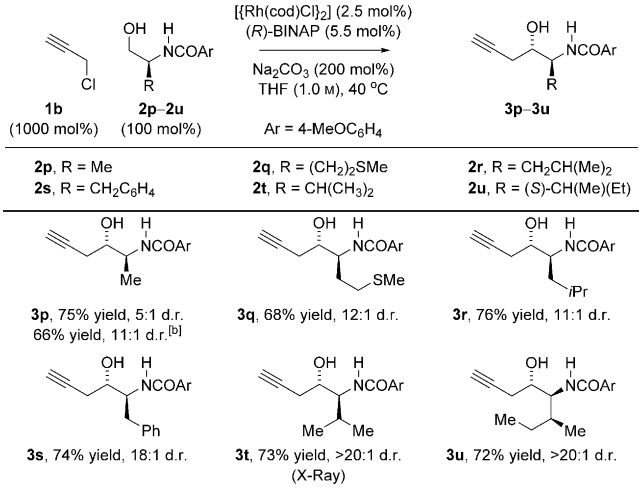
The products **3a–o** were generated using a racemic rhodium/BINAP catalyst (Table 1). By using enantiomerically pure BINAP, moderate levels of enantioselectivity are observed (40–55% *ee*). Efforts to improve enantioselectivity while maintaining high levels of conversion have, thus far, been unrequited. Hence, match-mismatch effects in the *C*-propargylation of the enantiomerically enriched α-stereogenic amino alcohol **2p** were explored [Eq. (5)]. First, to establish the intrinsic diastereofacial bias, the rhodium catalyst modified by racemic BINAP was used. The *anti*- and *syn*-diastereomers **3p** and *epi*-**3p** are formed in a 2.3:1 ratio. This diastereofacial bias suggests intervention of an internal NH–O hydrogen bond in the transient aldehyde *dehydro*-**2p**, which directs carbonyl addition to the sterically less encumbered face of the chelate. When the propargylation is conducted using (*S*)-BINAP, the mismatched case, **3p** and *epi*-**3p** are formed in a 1:2.6 ratio. When the reaction is conducted using (*R*)-BINAP (the matched case), **3p** and *epi*-**3p** are formed in a 5:1 ratio. It was reasoned that reactions conducted in a lower dielectric medium, which is more conducive to hydrogen bonding, would display higher diaste-



reoselectivities. Indeed, in toluene, **3p** and *epi*-**3p** are formed in an 11:1 ratio, albeit in slightly lower yield.

These reaction conditions were applied to the *C*-propargylation of enantiomerically enriched α-amino alcohols **2p–u** (Table 2). Because of the solubility issues, it was necessary to use THF as the solvent. Nevertheless, the products of asymmetric *C*-propargylation (**3p–u**) were formed in a stereoselective manner, with diastereoselectivities increasing with increasing size of the α-substituent. HPLC analysis of **3p**, prepared through asymmetric propargylation, was compared to a mixture of all four stereoisomers, revealing that racemization of the transient aldehyde does not occur (see the Supporting Information).

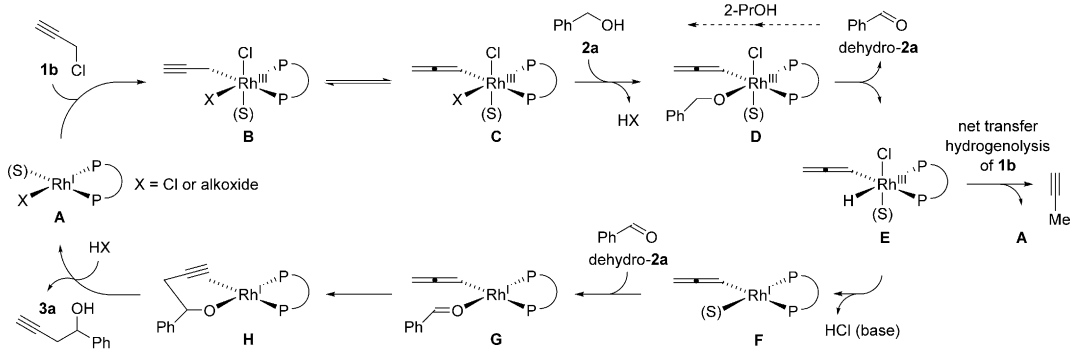
Table 2: Rhodium-catalyzed C–C coupling of **1b** with the α-amino alcohols **2p–u** to form the homopropargyl alcohols **3p–u**.[a]



[a] Yields are of material isolated by silica gel chromatography. See the Supporting Information for further experimental details. [b] Toluene (1.0 M).

Although at this early stage precise details of the catalytic mechanism are unknown, a very simple working model has been proposed as a basis for further refinement (Scheme 1). It is postulated that catalysis is initiated by oxidative addition of **1b** to the rhodium complex **A** to form the η^1-allenylrhodium(III) complex **C**. Precedent for this step in the catalytic mechanism is found in the oxidative addition of **1b** to Vaska's complex, which provides well-defined η^1-allenyliridium(III) complexes.[19] Equilibration may occur between **C** and the propargylrhodium(III) complex **B**, however, the η^1-allenylmetal isomers are thermodynamically preferred.[20] Complex **C** undergoes substitution with **2a** to form the rhodium(III) alkoxide complex **D**, which upon β-hydride elimination generates the rhodium(III) hydrochloride complex **E** and *dehydro*-**2a**. At this stage, **E** may undergo C–H reductive elimination to form propyne, which may account for the requirement of relatively high loadings of **1b**. An ion consistent with the molecular weight of propyne (or allene) is observed by GC-MS analysis of aliquots taken from reaction mixtures in the coupling of **1b** and **2a**. This pathway, which effects net catalytic transfer hydrogenolysis of **1b**, delivers unreacted aldehyde, which is converted back into the alcohol by 2-propanol-mediated reduction, reinitiating the catalytic cycle. Nonconjugated aldehydes derived from the alcohols **2k–u** appear more reactive toward addition; hence, 2-propanol is not required. Alternatively, **E** may eliminate HCl with the assistance of base, as documented in stoichiometric transformations.[21] The latter pathway delivers the η^1-allenylrhodium(I) complex **F**, which coordinates the aldehyde to the form complex **G**, which, in turn, triggers carbonyl addition to generate the homoallylic rhodium(I) alkoxide **H**. Protonolytic cleavage then releases the **3a** and regenerates **A** to close the catalytic cycle. The stereochemistry of the octahedral complexes **B**–**E** should be considered tentative.

In summary, new reactivity is the most fundamental basis for innovation in the field of chemical synthesis. Here, using the concepts of C–C bond formation transfer hydrogenation pioneered in our laboratory, the canonical S_N2 behavior displayed by alcohols and activated alkyl halides in basic media (*O*-alkylation) is superseded by an alternate pathway



Scheme 1. General catalytic mechanism for rhodium-catalyzed alcohol *C*-propargylation.[a]

leading to products of carbinol *C*-alkylation. This method enables direct conversion of primary alcohols, including simple aliphatic alcohols, into secondary homopropargyl alcohols using inexpensive, commercial reagents. More broadly, these studies further demonstrate how the native reducing features of alcohol reactants can mediate reductive carbonyl addition, thus bypassing preformed carbanions and discrete redox reactions.

Acknowledgments

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Keywords: alcohols · hydrogenation · reaction mechanisms · rhodium · synthetic methods

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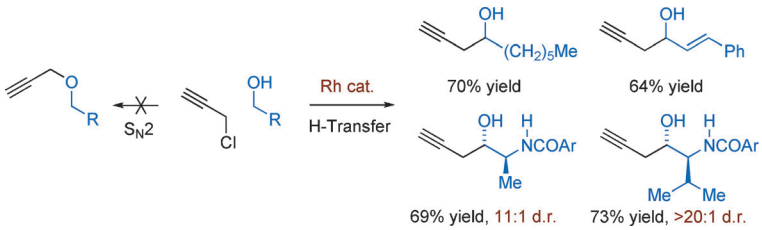
Communications

Hydrogenation

T. Liang, S. K. Woo,
M. J. Krische* ———— ■■■■–■■■■

C-Propargylation Overrides *O*-Propargylation in Reactions of Propargyl Chloride with Primary Alcohols: Rhodium-Catalyzed Transfer Hydrogenation



A path less travelled: The canonical S_N2 behavior displayed by alcohols and activated alkyl halides in basic media (*O*-alkylation) is superseded by a pathway leading to carbinol *C*-alkylation under the conditions of rhodium-catalyzed transfer hydrogenation. Racemic and asymmetric propargylations are described.