

Published in final edited form as:

Angew Chem Int Ed Engl. 2008 ; 47(28): 5220–5223. doi:10.1002/anie.200801359.

Carbonyl Propargylation from the Alcohol or Aldehyde Oxidation Level Employing 1,3-Enynes as Surrogates to Preformed Allenylmetal Reagents: A Ruthenium-Catalyzed C–C Bond-Forming Transfer Hydrogenation**

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Keywords

cross-coupling; enynes; propargylation; ruthenium; transfer hydrogenation

Over the past half century, numerous protocols for carbonyl propargylation using allenylmetal reagents have been developed.[1] Allenic Grignard reagents were used by Prévost et al.[2a] in carbonyl additions to furnish mixtures of β -acetylenic and α -allenic carbinols, which led to them to coin the term “propargylic transposition.”[2a,b] Subsequent studies by Chodkiewicz and co-workers[2c] demonstrated relative stereocontrol in such additions. Shortly thereafter, Lequam and Guillerm[2d] reported that isolable allenic stannanes provide products of carbonyl propargylation upon exposure to chloral. Later, Mukaiyama and Harada[2e] demonstrated that stannanes generated in situ from propargyl iodides and stannous chloride reacted with aldehydes to provide mixtures of β -acetylenic and α -allenic carbinols. Related propargylations employing allenylboron reagents were first reported by Favre and Gaudemar,[2f] and propargylations employing allenylsilicon reagents were first reported by Danheiser and Carini.[2g] Asymmetric variants followed (Scheme 1). Allenylboron reagents chirally modified at the boron center engage in asymmetric propargylation, as was first reported by Yamamoto and co-workers[2h] and Corey et al.[2i] Allenylstannanes chirally modified at the tin center also induce asymmetric carbonyl propargylation, as was first reported by Minowa and Mukaiyama.[2j] Axially chiral allenylstannanes, allenylsilanes, and allenylboron reagents propargylate aldehydes enantiospecifically, as was first described by Marshall et al.,[2k,l] and Hayashi and coworkers,[2m] respectively. Finally, asymmetric aldehyde propargylation using allenylmetal reagents may be catalyzed by chiral Lewis acids or chiral Lewis bases, as was first reported by Keck et al.,[2n] and Denmark and Wynn,[2o] respectively.

Here, we report a new approach to carbonyl propargylation based on ruthenium-catalyzed C–C bond-forming transfer hydrogenation.[3–5] Specifically, upon exposure of 1,3-enynes **1a–1g** to alcohols **2a–2o** in the presence of $[\text{RuHCl}(\text{CO})(\text{PPh}_3)_3]/\text{dppf}$ (dppf = 1,1'-bis(diphenylphosphino)ferrocene), hydrogen shuffling between reactants occurs to generate nucleophile–electrophile pairs that regioselectively combine to furnish products of carbonyl

** Acknowledgements are made to Merck, the Robert A. Welch Foundation, the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable, and the NIH (Grant No. RO1-GM069445) for partial support of this research.

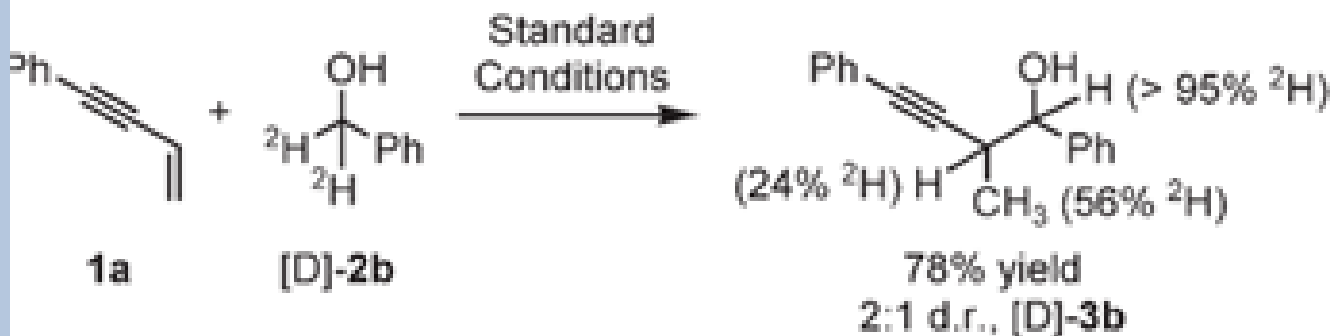
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Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.200801359>.

propargylation.[6] Under related transfer hydrogenation conditions and employing isopropanol as the terminal reductant, 1,3-enynes couple to aldehydes to furnish identical products of carbonyl propargylation. The observed regiochemistry is unique with respect to related enyne–carbonyl reductive coupling reactions that are catalyzed by rhodium[5,7] and nickel complexes, [8,9,10] which favor coupling at the acetylenic terminus of the enyne. Significantly, this protocol enables carbonyl propargylation from the alcohol or aldehyde oxidation level in the absence of preformed allenylmetal reagents (Scheme 2).

In connection with our efforts to exploit catalytic hydrogenation in C–C coupling reactions beyond hydroformylation,[5] we recently demonstrated that C–C bond formation may be achieved under the conditions of iridium- and ruthenium-catalyzed transfer hydrogenation. [11] These processes enable direct carbonyl allylation from the alcohol or aldehyde oxidation level by using commercially available allenes or dienes as allyl donors. Seeking to develop corresponding carbonyl propargylations, diverse iridium and ruthenium complexes were assayed for their ability to catalyze the coupling of enyne **1a** and alcohol **2a**. Gratifyingly, both [$\text{Ir}(\text{cod})\text{Cl}$]₂/biphep (biphep =diphenylphosphine, cod =cycloocta-1,5-diene) and [$\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$]/dppf catalyze the desired coupling. The ruthenium-based catalyst was most effective and, under optimized conditions, enyne **1a** coupled to benzylic, allylic, and aliphatic alcohols **2a–2o** to form homopropargyl alcohols **3a–3o** in good to excellent yields (Table 1). To probe the scope of the enyne coupling partner, enynes **1b–1g** were coupled to benzyl alcohol **2b** under standard reaction conditions. Good to excellent yields of propargylation products **3p–3u** were observed (Table 2). Substitution at the olefinic terminus of the enyne was found to diminish conversion to product. Finally, carbonyl allylation can also be achieved from the aldehyde oxidation level by employing isopropanol as the terminal reductant. Under standard reaction conditions, aldehydes **4a–4c** couple to enyne **1a** to provide the products of carbonyl propargylation **3a–3c**, respectively, in good to excellent yield. Thus, carbonyl propargylation may be achieved from either the alcohol or aldehyde oxidation level (Table 3). The coupling products **3a–3u** are remarkably resistant to over-oxidation to form the corresponding β,γ -acetylenic ketones. However, such over-oxidation is observed if cationic ruthenium complexes are employed as catalysts. This result suggests that, for the neutral ruthenium complexes employed in this study, the alkyne moiety of the coupling product blocks a coordination site required for β hydride elimination of the carbinol C–H bond. Other aspects of the catalytic mechanism, including determination of the structural and interactive features of the ruthenium complex that influence relative and absolute stereocontrol, are currently under investigation.

A general catalytic mechanism is likely to involve the following steps:[11] a) alcohol dehydrogenation to generate a ruthenium hydride is followed by b) enyne hydrometalation to generate an allenyl metal–aldehyde/nucleophile–electrophile pair, which undergoes c) carbonyl addition with propargylic transposition. Consistent with this interpretation, the coupling of enyne **1a** to [D]-**2b** under standard reaction conditions provides [D]-**3b**, in which deuterium is incorporated at the benzylic position (>95%), the allylic methyl group (56%), and the allylic methine position (24%), thus suggesting reversible olefin-hydrometalation [Eq. (1)].



(1)

Our collective studies on hydrogenative and transfer hydrogenative C–C coupling define a departure from the use of preformed organometallic reagents in carbonyl addition chemistry. [5,11] For such transfer hydrogenative coupling reactions, hydrogen embedded within isopropanol or an alcohol substrate is redistributed among reactants to generate nucleophile–electrophile pairs, thus enabling carbonyl addition from the aldehyde or alcohol oxidation level. In this way, carbonyl additions that transcend the boundaries of oxidation level are devised. In the present study, we have demonstrated that 1,3-enynes serve as allenylmetal equivalents under the conditions of transfer hydrogenative coupling, thus also enabling carbonyl propargylation from the alcohol or aldehyde oxidation level. These studies contribute to a growing body of catalytic methods for the direct functionalization of carbinol C–H bonds. [11,12] Future studies will focus on the development of related alcohol–unsaturate C–C coupling processes.

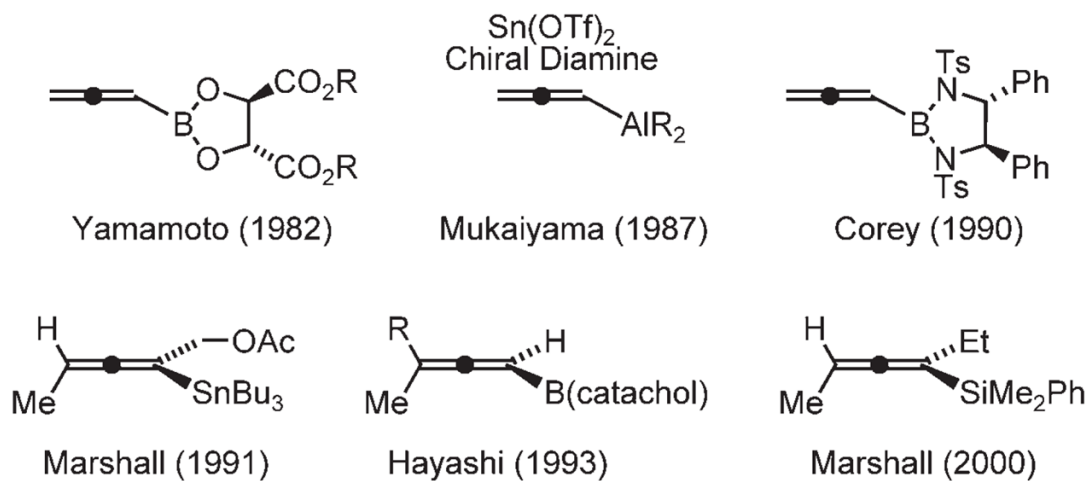
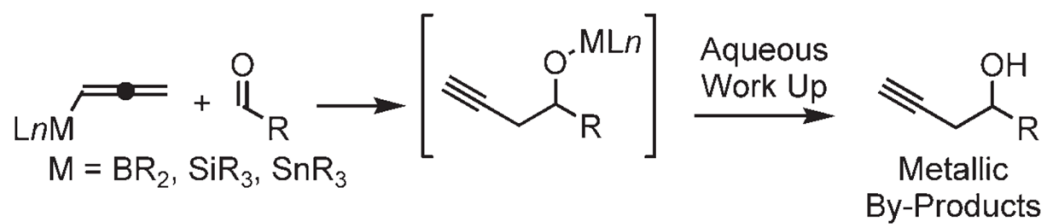
Supplementary Material

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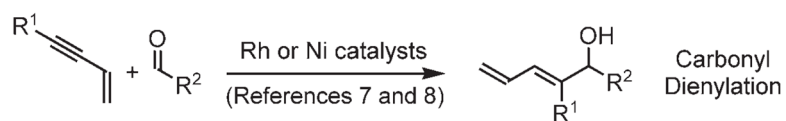
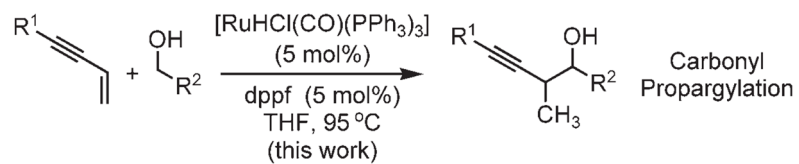
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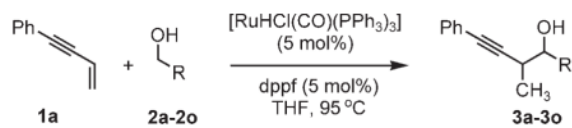
**Scheme 1.**

Chirally modified allenylmetal reagents for carbonyl propargylation. Tf =trifluoromethanesulfonyl, Ts =*para*-toluenesulfonyl.

Rh- and Ni-catalyzed enyne–aldehyde reductive coupling**Ru-catalyzed enyne–alcohol transfer hydrogenative coupling****Scheme 2.**

Divergent regioselectivity observed in metal-catalyzed enyne–carbonyl coupling.

Table 1

Carbonyl propargylation from the alcohol oxidation level by ruthenium-catalyzed transfer hydrogenation.^a2a, R = *p*-NO₂Ph

2b, R = phenyl

2c, R = *p*-MeOPh2d, R = *o*-MeOPh

2e, R = 5-piperonyl

2f, R = *p*-BrPh

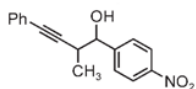
2g, R = 2-furyl

2h, R = 3-indolyl

2i, R = 2-(6-BrPy)

2j, R = cinnamyl

Coupling to benzylic alcohols



3a

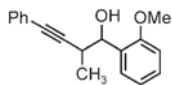
65% yield

1:1 d.r.

3b

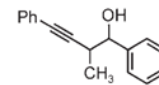
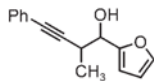
81% yield

1:1 d.r.

**3d**

91% yield

2:1 d.r.

**3e**

83% yield

2:1 d.r.

**3g**

71% yield

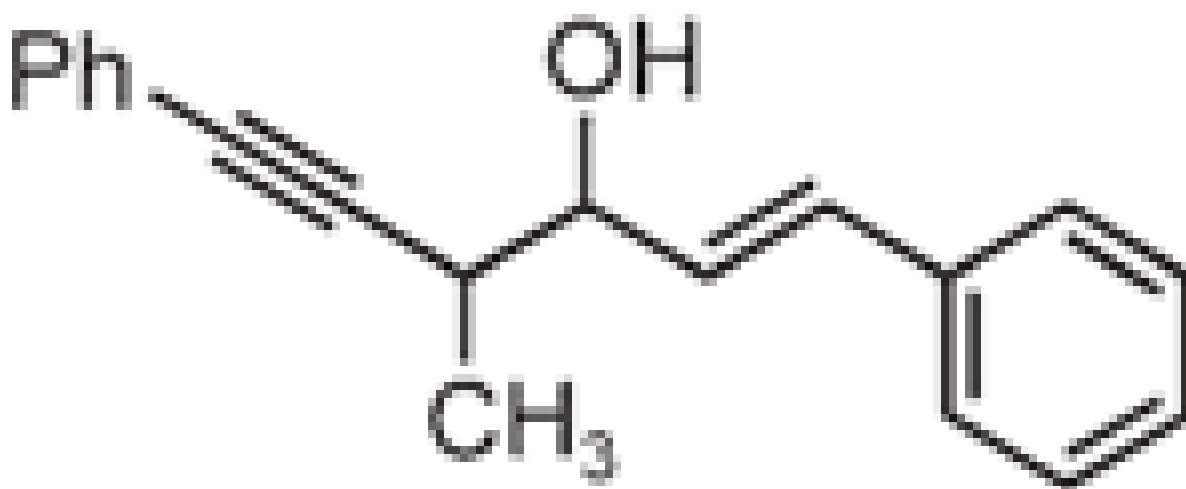
1.5:1 d.r.

Coupling to allylic alcohols

3h

94% yield

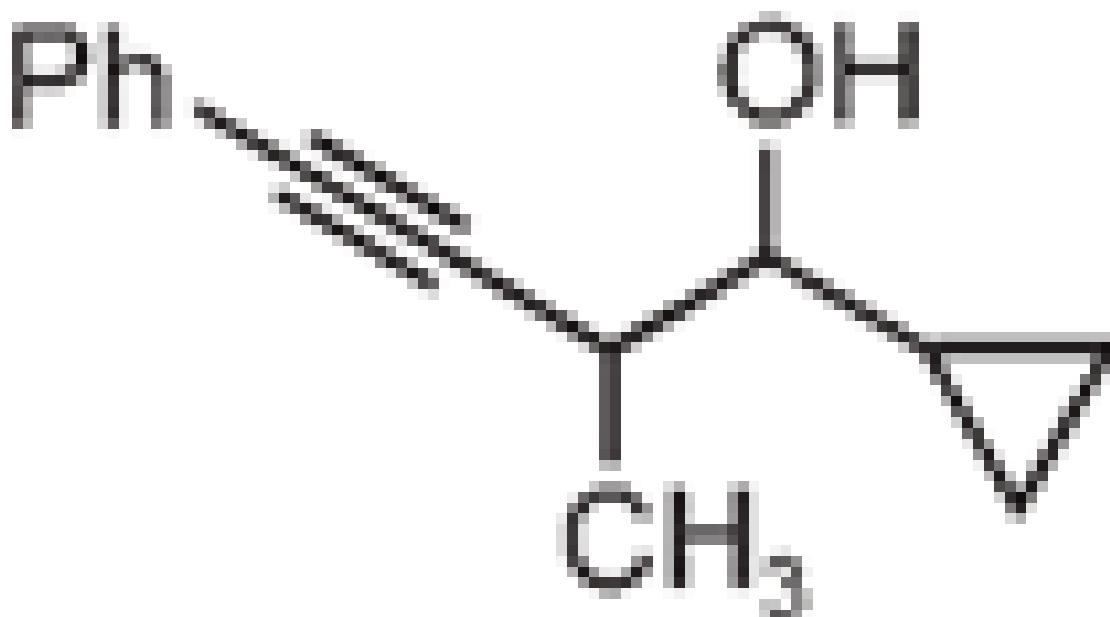
1:1 d.r.

**3j**

68% yield

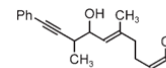
1:1 d.r.

Coupling to aliphatic alcohols

**3m**

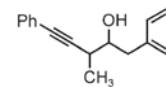
75% yield

2:1 d.r.

**3k**

63% yield

1.5:1 d.r.

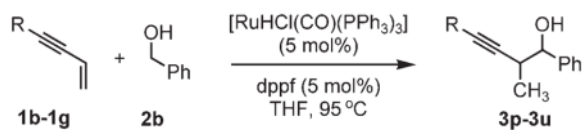
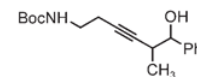
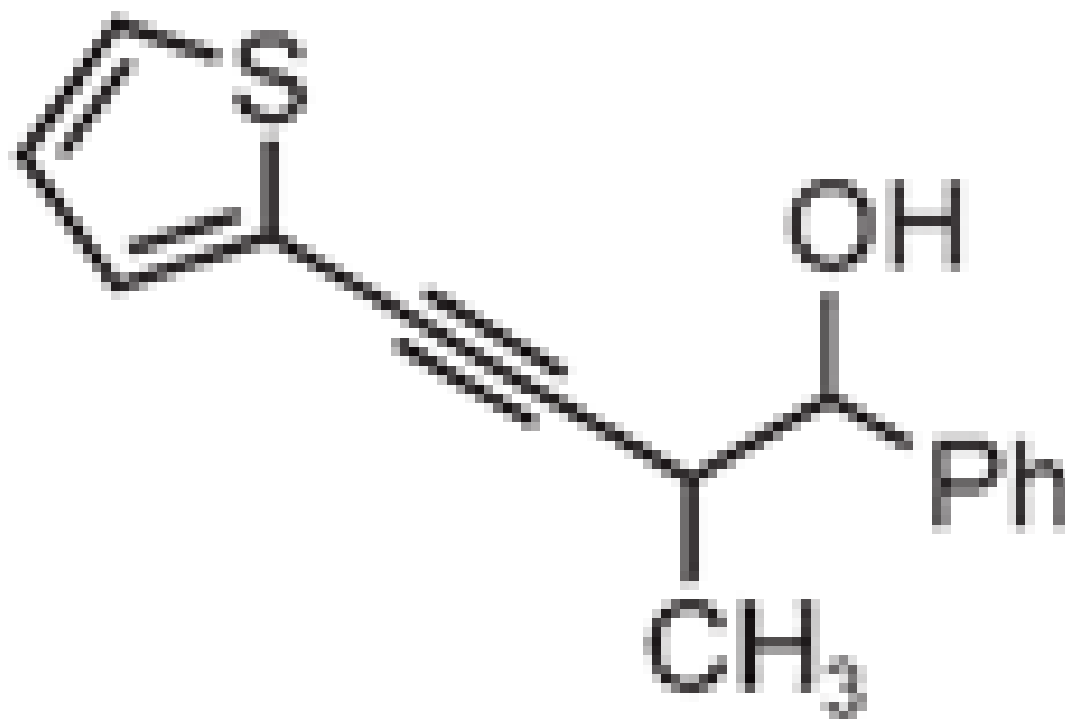
**3n**

70% yield

1:1 d.r.

^aYields of isolated material. Standard reaction conditions employed 1 equivalent of alcohol/aldehyde and 2 equivalents of enyne. See the Supporting Information for detailed experimental procedures. Py = pyridine.

Table 2

Coupling of enynes **1b–1g** to benzyl alcohol **2b** by ruthenium-catalyzed transfer hydrogenation.^a**1b**, R = 2-thienyl**1c**, R = BocNH(CH₂)₂**1d**, R = TBSO(CH₂)₄**1e**, R = TBSOCH₂**3p**^b

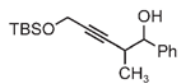
71% yield

1:1 d.r.

3q

54% yield

1:1 d.r.

**3s**

78% yield

1.5:1 d.r.

3t^b

56% yield

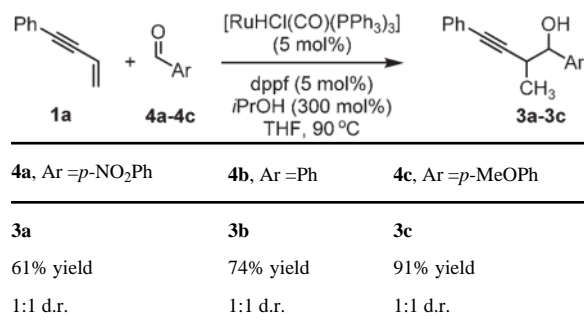
1:1 d.r.

^aSee the footnotes of Table 1 for details.

^b*m*-NO₂BzOH (5 mol%) was employed as a cocatalyst. Boc = *tert*-butoxycarbonyl, Bz = benzyl, TBS = *tert*-butyldimethylsilyl.

Table 3

Carbonyl propargylation from the aldehyde oxidation level by ruthenium-catalyzed transfer hydrogenation.^a



^a Formation of **3a** and **3b** were accompanied by about 10% alkyne reduction. See the Supporting Information for detailed experimental procedures.