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Direct Vinylation of Alcohols or Aldehydes Employing Alkynes as Vinyl Donors: A Ruthenium Catalyzed C-C Bond Forming Transfer Hydrogenation

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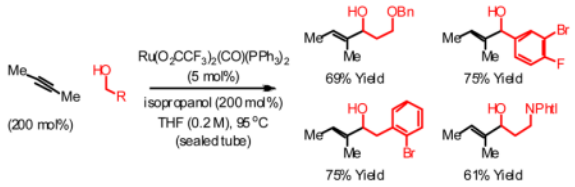
Abstract



Under the conditions of ruthenium catalyzed transfer hydrogenation, 2-butyne couples to benzylic and aliphatic alcohols **1a–1i** to furnish allylic alcohols **2a–2i**, constituting a direct C-H vinylation of alcohols employing alkynes as vinyl donors. Under related transfer hydrogenation conditions employing formic acid as terminal reductant, 2-butyne couples to aldehydes **4a, 4b, and 4e** to furnish identical products of carbonyl vinylation **2a, 2b, and 2e**. Thus, carbonyl vinylation is achieved from the alcohol or the aldehyde oxidation level in the absence of any stoichiometric metallic reagents. Nonsymmetric alkynes **6a–6c** couple efficiently to aldehyde **4b** to provide allylic alcohols **2m–2o** as single regioisomers. Acetylenic aldehyde **7a** engages in efficient intramolecular coupling to deliver cyclic allylic alcohol **8a**.

Carbonyl vinylation is a convergent protocol for the preparation of allylic alcohols. Following the seminal work of Oguni (1984) and Noyori (1986),[1] enantioselective catalytic addition of vinylzinc reagents to aldehydes were reported by Oppolzer (1992) and Wipf (1994).[2,3,4] Although such transformations exhibit high stereoselectivity, vinylzinc generation relies upon stoichiometric alkyne hydrometallation (R_2BH or Cp_2ZrHCl) with subsequent transmetallation to zinc using $ZnMe_2$. Thus, alkyne activation requires successive use of four stoichiometric organometallic reagents (Scheme 1).

Direct metal catalyzed alkyne-carbonyl reductive coupling bypasses the use of multiple stoichiometric organometallic reagents. This reactivity pattern was first observed in cyclizations of acetylenic aldehydes catalyzed by rhodium, titanium and nickel, as reported by Ojima (1994),[5] Crowe (1995)[6] and Montgomery (1997),[7] respectively. Intermolecular variants of the nickel catalyzed reactions soon followed.[8,9] However, while reductive couplings of this type signal a departure from stoichiometric organometallics, they employ reductants that generate molar equivalents of metallic byproducts.

Completely atom economical alkyne-carbonyl and imine-carbonyl reductive couplings are achieved under the conditions rhodium and iridium catalyzed hydrogenation.[10,11,12] This

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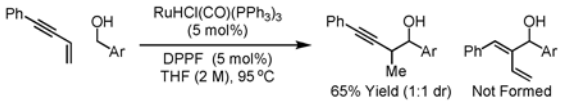
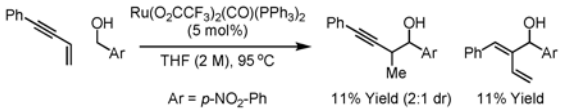
concept was extended to C-C bond forming transfer hydrogenation, wherein hydrogen embedded within an alcoholic reactant, typically isopropanol, serves as terminal reductant.[13,14] Most significantly, an alcohol may serve dually as hydrogen donor and precursor to the carbonyl electrophile, enabling byproduct-free carbonyl addition from the alcohol oxidation level.[10d,13,14a,c,d,15]

Under the conditions of ruthenium catalyzed transfer hydrogenation employing RuHCl(CO)$(PPh_3)_3$ as catalyst, carbonyl allylation and propargylation are achieved from the alcohol or aldehyde oxidation level using conjugated dienes and enynes as surrogates to preformed allyl and allenyl metal reagents, respectively.[14a,c] *Here, we report the first direct C-H vinylation of alcohols, which is achieved by way of alkyne-alcohol C-C bond-forming transfer hydrogenation employing $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$ as catalyst*.

Recently, we disclosed a method for carbonyl propargylation from the alcohol or aldehyde oxidation level *via* enyne-carbonyl transfer hydrogenative coupling employing RuHCl(CO)$(PPh_3)_3$ as catalyst (eqn. 1).[14c] In subsequent studies, it was found that the regiochemistry of C-C coupling is altered the upon the use of $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$ as catalyst in the absence of added ligand (eqn. 2). Interestingly, both regioselectivities differ from those observed under the conditions of rhodium[12] or nickel catalysis,[16] wherein coupling at the acetylenic terminus of the enyne is observed.



(eq. 1)

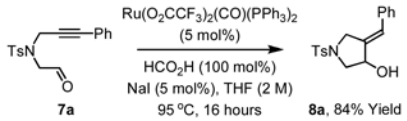


(eq. 2)

These results suggested the feasibility of using non-conjugated alkynes in transfer hydrogenative C-C coupling, which would constitute a direct C-H vinylation of alcohols employing alkynes as vinyl donors. After extensive optimization, it was found that 2-butyne (200 mol%) and *p*-nitrobenzyl alcohol **1b** (100 mol%) combine to form the desired product of C-H vinylation, allylic alcohol **2b**, in 78% isolated yield simply upon heating in THF solvent at 95 °C (sealed tube) in the presence of $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$ (5 mol%) and isopropanol (200 mol%). Enone **3b** also forms in 12% isolated yield. Under these conditions, diverse benzylic and aliphatic alcohols **1a–1l** are converted to the corresponding allylic alcohols **2a–2l**, accompanied by variable quantities of the corresponding enones **3a–3l** (Table 1). Added isopropanol (200 mol%) was found to minimize formation of enones **3a–3l**.

Carbonyl vinylation from the aldehyde oxidation level also was explored. Using isopropanol as terminal reductant, low conversion was observed. However, in reactions mediated by formic acid (100 mol%), aldehydes **4a**, **4b** and **4e** were converted to allylic alcohols **2a**, **2b** and **2e** in good yield, accompanied by products of olefin isomerization **5a**, **5b** and **5e**. Here, sodium iodide (5 mol%) was found to suppress over-oxidation leading to enone side-products (Table 2).

The coupling of nonsymmetric alkynes **6a–6c** also was explored from the aldehyde oxidation level employing aldehyde **4b**. Using formic acid as reductant, efficient vinylation occurs to provide allylic alcohols **2m–2o** as single regioisomers. Over-oxidation of **2m–2o** to form enones **3m–3o** was not observed. Under the standard conditions cited in Table 1, the coupling of nonsymmetric alkynes **6a–6c** to *p*-nitrobenzyl alcohol **1b** to form allylic alcohols **2m–2o** was less efficient (Table 2). Finally, whereas cyclization of acetylenic alcohols failed, the reductive cyclization of acetylenic aldehyde **7a** proceeds efficiently to deliver **8a** in 84% isolated yield (eqn. 1).



(eqn. 1)

In summary, through C-C bond forming transfer hydrogenation, direct vinylation of alcohols or aldehydes is achieved using alkynes as vinyl donors in the absence of any stoichiometric metallic reagents. Future studies will focus on the development of improved second generation catalysts for the transformations reported herein and related alcohol-unsaturate C-C couplings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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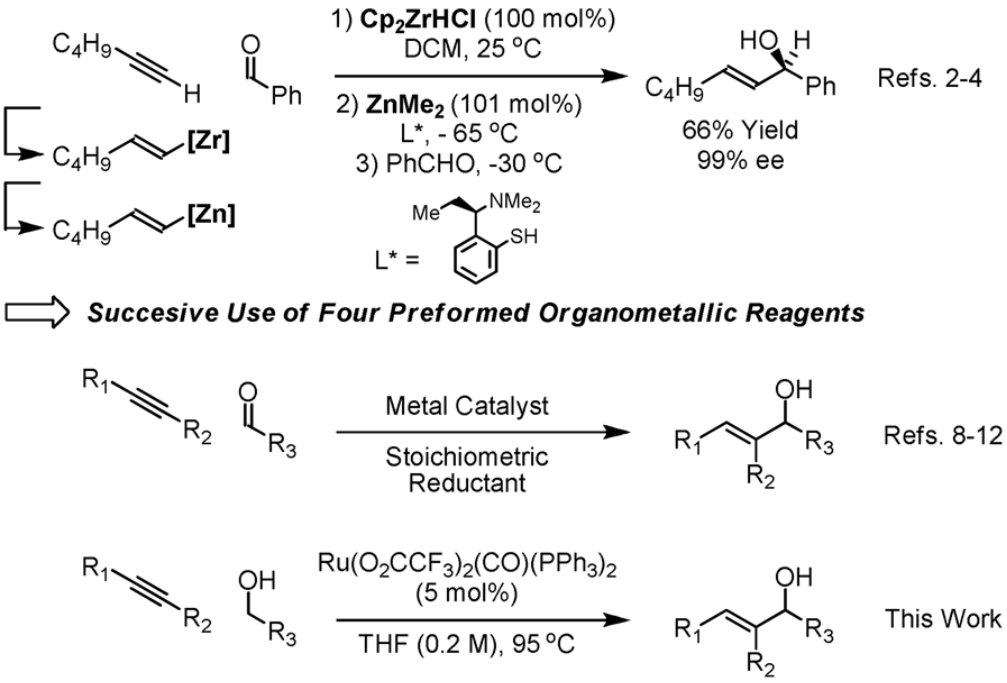
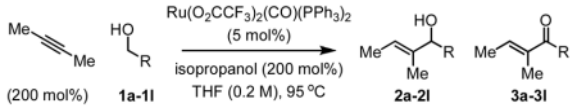


Scheme 1.
Selected milestones in carbonyl vinylation.

Table 1

Allylic alcohols **2a–2l** via ruthenium catalyzed transfer hydrogenative coupling of butyne to alcohols **1a–1l**.[a]



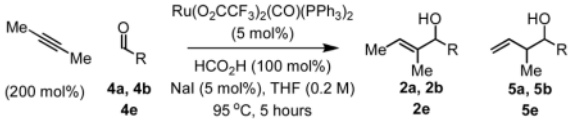
Entry	Alcohol	Product	R	Time (h)	Yield 2 (3)
1	**1a**	**2a** (**3a**)	Ph	9	72% (4%)[b]
2	**1b**	**2b** (**3b**)	*p*-NO_2-Ph	13	78% (12%)
3	**1c**	**2c** (**3c**)	*p*-Br-Ph	13	81% (7%)
4	**1d**	**2d** (**3d**)	*p*-CO_2Me-Ph	13	81% (10%)
5	**1e**	**2e** (**3e**)	*m*-MeO-Ph	13	78% (6%)
6	**1f**	**2f** (**3f**)	*m*-F-Ph	13	79% (11%)
7	**1g**	**2g** (**3g**)	3,5-Cl_2-Ph	13	76% (14%)
8	**1h**	**2h** (**3h**)	3-Br, 4-F-Ph	9	75% (< 1%)
9	**1i**	**2i** (**3i**)	$(CH_2)_2$OBn	13	69% (< 1%)
10	**1j**	**2j** (**3j**)	$(CH_2)_3$OBn	18	65% (< 1%)
11	**1k**	**2k** (**3k**)	$(CH_2)_2$NPhtl	18	61% (< 1%)
12	**1l**	**2l** (**3l**)	CH_2(*o*-Br-Ph)	13	75% (< 1%)[b]

[a] Cited yields are of material isolated by silica gel chromatography and refer to pure **2a–2l** free of any enone byproduct.

[b] The reaction was conducted at 0.6 M concentration.

Table 2

Ruthenium catalyzed transfer hydrogenative coupling of butyne to aldehydes **4a**, **4b** and **4e**.[a]

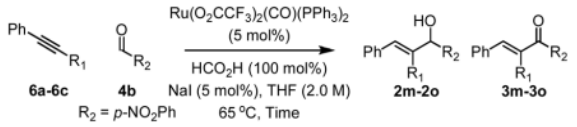


Entry	Aldehyde	Product	R	Yield (2:5)
1	**4a**	**2a** (**5a**)	Ph	88% (5:1)
2	**4b**	**2b** (**5b**)	*p*-NO_2-Ph	78% (10:1)
3	**4e**	**2e** (**5e**)	*m*-MeO-Ph	91% (7:1)

[a] See supporting information for detailed procedures.

Table 3

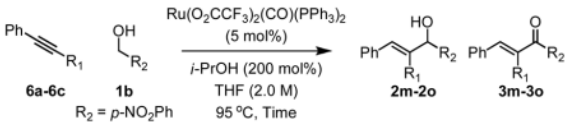
Ruthenium catalyzed transfer hydrogenative coupling of alkynes **6a–6c** to aldehyde **4b** (top) and alcohol **1b** (bottom).[a]



6a-6c 4b 2m-2o 3m-3o

R_2 = *p*-NO_2Ph

Entry	Alkyne (200 mol%)	Product	Time (hr)	Yield (2:3)
1	**6a**, R_1 = Ph	**2m (3m)**	24 hr	91% (>20:1)
2	**6b**, R_1 = $(CH_2)_2OBn$	**2n (3n)**	16 hr	84% (>20:1)
3	**6c**, R_1 = CH_2NHBoc	**2o (3o)**	13 hr	75% (>20:1)



6a-6c 1b 2m-2o 3m-3o

R_2 = *p*-NO_2Ph

Entry	Alkyne (200 mol%)	Product	Time (hr)	Yield 2 (3)
1	**6a**, R_1 = Ph	**2m (3m)**	37 hr	62% (12%)
2	**6b**, R_1 = $(CH_2)_2OBn$	**2n (3n)**	13 hr	58% (>1%)
3	**6c**, R_1 = CH_2NHBoc	**2o (3o)**	13 hr	15% (>1%)

[a] See supporting information for detailed procedures. Isolated yields refer to pure **2m–2o** free of any enone byproduct.