C–C Coupling Hot Paper

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# Redox-Triggered C–C Coupling of Diols and Alkynes: Synthesis of β,γ-Unsaturated α-Hydroxyketones and Furans by Ruthenium-Catalyzed Hydrohydroxyalkylation**

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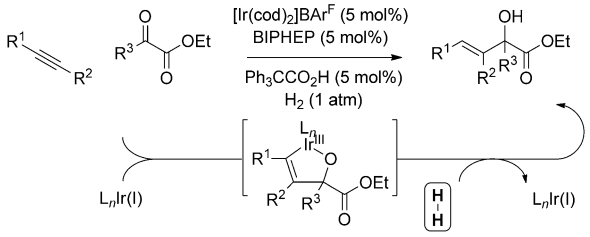
***Abstract:*** *Direct ruthenium-catalyzed C–C coupling of alkynes and vicinal diols to form β,γ-unsaturated ketones occurs with complete levels of regioselectivity and good to complete control over the alkene geometry. Exposure of the reaction products to substoichiometric quantities of p-toluenesulfonic acid induces cyclodehydration to form tetrasubstituted furans. These alkyne-diol hydrohydroxyalkylations contribute to a growing body of merged redox-construction events that bypass the use of premetalated reagents and, hence, stoichiometric quantities of metallic by-products.*

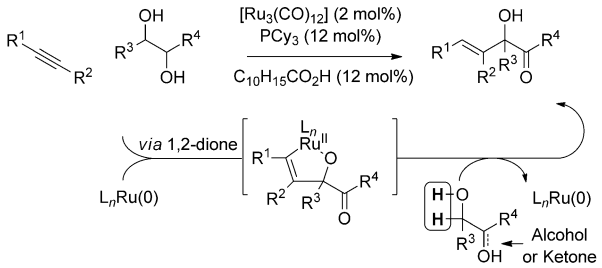
Metal-catalyzed reductive coupling reactions of π-unsaturated reactants bypass the use of premetalated C-nucleophiles in a range of carbonyl and imine additions.[1] Despite significant advances, catalytic intermolecular reductive coupling reactions of simple alkenes or alkynes to ketones (activated or unactivated) remain uncommon.[2–7] In connection with efforts aimed at the development of hydrogen-mediated reductive coupling reactions beyond hydroformylation,[1f,g,h] rhodium- or iridium-catalyzed hydrogenations of α-ketoesters in the presence of conjugated or nonconjugated alkynes were found to promote the formation of α-hydroxyesters (Scheme 1).[6b,c,7] More recently, under the conditions of ruthenium(0)-catalyzed transfer hydrogenation, it was found that activated secondary alcohols engage in C–C coupling to unsaturated reactants to form products of hydrohydroxyalkylation.[8–11] Specifically, the catalytic C–C coupling of α-hydroxy carbonyl compounds[8] or 1,2-diols[8d,f] with conjugated dienes,[8a,b,d,e] terminal olefins,[8c] and α,β-unsaturated esters[8f] was achieved. The feasibility of coupling secondary alcohols to alkynes[6,7,9,12] under the conditions of ruthenium(0)-catalyzed transfer hydrogenation was unclear, as ruthenium(0) complexes are efficient catalysts for alkyne [2+2+2] cycloaddition.[13,14] Here, we report that the ruthenium(0) catalyst formed in situ from $[Ru_3(CO)_{12}]$ and tricyclohexylphosphine ($PCy_3$) promotes regio- and stereoselective alkyne-diol hydrohydroxyalkylation to form α-hydroxy-β,γ-unsaturated ketones in good to excellent yields (Scheme 1). The reaction products engage in acid-catalyzed cyclodehydration to form tetrasubstituted furans.[15]

**Prior Work**: *J. Am. Chem. Soc.* **2007**, *129*, 280 (Ref. [7a])



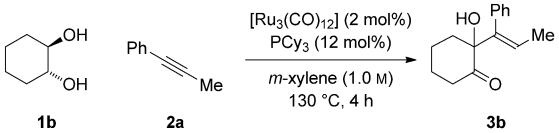

For related Rh-catalyzed reactions of 1,3-enynes or acetylene, see Ref. [6b,c]

**This Work**




***Scheme 1.*** Hydrogen-mediated reductive coupling of alkynes to activated ketones and related hydrohydroxyalkylations. cod = 1,5-cyclooctadiene, BIPHEP = 2,2′-bis(diphenylphosphino)-1,1′-biphenyl.

In a preliminary experiment, racemic *trans*-1,2-cyclohexane diol (**1b**) was exposed to 1-phenyl-1-propyne (**2a**) under conditions established for the C–C coupling of dienes to α-hydroxy esters or α-hydroxy amides.[8a,b] The anticipated product of hydrohydroxyalkylation **3b** was formed, but in only 14% yield [Eq. (1)]. In related rhodium- or iridium-catalyzed alkyne-α-ketoester reductive coupling reactions using elemental hydrogen as the terminal reductant,[6b,c,7] carboxylic acid co-catalysts were found to increase the rate and conversion. As supported by computational studies,[16] such acid co-catalysts bypass highly energetic four-centered transition structures for the direct hydrogenolysis of oxametallacyclic intermediates through σ-bond metathesis, instead protonating the metal–oxygen bond to form metal carboxylates, which then react with elemental hydrogen by way of lower energy six-centered transition structures. This acid co-

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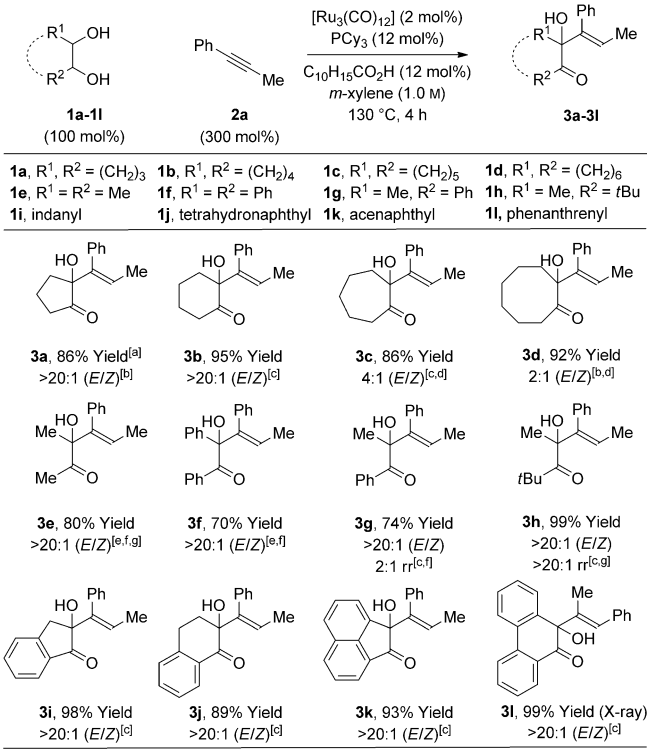
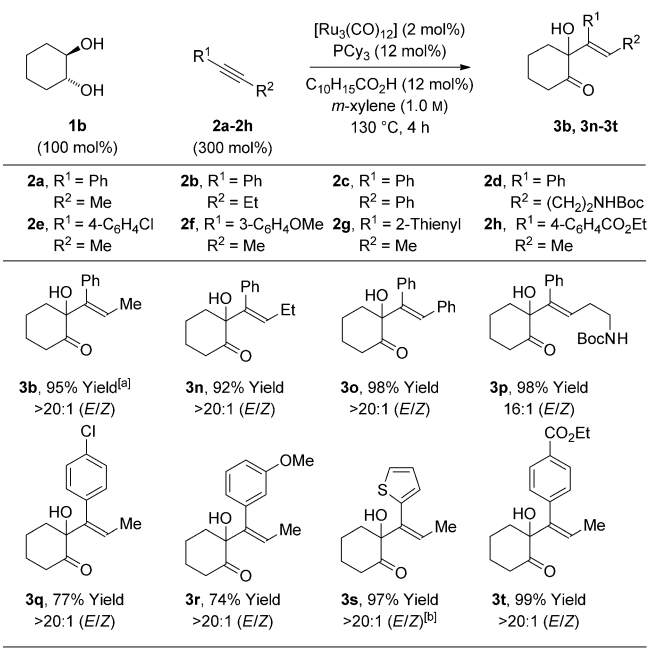
catalyst effect also is operative in ruthenium(0)-catalyzed hydrohydroxyalkylations[8c,f] that proceed through oxametallacyclic intermediates that are cleaved through transfer hydrogenolysis. As borne out experimentally, the use of 1-adamantanecarboxylic acid (12 mol%) under the aforesaid conditions led to a 95% yield of the isolated adduct **3b** as a single olefin stereoisomer [Eq. (1)].

Under these conditions, diverse diols **1a–1l** react with 1-phenyl-1-propyne (**2a**) to form the corresponding α-hydroxy ketones **3a–3l** (Scheme 2). The diol stereochemistry is unimportant, as both *cis* and *trans* diastereomers engage in efficient C–C coupling. Cyclic diols **1a–1d** and **1i–1l** as well as acyclic diols **1e–1h** deliver coupling products in good to excellent yields. In all but two cases, adducts **3c** and **3d**, complete levels of olefin stereocontrol are observed. For adducts **3c** and **3d**, longer reaction times result in a greater loss of the *E*/*Z* stereoselectivity, which suggests these products initially form with high levels of *E*/*Z* stereoselectivity but isomerize under the reaction conditions. As will be discussed, the coupling of diol **1l** proceeds with inversion of regioselectivity, as corroborated by single-crystal X-ray diffraction. By using this specific catalyst system, terminal vicinal diols that incorporate primary alcohols provide complex stereoisomeric mixtures of mono- and bis-C–C coupling



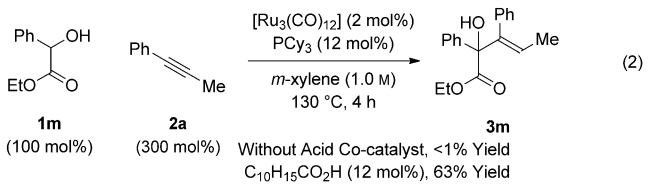

***Scheme 2.*** Ruthenium(0)-catalyzed hydrohydroxyalkylation of 1-phenyl-1-propyne (**2a**) with diols **1a–1l**. [a] Yields are of material isolated by chromatography on silica gel. $C_{10}H_{15}CO_2H$ refers to 1-adamantanecarboxylic acid. For acyclic 1,2-diols, the terminology "*cis*" and "*trans*" relates to the indicated reactant conformation. See the Supporting Information for further details. [b] The *cis*-1,2-diol was employed. [c] The *trans*-1,2-diol was employed. [d] 2 h. [e] A mixture of *cis*- and *trans*-1,2-diols was employed. [f] 1,1′-bis(diphenylphosphino)ferrecene (DPPF, 6 mol%) was used instead of $PCy_3$ (12 mol%). [g] 20 h.




***Scheme 3.*** Ruthenium(0)-catalyzed hydrohydroxyalkylation of alkynes **2a–2h** with cyclohexane diol **1b**. [a] Yields are of material isolated by chromatography on silica gel. $C_{10}H_{15}CO_2H$ refers to 1-adamantanecarboxylic acid. See the Supporting Information for further details. [b] 20 h. Boc = *tert*-butoxycarbonyl.

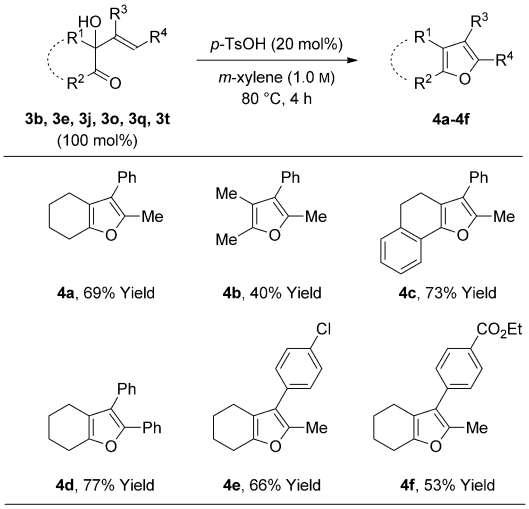
products. In the absence of diol, alkyne **2a** is converted into products of [2+2+2] cycloaddition.[13,14]

To further evaluate the scope of this process, the coupling of *trans*-1,2-cyclohexane diol (**1b**) to alkynes **2a–2h** was explored (Scheme 3). In all cases, good to excellent yields of the corresponding C–C coupling products **3b** and **3n–3t** were obtained. With the exception of adduct **3p**, complete levels of olefin *E*/*Z* stereoselectivity were observed, and for all nonsymmetric alkynes (**2a**, **2b**, **2d–2h**), complete levels of regioselectivity were observed. Terminal alkynes and dialkyl-substituted alkynes do not engage in efficient coupling under these conditions. As illustrated by the reaction of racemic ethyl mandelate (**1m**) to 1-phenyl-1-propyne (**2a**) to form adduct **3m**, other vicinally deoxygenated reactants participate in C–C bond formation under these conditions and require an acid co-catalyst [Eq. (2)]. Finally, in a preliminary evaluation of the utility of the coupling products, adducts **3b**, **3e**, **3j**, **3o**, **3q**, and **3t** were exposed to catalytic amounts of *p*-toluenesulfonic acid in *m*-xylene at 80 °C. Cyclodehydration to form the corresponding substituted furans **4a–4f** occurred in good yields (Scheme 4).[15]

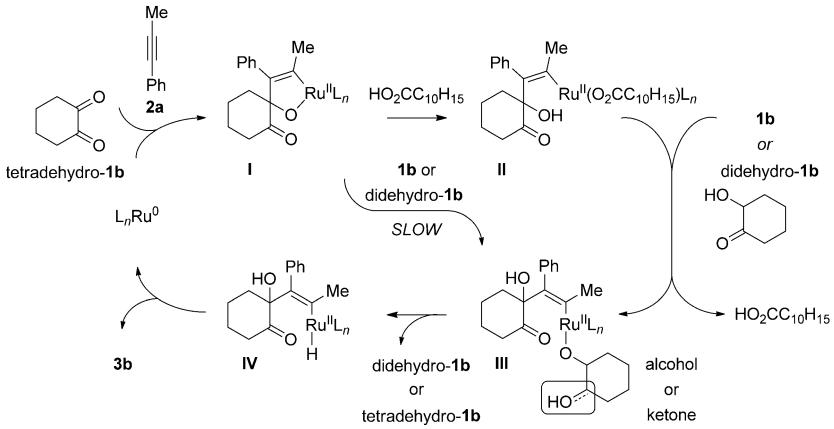



A plausible catalytic mechanism is illustrated for the coupling of *trans*-1,2-cyclohexane diol (**1b**) and 1-phenylpropyne (**2a**) to form adduct **3b** (Scheme 5). A mononuclear

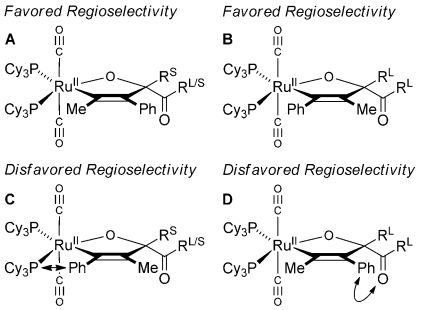



***Scheme 4.*** Acid-catalyzed cyclodehydration of adducts **3b**, **3e**, **3j**, **3o**, **3q**, and **3t** to form furans **4a**–**4f**. Yields are of material isolated by chromatography on silica gel. See the Supporting Information for further details. TsOH = p-toluenesulfonic acid.




***Scheme 5.*** Postulated mechanism for ruthenium(0)-catalyzed diol-alkyne hydrohydroxyalkylation as illustrated for the coupling of 1,2-cyclohexane diol (**1b**) and 1-phenyl-1-propyne (**2a**).

ruthenium(0) complex[17] promotes the oxidative coupling of dione tetradehydro-**1b** and 1-phenylpropyne (**2a**) to form oxaruthenacycle **I**.[18,19] As corroborated by low-resolution MS of crude reaction mixtures, which reveal the presence of alkene, the requisite dione tetradehydro-**1b** may be formed through successive $[Ru_3(CO)_{12}]$-catalyzed transfer of hydrogen from cyclohexanediol **1b** to the alkyne.[20–22] The protonation of oxaruthenacycle **I** by cyclohexanediol **1b**, or hydroxyketone didehydro-**1b** to form the ruthenium alkoxide **III**, is postulated to be slow compared to protonolytic cleavage of oxaruthenacycle **I** by 1-adamantanecarboxylic acid to form ruthenium carboxylate **II**. Exchange of the ruthenium carboxylate **II** with **1b** or didehydro-**1b** forms ruthenium alkoxide **III**, which upon β-hydride elimination delivers didehydro-**1b** or tetradehydro-**1b**, respectively, and ruthenium hydride **IV**. Subsequent C–H reductive elimination furnishes adduct **3b** and returns ruthenium to its zerovalent form. The indicated model accounts for the observed regioselectivity, including the inversion of the alkyne regioselectivity found in the coupling of diol **1l** (Scheme 6). The




***Scheme 6.*** Model to account for the observed regioselectivity of the alkyne coupling.

steric demand of the metal center promotes oxidative coupling at the less bulky carbonyl moiety of the transient dione, and controls the alkyne orientation (**A** and **C**, Scheme 6). The inversion of the alkyne regioselectivity evident in the formation of **3l** can be explained by the increase in steric repulsion between the dione and alkyne substituent (**B** and **D**, Scheme 6). The proposed structure of these complexes is analogous to that of related metallacycles obtained upon ruthenium(0)-mediated ketone-diene oxidative coupling.[8e]

In summary, we report the direct ruthenium-catalyzed C–C coupling of alkynes and vicinal diols to form β,γ-unsaturated ketones with complete levels of regioselectivity and good to complete control over alkene geometry. Exposure of the reaction products to substoichiometric quantities of *p*-toluenesulfonic acid induces cyclodehydration to form tetrasubstituted furans. The present alkyne-diol hydrohydroxyalkylations contribute to a growing body of merged redox-construction events that bypass the use of premetalated reagents and, hence, stoichiometric quantities of metallic by-products.

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