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

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Metal catalyzed reductive couplings of π -unsaturated reactants bypass use of premetallated C-nucleophiles in a range of carbonyl and imine additions.^[1] Despite significant advances, catalytic intermolecular reductive couplings of simple alkenes or alkynes to ketones (activated or unactivated) remain uncommon.^[2,3,4,5,6,7] In connection with efforts aimed at the development of hydrogen-mediated reductive couplings beyond hydroformylation,^[1f,g,h] rhodium or iridium catalyzed hydrogenations of α -ketoesters in the presence of conjugated or nonconjugated alkynes, respectively, were found to promote formation of α -hydroxyesters (Figure 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.^[8,9,10,11] 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]cycloaddition.^[13,14] Here, we report that the ruthenium(0) catalyst formed *in situ* from $\text{Ru}_3(\text{CO})_{12}$ and tricyclohexylphosphine, PCy_3 , promotes regio- and stereoselective alkyne-diol hydrohydroxyalkylation to form α -hydroxy- β,γ -unsaturated ketones in good to excellent yields (Figure 1). The reaction products engage in acid catalyzed cyclodehydration to form tetrasubstituted furans.^[15]

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

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iridium catalyzed alkyne- α -ketoester reductive couplings employing hydrogen as terminal reductant,^[6b,c,7] carboxylic acid co-catalysts were found to increase rate and conversion. As supported by computational studies,^[16] such acid co-catalysts bypass highly energetic 4-centered transition structures for direct hydrogenolysis of oxametallacyclic intermediates *via* σ -bond metathesis, instead protonating the metal-oxygen bond to form metal carboxylates, which then react with elemental hydrogen by way of lower energy 6-centered transition structures. This acid co-catalyst effect also is operative in ruthenium(0) catalyzed hydrohydroxyalkylations^[8c,f] that proceed through oxametallacyclic intermediates cleaved through *transfer hydrogenolysis*. As borne out experimentally, use of 1-adamantanecarboxylic acid (12 mol%) under the aforesaid conditions led to a 95% isolated yield of adduct **3b** as a single olefin stereoisomer (eq. 1).

(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** (Table 1). Diol stereochemistry is unimportant, as both *cis*- and *trans*-diastereomers engage in efficient C-C coupling. Both cyclic diols **1a-1d**, **1i-1l** and acyclic diols **1e-1h**, deliver couplings 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 *E/Z* stereoselectivity, suggesting 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. Using this specific catalyst system, terminal vicinal diols that incorporate primary alcohols provide complex stereoisomeric mixtures of *mono*- and *bis*-C-C coupling products. In the absence of diol, alkyne **2a** is converted to 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 (Table 2). In all cases, good to excellent isolated yields of the corresponding coupling products **3b**, **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 in 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 cocatalyst (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 *p*-toluenesulfonic acid in *m*-xylene at 80 °C. Cyclodehydration to form the corresponding substituted furans **4a-4f** occurred in good yields (Table 3).^[15]

(eq. 2)

A plausible catalytic mechanism is illustrated in the coupling of *trans*-1,2-cyclohexane diol **1b** and 1-phenylpropyne **2a** to form adduct **3b** (Scheme 1). A mononuclear 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 LRMS of crude reaction mixtures, which reveal the presence of alkene, the requisite dione *tetradehydro-1b* may be formed through successive Ru₃(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 zero-valent form. The indicated model accounts for the observed regioselectivity, including the inversion of alkyne regioselectivity found in the coupling of diol **1i** (Figure 2). The steric demand of the metal center promotes oxidative coupling at the less bulky carbonyl moiety of the transient dione and controls alkyne orientation (**A** and **C**, Figure 2). The inversion of alkyne regioselectivity evident in the formation of **3i** can be explained by the increase in steric repulsion between the dione and alkyne substituent (**B** and **D**, Figure 2). 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 of 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 premetallated reagents and, hence, stoichiometric quantities of metallic byproducts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

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

This Work

Figure 1.

Hydrogen-mediated reductive coupling of alkynes to activated ketones and related hydrohydroxyalkylations.

Favored Regioselectivity *Favored Regioselectivity* *Disfavored Regioselectivity* *Disfavored Regioselectivity*

Figure 2.

Model to account for the observed regioselectivity of alkyne coupling.

Scheme 1.

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

Table 1

Ruthenium(0) catalyzed hydrohydroxyalkylation of 1-phenyl-1-propyne **2a** with diols **1a-1l**.^a

1a-1l (100 mol%)	2a (300 mol%)	Ru ₃ (CO) ₁₂ (2 mol%) PCy ₃ (12 mol%) C ₁₀ H ₁₅ CO ₂ H (12 mol%) <i>m</i> -xylene (1.0 M) 130 °C, 4 h	3a-3l
1a , R ¹ , R ² = (CH ₂) ₃ 1e , R ¹ = R ² = Me 1i , indanyl	1b , R ¹ , R ² = (CH ₂) ₄ 1f , R ¹ = R ² = Ph 1j , tetrahydronaphthyl	1c , R ¹ , R ² = (CH ₂) ₅ 1g , R ¹ = Me, R ² = Ph 1k , acenaphthyl	1d , R ¹ , R ² = (CH ₂) ₆ 1h , R ¹ = Me, R ² = <i>t</i> Bu 1l , phenanthrenyl
3a , 86% Yield >20:1 (<i>E</i> : <i>Z</i>) ^b	3b , 95% Yield >20:1 (<i>E</i> : <i>Z</i>) ^c	3c , 86% Yield 4:1 (<i>E</i> : <i>Z</i>) ^{c,d}	3d , 92% Yield 2:1 (<i>E</i> : <i>Z</i>) ^{b,d}
3e , 80% Yield >20:1 (<i>E</i> : <i>Z</i>) ^{e,f,g}	3f , 70% Yield >20:1 (<i>E</i> : <i>Z</i>) ^{e,f}	3g , 74% Yield >20:1 (<i>E</i> : <i>Z</i>) 2:1 <i>rr</i> ^{c,f}	3h , 99% Yield >20:1 (<i>E</i> : <i>Z</i>) >20:1 <i>rr</i> ^{c,g}
3i , 98% Yield >20:1 (<i>E</i> : <i>Z</i>) ^c	3j , 89% Yield >20:1 (<i>E</i> : <i>Z</i>) ^e	3k , 93% Yield >20:1 (<i>E</i> : <i>Z</i>) ^e	3l , 99% Yield (X-ray) >20:1 (<i>E</i> : <i>Z</i>) ^e

^aYields are of material isolated by silica gel chromatography. C₁₀H₁₅CO₂H refers to 1-adamantanecarboxylic acid. For acyclic 1,2-diols, the terminology "cis" and "trans" relates to the indicated reactant conformation. See Supporting Information for further details.

^bThe *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 DPPF (6 mol%) was used instead PCy₃ (12 mol%).

^g 20 h.

Table 2

Ruthenium(0) catalyzed hydrohydroxyalkylation of alkynes **2a-2h** with cyclohexane diol **1b**.^a

1b (100 mol%)	2a-2h (300 mol%)		
2a , R ¹ = Ph R ² = Me	2b , R ¹ = Ph R ² = Et	2c , R ¹ = Ph R ² = Ph	2d , R ¹ = Ph R ² = (CH ₂) ₂ NHBoc
2e , R ¹ = 4-C ₆ H ₄ Cl R ² = Me	2f , R ¹ = 3-C ₆ H ₄ OMe R ² = Me	2g , R ¹ = 2-Thienyl R ² = Me	2h , R ¹ = 4-C ₆ H ₄ CO ₂ Et R ² = Me
3b , 95% Yield >20:1 (E:Z)	3n , 92% Yield >20:1 (E:Z)	3o , 98% Yield >20:1 (E:Z)	3p , 98% Yield 16:1 (E:Z)
3q , 77% Yield >20:1 (E:Z)	3r , 74% Yield >20:1 (E:Z)	3s , 97% Yield >20:1 (E:Z) ^b	3t , 99% Yield >20:1 (E:Z)

^aYields are of material isolated by silica gel chromatography. C₁₀H₁₅CO₂H refers to 1-adamantanecarboxylic acid. See Supporting Information for further details.^b20 h.

Table 3

Acid catalyzed cyclodehydration of adducts **3b**, **3e**, **3j**, **3o**, **3q**, and **3t** to form furans **4a-4f**.^a

^aYields are of material isolated by silica gel chromatography. See Supporting Information for further details.