Diols, α-Ketols, and Diones as $2_{2\pi}$ Components in [2+2+2] Cycloadditions of 1,6-Diynes via Ruthenium(0)-Catalyzed Transfer Hydrogenation

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S Supporting Information

ABSTRACT: The first use of vicinal diols, ketols, or diones as $2_{2\pi}$ components in metal-catalyzed [2+2+2] cycloaddition is described. Using ruthenium(0) catalysts, 1,6-diynes form ruthenacyclopentadienes that engage transient diones in successive carbonyl addition. Transfer hydrogenolysis of the resulting ruthenium(II) diolate mediated by the diol or ketol reactant releases the cycloadduct with regeneration of ruthenium(0) and the requisite dione.

Metal-catalyzed [2+2+2] cycloadditions of π-unsaturated reactants enable convergent construction of (poly)cyclic compounds.[1] Transformations of this type typically proceed through catalytic mechanisms wherein low-valent metal centers mediate π-bond oxidative coupling to form high-valent metallacyclopentadienes, which upon π-bond insertion–reductive elimination deliver cycloadducts and regenerate the catalyst (Figure 1, eq 1). The use of carbonyl compounds,[2] including carbon dioxide,[3] as $2_{2\pi}$ components in metal-catalyzed [2+2+2] cycloaddition is well established.[1–3] Here, carbonyl insertion is followed by C–O reductive elimination to form pyrans.[2,3] To our knowledge, mechanisms involving capture of the transient metallacyclopentadiene through an *exo*-type carbonyl addition to form hydroxy-substituted cycloadducts have not been described.[1–3]

As part of a broad program focused on the development of carbonyl reductive couplings via catalytic hydrogenation,[4] we imagined a pathway for 1,6-diyne-1,2-dione [2+2+2] cycloaddition involving hydrogen auto-transfer from a diol reactant (Figure 1, eq 2). Specifically, ruthenium(0)-mediated 1,6-diyne oxidative coupling would provide a ruthenacyclopentadiene complex that participates in successive carbonyl addition with a 1,2-dione to form a ruthenium(II) diolate. Diol- or ketol-mediated transfer hydrogenolysis of the diolate regenerates zerovalent ruthenium and ketol or dione, with release of cycloadduct to close the catalytic cycle (Figure 1, bottom). In this Communication, we report the first examples of such transfer hydrogenative [2+2+2] cycloadditions.[5]

To explore the feasibility of transfer hydrogenative [2+2+2] cycloaddition, racemic *trans*-cyclohexanediol **1b** (100 mol%) and 1,6-diyne **2a** (200 mol%) were exposed to various ruthenium(0) catalysts generated *in situ* through the combination of $Ru_3(CO)_{12}$ (2 mol%) and various phosphine ligands (Scheme 1). In the course of these optimization experiments, trace quantities of the desired product of [2+2+2] cyclo-
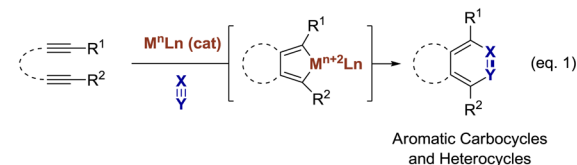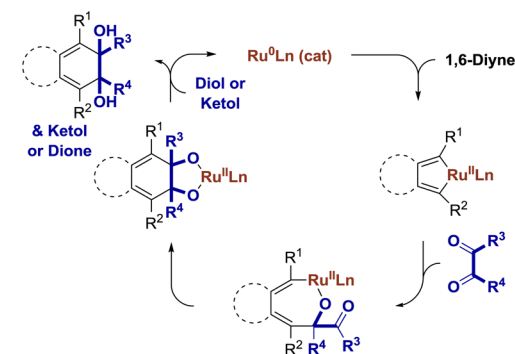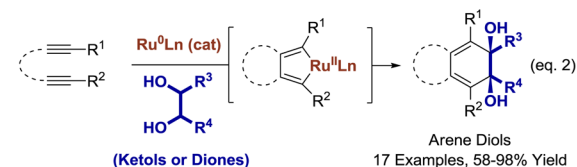

Figure 1. Top: Classical vs transfer hydrogenative [2+2+2] cycloaddition using 1,2-diols as $2_{2\pi}$ components. Bottom: General catalytic mechanism.
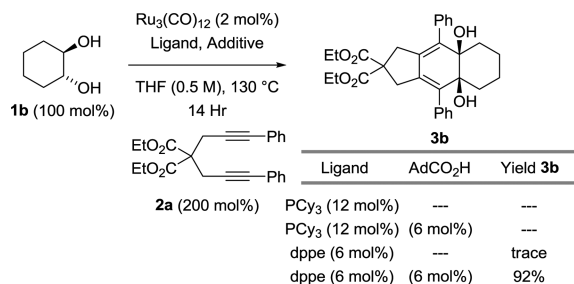
addition **3a** were observed when dppe was used as ligand. Carboxylic acid co-catalysts enhance rate and conversion in mechanistically related C–C couplings by accelerating the hydrogenolysis[6] or transfer hydrogenolysis[5b] of metallacyclic intermediates. The use of 1-adamantanecarboxylic acid (6 mol %) as a co-catalyst under otherwise identical conditions led to the formation of cycloadduct **3b** in 92% yield with complete levels of *syn*-diastereoselectivity.

To assess the generality of this process, these conditions were applied to the [2+2+2] cycloaddition of 1,6-diyne **2a** with diols **1a–1i** (Table 1). As illustrated by the formation of cycloadducts **3a–3c**, 5-, 6-, and 7-membered cycloalkanediols **1a–1c**

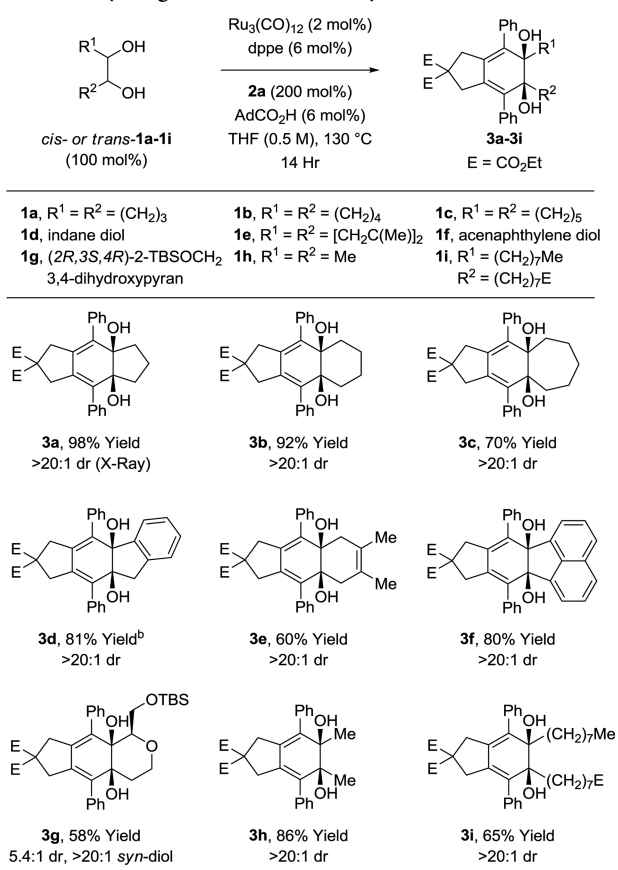**Scheme 1. Selected Optimization Experiments in the [2+2+2] Cycloaddition of 1,6-Diyne 2a with Cyclohexanediol 1b**[a]

Ligand	AdCO₂H	Yield 3b
PCy₃ (12 mol%)	---	---
PCy₃ (12 mol%)	(6 mol%)	---
dppe (6 mol%)	---	trace
dppe (6 mol%)	(6 mol%)	92%

[a]Yields of material isolated by silica gel chromatography. AdCO₂H refers to 1-adamantanecarboxylic acid. PCy₃ = tricyclohexylphosphine. dppe = bis-(diphenylphosphino)ethane. See Supporting Information for further experimental details.

Table 1. Survey of Diols 1a−1i in Ruthenium(0)-Catalyzed Transfer Hydrogenative [2+2+2] Cycloaddition[a]

1a, R¹ = R² = (CH₂)₃	**1b**, R¹ = R² = (CH₂)₄	**1c**, R¹ = R² = (CH₂)₅
1d, indane diol	**1e**, R¹ = R² = [CH₂C(Me)]₂	**1f**, acenaphthylene diol
1g, (2R,3S,4R)-2-TBSOCH₂ 3,4-dihydroxypyran	**1h**, R¹ = R² = Me	**1i**, R¹ = (CH₂)₇Me R² = (CH₂)₇E

3a, 98% Yield, >20:1 dr (X-Ray) — **3b**, 92% Yield, >20:1 dr — **3c**, 70% Yield, >20:1 dr

3d, 81% Yield[b], >20:1 dr — **3e**, 60% Yield, >20:1 dr — **3f**, 80% Yield, >20:1 dr

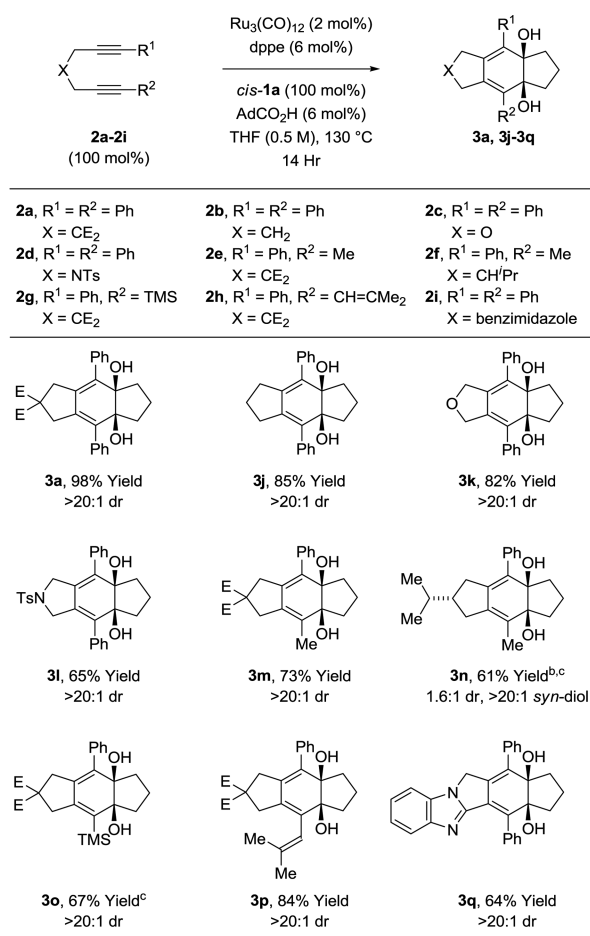**3g**, 58% Yield, 5.4:1 dr, >20:1 syn-diol — **3h**, 86% Yield, >20:1 dr — **3i**, 65% Yield, >20:1 dr

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

participate in cycloaddition. Tolerance of adjacent π-unsaturation is demonstrated by the conversion of indanediol **1d**, cyclohexenediol **1e**, and acenaphthalenediol **1f** to cycloadducts **3d**−**3f**, respectively. Notably, the transient dione derived from cyclohexenediol **1e** undergoes cycloaddition more rapidly than tautomerization to form the corresponding catechol. Diol **1g**, which incorporates a pre-existing stereogenic center, engages in cycloaddition to form **3g** with serviceable levels of 1,2-

asymmetric induction. Finally, acyclic vicinal diols, 2,3-butanediol **1h** and the diol **1i** derived from methyl oleate, are converted to cycloadducts **3h** and **3i**.

In a further evaluation of the reaction scope, 1,6-diynes **2a**−**2i** were exposed to cyclopentanediol **1a** under standard conditions (Table 2). As demonstrated by the reaction of

Table 2. Survey of Diynes 2a−2i in Ruthenium(0)-Catalyzed Transfer Hydrogenative [2+2+2] Cycloaddition[a]


2a, R¹ = R² = Ph, X = CE₂	**2b**, R¹ = R² = Ph, X = CH₂	**2c**, R¹ = R² = Ph, X = O
2d, R¹ = R² = Ph, X = NTs	**2e**, R¹ = Ph, R² = Me, X = CE₂	**2f**, R¹ = Ph, R² = Me, X = CH^iPr
2g, R¹ = Ph, R² = TMS, X = CE₂	**2h**, R¹ = Ph, R² = CH=CMe₂, X = CE₂	**2i**, R¹ = R² = Ph, X = benzimidazole

3a, 98% Yield, >20:1 dr — **3j**, 85% Yield, >20:1 dr — **3k**, 82% Yield, >20:1 dr

3l, 65% Yield, >20:1 dr — **3m**, 73% Yield, >20:1 dr — **3n**, 61% Yield[b,c], 1.6:1 dr, >20:1 syn-diol

3o, 67% Yield[c], >20:1 dr — **3p**, 84% Yield, >20:1 dr — **3q**, 64% Yield, >20:1 dr

[a]Yields of material isolated by silica gel chromatography. See Supporting Information for further experimental details. [b]120 °C. [c]24 h.

diyne **2b** to form **3j**, pre-organization via geminal substitution of the diyne partner is not required for efficient cycloaddition.[7] The formation of cycloadducts **3k** and **3l** from diynes **2c** and **2d**, respectively, establishes the tolerance of both O- and N-tethers. Compatibility of substituents at the acetylenic terminus beyond phenyl moieties is illustrated by the cycloaddition of diynes **2e**−**2h** to form adducts **3m**−**3p**. Finally, generation of the benzimidazole-containing cycloadduct **3q** establishes compatibility with Lewis-basic N-heterocycles. 1,6-Diynes that are unsubstituted at the acetylenic terminus and 1,7-diynes do not engage in efficient cycloaddition under these initially developed conditions.

Cycloaddition is postulated to occur through a general catalytic mechanism involving successive dehydrogenation of the diol reactant to form a transient α-ketol and, ultimately, the vicinal dione partner that is required for oxidative coupling (Figure 1). Thus, in addition to diols, α-ketols and vicinal

diones should be viable reactants. Whereas the cycloaddition of diols is an oxidative transformation for which excess diyne likely serves as hydrogen acceptor, the cycloaddition of α-ketols is redox-neutral, and the cycloaddition of vicinal diones is reductive. To demonstrate that the present cycloaddition may be conducted in oxidative, redox-neutral, and reductive modes, the reactions of diol **1f**, α-ketol *dehydro*-**1f**, and vicinal dione *didehydro*-**1f** were explored (Scheme 2). Standard conditions

Scheme 2. Redox-Level Independent [2+2+2] Cycloadditions of Diol 1f, α-Ketol *dehydro*-1f, and Vicinal Dione *didehydro*-1f[a]
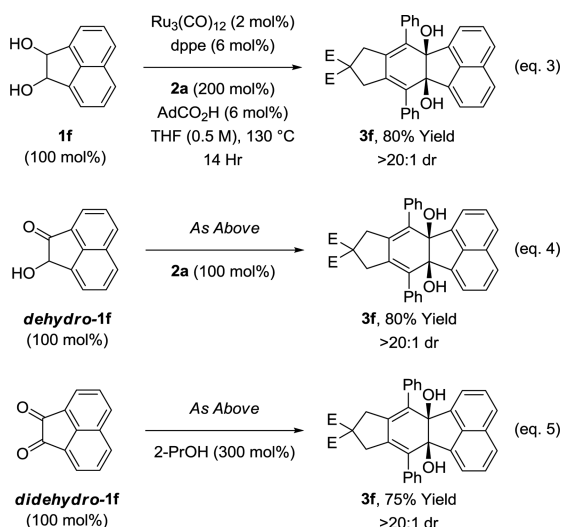
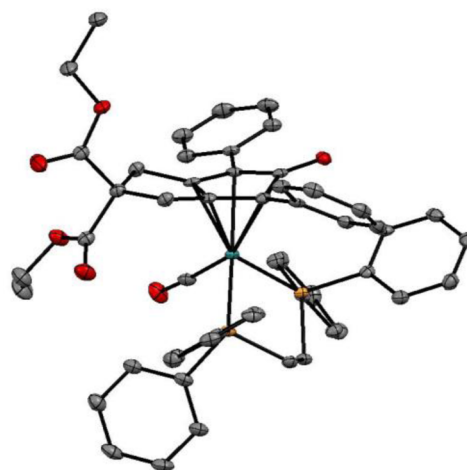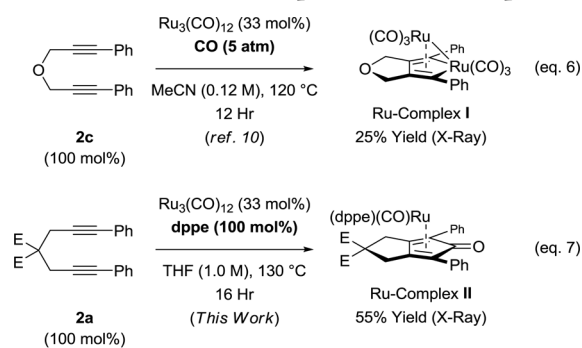[a]Yields of material isolated by silica gel chromatography. See Supporting Information for further experimental details.

used for the cycloaddition of diol **1f** (Scheme 2, eq 3), when applied to α-ketol *dehydro*-**1f** (Scheme 2, eq 4), led to the formation of cycloadduct **3f** in 80% yield. Reductive cycloaddition of vicinal dione *didehydro*-**1f** to form **3f** also was possible using 2-propanol as a source of hydrogen under otherwise standard conditions (Scheme 2, eq 5). Recently, a variety of oxidative[5a,8] and reductive[5a,9] cycloaddition reactions have been reported that provide access to cyclic compounds from unconventional substrates. To our knowledge, the conversion of dione *didehydro*-**1f** to **3f** represents the first example of a reductive [2+2+2] cycloaddition reaction.[1]

The proposed general catalytic mechanism (Figure 1) is corroborated by the following data. As reported by Yamamoto,[10] the stoichiometric reaction of 1,6-diyne **2c** with $Ru_3(CO)_{12}$ in the presence of carbon monoxide delivers the dinuclear ruthenacyclopentadiene complex, Ru-complex **I** (Scheme 3, eq 6). It is reported that exposure of $Ru_3(CO)_{12}$ to dppe in benzene solvent provides the mononuclear complex $Ru(CO)_3(dppe)$.[11] As might be anticipated on the basis of these two observations, we have found that, in the absence of carbon monoxide, the stoichiometric reaction of 1,6-diyne **2a** with $Ru_3(CO)_{12}$ and dppe provides the mononuclear ruthenium cyclopentadienone complex, Ru-complex **II** (Scheme 3, eq 7).[12] Together, these data corroborate diyne oxidative coupling mediated by a mononuclear ruthenium–phosphine complex as a key feature of the catalytic mechanism.[13] The addition of metallacyclopentadienes to π-electrophiles has been demonstrated in rhodium-catalyzed reductive couplings of acetylene with aldehydes and imines

Scheme 3. Stoichiometric Reaction of Diynes 2c and 2a with $Ru_3(CO)_{12}$ To Form Ru-Complex I and Ru-Complex II[a]

[a]Structure of Ru-complex **II** as determined by single-crystal X-ray diffraction (H-atoms omitted for clarity). Yields of material isolated by silica gel chromatography (eq 6) or precipitation (eq 7). Displacement ellipsoids are scaled to the 50% probability level. See Supporting Information for crystallographic data and further experimental details.

mediated by elemental hydrogen.[6] Finally, carboxylic acid co-catalyzed transfer hydrogenolysis of oxoruthenacycle intermediates, the final stage of the catalytic mechanism, has been established in our prior work.[5b] A model accounting for *syn*-diastereoselectivity can be found in the Supporting Information.

In summary, adding a broad, new dimension to a longstanding field,[14] we report the first examples of vicinal diols, ketols, or diones as $2_{2\pi}$ components in metal-catalyzed [2+2+2] cycloaddition. The collective data corroborate a mechanism in which ruthenium(0)-mediated oxidative coupling of a 1,6-diyne is followed by successive carbonyl addition between the resulting ruthenacyclopentadiene and a transient dione. Transfer hydrogenolysis of the resulting ruthenium(II) diolate releases the cycloadduct, an arene diol, and returns ruthenium to its zerovalent form with concomitant regeneration of the vicinal dicarbonyl partner. Future studies will focus on the development of related hydrogen-transfer-mediated cycloadditions, as well as application of the present methodology to the synthesis of polycyclic aromatic hydrocarbons.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b11746.

Experimental procedures and spectral data (PDF)

Single-crystal X-ray diffraction data for Ru-complex **II** (CIF)

Single-crystal X-ray diffraction data for **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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