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Successive C-C Coupling of Dienes to Vicinally Dioxygenated Hydrocarbons: Ruthenium Catalyzed [4+2] Cycloaddition across the Diol, Hydroxycarbonyl or Dione Oxidation Levels

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Abstract

The ruthenium(0) catalyst generated from $Ru_3(CO)_{12}$ and tricyclohexylphosphine or BIPHEP promotes successive C-C coupling of dienes to vicinally dioxygenated hydrocarbons across the diol, hydroxyketone and dione oxidation levels to form products of [4+2] cycloaddition. A mechanism involving diene-carbonyl oxidative coupling followed by intramolecular carbonyl addition from the resulting allylruthenium intermediate is postulated.

Vicinal diols are ubiquitous in Nature and are of interest *vis-à-vis* biomass conversion,[1,2] yet there exist no examples of their direct catalytic C-C coupling. We have developed a broad family of transformations wherein hydrogen transfer between alcohols and π-unsaturated reactants produces organ-ometal-carbonyl pairs that combine to form products of addition.[3] In the course of these studies, a ruthenium(0) catalyst recently was identified that promotes alcohol C-C coupling through an alternate mechanism, wherein alcohol dehydrogenation drives carbonyldiene oxidative coupling to form metallacyclic intermediates, as illustrated in couplings of α-hydroxy esters to isoprene or myrcene to form products of prenylation or geranylation, respectively.[4] It was posited that the allylruthenium species arising transiently upon diene-carbonyl oxidative coupling might be intercepted *via* allylruthenation onto a tethered carbonyl moiety to form products of cycloaddition, suggesting the feasibility of utilizing diols as partners for C-C coupling. Here, we report that vicinal diols and their more highly oxidized forms (hydroxyketones and diones) engage in [4+2] cycloaddition with a diverse range of conjugated dienes – a powerful, new cycloaddition that may be conducted in reductive, redox-neutral or oxidative modes (Figure 1).[5,6]

Following the mechanism postulated above, the phenethyl diol **1a** was exposed to isoprene **4b** in the presence of sub-stoichiometric quantities of $Ru_3(CO)_{12}$ and tricyclohexylphosphine, PCy_3, at 130 °C in toluene solvent. Remarkably, the product of cycloaddition **5a** was obtained in 78% isolated yield as a 6:1 mixture of regioisomers. Whereas PCy_3 was the preferred ligand for terminal 1,2-diols **1a**-**1b**, a screen of phosphine ligands revealed that the chelating phosphine ligand BIPHEP, 2,2′-bis(diphenylphosphino)-1,1′-biphenyl, was the better for internal 1,2-diols **1c**-**1h**. For internal diols **1c**-**1h**, *cis*- or *trans*-diastereomers react with equal facility (Table 1).

The scope of the diene partner is illustrated in cycloadditions of *rac*-cyclohexanediol **1f**. Butadiene **4a** and a range of substituted dienes **4b**-**4h** participate in the ruthenium catalyzed cycloaddition to furnish decalins **5f**, **5i**-**5o** in excellent yield. A single substituent is tolerated

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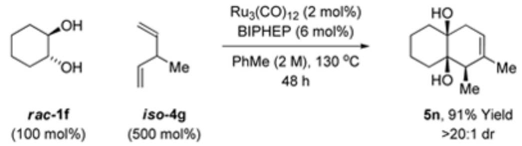
Supporting Information Available: Experimental procedures and spectral data. Single crystal X-ray diffraction data for compound **5j**. This material is available free of charge *via* the internet at http://pubs.acs.org.

at any position of the diene. For the dimethyl substituted butadienes **4e**-**4g**, good to excellent yields of cycloadducts **5l**-**5o**, respectively, are obtained. For the terminally disubstituted diene **4h**, 2,4-hexadiene, substantial olefin isomerization in advance of cycloaddition is observed (Table 2). Indeed, $Ru_3(CO)_{12}$ catalyzed olefin isomerization has been documented.[7] This phenomena is advantageous in terms of recruiting non-conjugated dienes as partners for cycloaddition. For example, *rac*-cyclohexanediol **1f** was reacted with the non-conjugated diene *iso*-**4g** (eqn. 1). Remarkably, *iso*-**4g** and **4g** produce cycloadduct **5n** with roughly equal facility.



(1)

The cycloadditions of diols **1a**-**1h** are oxidative processes wherein excess diene presumably serves as the hydrogen acceptor (Tables 1 and 2). The feasibility of cycloaddition from more highly oxidized congeners of diols **1a**-**1d** and **1f** were evaluated in reactions with isoprene **4b** (Table 3). In the event, exposure of the α-hydroxycarbonyl compounds **2a**-**2d** and **2f** to standard conditions employing substoichiometric quantities of $Ru_3(CO)_{12}$ and either PCy_3 or BIPHEP as ligand provided the cycloadducts **5a**-**5d** and **5f** in good to excellent yield. Whereas reactions of α-hydroxycarbonyl compounds **2a**-**2d** and **2f** are redox-neutral processes, cycloadditions of the corresponding dicarbonyl compounds **3a**-**3d** and **3f** are reductive processes requiring a stoichiometric hydrogen donor. For such dicarbonyl reactants, formic acid proved to be most effective reductant, and use $RuH_2CO(PPh_3)_3$ as precatalyst was advantageous in certain cases.[8] While glyoxals **3a** and **3b** failed to deliver any cycloadduct, the vicinal diketones **3c**, **3d** and **3f** provided the anticipated products **5c**, **5d** and **5f** in modest yields. Thus, ruthenium catalyzed [4+2] cycloaddition is achieved from the diol, hydroxycarbonyl and dicarbonyl oxidation levels.

A general catalytic mechanism has been proposed, as illustrated in the cycloaddition of *rac*-cyclohexanediol **1f** and isoprene **4b** (Scheme 1). It is well established that exposure of $Ru_3(CO)_{12}$ to chelating phosphine ligands provides complexes of the type $Ru(CO)_3$(diphosphine).[9] Hence, intervention of a discrete, mono-metallic catalyst is anticipated. The $Ru_3(CO)_{12}$ catalyzed oxidation of alcohols employing olefins and alkynes as hydrogen acceptors has been described.[10,11] Further, mechanistically related $Ru_3(CO)_{12}$ catalyzed secondary alcohol aminations involving dehydrogenation of 1,2-diols[12a] and α-hydroxy esters[12c] are known. These data suggest the present $Ru_3(CO)_{12}$-phosphine catalyst system is capable of converting 1,2-diol **1f** to the hydroxyketone **2f** and, ultimately, the corresponding 1,2-dione **3f** using diene **4b** as the hydrogen acceptor.[10] The diol *rac*-**1f**, which is introduced as the isomerically pure *trans*-stereoisomer, appears as a mixture of *cis*- and *trans*-diastereomers when recovered from the reaction mixture, suggesting dehydrogenation of **1f** is reversible. Small quantities of hydroxyketone **2f** also can be recovered from reaction mixtures. Oxidative coupling of 1,2-dione **3f** and diene **4b** to form oxametallacycle **I** finds precedent in the work of Chatani and Murai on Pauson-Khand type reactions of 1,2-diones,[13] and our own work on the prenylation of substituted mandelic esters.[4] Protonolytic cleavage of oxametallacycle **I** by **1f** or **2f** to form the allylruthenium complex **II** triggers intramolecular allylruthenation to form the ruthenium(II) alkoxide **III**.

Finally, β-hydride elimination forms ruthenium hydride **IV** and OH reductive elimination delivers the product **5f** and returns ruthenium to its zero-valent form to close the cycle.[14]

The assignment of regio- and stereochemistry merit discussion. Single crystal X-ray diffraction analysis of cycloadduct **5j** revealed the *cis*-diastereomer. Additionally, the ^{1}H NMR spectral characteristics of cycloadducts **5i** and **5l** are consistent with the indicated *meso*-stereoisomers, not the corresponding C_2-symmetric stereoisomers. The stereochemical assignment of other cycloadducts was made in analogy to compounds **5j**, **5i** and **5l**. A model accounting for the observed *syn*-diastereoselectivity is presented has been postulated, which involves intramolecular allylruthenation through a boat-like transition structure. Finally, aromatization of cycloadduct **5a** *via* acid catalyzed double dehydration enabled the regiochemical assignment of this cycloadduct (see supporting information). Indeed, a systematic investigation of diol cycloaddition-aromatization is now underway in our laboratory.

In summary, since the advent of the photocycloaddition in 1908[15a] and the Diels-Alder reaction in 1928,[15b] several distinct and powerful classes of cycloaddition reactions have been developed, including diverse metal catalyzed processes.[16] However, despite decades of intensive investigation, reductive and oxidative variants of cycloaddition reactions remain highly uncommon.[5,6] Here, we report a powerful and conceptually novel strategy for the [4+2] cycloaddition of dienes with 1,2-diols and their higher vicinally dioxygenated congeners. This work demonstrates that merged redox-construction events[17] can be exploited in succession to form multiple C-C bonds, enabling generation of complex polycyclic frameworks in the absence of premetallated reagents. The development of related transformations and application of this methodology to the direct modification of abundant renewable polyols is ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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8. The precatalyst $RuH_2CO(PPh_3)_3$ may reductively eliminate elemental hydrogen or transfer hydrogen to the diene to furnish the zero-valent ruthenium species required for diene-carbonyl oxidative coupling.
9. For example, exposure of $Ru_3(CO)_{12}$ to dppe in benzene solvent provides $Ru(CO)_3$(dppe): Sanchez-Delgado RA, Bradley JS, Wilkinson G. J Chem Soc Dalton Trans. 1976:399.
10. (a) Blum Y, Reshef D, Shvo Y. Tetrahedron Lett. 1981; 22:1541.(b) Shvo Y, Blum Y, Reshef D, Menzin M. J Organomet Chem. 1982; 226:C21.(c) Meijer RH, Ligthart GBWL, Meuldijkb J, Vekemans JAJM, Hulshof LA, Mills AM, Kooijmanc H, Spek AL. Tetrahedron. 2004; 60:1065.
11. For mechanistically related $Ru_3(CO)_{12}$ catalyzed transfer hydrogenation of ketones mediated by isopropanol, see: Johnson TC, Totty WG, Wills M. Org Lett. 2012; 14:5230. [PubMed: 23025546]
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14. A Diels-Alder mechanism involving pericyclic [4+2] cycloaddition of a ruthenium-bound enediolate can be excluded as β-hydroxy ketones were found to participate in the cycloaddition. A detailed account of this process will be reported in due course.
15. (a) Ciamician G, Silber P. Chem Ber. 1908; 41:1928.(b) Diels O, Alder K. Ann. 1928; 460:98.
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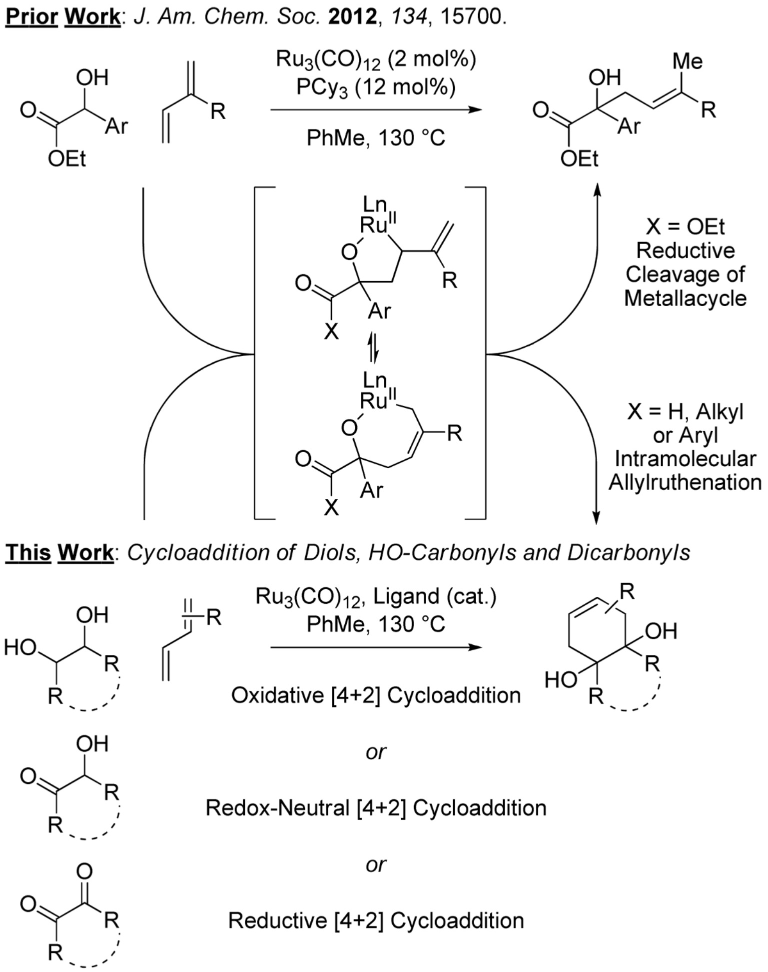
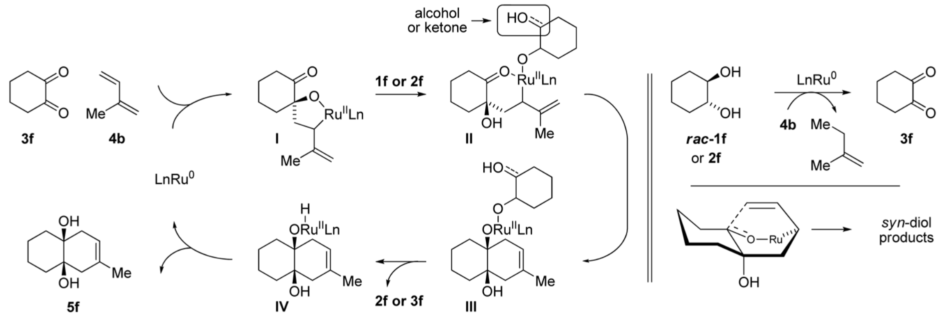


Figure 1.

Cycloaddition of vicinally dioxygenated hydrocarbons through interception of an allylruthenium intermediate.

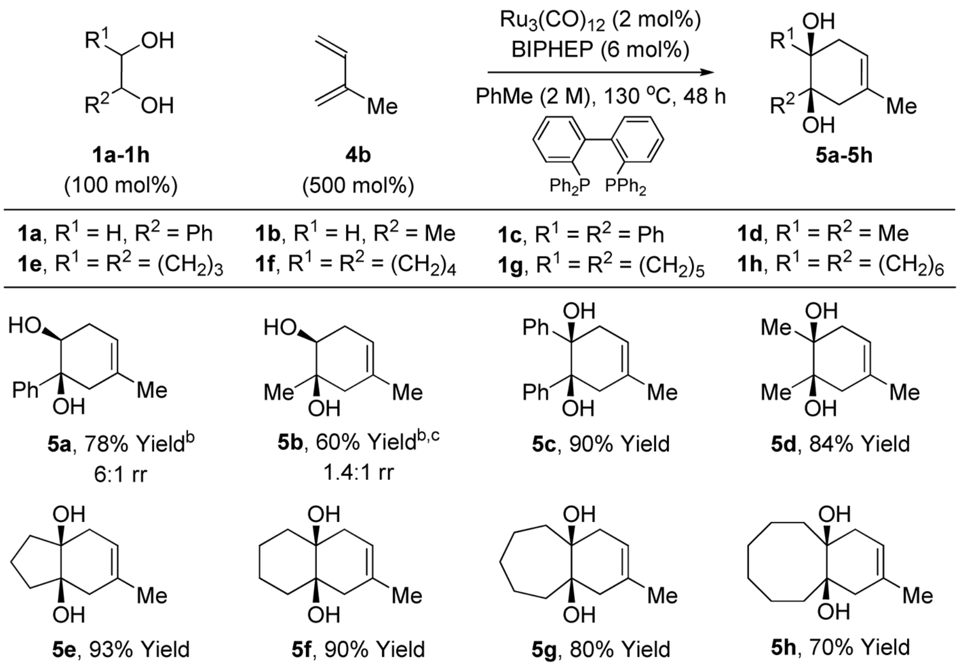


Scheme 1.

Proposed mechanism and stereochemical model for the cycloaddition of *rac*-cyclohexanediol **1f** and isoprene **4b**.

Table 1

Oxidative ruthenium catalyzed [4+2] cycloaddition of isoprene **4b** with diols **1a**-**1h**.[a]



1a-1h (100 mol%)

4b (500 mol%)

5a-5h

1a, $R^1 = H$, $R^2 = Ph$
1e, $R^1 = R^2 = (CH_2)_3$
1b, $R^1 = H$, $R^2 = Me$
1f, $R^1 = R^2 = (CH_2)_4$
1c, $R^1 = R^2 = Ph$
1g, $R^1 = R^2 = (CH_2)_5$
1d, $R^1 = R^2 = Me$
1h, $R^1 = R^2 = (CH_2)_6$

5a, 78% Yield[b]
6:1 rr

5b, 60% Yield[b,c]
1.4:1 rr

5c, 90% Yield

5d, 84% Yield

5e, 93% Yield

5f, 90% Yield

5g, 80% Yield

5h, 70% Yield

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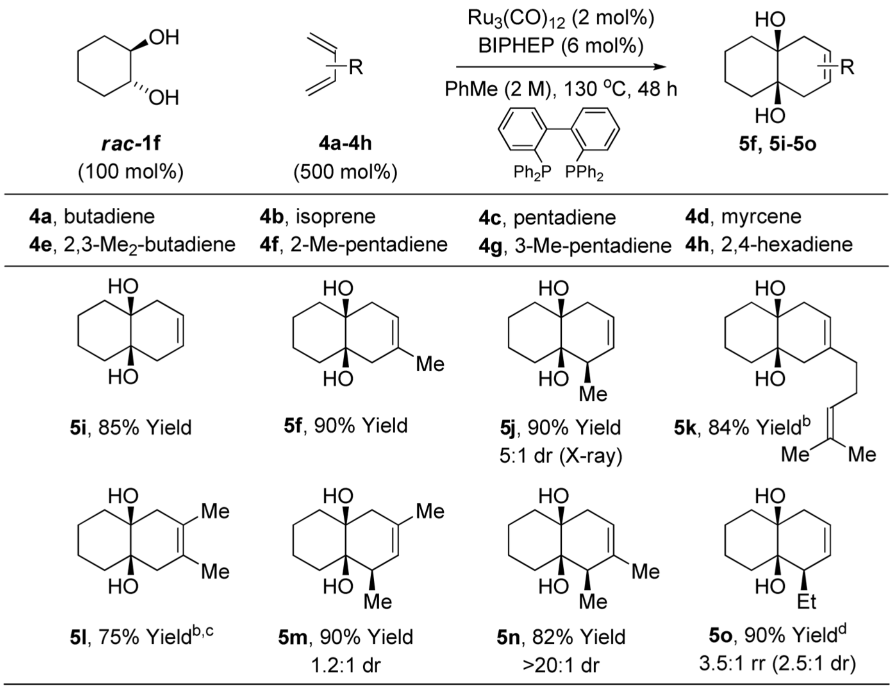
[a] Yields are of material isolated by silica gel chromatography.

[b] PCy_3 (12 mol%).

[c] 150 °C. See Supporting Information for further details and structural assignments.

Table 2

Ruthenium catalyzed [4+2] cycloaddition of *rac*-cyclohexanediol **1f** with dienes **4a-4h**.[a]



[a] Yields are of material isolated by silica gel chromatography.

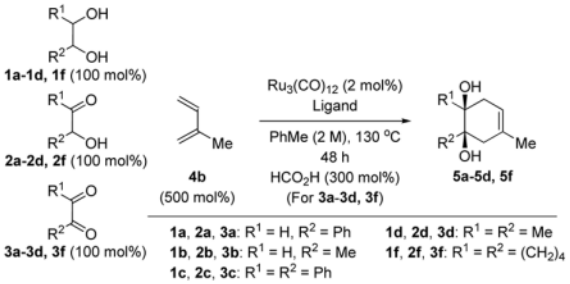
[b] 300 mol% diene.

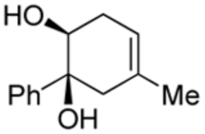
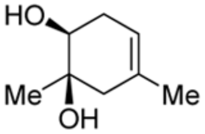
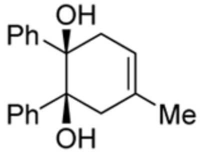
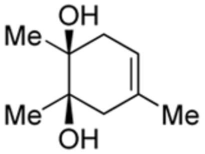
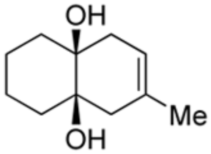
[c] 150 °C.

[d] The same products are generated in the same distribution using 1,5-hexadiene. See Supporting Information for further details and structural assignments.

Table 3

Ruthenium catalyzed [4+2] cycloaddition of isoprene **4b** with vicinally dioxygenated hydrocarbons **1a-1d**, **1f**, **2a-2d**, **2f**, and **3a-3d**, **3f**.[a]



Entry	Cycloadduct	Reactant	Yield %
1		Diol **1a**	78[b]
		Hydroxyketone **2a**	75[b]
		Dicarbonyl **3a**	Trace
2		Diol **1b**	60[b,e]
		Hydroxyketone **2b**	72[b]
		Dicarbonyl **3b**	Trace
3		Diol **1c**	90[c]
		Hydroxyketone **2c**	98[c]
		Dicarbonyl **3c**	70[d]
4		Diol **1d**	84[b]
		Hydroxyketone **2d**	61[b]
		Dicarbonyl **3d**	35[d,f]
5		Diol **1f**	90[b]
		Hydroxyketone **2f**	68[b]
		Dicarbonyl **3f**	54[d,f]

[a] Yields are of material isolated by silica gel chromatography.

[b] PCy_3 (12 mol%).

[c] BIPHEP (6 mol%).

[d] $RuH_2CO(PPh_3)_3$ (6 mol%), BIPHEP (6 mol%).

[e] 150 °C.

[f] HCO_2H (300 mol%). See Supporting Information for further details and structural assignments.