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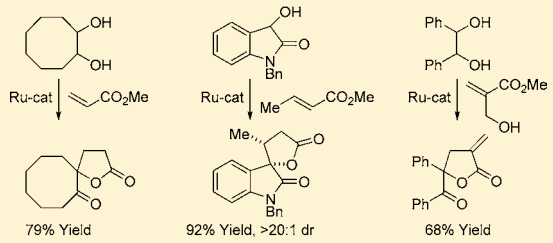
Ruthenium-Catalyzed Hydrohydroxyalkylation of Acrylates with Diols and α-Hydroxycarbonyl Compounds To Form Spiro- and α-Methylene-γ-butyrolactones

Emma L. McInturff, Jeffrey Mowat, Andrew R. Waldeck, and Michael J. Krische*

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712, United States

Supporting Information

ABSTRACT: Under the conditions of ruthenium(0)-catalyzed hydrohydroxyalkylation, vicinal diols **1a**−**1l** and methyl acrylate **2a** are converted to the corresponding lactones **3a**−**3l** in good to excellent yield. The reactions of methyl acrylate **2a** with hydrobenzoin **1f**, benzoin *didehydro*-**1f**, and benzil *tetradehydro*-**1f** form the same lactone **3f** product, demonstrating that this process may be deployed in a redox level-independent manner. A variety of substituted acrylic esters **2a**−**2h** participate in spirolactone formation, as illustrated in the conversion of *N*-benzyl-3-hydroxyoxindole **1o** to cycloadducts **4a**−**4h**. Hydrohydroxyalkylation of hydroxyl-substituted methacrylate **2i** with diols **1b**, **1f**, **1j**, and **1l** forms α-*exo*-methylene-γ-butyrolactones **5b**, **5f**, **5j**, and **5l** in moderate to good yield. A catalytic cycle involving 1,2-dicarbonyl−acrylate oxidative coupling to form oxaruthenacyclic intermediates is postulated. A catalytically competent mononuclear ruthenium(II) complex was characterized by single-crystal X-ray diffraction. The influence of electronic effects on regioselectivity in reactions of nonsymmetric diols was probed using *para*-substituted 1-phenyl-1,2-propanediols **1g**, **1m**, and **1n** and density functional theory calculations.



INTRODUCTION

Our laboratory has developed ruthenium and iridium "hydrohydroxyalkylations" wherein hydrogen transfer from primary alcohols to π-unsaturated reactants generates organometal−aldehyde pairs that combine to form products of carbonyl addition.[1−3] Such C−C bond-forming transfer hydrogenations may be viewed as alternatives to classical carbonyl additions, for which discrete alcohol-to-aldehyde oxidation and use of premetallated *C*-nucleophiles are often required. To expand the scope of this emerging family of C−C bond formations, the development of corresponding *secondary* alcohol-mediated hydrohydroxyalkylations was undertaken. However, our initial efforts to promote hydrohydroxyalkylations with secondary alcohols using previously developed ruthenium[2] and iridium[3] catalysts resulted in conventional transfer hydrogenation to form ketone products. Products of C−C coupling were not observed.

It was postulated that secondary alcohols that form vicinal dicarbonyl compounds upon dehydrogenation, for example, α-hydroxy esters or vicinal cycloalkane diols, should engage more readily in carbonyl addition or oxidative coupling pathways *en route* to products of C−C coupling. However, this enhanced reactivity also renders vicinal dicarbonyl compounds more susceptible to reduction. Hence, if dehydrogenation is reversible, the short lifetime of the transient vicinal dicarbonyl might impede C−C coupling pathways. In view of this issue, we were inspired by recent reports of $Ru_3(CO)_{12}$-catalyzed aminations of 1,2-diols[4a,b] and α-hydroxy amides,[4c] which occur via reductive amination of transient vicinal dicarbonyl species. This result, along with Chatani's observation of oxidative coupling pathways in Pauson−Khand reactions of 1,2-diones,[5] suggested the feasibility of hydrohydroxyalkylations by way of oxidative coupling−secondary alcohol transfer hydrogenation pathways.

Ruthenium(0) catalysts derived from $Ru_3(CO)_{12}$ and phosphine ligands were found to promote the C−C coupling of α-hydroxy esters and amides to isoprene and myrcene to furnish products of prenylation and geranylation, respectively (Figure 1, top).[6a,b] More recently, a mechanistically related ruthenium(0)-catalyzed [4+2] cycloaddition of vicinal diols via successive hydrohydroxyalkylation of dienes was developed (Figure 1, middle).[6c] Here, we report that ruthenium(0)-catalyzed hydrohydroxyalkylation of acrylates with vicinal diols or their more highly oxidized congeners delivers spiro- and α-methylene-γ-butyrolactones, structural motifs that are ubiquitous in nature (Figure 1, bottom).[7]

RESEARCH DESIGN AND METHODS

It was reasoned that ruthenium(0)-catalyzed hydrohydroxyalkylation of acrylates with vicinal diols would provide transient oxaruthenacycles that would spontaneously cyclize to form lactone products (Figure 1, bottom). This method would complement alternate approaches to spirocyclic γ-butyrolactones,[7a] which include cationic rearrangements of epoxides[8] and bromonium ions,[9] Stetter-type reactions,[10] oxidative dearomatization,[11] C−H hydroxylation of carboxylic

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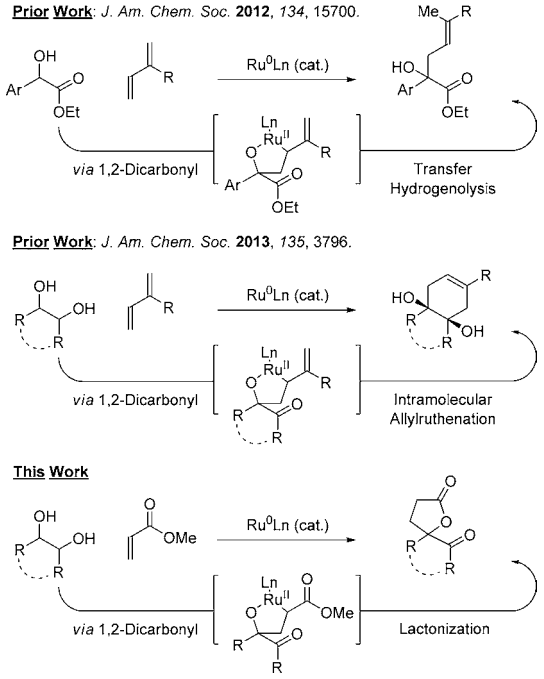


Figure 1. Ruthenium(0)-catalyzed hydrohydroxyalkylations.

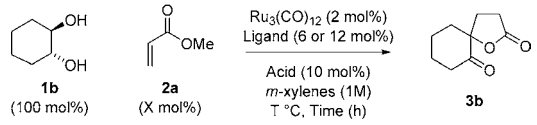
acids,[12] reductive cyclizations of α,β-unsaturated esters onto ketones,[13] Pauson–Khand-type reactions of olefins with vicinal diones,[5] and the 2-(alkoxycarbonyl)allylation of carbonyl compounds.[14]

To probe the feasibility of the proposed transformation, racemic *trans*-1,2-cyclohexane diol **1b** was exposed to methyl acrylate **2a** (300 mol%) in the presence of $Ru_3(CO)_{12}$ (2 mol %) and various nitrogen or phosphorus containing ligands. It was found that the ruthenium catalyst modified by DPPP (6 mol%) was uniquely effective, providing the desired spirolactone **3b** in 76% yield (Table 1, entry 4). Although increased loadings of methyl acrylate **2a** were found to improve the isolated yield of spirolactone **3b** (Table 1, entries 6 and 7), enhancing the intrinsic reaction efficiency so as to minimize the loading of methyl acrylate **2a** was preferred. As further variation of the reaction parameters, including temperature (Table 1, entries 8 and 9), did not avail further improvement, carboxylic acid additives, which are known to co-catalyze hydrogenolysis of oxa- and azametallacycles, were evaluated.[15] Using 1-adamantanecarboxylic acid (10 mol%) as a cocatalyst, the isolated yield of spirolactone **3b** was increased from 76% to 96% (Table 1, entries 4 and 11).

Optimal conditions identified for formation of spirolactone **3b** were applied to the C–C coupling of cyclic and acyclic diols **1a–1l** and methyl acrylate **2a**. The corresponding lactones **3a–3l** were generated in good to excellent yield (Table 2). Both *cis*- and *trans*-diols react with equal efficiency. As illustrated in the conversion of diols **1a–1d** to **3a–3d**, five-, six-, seven-, and eight-membered ring cycloalkanes participate in spirolactone formation. Acyclic vicinal diols **1e–1h** form lactone products **3e–3h**. Whereas nonsymmetric diols **1g** and **1h** are converted to lactones **3g** and **3h** with incomplete control of regioselectivity, the reactions of cyclic diols **1i**, **1j**, and **1l** are completely regioselective, providing spirolactones **3i**, **3j**, and **3l** as single constitutional isomers.

As illustrated in the conversion of hydrobenzoin **1f**, benzoin *didehydro*-**1f**, and benzil *tetradehydro*-**1f** to lactone **3f**, catalytic

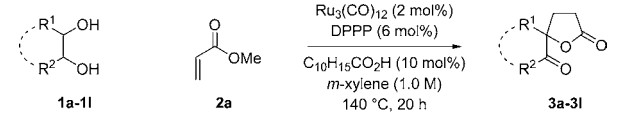
Table 1. Selected Optimization Experiments in the Ruthenium-Catalyzed C–C Coupling of Diol 1b and Methyl Acrylate 2a[a]

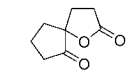
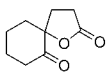
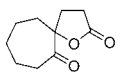
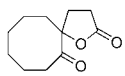
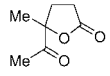
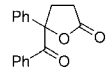
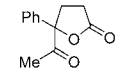
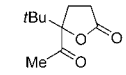
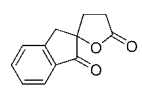
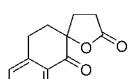
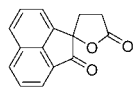
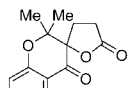


entry	ligand	additive	**2a** (mol%)	time (h)	T (°C)	yield (%)
1	BIPY	–	300	20	140	trace
2	Phen	–	300	20	140	trace
3	PCy_3	–	300	20	140	trace
4	DPPP	–	300	20	140	76
5	DPPP	–	200	20	140	56
6	DPPP	–	400	20	140	88
7	DPPP	–	500	20	140	79
8	DPPP	–	300	20	130	33
9	DPPP	–	300	20	150	69
10	DPPP	benzoic acid	300	20	140	93
11	**DPPP**	**$C_{10}H_{15}CO_2H$**	**300**	**20**	**140**	**96**
12	DPPP	$C_{10}H_{15}CO_2H$	300	4	140	73
13	DPPP	$C_{10}H_{15}CO_2H$	300	8	140	83
14	DPPP	$C_{10}H_{15}CO_2H$	300	20	120	62
15	DPPP	$C_{10}H_{15}CO_2H$	300	20	140	55[b]

[a]Cited yields are of material isolated by silica gel chromatography. $C_{10}H_{15}CO_2H$ refers to 1-adamantanecarboxylic acid. [b]0.5 mol% $Ru_3(CO)_{12}$. See Supporting Information for further experimental details.

Table 2. Ruthenium(0)-Catalyzed Hydrohydroxyalkylation of Methyl Acrylate 2a with Diols 1a–1l to Form Lactones 3a–3l[a]



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 = Ph, R^2 = Me **1k**, acenapthyl	**1d**, $R^1, R^2 = (CH_2)_6$ **1h**, R^1 = *t*Bu, R^2 = Me **1l**, dimethylchromanyl
			
3a, 85% Yield[b,e]	**3b**, 96% Yield[c]	**3c**, 64% Yield[c]	**3d**, 79% Yield[b]
			
3e, 93% Yield[d]	**3f**, 90% Yield[d]	**3g**, 71% Yield[c] 4:1 rr	**3h**, 75% Yield[c] 1.3:1 rr
			
3i, 79% Yield[c] > 20:1 rr	**3j**, 88% Yield[d] > 20:1 rr	**3k**, 59% Yield[d]	**3l**, 74% Yield[b] > 20:1 rr

[a]Cited yields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details. [b]The *cis*-1,2-diol was employed. [c]The *trans*-1,2-diol was employed. [d]A mixture of *cis*- and *trans*-1,2-diols was employed. [e]**2a** (400 mol%).

C–C coupling may be accomplished in oxidative, redox-neutral, and reductive modes, respectively (Table 3). For the latter

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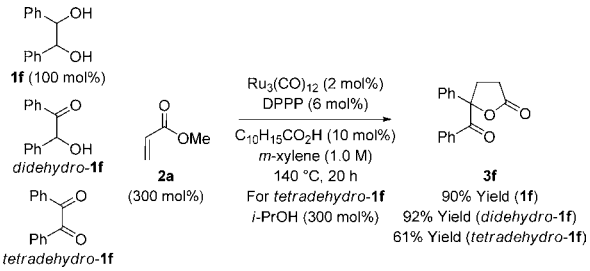
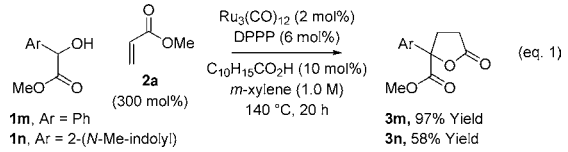
Table 3. Redox Level-Independent Formation of Lactone 3f[a]



[a]Yields are of material isolated by silica gel chromatography. $C_{10}H_{15}CO_2H$ refers to 1-adamantanecarboxylic acid. See Supporting Information for further details.

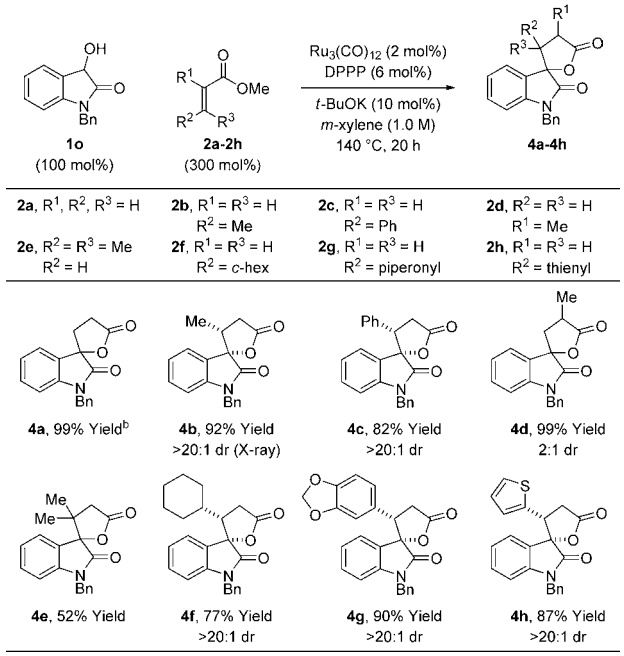
reaction involving benzil *tetradehydro*-**1f**, isopropanol (300 mol %) is employed as terminal reductant. Additionally, it was found that other vicinally deoxygenated compounds participate in lactone formation. For example, exposure of α-hydroxy esters **1m** and **1n** to methyl acrylate **2a** under standard reaction conditions provided the corresponding spirolactones **3m** and **3n** in 97% and 58% yields, respectively (eq 1).



Having explored the scope of the diol and hydroxyester partners **1a**−**1n**, substituted α,β-unsaturated esters **2a**−**2h** were investigated. Attempted reactions of esters **2b**−**2h** with diols **1a**−**1l** under standard conditions did not provide products of C−C coupling. In contrast, the reactions of *N*-benzyl-3-hydroxyoxindole **1o** with esters **2a**−**2h** proceed in good to excellent yield to furnish spirooxindole products **4a**−**4h** (Table 4). As illustrated, β-substituted acrylic esters **2b**, **2c**, **2f**, **2g**, and **2h** provide the corresponding spirolactones **4b**, **4c**, **4f**, **4g**, and **4h**, respectively, in good to excellent isolated yields as single diastereomers. Relative stereochemistry was assigned by single-crystal X-ray diffraction analysis of **4b**. The relative stereochemistry of cycloadducts **4c**, **4f**, **4g**, and **4h** is assigned in analogy to **4b**. As will be discussed in greater detail, for cycloadditions of acrylic esters **2a**−**2h** with *N*-benzyl-3-hydroxyoxindole **1o**, catalytic amounts of potassium *tert*-butoxide are required to enforce complete levels of diastereoselectivity. Finally, it is notable that even β,β-substituted acrylic ester **2e** participates in spirolactone formation, albeit in moderate yield.

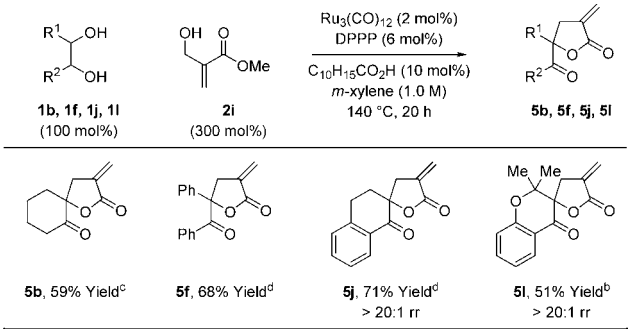
The fact that diols **1a**−**1l** did not react with substituted α,β-unsaturated esters **2b**−**2h** may be due to reversible oxaruthenacycle formation. If so, one can envision decorating the enoate reactant such that the transient metallacyclic intermediate is captured and driven to product. As the oxaruthenacycle intermediate may be viewed as a ruthenium enolate (Figure 1, bottom), it was reasoned that the hydroxyl-substituted methacrylate **2i** might engage in E1cB elimination to furnish α-methylene-γ-butyrolactones. In the event, upon exposure of diols **1b**, **1f**, **1j**, and **1l** to acrylic ester **2i** under standard conditions the α-*exo*-methylene γ-butyrolactones **5b**, **5f**, **5j**, and **5l**, respectively, were formed in moderate yield.[14] The modest yields in the formation of **5b**, **5f**, **5j**, and **5l** are, in part, attributed to reduction of the exocyclic double bond (Table 5).

Table 4. Ruthenium(0)-Catalyzed Hydrohydroxyalkylation of Acrylic Esters 2a−2h with *N*-Benzyl-3-hydroxyoxindole 1o to Form Spirolactones 4a−4h[a]



[a]Cited yields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.

Table 5. Hydrohydroxyalkylation of Hydroxyl-Substituted Methacrylate 2i with Diols 1b, 1f, 1j, and 1l to Form α-*exo*-Methylene-γ-butyrolactones 5b, 5f, 5j, and 5l[a]



[a]Yields are of material isolated by silica gel chromatography. $C_{10}H_{15}CO_2H$ refers to 1-adamantanecarboxylic acid. See Supporting Information for further details. [b]The *cis*-1,2-diol was employed. [c]The *trans*-1,2-diol was employed. [d]A mixture of *cis*- and *trans*-1,2-diols was employed.

MECHANISM AND DISCUSSION

A plausible general catalytic mechanism for the ruthenium-catalyzed C−C coupling of cyclohexanediol **1b** and methyl acrylate **2a** to form spirolactone **3b** is as follows (Scheme 1). Based on literature precedent, intervention of a discrete, mononuclear ruthenium(0) complex is anticipated.[16] Consistent with this expectation, upon heating a solution of $Ru_3(CO)_{12}$, DPPP, and 1-adamantanecarboxylic acid, the mononuclear ruthenium(II) species, $Ru(CO)(dppp)(C_{10}H_{15}CO_2)_2$ is formed, as established by single-crystal X-ray diffraction analysis (Figure 2). It should be noted that $Ru(CO)(dppp)(C_{10}H_{15}CO_2)_2$ is a competent precatalyst for catalytic C−C coupling (eq 2). Oxidative coupling of

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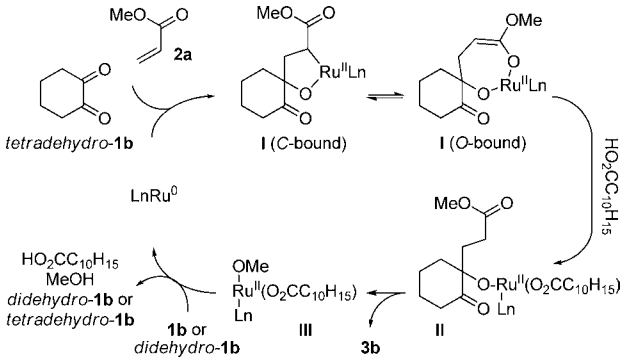
Scheme 1. A Plausible General Mechanism for Ruthenium(0)-Catalyzed Spirolactone Formation as Illustrated in the Coupling of Diol 1b and Methyl Acrylate 2a



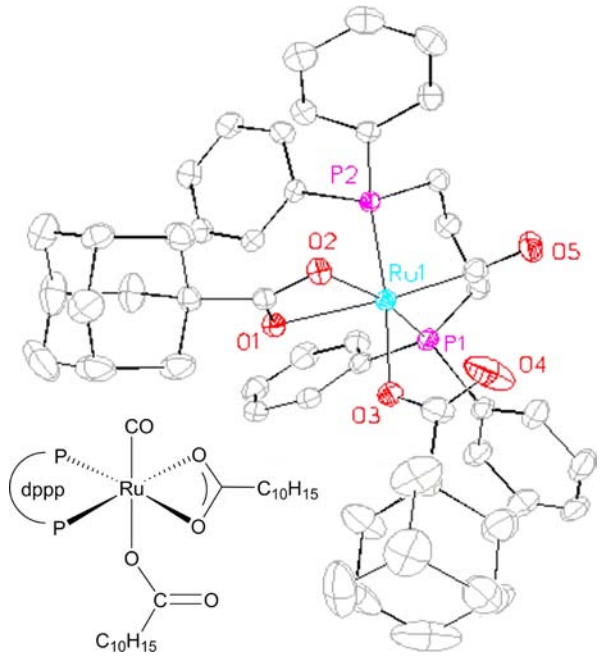
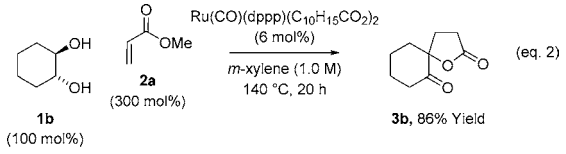


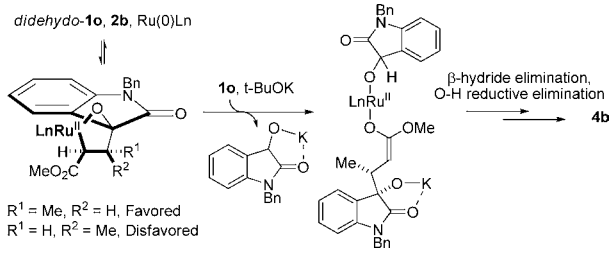
Figure 2. Single-crystal X-ray diffraction data of Ru(CO)(dppp)-$(C_{10}H_{15}CO_2)_2$. Displacement ellipsoids are scaled to the 50% probability level. Hydrogen atoms have been omitted for clarity. $C_{10}H_{15}CO_2H$ refers to 1-adamantanecarboxylic acid.



tetradehydro-**1b** and methyl acrylate **2a** forms oxaruthenacycle **I**,[5,6] which is anticipated to reside as the *O*-bound haptomer.[17] The requisite dione *tetradehydro*-**1b** likely arises through $Ru_3(CO)_{12}$-catalyzed oxidation of cyclohexanediol **1b** employing methyl acrylate **2a** as the hydrogen acceptor.[18−20] Protonation of oxaruthenacycle **I**[15] by cyclohexanediol **1b** or *didehydro*-**1b** may be slow compared to protonation of oxaruthenacycle **I** by 1-adamantanecarboxylic acid to form ruthenium carboxylate **II**, which lactonizes to form the spirocycle **3b**. The resulting ruthenium(II) complex **III** may engage in substitution with cyclohexanediol **1b** or α-hydroxy ketone *dihydro*-**1b**. Upon β-hydride elimination, *dihydro*-**1b** or *tetradehydro*-**1b** would be generated, respectively, along with a ruthenium hydride, which upon O−H reductive elimination would regenerate ruthenium(0).

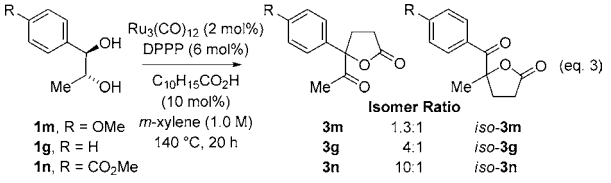
Whereas couplings of methyl acrylate **2a** with diols **1a**−**1l** require an acidic cocatalyst (Table 2), cycloadditions of acrylic esters **2a**−**2h** with *N*-benzyl-3-hydroxyoxindole **1o** require catalytic amounts of potassium *tert*-butoxide to enforce complete levels of diastereoselectivity. Based on the postulated mechanism (Scheme 1), one possible interpretation is as follows. If oxidative coupling is reversible via *retro*-Michael addition, complete kinetic stereoselectivity will be eroded if transfer hydrogenolysis of the metallacycle is not fast. Deprotonation of *N*-benzyl-3-hydroxyoxindole **1o** may accelerate transfer hydrogenolysis with respect to *retro*-Michael addition through alkoxide exchange as indicated (Scheme 2).

Scheme 2. Diastereoselection in the Formation of Spirolactones 4b, 4c, 4f, 4g, and 4h and Potential Effect of *tert*-Butoxide



The inversion in regioselectivity observed in the reaction of diol **1g** versus diols **1i** and **1j** merits discussion. As observed across numerous carbonyl additions, 1,2-indanedione reacts at the carbonyl moiety distal to the aromatic ring,[21] whereas 1-phenyl-2,3-propanedione reacts predominantly at the carbonyl moiety proximal to the aromatic ring.[22] Such trends in regioselectivity are evident in metal-catalyzed transformations, for example, hydrogenations of 1,2-indanedione and 1-phenyl-1,2-propanedione.[23] Naturally, regioselectivities observed in the aforementioned carbonyl additions and the present ruthenium-catalyzed C−C couplings are governed by the interaction of frontier molecular orbitals. Thus, notwithstanding steric effects, C−C coupling will occur predominantly at the dione carbonyl bearing the largest LUMO coefficient. Indeed, as posited by Hoffmann, the conversion of polarized bis(olefin) complexes to metallacyclopentanes should occur such that C−C bond formation occurs at the atom bearing the largest LUMO coefficient.[24]

To challenge this hypothesis, a series of *para*-substituted 1-phenyl-1,2-propanediols **1g**, **1m**, and **1n** were prepared and subjected to standard conditions for spirolactone formation (eq 3). For the *para*-methoxy-substituted diol **3m**, the electro-



philicity of the resulting dione at the carbonyl moiety proximal to the arene is attenuated and the proportion of regioisomer derived from C−C coupling to this position decreases.

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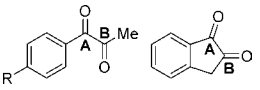
Conversely, for the 1,2-dione derived from the *para*-carbomethoxy-substituted diol **3n**, the electrophilicity of the carbonyl moiety proximal to the arene is now augmented and the proportion of regioisomer derived from C−C coupling to this position increases. To more quantitatively correlate regioselectivity with the magnitude of the respective dione LUMO coefficients, density functional theory (DFT) calculations were used to evaluate the dione LUMO coefficients. Although these data correspond to the diones in the ground state, and not the ruthenium bound diones that would be evident in the transition state, the observed trends are in alignment with the experimental results. That is, while the LUMO coefficients are always larger at the carbonyl moiety proximal to the arene, the proportion of regioisomers derived from coupling to the carbonyl moiety distal to the arene increases as the difference between the LUMO coefficients become smaller. Notably, indane diol **1i** engages in completely regioselective coupling, and the corresponding dione **5i** is predicted to have the smallest difference between the LUMO coefficients (Table 6).

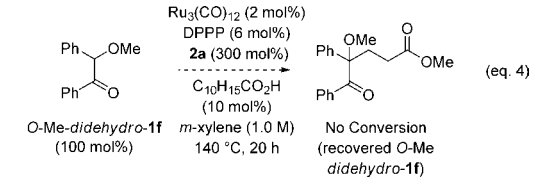
Table 6. Magnitude of Dione LUMO Coefficients Determined by DFT Calculations Correlate to Regioselectivity[a]

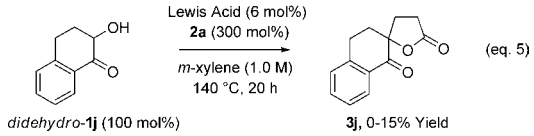


	LUMO coefficient			
dione	*A*	*B*	Δ(*A* − *B*)	experimental isomeric ratio (*A*:*B*)
5i, indane dione	−0.12189	−0.10896	0.013	1:>20
5m, R = OMe	−0.13750	−0.11802	0.019	1.3:1
5g, R = H	−0.13943	−0.11213	0.027	4:1
5n, R = CO_2Me	−0.13353	−0.09587	0.038	10:1

[a]DFT calculations were carried out with QChem 4.0 using the B3LYP hybrid functional and 6-311G(d,p) basis set.

To further challenge the veracity of the proposed oxidative coupling mechanism, several control experiments were performed. To evaluate the possibility of a mechanistic pathway involving conventional Michael addition, benzoin *didehydro*-**1f** was converted to the methyl ether *O*-Me-*didehydro*-**1f** and subjected to standard conditions for ruthenium(0)-catalyzed lactone formation, however, no reaction was observed and the starting materials were recovered unchanged (eq 4). Additionally, hydroxyketone *didehydro*-**1j** was subjected to methyl acrylate **2a** in the presence of various Lewis acids ($RuCl_3$, $B(OMe)_3$, $InCl_3$, ZnI_2, $MgCl_2$). Here, only small quantities of the spirolactone were obtained along with recovered starting materials (eq 5).





CONCLUSIONS

In summary, we report a convergent synthesis of γ-butyrolactones, including spiro- and α-methylene-γ-butyrolactones, through the ruthenium(0)-catalyzed C−C coupling of vicinal diols and acrylic esters. As demonstrated in the reactions of methyl acrylate **2a** with hydrobenzoin **1f**, benzoin *didehydro*-**1f**, and benzil *tetradehydro*-**1f**, such transformations can be conducted in a redox level-independent manner. As shown in the conversion of α-hydroxy esters **1m** and **1n** to lactones **3m** and **3n**, respectively, the reaction is applicable to other vicinally dioxygenated systems. Additionally, diverse α,β-unsaturated esters **2a**−**2h** participate in spirolactone formation to form cycloadducts **4a**−**4h**. A catalytically competent ruthenium(II) complex, $Ru(CO)(dppp)(C_{10}H_{15}CO_2)_2$, was characterized by single-crystal X-ray diffraction, and the influence of electronic effects on regioselectivity in reactions of nonsymmetric diols was probed experimentally and computationally. Future studies will focus on the development of related atom-efficient C−C couplings that result in formal alcohol C−H functionalization.

EXPERIMENTAL SECTION

General Experimental Procedure for Hydrohydroxyalkylation of Methyl Acrylate with Diol 1b. To a resealable pressure tube (13 × 100 mm) equipped with a magnetic stir bar were added *trans*-1,2-cyclohexanediol **1b** (35 mg, 0.30 mmol), $Ru_3(CO)_{12}$ (3.8 mg, 0.006 mmol, 2 mol%), 1,3-bis(diphenylphosphino)propane (7.4 mg, 0.018 mmol, 6 mol%), and 1-adamantanecarboxylic acid (5.4 mg, 0.03 mmol, 10 mol%). The tube was sealed with a rubber septum and purged with argon. Methyl acrylate **2a** (81 μL, 0.90 mmol, 300 mol%) and *m*-xylenes (0.22 mL) were added. The rubber septum was replaced with a screw cap. The mixture was heated at 140 °C (oil bath temperature) for 20 h, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated, and the residue was subjected to flash column chromatography (SiO_2; hexanes:ethyl acetate = 1:1) to furnish the title compound (48.4 mg, 0.29 mmol, 96%) as a clear yellow oil.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for all new compounds (^1H NMR, ^{13}C NMR, IR, HRMS), including NMR spectra; single-crystal X-ray diffraction data (CIF files) for spirolactone **4b** and the ruthenium complex $Ru(CO)(dppp)(C_{10}H_{15}CO_2)_2$. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

mkrische@mail.utexas.edu

Notes

The authors declare no competing financial interest.

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