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Enantioselective Ruthenium-BINAP-Catalyzed Carbonyl Reductive Coupling of Alkoxyallenes: Convergent Construction of *syn-sec,tert*-Diols via (*Z*)-σ-Allylmetal Intermediates

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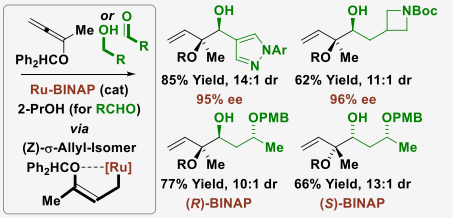
ABSTRACT: The first catalytic enantioselective ruthenium-catalyzed carbonyl reductive couplings of allene pronucleophiles is described. Using an iodide-modified ruthenium-BINAP-catalyst and *O*-benzhydryl alkoxyallene **1a**, carbonyl (α-alkoxy)-allylation occurs from the alcohol or aldehyde oxidation level to form enantiomerically enriched *syn-sec,tert*-diols. Internal chelation directs intervention of (*Z*)-σ-alkoxyallyl-ruthenium isomers, which engage in stereospecific carbonyl addition.



INTRODUCTION

Convergent construction of enantiomerically enriched acylic stereodiads bearing fully substituted carbon stereocenters remains a persistent challenge in chemical synthesis.[1] Among such motifs, *syn-sec,tert*-diols appear ubiquitously as substructures across diverse secondary metabolites, especially type I polyketides. One approach to their preparation involves stereospecific aldehyde addition of geometrically defined γ,γ-disubstituted chiral allylboron reagents through closed chairlike transition structures (Figure 1).[2,3] Corresponding catalytic enantioselective processes that generate *syn-sec,tert*-diols from tractable alkoxyallene pronucleophiles represents an alternate approach that is hitherto undescribed.[3,4] In connection with our studies of carbonyl reductive coupling via hydrogenation, transfer hydrogenation, and hydrogen autotransfer,[5] which includes the use of allene pronucleophiles,[6,7] an iridium-catalyzed reductive coupling of 1,1-disubstituted allenes with fluoral to form acyclic stereodiads bearing quaternary carbon centers was developed.[7] We posited that the enhanced oxaphilicity of ruthenium[8] might enable asymmetric couplings

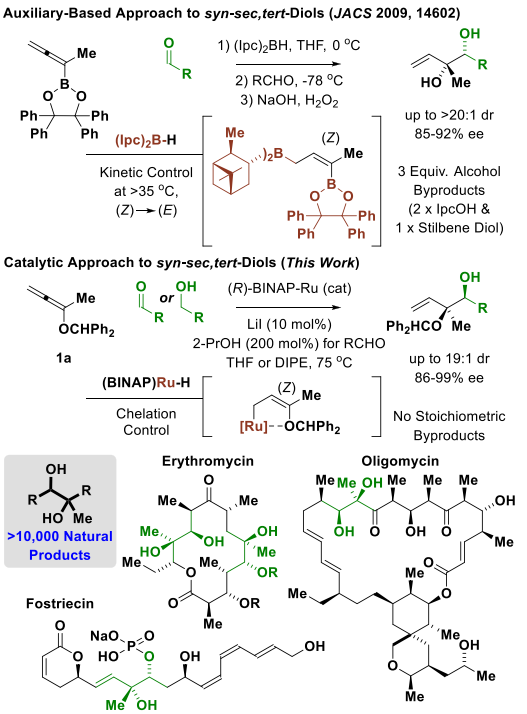


Figure 1. Stoichiometric vs catalytic synthesis of enantiomerically enriched *syn-sec,tert*-diols, a pervasive substructure among type I polyketide natural products.

Scheme 1. Potential Multiplicity of Chair-Like Transition Structures in Ruthenium-Catalyzed Carbonyl (α-Alkoxy)allylation To Form *syn-sec,tert*-Diols

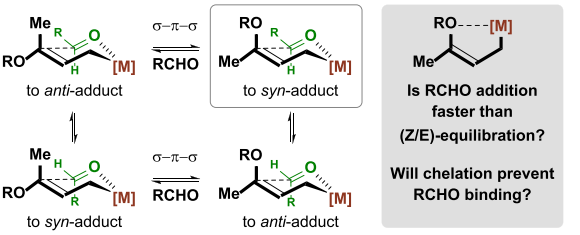


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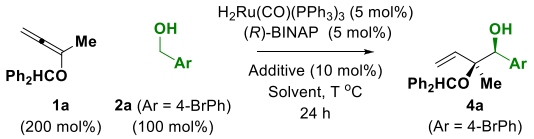
Table 1. Selected Optimization Experiments in the Enantioselective Ruthenium-Catalyzed C−C Coupling of Alkoxyallene 1a with Alcohol 2a[a]



Entry	Solvent [M]	Additive	T (°C)	3a (Yield)	dr	ee
1	CPME [0.4]	–	70	18%	4:1	73%
2	CPME [0.4]	LiCI	70	50%	6:1	59%
3	CPME [0.4]	LiBr	70	76%	7:1	79%
4	CPME [0.4]	LiI	70	80%	8.5:1	86%
5[c]	CPME [0.4]	–	70	56%	6:1	58%
6[c]	CPME [0.4]	LiI	70	65%	8:1	87%
7	THF [0.4]	LiI	70	73%	9.5:1	87%
8	THF [0.4]	LiI	75	75%	9:1	89%
9	**THF [0.3]**	**LiI**	**75**	**78%**	**9:1 (10:1)[b]**	**90%**
10[c]	THF [0.3]	LiI	75	72%	7.5:1	88%

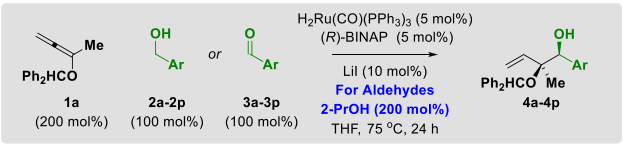
[a]Yields are of material isolated by silica gel chromatography. Diastereoselectivities were determined by ^{1}H NMR of crude reaction mixtures. Enantioselectivities were determined by chiral stationary phase HPLC analysis. [b]Diastereoselectivity was determined after chromatographic purification. [c]$HClRu(CO)(PPh_3)_3$ (5 mol %). See Supporting Information for experimental details.

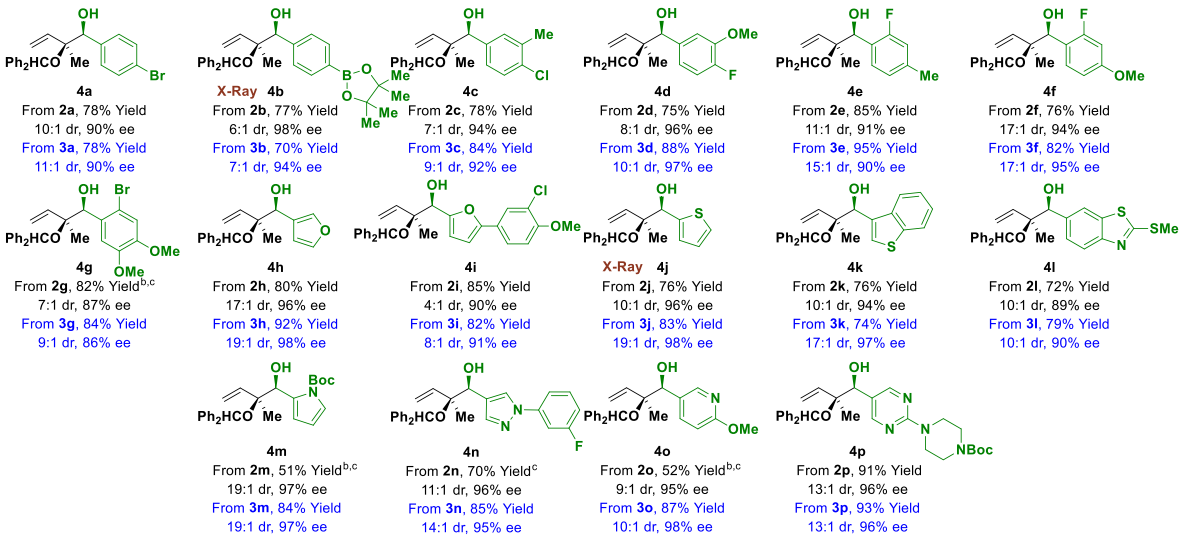
to unactivated aldehydes. In the case of alkoxyallenes, such oxaphilicity might also result in internal chelation to form (*Z*)-*σ*-allylmetal nucleophiles (Scheme 1).[9,10] Hence, to accommodate aldehyde binding, such chelation must be reversible and, to preserve *syn*-diastereoselectivity, carbonyl addition must be fast relative to (*Z*)-to-(*E*)-isomerization of the fluxional allylruthenium intermediates.[11] Furthermore, as described by Marek,[12] for *γ*,*γ*-disubstituted allylmetal nucleophiles gauche interactions associated with the developing C−C bond can reverse the equatorial vs axial preference of the aldehyde substituent to erode or invert diastereoselectivity. Despite these challenges, we herewith report ruthenium-BINAP-catalyzed *syn*-diastereo- and enantioselective carbonyl reductive couplings of *O*-benzhydryl 3-alkoxy-1,2-butadiene to form *syn-sec,tert*-diols from primary alcohol reactants (via hydrogen autotransfer) or aldehyde reactants (via 2-propanol-mediated reductive coupling).[13,14] *These processes represent the first catalytic enantioselective ruthenium-catalyzed carbonyl reductive couplings of allene pronucleophiles.*[4,6,7,15,16]

RESULTS AND DISCUSSION

Recently, we found that ruthenium catalysts bearing iodide counterions[17] display enhanced selectivity and productivity in *anti*-diastereo- and enantioselective couplings of primary alcohol proelectrophiles with arylpropynes to form products of aldehyde (*α*-aryl)allylation.[18] This observation suggested the feasibility of utilizing chiral ruthenium iodide complexes to catalyze alcohol-mediated carbonyl reductive couplings of *O*-benzhydryl 3-alkoxy-1,2-butadiene **1a**. Branch-selective couplings of this type would generate fully substituted carbon stereocenters in the form of monoprotected *syn-sec,tert*-diols. With these thoughts in mind, a series of experiments were conducted to assess the influence of counterion in reactions of alkoxy allene **1a** with *p*-bromo benzyl alcohol **2a** using the catalyst assembled from $H_2Ru(CO)(PPh_3)_3$ (5 mol %) and (*R*)-BINAP (5 mol %) in

Table 2. Diastereo- and Enantioselective Ruthenium-Catalyzed C−C Coupling of Alkoxyallene 1a with Benzylic Alcohols 2a−2p and Aryl Aldehydes 3a−3p To Form Mono-protected *syn-sec,tert*-Diols 4a−4p[a]





[a]Yields are of material isolated by silica gel chromatography. Diastereoselectivities were determined by ^{1}H NMR of purified materials. Enantioselectivities were determined by chiral stationary phase HPLC. Standard conditions: 0.2 mmol scale. See Supporting Information for experimental details. [b]10% catalyst. [c]48 h.

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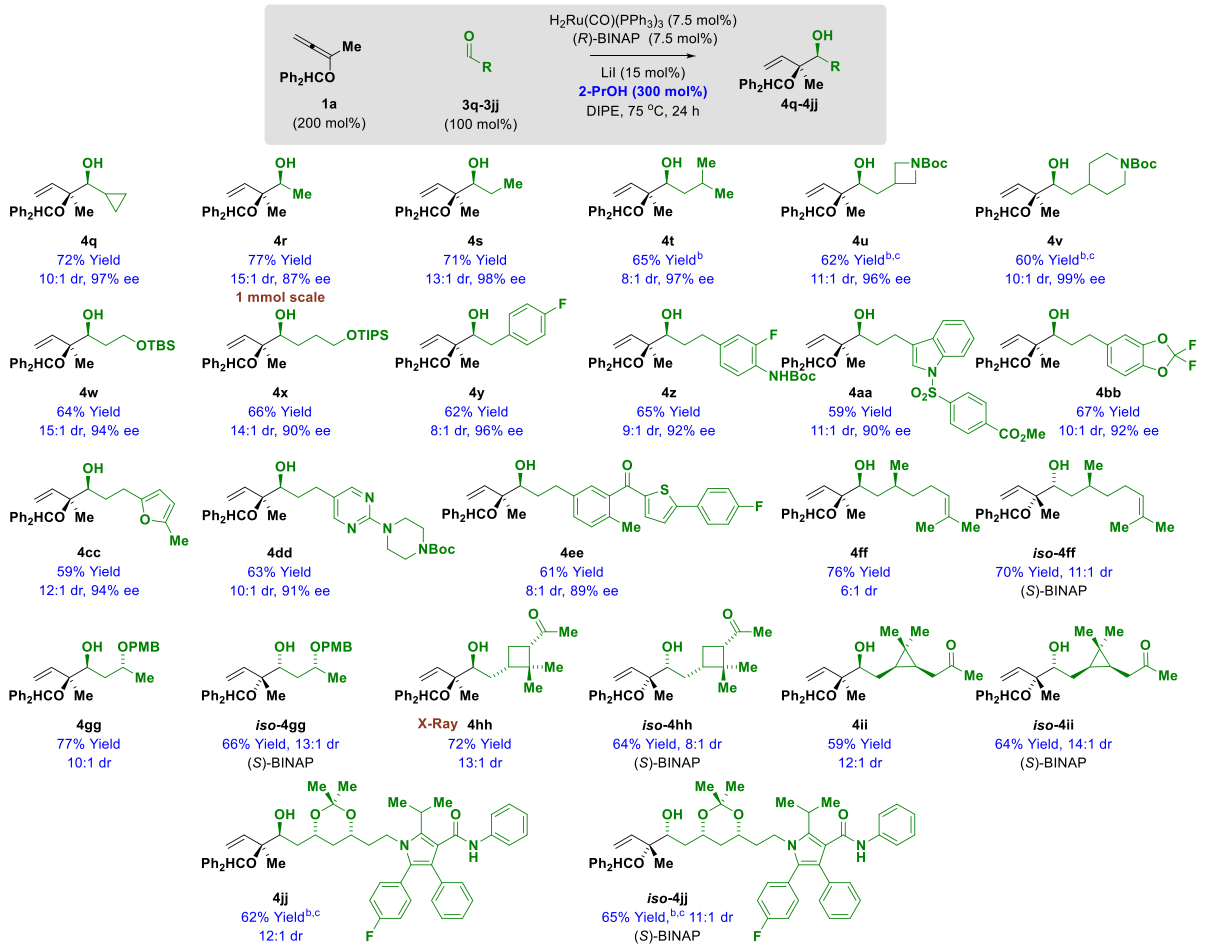
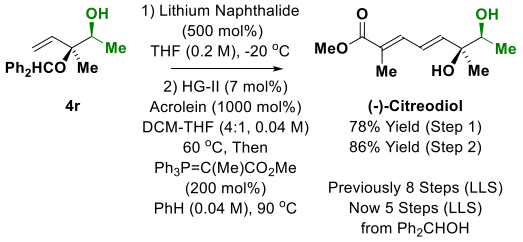
Table 3. Diastereo- and Enantioselective Ruthenium-Catalyzed Reductive C−C Coupling of Alkoxyallene 1a with Aliphatic Aldehydes 3q−3jj To Form Mono-protected *syn-sec,tert*-Diols 4q−4jj Mediated by 2-Propanol[a]



[a]Yields are of material isolated by silica gel chromatography. Diastereoselectivities were determined by ^{1}H NMR of purified materials. Enantioselectivities were determined by chiral stationary phase HPLC. Standard conditions: 0.2 mmol scale. See Supporting Information for experimental details. [b]10% catalyst. [c]48 h.

Scheme 2. Total Synthesis of (−)-Citreodiol



cyclopentyl methyl ether (CPME) solvent at 70 °C. In the absence of added halide ion, the anticipated product of (α-alkoxy)crotylation **4a** was formed in 18% yield with an enantiomeric enrichment of 73% (Table 1, entry 1). Notably, a 4:1 mixture of diastereomers in favor of the *syn*-isomer was observed. Under these conditions, the introduction of the halide additives LiX = Cl, Br, I (10 mol %) led to progressively higher yields and stereoselectivities (Table 1, entries 2−4), with the iodide-bound catalyst providing **4a** in 80% yield, 8.5:1 diastereomeric ratio, and 86% ee (Table 1, entry 4). The selectivities obtained using $HClRu(CO)(PPh_3)_3$ as precatalyst (for which chloride is preinstalled) are in excellent alignment with the outcome observed using $H_2Ru(CO)(PPh_3)_3$ and LiCl (Table 1, entry 2 vs 5). The stereoselectivities obtained upon addition of LiI to either $H_2Ru(CO)(PPh_3)_3$ or $HClRu(CO)(PPh_3)_3$ are also strikingly similar (Table 1, entry 4 vs 6), corroborating efficient formation of the halide-modified catalyst. As slightly better performance was observed using $H_2Ru(CO)(PPh_3)_3$, subsequent optimization focused on this precatalyst. Conducting the reaction in THF (Table 1, entry 7), increasing temperature (Table 1, entry 8), and slightly decreasing concentration were all beneficial, enabling formation of **4a** in 78% yield with excellent control of *syn*-diastereo- and enantioselectivity (Table 1, entry 9). The catalyst derived from $HClRu(CO)(PPh_3)_3$ and LiI gave **4a** in similar, but slightly lower, yields and selectivities (Table 1, entry 10).

Optimal conditions identified for the formation of **4a** were applied to structurally diverse benzylic and heterobenzylic alcohols **2b**−**2p** (Table 2). As illustrated by the formation of adducts **4a**−**4g**, diverse substitution patterns of the benzene ring, including *ortho*-substituents, are tolerated. Additionally, as demonstrated by the formation of adduct **4b**, the reaction conditions are sufficiently mild that pinacol boronates are tolerated. Adducts **4h**−**4p** derived from heterobenzylic alcohols incorporating furan, thiophene, benzothiazole, pyrrole, pyrazole, pyridine, and pyrimidine rings also were formed in an efficient

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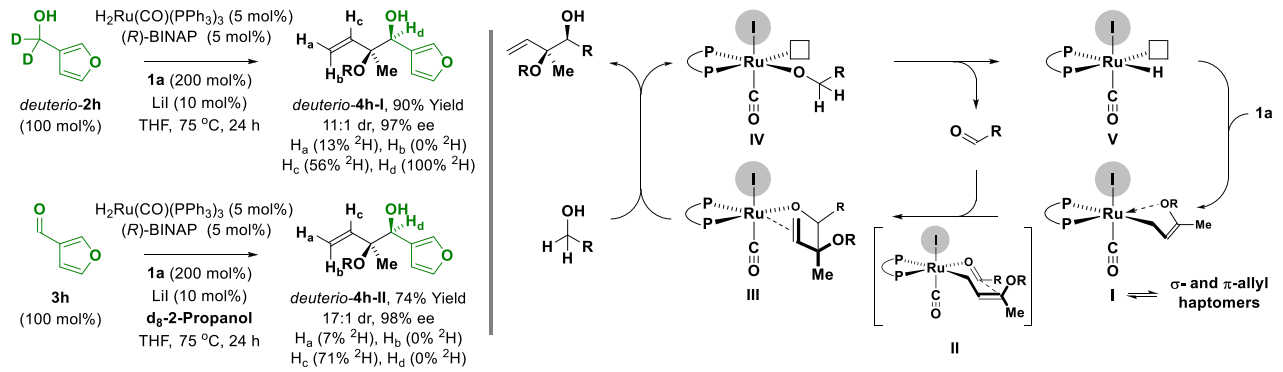
Scheme 3. General Catalytic Mechanism As Corroborated by Isotopic Labeling Studies

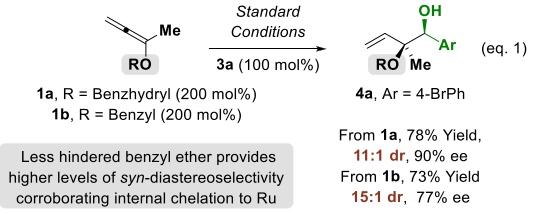


and selective manner. The conversion of alcohols **2a**−**2p** to adducts **4a**−**4p** represent redox-neutral hydrogen autotransfer processes. The corresponding aldehydes **3a**−**3p** also can be transformed to adducts **4a**−**4p** via 2-propanol-mediated reductive coupling under otherwise identical reaction conditions. Notably, reactions conducted from the aldehyde oxidation level generally displayed slightly higher yields and stereoselectivities, which is attributed to more efficient capture of the transient allylruthenium nucleophiles.

Aliphatic alcohols did not react efficiently under the optimal conditions for the formation of **4a**. To facilitate the carbonyl addition process, the reaction was conducted from the aldehyde oxidation level at slightly higher catalyst loadings in a less Lewis basic solvent, DIPE (diisopropyl ether), to promote association of the aldehyde with the allylruthenium intermediate (see Supporting Information for selected optimization experiments). Under these conditions, aliphatic aldehydes **3q**−**3ee** engage in efficient 2-propanol-mediated reductive coupling with allene **1a** to furnish adducts **4q**−**4ee** (Table 3). *syn*-Diastereoselectivities ranging from 8:1 to 15:1 were accompanied by excellent levels of enantioselectivity (87−99% ee). Additionally, a series of chiral *β*-stereogenic aldehydes **3ff**, **3gg**, **3hh**, **3ii**, and **3jj** were subjected to reductive coupling with allene **1a** using catalysts modified by (*R*)- and (*S*)-BINAP. In each case, excellent levels of catalyst-directed asymmetric induction were observed. The utility of this method is highlighted by conversion of adduct **4r** to (−)-citreodiol, a secondary metabolite of the ascomycetous fungi *Penicillium citreoviride B* (Scheme 2).[19,20]

To corroborate the catalytic mechanism, a series of deuterium labeling experiments were performed (Scheme 3). Under standard reaction conditions, d_2-3-furfuryl alcohol *deuterio*-**2h** is converted to *deuterio*-**4h**-**I** which completely retains deuterium at the carbinol position. Deuterium is transferred to the internal vinylic position (56% ^{2}H at H_c) and the terminal vinylic position (13% ^{2}H at H_a). These data suggest dehydrogenation of the primary alcohol is irreversible due to rapid allene hydroruthenation at the central allene carbon atom, and that the secondary alcohol product is resistant to dehydrogenation due to internal coordination of the alkene. In a related experiment, 3-furfural **3h** is subjected to standard reductive coupling conditions mediated by d_8-2-propanol. Deuterium is transferred to the internal vinylic position (71% ^{2}H at H_c) and the terminal vinylic position (7% ^{2}H at H_a). The absence of deuterium at the carbinol position again suggests the secondary alcohol product is inert with respect to dehydrogenation and that allylruthenium generation occurs via hydroruthenation at the central allene carbon atom. In both experiments, deuterium loss is attributed to H/D-exchange involving adventitious water and, in the former experiment, the hydroxyl functional group of the primary alcohol reactant.[21] It is notable that deuterium is incorporated at H_a but not H_b in both experiments, suggesting strong kinetic stereocontrol in the allene hydroruthenation event, possibly due to coordination of ruthenium to the ether oxygen.

Based on these data, the indicated reaction mechanism is proposed (Scheme 3). Hydroruthenation of alkoxyallene **1a** delivers (*Z*)-*σ*-allylruthenium species **I** in which internal coordination of the benzhydryl ether oxygen to ruthenium defines alkene stereochemistry. Aldehyde coordination triggers carbonyl addition by way of a closed six-centered transition structure **II**, resulting in the formation of the homoallylic ruthenium alkoxide **III**. Exchange with a primary alcohol reactant releases product and forms the ruthenium alkoxide **IV**, which upon *β*-hydride elimination generates the aldehyde and the ruthenium hydride **V**. That internal chelation defines (*Z*)-stereochemistry of the transient allylruthenium intermediate is corroborated by reactions of alkoxyallenes **1a** vs **1b** (eq 1).



Alkoxyallene **1b** contains a smaller benzyl ether and, hence, is anticipated to form a more stable chelate than alkoxyallene **1a**, which incorporates a larger benzhydryl ether. Indeed, the reaction of the less hindered alkoxyallene **1b** proceeds with higher levels of *syn*-diastereoselectivity but with significantly lower levels of enantioselectivity. A related bis(1-naphthyl)-alkoxyallene was prepared, but coupling product was not observed upon exposure to **3a** under standard conditions. Preparation of tertiary allenic ethers could not be achieved, as lithiation occurs predominately at the *γ*-position.[22] Attempted synthesis of the ethyl-substituted allene via lithiation of the monosubstituted alkoxyallene followed by reaction with ethyl iodide resulted in incomplete ethylation, possibly due to competing elimination.

CONCLUSIONS

In summary, we report the first enantioselective ruthenium-catalyzed carbonyl reductive couplings of allene pronucleophiles. This method employs an inexpensive ruthenium-BINAP-

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catalyst and *O*-benzhydryl 3-alkoxy-1,2-butadiene **1a**, which can be prepared in 2 steps from benzhydryl alcohol on >15 g scale (see Supporting Information)—attributes that make this method a practical protocol for the generation of enantiomerically enriched *syn-sec,tert*-diols, which appear ubiquitously among type I polyketide natural products. Two remarkable effects were uncovered: (a) the enhanced selectivity and productivity of ruthenium catalysts bearing iodide counterions,[17] and (b) the oxaphilicity of the ruthenium(II) center is sufficient to direct internal chelation to form (*Z*)-*σ*-alkoxyallylruthenium intermediates. The physical basis of the "iodide effect" remains unclear; however, due to its size and stronger binding,[17,23] we speculate that the iodide counterion may accentuate energetic differences between diastereomeric transition structures and suppress catalyst decomposition pathways. Computational studies aimed at establishing the veracity of this interpretation are ongoing. This work contributes to a growing class of catalytic enantioselective carbonyl reductive couplings beyond premetalated reagents.[24]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c03480.

Experimental procedures and spectral data for all new compounds; X-ray diffraction data for compounds **4b**, **4j**, and **4hh** (PDF)

Accession Codes

CCDC 2043407 and 2068895−2068896 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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