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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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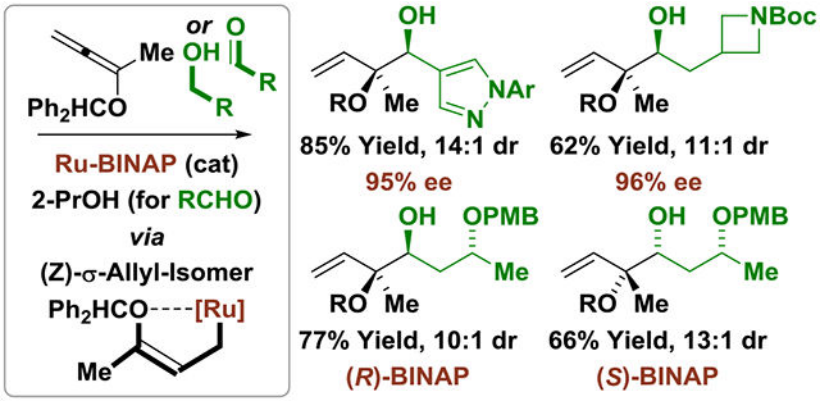
Abstract

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-alkoxyallylruthenium isomers, which engage in stereospecific carbonyl addition.

Graphical Abstract



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

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. X-Ray diffraction data for compounds **4b**, **4j** and **4hh**. This material is available free of charge *via* the internet at http://pubs.acs.org.

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involves stereospecific aldehyde addition of geometrically defined γ,γ-disubstituted chiral allylboron reagents through closed chair-like 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 auto-transfer,[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 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 auto-transfer) 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 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).

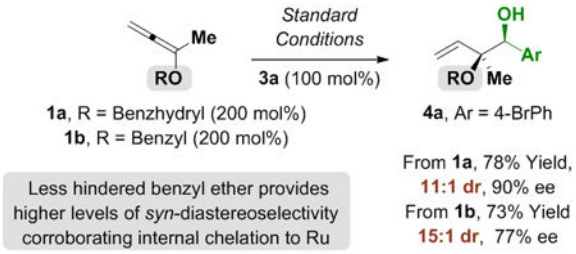
Optimal conditions identified for the formation of **4a** were applied to structurally diverse benzylic and hetero-benzylic alcohols **2b**-**2p** (Table 2). As illustrated by the formation of adducts **4a**-**4g**, diverse substitution patterns of the benzene ring, including *ortho*-substituents, are 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 hetero-benzylic alcohols incorporating furan, thiophene, benzothiazole, pyrrole, pyrazole, pyridine and pyrimidine rings also were formed in an efficient and selective manner. The conversion of alcohols **2a**-**2p** to adducts **4a**-**4p** represent redox-neutral hydrogen auto-transfer 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 labelling 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% ^2H at H_c) and the terminal vinylic position (13% ^2H 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 Ha but not Hb in both experiments, suggesting a 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-napthyl)-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 mono-substituted alkoxyallene followed by reaction with ethyl iodide resulted in incomplete ethylation, possibly due to competing elimination.



(eq. 1)

CONCLUSIONS

In summary, we report the first enantioselective ruthenium-catalyzed carbonyl reductive couplings of allene pronucleophiles. This method employs an inexpensive ruthenium-BINAP-catalyst and *O*-benzhydryl 3-alkoxy-1,2-butadiene **1a**, which can be prepared in 2 steps from benzhydryl alcohol on >15 gram 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]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments.

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REFERENCES

(1). (a)For selected reviews on the synthesis of enantiomerically enriched stereodiads bearing fully substituted carbonyl stereocenters, see:Marek I; Sklute G Creation of Quaternary Stereocenters in Carbonyl Allylation Reactions. Chem. Commun 2007, 1683–1691.(b)Feng J; Holmes M; Krische MJ Acyclic Quaternary Carbon Stereocenters *via* Enantioselective Transition Metal Catalysis. Chem. Rev 2017, 117, 12564–12580. [PubMed: 28910092] (c)Pierrot D; Marek I Synthesis of Enantioenriched Vicinal Tertiary and Quaternary Carbon Stereogenic Centers within an Acyclic Chain. Angew. Chem., Int. Ed 2020, 59, 36–49.

(2). Chen M; Handa M; Roush WR Enantioselective Synthesis of 2-Methyl-1,2-*syn*- and 2-Methyl-1,2-*anti*-3-butenediols via Allene Hydroboration-Aldehyde Allylboration Reaction Sequences. J. Am. Chem. Soc 2009, 131, 14602–14603. [PubMed: 19778012]

(3). (a)For selected reviews on enantioselective carbonyl allylation, see:Denmark SE; Fu J Catalytic Enantioselective Addition of Allylic Organometallic Reagents to Aldehydes and Ketones. Chem. Rev 2003, 103, 2763–2794. [PubMed: 12914480] (b)Hall DG Lewis and Brønsted Acid Catalyzed Allylboration of Carbonyl Compounds: From Discovery to Mechanism and Applications. Synlett 2007, 11, 1644–1655.(c)Hargaden GC; Guiry PJ The Development of the Asymmetric Nozaki–Hiyama–Kishi Reaction. Adv. Synth. Catal 2007, 349, 2407–2424.(d)Yus M; González-Gómez JC; Foubelo F Catalytic Enantioselective Allylation of Carbonyl Compounds and Imines. Chem. Rev 2011, 111, 7774–7854. [PubMed: 21923136] (e)Huo H-X; Duvall JR; Huang M-Y; Hong R Catalytic Asymmetric Allylation of Carbonyl Compounds and Imines with Allylic Boronates. Org. Chem. Front 2014, 1, 303–320.(f)Spielmann K; Niel G; de Figueiredo RM; Campagne J-M Catalytic Nucleophilic 'Umpoled' π-Allyl Reagents. Chem. Soc. Rev 2018, 47, 1159–1173. [PubMed: 29323678]

(4). (a)For selected reviews on allene-mediated C-C coupling, see:Neff RK; Frantz DE Recent Applications of Chiral Allenes in Axial-to-Central Chirality Transfer Reactions. Tetrahedron 2015, 71, 7–18.(b)Pulis AP; Yeung K; Procter DJ Enantioselective Copper Catalysed, Direct Functionalisation of Allenes via Allyl Copper Intermediates. Chem. Sci 2017, 8, 5240–5247. [PubMed: 28959423] (c)Holmes M; Schwartz LA; Krische MJ Intermolecular Metal-Catalyzed Reductive Coupling of Dienes, Allenes and Enynes with Carbonyl Compounds and Imines. Chem. Rev 2018, 118, 6026–6052. [PubMed: 29897740] (d)Schmiedel VM; Reissig H-U Alkoxyallenes as Starting Materials for the Synthesis of Natural Products. Curr. Org. Chem 2019, 23, 2976–3003.(e)Li G; Huo X; Jiang X; Zhang W Asymmetric Synthesis of Allylic Compounds

via Hydrofunctionalisation and Difunctionalisation of Dienes, Allenes, and Alkynes. Chem. Soc. Rev 2020, 49, 2060–2118. [PubMed: 32150186] (f)Blieck R; Taillefer M; Monnier F Metal-Catalyzed Intermolecular Hydrofunctionalization of Allenes: Easy Access to Allylic Structures via the Selective Formation of C-N, C-C and C-O Bonds. Chem. Rev 2020, 120, 13545–13598. [PubMed: 33301308]

(5). (a)For selected reviews on enantioselective carbonyl reductive coupling via hydrogenation, transfer hydrogenation and hydrogen auto-transfer, see:Kim SW; Zhang W; Krische MJ Catalytic Enantioselective Carbonyl Allylation and Propargylation via Alcohol-Mediated Hydrogen Transfer: Merging the Chemistry of Grignard and Sabatier Acc. Chem. Res 2017, 50, 2371–2380. [PubMed: 28792731] (b)Doerksen RS; Meyer CC; Krische MJ Feedstock Reagents in Metal-Catalyzed Carbonyl Reductive Coupling: Minimizing Preactivation for Efficiency in Target-Oriented Synthesis. Angew. Chem. Int. Ed 2019, 58, 14055–14064.

(6). (a)For seminal examples of allene pronucleophiles in allylative metal-catalyzed carbonyl reductive coupling, see:Skucas E; Bower JF; Krische MJ Carbonyl Allylation in the Absence of Preformed Allyl Metal Reagents: Reverse Prenylation *via* Iridium Catalyzed Hydrogenative Coupling of Dimethylallene. J. Am. Chem. Soc 2007, 129, 12678–12679. [PubMed: 17900123] (b)Bower JF; Skucas E; Patman RL; Krische MJ Catalytic C-C Coupling *via* Transfer Hydrogenation: Reverse Prenylation, Crotylation and Allylation from the Alcohol or Aldehyde Oxidation Level. J. Am. Chem. Soc 2007, 129, 15134–15135. [PubMed: 18020342] (c)Ngai M-Y; Skucas E; Krische MJ Ruthenium Catalyzed C-C Bond Formation *via* Transfer Hydrogenation: Branch-Selective Reductive Coupling of Allenes to Paraformaldehyde and Higher Aldehydes. Org. Lett 2008, 10, 2705–2708. [PubMed: 18533665]

(7). Schwartz LA; Holmes M; Brito GA; Gonçalves TP; Richardson J; Ruble JC; Huang K-W; Krische MJ Cyclometallated Iridium-PhanePhos Complexes Are Active Catalysts in Enantioselective Allene-Fluoral Reductive Coupling and Related Alcohol-Mediated Carbonyl Additions that Form Acyclic Quaternary Carbon Stereocenters. J. Am. Chem. Soc 2019, 141, 2087–2096. [PubMed: 30681850]

(8). For evidence of ruthenium's relatively oxaphilic character, see: Trost BM; Ferreira EM; Gutierrez AC Ruthenium- and Palladium-Catalyzed Enyne Cycloisomerizations: Differentially Stereoselective Syntheses of Bicyclic Structures. J. Am. Chem. Soc 2008, 130, 16176–16177. [PubMed: 18998647]

(9). Internal chelation of alkoxy-substituted allylindium reagents has been observed. For a review, see: Zambron BK Internal Chelation within Functionalized Organoindium Reagents: Prospects for Regio- and Stereocontrol in the Allylation, Propargylation and Allenylation of Carbonyl Compounds. Synthesis 2020, 52, 1147–1180.

(10). For internal chelation of alkoxy-substituted allyltin trihalides, see: Almendros P; Thomas EJ On The Stereoselectivity of Reactions of Alkoxyallylstannanes and Alkoxy Aldehydes. J. Chem. Soc., Perkin Trans 1, 1997, 2561–2568.

(11). Zbieg JR; McInturff EL; Leung JC; Krische MJ Amplification of *anti*-Diastereoselectivity *via* Curtin-Hammett Effects in Ruthenium Catalyzed Hydrohydroxyalkylation of 1,1-Disubstituted Allenes: Diastereoselective Formation of All-Carbon Quaternary Centers. J. Am. Chem. Soc 2011, 133, 1141–1144. [PubMed: 21175178]

(12). Mejuch T; Gilboa N; Gayon E; Wang H; Houk KN; Marek I Axial Preferences in Allylation Reactions via The Zimmerman-Traxler Transition State. Acc. Chem. Res 2013, 46, 1659–1669. [PubMed: 23672428]

(13). (a)For selected reviews on the convergent construction of monoprotected priopionate-based *syn-sec,tert*-diols via diastereoselective additions of *C*-nucleophiles to chiral α-alkoxy ketones., see:Reetz MT Chelate- or Nonchelate Control in Addition Reactions of Chiral α- and β-Alkoxycarbonyl Compounds. Angew. Chem. Int. Ed 1984, 23, 556–569.(b)Mengel A; Reiser O Around and Beyond Cram's Rule. Chem. Rev 1999, 99, 1191–1223. [PubMed: 11749444] (c)Braun M Selected Diastereoselective Reactions: Additions of Achiral Carbanions to Chiral Aldehydes and Ketones. In Comprehensive Chirality, Carreira EM, Yamamoto H, Eds.; Elsevier: London, U.K., 2012; Vol. 2; pp 346–369.

(14). Nonconvergent construction of *syn-sec,tert*-diols may be achieved via catalytic enantioselective dihydroxylation of trisubstituted olefins. For a review, see: Kolb HC; VanNieuwenhze MS; Sharpless KB Catalytic Asymmetric Dihydroxylation. Chem. Rev 1994, 94, 8, 2483–2547.

(15). (a)For selected examples of enantioselective copper-catalyzed allene-carbonyl reductive coupling, see:Tsai EY; Liu RY; Yang Y; Buchwald SL A Regio- and Enantioselective CuH-Catalyzed Ketone Allylation with Terminal Allenes. J. Am. Chem. Soc 2018, 140, 2007–2011. [PubMed: 29376366] (b)Liu RY; Zhou YZ; Yang Y; Buchwald SL Enantioselective Allylation Using Allene, a Petroleum Cracking Byproduct J. Am. Chem. Soc 2019, 141, 2251–2256. [PubMed: 30685967]

(16). (a)For general reviews on catalytic enantioselective processes that involve alcohol dehydrogenation, see:Quintard A; Rodriguez J Catalytic Enantioselective OFF ↔ ON Activation Processes Initiated by Hydrogen Transfer: Concepts and Challenges. Chem. Commun 2016, 52, 10456–10473.(b)Kwok T; Hoff O; Armstrong RJ; Donohoe TJ Chem. Eur. J 2020, 26, 12912–12926. [PubMed: 32297370]

(17). (a)For reviews on halide effects in transition metal catalysis, see:Maitlis PM; Haynes A; James BR; Catellani M; Chiusoli GP Iodide Effects in Transition Metal Catalyzed Reactions. Dalton Trans. 2004, 3409–3419. [PubMed: 15510253] (b)Fagnou K.l; Lautens M Halide Effects in Transition Metal Catalysis. Angew. Chem. Int. Ed 2002, 41, 26–47.

(18). Xiang M; Ghosh A; Krische MJ Diastereo- and Enantioselective Ruthenium-Catalyzed C-C Coupling of 1-Arylpropynes and Alcohols: Alkynes as Chiral Allylmetal Precursors in Carbonyl anti-(α-Aryl)allylation. J. Am. Chem. Soc 2021, 143, 2838–2845. [PubMed: 33555867]

(19). (a)For isolation of citreodiol, see:Shizuri Y, Nishiyama S, Imai D & Yamamura S Isolation and Stereostructures of Citreoviral, Citreodiol, and Epicitreodiol. Tetrahedron Lett. 1984, 25, 4771–4774.(b)Cao Z; Yoshida R; Kinashi H; Arakawa K Blockage of The Early Step of Lankacidin Biosynthesis Caused a Large Production of Pentamycin, Citreodiol and *epi*-Citreodiol in *Streptomyces rochei*. J. Antibiot 2015, 68, 328–333.

(20). (a)For the total synthesis of citreodiol and *epi*-citreodiol, see:Ghosh P; Cusick JR; Inghrim J; Williams LJ Silyl-Substituted Spirodiepoxides: Stereoselective Formation and Regioselective Opening. Org. Lett 2009, 11, 4672–4675. [PubMed: 19810767] (b)Giovannini PP; Fantin G; Massi A; Venturi A; Pedrini P Enzymatic Diastereo- and Enantioselective synthesis of α-Alkyl-α,β-Dihydroxyketones Org. Biomol. Chem 2011, 9, 8038–8045. [PubMed: 22006343]

(21). (a)Tse SKS; Xue P; Lin Z; Jia G Hydrogen/Deuterium Exchange Reactions of Olefins with Deuterium Oxide Mediated by the Carbonylchlorohydrido-tris(triphenylphosphine)ruthenium(II) Complex. Adv. Synth. Catal 2010, 352, 1512–1522.(b)Isbrandt ES; Vandavasi JK; Zhang W; Jamshidi MP; Newman SG Catalytic Deuteration of Aldehydes with D_2O. Synlett 2017, 28, 2851–2854.

(22). (a)Clinet JC; Linstrumelle G A New Simple Stereoselective Synthesis of *trans*-α,β-Unsaturated Carbonyl Compounds. Tetrahedron Lett. 1978, 19, 1137–1140.(b)Gschwend HW; Rodriguez HR Heteroatom-Facilitated Lithiations. Org. React 1979, 26, 1–360.

(23). (a)Pitteri B; Marangoni G; Cattalini L; Canovese L Nucleophilic Displacement of Halides from Dihalogeno-platinum(II) Complexes Containing a Chelating Thioether. Kinetics and Equilibria. J. Chem. Soc. Dalton Trans 1994, 169–174.(b)Poulton JT; Sigalas MP; Folting K; Streib WE; Eisenstein O; Caulton KG RuHX(CO)$(PR_3)_2$: Can ν_{CO} Be a Probe for the Nature of the Ru-X Bond? Inorg. Chem 1994, 33, 1476–1485.

(24). For a general review on catalytic carbonyl reductive couplings of π-unsaturated pronucleophiles, see: Nguyen KD; Park BY; Luong T; Sato H; Garza VJ; Krische MJ Metal-Catalyzed Reductive Coupling of Olefin-Derived Nucleophiles: Reinventing Carbonyl Addition. Science 2016, 354, aah5133. [PubMed: 27846504]

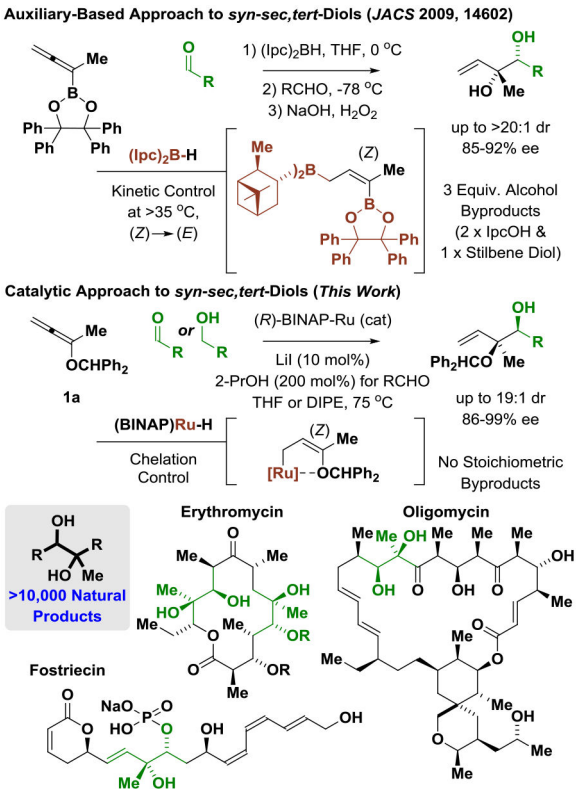
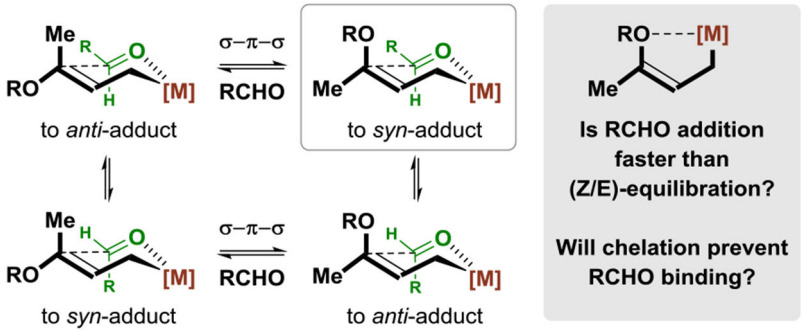


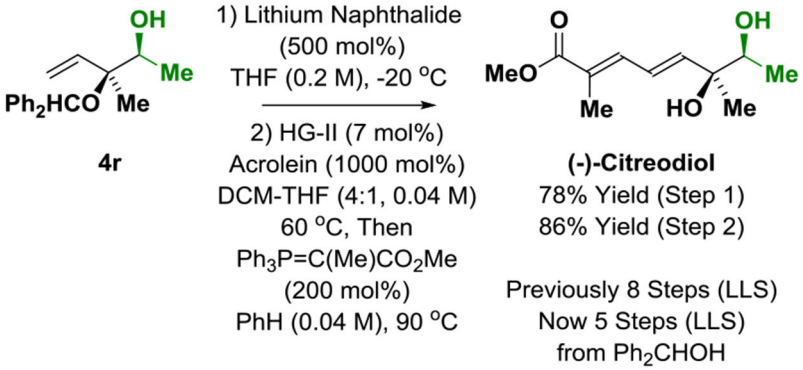
Figure 1.

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

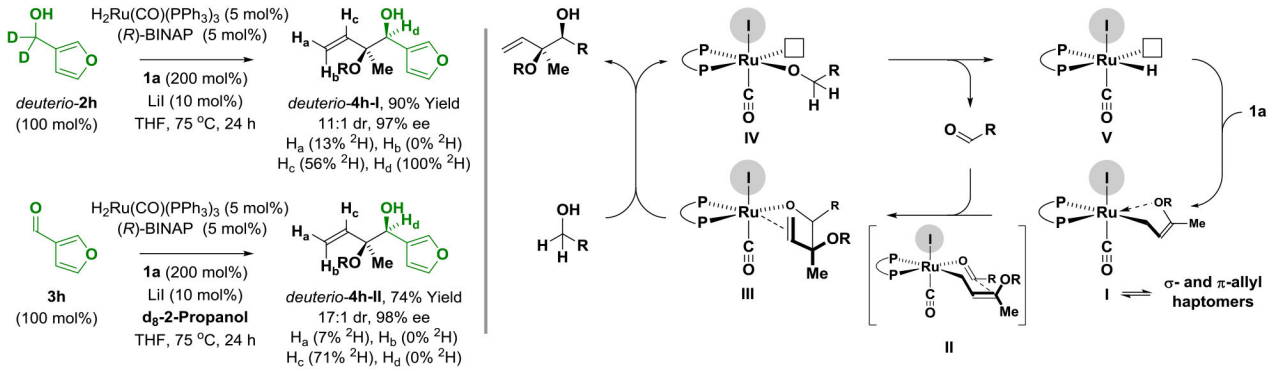


Scheme 1.

Potential multiplicity of chair-like transition structures in ruthenium-catalyzed carbonyl (α-alkoxy)allylation to form *syn-sec,tert*-diols.



Scheme 2.
Total synthesis of (−)-citreodiol.

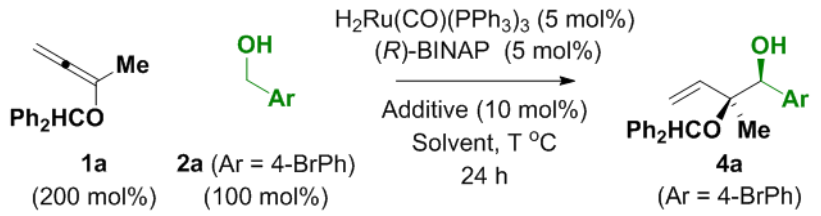


Scheme 3.

General catalytic mechanism as corroborated by isotopic labeling studies.

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]	LiCl	70	50%	6:1	59%
	3	CPME [0.4]	LiBr	70	76%	7:1	79%
	4	CPME [0.4]	Lil	70	80%	8.5:1	86%
	5[c]	CPME [0.4]	---	70	56%	6:1	58%
	6[c]	CPME [0.4]	Lil	70	65%	8:1	87%
	7	THF [0.4]	Lil	70	73%	9.5:1	87%
	8	THF [0.4]	Lil	75	75%	9:1	89%
→	9	THF [0.3]	Lil	75	78%	9:1 (10:1)[b]	90%
	10[c]	THF [0.3]	Lil	75	72%	7.5:1	88%

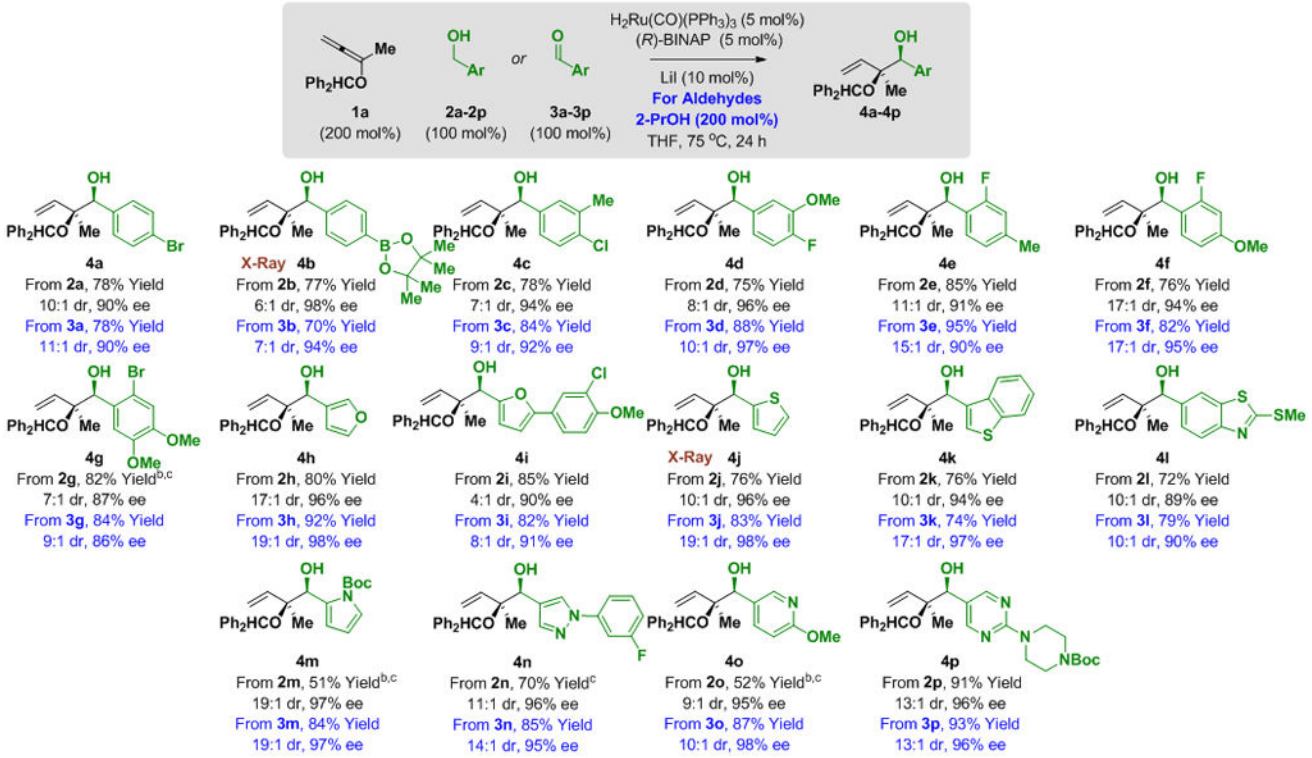
[a] Yields are of material isolated by silica gel chromatography. Diastereoselectivities were determined by ^{1}H NMR of crude reaction mixtures. Enantioselectivities were determined by chiral stationary phase HPLC analysis.

[b] Diastereoselectivity was determined after chromatographic purification.

[c] HClRu(CO)(PPh3)3 (5 mol%). See Supporting Information for experimental details.

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] 48h.

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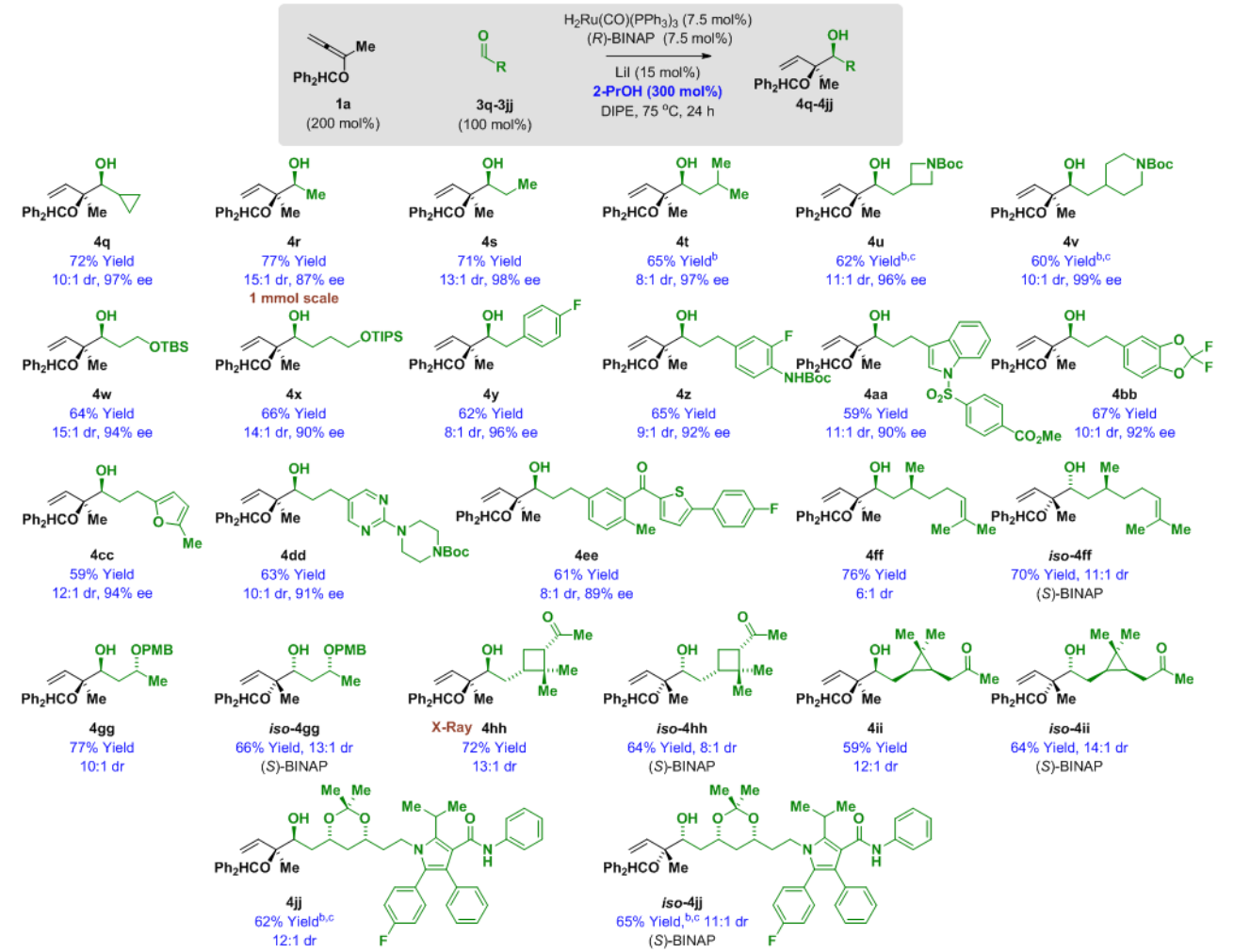
Table 3.

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.