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Stereo- and Site-Selective Crotylation of Alcohol Proelectrophiles via Ruthenium-Catalyzed Hydrogen Auto-Transfer Mediated by Methylallene and Butadiene

Eliezer Ortiz[§],

Brian J. Spinello[§],

Yoon Cho,

Jessica Wu,

Michael J. Krische[*]

University of Texas at Austin, Department of Chemistry, Austin, TX 78712-1167 (USA)

Abstract

Iodide-bound ruthenium-JOSIPHOS complexes catalyze the redox-neutral C-C coupling of primary alcohols with methylallene (1,2-butadiene) or 1,3-butadiene to form products of *anti*-crotylation with good to excellent levels of diastereo- and enantioselectivity. Distinct from other methods, direct crotylation of primary alcohols in the presence of unprotected secondary alcohols is possible, enabling generation of spirastrellolide B (C9-C15) and leucascandrolide A (C9-C15) substructures in significantly fewer steps than previously possible.

Graphical Abstract

Ruthenium-JOSIPHOS-catalysts affect *anti*-crotylation of primary alcohols mediated by methylallene or 1,3-butadiene to provide polyketide propionate motifs. These C-C bond formations are byproduct-free and can be conducted in the presence of unprotected secondary alcohols.

Keywords

Alcohols; Dienes; Crotylation; Enantioselectivity; Ruthenium Catalysis

[*] mkrische@mail.utexas.edu .

[§]These authors contributed equally to this work.

Introduction

Polyketides and their derivatives are used more frequently in human medicine than any other class of natural products, and are estimated to comprise roughly 20% of top-selling small-molecule drugs.[1] Despite their importance, nearly all polyketide drugs are prepared via fermentation or semi-synthesis, as current methods for their *de novo* synthesis have not availed sufficiently concise or scalable manufacturing routes. As illustrated in the structure of erythromycin A, polyketides often comprise so-called "propionate subunits," which, classically, are assembled via organometal-mediated carbonyl additions, such as the aldol reaction, or as shown, the "Brown crotylation" (Figure 1).[2,3] The use of π-unsaturated petrochemical feedstocks as pronucleophiles in metal-catalyzed carbonyl addition offers an alternative to the use of discrete organometallic reagents, which are often hazardous and functional group intolerant.[4] Inspired by the extensive use of hydrogenation in reactions used to prepare small-molecule clinical candidates,[5] we have developed a broad family of metal-catalyzed carbonyl reductive couplings mediated by hydrogen or 2-propanol, and related hydrogen auto-transfer processes in which alcohol reactants function dually as carbonyl proelectrophile and reductant.[6,7] In this context, the use of allene and diene feedstocks as allylmetal pronucleophiles was explored (Figure 1),[8,9,10] resulting in the first use of commercially available allene (propadiene), methylallene (1,2-butadiene) and dimethylallene (3-methyl-1,2-butadiene) as allylmetal pronucleophiles in metal-catalyzed carbonyl addition (2007).[10] Despite progress toward the development of enantioselective variants,[11] catalytic asymmetric crotylations using methylallene have not been reported,[8] even though it could potentially serve as an atom-efficient reagent for carbonyl crotylation. Additionally, first-generation conditions for butadiene-mediated carbonyl crotylation[12] suffer from significant limitations: (a) 2-trialkylsilyl groups[12b] or non-commercial chiral counterions[12d] are required to enforce *syn*-diastereoselectivity[13] and, most importantly, (b) asymmetric reactions that display *anti*-diastereoselectivity are restricted to benzylic alcohols.[12c] These processes and related enantioselective ruthenium-catalyzed alcohol C-C couplings relevant to polyketide construction[14] are summarized in Figure 2.

Here, we report that iodide-bound ruthenium-JOSIPHOS catalysts recently developed in our laboratory[15,16] promote methylallene- and butadiene-mediated carbonyl crotylations of primary alcohol reactants via hydrogen auto-transfer with good to excellent levels of *anti*-diastereo- and enantioselectivity. Furthermore, distinct from conventional chiral crotylmetal reagents,[2,3] the crotylation of primary alcohols can be achieved in the presence of unprotected secondary alcohols via site-selective dehydrogenation, enabling the streamlined synthesis of type-I polyketide substructures in the absence of secondary hydroxyl protecting groups or generation of stoichiometric byproducts, as demonstrated by the construction of C9-C15 of spirastrellolide B and C9-C15 of leucascandrolide A.[17,18,19]

Results and Discussion

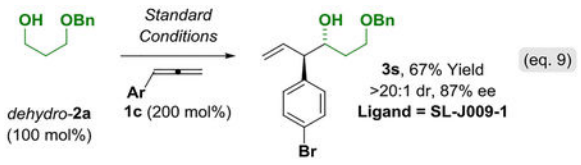
In connection with studies on the ruthenium-catalyzed C-C coupling of primary alcohols with 1-aryl-1-propynes to form products of carbonyl *anti*-(α-aryl)allylation, the ruthenium complexes, RuX(CO)(η^3-C_3H_5)(JOSIPHOS), where X = Cl, Br, I, were characterized by single crystal X-ray diffraction, revealing a halide-dependent diastereomeric preference that

defines stereogenicity at the ruthenium center in the solid state.[15,20] As supported by computational studies,[15] iodide counterions were unique in their ability to (a) enforce control of stereochemistry at ruthenium, which enables high levels of enantioselectivity and, (b) engage the aldehyde in formyl CH···I hydrogen-bonding, which stabilizes the favored transition state for carbonyl addition.[21] From these studies, an improved ruthenium catalyst system was developed in which the active metal complex is assembled *in situ* from the iodide-containing precursor $RuI(CO)_3(\eta^3\text{-}C_3H_5)$ and a commercially available JOSIPHOS ligand. Eager to assess the capabilities of this improved iodide-bound ruthenium-JOSIPHOS catalyst, the redox-neutral C-C coupling of methylallene **1a** with propanediol benzyl ether **2a** was attempted (Table 1). To this end, a pressure tube charged with a THF solution (0.5 M) of **2a** (100 mol%), trifluoroethanol (300 mol%), $RuI(CO)_3(\eta^3\text{-}C_3H_5)$ (5 mol%) and the JOSIPHOS ligand SL-J011–01 (5 mol%) was backfilled with methylallene **1a** and the reaction vessel was sealed and placed in a 100 °C temperature bath. To our delight, the desired product of carbonyl crotylation **3a** was formed in 72% isolated yield with a 5:1 preference for the *anti*-diastereomer and 80% ee. Under otherwise identical conditions using the JOSIPHOS ligand SL-J502–01, the level of enantiomeric enrichment increased to 85% ee. Finally, using the JOSIPHOS ligand SL-J009–01, adduct **3a** was generated in 90% isolated yield with a 7:1 preference for the *anti*-diastereomer and 90% ee. Deviation from these conditions did not avail any further improvement. Upon omission of trifluoroethanol (TFE), conversion to adduct **3a** was not observed. These data and prior computational studies suggest TFE catalyzes exchange of the homoallylic alkoxide with the primary alcohol reactant to release product (*vide infra*).[15] In an analogous series of experiments, butadiene **1b** and propanediol benzyl ether **2a** were exposed to identical conditions. Here, optimal results were obtained using the JOSIPHOS ligand SL-J502–01, revealing methylallene **1a** and butadiene **1b** display distinct reactivities, although identical crotylruthenium intermediates are anticipated (*vide infra*).

Using the iodide bound ruthenium catalyst assembled from $RuI(CO)_3(\eta^3\text{-}C_3H_5)$ and the JOSIPHOS ligand SL-J009–01, a range of primary alcohols **2a**-**2q** were surveyed as participants for methylallene-mediated crotylation via hydrogen auto-transfer (Table 2). Good levels of *anti*-diastereo- and enantioselectivity were observed in reactions of achiral primary alcohols **2a**-**2f**. Additionally, methylallene-mediated crotylation of diverse chiral primary alcohols **2g**-**2q** were explored using the enantiomeric ruthenium catalysts modified by the JOSIPHOS ligands SL-J009–01 and SL-J009–02. Adducts **3g**-**3q** were formed with good levels of catalyst-directed diastereoselectivity in both the matched and mismatched cases. Remarkably, these data encompass reactions of chiral β-stereogenic 1°,2°-1,3-diols **2g**-**2j**, **2p**, which were found to undergo C-C coupling to form **3g**-**3j**, **3p** without competing dehydrogenation of the secondary hydroxyl groups. One limitation of the present catalytic system resides in couplings of benzylic alcohols, which occur in good yield, but with modest levels of enantiocontrol (ca. 70% ee). Additionally, 1,2-diols are inefficient reaction partners as the vicinal oxygen atom destabilizes the transition state for dehydrogenation due to its negative inductive effect. Finally, as illustrated by the conversion of *dehydro*-**2c**, *dehydro*-**2e**, and *dehydro*-**2m** to adducts **3c**, **3e**, **3m** and *epi*-**3m**, respectively, methylallene-mediated crotylation can be conducted from the aldehyde oxidation level using 2-propanol (200 mol%) as reductant under otherwise identical conditions with roughly equivalent levels of

diastereo- and enantioselectivity (Scheme 1, eq. 1–4). The stereochemical assignments of adducts **3a**-**3q** were made in analogy to that determined for the dinitrobenzoate of **3b**, which was established via single crystal X-ray diffraction.

To assess the scope of related butadiene-mediated crotylations, a duplicate set of adducts **3a**-**3q** were prepared using the ruthenium catalyst modified by JOSIPHOS ligand SL-J502–01 under otherwise identical conditions, notwithstanding use of *iso*-octane as solvent (Table 3). Due to issues of solubility, the solvent MTBE was substituted *iso*-octane in certain cases. In nearly all cases, roughly equivalent diastereoselectivities and enantioselectivities were observed. Thus, chiral primary alcohols **2g**-**2q** were converted to adducts **3g**-**3q** using the ruthenium catalysts modified by the enantiomeric ligands SL-J502–01 and SL-J502–02 with good levels of catalyst-directed diastereoselectivity, and chiral β-stereogenic 1°,2°-1,3-diols **2g**-**2j**, **2p** were converted to adducts **3g**-**3j**, **3p** in the absence of secondary hydroxyl protecting groups. However, as illustrated by the divergent selectivities observed in reactions of **3f-a** and **3f-b**, certain alcohol proelectrophiles display distinctly different selectivities in reactions of methylallene **1a** vs butadiene **1b**. Additionally, perhaps due to its greater stability, reactions of butadiene **1b** are more efficient, often not requiring chromatographic purification. Indeed, diastereo- and enantioselective butadiene-mediated crotylation can be conducted in excellent yield on gram-scale at lower catalyst loadings (2 mol%), underscoring the practicality of this method (Scheme 1, eq. 5 and 6). As illustrated in the asymmetric crotylation of alcohols **2h** and **2q**, which are derived from Lovastatin (Mevacor®) and atorvastatin (Lipitor®), respectively, structurally complex reactants that incorporate diverse functional groups are tolerated, suggesting applicability of this method to even more challenging "late-stage functionalizations."[22] To probe the limits of functional group compatibility, the enantiomeric ruthenium catalysts modified by SL-J502–01 and SL-J502–02 were reacted with an alcohol derived from the type I polyketide antibiotic mupirocin, specifically, pseudomonic acid A (Bactroban®). Despite the presence of sensitive epoxide and secondary hydroxyl functional groups, the diastereomeric adducts were obtained in good isolated yield with high levels of catalyst-directed diastereocontrol (Scheme 1, eq. 7 and 8). Finally, as demonstrated by the reaction of the *p*-bromophenyl-substituted allene **1c**, the conditions optimized for catalytic enantioselective allene-mediated crotylation are transferable to other allene pronucleophiles (eq. 9).



A unique feature of the present method resides in the ability to affect the crotylation of primary alcohols in the presence of unprotected secondary hydroxyl groups. To demonstrate how this capability streamlines type I polyketide construction, two different C9-C15 spirastrellolide B substructures were prepared via stereo- and site-selective crotylation of the chiral β-stereogenic 1°,2°-1,3-diol *ent*-**2i** and a comparison of step-count (Longest Linear Sequence, LLS) to previously reported C9-C15 spirastrellolide B substructures

was made (Scheme 2, Top). The C9-C15 spirastrellolide B substructure *ent-epi*-**3i**, which was previously made in 10 steps (LLS) by Hanson,[23a] is accessible in 3 steps (LLS) via butadiene-mediated crotylation. Ozonolysis-reduction of *ent-epi*-**3i** delivers compound **4a** in 4 steps (LLS), whereas the related compound **4b** was prepared by Chandrasekhar in 8 steps (LLS).[23b] The ability to directly deploy butadiene, an abundant feedstock chemical, in catalytic enantioselective crotylation offers another advantage. Many methods for crotylation rely on the use of chiral crotylmetal reagents, which are prepared through multi-step sequences, which impact the number of total steps (TS). To illustrate, the C9-C15 leucascandrolide A substructure prepared by Cossy requires 6 steps (LLS), but 8 total steps (TS),[24] as it uses the chiral crotyltitanium reagent developed by Hafner and Duthaler, which requires a 3 step synthesis.[25] The identical compound is prepared via butadiene-mediated crotylation in 4 steps (LLS = TS) (Scheme 2, Bottom).

A general catalytic mechanism for enantioselective methylallene-mediated carbonyl crotylation via ruthenium-JOSIPHOS-catalyzed hydrogen auto-transfer has been proposed (Scheme 3). Entry into the catalytic cycle occurs via protonolysis of the π-allylruthenium precatalyst by TFE followed by substitution with a reactant alcohol to form the primary ruthenium alkoxide **I**.[15] β-Hydride elimination of ruthenium alkoxide **I** releases aldehyde and forms the ruthenium hydride **II**. Hydroruthenation of methylallene provides an equilibrating mixture of π- and σ-crotylruthenium species **III**.[26] Carbonyl addition from the (*E*)-σ-crotylruthenium isomer by way of a closed Zimmerman-Traxler type transition structure[27] provides the homoallylic ruthenium alkoxide **IV**. The stereospecific nature of the carbonyl addition event is inferred by the anticipated influence of steric effects on the geometry of σ-allyl intermediates and, therefrom, diastereoselectivity in reactions of substituted allenes[28] and dienes.[14b] TFE-assisted exchange of the homoallylic ruthenium alkoxide **IV** with reactant alcohol releases the product of crotylation and regenerates the primary ruthenium alkoxide **I** to close the catalytic cycle.[15] This mechanism is consistent with the outcome of the indicated deuterium labelling experiment, in which *deuterio*-**2a** is exposed to methylallene **1a** (800 mol%) under otherwise standard conditions. The relatively low level of deuterium transfer to the internal vinylic position (11% ^{2}H) is due to exchange of the transient ruthenium deuteride akin to **II** with the hydroxyl hydrogen of TFE and *deuterio*-**2a**.[29] An analogous mechanism is postulated for corresponding reactions of butadiene **1b**. Slight differences in reactivity and selectivity displayed by methylallene **1a** and butadiene **1b** are attributed to differences in kinetic stereoselectivity in the hydrometalation event to generate the initially formed chiral-at-metal crotylruthenium intermediate. Butadiene cannot be detected in reactions of methylallene, indicating that allene-to-diene isomerization does not occur in methylallene-mediated crotylation. Attempted reactions of 1,4-pentadiene under the present conditions provides a 25% yield of C-C coupling product with low levels of stereocontrol (not shown).

Conclusion

The development of practical methods for the *de novo* construction of polyketide natural products remains an important challenge in chemical synthesis. Here, using iodide-bound ruthenium-JOSIPHOS complexes recently developed in our laboratory, we report the

reaction of primary alcohols with methylallene (1,2-butadiene) or 1,3-butadiene to form products of carbonyl crotylation with good to excellent levels of *anti*-diastereo- and enantioselectivity, providing *byproduct-free* entry to propionate substructures that are the ubiquitous among polyketides. A remarkable feature of these processes resides in the kinetic preference for primary alcohol dehydrogenation, which enables asymmetric crotylation of primary alcohols in the presence of unprotected secondary alcohols. As illustrated in concise syntheses of spirastrellolide B (C9-C15) and leucascandrolide A (C9-C15) substructures, this capability streamlines type I polyketide construction. Future studies will focus on related hydrogen auto-transfer process for byproduct-free enantioselective carbonyl addition that exploit feedstock pronucleophiles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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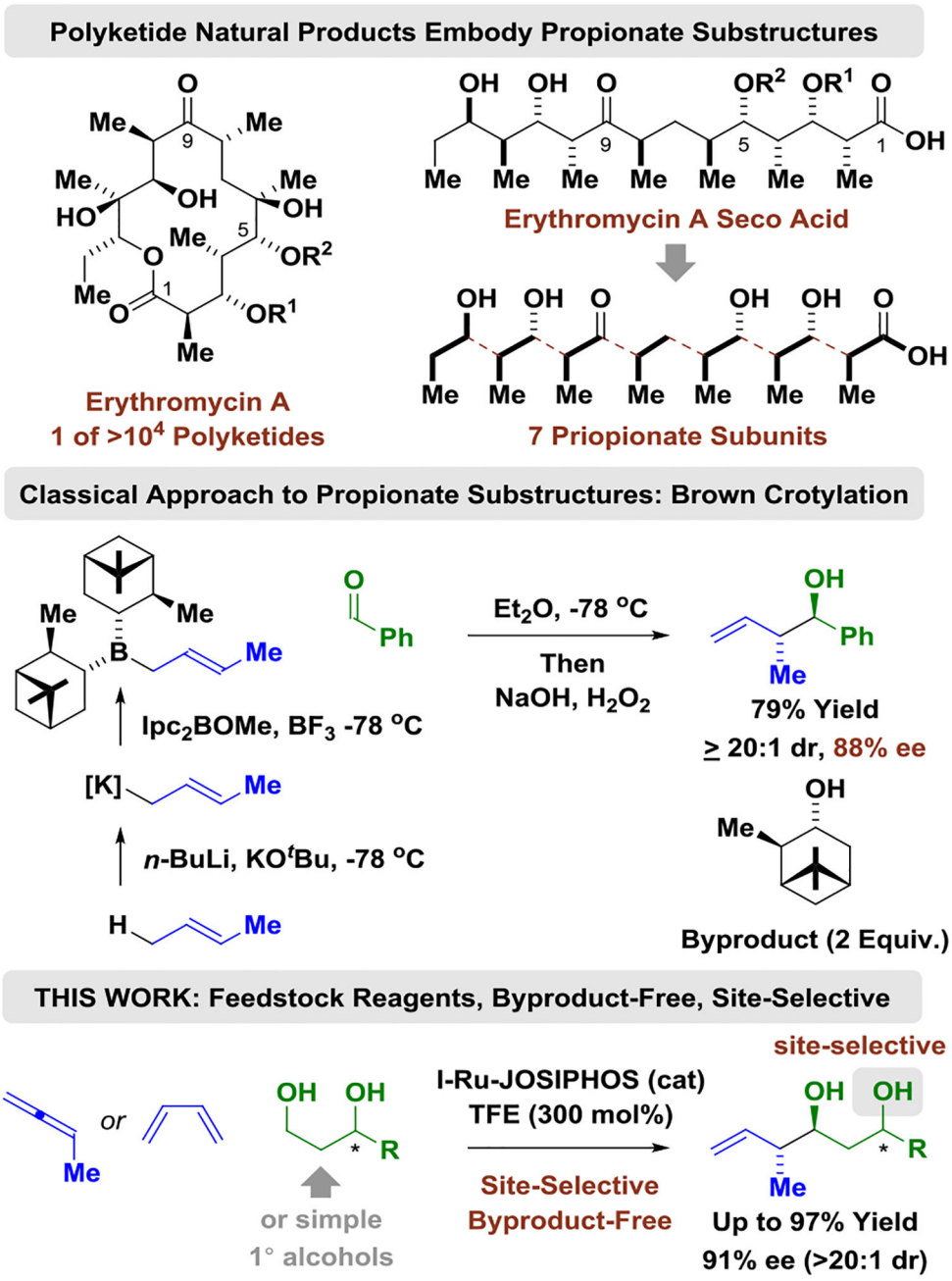


Figure 1.
Asymmetric carbonyl crotylation: A gateway to polyketide structural motifs.

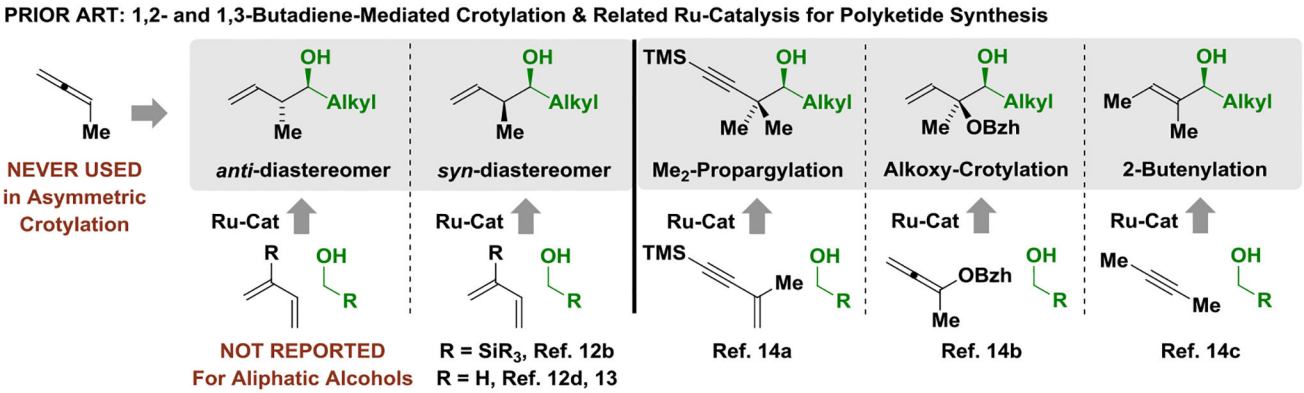
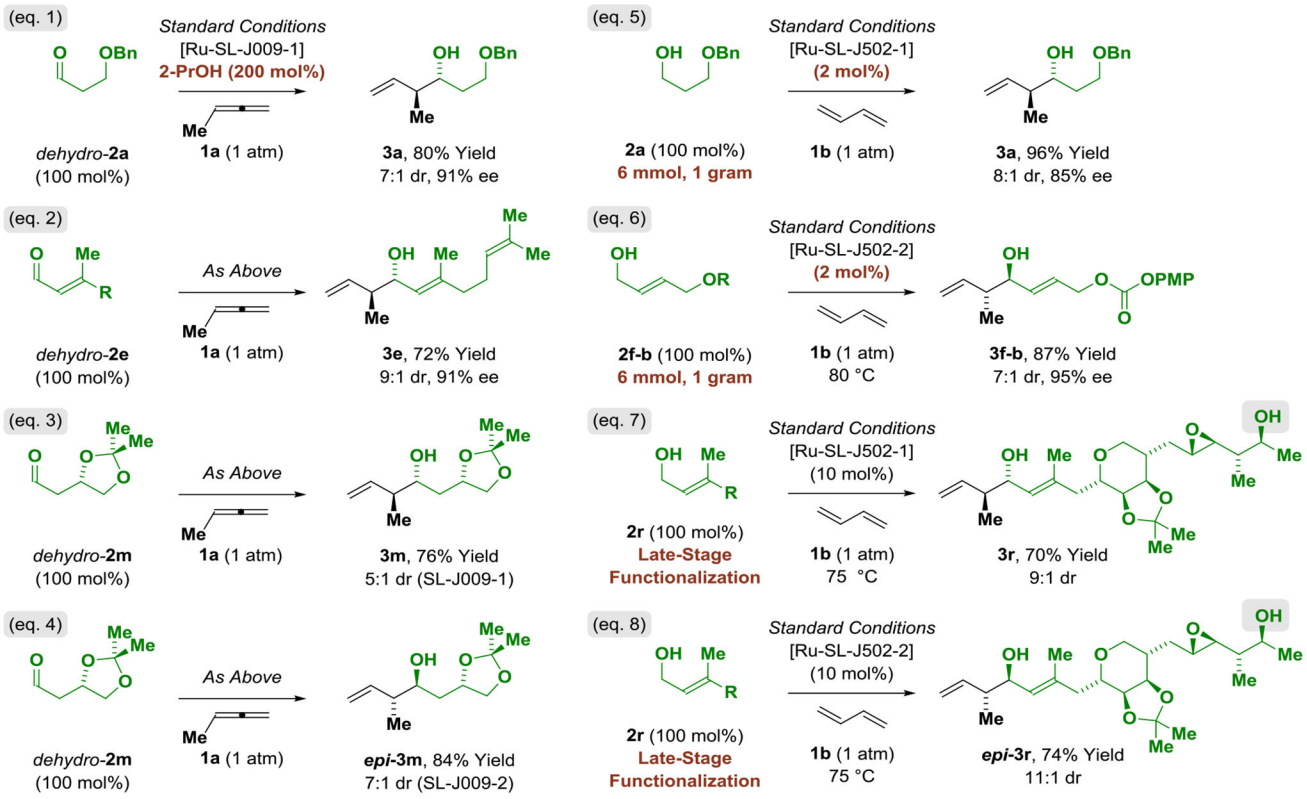


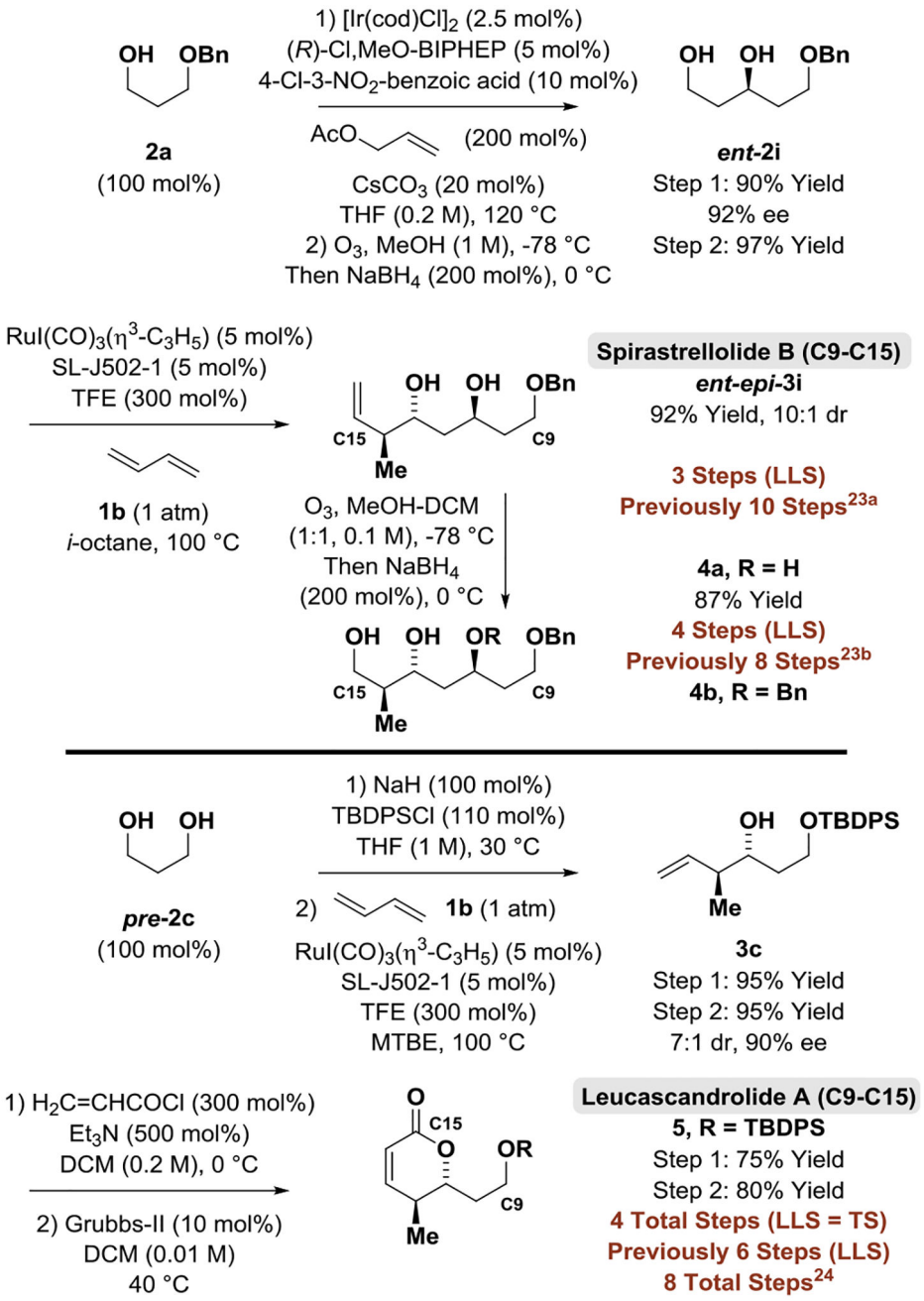
Figure 2.
Enantioselective ruthenium-catalyzed C-C coupling of alcohols.



Scheme 1.

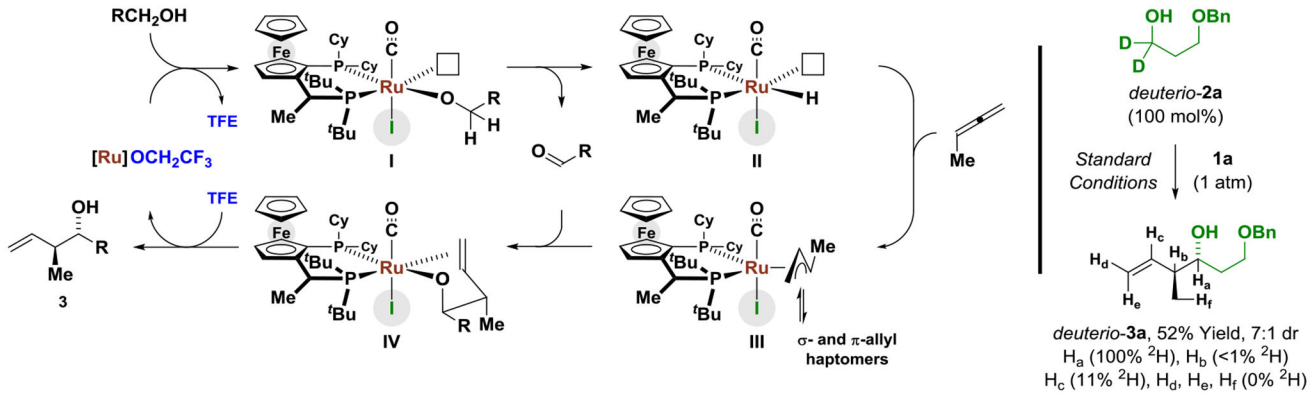
Stereo- and site-selective methylallene-mediated carbonyl crotylation from the aldehyde oxidation level, gram-scale butadiene-mediated crotylations and late-stage functionalizations.[a]

[a]Yields of material isolated by silica gel chromatography. Enantioselectivities determined by HPLC analysis. Diastereoselectivities determined by ^{1}H NMR analysis of crude reaction mixtures and refer to the major isomer vs all other isomers.



Scheme 2.

Generation of spirastrellolide B (C9-C15) and leucascandrolide A (C9-C15) substructures. [a]Yields of material isolated by silica gel chromatography. Enantioselectivities determined by HPLC analysis. Diastereoselectivities determined by ^{1}H NMR analysis of crude reaction mixtures and refer to the major isomer vs all other isomers. LLS = Longest linear sequence.



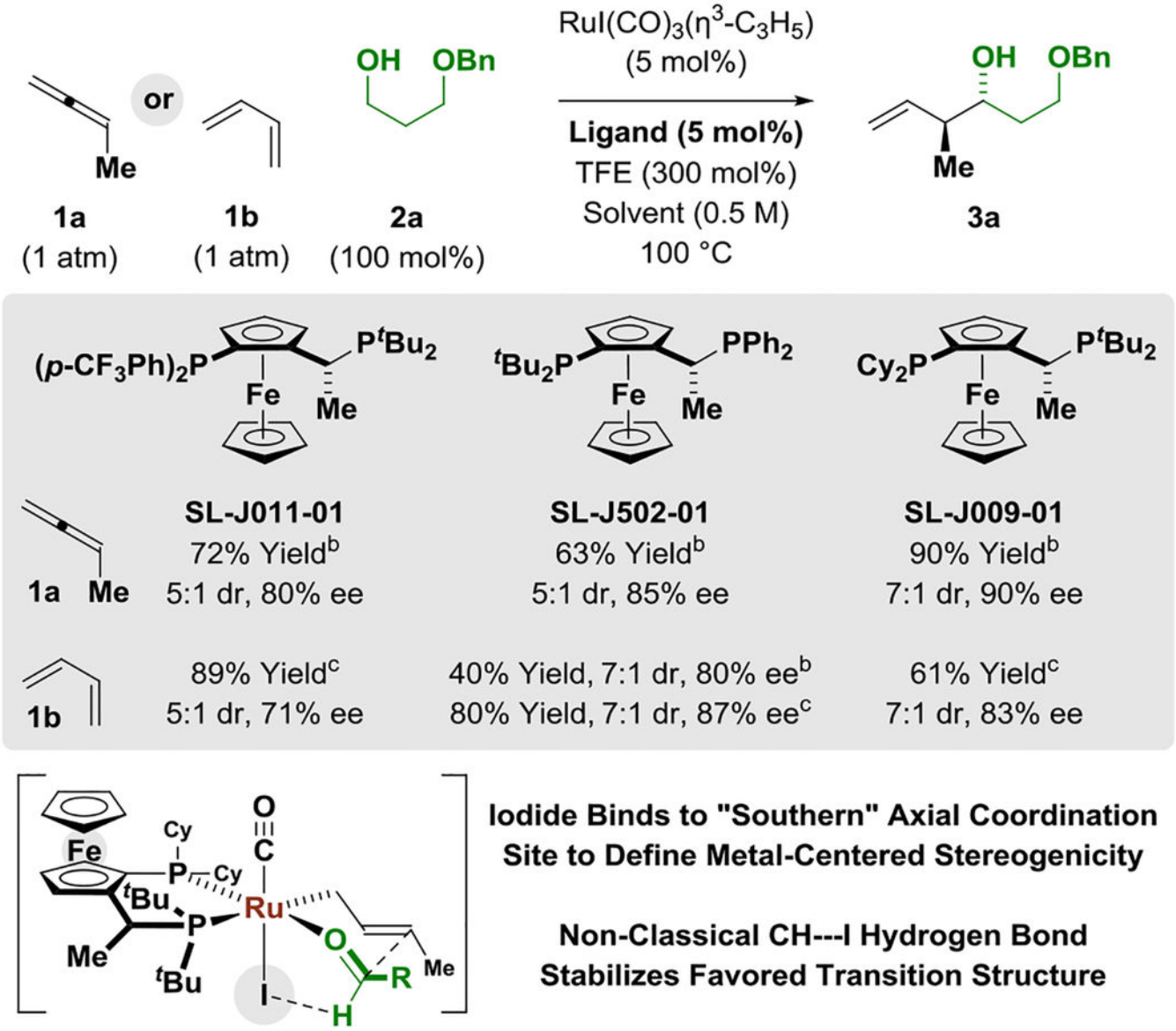
Scheme 3.

Proposed mechanism for enantioselective methylallene-mediated carbonyl crotylation via ruthenium-JOSIPHOS-catalyzed hydrogen auto-transfer of primary alcohols and deuterium labelling experiment.[a]

[a]The pattern of deuterium incorporation in *deuterio*-**3a** was assigned by ^{1}H NMR, ^{2}H NMR and HRMS. See Supporting Information for further details.

Table 1.

Ruthenium-JOSIPHOS-catalyzed C-C coupling of methylallene **1a** or butadiene **1b** with alcohol **2a** to form adduct **3a** and stereochemical model for carbonyl addition.[a]



[a]Yields of material isolated by silica gel chromatography. Enantioselectivities were determined by HPLC analysis. TFE = trifluoroethanol.

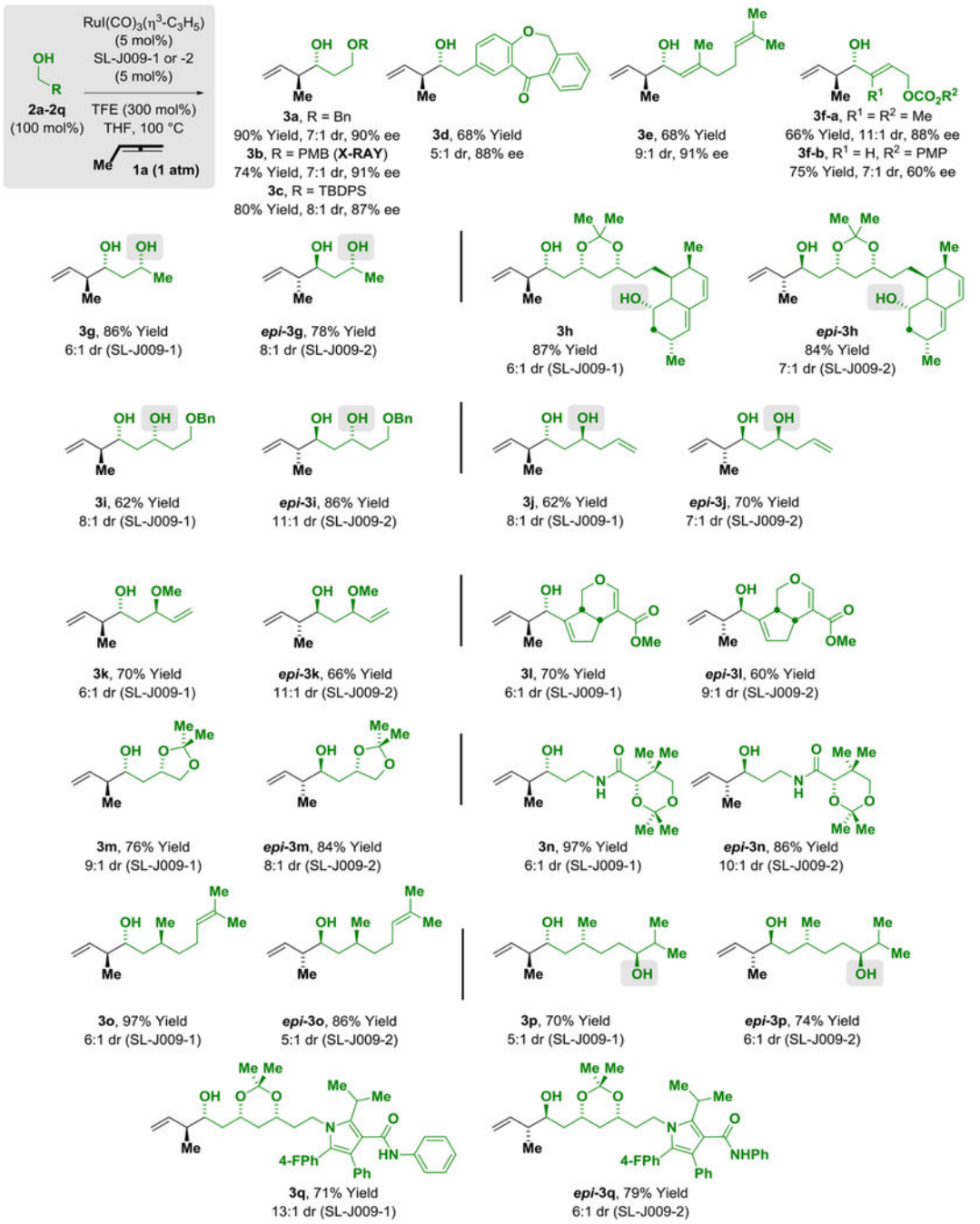
[b]THF,

[c]Isoctane.

See Supporting Information for further details.

Table 2.

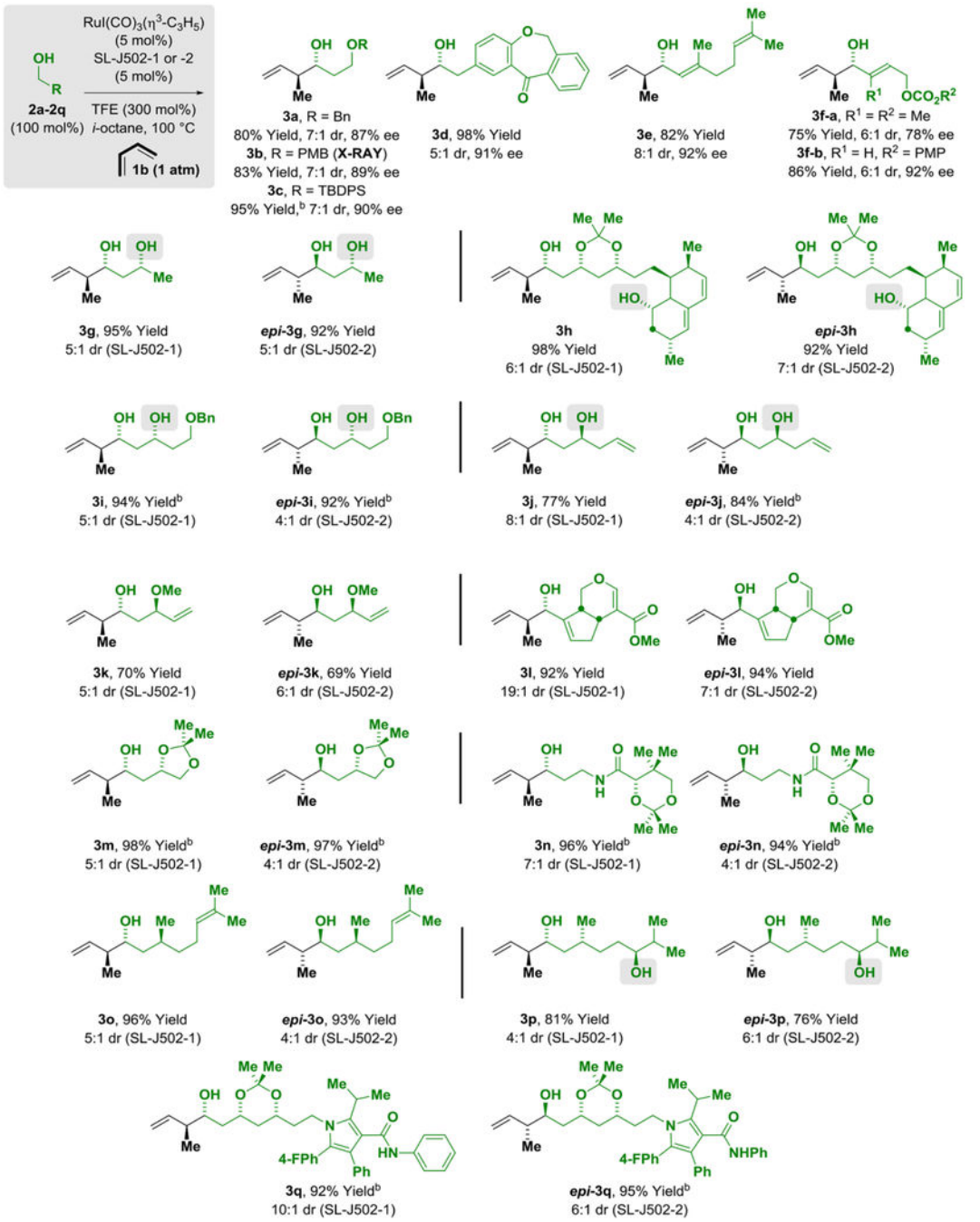
Stereo- and site-selective methylallene-mediated carbonyl crotylation via ruthenium-JOSIPHOS-catalyzed hydrogen auto-transfer of primary alcohols **2a-2q** hydrogen-auto transfer.[a]



[a]Yields of material isolated by silica gel chromatography. Enantioselectivities determined by HPLC analysis. Diastereoselectivities determined by ^{1}H NMR analysis of crude reaction mixtures and refer to the major isomer vs all other isomers. See Supporting Information for further details.

Table 3.

Stereo- and site-selective butadiene-mediated carbonyl crotylation via ruthenium-JOSIPHOS-catalyzed hydrogen auto-transfer of primary alcohols **2a-2q** hydrogen-auto transfer.[a]



[a]Yields of material isolated by silica gel chromatography. Enantioselectivities determined by HPLC analysis. Diastereoselectivities determined by ^{1}H NMR analysis of crude reaction mixtures and refer to the major isomer vs all other isomers.

[b] MTBE (0.5 M). See Supporting Information for further details.