Synthesis E. Ortiz et al. Short Review

Carbonyl Allylation and Crotylation: Historical Perspective, Relevance to Polyketide Synthesis, and Evolution of Enantioselective Ruthenium-Catalyzed Hydrogen Auto-Transfer Processes

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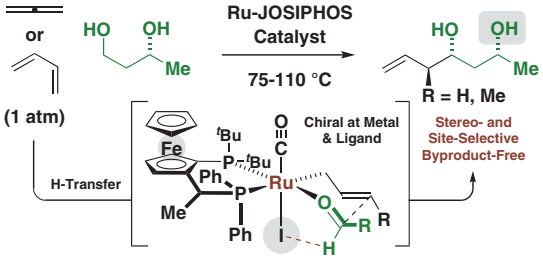

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Abstract The evolution of methods for carbonyl allylation and crotylation of alcohol proelectrophiles culminating in the design of iodide-bound ruthenium-JOSIPHOS catalysts is prefaced by a brief historical perspective on asymmetric carbonyl allylation and its relevance to polyketide construction. Using gaseous allene or butadiene as precursors to allyl- or crotylruthenium nucleophiles, respectively, new capabilities for carbonyl allylation and crotylation have been unlocked, including stereo- and site-selective methods for the allylation and crotylation of 1,3-diols and related polyols.

Key words polyketide, ruthenium, feedstock, allene, butadiene, allylation

1 Introduction and Historical Perspective

Carbonyl allylation is longstanding and has traditionally relied on the use of allylmetal reagents based on zinc (1876),[1a–c] magnesium (1904),[1d] boron (1964),[1e] tin (1967),[1f] silicon (1976),[1g] and chromium (1977).[1h] The first enantioselective carbonyl allylations were developed by Hoffmann (1978)[2a,b] using a chiral allylboronate derived from camphor. This finding led to the design of increasingly effective chiral allylmetal reagents,[2] as well as the development of catalytic enantioselective carbonyl allylation protocols,[3] as first reported by Yamamoto (1991).[3a] 'Umpoled' catalytic enantioselective allyl halide-carbonyl reductive couplings (asymmetric Nozaki–Hiyama allylations) reported by Cozzi and Umani-Ronchi (1999) soon followed (Figure 1).[3f] These methods were uniformly reliant on preformed allylmetal reagents or stoichiometric metallic reductants, as were corresponding enantioselective crotylation protocols.[4]

The development of asymmetric carbonyl allylation and crotylation protocols were, in part, incentivized by the prospect of preparing polyketide natural products via *de novo* chemical synthesis (Figure 2).[5] Polyketides are a broad class of microbial metabolites that are used frequently in human and veterinary medicine, as well as crop protection.[6] As shown in the structure of roxaticin,[7] an oxopolyene macrolide, 2-carbon 'acetate' subunits are common polyketide substructures. Similarly, the macrolide antibiotic erythromycin A,[8] the first polyketide approved for use in human medicine, comprises recurring 3-carbon 'propionate' subunits. The challenge of preparing these structural motifs impelled advances in acyclic stereocontrol, especially stereospecific methods for diastereo- and enantioselective carbonyl addition such as the aldol reaction[9] and, as described in the present monograph, carbonyl allylation and crotylation.[4]

Despite decades of work on polyketide total synthesis, commercial polyketides (with the exception of eribulin)[10] continue to be prepared via fermentation or semi-synthesis,[11] suggesting the classical lexicon of synthetic methods do not avail efficient entry to these stereochemically complex compounds. Indeed, the commercial manufacturing route to eribulin (halaven™),[10] a truncated congener of the marine polyketide halichondrin B and FDA-approved treatment for metastatic breast cancer, requires 65 steps, of which >50% are redox and protecting group manipulations. Thus, stereo- and site-selective methods for polyketide construction that bypass protecting groups and oxidation level adjustments should streamline routes to medicinally relevant polyketides. As Earth's biosphere encompasses >1 trillion microbial species,[12] next-generation methods for bacterial culture will augment the rate of polyketide discov-

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ery,[13] and improved methods for *de novo* polyketide construction[5] would facilitate preparation of polyketide-inspired clinical candidates that are inaccessible via fermentation or semi-synthesis.[14]

In a departure from classical methods for asymmetric carbonyl addition[15] and related metal-catalyzed carbonyl reductive couplings,[16] our laboratory has pioneered a new class of hydrogen auto-transfer reactions for the direct conversion of lower alcohols into higher alcohols.[17] These processes occur via hydrogen transfer from alcohol proelectrophiles to π-unsaturated pronucleophiles to form transient carbonyl-organometal pairs that combine via carbonyl addition. In this manner, carbonyl addition occurs from the alcohol oxidation level in the absence of stoichiometric organometallic reagents. These reactions are distinct from related 'borrowing hydrogen' processes, which affect formal hydroxyl substitution via successive alcohol dehydrogenation–carbonyl condensation–π-bond reduction (Figure 3).[18]

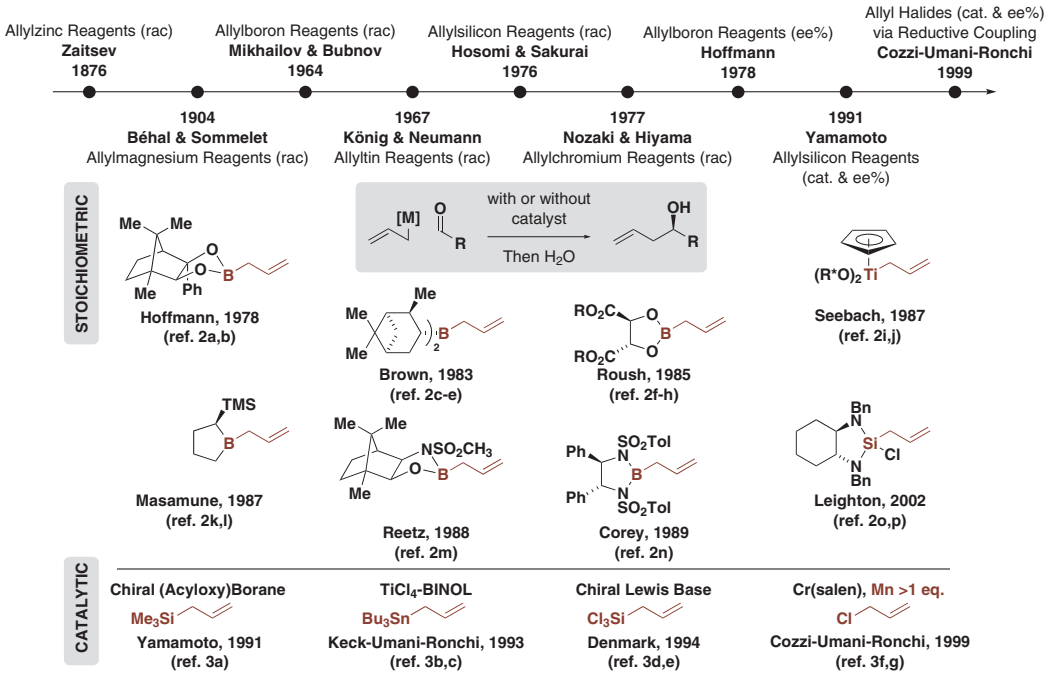


Figure 1 Selected milestones in carbonyl allylation from racemic reactions to catalytic enantioselective processes

The first carbonyl additions via hydrogen auto-transfer were discovered in 2007 using iridium catalysts.[19] Enantioselective iridium-catalyzed carbonyl allylations and crotylations were reported shortly thereafter.[20] In 2008, related ruthenium-catalyzed reactions were developed, which begins the topic of this review.[21]

2 Ruthenium-Catalyzed Conversion of Lower Alcohols into Higher Alcohols

Initially developed ruthenium-catalyzed carbonyl additions were achieved through exposure of primary alcohol proelectrophiles to diene pronucleophiles in the presence of the chloride-bound catalyst derived from HCl-$Ru(CO)(PPh_3)_3$ and added *rac*-BINAP or P(*p*-MeOPh)$_3$ (Scheme 1, left).[21a] In these reactions, ruthenium hydrides promote diene hydrometalation to form nucleophilic π-allylruthenium species[22] that engage in carbonyl addition to aldehydes obtained via primary alcohol dehydrogenation. As carbonyl addition occurs by way of the primary σ-allylruthenium haptomer with allylic inversion, secondary homoallylic alcohols are generated with complete levels of branched regioselectivity. Notably, while the primary alcohol reactant is subject to dehydrogenation, the resulting secondary alcohol product resists a less endothermic oxidation to form the ketone. This phenomenon is attributed to chelation of the homoallylic olefin, which suppresses β-hydride elimination by occupying the last available coordination site on ruthenium. In agreement with this interpretation, β,γ-enones are formed if the catalyst experiences coordinative unsaturation,[21b] which can be achieved through the omission of exogenous ligand and use of trifluoroacetate as counterion,[23] which can equilibrate between η^1 and η^3-binding modes (Scheme 1, right).

Managing relative and absolute stereocontrol in diene-mediated crotylations of primary alcohols raised the question of whether carbonyl addition occurs through closed chairlike transition structures in a stereospecific manner (Figure 4). To probe this issue, the indicated 2-silyl-substituted butadiene, which upon hydrometalation should exist predominantly as a single geometrical isomer due to allylic 1,2-strain,[24] was exposed to primary alcohols in the presence of the ruthenium catalyst derived from HCl-$Ru(CO)(PPh_3)_3$ and (*R*)-DM-SEGPHOS.[25a] The products of crotylation were formed with complete control of regio- and *syn*-diastereoselectivity and high levels of enantioselectivity, corroborating intervention of closed chairlike transition structures. This method was used to construct the C12–C13 and C6–C7 stereodiads of the polyketide natural products trienomycins A and F and soraphen A, respectively.[26] Finally, in a beautiful application of this method, Brimble and Furkert deployed enantiomeric ruthenium catalysts in couplings of the 2-silyl-substituted butadiene with the chiral alcohol derived from the Roche ester to generate the *syn*,*anti*- or *syn*,*syn*-stereotriads with complete levels of catalyst-directed diastereoselectivity (Scheme 2).[25b]

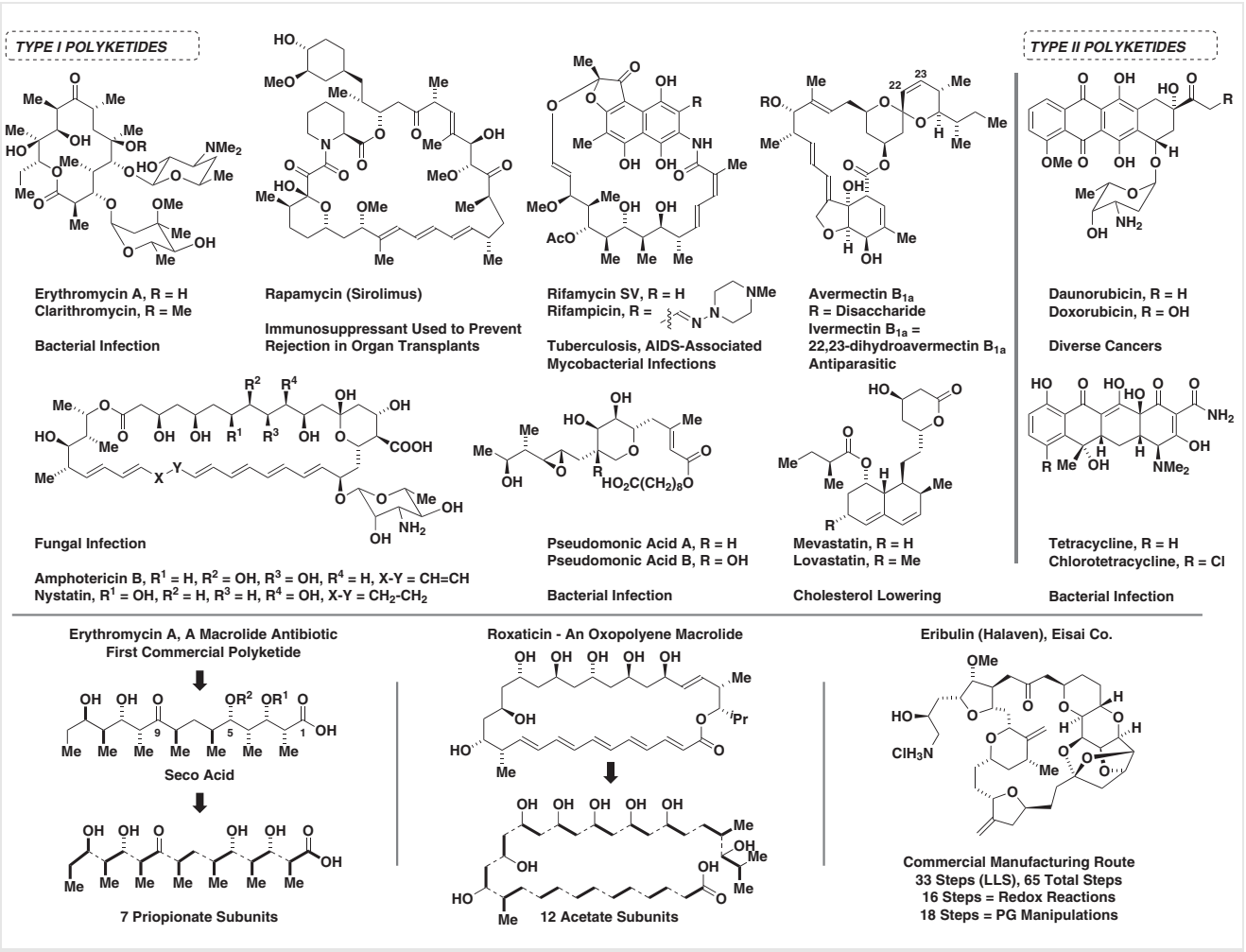


Figure 2 Selected FDA-approved polyketides medicines often comprise recurring acetate and propionate motifs

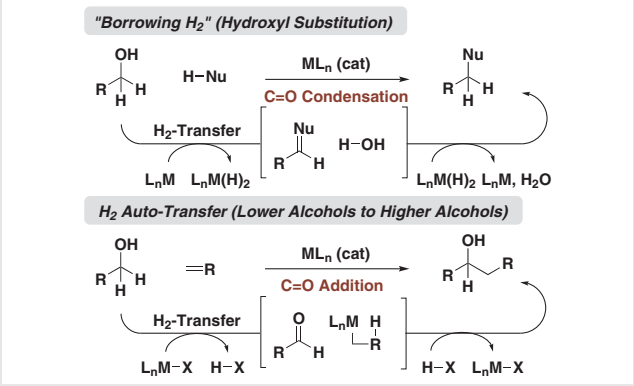


Figure 3 'Borrowing H_2' vs H_2 auto-transfer

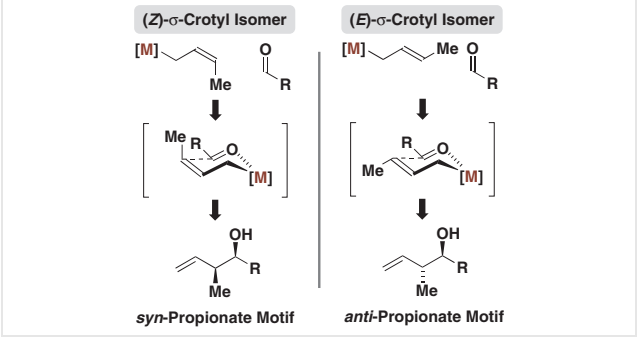
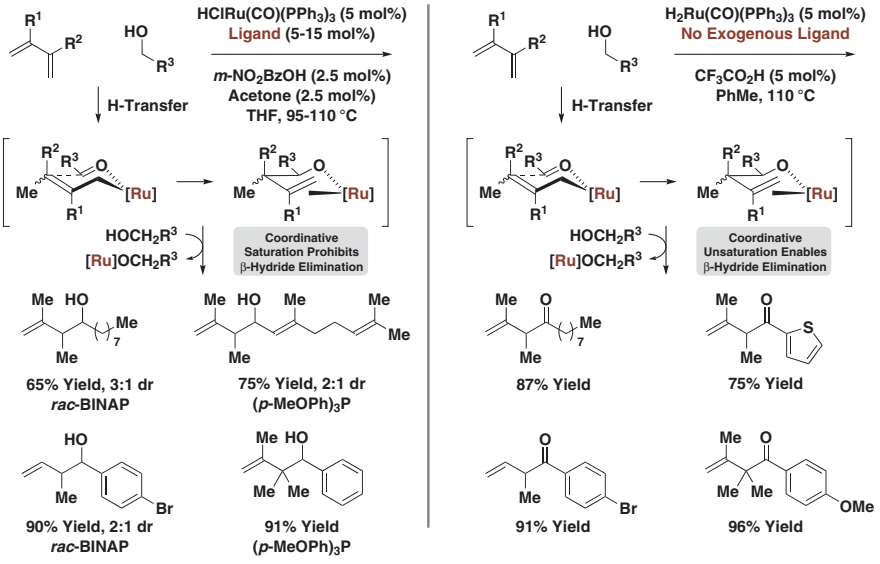


Figure 4 Stereospecific carbonyl crotylation

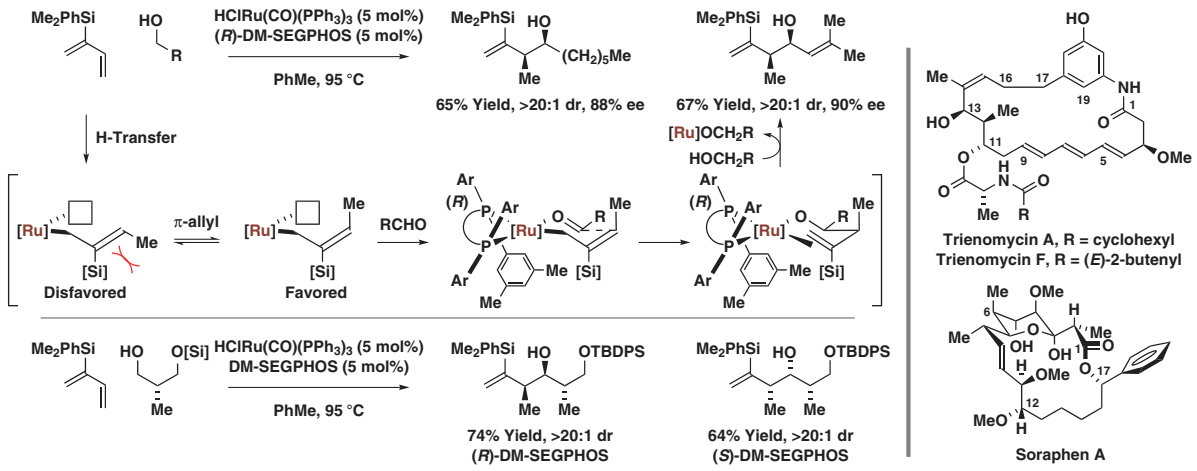
Having established stereospecificity, it was posited that a large chiral counterion at ruthenium might bias partitioning of (*Z*)- and (*E*)-σ-crotylruthenium intermediates to favor the latter, potentially enabling *anti*-diastereo- and enantioselective butadiene-mediated crotylations. After much effort, it was found that the indicated C_1-symmetric BINOL-derived phosphate counterion, which is installed via acid-base reaction of the phosphoric acid with the precatalyst $H_2Ru(CO)(PPh_3)_3$,[23] enabled *anti*-diastereo- and enantioselective crotylations of benzylic alcohols in the absence of a



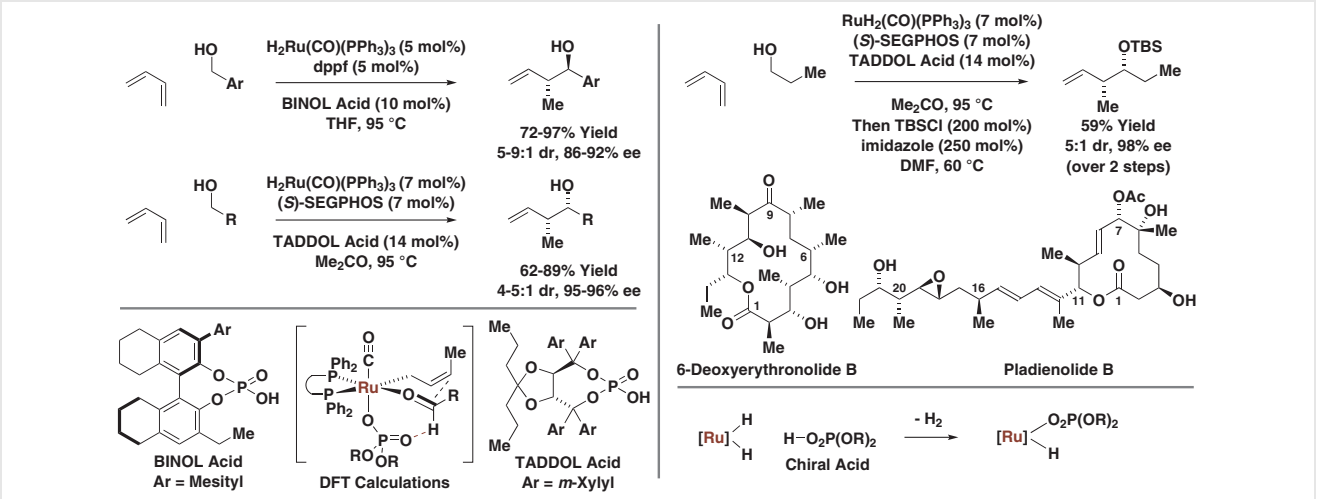
Scheme 1 Dienes as allylmetal pronucleophiles in ruthenium-catalyzed carbonyl addition via hydrogen auto-transfer

chiral phosphine ligand (Scheme 3).[27a] Remarkably, upon use of the indicated tartaric acid derived phosphate counterion in combination with (*S*)-SEGPHOS, *syn*-diastereo- and enantioselective crotylation was observed.[27b] DFT calculations suggest that the more Lewis basic TADDOL-phosphate counterion stabilizes the transition structure *en route* to the *syn*-diastereomer by contributing a formyl hydrogen bond.[28,29] The *syn*-diastereoselective reaction was used to construct the C12–C13 and C20–C21 stereodiads of 6-deoxyerythronolide B[8] and pladienolide B,[30] respectively.

These studies and prior work from our laboratory[31] impelled a systematic investigation of counterion effects in ruthenium-catalyzed C–C couplings of alcohols via hydrogen auto-transfer.[32,33] In our previously developed ruthenium-catalyzed reactions, enhanced yields, isomer selectivities and stereoselectivities were observed upon use of iodide counterions in combination with JOSIPHOS ligands.[31a–c] It was recognized that the C_1-symmetry of JOSIPHOS[34] made the catalyst stereogenic at ruthenium. Single crystal X-ray diffraction analysis of the complexes RuX(CO)(JOSIPHOS)(η^3-C_3H_5), where X = Cl, Br, I, revealed a halide-dependent diastereomeric preference in the solid state: whereas the iodide complex formed as a single diastereomer, the chloride and bromide complexes formed as diastereomeric mixtures.[32] While these preferences may reflect crystal-packing forces, computational studies corroborate iodide's capacity to direct formation of a single diastereomeric chiral-at-metal complex and its capacity for formyl hydrogen bonding.[32] Quantum theory of atoms in molecules (QTAIM) analysis identified the bond critical point be-



Scheme 2 *syn*-Diastereo- and enantioselective crotylation of primary alcohols mediated by a 2-silyl-substituted butadiene



Scheme 3 Chiral phosphate counterion-dependent inversion of diastereoselectivity in the enantioselective crotylation of primary alcohols mediated by butadiene

tween the I···H atoms, which aligns with natural bond orbital (NBO) analysis. The fuzzy bond order (FBO) of 0.069 was computed, indicating an overall stabilization energy of 4.44 kcal/mol (*E*(2)-NBO) in the transition state for carbonyl addition via interaction of iodide's lone pairs with the σ* orbital of the formyl CH bond (Figure 5).[32]

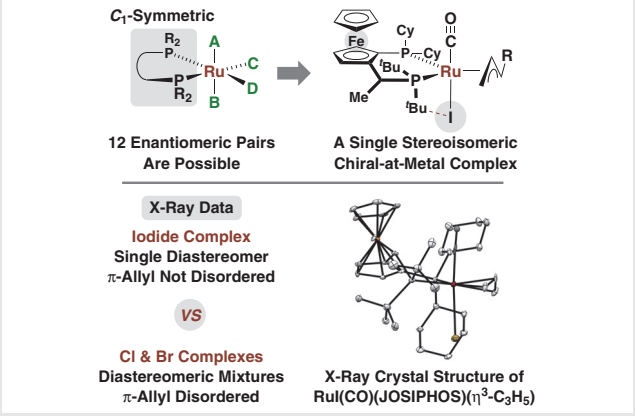
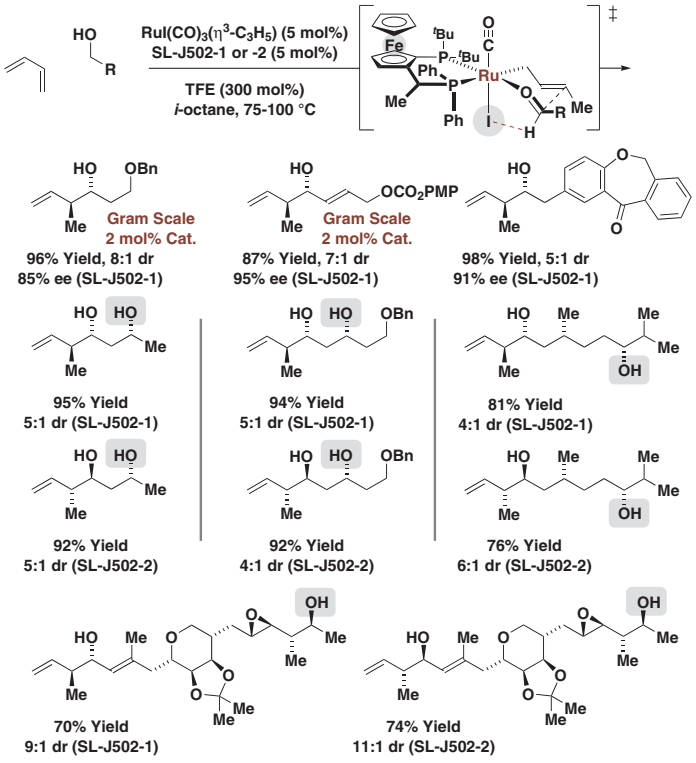


Figure 5 Iodide directs stereogenicity at ruthenium

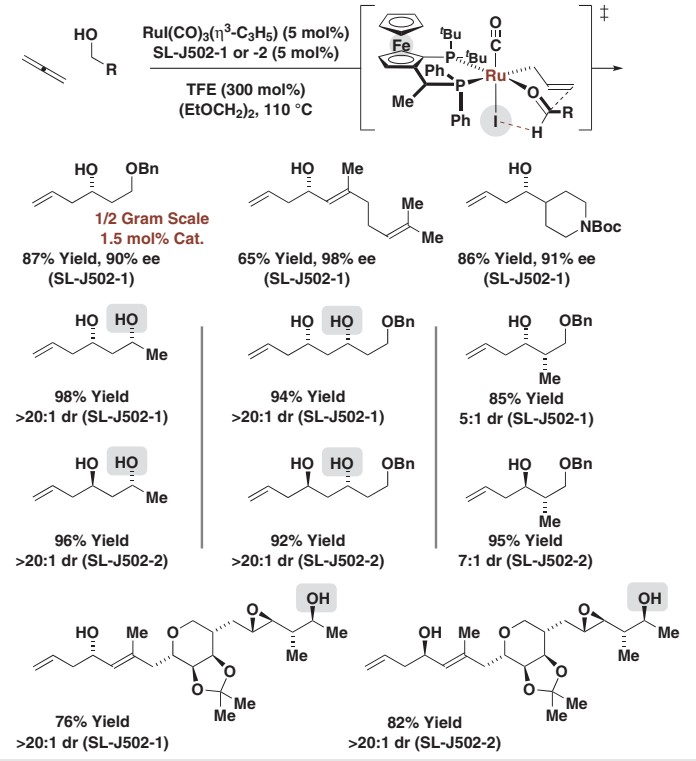
These insights informed the design of an effective catalytic system for *anti*-diastereo- and enantioselective butadiene-mediated crotylation of alcohol proelectrophiles of exceptionally broad scope (Scheme 4).[35a] Using the catalyst assembled from the iodide-bound ruthenium precatalyst $RuI(CO)_3(\eta^3\text{-}C_3H_5)$ and the JOSIPHOS ligand SL-J502-01 (or its enantiomer SL-J502-02), primary alcohols and butadiene combine to form products of crotylation as single regioisomers with good to excellent control of *anti*-diastereo- and enantioselectivity. These reactions can be conducted on gram scale with relatively low loadings of catalyst (2 mol%).

Using the enantiomeric ruthenium catalysts, crotylations of chiral primary alcohol proelectrophiles occur with good levels of catalyst-directed diastereoselectivity. One powerful feature of this catalyst system resides in the ability to promote site-selective couplings of primary alcohols in the presence of unprotected secondary alcohols, which circumvents installation/removal of hydroxyl protecting groups. This capability stems from the relatively rapid kinetics of primary vs secondary alcohol dehydrogenation, even though dehydrogenation of the primary alcohol is more endothermic. This method was used to assemble previously reported substructures of spirastrellolide B (C9–C15, 3 vs 10 steps) and leucascandrolide A (C9–C15, 4 vs 6 or 8 steps),[35a] and was used to construct the C1–C19 and C23–C35 substructures of neaumycin B (not shown).[36] Finally, using methylallene (buta-1,2-diene) as the crotyl donor, an identical set of products can be formed with roughly equivalent yields and selectivities (not shown).[35a] However, the use of butadiene is preferred due to its greater abundance (>1 × 10^7 tons/year).[37]

Allene (propadiene) is an abundant byproduct of C3 petroleum cracking fractions (>1 × 10^5 tons/year)[37] of untapped potential, as the majority is hydrogenated and recycled to prepare propylene. Our laboratory described the first allene-mediated carbonyl allylations in 2007.[19a] Enantioselective allene-mediated allylations of aldehydes[38a] and ketones[38b] appeared in 2019 using iridium and copper catalysts, respectively.[38] Using the iodide-bound ruthenium-JOSIPHOS catalyst, we very recently developed the first enantioselective allene-mediated carbonyl allylations via hydrogen auto-transfer from alcohol proelectrophiles (Scheme 5).[35b] As shown, these reactions are efficient at catalyst loadings as low as 1.5 mol% and, like the closely related butadiene-mediated crotylations, primary alcohols are subject to allylation in the presence of unprotected sec-



Scheme 4 Stereo- and site-selective ruthenium-JOSIPHOS catalyzed crotylation of primary alcohols mediated by butadiene



Scheme 5 Stereo- and site-selective ruthenium-JOSIPHOS catalyzed allylation of primary alcohols mediated by allene

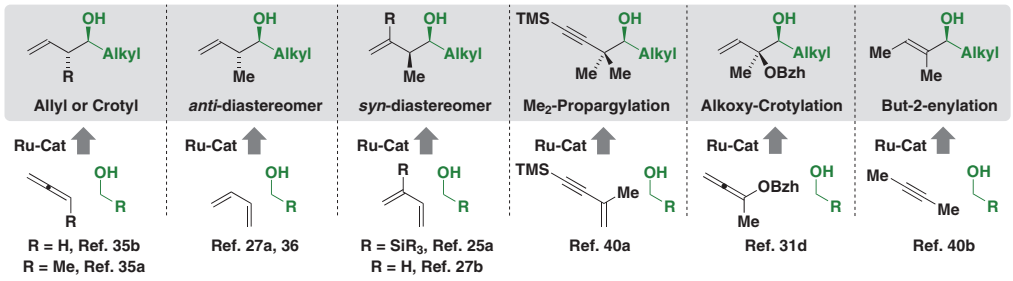


Figure 6 Enantioselective entry to polyketide motifs via ruthenium-catalyzed hydrogen auto-transfer

ondary alcohols. This method was used to construct previously reported substructures of spirastrellolide B and F (C7–C15, 7 vs 17 steps), cryptocarya diacetate (C3–C10, 3 vs 7 or 9 steps), mycolactone F (C8′–C14′, 1 vs 4 steps), and marinomycin A (C22–C28, 1 vs 9 steps) in fewer steps than previously possible (not shown).

3 Conclusion and Future Outlook

The methodological challenges posed by the stereochemical complexity of polyketide natural products continue to drive development of increasingly effective protocols for their preparation.[5] Whereas traditional approaches to polyketide construction are largely reliant on carbonyl additions mediated by premetalated reagents, our laboratory is advancing a broad, new family of hydrogen auto-transfer reactions that affect byproduct-free carbonyl addition from alcohol proelectrophiles using abundant π-unsaturated hydrocarbons as precursors to transient organometallic nucleophiles. Ruthenium(II) catalysts are especially effective in reactions of this type, as they are octahedral d^6 metal ions with unoccupied d_{x2-y2} orbitals that facilitate alkoxide β-hydride elimination. The evolution of methods for butadiene-mediated crotylation described in this review culminates in the design of iodide-bound ruthenium JOSIPHOS complexes, which represent a new and highly effective class of enantioselective catalysts that are ‘chiral-at-metal-and-ligand’.[39] Such iodide-bound ruthenium JOSIPHOS complexes allow the reactivity of ruthenium to be leveraged vis-à-vis an expanded lexicon of asymmetric methods for the catalytic conversion of lower alcohols to higher alcohols, including methods for polyketide construction (Figure 6).[17c,40] It is the authors’ hope this monograph will inform future advances in the development of related atom-efficient methods for chemical synthesis.

Conflict of Interest

The authors declare no conflict of interest.

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