Enantioselective Catalysis

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Catalytic Enantioselective C–H Functionalization of Alcohols by Redox-Triggered Carbonyl Addition: Borrowing Hydrogen, Returning Carbon

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The use of alcohols and unsaturated reactants for the redox-triggered generation of nucleophile–electrophile pairs represents a broad, new approach to carbonyl addition chemistry. Discrete redox manipulations that are often required for the generation of carbonyl electrophiles and premetalated carbon-centered nucleophiles are thus avoided. Based on this concept, a broad, new family of enantioselective C–C coupling reactions that are catalyzed by iridium or ruthenium complexes have been developed, which are summarized in this Minireview.

1. Introduction

As organic molecules are defined as compounds composed of carbon and hydrogen, stereoselective, atom-efficient methods for skeletal assembly involving the addition, removal, or redistribution of hydrogen in the absence of discrete oxidation level adjustment, or non-constructive functional group interconversions represent a natural endpoint in the evolution of synthetic methods.[1] This view of synthetic efficiency tacitly recognizes the value of merged redox-construction events ("redox economy"),[2] chemo- (site-), regio-, and stereoselectivity,[3] protecting-group-free chemical synthesis,[4] as well as the minimization of preactivation, defined as the degree of separation between reagent and feedstock.[5] Transformations and strategies that adhere to these ideals are inherently process-relevant.[6]

The application of these concepts to the chemistry of carbonyl addition reveals a significant opportunity for invention. In classical carbonyl additions, premetalated C-centered nucleophiles and carbonyl compounds are typically generated through separate streams of redox reactions: Discrete alcohol-to-aldehyde oxidation is frequently used to generate carbonyl electrophiles, and discrete reduction is often used to generate organometallic nucleophiles. By exploiting the native reducing capability of alcohols, redox-triggered carbonyl additions may be developed wherein hydrogen exchange between alcohols and unsaturated reactants generates transient electrophile–nucleophile pairs en route to products of formal alcohol C–H functionalization by carbonyl addition.[7] To date, three major mechanistic pathways for C–C coupling have been identified; alcohol oxidation may be balanced by 1) C=C π-bond hydrometalation, 2) reductive cleavage of a C–X bond, or 3) transfer hydrogenolysis of oxametallacycles (Figure 1).

In this review, catalytic enantioselective methods for C–C bond formation by alcohol C–H functionalization are surveyed on the basis of the aforementioned mechanistic pathways. Related redox-triggered alcohol C–H functionalizations that have not been rendered asymmetric are covered elsewhere.[7] For most alcohol C–C couplings described in this account, corresponding aldehyde reductive couplings have been reported,[7] but for the sake of brevity, they are not described. Dehydrogenative C–C bond formations that result in formal alcohol substitution, that is, so-called "borrowing hydrogen" or "hydrogen auto-transfer" processes, radical-mediated alcohol C–C couplings, and processes involving stoichiometric oxidants are also not discussed.[8,9]

2. Hydrometallative Pathways

In a series of experiments conducted in 2007, the first catalytic C–C couplings of primary alcohols based on the generation of nucleophile–electrophile pairs from reactant

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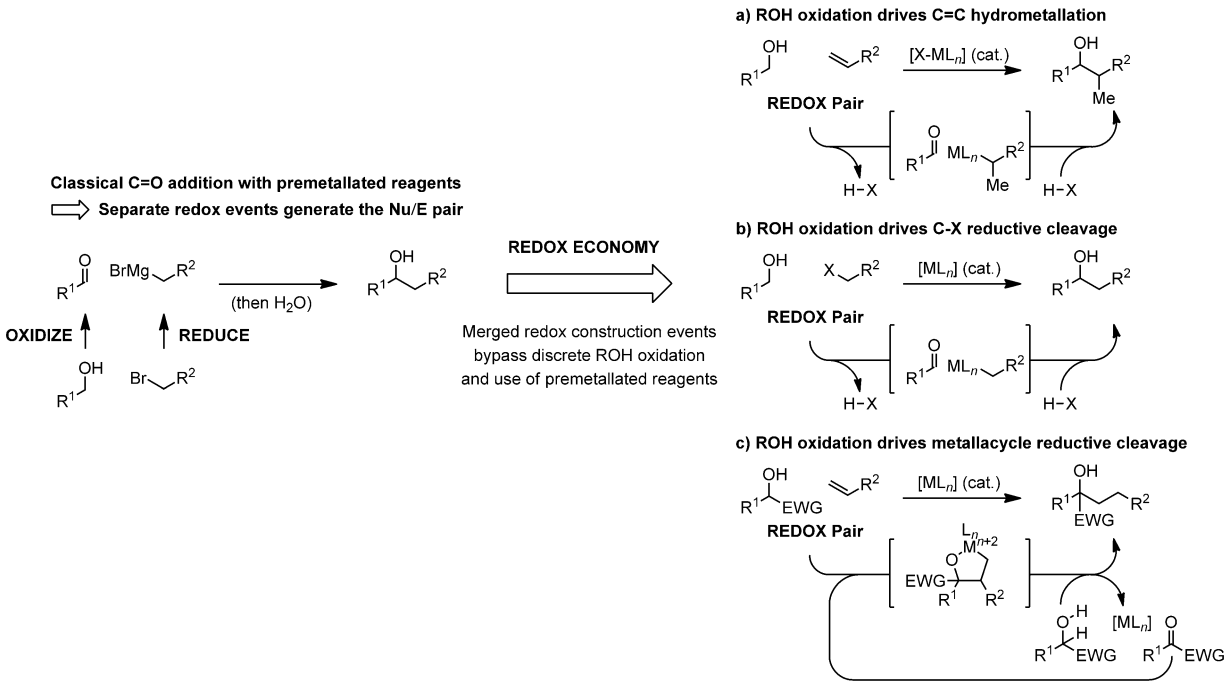


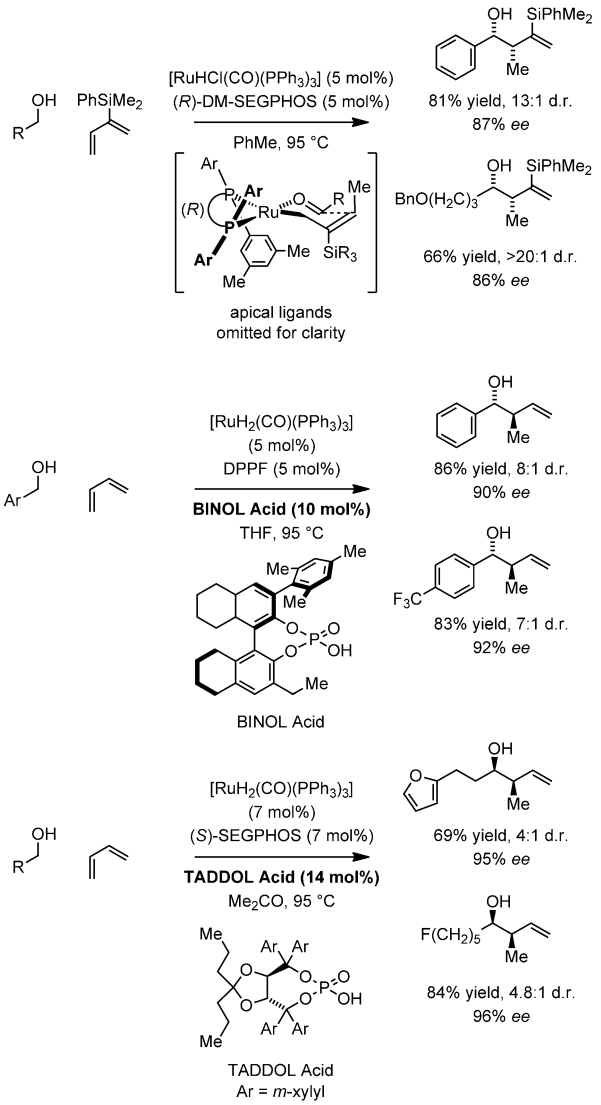
Figure 1. Redox economy in carbonyl addition: three general mechanistic pathways identified for redox-triggered alcohol C–H functionalization.

redox pairs were performed in our laboratory.[10a] For these initially developed transformations, which employ iridium[10] and ruthenium[11] catalysts, alcohol dehydrogenation triggers hydrometalation of a π-unsaturated reactant (allenes,[10a,d,11d,f] dienes,[10b,c,11a,e] enynes,[11b] or alkynes[11c]) to furnish aldehyde–organometal pairs that engage in carbonyl addition (Figure 1, mechanism A). Based on this pattern of reactivity, a series of catalytic enantioselective diene hydrohydroxyalkylations were developed (Scheme 1).[12] Using the indicated 2-silyl-substituted butadiene prepared from chloroprene in combination with chiral ruthenium catalysts modified by (*R*)-DM-SEGPHOS, *syn*-diastereo- and enantioselective C–C couplings were achieved by way of geometrically defined σ-allylruthenium intermediates.[12a] The direct use of butadiene itself, an abundant product of petroleum cracking, would be ideal. Using a chiral ruthenium catalyst modified by the indicated H_8-BINOL-derived phosphate counterion, which is installed through the acid–base reaction of $[RuH_2(CO)(PPh_3)_3]$ with the chiral phosphoric acid in the presence of DPPF, butadiene hydrohydroxyalkylation with primary benzylic alcohols occurred with good levels of *anti*-diastereo- and enantioselectivity.[12b] Remarkably, using the ruthenium catalyst that was generated in situ from $[RuH_2(CO)(PPh_3)_3]$, (*S*)-SEGPHOS, and the indicated TADDOL-derived phosphoric acid, an inversion in diastereoselectivity was observed.[12c] It appears that the more basic TADDOL-derived phosphate counterion preserves kinetic selectivity in the hydrometalation of the *s-cis* conformer of butadiene to form the (*Z*)-σ-crotylruthenium haptomer by attenuating the degree of coordinative unsaturation, which would otherwise accelerate isomerization to the (*E*)-σ-crotylruthenium haptomer. Such diene hydrohydroxyalkylations bypass the generation of stoichiometric byproducts and may be viewed as carbonyl crotylations from the alcohol oxidation level.

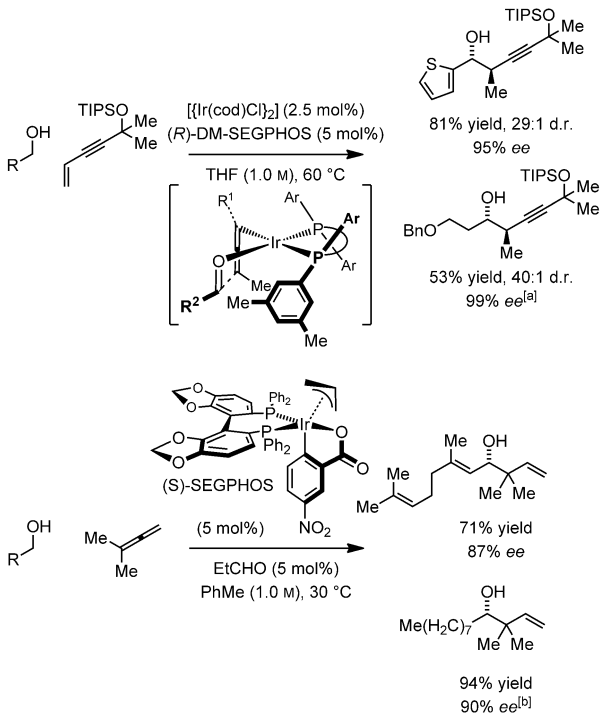
Iridium complexes also catalyze enantioselective C–C couplings wherein hydrogen is transferred from alcohols to π-unsaturated reactants, triggering the formation of nucleophile–electrophile pairs (Scheme 2).[13] Exposure of alcohols to 1,3-enynes in the presence of an iridium catalyst modified by (*R*)-SEGPHOS or (*R*)-DM-SEGPHOS gave rise to aldehyde–allenyliridium pairs, which combined to form enantiomerically enriched products of carbonyl *anti*-(α-methyl)propargylation.[13c] In these transformations, axial-to-axial-to-point chirality transfer from the phosphine ligand to the allenyliridium intermediate and then to the reaction product occurred with high fidelity. Using the indicated *ortho*-cyclometalated iridium *C*,*O*-benzoate complex prepared from $[\{Ir(cod)Cl\}_2]$, (*S*)-SEGPHOS, allyl acetate, and 3-nitrobenzoic acid,[14] alcohols and 1,1-dimethylallene combined by way of *n*-prenyliridium intermediates to form products of *tert*-prenylation. Here, enantiofacial selectivity is opposite to that observed in related allylations and crotylations catalyzed by *ortho*-cyclometalated iridium *C*,*O*-benzoates in combination with allyl acetate or α-methyl allyl acetate, respectively.[13b]

3. Reductive Cleavage of C–X bonds

In a significant step towards the long-term goal of developing Grignard-type carbonyl additions wherein alcohol oxidation drives reductive C–X (X = halide or pseudo-halide) bond cleavage to form carbonyl–organometal pairs, redox-triggered C–C couplings of primary alcohols and allyl acetate were developed (Scheme 3).[15] In initial studies, the *ortho*-cyclometalated iridium *C*,*O*-benzoate catalyst generated



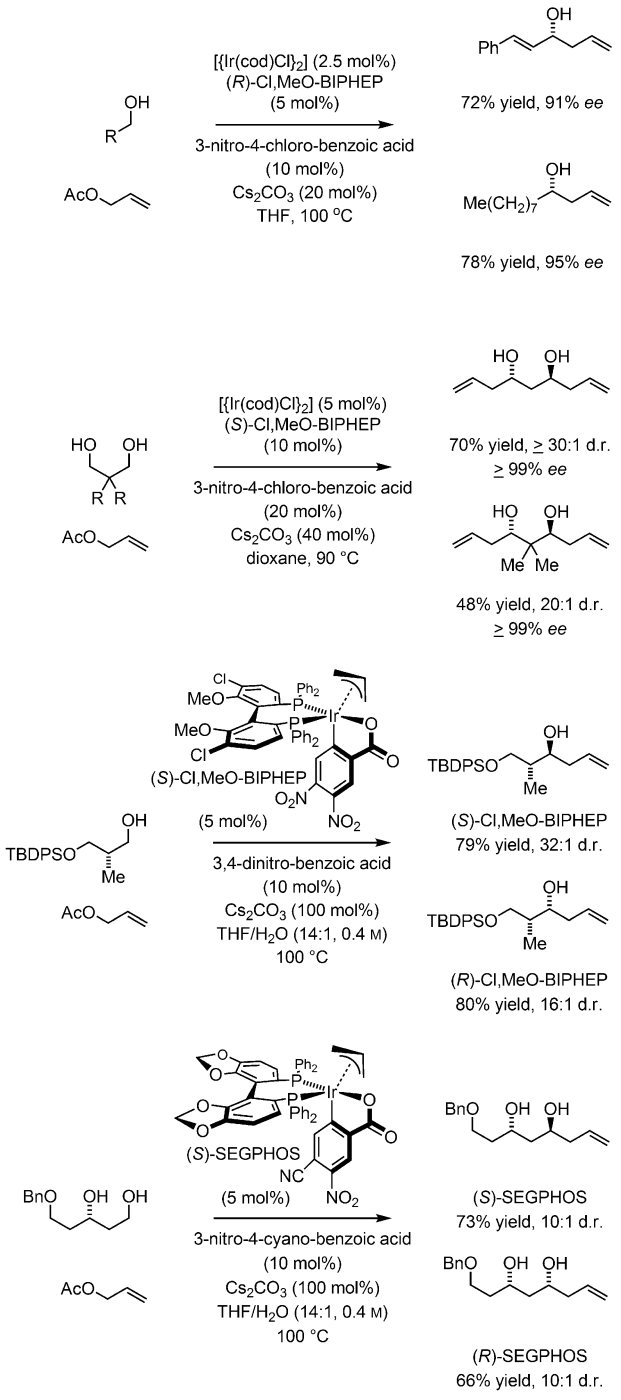
Scheme 1. Ruthenium-catalyzed diene hydrohydroxyalkylation: diastereo- and enantioselective carbonyl crotylation from the alcohol oxidation level. In all Schemes in this Minireview, the yields correspond to the material isolated by column chromatography on silica gel. Bn = benzyl, (*R*)-DM-SEGPHOS = (*R*)-(+)-5,5′-bis(di[3,5-xylyl]phosphino)-4,4′-bi-1,3-benzodioxole, DPPF = 1,1′-bis(diphenylphosphino)ferrocene, (*S*)-SEGPHOS = (*S*)-(−)-5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole.



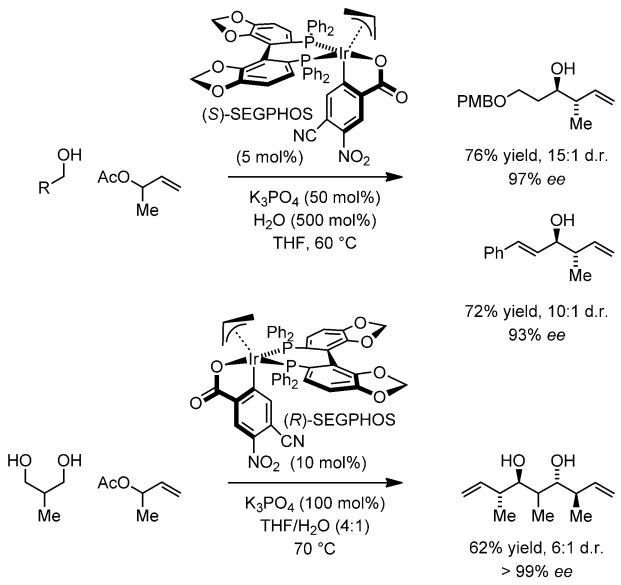
Scheme 2. Iridium-catalyzed 1,3-enyne and allene hydrohydroxyalkylation: enantioselective carbonyl propargylation and *tert*-prenylation from the alcohol oxidation level. [a] (*R*)-SEGPHOS was used as the ligand, and $PhCF_3$ was used as the solvent. [b] 50 °C. cod = cycloocta-l,5-diene, TIPS = triisopropylsilyl.

in situ from [{Ir(cod)Cl}$_2$], a chiral phosphine ligand, allyl acetate, and 3-nitrobenzoic acid were used. Aliphatic, allylic, and benzylic alcohols were converted into the corresponding homoallylic alcohols with uniformly high levels of enantioselectivity.[15a–c] Most significantly, the ability to directly engage alcohols as partners for C–C couplings opens the door to carbonyl allylation processes that are not possible using conventional allyl metal reagents.[16] For example, the enantioselective double allylation of 1,3-diols provides access to C_2-symmetric adducts that otherwise require rather lengthy preparations.[15d] Here, the reaction products were isolated as single enantiomers, as the minor enantiomer of the monoadduct was transformed into the *meso* stereoisomer.[17] The enhanced efficiency observed for iridium complexes that were purified by conventional flash column chromatography on silica gel availed further capabilities, such as highly diastereoselective C–H allylations of chiral β-stereogenic alcohols.[15e] This method bypasses the discrete generation of configurationally labile chiral α-stereogenic aldehydes, which often cannot be stored or subjected to column chromatography on silica gel without erosion of enantiomeric purity.[18] Remarkably, because of a pronounced kinetic preference for primary alcohol dehydrogenation, the indicated chromatographically purified iridium complex catalyzes the site-selective C–H allylation of polyols,[15f] streamlining synthesis by removing steps otherwise required for the installation and removal of protecting groups and avoiding discrete alcohol-to-aldehyde redox manipulations.

For alcohol C–H functionalizations catalyzed by *ortho*-cyclometalated iridium *C*,*O*-benzoate complexes, the collective data are consistent with the indicated general catalytic mechanism (Figure 2). Alcohol dehydrogenation results in the formation of an aldehyde and an iridium(III) hydride, which suffers deprotonation to form an anionic iridium(I) *C*,*O*-benzoate. Ionization of allyl acetate delivers a π-allyl species, which adds to the aldehyde by way of the σ-allyl intermediate to form the homoallylic iridium alkoxide. Protonolysis of this intermediate by the primary alcohol reactant closes the catalytic cycle. As supported by mechanistic studies, remote electron-withdrawing groups at the 4-position of the benzoate moiety enhance Lewis acidity at iridium, accelerating turnover-limiting carbonyl addition with



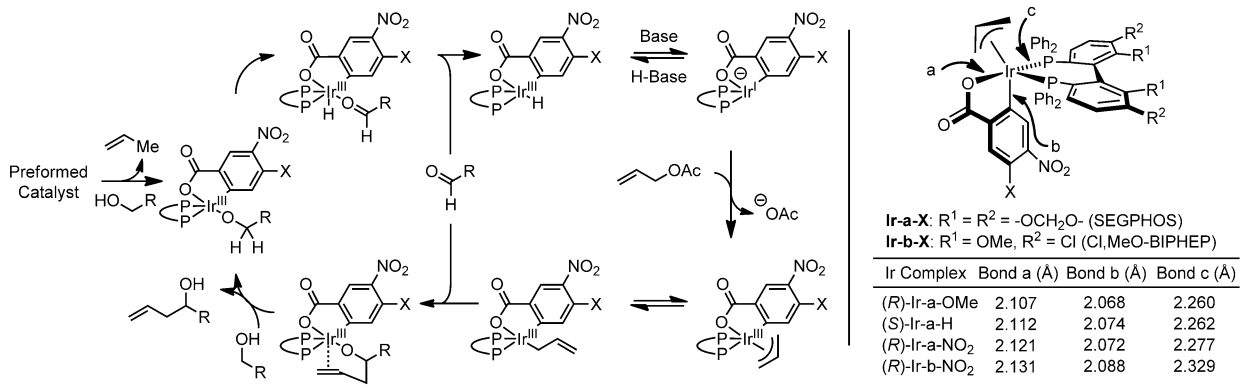
Scheme 3. Iridium-catalyzed C–C coupling of primary alcohols with allyl acetate: enantioselective carbonyl allylation from the alcohol oxidation level. TBDPS = *tert*-butyldiphenylsilyl.



Scheme 4. Iridium-catalyzed C–C coupling of primary alcohols with α-methyl allyl acetate: enantioselective carbonyl crotylation from the alcohol oxidation level.

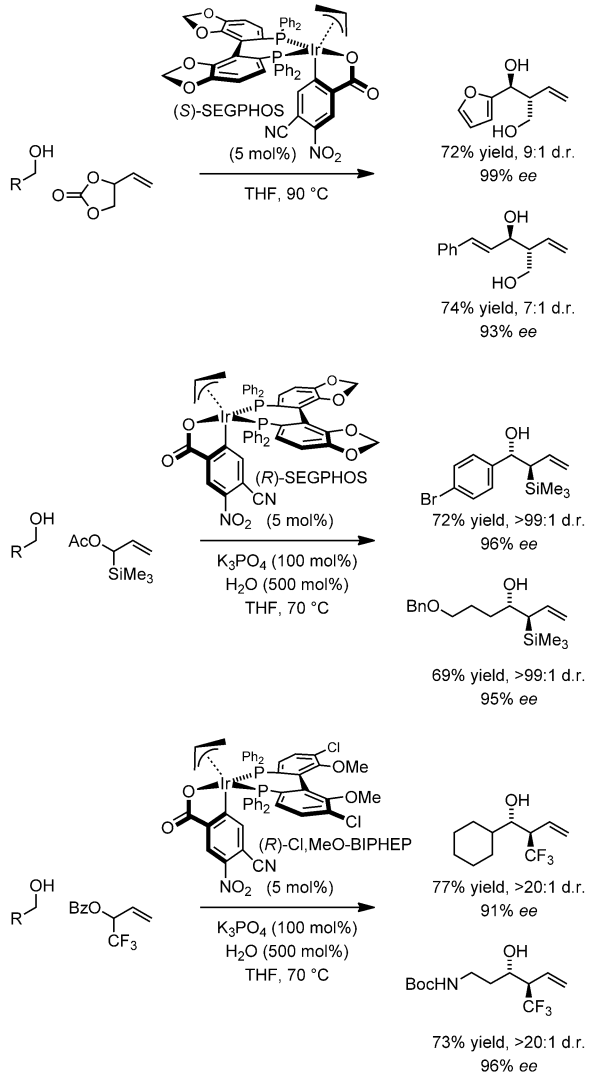
respect to competing processes. For example, in the reaction of primary alcohols with α-methyl allyl acetate to form C–H crotylation products (Scheme 4),[19a,b] the kinetic selectivity that is observed in the generation of the (*E*)-σ-crotyliridium intermediate, which reacts stereospecifically to deliver the *anti*-diastereomer, is preserved when the rate of carbonyl addition is accelerated with respect to isomerization of the σ-crotyliridium intermediate to the *Z* isomer, which reacts stereospecifically to form the *syn*-diastereomer. Indicative of enhanced Lewis acidity at the iridium center, longer C–Ir, O–Ir, and P–Ir bonds are evident in the more electron-deficient *C*,*O*-benzoate complexes, as determined by single-crystal X-ray diffraction analysis.[15e] Exploiting these subtle effects, a double alcohol C–H crotylation of 2-methyl-1,3-propane diol to form the indicated pseudo-C_2-symmetric polypropionate stereoquintet was developed.[19c] Because of the aforementioned amplification effect,[17] the double crotylation of 2-methyl-1,3-propanediol delivered predominantly one of 16 possible stereoisomers (Scheme 4).

In terms of scope, such cyclometalated iridium *C*,*O*-benzoate complexes catalyze the C–C coupling of benzylic, allylic, and aliphatic primary alcohols with a remarkably diverse range of π-allyl precursors. For example, as illustrated in the *anti*-diastereo- and enantioselective α-(hydroxymethyl)allylation,[20a] α-(trimethylsilyl)allylation,[20b] and α-(trifluoromethyl)allylation[20c] of primary alcohols, reactions employing α-substituted allylic carboxylates with monosubstituted alkenes are especially facile (Scheme 5). For allylic pronucleophiles that possess higher degrees of olefin substitution (Scheme 6),[21] the diminished stability of the olefin π-complex[22] impedes ionization of the allylic leaving group to form the nucleophilic π-allyliridium intermediate. In catalytic enantioselective alcohol C–H methallylations,[21a] the use of a more reactive chloride leaving group compensates for the shorter lifetime of the more highly substituted olefin π-complex. Alternatively, steric destabilization of the olefin π-complex stemming from higher degrees of olefin substitution can be offset by the introduction of LUMO-lowering substituents, which increase the degree of π-backbonding.[23] For the indicated γ-acyloxy crotonate,[21b] enhanced π-acidity of the allyl donor enables the C–H functionalization of primary alcohols to form vinylogous aldol-type products. Here, linear regioselectivity in response to increased steric

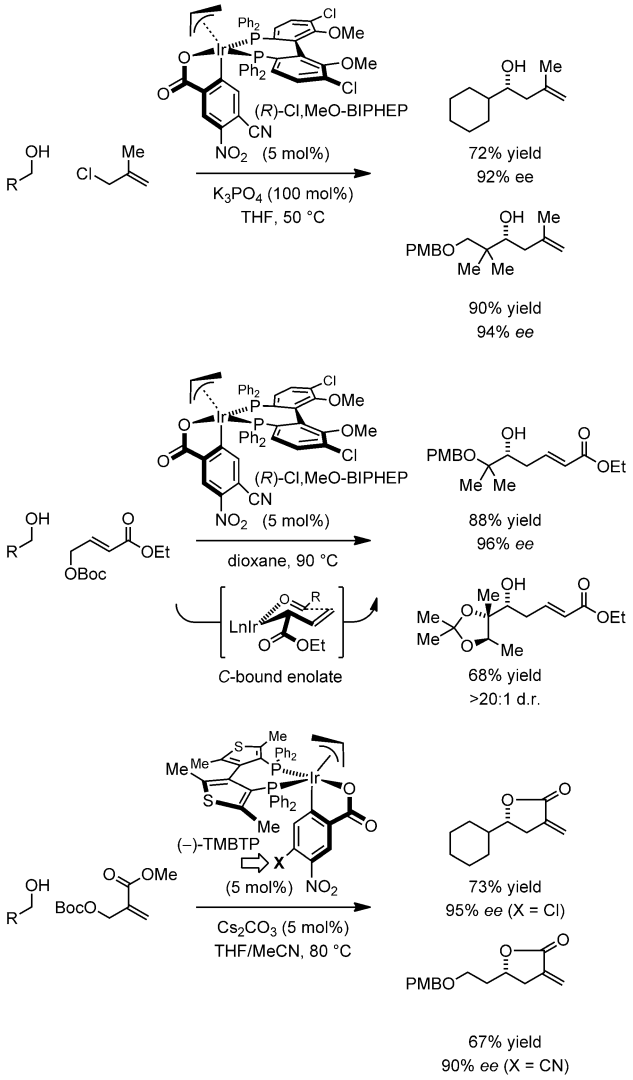


Ir Complex	Bond a (Å)	Bond b (Å)	Bond c (Å)
(*R*)-Ir-a-OMe	2.107	2.068	2.260
(*S*)-Ir-a-H	2.112	2.074	2.262
(*R*)-Ir-a-NO_2	2.121	2.072	2.277
(*R*)-Ir-b-NO_2	2.131	2.088	2.329

Figure 2. General catalytic mechanism and selected bond lengths obtained by single-crystal X-ray diffraction analysis of a series of π-allyliridium *C*,*O*-benzoate complexes.

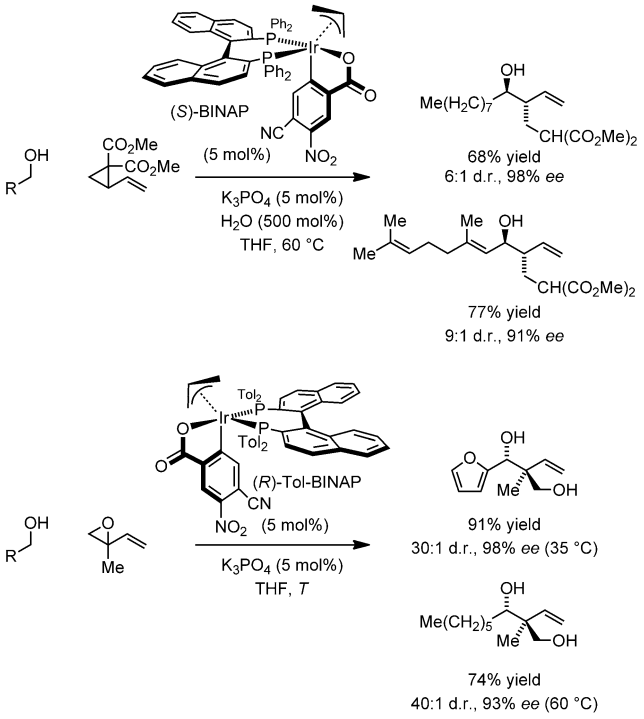


Scheme 5. Iridium-catalyzed C–C coupling of primary alcohols with α-substituted allyl donors. Bz = benzoyl.

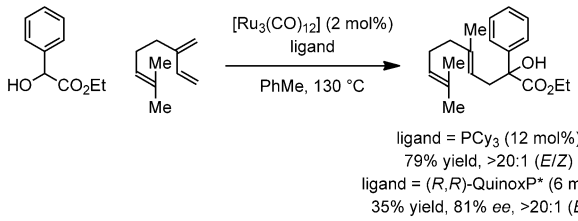


Scheme 6. Iridium-catalyzed C–C coupling of primary alcohols and allyl donors with substituents on the olefin moiety.

demand of the transient aldehyde suggests a Curtin–Hammett-type scenario where carbonyl addition occurs selectively from an equilibrating mixture of primary and secondary σ-allyl haptomers. Similarly, using 2-(alkoxycarbonyl)allyl carbonates, the C–H allylation of primary alcohols is accompanied by lactonization to form 5-substituted α-*exo*-



Scheme 7. Iridium-catalyzed C–C coupling of primary alcohols with vinylcyclopropanes and vinylepoxides.



Scheme 8. Ruthenium(0)-catalyzed C–C coupling of secondary alcohols.

methylene γ-butyrolactones,[21c] a structural motif found in approximately 10% of the >30000 known natural products.[24]

The strained C–C bond evident in the indicated donor–acceptor vinyl cyclopropane is subject to ionization to form aldehyde–allyliridium pairs en route to products of formal alcohol C–H functionalization.[25a] In an analogous manner, primary alcohols and isoprene oxide deliver aldehyde–allyliridium pairs that combine to form products of *tert*-(hydroxy)prenylation,[25b] a motif found in over 2000 terpenoid natural products. Here, carbonyl addition occurs predominantly by way of a single geometrical isomer of the transient allyliridium intermediate because of Curtin–Hammett effects, enabling the highly diastereo- and enantioselective formation of an all-carbon quaternary center (Scheme 7).

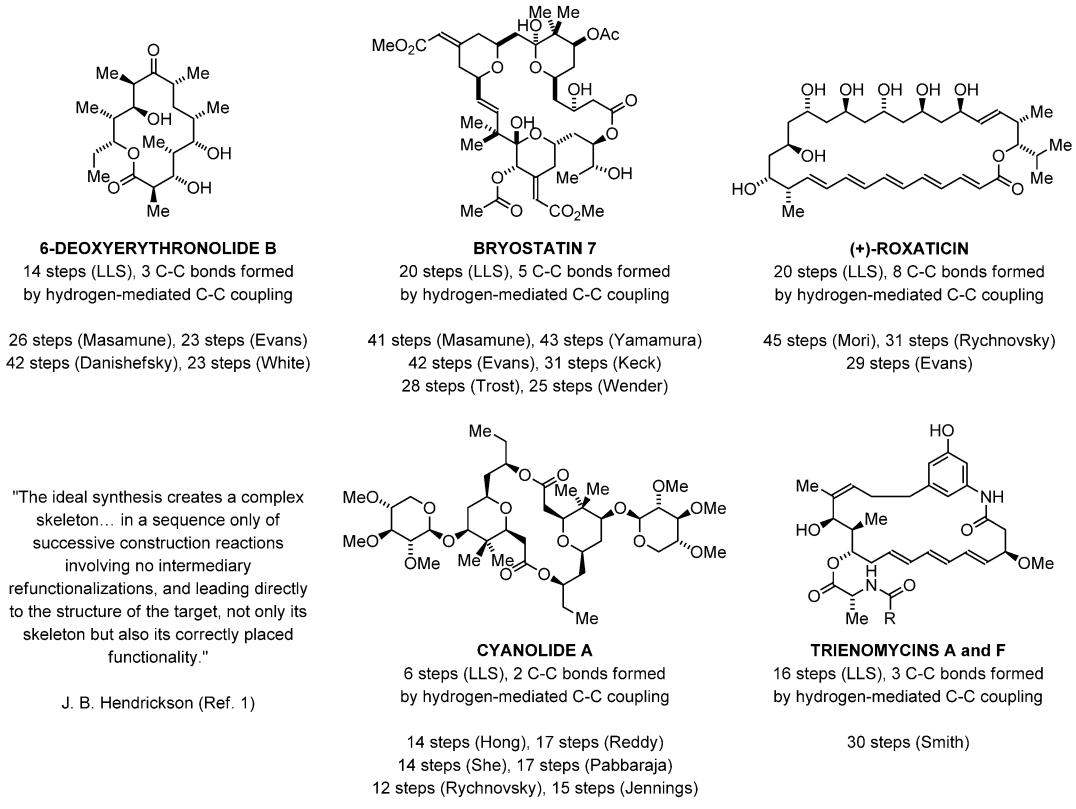


Figure 3. Catalytic alcohol C–C coupling streamlines organic synthesis, as illustrated in the total syntheses of polyketide natural products (Ref. [28]).

4. Metallacycle Hydrogenolysis

A third general mechanistic pathway for the C–C coupling of alcohols involves the transfer hydrogenolysis of oxametallacycles. This pathway was recently uncovered in connection with efforts to exploit secondary alcohols as partners for C–C coupling.[26] It was found that ruthenium(0) catalysts formed in situ from $[Ru_3(CO)_{12}]$ and certain phosphine ligands promote the C–C coupling of α-hydroxy carbonyl compounds[26] or 1,2-diols[26d,f,g] with conjugated dienes,[26a,b,d,e] terminal olefins,[26c] α,β-unsaturated esters,[26f] or alkynes.[26g] Asymmetric variants of these processes are currently under development, and promising levels of enantioselectivity have been observed (Scheme 8).

5. Summary and Outlook

The direct use of alcohols as partners for C–C coupling in redox-triggered carbonyl addition streamlines synthesis by avoiding discrete redox reactions often required for the generation of carbonyl electrophiles and premetalated C-centered nucleophiles. Further, the chemoselectivity displayed by these processes allows polyfunctional molecules to be engaged in a site-selective manner in the absence of protecting groups, inducing a shift in retrosynthetic paradigm. As demonstrated by the total syntheses of the polyketide natural products (+)-roxaticin,[27a] bryostatin 7,[27b] cyanolide A,[27c] trienomycins A and F,[27d] and 6-deoxyerythronolide B,[27e] such alcohol C–H functionalizations have availed a pronounced increase in synthetic efficiency, opening up the most concise routes to any member of these respective natural product families (Figure 3).[27–29] More broadly, the merged redox-construction events described herein suggest that other processes that have traditionally employed one or more organometallic reagents can now be conducted catalytically in the absence of stoichiometric metals by utilizing reactants as redox pairs.

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