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

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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]

Application of these concepts to the chemistry of carbonyl addition reveals a significant opportunity for invention. In classical carbonyl additions, premetallated *C*-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 *via* carbonyl addition.[7] To date, three major mechanistic pathways for C-C coupling have been identified wherein alcohol oxidation is balanced by (A) C=C π-bond

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hydrometallation, (B) C-X reductive cleavage, and (C) transfer hydrogenolysis of oxametallacycles (Figure 1).

In this review, catalytic enantioselective methods for C-C bond formation *via* alcohol CH 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 are reported,[7] but for the sake of brevity are not covered. 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 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 redox pairs were performed in our laboratory.[10a] For these initially developed transformations, which employ iridium[10] and ruthenium[11] catalysts, alcohol dehydrogenation triggers hydrometallation of a π-unsaturated reactant (allenes,[10a,d,11d,f] dienes,[10b,c,11a,d] 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-silylsubstituted butadiene prepared from chloroprene in combination with chiral ruthenium catalysts modified by (*R*)-DM-SEGPHOS, *syn*-diastereo-and enantioselective C-C coupling is 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 employing primary benzylic alcohols occurs with good levels of *anti*-diastereo-and enantioselectivity.[12b] Remarkably, using the ruthenium catalyst generated *in situ* from $RuH_2(CO)(PPh_3)_3$, (*S*)-SEGPHOS and the indicated TADDOL-derived phosphoric acid, an inversion in diastereoselectivity is observed.[12c] It appears the more basic TADDOL-derived phosphate counterion preserves kinetic selectivity in the hydrometallation 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 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 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 gives rise to aldehyde-allenyliridium pairs, which combine 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 the reaction product, respectively, occurs with high fidelity. Using the indicated *ortho*-cyclometallated 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 combine by way of *n*-prenyliridium intermediates to form products of *tert* prenylation. Here, the observed enantiofacial selectivity is opposite to that observed in related allylations and crotylations catalyzed by *ortho*-cyclometallated iridium *C,O*-benzoates in combination with allyl acetate or α-methyl allyl acetate, respectively.[13b]

3. C-X Reductive Cleavage

In a significant step toward 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, the redox-triggered C-C couplings of primary alcohols and allyl acetate were developed (Scheme 3).[15] In initial studies, the *ortho*-cyclometallated iridium *C,O*-benzoate catalyst generated *in situ* from $[Ir(cod)Cl]_2$, a chiral phosphine ligand, allyl acetate and 3-nitrobenzoic acid was used. Aliphatic, allylic and benzylic alcohols were converted to 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 coupling opens the door to carbonyl allylation processes that are not possible using conventional allylmetal reagents.[16] For example, 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 are isolated as single enantiomers, as the minor enantiomer of the *mono*-adduct is transformed to the *meso*-stereoisomer.[17] The enhanced efficiency observed for iridium complexes purified by conventional flash silica gel chromatography availed further capabilities, such as highly diastereoselective C-H allylations of chiral β-stereogenic alcohols.[15e] This protocol bypasses discrete generation of configurationally labile chiral α-stereogenic aldehydes, which often cannot be stored or subjected to silica gel chromatography without erosion of enantiomeric purity.[18] Remarkably, due to 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*-cyclometallated iridium *C,O*-benzoate complexes, the collective data are consistent with the indicated general catalytic mechanism (Figure 2). Alcohol dehydrogenation results in 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, which adds to the aldehyde by way of the σ-allyl to form the homoallylic iridium alkoxide. Protonolysis of the homoallylic iridium alkoxide 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 respect to competing processes. For example, in the reaction of primary alcohols with

α-methyl allyl acetate to form products C-H crotylation (Scheme 4),[19a,b] kinetic selectivity 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, longer C-Ir, O-Ir, and P-Ir bonds are evident in 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] Due to the aforesaid amplification effect,[17] the double crotylation of 2-methyl-1,3-propanediol delivers predominantly one of 16 possible stereoisomers (Scheme 4).

In terms of scope, such cyclometallated 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 possessing monosubstituted alkenes are especially facile (Scheme 5). For allylic pronucleophiles that possess higher degrees of olefin substitution (Scheme 6),[21] 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] 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 that increase the degree of π-backbonding.[23] For the indicated γ-acyloxy crotonate,[21b] enhanced π-acidity of the allyl donor enables primary alcohol C-H functionalization to form vinylogous aldol-type products. Here, linear regioselectivity in response to increased steric 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, primary alcohol C-H allylation is accompanied by lactonization to form 5-substituted α-exomethylene γ-butyrolactones,[21c] a structural motif embodied by approximately 10% of the >30,000 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*-(hydroxyl)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 due to Curtin- Hammett effects, enabling highly diastereo- and enantioselective formation of an all-carbon quaternary center (Scheme 7).

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 premetallated *C*-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 in 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 step-function change in synthetic efficiency, opening up the most concise routes to any member of these respective natural products families (Figure 3).[27–29] More broadly, the merged redox-construction events described herein suggest other processes that traditionally have 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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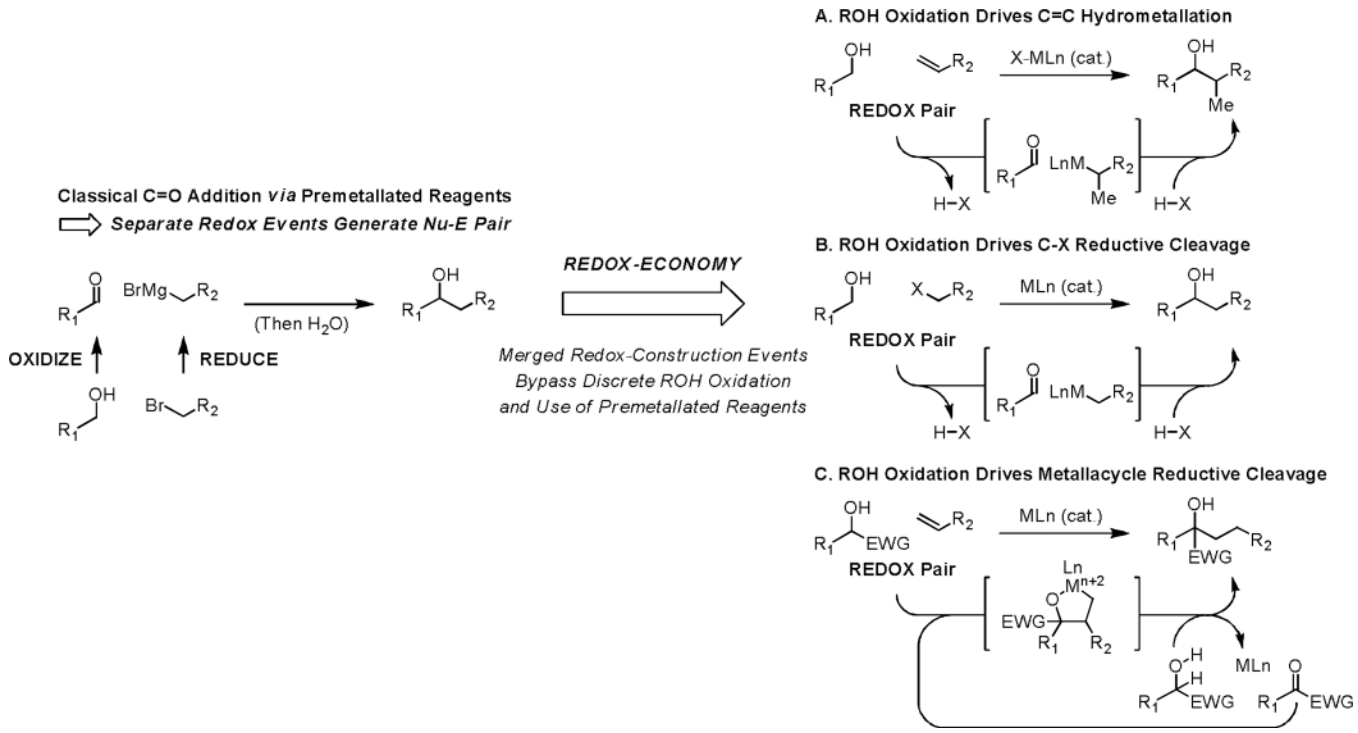
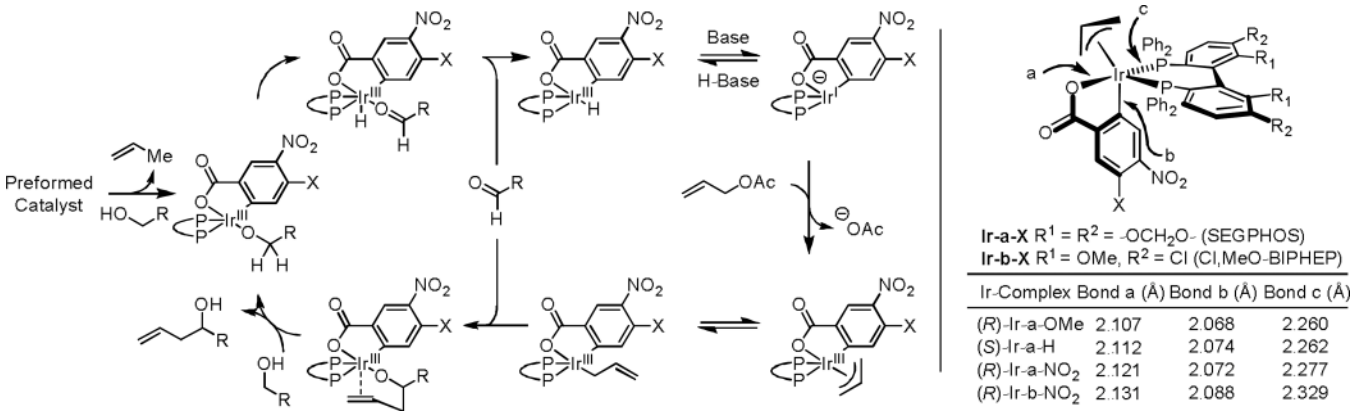


Figure 1.

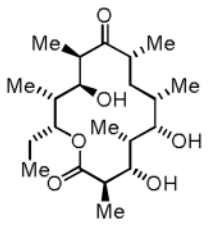
Redox-economy in carbonyl addition: three general mechanistic pathways identified for redox-triggered alcohol C-H functionalization.



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

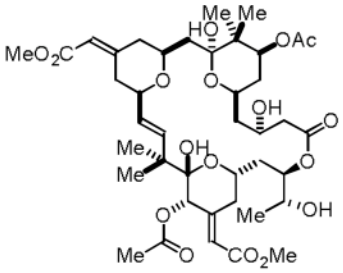
Figure 2.

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



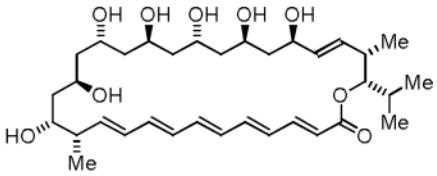
6-DEOXYERYTHRONOLIDE B
14 Steps (LLS), 3 C-C Bonds Formed
via Hydrogen Mediated C-C Coupling

26 Steps (Masamune), 23 Steps (Evans)
42 Steps (Danishefsky), 23 Steps (White)



BRYOSTATIN 7
20 Steps (LLS), 5 C-C Bonds Formed
via Hydrogen Mediated C-C Coupling

41 Steps (Masamune), 43 Steps (Yamamura)
42 Steps (Evans), 31 Steps (Keck)
28 Steps (Trost), 25 Steps (Wender)

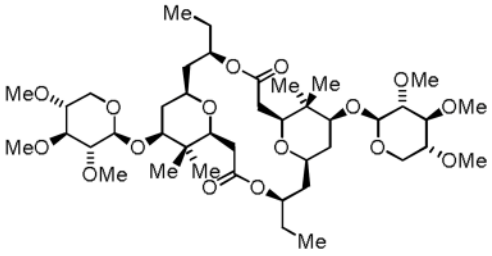


(+)-ROXATICIN
20 Steps (LLS), 8 C-C Bonds Formed
via Hydrogen Mediated C-C Coupling

45 Steps (Mori), 31 Steps (Rychnovsky)
29 Steps (Evans)

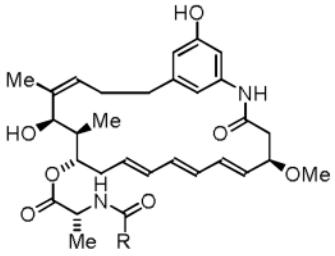
"The ideal synthesis creates a complex skeleton… in a sequence only of successive construction reactions involving no intermediary refunctionalizations, and leading directly to the structure of the target, not only its skeleton but also its correctly placed functionality."

J. B. Hendrickson (ref. 1)



CYANOLIDE A
6 Steps (LLS), 2 C-C Bonds Formed
via Hydrogen Mediated C-C Coupling

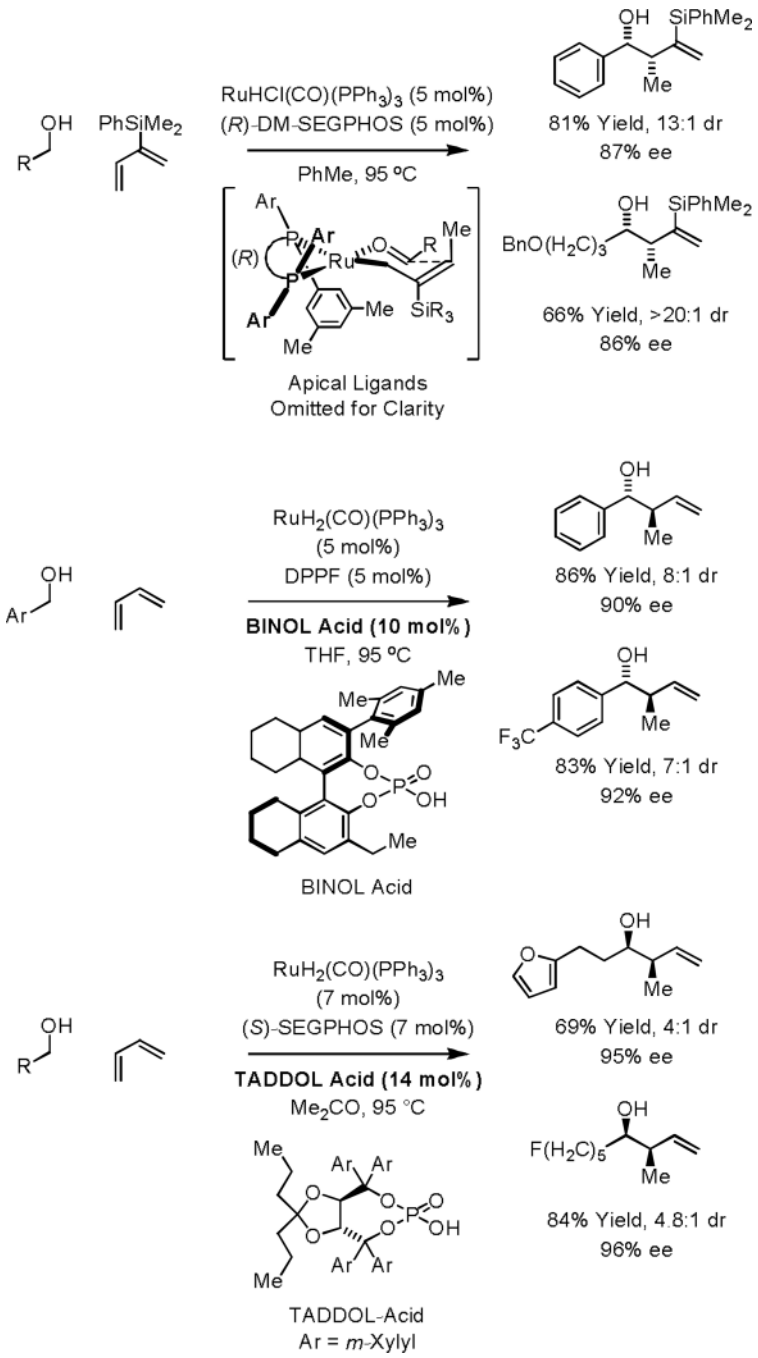
14 Steps (Hong), 17 Steps (Reddy)
14 Steps (She), 17 Steps (Pabbaraja)
12 Steps (Rychnovsky), 15 Steps (Jennings)



TRIENOMYCINS A and F
16 Steps (LLS), 3 C-C Bonds Formed
via Hydrogen Mediated C-C Coupling

30 Steps (Smith)

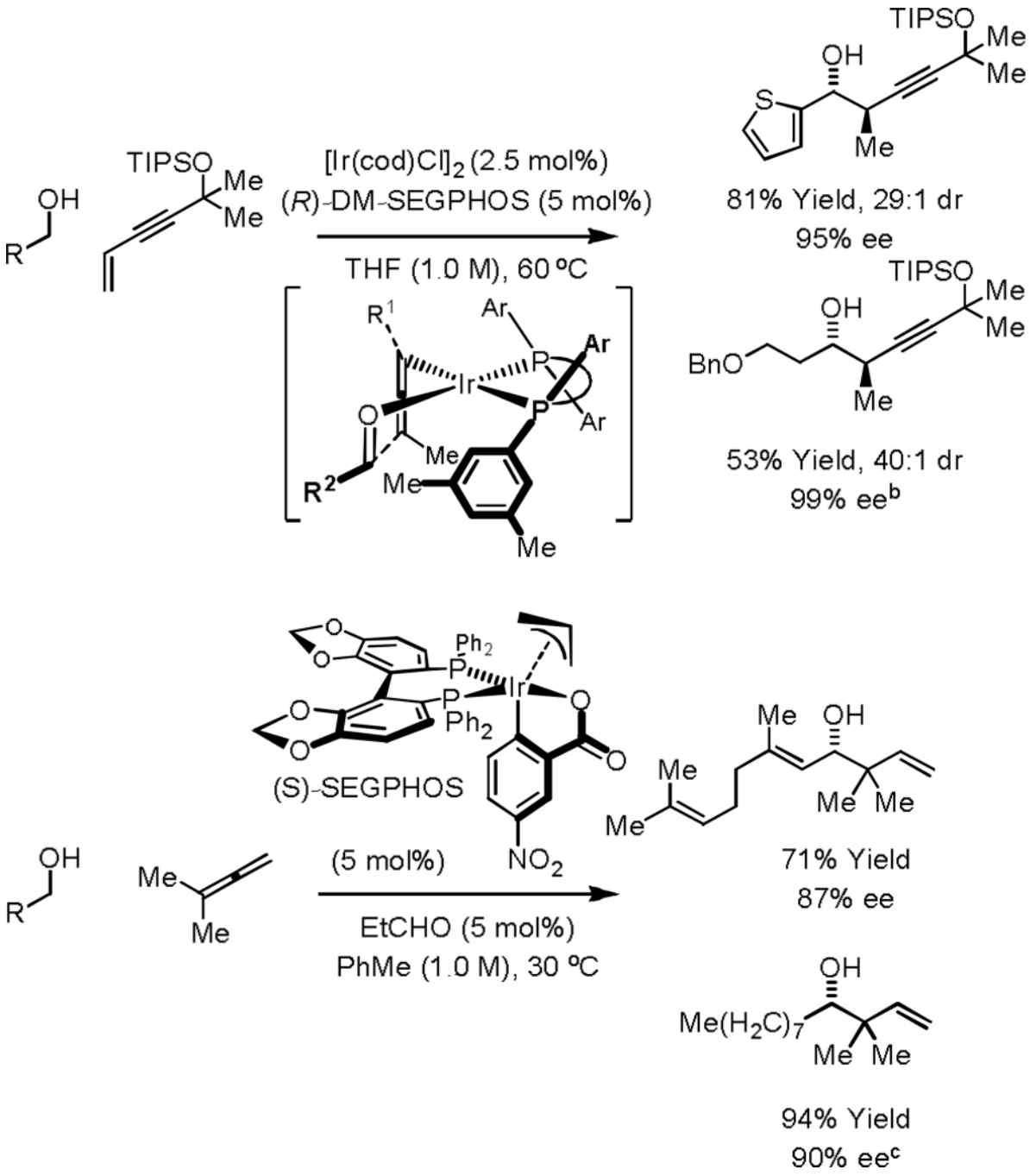
Figure 3.
Catalytic alcohol C-C coupling streamlines organic synthesis, enabling a step-function change in efficiency (ref. 28).



scheme 1.

Ruthenium catalyzed diene hydrohydroxyalkylation: diastereo- and enantioselective carbonyl crotylation from the alcohol oxidation level.a

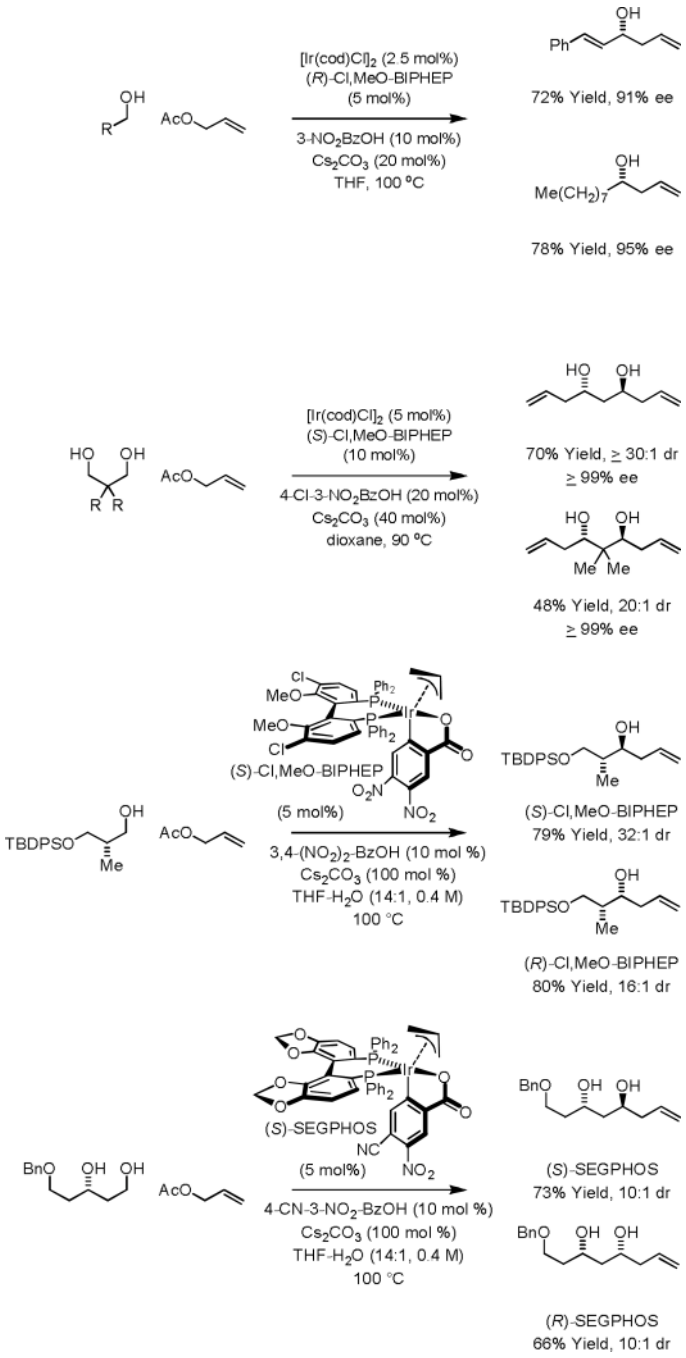
[a]Yields are of material isolated by silica gel chromatography. (*R*)-DM-SEGPHOS = [*R*)-(+)-5,5’-bis(di[3,5–xylyl]phosphino)-4,4’-bi-1,3-benzodioxole]; DPPF = 1,1’-bis(diphenylphosphino)ferrocene; (*S*)-SEGPHOS = (S)-(−)-5,5’-bis-(diphenylphosphino)-4,4’-bi-1,3-benzodioxole.



scheme 2.

Iridium catalyzed 1,3-enyne and allene hydrohydroxyalkylation: enantioselective carbonyl propargylation and *tert*-prenylation from the alcohol oxidation level[a]

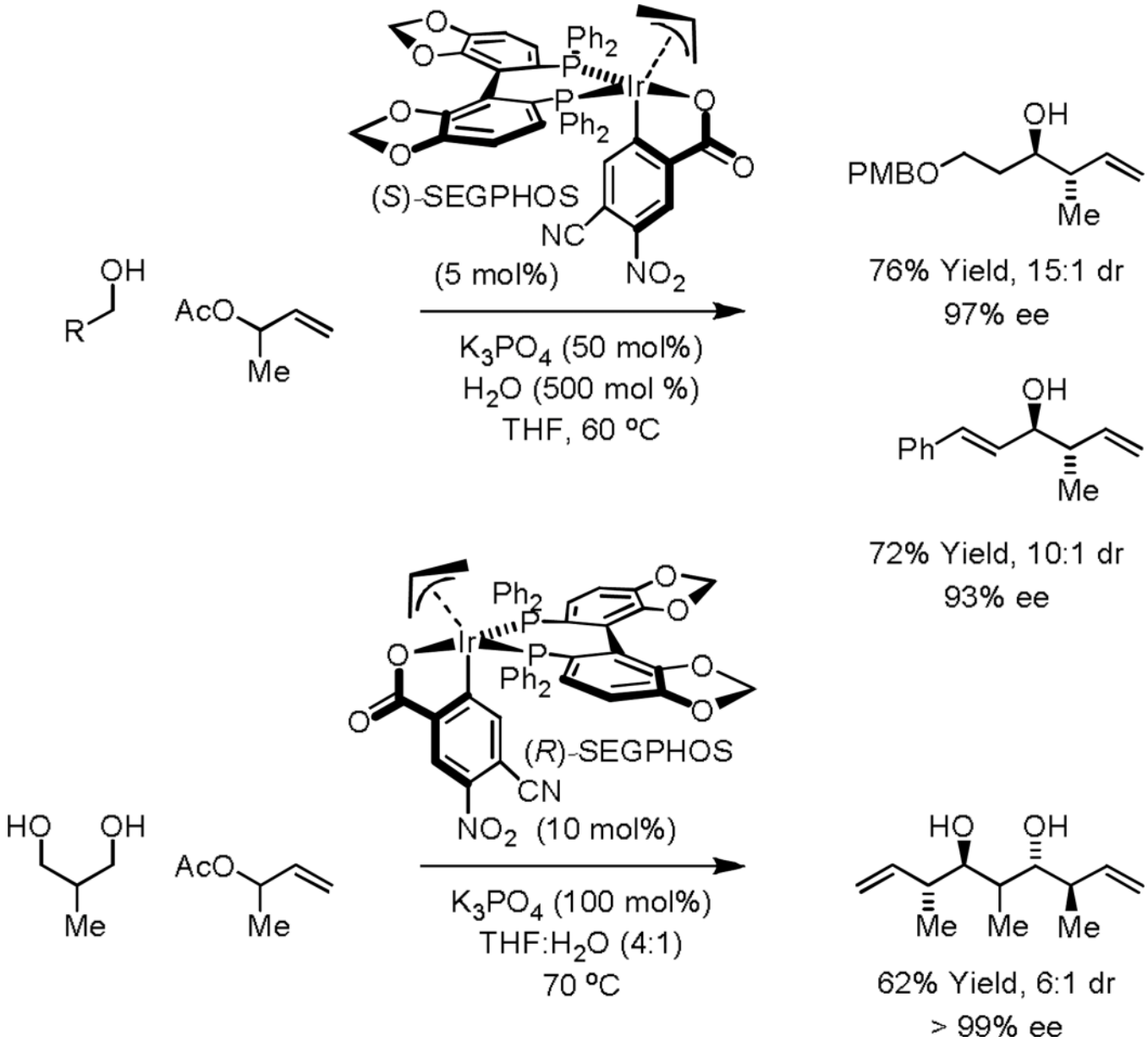
[a]As described in Scheme 1.[b](*R*)-SEGPHOS was used as ligand and $PhCF_3$ was used as solvent.[c]50°C.



scheme 3.

Iridium catalyzed C-C coupling of primary alcohols with allyl acetate: enantioselective carbonyl allylation from the alcohol oxidation level.a

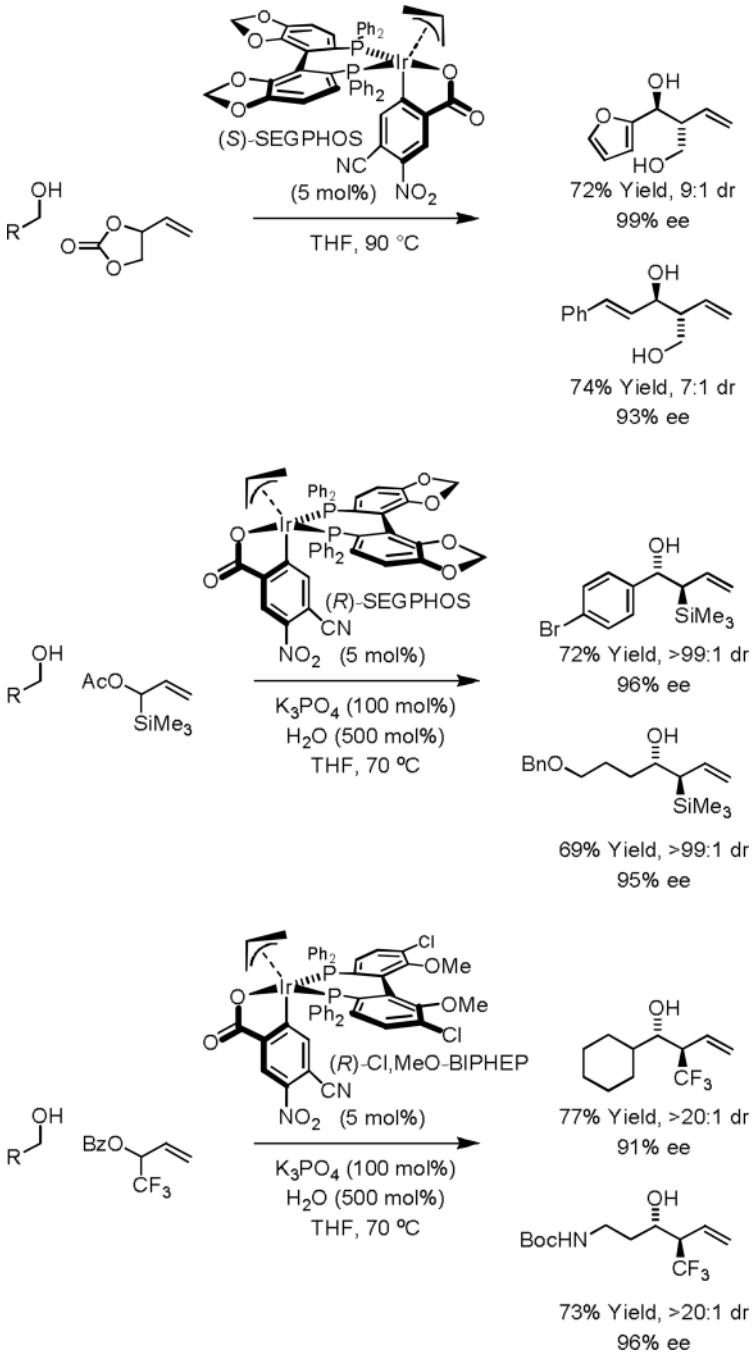
[a]As described in Scheme 1



scheme 4.

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

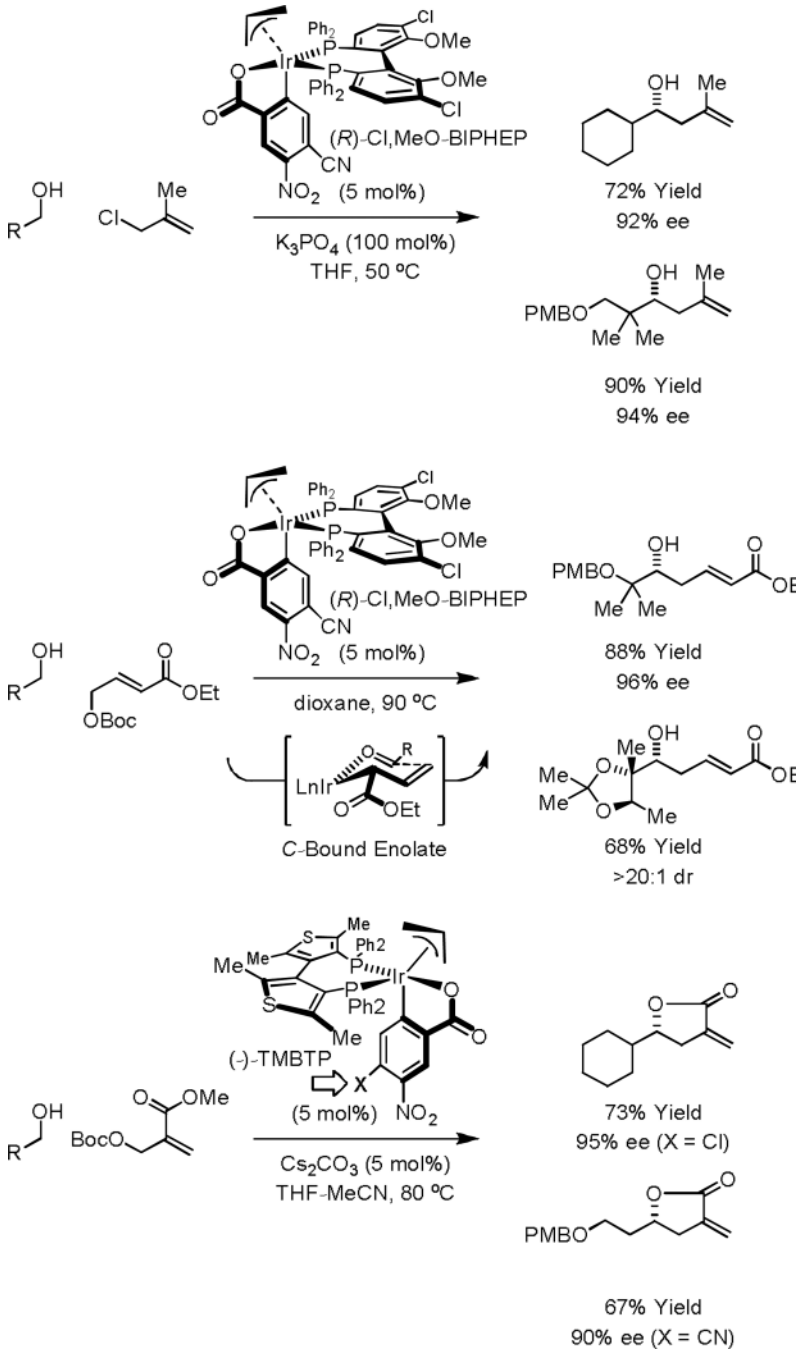
[a]As described in Scheme 1.



scheme 5.

Iridium catalyzed C-C coupling of primary alcohols with α-substituted allyl donors.a

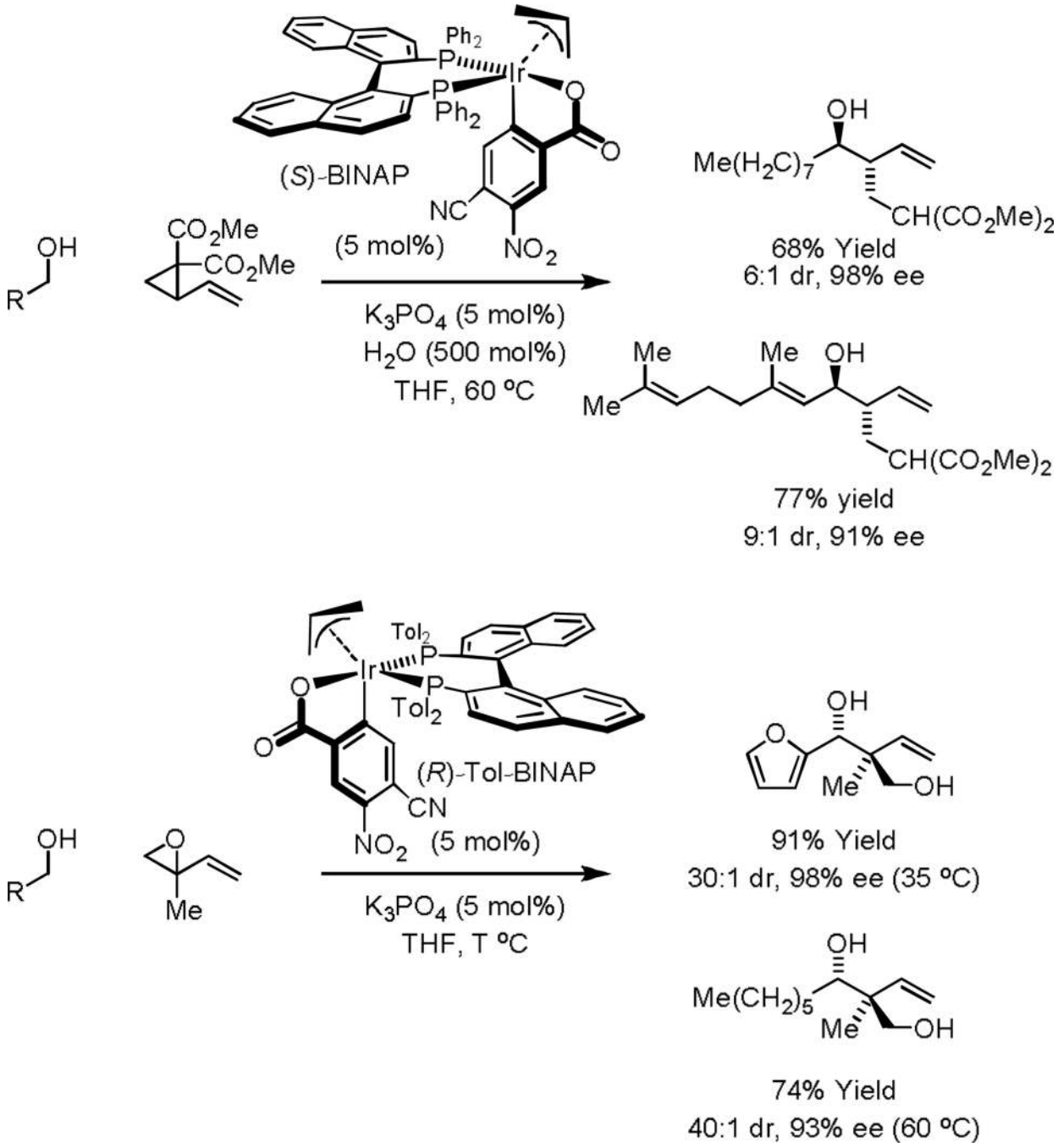
[a]As described in Scheme 1.



scheme 6.

Iridium catalyzed C-C coupling of primary alcohols with allyl donors possessing olefinic substitution.a

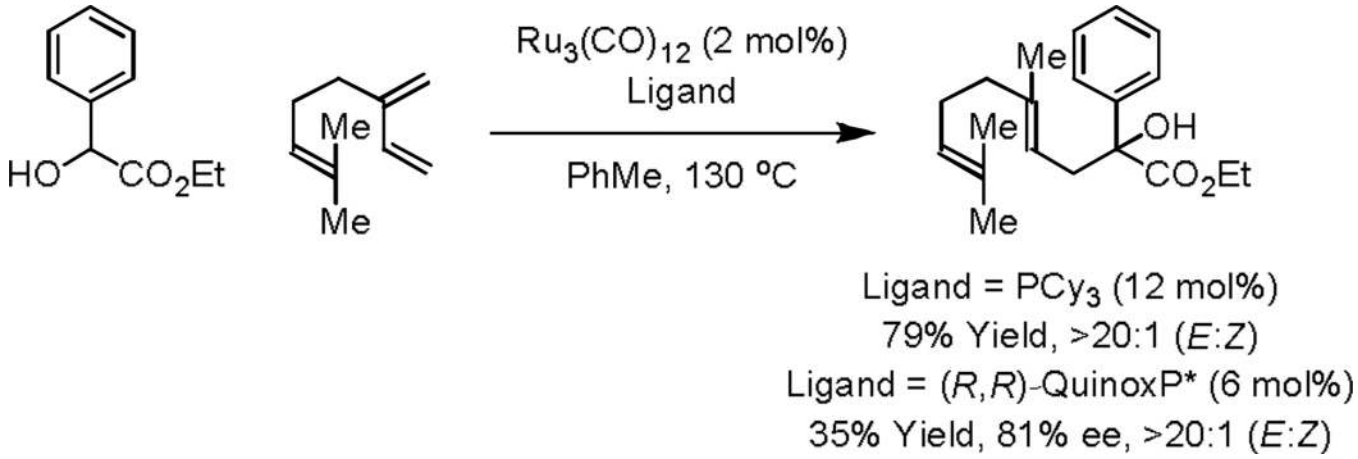
[a]As described in Scheme 1.



scheme 7.

Iridium catalyzed C-C coupling of primary alcohols with vinylcyclopropanes and vinylepoxides.a

[a]As described in Scheme 1.



scheme 8.

Ruthenium(0) catalyzed C-C coupling of secondary alcohols.a

[a]As described in Scheme 1.