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Intermolecular Metal-Catalyzed Reductive Coupling of Dienes, Allenes and Enynes with Carbonyl Compounds and Imines

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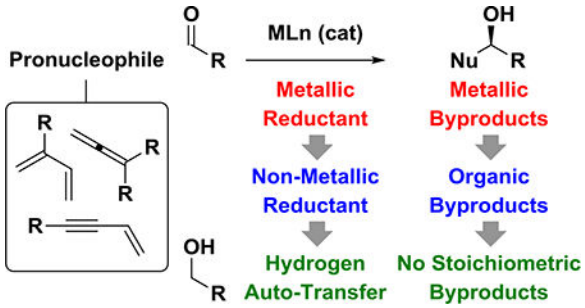
Abstract

Metal-catalyzed reductive coupling has emerged as an alternative to the use of stoichiometric organometallic reagents in an increasingly diverse range of carbonyl and imine additions. In this monograph, the use of diene, allene and enyne pronucleophiles in intermolecular carbonyl and imine reductive couplings are surveyed along with related hydrogen auto-transfer processes.

Graphical Abstract



1. Introduction and Historical Perspective on Carbonyl Addition

Following Frankland's preparation of diethylzinc in 1849[1–3] were the first reports of the addition of premetalated *C*-nucleophiles to carbonyl compounds. For example, in 1858, Frankland's protégé James Wanklyn described the addition of ethylsodium to carbon dioxide to form propionic acid assisted by sodium triethylzincate, $NaZn(C_2H_5)_3$.[4,5] Literature from this time period include references to the reaction of transient organometallics with carbonyl compounds, however, it was not until the systematic studies of Butlerov[6,7] (and his "Kazan school" progeny)[8,9] and Grignard[10,11] that the addition of premetalated *C*-nucleophiles to carbonyl compounds took root as a major method for chemical synthesis. Subsequent milestones in organometallic and carbonyl addition chemistry include the generation of organolithium reagents[12,13] and, therefrom, cuprates,[14] the advent of palladium-mediated C-C coupling.[15,16] Finally, in 1986 Noyori reported the first highly enantioselective catalytic method for carbonyl addition[17] – a progenitor to the numerous methods now available for

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the catalytic enantioselective addition of non-stabilized carbanions and their equivalents to carbonyl compounds and imines (Figure 1).[18–24]

While carbonyl addition mediated by premetalated reagents continues to play an important role in chemical synthesis,[25] the requisite organometallic reagents are hazardous, frequently require cryogenic conditions and generate stoichiometric quantities of metallic byproducts, which complicates large-volume applications. Metal-catalyzed reductive couplings of π-unsaturated reagents with carbonyl compounds provides a more ideal alternative to the use of stoichiometric organometallic reagents. Fischer-Tropsch type reactions (1922)[26,27] and alkene hydroformylation (1938)[28] may be considered the prototypical metal-catalyzed reductive C-C couplings. However, even with the advent of heterogeneous[25] and homogenous hydrogenation,[30] catalytic reductive couplings beyond carbon monoxide did not appear until much later and hydrogen-mediated reductive couplings were not systematically studied until the work of Krische.[31–33] The discovery that nickel salts catalyze chromium(II)mediated couplings of organic halides to carbonyl compounds (the Nozaki-Hiyama-Kishi reaction)[34–37] advanced the concept of metal-catalyzed reductive carbonyl addition, as well as the quest for more benign, less mass-intensive terminal reductants. Metal-catalyzed reductive coupling gradually emerged as a discrete field of inquiry.[31–33,37–48]

The arc of science traced from these early advances in organometallic chemistry to the current state-of-the-art in carbonyl addition chemistry defines a progression from (a) classical reactions of premetalated *C*-nucleophiles (with or without a metal catalyst)[18–23] to (b) metal-catalyzed reductive couplings of π-unsaturated reactants (with metallic or non-metallic terminal reductants)[38–48] and, finally, (c) carbonyl additions that proceed through alcohol-mediated hydrogen auto-transfer (Figure 1).[24,43–48] The selective pressure of efficiency has guided this evolution: many reactions that traditionally exploit premetalated reagents can now be conducted catalytically in the absence of stoichiometric metals or byproducts with high levels of stereocontrol. Additionally, many transformations that have no counterpart in classical carbonyl or imine addition chemistry have been discovered.

In this review, intermolecular metal-catalyzed reductive couplings of 1,3-dienes, allenes or 1,3-enynes with carbonyl compounds and imines are surveyed. Discussion is restricted to processes that result in both C-H and C-C bond formation, ideally in (formal) additions of H_2 across the π-unsaturated pronucleophile and C=X (X = O, NR) π-bond. Related reductive cyclizations,[39] multi-component reductive couplings (alkylative/arylative,[49–51] borylative[52–58] or, more generally, bismetalative[59–61]) and reductive couplings to carbon dioxide[62–67] are not covered and the reader is referred to the review literature and selected examples. Processes wherein the π-unsaturated pronucleophile is stoichiometrically reduced to a discrete nucleophilic species (for example, through hydrometalation) to which the carbonyl or imine partner is subsequently exposed, are not covered.[68–70]

2. Diene-C=X (X = O, NR) Reductive Coupling

2.1. Nickel

Following Mori and Sato's seminal report in 1994 on the nickel-catalyzed reductive cyclization of dienyl aldehydes mediated by silane,[71] related intermolecular diene-aldehyde reductive couplings were developed by Tamaru and Kimura in 1998 using triethylborane as terminal reductant.[72] As illustrated in homoallylations of benzaldehyde, feedstock dienes such as isoprene and myrcene engage in C-C coupling with exceptional levels of regio- and 1,3-*anti*-diastereoselectivity at ambient temperature. The same year, an intermolecular silane-mediated variant of this process was reported by Mori and Sato using terminal dienes.[73] While uniformly high levels of regioselectivity were accompanied by complete olefin (*E*:*Z*)-stereocontrol in additions to aryl aldehydes, related couplings of aliphatic aldehydes displayed incomplete levels of alkene stereoselectivity. Mori and Sato later showed that in reductive couplings of aldehydes with trialkylsilyl substituted dienes, Ph_3P-modified nickel catalysts enable (*E*)selective allylation (not shown) whereas NHC-modified nickel catalysts enable (*Z*)-selective allylation.[74] Further studies by Tamaru and Kimura revealed that diene-aldehyde reductive couplings mediated by diethylzinc are particularly effective for couplings of aliphatic aldehydes and ketones, although erosion of regioselectivity is observed in the latter case.[75] Using the $Ni(acac)_2/Et_3B$ catalyst system, lactols and aqueous glutardialdehyde undergo highly diastereoselective homoallylation illustrating compatibility with hydroxyl functional groups (Scheme 1).[76] Diisobutylaluminum acetylacetonate is also a viable reductant in couplings of dienes bearing terminal aryl substituents, however, mixtures of linear and branched regioisomers are observed (not shown).[77] Using the $Ni(acac)_2/Et_3B$ catalyst system, cyclohexadiene-aldehyde reductive coupling is possible but roughly equimolar diastereomeric mixtures are observed (not shown).[78]

A general mechanism for $Ni(acac)_2/Et_3B$-catalyzed diene-aldehyde reductive coupling that accounts for the observed regio- and 1,3-*anti*-diastereoselectivity has been proposed (Scheme 2).[79] Coordination of diene and aldehyde by nickel generates a nucleophilic π-complex, which upon triethylborane assisted oxidative coupling delivers the indicated π-allyl-oxanickelacycle. Computational studies on related nickel(0)-catalyzed alkyne-aldehyde reductive couplings mediated by triethylborane suggest the LUMOlowering effect evident upon the binding of triethylborane to the aldehyde accelerates oxidative coupling.[80] As illustrated in elegant work by Ogoshi,[81] reversible diene-aldehyde oxidative coupling is observed in stoichiometric reactions with nickel(0) to provide isolable π-allylalkoxynickel(II) complexes that have been characterized by single crystal X-ray diffraction analysis. Ethyl transfer to the nickel(II) center followed by β-hydride elimination provides a π-allylnickel hydride, which upon reductive elimination delivers the product of reductive coupling and returns nickel(II) to its zero-valent form.

The development of general methods for enantioselective nickel(0)-catalyzed diene-aldehyde reductive coupling remains a largely unresolved challenge. In 2007, Zhou reported the *anti*-diastereo- and enantioselective reductive coupling of 1,4-diphenylbutadiene with aromatic aldehydes mediated by diethylzinc using a nickel catalyst modified by a monodentate spiro-phosphoramidite, ligand-**II**.[82] The same year, Sato reported a silane-

mediated diene-aldehyde reductive coupling using the C_2-symmetric ligand-**III**.[83] While this process delivers (*Z*)-homoallylic silyl ethers with excellent control of olefin geometry and diastereoselectivity, high levels of enantioselectivity were again only evident in reactions of 1,4-diphenylbutadiene (Scheme 3).

The requirement of reductants that are pyrophoric (Et_2Zn and Et_3B) or those that are costly and mass-intensive (R_3SiH) represents a major limitation associated with the methods described above. In a significant departure from prior art, Krische and Breit reported the reductive coupling of 2-substituted dienes wherein formaldehyde serves as both electrophile and reductant (Scheme 4).[84] In these processes, the transient π-allylalkoxynickel(II) complex inserts formaldehyde and undergoes β-hydride elimination to deliver coupling products as the formate esters, which are cleaved in the course of isolation. Depending on the diene 2-substituent, a preference for C-C bond formation at either the C1 or C4 position is observed. For dienes incorporating alkyl or aryl groups at the 2-substituent, dieneformaldehyde oxidative coupling at C1 is kinetically preferred. For corresponding silicon- and tinsubstituted dienes, hyperconjugation between the C–Si or C–Sn σ-bond and the σ* orbital of the newly formed C-C bond renders oxidative coupling at C1 reversible, enabling oxidative coupling at C4 which is thermodynamically preferred. Reversibility in diene-carbonyl oxidative coupling and the kinetic vs thermodynamic preference for C1 vs C4 oxidative coupling, respectively, has been demonstrated in mechanistic studies by Ogoshi.[81]

In 2004, Tamaru and Kimura reported the first nickel(0)-catalyzed reductive coupling of dienes and imines.[85] This process conveniently generates the imine *in situ* from the aldehyde and *p*-anisidine with subsequent introduction of the nickel acetylacetonate, diene and diethylzinc. Coupling occurs predominantly at the diene C1 position to provide the products with good to complete levels of 1,3-*syn*diastereoselectivity. Using triethylborane as terminal reductant, the authors later extended this process to encompass imines derived from lactols.[86] As reported by Singh in 2015, exposure of *p*-anisidine to aryl aldehydes bearing *ortho*-carboxy substituents enables tandem nickel(0)-catalyzed diene-imine reductive coupling-lactam formation to form isoindolinones and isoquinolinones (Scheme 5).[87] For related 3component couplings of dienes, imines and organozinc reagents, the reader is referred to the review literature.[50]

2.2. Ruthenium

The first ruthenium(II)-catalyzed diene-carbonyl reductive coupling was reported in 2008 by Krische (Scheme 6).[88] Using 2-propanol or formic acid as reductants, butadiene, isoprene or 2,3dimethylbutadiene react with aldehydes to form branched products of C-C coupling as single regioisomers. Unlike the nickel(0)-based catalysts systems, which operate through pathways involving diene-carbonyl oxidative coupling, the present ruthenium(II)-catalyzed processes involve diene hydrometalation to provide nucleophilic allylruthenium(II) intermediates. Related stoichiometric reactions of $HClRu(CO)(PPh_3)_3$ with 1,3-dienes to form well defined π-allylruthenium complexes have been documented.[89] Carbonyl addition occurs by way of the primary σ-allyl haptomer through the indicated closed six-centered transition state. Under these conditions, primary alcohols transfer hydrogen to dienes to

form aldehyde-allylruthenium pairs that combine to form homoallylic alcohols. The reaction of isoprene with d_2-benzyl alcohol results in deuterium transfer to the allylic methyl (32% ^{2}H) and allylic methine (14% ^{2}H), corroborating reversible hydrometalation of the less substituted olefin with incomplete regiocontrol. The reaction products resist further dehydrogenation by coordination of the homoallylic olefin to the ruthenium center.[90]

Relative and absolute stereocontrol is enforced using chiral ruthenium(II) complexes modified by (*R*)-DM-SEGPHOS in combination with 2-trialkylsilyl-butadienes (Scheme 7).[91] Hydrometalation of 2trialkylsilyl-substituted dienes delivers crotylmetal species that exist predominantly as single geometrical isomers due to allylic strain.[92,93] Stereospecific carbonyl addition provides the branched products of reductive coupling with high levels of *syn*-diastereo- and enantioselectivity. Carbonyl addition can be conducted from the aldehyde oxidation level using 2-propanol as terminal reductant or from the alcohol oxidation level *via* hydrogen auto-transfer. A significant extension in scope was made in 2017 by Brimble, who reports the crotylation of chiral alcohols to form polyketide stereotriads, which avoids the use of configurationally labile chiral α-stereogenic aldehydes.[94]

The ability to exploit butadiene itself, an abundant petrochemical feedstock, in regio- and stereocontrolled diene-carbonyl reductive coupling would represent a powerful alternative to stoichiometric reactions of chiral crotylmetal reagents.[95] Using a ruthenium catalyst modified by a chiral phosphate counterion derived from H_8-BINOL, direct *anti*-diastereo- and enantioselective hydrohydroxyalkylations of butadiene can be achieved from the alcohol or aldehyde oxidation level (Scheme 8).[96] In the latter case, 1,4-butanediol is used as terminal reductant.[97] Notably, the chiral counterion is the sole chiral inducing element. Corresponding *syn*-diastereo- and enantioselective butadiene-mediated carbonyl crotylations take advantage of match-mismatch effects between the indicated TADDOL-derived phosphate counterion and the chiral ligand, (S)-SEGPHOS.[98] In both processes, butadiene hydroruthenation from the *s-cis* conformer delivers the (*Z*)-σ-crotylruthenium haptomer. For the more Lewis basic TADDOL-phosphate counterion, formation of a contact ion-pair with the ruthenium(II) center preserves kinetic (*Z*)-selectivity and stereospecific carbonyl addition provides the product of *syn*-crotylation. For the less Lewis basic BINOL-phosphate counterion, open coordination sites on ruthenium enable isomerization of the initially formed (*Z*)-σ-crotylruthenium haptomer to the thermodynamically preferred (*E*)-σ-crotylruthenium haptomer, which, in turn, provides the product of *anti*-crotylation. Computational studies suggest the transition state for aldehyde addition from the (*Z*)-σcrotylruthenium haptomer is facilitated by formation of a formyl hydrogen bond between the aldehyde C-H and phosphate oxo-moiety.[99]

For 2-substituted dienes, the divergent behavior of neutral *vs* cationic ruthenium(II) catalysts manifests as regioisomeric carbonyl addition pathways. 2-Propanol-mediated reductive couplings of 2substituted dienes with paraformaldehyde illustrate this effect (Scheme 9).[84,100–102] Whereas neutral ruthenium catalysts promote coupling at C3,[83] ruthenium catalysts with greater cationic character promote coupling at C2.[101] However, upon use of higher carbonyl partners, such as acetaldehyde (from ethanol), an erosion in C2-regioselectivity is observed.[102] As corroborated by deuterium labelling studies (not shown), the collective data suggest the following mechanistic interpretation. Diene hydroruthenation

at the less substituted olefin to form π-allyl **A** is kinetically preferred. For neutral ruthenium catalysts, this kinetic preference is preserved and C3 adducts are formed. In contrast, vacant coordination sites of cationic ruthenium complexes enable reversible diene hydroruthenation, allowing equilibration between π-allyl **A** and π-allyl **B**.[103] A Curtin-Hammett scenario becomes operative. For small aldehydes (R^1 = H), the transition state *en route* to C2-adducts is lower in energy. For larger aldehydes (R^1 = Me), formation of a more congested quaternary carbon stereocenter elevates the energetic barrier to carbonyl addition, eroding C2-regioselectivity.

Ruthenium(0) complexes derived from $Ru_3(CO)_{12}$ and tricyclohexylphosphine catalyze the reductive coupling of dienes with α-ketoesters from the α-hydroxy ester oxidation level *via* hydrogen auto-transfer (Scheme 10).[104] Butadiene, isoprene and myrcene deliver products of carbinol C-H (*Z*)-butenylation, prenylation and geranylation, respectively, as single regioisomers. A discrete mononuclear ruthenium(0) catalyst[105] initiates the catalytic cycle by diene-carbonyl oxidative coupling.[106,107] Transfer hydrogenolytic cleavage of the resulting oxaruthenacycle occurs through protonation at oxygen mediated by the α-hydroxy ester reactant followed by β-hydride elimination and C-H reductive elimination. This interpretation of the mechanism was corroborated by deuterium labelling studies. Upon use of deuterated *rac*-ethyl mandelate, the *n*-prenylated adduct incorporating deuterium exclusively at the *cis*-methyl group (^{2}H 50%) was obtained. Under nearly identical conditions, related diene reductive couplings to isatins were achieved from the 3-hydroxy-2-oxindole oxidation level *via* hydrogen auto-transfer.[108]

Heteroaromatic ketones with vicinal dicarbonyl character undergo ruthenium(0)-catalyzed diene-carbonyl reductive coupling mediated by 2-propanol (Scheme 11).[109] Alternatively, diene-carbonyl reductive coupling can be conducted from the secondary alcohol oxidation level *via* hydrogen autotransfer. The putative oxaruthenacycle intermediate was isolated and characterized by single crystal Xray diffraction. Remarkably, experiments involving diene exchange demonstrate reversible metallacycle formation.

As illustrated in formic acid-mediated reductive diene-dione [4+2] cycloadditions, πallylruthenium intermediates obtained upon diene-carbonyl oxidative coupling can be captured through intramolecular addition to the carbonyl moiety of a vicinal dione precursor (Scheme 12).[110–113] Cycloaddition is possible from dione, ketol (not shown) or diol oxidation levels. Given the greater tractability and abundance of 1,2-diols, a focus was placed on diene-dione [4+2] cycloadditions *via* hydrogen auto-transfer. Acyclic dienes react with cyclic or acyclic diols to form [4+2] cycloadducts bearing bridgehead diols with complete *syn*-diastereoselectivity. Similarly, in reactions of cyclohexadiene, cyclic or acyclic diols provide *syn*-configured cycloadducts with complete levels of *exo*selectivity.[112]

Using ruthenium(II) catalysts, 2-propanol-mediated reductive coupling of butadiene with the trimeric imine, dihydropyrrole, provides the branched product of addition in a completely regio- and *anti*-diastereoselective manner (Scheme 13).[114] In related reactions of 4-aminobutanol, hydrogen transfer from the primary alcohol triggers cyclocondensation to form the imine, dihydropyrrole. The resulting allylruthenium-imine pair undergoes stereospecific addition through a closed transition structure to deliver the branched adducts

with good to complete levels of *anti*-diastereoselectivity. Pyrrole itself can serve dually as reductant and imine proelectrophile to deliver identical products of addition. Other imines participate in ruthenium(II)-catalyzed diene reductive coupling mediated by 2propanol. For example, 1,3,5-*tris*(4-methoxyphenyl)-hexahydro-1,3,5-triazine, which undergoes thermal cycloreversion to generate formaldimines *in situ*, provides products of hydroaminomethylation as single regioisomers.[115] Additionally, iminoacetates engage in regioselective 2-propanol-mediated reductive coupling with dienes, albeit with modest levels of *anti*-diastereoselectivity.[116]

A single report of ruthenium(0)-catalyzed diene-imine reductive coupling via hydrogen autotransfer appears in the literature.[117] Using a ruthenium(0) catalyst derived from $Ru_3(CO)_{12}$ and triphos [$PhP(CH_2CH_2PPh_2)_2$], isoprene reacts with aryl substituted hydantoins to give products of *n*-prenylation as single regioisomers (Scheme 14). In this process, hydantoin dehydrogenation is followed by dieneimine oxidative coupling to furnish a transient aza-ruthenacycle. Transfer hydrogenolysis of the azaruthenacycle mediated by the hydantoin releases the product and regenerates the requisite imine to close the catalytic cycle.

2.3. Rhodium

Only two reports on rhodium catalyzed diene-carbonyl reductive coupling appear in the literature. In 2003, Krische described a reductive coupling of cyclohexadiene with α-ketoaldehydes mediated by hydrogen (Scheme 15).[118] In 2009, Kimura described a triethylborane-mediated dienealdehyde reductive coupling, which displayed good levels of regio- and *syn*-diastereoselectivity.[119]

2.4. Iridium

Under the conditions of iridium catalyzed transfer hydrogenation, 2-propanol-mediated reductive coupling of 1,3-cyclohexadiene with aryl aldehydes provide products of carbonyl cyclohexenylation in good yield with complete levels of diastereocontrol (Scheme 16).[120] Under nearly identical conditions, but in the absence of 2-propanol, 1,3-cyclohexadiene reductively couples to primary benzylic alcohols via hydrogen auto-transfer to furnish identical products with comparable levels of selectivity. In each case, small quantities of the regioisomeric γ,δ-unsaturated alcohols could be detected.

Cyclometalated π-allyliridium *C,O*-benzoates catalyze butadiene-aldehyde reductive coupling mediated by 1,4-butanediol[97] to furnish products of carbonyl crotylation.[121] Although enantioselective variants of this process were disclosed, diastereomeric mixtures were obtained (not shown). Under identical conditions, but in the absence of 1,4-butanediol, butadiene reductively couples to primary benzylic alcohols via hydrogen auto-transfer to furnish identical products with similar levels of selectivity.

Using an iridium catalyst modified by (*R*)-PhanePhos, 2-substituted dienes engage in reductive couplings to formaldehyde *via* methanol-mediated hydrogen auto-transfer (Scheme 18).[122] Notably, this process enables enantioselective formation of acyclic quaternary carbon stereocenters in the absence of stoichiometric byproducts.[123] Whereas the indicated reactions of formaldehyde display complete C2-regioselectivity, reactions of

higher aldehydes display complete C3-regioselectivity (not shown). The origins of regiodivergence were explored using deuterium labelling studies, which corroborate a CurtinHammett scenario wherein methanol dehydrogenation triggers rapid, reversible diene hydrometalation *en route* to regioisomeric allyliridium-carbonyl pairs. The energetic barrier to formaldehyde addition is lowest from the terminally disubstituted σ-allyliridium isomer. For higher aldehydes, the transition state energy for carbonyl addition at C2 increases due to greater steric congestion in formation of a quaternary carbon center. Hence, the 1,2-disubstituted allyliridium isomers become kinetically more reactive.

2.5. Titanium

A single study of titanium catalyzed diene-carbonyl reductive coupling was disclosed in 2005 by Moïse and Le Gendre (Scheme 19).[124] Using substoichiometric quantities of titanocene dichloride in combination with poly(methylhydrosiloxane) (PMHS) as terminal reductant, diene-aldehyde reductive coupling occurred with complete regioselectivity and modest levels of *anti*-diastereoselectivity. Entry into the catalytic cycle occurs through the reaction of titanocene dichloride with *n*-BuLi in the presence of PMHS to form a titanium hydride. Diene hydrometalation generates a nucleophilic allyltitanium(IV) species, which engages in aldehyde addition. σ-Bond metathesis of the resulting titanium alkoxide with PMHS delivers the crotylation product and regenerates the titanium hydride to close the catalytic cycle.

2.6. Copper

While the use of diene pronucleophiles in copper-catalyzed carbonyl reductive coupling is unknown, Malcolmson and co-workers recently demonstrated the viability of structurally related 2-azadienes (Scheme 20).[125] Specifically, using a chiral copper catalyzed modified by (*S*,*S*)-Ph-BPE and silane as terminal reductant, 2-azadienes reacts with aryl ketones to generate 1,2-amino alcohols in a highly regio- and enantioselectives fashion. Entry into the catalytic cycle involves the conversion of $Cu(OAc)_2$ to a copper(I) hydride. Hydrocupration of 2-azadiene delivers a nucleophilic azaallylcopper(I) species that undergoes ketone addition to form a copper(I) alkoxide, which upon σ-bond metathesis with the silane regenerates the copper hydride to close the catalytic cycle. Further imine reduction and cleavage of the silyl ether gives the benzhydryl-protected *anti*-1,2-amino alcohol products. More recently, the same authors successfully developed related 2-azadiene-imine reductive couplings to form differentially protected vicinal diamines with excellent control of diastereo- and enantioselectivity.[126]

3. Allene-C=X (X = O, NR) Reductive Coupling

3.1. Nickel

Nickel(0) complexes modified by carbene ligand-**IV** were reported by Jamison to catalyze the silane-mediated reductive coupling of chiral nonracemic 1,3-disubstituted allenes with aldehydes (Scheme 21).[127–129] The reaction mechanism is initiated by stereospecific allene-aldehyde oxidative coupling to form an oxanickelacycle. σ-Bond metathesis with silane forms an 1,3-*anti*-π-allylnickel hydride, which upon regio- and stereoselective C-H reductive elimination delivers the product of carbonyl reductive coupling with excellent

levels of axial-to-central chirality transfer and alkene (*Z*)stereoselectivity. In each case, small quantities of the isomeric homoallylic alcohols were formed.

3.2. Ruthenium

Phosphine-modified ruthenium(II) complexes bearing carbonyl ligands catalyze the 2-propanol-mediated reductive coupling of allenes to paraformaldehyde and higher aldehydes (Scheme 22).[130] The mechanism involves allene hydrometalation to form a nucleophilic allylruthenium species that undergoes aldehyde addition through a closed 6-centered transition structure. In reactions of *mono*substituted allenes, an appropriately defined allene substituent can enforce intervention of geometrically defined allylruthenium intermediates. For example, in 2-propanol-mediated reductive coupling of allenamides, stereospecific carbonyl addition occurs by way of the (*E*)-σ-allylruthenium haptomer to form vicinal *anti*-aminoalcohols as single diastereomers.[131] Primary alcohols can serve dually as reductant and aldehyde pronucleophile in reductive couplings with allenamides under the conditions of hydrogen auto-transfer.[132] Comparable levels of selectivity are observed from the aldehyde or alcohol oxidation level. In contrast, using 1,1-disubstituted allenes, high levels of *anti*diastereoselectivity are only evident in reactions conducted from the alcohol oxidation level.[133] Furthermore, diastereoselectivities are highly concentration dependent and at lower concentrations higher diastereoselectivities are observed. A Curtin-Hammett scenario appears to be operative. As carbonyl addition is hindered sterically due to the formation of a quaternary carbon stereocenter, it is turn-over limiting. The transition state energy for carbonyl addition from the (*E*)-σ-allylruthenium haptomer, which leads to the *anti*-diastereomer, is lower than that from the corresponding (Z)-isomer, which provides the *syn*-diastereomer. At lower concentrations, equilibration of the transient (*E*)- and (*Z*)σ-allylruthenium isomers is fast with respective to carbonyl addition, allowing the (*E*)-isomer to be replenished.

The formation of highly congested CF_3-bearing quaternary carbon stereocenters is achieved upon ruthenium(II) catalyzed reductive coupling of CF_3-allenes with paraformaldehyde mediated by 2propanol (Scheme 23).[134] Formate esters, which are cleaved upon isolation, appear as minor reaction products, suggesting paraformaldehyde contributes to some extent as a terminal reductant. Under similar conditions, allene-aldehyde reductive coupling can be achieved using fluorinated alcohols as reductants and proelectrophiles.[135] This capability is significant as the corresponding fluorinated aldehydes are highly intractable and, in many cases, are not commercially available. As dehydrogenation of fluorinated alcohols is significantly more endothermic than the corresponding aliphatic alcohols,[136,137] reactions of monofluoro-, difluoro- and trifluoroethanol become increasingly inefficient.

The ability to exploit alkynes as latent allenes[138] has expanded the scope of ruthenium catalyzed allene-aldehyde reductive coupling (Scheme 24).[139–141] Using a cationic ruthenium catalyst generated upon the acid-base reaction of $H_2Ru(CO)(PPh_3)_3$ and 2,4,6-(2-$Pr)_3PhSO_3H$, two discrete catalytic processes are enacted: (a) alkyne-to-allene isomerization and (b) allene-carbonyl reductive coupling via hydrogen auto-transfer. The cationic ruthenium(II) exists in equilibrium with a zero-valent ruthenium that promotes allene-aldehyde oxidative coupling. The resulting oxaruthenacycle ultimately provides the (*Z*)-

homoallylic alcohol.[139] The introduction of iodide and ligand-**V** (Josiphos SL-J009–1) enables suppression of oxidative coupling pathways. With these subtle changes, alkyne-to-allene isomerization pathways persist, however, the allene undergoes hydrometalation to form a nucleophilic allylruthenium species. Carbonyl addition by way of a closed transition structure provides the branched homoallylic alcohols with exceptional levels of *anti*-diastereo- and enantioselectivity.[140] The ruthenium(II) complex derived from HClRu(CO)$(PPh_3)_3$ and dippf, bis(diisopropylphosphino)ferrocene, catalyzes conversion of acetylenic pyrroles to allenes, which participate in allene-aldehyde reductive coupling via hydrogen auto-transfer.[141] The products, protected vicinal aminoalcohols, are generated with complete regio- and *anti*-diastereoselectivity.

Only one study on ruthenium catalyzed allene-imine reductive coupling appears in the literature. Using a ruthenium(II) catalyzed modified by the chelating phosphine ligand 1,2bis(dicyclohexylphosphino)ethane (dCype), 1,1-disubstituted allenes and formaldimines engage in 2propanol-mediated reductive coupling to form homoallylic amines with complete branched regioselectivity (Scheme 25).[142] The formaldimines are generated *in situ* through cycloreversion of PMPprotected hexahydro-1,3,5-triazines. This process represents a method for the hydroaminomethylation of π-unsaturated reactants beyond classical hydroformylation/reductive amination.

3.3. Iridium

In 2007, Krische reported the first allene-aldehyde reductive coupling catalyzed by iridium (Scheme 26).[143] Specifically, hydrogenation of dimethyl allene in the presence of activated aldehydes provided the products of carbonyl *tert*-prenylation with complete branched regioselectivity. Under an atmosphere of deuterium, deuterium is incorporated exclusively at the interior vinylic position (80% ^2H). This result is consistent with a catalytic mechanism involving allene-aldehyde oxidative coupling, however, hydrometalative pathways involving allyliridium species cannot be excluded on the basis of this data alone. Shortly thereafter, related allene-aldehyde reductive couplings mediated by 2-propanol and hydrogen auto-transfer were demonstrated.[144] Using d_8-isopropanol as reductant, the indicated product of *tert*-prenylation incorporates deuterium predominantly at the internal vinylic position (85% ^2H). A similar pattern of deuterium incorporation is observed in hydrogen auto-transfer reactions of $d_2$benzyl alcohol, corroborating its dual role as reductant and carbonyl proelectrophile.

The cyclometalated π-allyliridium *C,O*-benzoate complex modified by (S)-SEGPHOS catalyzes the regio- and enantioselective reductive coupling of dimethylallene with aldehydes mediated by 2-propanol (Scheme 27).[145,146] Aliphatic, α,β-unsaturated and aromatic aldehydes are converted to the products of carbonyl *tert*-prenylation with uniformly high levels of selectivity. Under the conditions of hydrogen auto-transfer, primary alcohols are converted to an identical set of products with similar levels of selectivity. This process represents a departure from the longstanding use of stoichiometric organometallic reagents in enantioselective carbonyl *tert*-prenylation.[147]

The cyclometalated π-allyliridium *C,O*-benzoate complex modified by DPPF catalyzes allene- formaldehyde reductive coupling via methanol-mediated hydrogen autotransfer

(Scheme 28).[148] This process enables direct, byproduct-free coupling of methanol, an abundant feedstock (35 million metric tons per year), to form highly congested quaternary carbon stereocenters. Using an iridium catalyst modified by (*R*)-PhanePhos, CF_3-allenes react with methanol to form homoallylic alcohols with CF_3-bearing quaternary carbon stereocenters with high levels of regio- and enantioselectivity.[149] Such congested acyclic quaternary carbon stereocenters are exceptionally difficult to prepare in enantiomerically enriched form, with existing protocols for their construction largely restricted to conjugate additions to β,β-disubstituted CF_3-enones and nitroolefins.[123]

3.4. Palladium

In 2000, a palladium(0) catalyzed allene-aldehyde reductive coupling mediated by tin(II) chloride was reported by Cheng (Scheme 29).[150] Using dimethylallene, products of *tert*-prenylation were formed with complete regioselectivity. Additionally, monosubstituted allenes provided branched adducts with complete *anti*-diastereoselectivity. The authors propose the reaction proceeds through palladium catalyzed allene hydrostannylation to furnish an allylstannane that undergoes spontaneous aldehyde addition through a six-member chair-like transition state.

In 2015, a palladium(0)-catalyzed allene-anhydride reductive coupling mediated by silane was reported by Tsuiji and Fujihara (Scheme 30).[151] The catalytic cycle is initiated by anhydride oxidation addition to form an acylpalladium(II) species, which upon allene carbopalladation forms a πallylpalladium intermediate. Silane-mediated hydride transfer to palladium followed by C-H reductive elimination delivers the reductive coupling product and returns palladium to its zero-valent form. The reaction products form as single regioisomers, albeit with incomplete control of alkene geometry. This method provides an alternative to the use of aldehydes as acyl donors in allene hydroacylation.[152]

3.5. Copper

In 2018, Buchwald reported an enantioselective copper(I)-catalyzed allene-ketone reductive coupling mediated by silane (Scheme 31).[153] Using a copper complex modified by ligand-**VI**, a wide range of methyl ketones were converted to the tertiary homoallylic alcohols with moderate to good levels of *anti*-diastereo- and enantioselectivity. The highest stereoselectivities were observed for allenes bearing branched alkyl substituents. The catalytic mechanism is postulated to involve allene hydrocupration to form a nucleophilic allylcopper(I) species. Ketone addition generates a copper(I) alkoxide, which upon σbond metathesis with silane delivers the homoallylic silyl ether (hydrolyzed upon isolation) and copper(I) hydride to close the catalytic cycle.

In an earlier report (2016) by the same author, closely related conditions for copper-catalyzed allene-imine reductive coupling were described (Scheme 32).[154] Remarkably, regiodivergent reductive coupling to form either branched or linear adducts was observed in response to the choice of nitrogen protecting group. The origins of this regiodivergence were probed using DFT calculations. Irreversible allene hydrocupration provides a primary σ-allylcopper intermediate. For the phosphinoyl imine, the phosphinoyl oxygen binds to the copper center in the transition state and allyl transfer provides the linear product. In contrast,

for *N*-benzyl imines, the nitrogen atom coordinates the copper center causing imine addition to occur with allylic inversion to furnish the branched product.

4. Enyne-C=X (X = O, NR) Reductive Coupling

4.1. Nickel

In 2004, Jamison reported an intermolecular nickel(0)-catalyzed enyne-aldehyde reductive coupling mediated by triethylborane (Scheme 33).[155] High levels of regioselectivity in favor of C-C coupling at the acetylenic terminus of the enyne were accompanied by complete control of alkene geometry. Subsequent attempts to develop enantioselective variants of this process proved challenging. Using the monodentate *P*-chiral ferrocenyl phosphine ligand-**VII**, moderate levels of asymmetric induction were observed.[156] Remarkably, under closely related reductive coupling conditions using the *P*-chiral ligand-**VIII**, unactivated ketones were competent electrophilic partners.[157] Again, high levels of regioselectivity in favor of coupling at the acetylenic terminus were accompanied by complete control of alkene geometry and moderate enantioselectivities.

Computational studies by Houk[158] and experimental studies by Montgomery,[159] who observed a ligand-dependent inversion of regioselectivity, illuminate the origins of regioselectivity in enynealdehyde reductive coupling (Scheme 34). The collective data are consistent with the following interpretation. An oxidative coupling mechanism is operative in which an electronic bias for coupling at the acetylenic terminus is observed.[160] For the large ligand-**IX**, this intrinsic bias is accentuated due to increased steric interactions between the ligand and the substituent at the acetylenic terminus. Hence, the substituent at the acetylenic terminus prefers to be placed distal to the metal center in the oxanickelacycle. Upon use of the smaller ligand-**I**, steric repulsion between the aldehyde and acetylenic substituents is greater than steric repulsion between the ligand and acetylenic substituent, which results in an inversion in regioselectivity.

4.2. Rhodium

Highly enantioselective and byproduct-free enyne-carbonyl reductive coupling is achieved under the conditions of catalytic hydrogenation using chiral rhodium complexes modified by ligand-**X** or ligand**XI** (Scheme 35).[161–163] Activated carbonyl compounds, such as glyoxalates[161] and pyruvates,[162] are required. The resulting dienyl alcohols form as single regioisomers with excellent levels of enantiomeric enrichment and, remarkably, conventional hydrogenation of the diene-containing products is not observed. This result can be explained as follows. The enyne reactant is a stronger **π**-acid than the diene product. Hence, once the carbonyl electrophile is fully consumed, excess enyne preferentially binds rhodium(I), retarding the rate of product hydrogenation. Beyond vicinal dicarbonyl electrophiles, certain heterocyclic aromatic aldehydes and ketones undergo reductive coupling with enyne pronucleophiles under hydrogenation conditions.[163] Again, the resulting heteroaryl substituted secondary and tertiary dienyl alcohols are generated as single regioisomers in highly enantiomerically enriched form (Scheme 35).

A mechanism for hydrogen-mediated enyne-carbonyl reductive coupling has been proposed and is supported by computational studies (Scheme 36).[164,165] The catalytic cycle is initiated by alkyne-C=O oxidative coupling. Direct hydrogenolysis of the oxarhodacyclopentene by σ-bond metathesis with hydrogen through the 4-centered transition structure **A** is slow compared to metallacycle protonolysis by the carboxylic acid cocatalyst through the 6-centered transition structure **B**. The resulting rhodium carboxylate engages hydrogen in σ-bond metathesis through the 6-centered transition structure **C** to form an alkenylrhodium hydride, which upon C-H reductive elimination releases product and rhodium(I). Cationic rhodium complexes are essential, as these square planar non-contact ion pairs offer an additional coordination site, enabling simultaneous binding of enyne and carbonyl reactants. Additionally, unlike neutral rhodium complexes, the cationic complexes are slow to engage in hydrogen oxidative addition.[166] These two factors act in concert to promote alkyne-C=O oxidative coupling pathways.

Rhodium catalyzed hydrogenation of 1,3-enynes in the presence of ethyl (*N*-*tert*butanesulfinyl)iminoacetate results in reductive coupling to furnish diene-containing α-amino acid esters (Scheme 37).[167] Coupling occurs in a completely regioselective manner at the acetylenic terminus of the enyne. Additionally, the nitrogen-bearing stereogenic center of the product is formed as a single diastereomer. Under an atmosphere of elemental deuterium, reductive coupling occurs with incorporation of a single deuterium atom at the former 2-position of the enyne, which is consistent with a mechanism involving enyne-imine oxidative coupling followed by hydrogenolytic cleavage of the resulting metallacycle.

4.3. Ruthenium

The first enyne-mediated carbonyl propargylations were reported by Krische in 2008, who used a ruthenium(II) complex modified by dppf [*bis*(diphenylphosphino)ferrocene] to catalyze 2-propanolmediated enyne-aldehyde reductive coupling (Scheme 38).[168] In these reactions, enyne hydrometalation delivers a nucleophilic allenylruthenium species that undergoes aldehyde addition. The stoichiometric reaction of $HClRu(CO)(PPh_3)_3$ with enynes to form σ-allenylruthenium complexes, which were characterized by single crystal X-ray diffraction, has been reported.[169] Under these conditions, primary alcohols react with enynes to form products of carbonyl propargylation via hydrogen auto-transfer. The pattern of deuterium incorporation in isotopic labelling studies using α,α-d_2-benzyl alcohol corroborate reversible and non-regioselective enyne hydroruthenation in advance of carbonyl addition. Deuterium is completely retained at the carbinol methine, suggesting the product is kinetically inert with respect to dehydrogenation due to internal alkyne coordination to ruthenium. It was later found that good to complete levels of *anti*-diastereoselectivity could be achieved in 2-propanol-mediated enyne-aldehyde reductive couplings using the indicated 2-propoxy-substituted enyne.[170] Finally, (*R*)-BINAP-modified ruthenium complexes were shown to catalyze highly enantioselective 2-propanol-mediated enynealdehyde reductive couplings.[171] Secondary homopropargyl alcohols bearing gem-dimethyl groups were obtained with uniformly high levels of enantioselectivity. Under these conditions, reductive coupling also could be achieved via hydrogen auto-transfer from aliphatic, allylic and benzylic alcohols. These processes represent an alternative to the use of preformed allenylmetal reagents in enantioselective carbonyl propargylation.[172]

4.4. Iridium

The sole examples of iridium catalyzed enyne-carbonyl reductive coupling were reported by Krische in 2012 (Scheme 39).[173] Using an iridium(I) catalyst in combination with commercially available SEGPHOS or DM-SEGPHOS ligands, aldehydes are subject to highly *anti*-diastereo- and enantioselective formic acid mediated propargylation. These transformations proceed via enyne hydrometalation to form an allenyl-iridium(I) species, which engages the aldehyde in addition through a closed six-centered transition state. Enyne-mediated propargylation from the alcohol oxidation level via hydrogen autotransfer displayed higher levels of *anti*-diastereo- and enantioselectivity. Deuterium labelling studies corroborate reversible, non-regioselective enyne hydrometalation in advance of carbonyl addition. Complete retention of deuterium at the carbonyl methine suggests the reaction products are inert with respect to dehydrogenation.

4.5. Copper

Recently, the first copper-catalyzed enyne-carbonyl reductive couplings were reported by Buchwald (Scheme 40).[174] Using a copper complex modified by the chiral bidentate phosphine ligand (*S*,*S*)-Ph-BPE and $(MeO)_2MeSiH$ as terminal reductant, diverse ketones were converted to tertiary homopropagyl alcohols with good levels of *syn*-diastereo- and enantioselectivity. Aryl-methyl ketones underwent propargylation with highest levels of stereocontrol. Notably, the reaction could be run efficiently on 50 mmol scale with catalyst loadings as low as 0.2 mol%. A catalytic mechanism involving enyne hydrocupration to generate an allenylcopper(I) nucleophile is postulated. Ketone addition then generates a copper(I) alkoxide, which upon σ-bond metathesis regenerates the copper(I) hydride to close the catalytic cycle.

5. Applications in Natural Product Synthesis

Although enantioselective carbonyl reductive couplings have only recently been developed, applications in natural product total synthesis have begun to emerge. Krische and coworkers prepared bryostatin 7[175] and related *seco*-B-ring analogues (not shown)[176,177] using enyne-carbonyl[178] and allenecarbonyl[179] reductive couplings (Scheme 41). To construct the bryostatin C-ring, a rhodium-catalyzed hydrogen-mediated enyne-α-ketoaldehyde reductive coupling forms the C20-C21 bond with control of the C20 carbinol stereochemistry and the C21 alkene geometry. The neopentyl carbinol motif of the bryostatin A-ring is generated through iridium-catalyzed reductive coupling of dimethyl allene with the indicated aldehyde using 2-propanol as terminal reductant. Using these hydrogenative and transferhydrogenative methods, the total synthesis of bryostatin 7 was achieved in fewer steps than any prior synthesis of a bryostatin family member.

The triene-containing C17-benzene ansamycins, trienomycins A and F,[180] and 6deoxyerythronolide B[181] were prepared by Krische and coworkers *via* ruthenium-catalyzed *syn*diastereo- and enantioselective diene-carbonyl reductive coupling mediated by hydrogen auto-transfer (Scheme 42). For trienomycins A and F, a ruthenium catalyst modified by DM-SEGPHOS is used to react the indicated trisubstituted (*Z*)-allylic alcohol with a 2-trialkylsilyl substituted diene to form the product of carbonyl *syn*-crotylation. The ability to

conduct carbonyl crotylation from the alcohol oxidative level avoids the use of the (*Z*)-enal, which is prone to geometrical isomerization. For the synthesis of deoxyerythronolide B, a ruthenium catalyst modified by SEGPHOS and a chiral phosphate counterion (previously indicated in Scheme 8) enabled direct use of butadiene itself as a crotyl donor.

Menche and coworkers prepared the C8-C22 substructure of the actin-binding macrodiolide rhizopodin using an enantioselective iridium-catalyzed dimethyl allene-aldehyde reductive coupling under the conditions of alcohol-mediated hydrogen auto-transfer (Scheme 43).[182,183] The reaction, which forms the C16-carbinol stereocenter, was conducted on multi-gram scale to furnish the product of *tert*prenylation in 98% yield. Chromatographic purification of the cyclometalated π-allyliridium catalyst (depicted in Scheme 41) led to an improvement in enantiomeric excess from 82% to 90% ee.[183]

6. Conclusion and Outlook

Carbonyl and imine addition mediated by premetalated reagents has played a central role in chemical synthesis since the inception of Organic Chemistry as a field. However, the requisite organometallic reagents often pose issues of safety, selectivity, cost and waste. Metal catalyzed reductive coupling has emerged as an alternative to stoichiometric organometallic reagents in classical carbonyl and imine additions, but many important challenges remain. For example, many reductive couplings require pyrophoric (Et_3B) or expensive/mass-intensive (R_3SiH) terminal reductants. It would be preferable to exploit safe, inexpensive terminal reductants with low molecular weights, such as 2-propanol or H_2. Perhaps most ideal are reductive couplings mediated by hydrogen auto-transfer, which altogether preclude the use of an exogenous terminal reductant (Scheme 44). Another major challenge involves the development of catalysts for the reductive coupling of ethylene and α-olefins,[48] which are abundant feedstocks with production volumes exceeded only by alkanes. Late transition metals will likely be the key to unlock these unmet challenges, as their low oxaphilicity enables chemoselective reduction of π-unsaturated pronucleophiles in the presence of carbonyl and imine electrophiles. It is the authors' hope that the collective efforts presented in this monograph will encourage future research toward catalytic carbonyl additions beyond stoichiometric metals.

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Biography

Professor Michael J. Krische obtained a B.S. degree in Chemistry from the University of California at Berkeley (1989), where he performed research with Professor Henry Rapoport. After a year abroad as a Fulbright Fellow, he initiated doctoral studies at Stanford University with Professor Barry Trost as a Veatch Graduate Fellow. Following receipt of his Ph.D. degree (1996), he joined the laboratory of Professor Jean-Marie Lehn at the Université Louis Pasteur as an NIH Post-Doctoral Fellow. In 1999, he joined the faculty at the University of Texas at Austin. He was promoted directly to the rank of full professor (2004) and shortly

thereafter appointed the Robert A. Welch Chair in Science (2007). Professor Krische has pioneered a new class of C-C bond formations that merge the characteristics of carbonyl addition and catalytic hydrogenation. Professor Krische's research has garnered numerous awards, including the NSF-CAREER Award (2000), Cottrell Scholar Award (2002), Eli Lilly Granteeship for Untenured Faculty (2002), Frasch Award in Chemistry (2002), Dreyfus Teacher-Scholar Award (2003), Sloan Fellowship (2003), Johnson & Johnson Focused Giving Award (2005), Solvias Ligand Prize (2006), Presidential Green Chemistry Award (2007), ACS Corey Award (2007), Dowpharma Prize (2007), Novartis Lectureship (2008), Tetrahedron Young Investigator Award (2009), Humboldt Senior Research Award (2009–2011), Mukaiyama Award (2010), Glaxo-Smith-Kline Scholar Award (2011), ACS Cope Scholar Award (2012), and JSPS Fellow (2013), Eun Lee Lectureship, Korea (2015), Royal Society of Chemistry, Pedlar Award (2015), AAAS Fellow (2017).

Leyah A. Schwartz obtained a B.S. degree in chemistry from the University of Alabama at Birmingham in 2016, where she conducted undergraduate research in the laboratory of Professor Pengfei Wang. In Fall 2016, she entered the doctoral degree program at the University of Texas at Austin in the laboratory of Professor Michael J. Krische, where she is developing enantioselective alcohol-mediated iridiumcatalyzed reductive couplings of allene pronucleophiles.

Michael Holmes obtained a B.S. degree in Chemistry and Mathematics from the University of Canterbury in 2010 where he performed research in the laboratory of Professor Owen Curnow. He initiated doctoral studies under the supervision of Professor Robert Britton at Simon Fraser University in 2011, where he developed methods for the construction of tetrahydrofuranol containing natural products. Following receipt of his Ph.D. degree in 2016, he joined the laboratory of Professor Michael J. Krische at the University of Texas at Austin as an Eli Lilly postdoctoral fellow, where he is developing enantioselective alcohol-mediated iridium-catalyzed reductive couplings of allene pronucleophiles.

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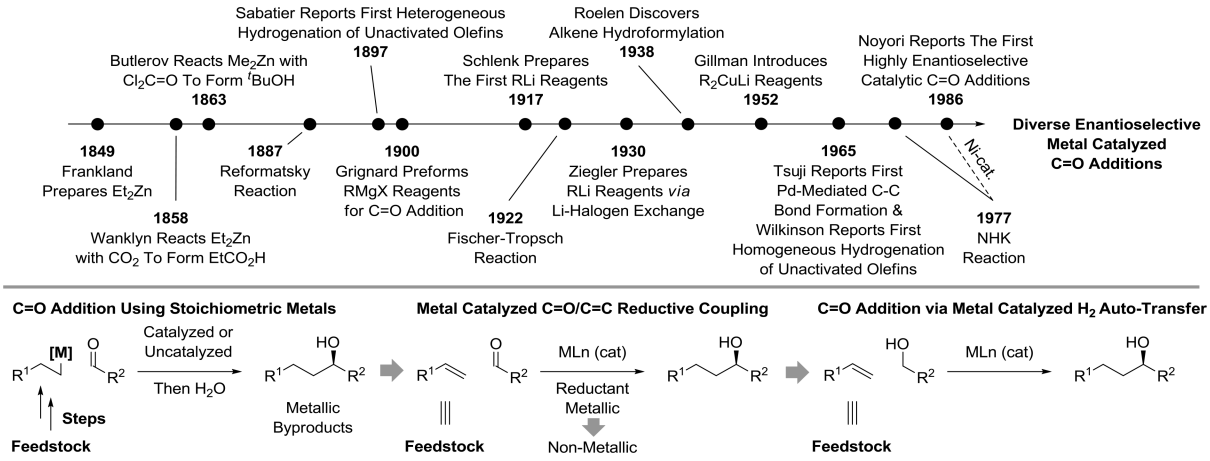
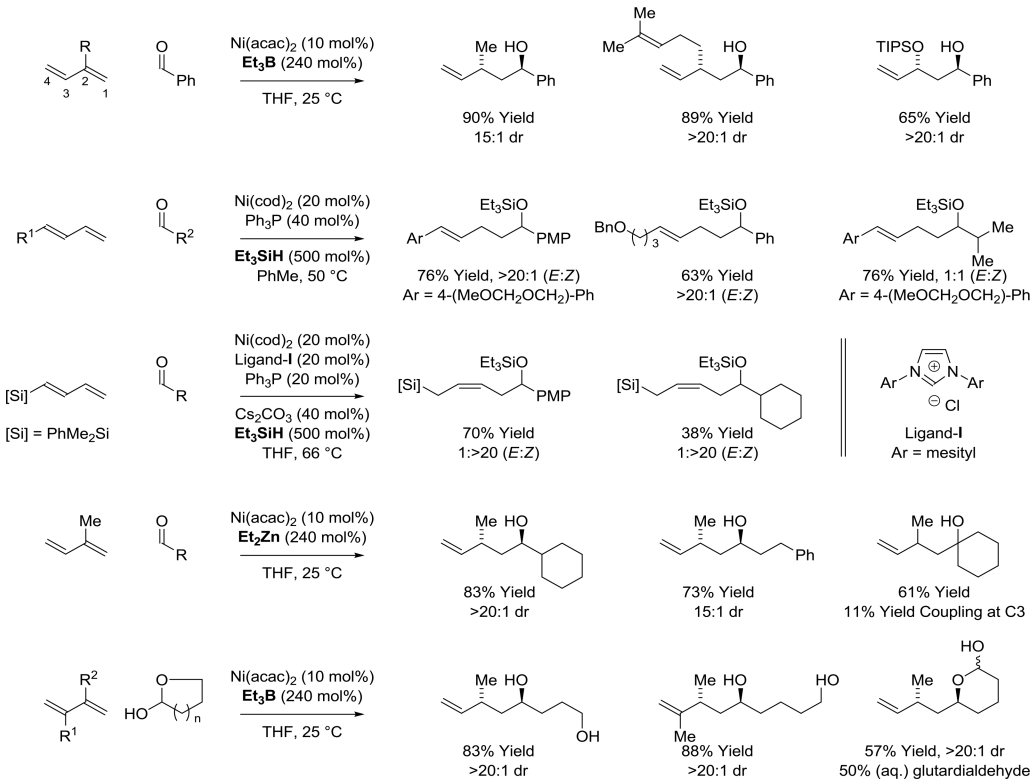


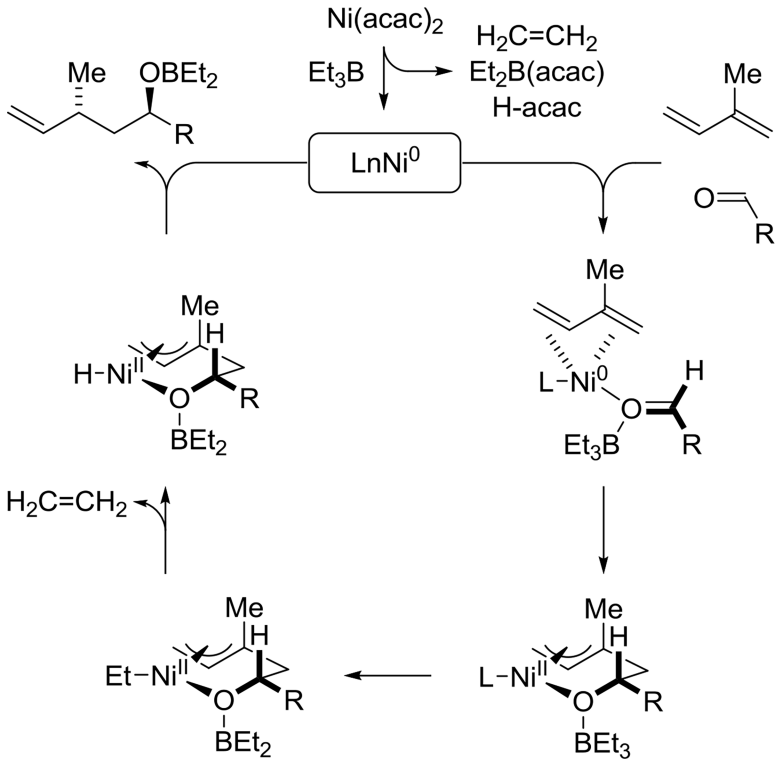
Figure 1.

Selected milestones in organometallic and carbonyl addition chemistry.

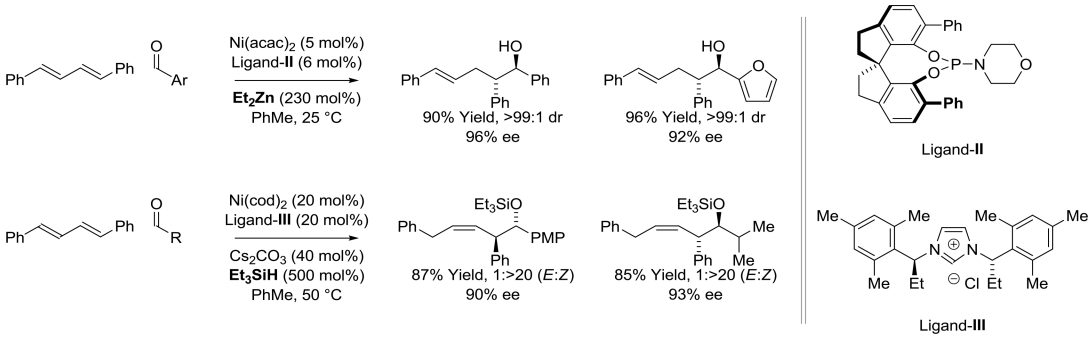


Scheme 1.

Nickel(0)-catalyzed diene-aldehyde reductive coupling

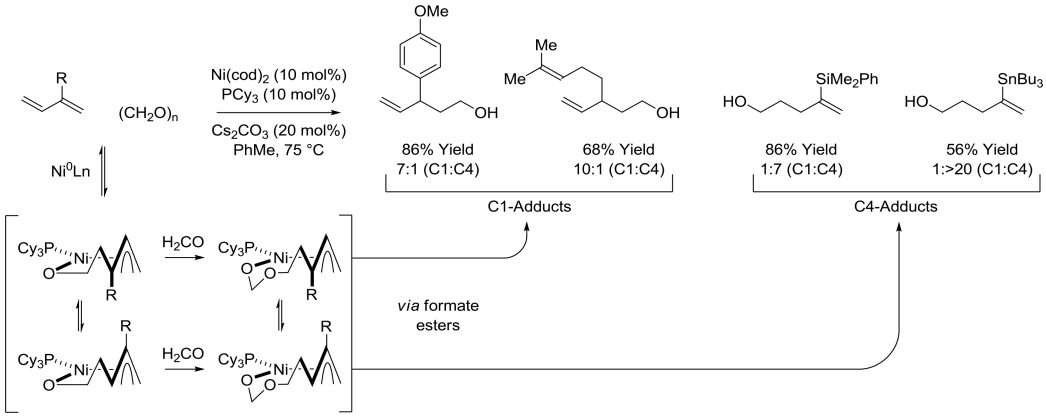


Scheme 2.
Catalytic mechanism for nickel(0)-catalyzed diene-aldehyde reductive coupling



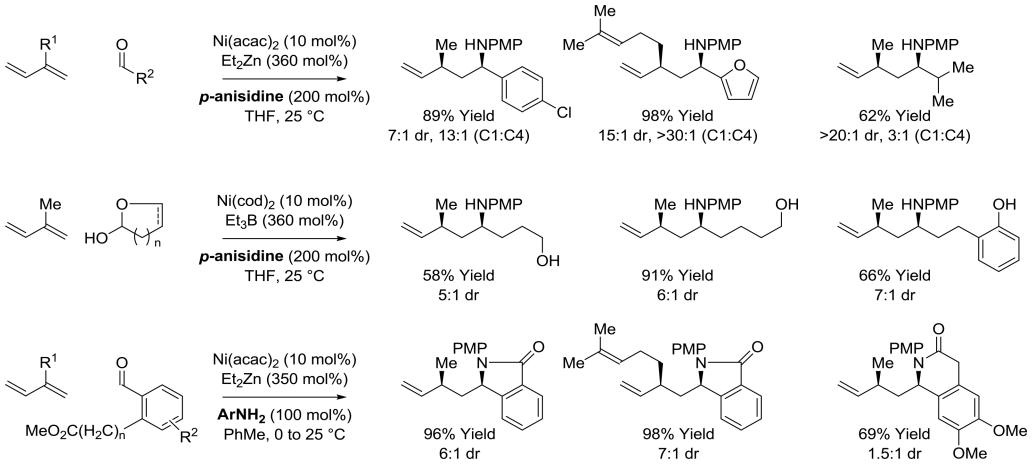
Scheme 3.

Enantioselective nickel(0)-catalyzed diene-aldehyde reductive couplings



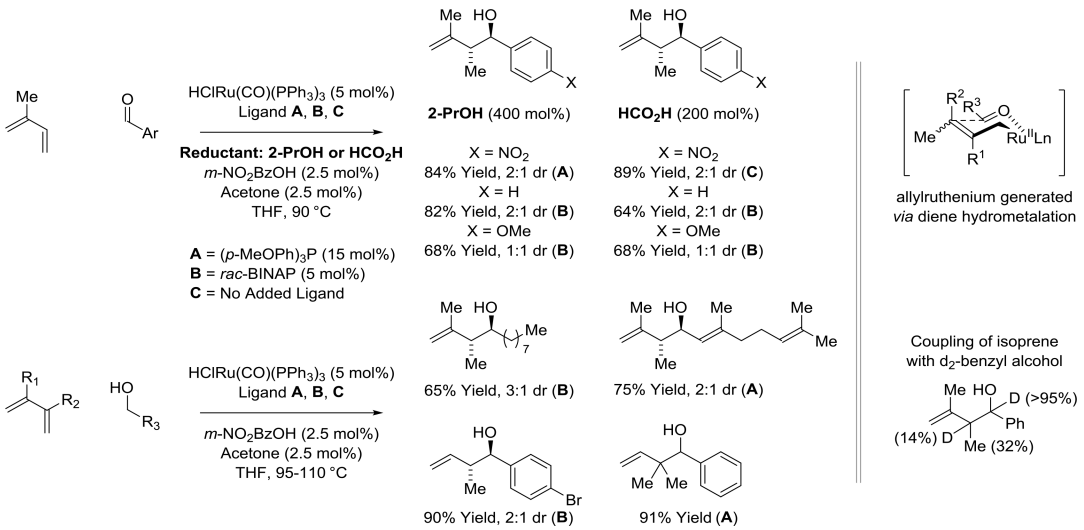
Scheme 4.

Formaldehyde as electrophile and reductant in nickel(0)-catalyzed reductive couplings to 2substituted dienes



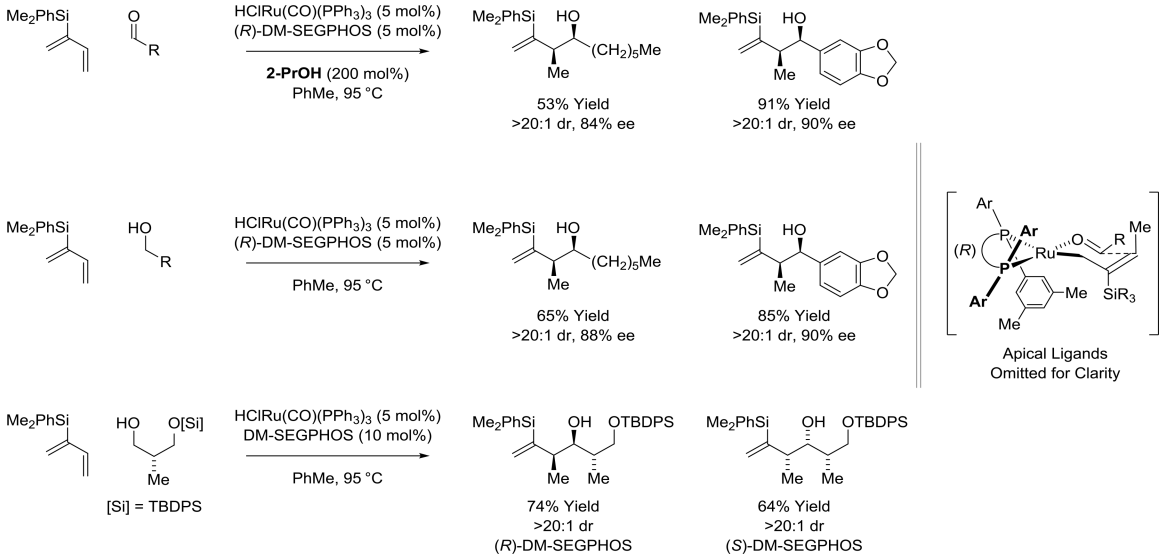
Scheme 5.

Nickel(0)-catalyzed diene-imine reductive couplings



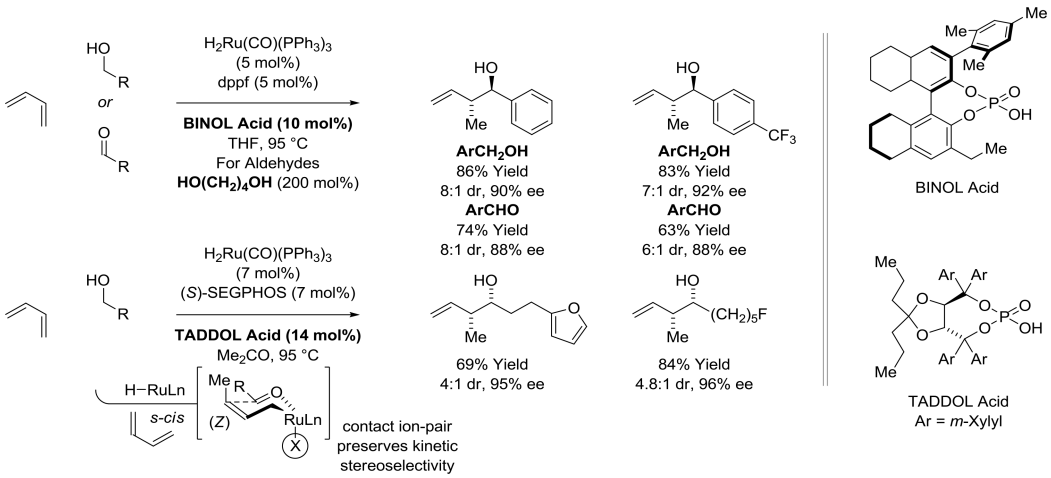
Scheme 6.

Ruthenium(II)-catalyzed diene-aldehyde reductive couplings mediated by 2-propanol, formic acid or hydrogen auto-transfer



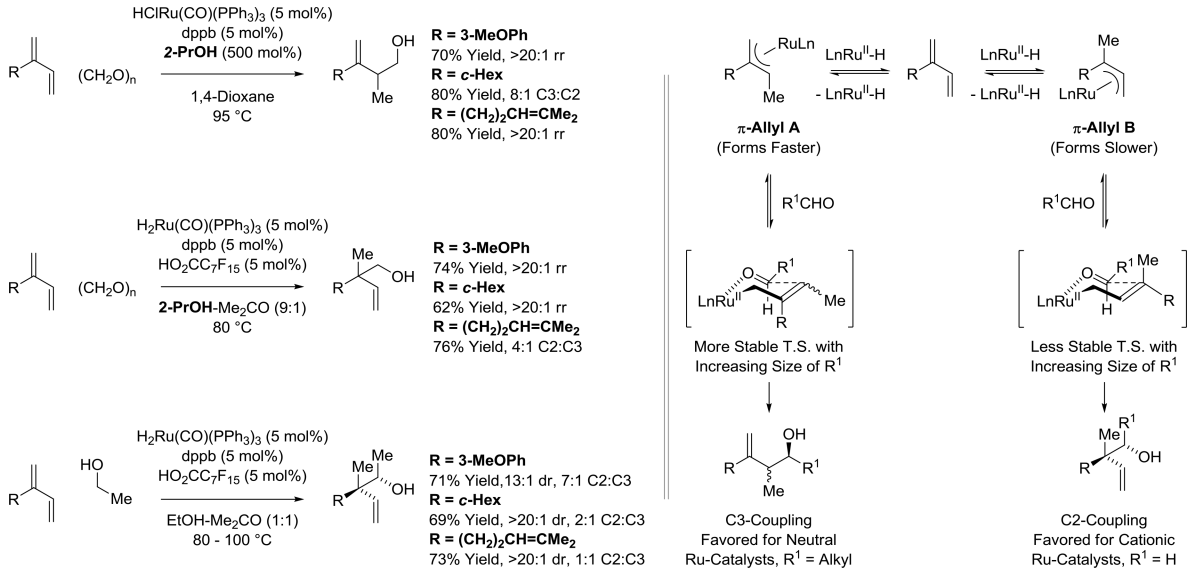
Scheme 7.

syn-Diastereo- and enantioselective ruthenium(II)-catalyzed reductive coupling of aldehydes with 2-trialkylsilyl substituted dienes mediated by 2-propanol or hydrogen auto-transfer



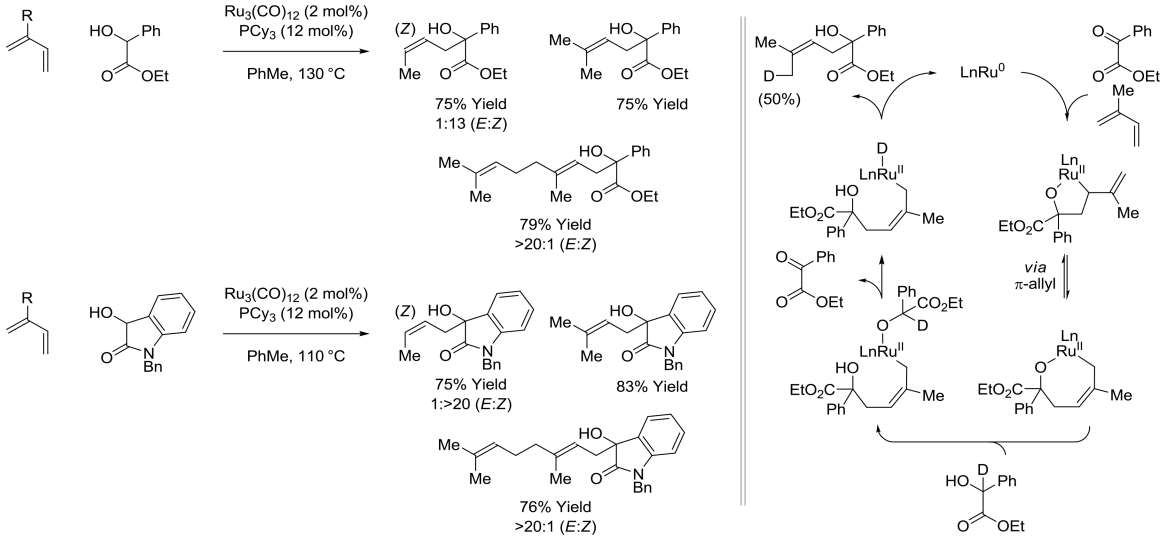
Scheme 8.

Divergent diastereoselectivity in asymmetric ruthenium(II)-catalyzed butadiene-aldehyde reductive couplings



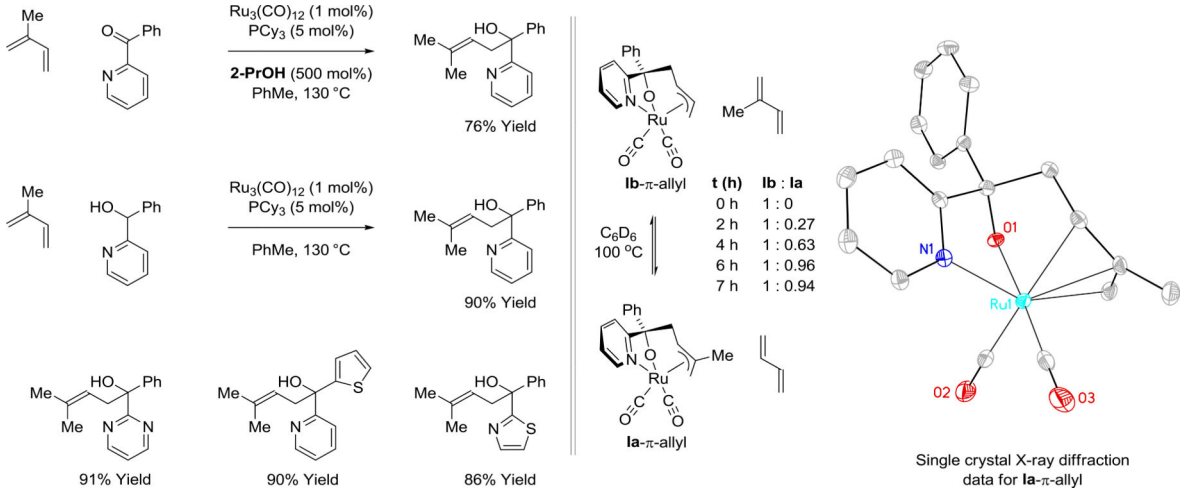
Scheme 9.

Divergent regioselectivity in ruthenium(II)-catalyzed diene-carbonyl reductive couplings



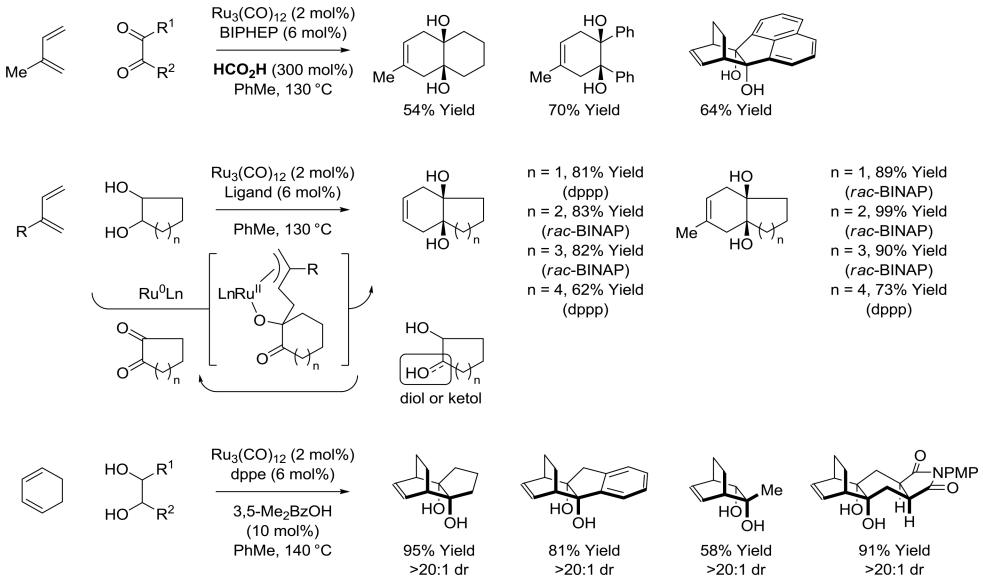
Scheme 10.

Ruthenium(0)-catalyzed diene-ketone reductive coupling *via* hydrogen auto-transfer



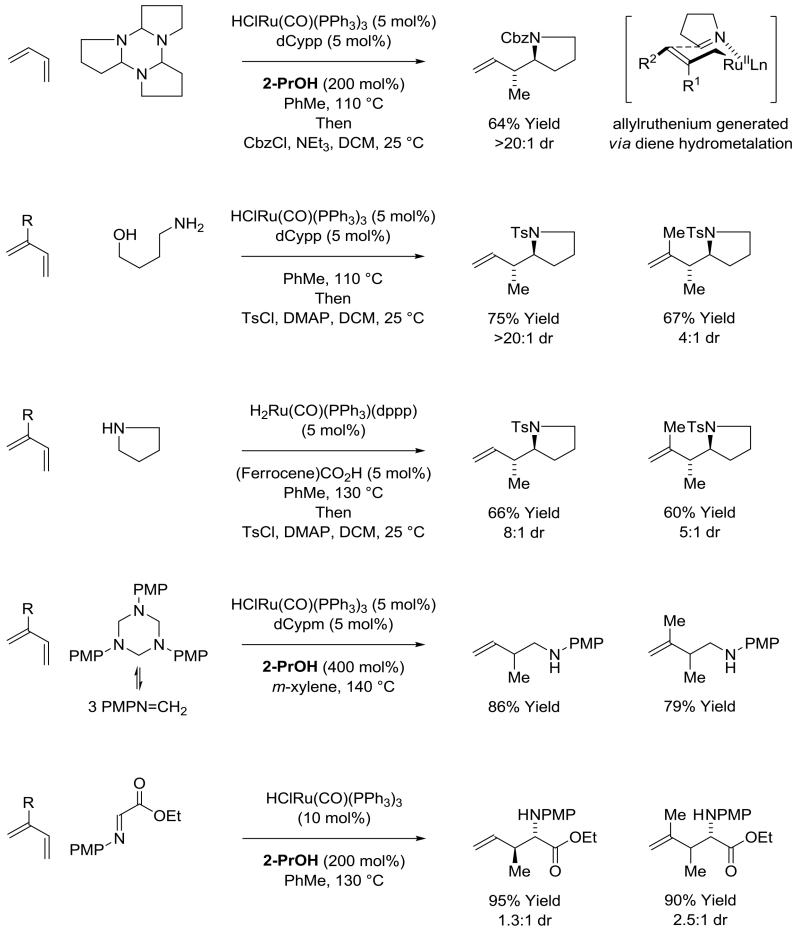
Scheme 11.

Reversible oxidative coupling pathways in ruthenium(0)-catalyzed diene-ketone reductive coupling



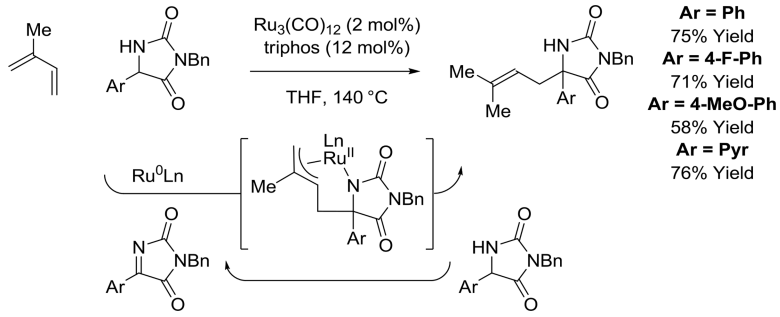
Scheme 12.

Ruthenium(0)-catalyzed diene-dione reductive coupling resulting in [4+2] cycloaddition



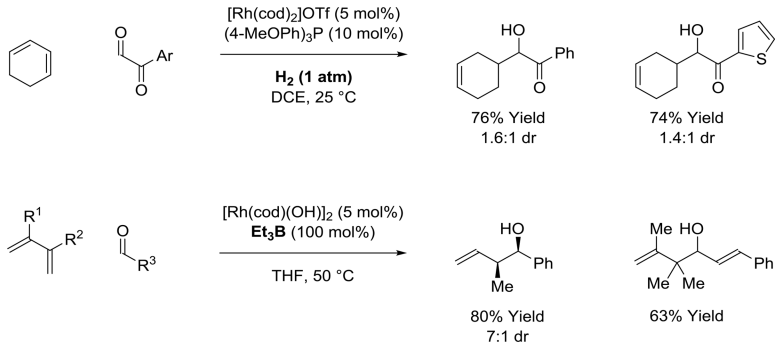
Scheme 13.

Ruthenium(II)-catalyzed diene-imine reductive coupling mediated by 2-propanol or hydrogen auto-transfer



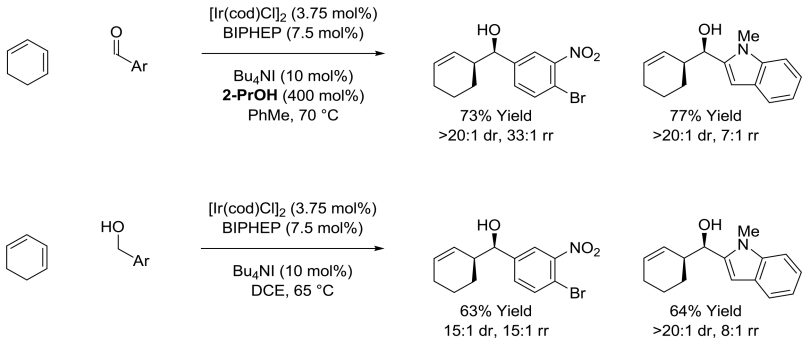
Scheme 14.

Ruthenium(0)-catalyzed diene-imine reductive coupling via hydrogen auto-transfer



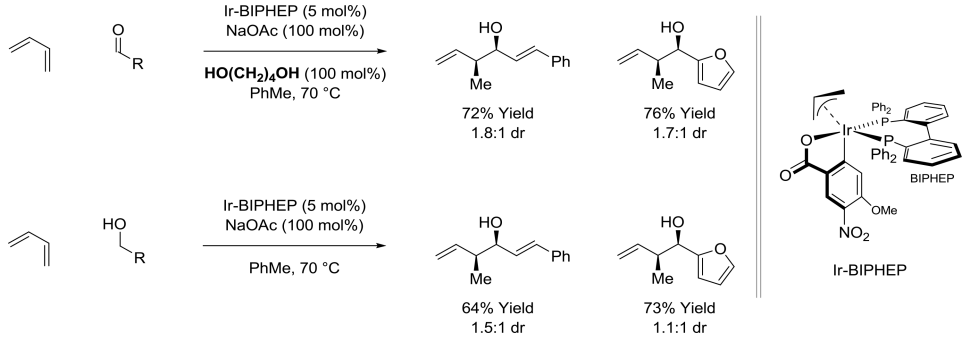
Scheme 15.

Rhodium(I)-catalyzed diene-carbonyl reductive couplings mediated by hydrogen and triethylborane



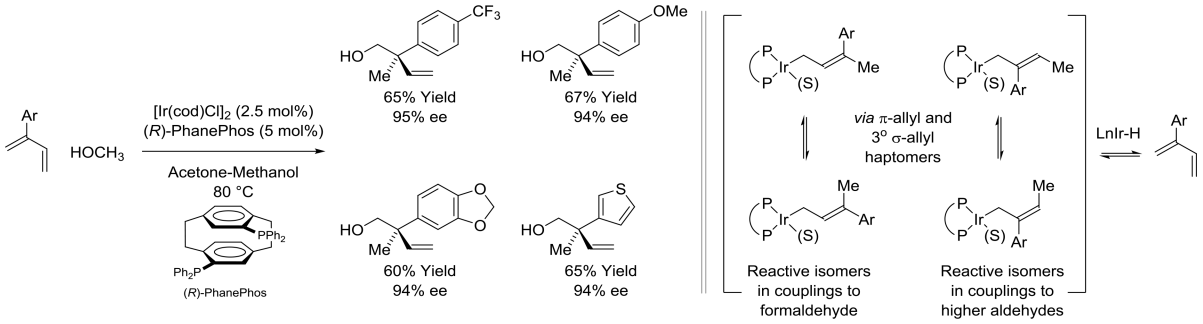
Scheme 16.

Iridium(I)-catalyzed cyclohexadiene-aldehyde reductive coupling mediated by 2-propanol or hydrogen auto-transfer



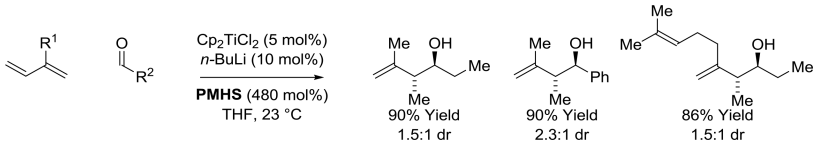
Scheme 17.

Iridium(I)-catalyzed butadiene-aldehyde reductive coupling mediated by 1,4-butanediol or hydrogen auto-transfer



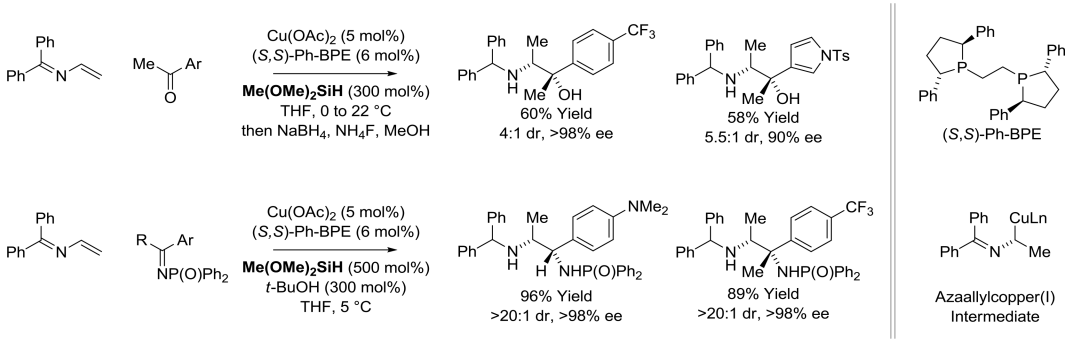
Scheme 18.

Iridium(I)-catalyzed reductive coupling of 2-substituted dienes with methanol *via* hydrogen auto-transfer



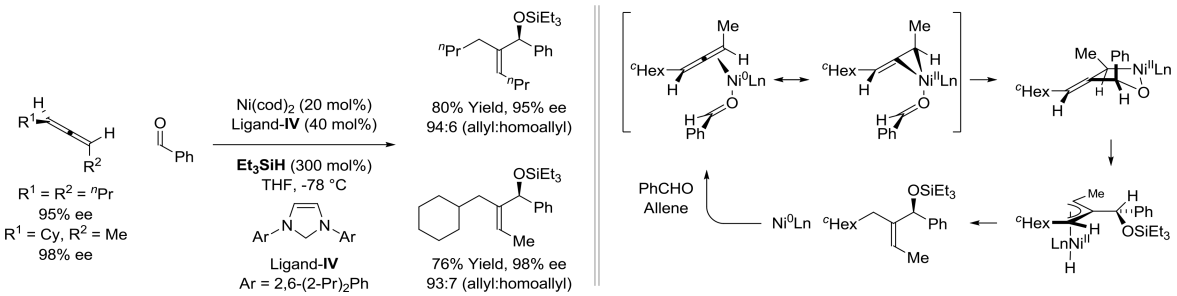
Scheme 19.

Titanium catalyzed diene-aldehyde reductive coupling mediated by silane



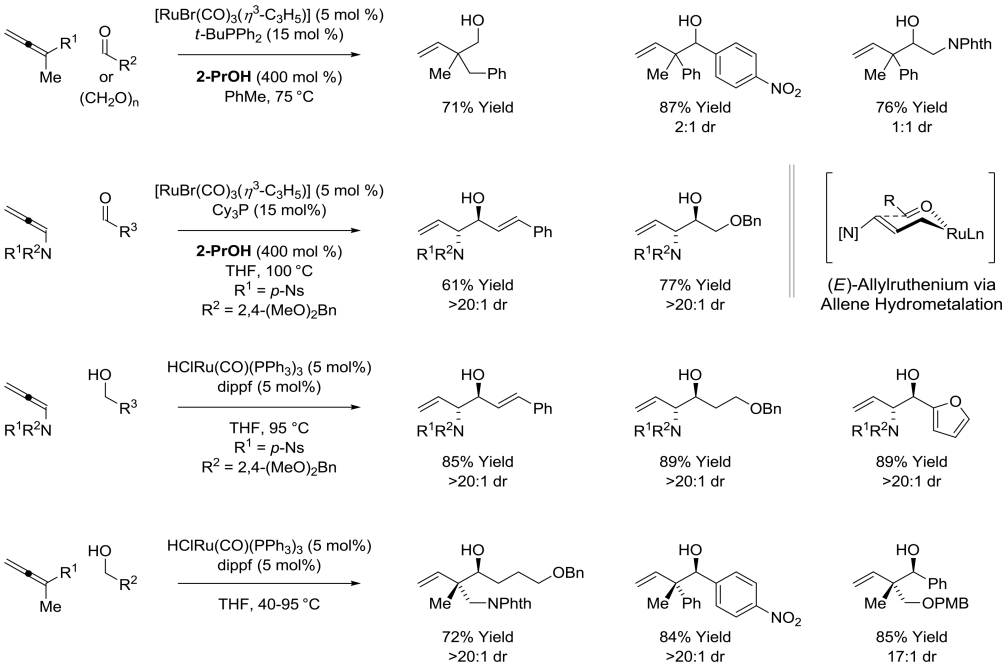
Scheme 20.

Copper-catalyzed reductive coupling of 2-azadienes with aryl ketones and imines mediated by silane



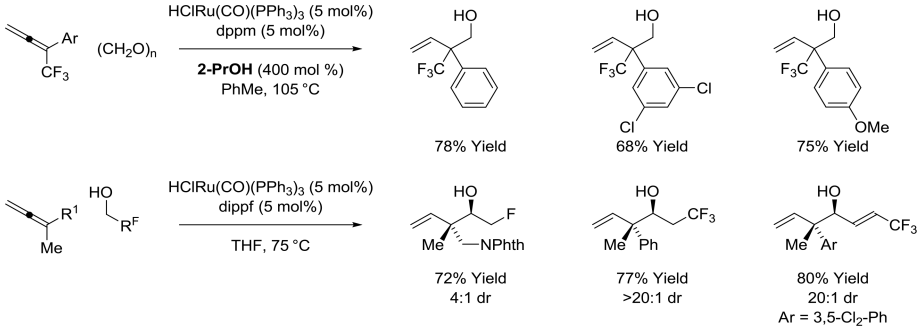
Scheme 21.

Nickel(0)-catalyzed reductive coupling of chiral nonracemic allenes and aldehydes mediated by triethylsilane



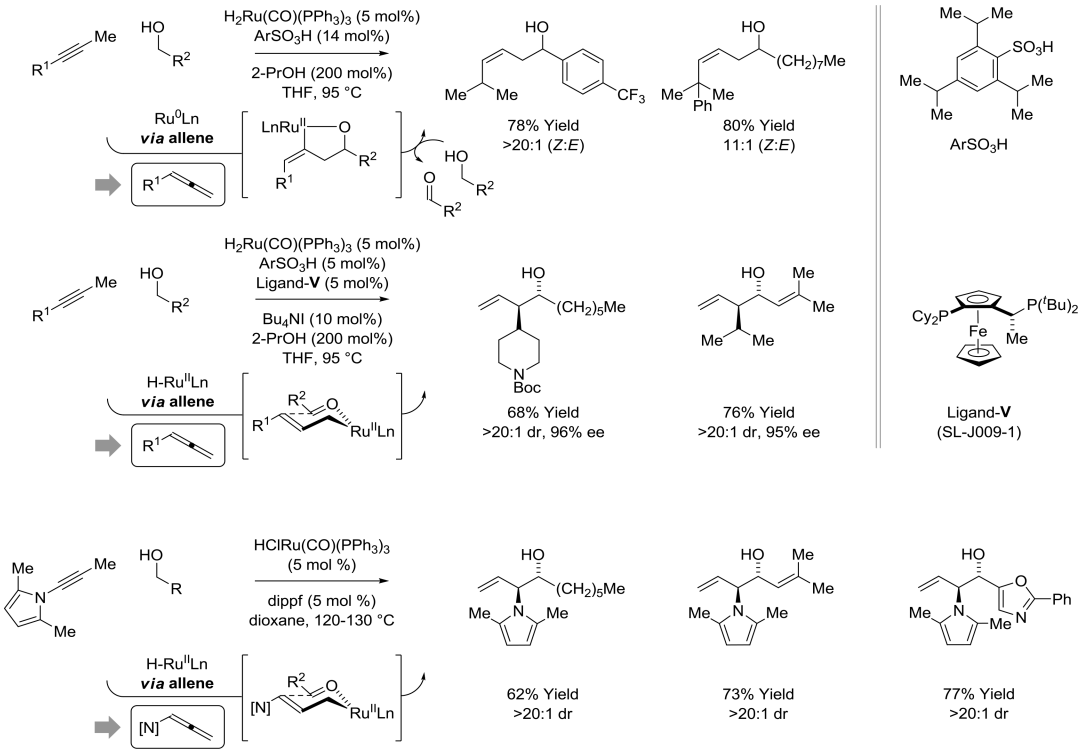
Scheme 22.

Ruthenium(II)-catalyzed allene-aldehyde reductive coupling mediated by 2-propanol or hydrogen auto-transfer



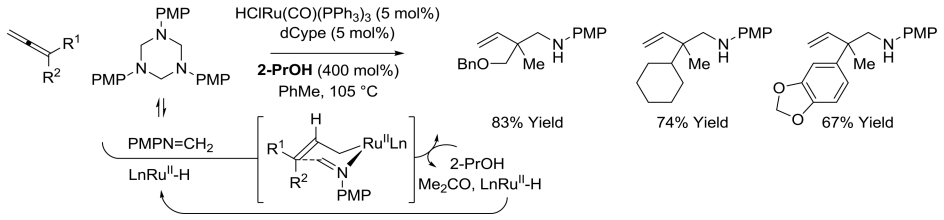
Scheme 23.

Use of CF_3-allenes and fluorinated alcohols in ruthenium(II)-catalyzed allene-aldehyde reductive coupling mediated by 2-propanol or hydrogen auto-transfer



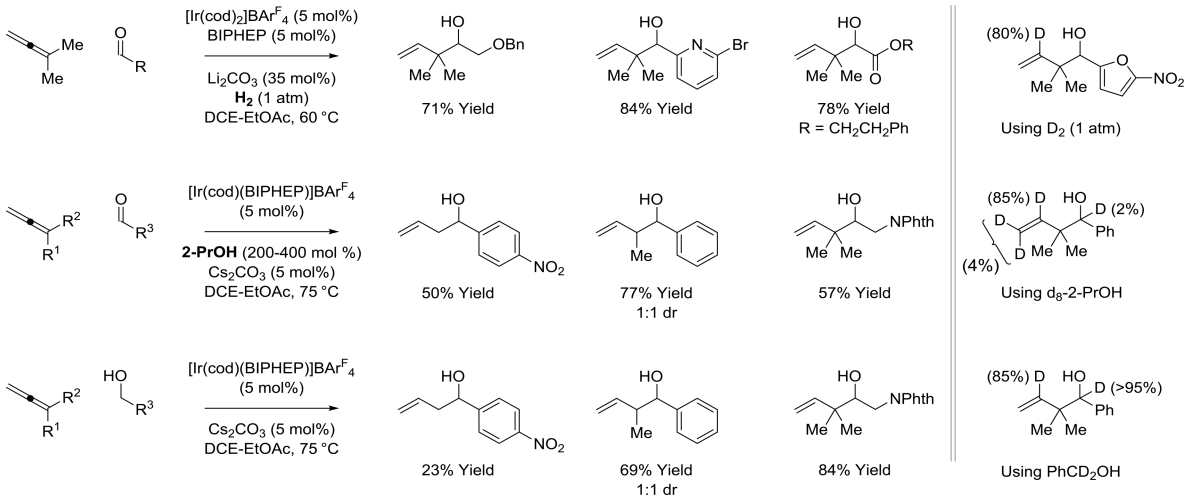
Scheme 24.

Alkynes as latent allenes in ruthenium(0) and ruthenium(II) catalyzed allene-aldehyde reductive couplings via hydrogen auto-transfer



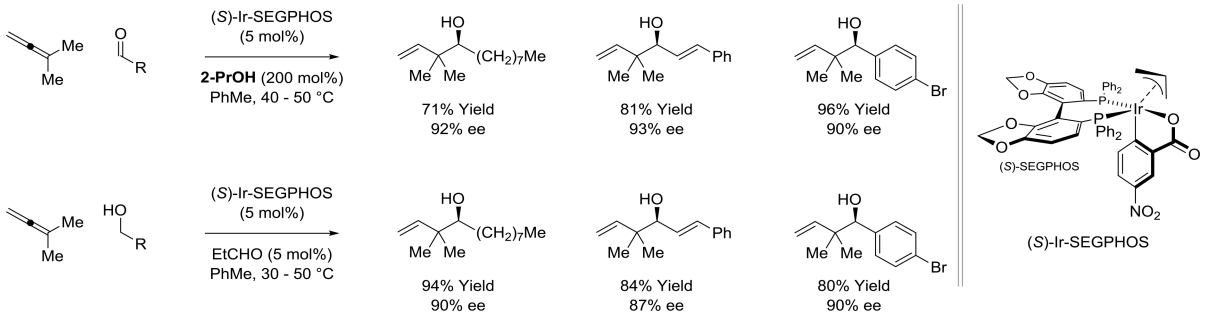
Scheme 25.

Ruthenium(II)-catalyzed allene-imine reductive coupling mediated by 2-propanol



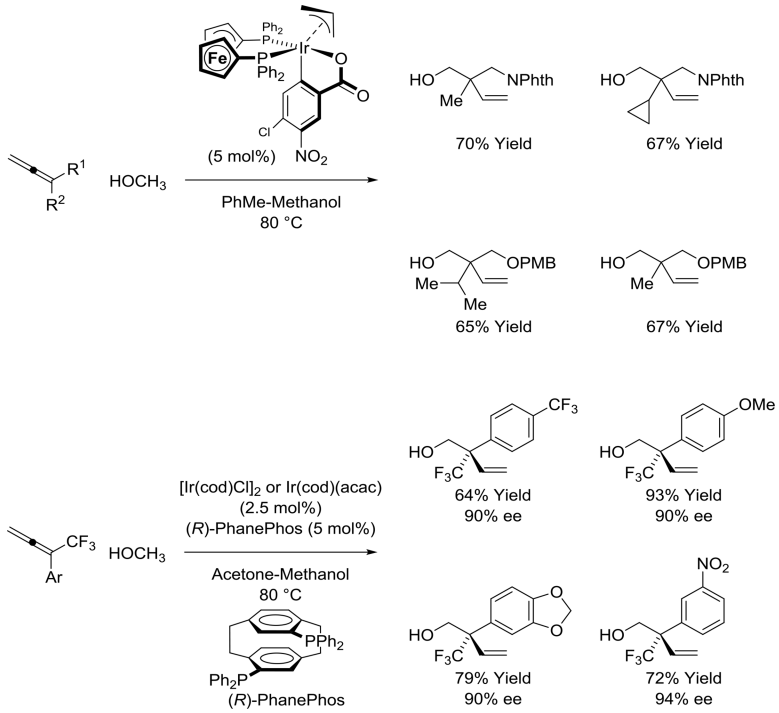
Scheme 26.

Iridium(I)-catalyzed allene-aldehyde reductive coupling mediated by hydrogen, 2propanol or hydrogen auto-transfer



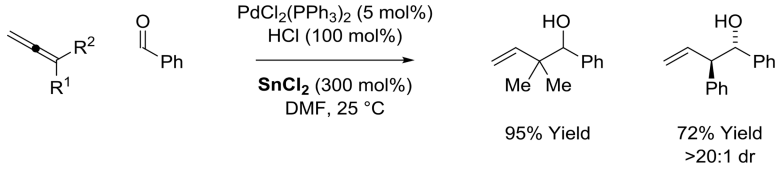
Scheme 27.

Enantioselective carbonyl *tert*-prenylation *via* iridium(I)-catalyzed dimethylallenealdehyde reductive coupling mediated by 2-propanol or hydrogen auto-transfer



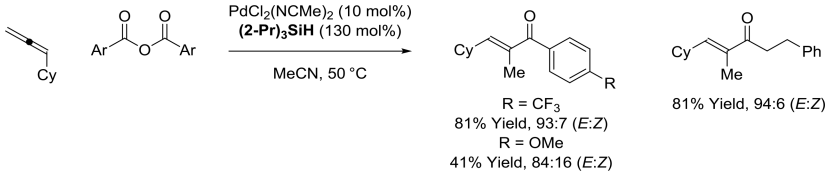
Scheme 28.

Iridium(I)-catalyzed reductive coupling of 1,1disubstituted allenes *via* methanol-mediated hydrogen auto-transfer



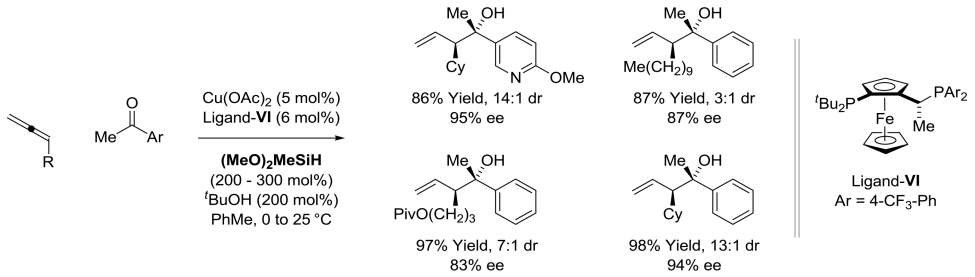
Scheme 29:

Palladium catalyzed allene-aldehyde reductive coupling mediated by stannous chloride



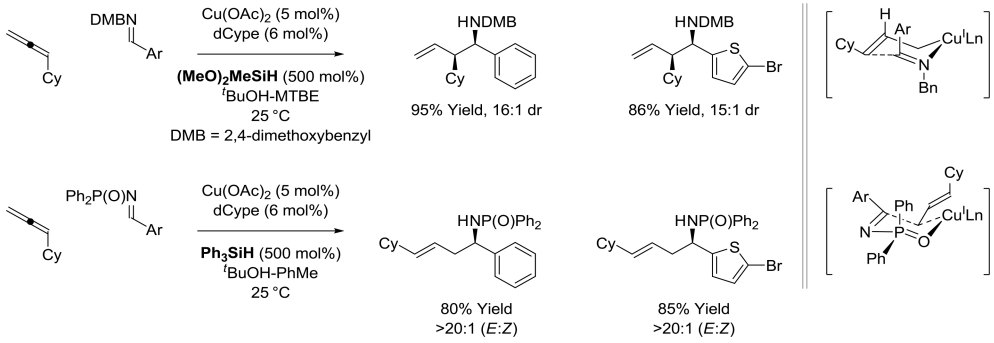
Scheme 30.

Palladium(0)-catalyzed allene-anhydride reductive coupling mediated by silane



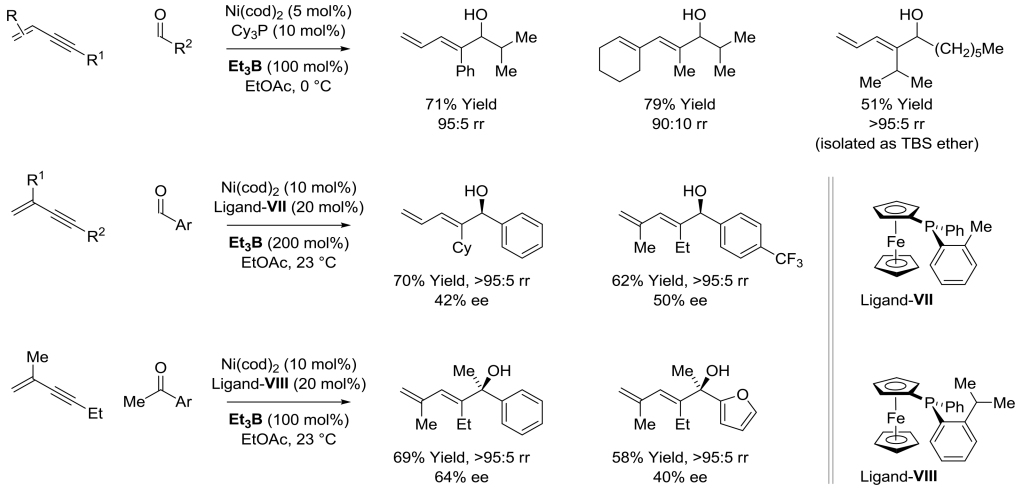
Scheme 31.

Copper(I)-catalyzed allene-ketone reductive coupling mediated by silane



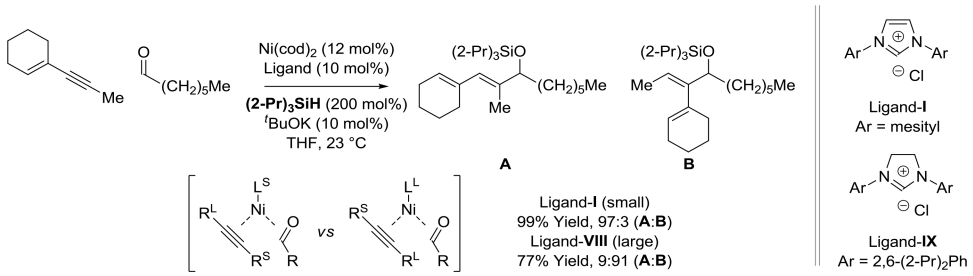
Scheme 32.

Regiodivergent copper(I)-catalyzed allene-imine reductive coupling mediated by silane



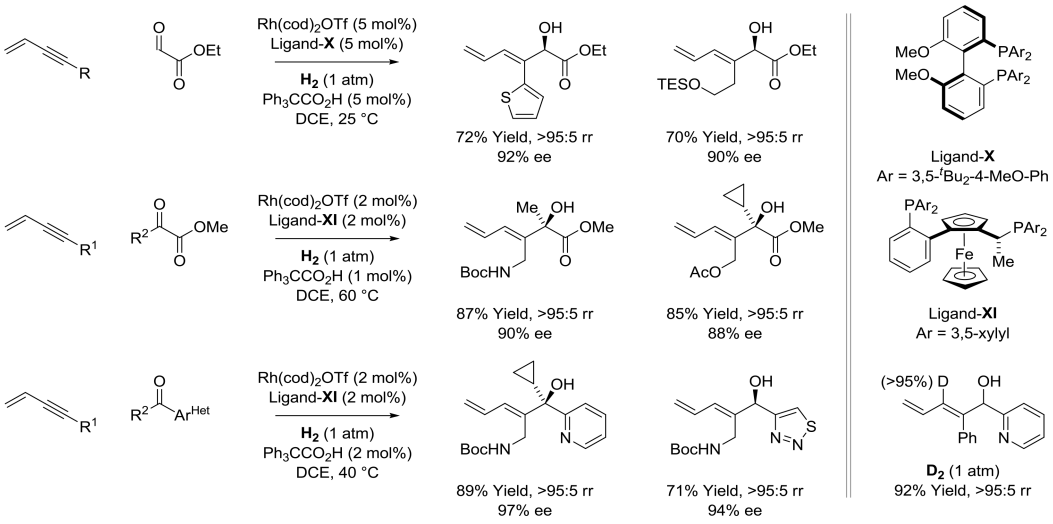
Scheme 33.

Nickel(0)-catalyzed enyne-aldehyde reductive coupling mediated by triethylborane



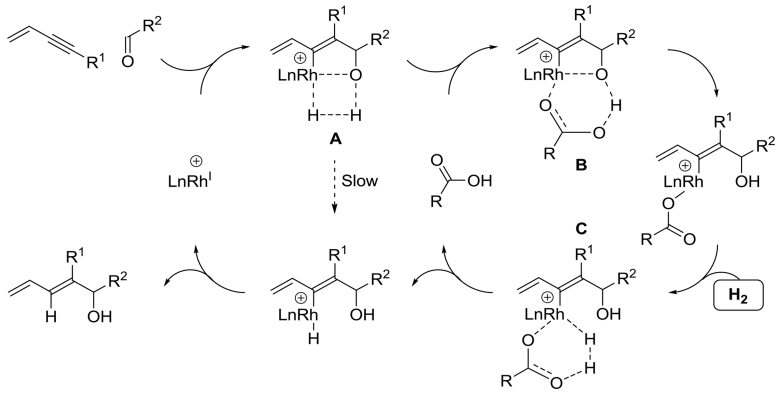
Scheme 34.

Ligand-dependent inversion of regioselectivity in nickel(0)-catalyzed enyne-aldehyde reductive coupling mediated by silane



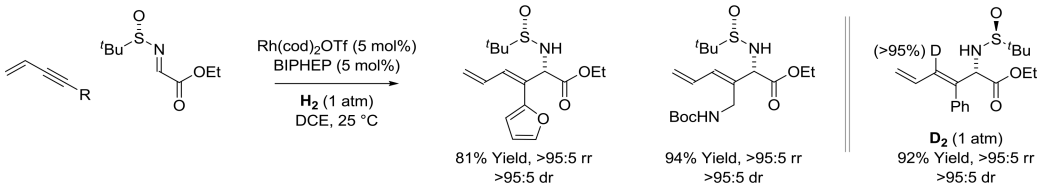
Scheme 35.

Enantioselective rhodium(I)-catalyzed enyne-aldehyde and enyne-ketone reductive coupling mediated by hydrogen



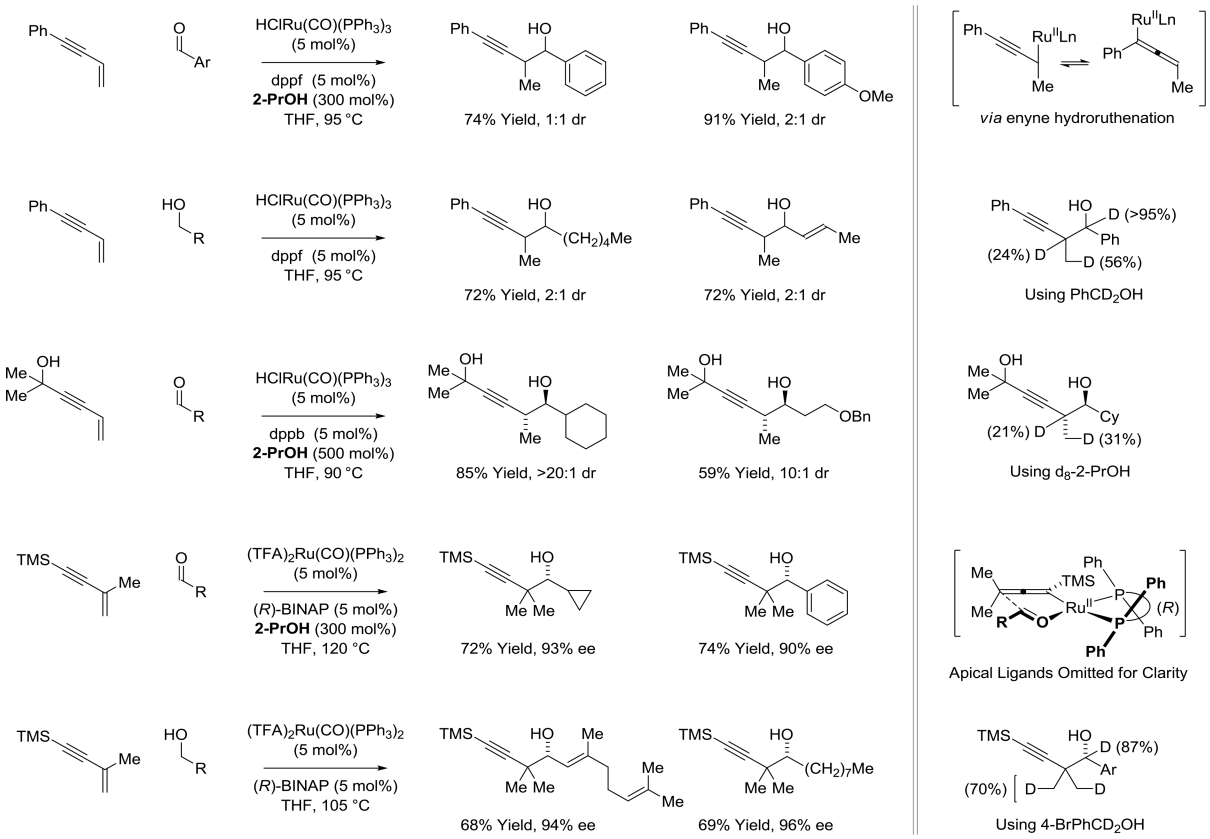
Scheme 36.

Catalytic mechanism for rhodium(I)-catalyzed enyne-carbonyl reductive coupling mediated by hydrogen



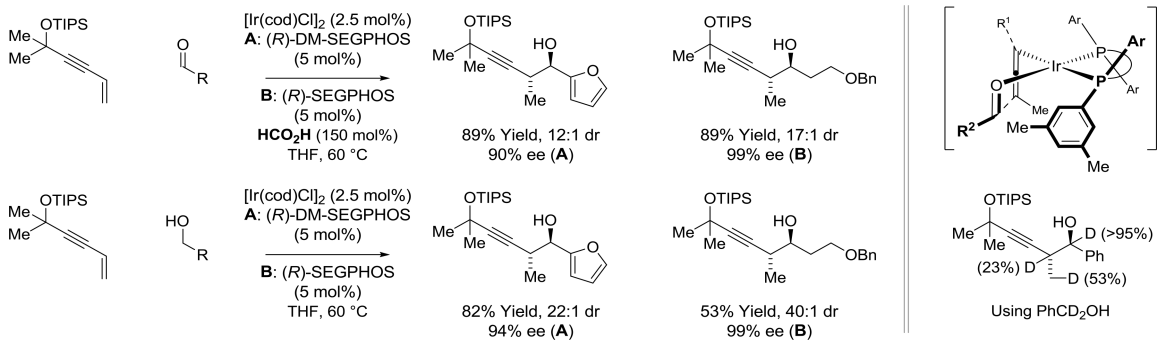
Scheme 37.

Asymmetric rhodium(I)-catalyzed enyne-imine reductive coupling mediated by hydrogen



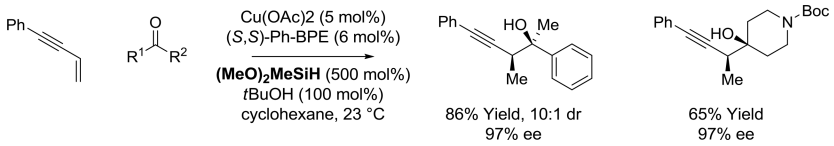
Scheme 38.

Ruthenium(II)-catalyzed enyne-aldehyde reductive coupling mediated by 2-propanol and hydrogen auto-transfer



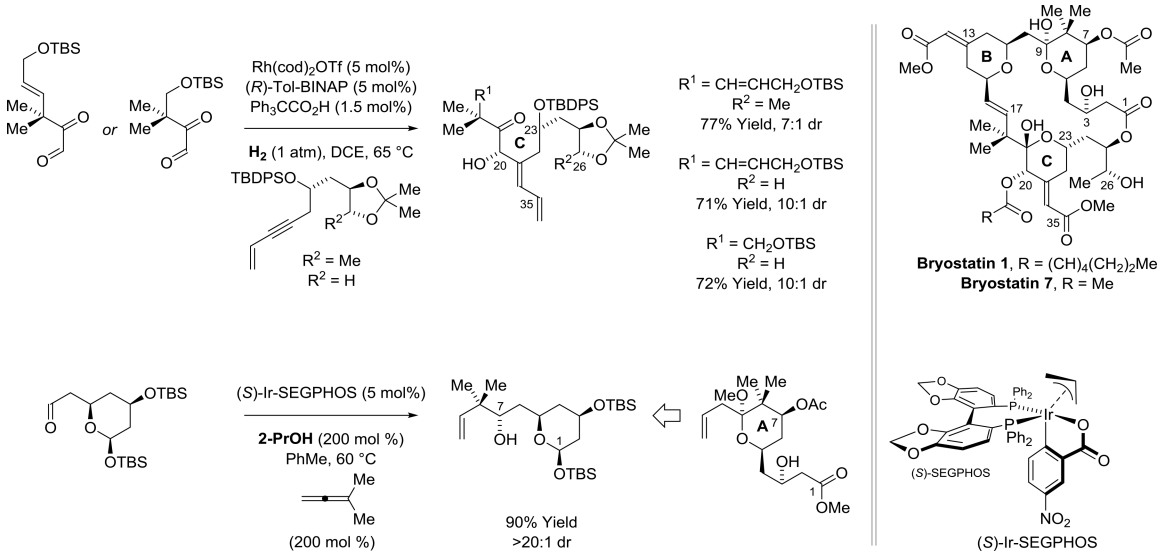
Scheme 39.

anti-Diastereoselective iridium(I)-catalyzed enyne-aldehyde reductive coupling mediated by formic acid or hydrogen auto-transfer



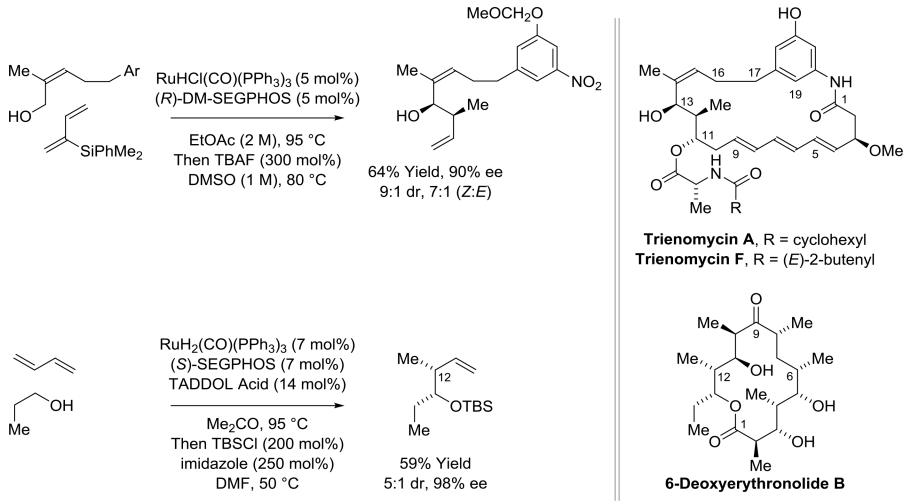
Scheme 40.

Diastereoselective copper(I)-catalyzed enyne-ketone reductive coupling mediated by silane



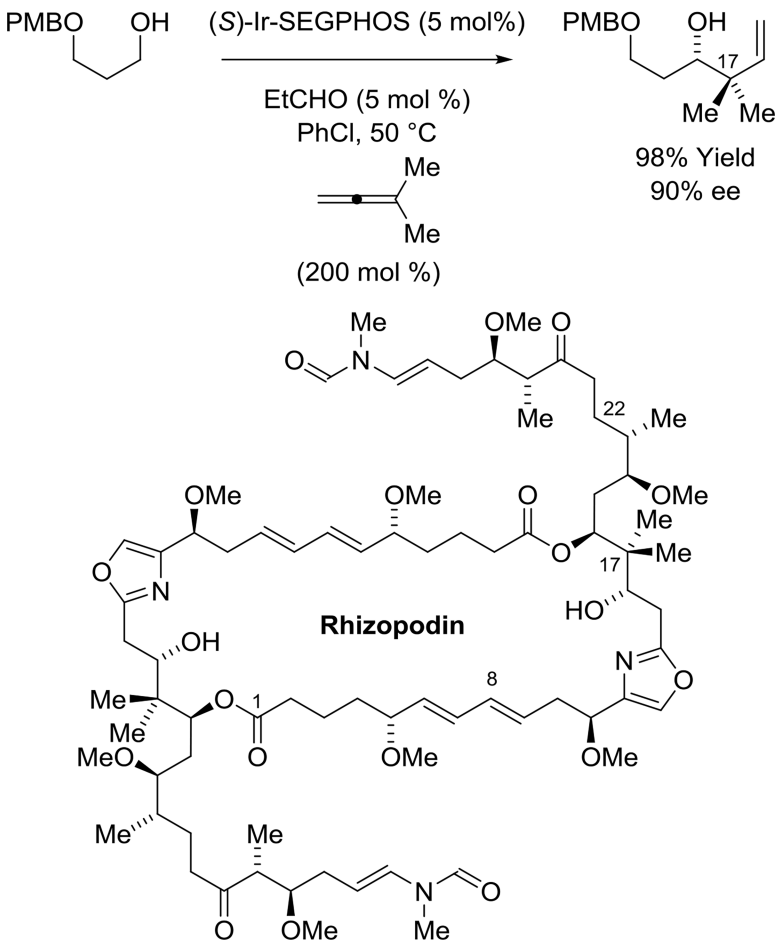
Scheme 41.

Total synthesis of bryostatin 7 via asymmetric rhodium- and iridium-catalyzed hydrogenative and transfer-hydrogenative reductive couplings, respectively



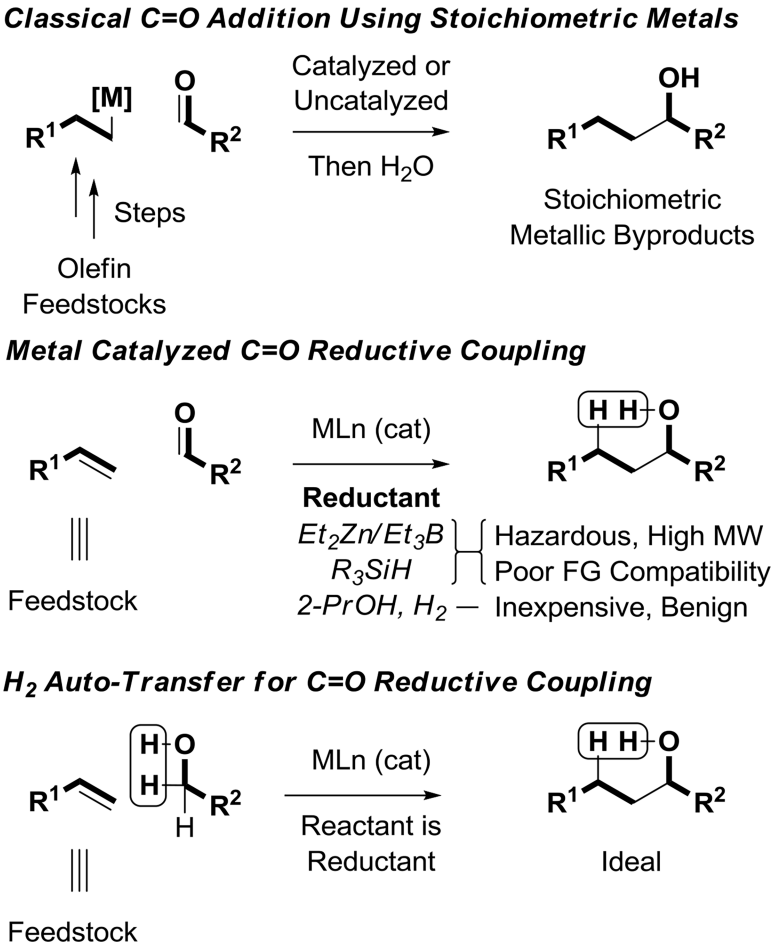
Scheme 42.

Total syntheses of trienomycins A and F and 6-deoxyerythronolide B *via* rutheniumcatalyzed *syn*-diastereo- and enantioselective diene-carbonyl reductive coupling mediated by hydrogen auto-transfer



Scheme 43.

Syntheses of the C8-C22 substructure of rhizopodin via enantioselective iridium-catalyzed allene-aldehyde reductive coupling via hydrogen auto-transfer



Scheme 44.
Catalytic reductive coupling for carbonyl addition