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Metal catalyzed reductive coupling of olefin-derived nucleophiles: reinventing carbonyl addition

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Abstract

α-Olefins are the most abundant petrochemical feedstock beyond alkanes, yet their use in commodity chemical manufacture is largely focused on polymerization and hydroformylation. The development of byproduct-free catalytic C-C bond forming reactions that convert olefins to value-added products remains an important objective. Here, we review catalytic intermolecular reductive couplings of unactivated and activated olefin-derived nucleophiles with carbonyl partners. These processes represent an alternative to the longstanding use of stoichiometric organometallic reagents in carbonyl addition.

Graphical abstract

One Sentence Summary: The development of catalytic intermolecular olefin-carbonyl reductive coupling is reviewed.

Byproduct-free catalytic C-C bond forming reactions of α-olefins are of great commercial interest. Hydroformylation (1,2) and single-site alkene polymerization (3) are now among the largest volume applications of homogenous metal catalysis. Carbonyl compounds represent another abundant class of chemical feedstock that are derived from α-olefins *via* hydroformylation (oxo-products) (1,2) or Wacker oxidation (4). Despite the availability of α-olefins and carbonyl compounds, there is a striking paucity of catalytic processes for the coupling of these orthogonal feedstocks. Here, we review direct methods for the metal catalyzed reductive coupling of olefins with carbonyl compounds. Transformations are catalogued based on their use of (i) unactivated or less activated olefins (α-olefins, styrenes), (ii) conjugated olefins (1,3-dienes, 1,3-enynes) and (iii) highly activated olefins (enones, acrylates, vinyl azines) (Figure 1). Multicomponent reactions, reductive couplings of allenes, reductive carboxylation and carbonyl additions wherein olefins are reduced *in situ* to form stoichiometric quantities of premetalated reagent, for example through hydroboration or hydrozirconation, are not covered.

α-Olefins and Styrenes

Intermolecular catalytic reductive coupling of simple linear α-olefins with unactivated carbonyl partners remains an unmet challenge. Titanocene-catalyzed silane-mediated reductive cyclizations of 1,5-enones and enals were reported by Buchwald (5,6) and Crowe (7) in 1995; however, intermolecular variants remain elusive. The concept of transfer hydrogenative carbonyl addition introduced by our laboratory (8-10) provides an important

inroad to this problem. Using ruthenium(0) catalysts, vicinally oxygenated secondary alcohols serve dually as reductants and carbonyl precursors (11, 12) (Figure 2). Ethylene, propylene, 1-octene, styrene and a host of other terminal olefins were found to engage in highly regio- and diastereoselective C-C coupling with 3-hydroxy-2-oxindoles to form the corresponding tertiary alcohols (11). The scope of this process was extended through the use of related osmium(0) catalysts (12), which promote the C-C couplings of ethylene and 1-octene with diols, α-ketols or α-hydroxy esters by way of vicinal dicarbonyl intermediates. The collective data corroborate a catalytic mechanism involving oxametalacyclopentane formation via olefin-carbonyl oxidative coupling. Transfer hydrogenolysis of the metalacycle mediated by the reactant alcohol releases the product and regenerates the requisite carbonyl partner. As indicated in the general catalytic mechanism, carboxylic acid cocatalysts dramatically enhance rate and conversion in these processes (Figure 2); an effect that may be attributed to intervention of 6-centered transition structures for both protonolytic cleavage of the metalacycle and substitution of the carboxylate ligand by the reactant alcohol at the metal center. Related C-C couplings of vinyl carboxylates with activated secondary alcohols results in metalacycle fragmentation to form products of vinyl transfer (13) (not shown).

Anhydrides represent an alternate class of carbonyl electrophile that have proven effective in catalytic reductive couplings with styrenes and certain α-olefins (Figure 3). Following initial observations by Miura (14), we reported a highly regioselective rhodium catalyzed olefin-anhydride reductive coupling mediated by elemental hydrogen (15). Subsequently, an enantioselective variant of this process involving copper catalysts was developed by Buchwald (16). Oxidative coupling-metalacycle fragmentation pathways are proposed for the hydrogen-mediated processes, whereas the copper catalyzed reactions are postulated to operate *via* olefin hydrometalation to form σ-benzyl copper intermediates. While hydroacylations employing aldehydes as acyl donors require chelating groups to suppress conversion of the transient acyl metal intermediates to catalytically inactive carbonyl complexes, the present anhydride reductive couplings overcome this limitation (17).

Recently, an iron catalyzed Prins-Meerwein-Ponndorf-Verley-type olefin-aldehyde reductive coupling mediated by 2-propanol was reported by Ye (18) (Figure 4). Deuterium labelling studies corroborate a catalytic mechanism wherein condensation of the aldehyde with 2-propanol triggers nucleophilic attack by the olefin. The nascent cation is reduced *via* internal hydride transfer. As anticipated on the basis of this non-concerted or asynchronous oxonia-ene mechanism, olefins that best stabilize the developing cation are the most efficient reactants. The use of unactivated α-olefins in these couplings would represent a major advance.

Dienes and Enynes

Butadiene (12×10^6 tons/year), isoprene (0.8×10^6 tons/year), and myrcene (30×10^3 tons/year) are important chemical feedstocks. The first intermolecular metal-catalyzed reductive coupling of dienes with carbonyl compounds, a process mediated by triethylborane, was reported by Kimura and Tamaru in 1998 (19, 20) (Figure 5). Diverse dienes may be converted to the respective homoallylation products in good yields and excellent levels of

anti-1,3-diastereoselectivity. Regioselectivity in favor of coupling to the more substituted olefin moiety is observed. A mechanism involving diene-carbonyl oxidative coupling to form transient oxo-nickelacycles is postulated (19, 20). Corresponding ketone homoallylations were developed using diethylzinc as terminal reductant (21). Asymmetric variants of the nickel-catalyzed diene-aldehyde reductive couplings are limited to 1,4-diaryl-butadienes (22, 23). Whereas rhodium-catalyzed diene-carbonyl reductive coupling mediated by elemental hydrogen require use of α-ketoaldehydes (24), ruthenium catalysts promote the reductive coupling of diverse dienes to unactivated aldehydes *via* transfer hydrogenation (25). Here, 2-propanol or formic acid may serve as terminal reductant or, remarkably, the reactant itself may serve dually as reductant and carbonyl precursor. Enantioselective variants of the ruthenium catalyzed reductive couplings have been developed (26-29). Whereas initial studies relied on the use of 2-silyl-substituted dienes to direct *syn*-diastereo and enantioselectivity (26), chiral phosphate counterions (28) enable access to either the *anti*- or *syn*- diastereomers with good control of enantioselectivity (27, 28, 30). The collective data are consistent with a catalytic mechanism wherein alcohol dehydrogenation triggers diene hydrometalation (Figure 5).

Ruthenium complexes that embody cationic character catalyze the reductive coupling of 2-substituted dienes to form all-carbon quaternary centers, as illustrated in 2-propanol mediated reductive couplings with paraformaldehyde (31, 32) (Figure 6). Here, a vacant or labile coordination site at the metal center facilitates reversible diene hydrometalation, enabling conversion of the kinetic π-allylruthenium isomer to the thermodynamically more stable terminally disubstituted π-allyl species. Related hydrohydroxymethylations that directly employ methanol (36×10^6 tons/year) as a coupling partner were reported for the first time using an iridium catalyst and 1,1-disubstituted allenes as pronucleophiles (33). Indeed, iridium complexes also catalyze the reaction of dienes with carbonyl compounds to form secondary homoallylic alcohols (33, 34). Cyclohexadiene (34) and butadiene (35) engage in either 2-propanol-mediated reductive coupling or, as shown, direct primary alcohol C-C coupling *via* hydrogen auto-transfer (Figure 6).

Ruthenium(0) catalysis enables reductive coupling of dienes with activated ketones from the secondary alcohol oxidation level *via* hydrogen auto-transfer (36-38) (Figure 7). Mechanistic studies corroborate a catalytic mechanism involving diene-carbonyl oxidative coupling to form an oxaruthenacycle. Hydrogen transfer from the secondary alcohol reactant mediates metalacycle hydrogenolysis, releasing the products of C-C coupling and regenerating the activated ketone to close the catalytic cycle. The regioselectivity of C-C coupling at the diene C4-position is unique among diene-carbonyl reductive couplings. Beyond α-hydroxy esters (36), this process applies to 3-hydroxy-2-oxindoles (37) and heteroaryl substituted secondary alcohols (38). In the latter case, the oxaruthenacycle intermediate was isolated and characterized and reversible metalacycle formation was established through experiments involving diene exchange.

The reductive coupling of conjugated enynes with carbonyl compounds to form homopropargylic alcohols was first reported in 2008 (39) (Figure 8). Using the ruthenium catalyst derived *in situ* from $HClRu(CO)(PPh_3)_3$ and dppf, hydrogen is transferred from primary alcohols to 1,3-enynes to form aldehyde-allenylruthenium pairs that combine to

deliver the products of C-C coupling as single regioisomers in the absence of stoichiometric byproducts. In corresponding 2-propanol mediated reductive couplings of aldehydes with 2-propoxy substituted enynes, good levels of *anti*-diastereoselectivity are achieved (40). The 2-propoxy group of the product readily eliminates acetone upon exposure to aqueous sodium hydroxide to reveal the terminal alkyne. More recently, using the chiral ruthenium complex derived *in situ* from $(TFA)_2Ru(CO)(PPh_3)_2$ and (*R*)-BINAP, the enantioselective C-C couplings of diverse primary alcohols with the commercially available 1,3-enyne, $TMSC{\equiv}CC(Me){=}CH_2$, were reported (41). Metals other than ruthenium catalyze enyne-carbonyl reductive coupling. For example, an iridium catalyst with (*R*)-SEGPHOS or (*R*)-DM-SEGPHOS ligands catalyzes highly enantioselective enyne-carbonyl reductive coupling from the alcohol or aldehyde oxidation level (42). In the latter case, formic acid serves as terminal reductant. Finally, copper complexes recently were found to catalyze the silane mediated reductive coupling of 1,3-enynes with diverse ketones with excellent control of *syn*-diastereo- and enantioselectivity (43) (Figure 8).

Acrylates, Enones and Vinyl Azines

The use of α,β-unsaturated carbonyl compounds as pronucleophiles in reductive couplings with carbonyl compounds is known as the “reductive aldol reaction” (44). Following seminal studies by Revis in 1987 on the rhodium-catalyzed reductive aldol reaction of acrylates with aldehydes and ketones mediated by silane (45), numerous processes of this type were developed using different metal catalysts. We focus here on enantioselective intermolecular reductive aldol reactions (Figure 9). Catalytic carbonyl reductive couplings of α,β-unsaturated carbonyl compounds that occur at the β-position are not covered (46).

The first enantioselective reductive aldol reaction was reported by Morken in 2000 (47). This reductive coupling of acrylic esters with aldehydes was catalyzed by a rhodium-BINAP catalyst using Et_2MeSiH as the terminal reductant. High levels of enantioselectivity were accompanied by modest levels of *syn*-diastereoselectivity (Figure 9). Mechanistic studies implicate hydrometalative pathways *en route* to rhodium enolates. Using an Ir(pybox) catalyst, improved *syn*-diastereo- and enantioselectivities were observed; however, inductively activated aldehydes are required (48). A remarkably general Rh(phebox) catalyst for asymmetric reductive aldol addition was subsequently reported by Nishiyama (49). Uniformly high levels of *anti*-diastereoselectivity and enantioselectivity were observed across a diverse range of substrates, including additions to ketones (50). Ketone electrophiles are also accommodated by copper catalysts (51). The preceding examples of asymmetric reductive aldol coupling pair acrylate pronucleophiles with hydrosilane as terminal reductant. Vinyl ketones serve as pronucleophiles with rhodium catalysts and H_2 as reductant (52). Substituting deuterium as the reductant leads to transfer of a single deuterium atom to the former enone β-position, consistent with a catalytic mechanism involving oxidative coupling followed by hydrogenolysis of the resulting metalacycle *via* σ-bond metathesis. Hydrometalative pathways cannot be excluded on the basis of these results; however, reversible hydrometalation-β-hydride elimination would be anticipated to diminish the extent of deuterium incorporation.

Vinyl azines are isostructural with respect to α,β-unsaturated carbonyl compounds and, as described in the review literature (53), display analogous reactivity. However, their use as pronucleophiles in catalytic reductive coupling has only recently begun to be explored. In 2008, the first example of vinyl azine reductive coupling to a π-electrophile was achieved *via* rhodium catalyzed hydrogenation of vinyl azines in the presence of imines (54) (Figure 10). Good levels of *syn*-diastereoselectivity were observed. The Lam laboratory subsequently reported a copper catalyzed coupling of vinyl azines to ketone electrophiles with good levels of *syn*-diastereoselectivity and excellent enantioselectivity (55). For both processes, optimal results are obtained using vinyl azines where both positions adjacent to nitrogen are substituted.

Conclusion and Outlook

Intermolecular catalytic reductive coupling of simple linear α-olefins with unactivated carbonyl partners remains an important unmet challenge in chemical synthesis. For such abundant feedstocks, an additional consideration resides in identifying terminal reductants that are equally inexpensive and minimize or eliminate byproduct formation. Hence, byproduct-free processes mediated by elemental hydrogen or transfer hydrogenative C-C couplings of alcohol reactants are especially attractive. Conversely, processes mediated by reductants that are pyrophic ($ZnEt_2$, BEt_3) or those that are costly and mass-intensive (R_3SiH) can only be viewed as interim solutions. Despite the many unrequited challenges, progress made in the area of metal catalyzed reductive coupling clearly show that classical methods for carbonyl addition that traditionally have exploited stoichiometric organometallic reagents may be replaced by catalytic processes that bypass premetalated reagents. It is our hope this monograph will inspire and guide future research aimed at unlocking carbonyl addition chemistry beyond stoichiometric metals.

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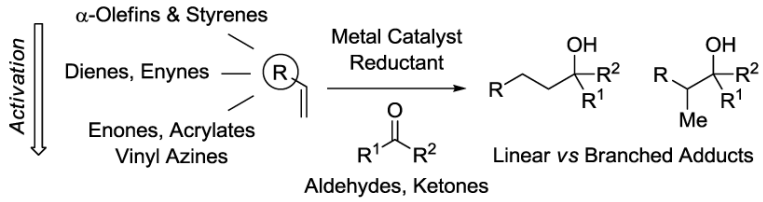

Figure 1.

Metal catalyzed reductive coupling of unactivated and activated olefin-derived nucleophiles with carbonyl compounds.

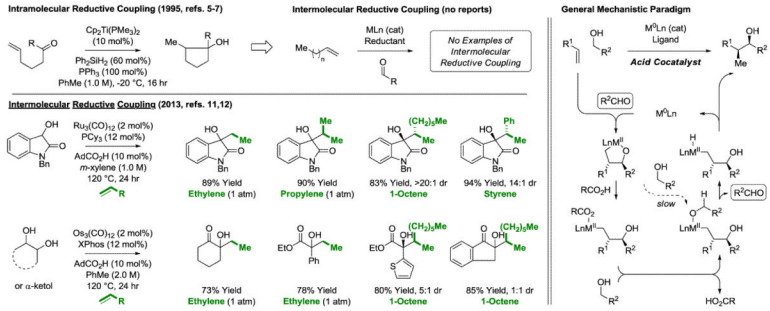

Figure 2.

Metal catalyzed reductive coupling of α-olefins with carbonyl partners.[a]

[a]$AdCO_2H$ refers to 1-adamantane carboxylic acid. X-Phos = 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

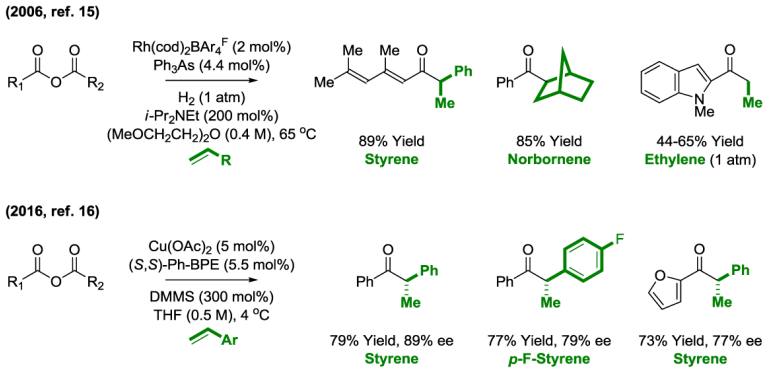

Figure 3.

Metal catalyzed reductive coupling of olefins with anhydrides.[a]

[a](*S,S*)-Ph-BPE = 1,2-*bis*[(*2S,5S*)-2,5-diphenylphospholano]ethane. DMMS = dimethoxymethylsilane.

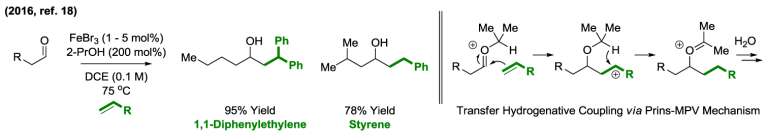

Figure 4.
Iron catalyzed Prins-Meerwein-Ponndorf-Verley-type olefin-aldehyde reductive coupling.

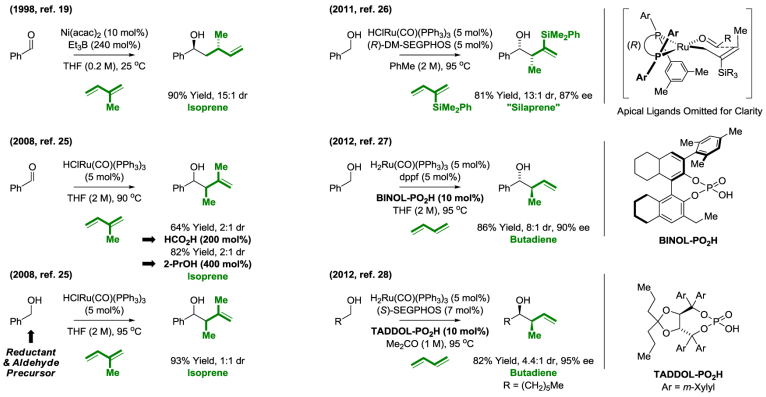

Figure 5.

Metal catalyzed diene-carbonyl reductive coupling.

[a]dppf = 1,1-*bis*-(diphenylphosphino)ferrocene. (*R*)-DM-SEGPHOS = (*R*)-(+)-5,5′−*bis*-[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole. (*S*)-SEGPHOS = (*S*)-(−)-5,5′-*bis*-(diphenylphosphino)-4,4′-bi-1,3-benzodioxole. acac = acetylacetonate.

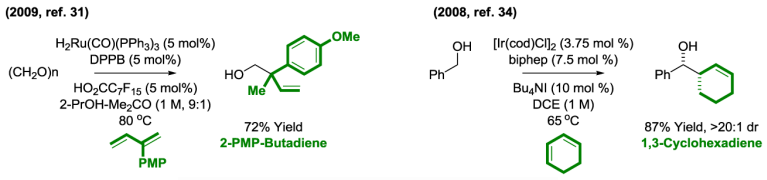

Figure 6.

Alternate regioselectivity and use of cyclic dienes in metal catalyzed carbonyl reductive coupling.[a]

[a]dppb = *bis*-(diphenylphosphino)butane. biphep = 2,2′-*bis*-(diphenylphosphino)-1,1′-biphenyl.

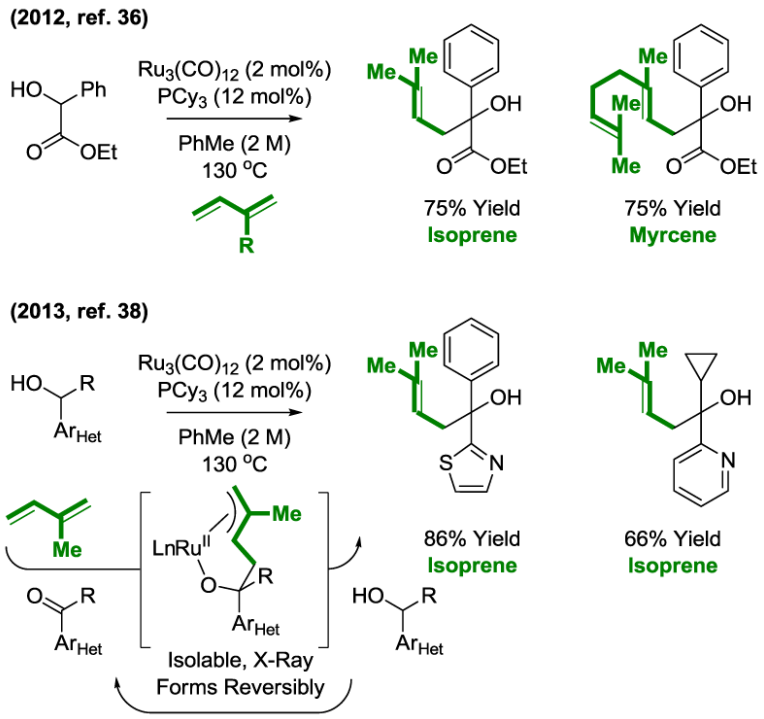

Figure 7.

Ruthenium(0) catalyzed diene-ketone reductive coupling *via* hydrogen auto-transfer.[a]

[a]PCy_3 = tricyclohexylphosphine.

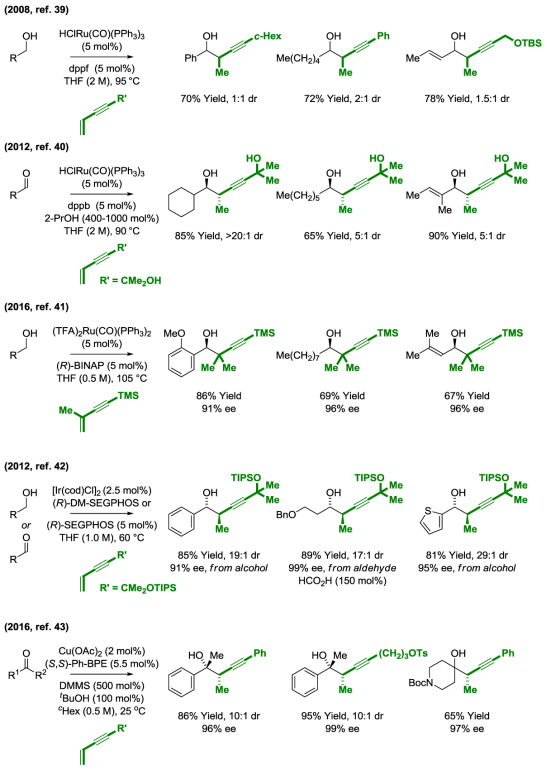

Figure 8.

Metal catalyzed enyne-carbonyl reductive coupling.[a]

[a]DMMS = dimethoxymethylsilane. (*R*)-BINAP = (*R*)-(+)-2,2′-*bis*-(diphenylphosphino)-1,1′-binaphthyl

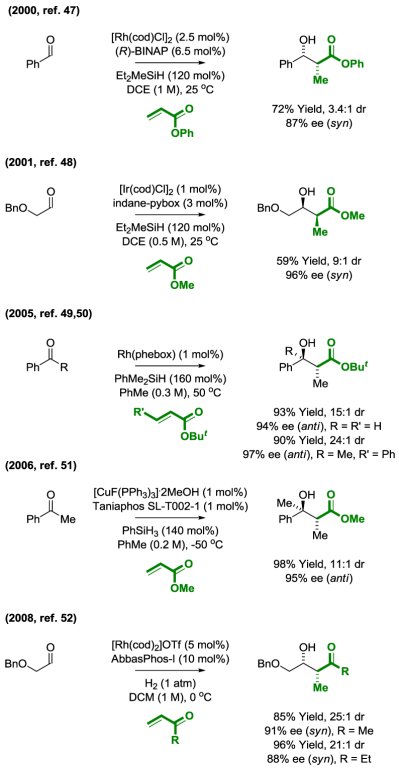

Figure 9.

Enantioselective metal catalyzed reductive aldol reactions.[a]

[a]See primary literature for the structures of indane-pybox, phebox, taniaphos and AbbasPhos-I.

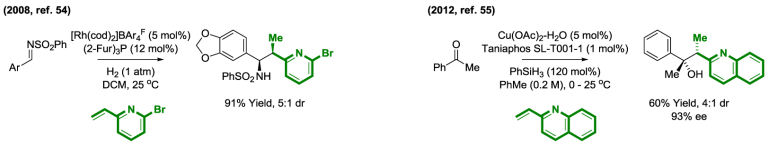

Figure 10.
Metal catalyzed reductive coupling of vinyl azines.[a]

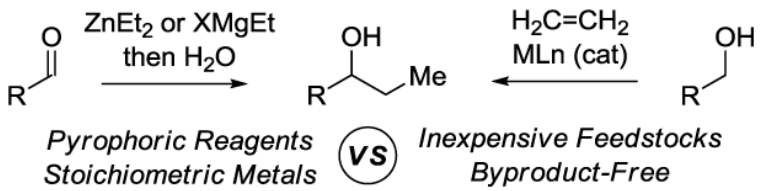

Figure 11.
A departure from preformed organometallic reagents in carbonyl addition.