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Catalytic Reductive Aldol and Mannich Reactions of Enone, Acrylate and Vinyl Heteroaromatic Pronucleophiles

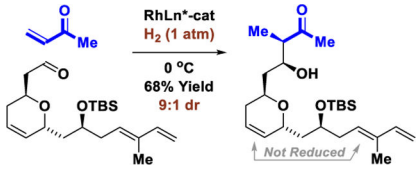
Cole C. Meyer, **Eliezer Ortiz**, **Michael J. Krische***

University of Texas at Austin, Department of Chemistry, Welch Hall (A5300), 105 E 24th St., Austin, TX 78712, USA

Abstract

Catalytic reductive coupling of enone, acrylate or vinyl heteroaromatic pronucleophiles with carbonyl or imine partners offers an alternative to base-mediated enolization in aldol and Mannich type reactions. In this monograph, direct catalytic reductive aldol and Mannich reactions are exhaustively catalogued on the basis of metal or organocatalyst. Step-wise processes involving enone conjugate reduction to form discrete enol or (metallo)enolate derivatives followed by introduction of carbonyl or imine electrophiles and aldol reactions initiated via enone conjugate addition are not covered.

Graphical Abstract



1. Introduction: Historical Perspective and Scope of Review

With initial observations by Kane (1838),[1,2] but attributed to independent reports by Borodin (1869)[3,4] and Würtz (1872),[5,6] the aldol reaction is the Proteus of enolate-mediated C-C bond formations and persists as one of the most broadly utilized transformations in chemical synthesis. Core physical organic and stereochemical principles associated with the aldol reaction,[7–13] applications of the aldol reaction in the total synthesis of natural products,[14–19] and catalytic enantioselective aldol reactions[20–24] have been reviewed. Indeed, the maturation of organic chemistry as a field, from its very inception to the current state-of-the-art, may be viewed through the lens of the aldol reaction and the diverse issues of selectivity posed by this fundamental transformation. The development of methods for base-mediated enolization of carbonyl compounds to furnish structurally defined (metallo)enolates had a pronounced impact on the field of aldol chemistry. Discrete formation of lithium enolates was first reported by Hauser (1951) using lithium amide.[25–28] Wittig (1963) later described the use of lithium diisopropylamide (LDA) in deprotonations of aldimines in so-called

*Corresponding Author: mkrische@mail.utexas.edu.

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"Wittig directed aldol condensations."[29–31] More detailed studies into dialkylamide bases ensued, which defined methods for stereoselective enolization under kinetically controlled conditions, as understood by Irelands model (1976),[32] or under thermodynamic conditions. These advances, combined with the observations of Dubois (1967)[33–35] and Heathcock (1980)[36] that (*Z*)- and (*E*)-enolates undergo carbonyl addition stereospecifically through closed "Zimmerman-Traxler"[37] transition structures to provide *syn*- and *anti*-addition products, respectively, laid the foundation for absolute stereocontrol, as exemplified by the use of Evan's auxiliary (1981).[38] Finally, in parallel with progress on stereocontrolled aldol additions of lithium[12] and boron[13,14,39] enolates, alternate, mechanistically distinct strategies for stereoselective aldol addition arose. The Mukaiyama aldol reaction (1973)[40,18] intermolecular variants of the Hajos-Parrish-Eder-Sauer-Wiechert reaction (1971),[41–43] metal-catalyzed asymmetric aldol additions reported by Hayashi and Ito (1986)[44] and "direct" metal-catalyzed asymmetric aldol additions reported by Shibasaki (1997)[45,46] offered powerful complementary approaches to stereoselective aldol addition (Figure 1).

Along with this expansion in scope in aldol chemistry, certain limitations were brought to light. For example, whereas regioselective enolization is readily achieved for nonsymmetric ketones possessing different degrees of substitution at the α-positions, such as methylcyclohexanone, upon deprotonation under kinetically or thermodynamically controlled conditions,[47,48] divergent regioselectivity is seldom attained in enolizations of non-symmetric ketones that possess identical degrees of substitution at the α-positions. The deprotonation of cholesterane-3-one represents a classic case.[49–53] Thermodynamically controlled enolization delivers the Δ^3-enolate with good isomer selectivity. In contrast, the Δ^2-enolate cannot be formed selectively *via* deprotonation under kinetic or thermodynamic conditions. Further, introduction of 7,8-unsaturation results in an inversion of regioselectivity. An overwhelming thermodynamic preference in favor of the Δ^2-enolate is observed, and the Δ^3-enolate cannot be formed selectivity under kinetically or thermodynamically controlled deprotonation conditions. Reductive enolate generation, initially realized in the context of the Reformatsky reaction (1887),[54] enables regiospecific formation of enolate isomers that are often inaccessible via base-mediated deprotonation. In what may be viewed as a prelude to the catalytic reductive aldol reaction, reductive enolization based on the dissolving metal reduction (Li/NH_3) of conjugated enones was reported by Stork (1965) (Scheme 1).[55,56]

Following Stork's seminal studies, a diverse array of metal catalysts for the conjugate reduction of α,β-unsaturated carbonyl compounds were developed utilizing molecular hydrogen,[57–63] silanes or borohydrides.[64–71] This work encompasses enantioselective conjugate reductions of α,β-unsaturated carbonyl compounds catalyzed by ruthenium,[72–80] rhodium,[81–93] iridium,[94–109] palladium,[110–113] copper[114–120] and cobalt complexes,[121–128] as well as enantioselective Lewis base-catalyzed conjugate reductions.[129–131,226] Additionally, preformation of enol derivatives in the context of tandem 1,4-reduction-carbonyl addition sequences have been disclosed.[132–146] As described in the review literature, this abundance of prior art laid the foundation for catalytic reductive couplings of α,β-unsaturated carbonyl compounds partners with carbonyl electrophiles, termed "*reductive aldol reactions.*"[147–162] Discovered over 30 years ago by Revis (1987),[163] catalysts for reductive aldol coupling based on rhodium,[163–189] cobalt,[190–195] iridium,[175,196]

ruthenium,[197–199] palladium,[200] nickel,[201–203] platinum,[204] copper,[205–220] zinc[221] and indium[222–225] have been described. Additionally, Lewis base-catalyzed reductive aldol additions have been described.[226–229] Related catalytic reductive Mannich reactions[230–237] and reductive couplings of vinyl heteroaromatic pronucleophiles to carbonyl and imines partners were developed in parallel.[238–241]

As shown herein, the catalytic reductive aldol reaction complements the scope of preexisting protocols for aldol addition. One advantage of the reductive aldol reaction resides in the ability to directly deploy feedstock pronucleophiles such as acrylates and methyl vinyl ketone, which enhances step-economy and minimizes mass-intensity (Figure 2).[242] That is, for chiral auxiliary-based aldol additions, for example, the Evans aldol reaction,[38,243] multiple steps are required for auxiliary synthesis and attachment, enolization and auxiliary removal, with each step utilizing sacrificial reagents that generate stoichiometric byproducts. Another advantage of the reductive aldol reaction relates to its regiospecificity, and the ability to access aldol isomers that are otherwise difficult to prepare (Scheme 2). For example, in direct metal-catalyzed[45,46,244,245] or secondary amine-catalyzed aldol additions,[246–250] the nonsymmetric ketone 2-butanone undergoes C-C coupling at the less substituted enolizable position. In contrast, enantioselective rhodium-catalyzed reductive aldol reactions of methyl vinyl ketone provide the corresponding branched isomers with complete levels of regiocontrol.[188]

In this review, catalytic reductive coupling of enone, acrylate and vinyl heteroaromatic pronucleophiles to carbonyl and imine partners are exhaustively catalogued on the basis of metal catalyst or organocatalyst.[147–241] Catalytic reductive Michael reactions are described elsewhere.[191,192,204,251–254] Step-wise processes involving conjugate reduction to form discrete (metallo)enolate derivatives followed by introduction of carbonyl or imine electrophiles,[132–146] and aldol reactions initiated via conjugate addition[255–262] have been reviewed elsewhere.[263–266] For enone-C=X (X = O, NR) reductive couplings that result in functionalization at the β-position of the α,β-unsaturated pronucleophile, the reader is referred to the review literature.[267–270] The catalytic reductive couplings described herein contribute to a departure from the use of premetalated reagents in carbonyl addition.[242, 271–281]

2. Catalytic Reductive Aldol and Mannich Reactions

2.1. General Catalytic Mechanisms

To streamline the discussion of mechanism, representative pathways for metal-catalyzed reductive aldol coupling are shown for rhodium-catalyzed reactions that employ the generic terminal reductant “H-Y”, where, for example, Y = SiR_3 or H (Scheme 3). Organocatalyzed reductive aldol couplings are less common and their mechanisms will be discussed ad hoc. Catalytic cycle **A** is initiated via H-Y oxidative addition to rhodium(I) to form the rhodium(III) hydride **I**. Oxidative additions of hydrosilane (Y = SiR_3)[282] or hydrogen (Y = H) to neutral[283–285] or cationic[286–289] rhodium(I) complexes have been reviewed.[290–292] Insertion of the aldehyde carbonyl into the Rh-Y bond to deliver complex **II** finds precedent in aldehyde silylformylations (Y = SiR_3) catalyzed by cobalt[293] and rhodium,[294,295] but is unknown for other reductants. Enone or acrylate hydrometalation forms complex **III**, which

upon C-C reductive elimination provides the aldol adduct (as the silyl ether for Y = SiR_3) with regeneration of low valent rhodium to close the catalytic cycle. In catalytic mechanism **B**, enone or acrylate hydrometalation mediated by complex **I** furnishes rhodium(III) enolate **IV**, which upon aldehyde addition provides the rhodium(III) aldolate **V**. Reductive elimination of "H-Y"[296,297] releases the aldol adduct (as the silyl ether for Y = SiR_3) and low valent rhodium to close the catalytic cycle. This pathway finds precedent in aldol additions of preformed late transition metal enolates.[298–302] Though not depicted, oxygen-silicon reductive elimination[296,297] from enolate **IV** formation followed by Mukaiyama-type aldol addition also may affect formation of aldolate **V**. In catalytic cycle **C**, oxidative coupling of the reactants delivers oxarhodacyclopentane **VI**.[303] σ-Bond metathesis with hydrosilane (Y = SiR_3)[304–306] or hydrogen (Y = H)[307] provides complex **VII**, which upon C-H reductive elimination affords the aldol adduct and low valent rhodium to close the catalytic cycle. Finally, for catalytic cycle **D**, a rhodium(I) hydride, which in the case of elemental hydrogen as reductant is derived upon formal heterolytic hydrogen activation,[308–310] promotes enone or acrylate hydrometalation to form rhodium(I) enolate **VIII**. Aldol addition affords aldolate **IX**, which upon hydrogen oxidative addition and O-H reductive elimination delivers aldol product.

2.2. Rhodium

2.2.1 Reductant ≠ Hydrogen—In 1987, Revis reported the first examples of reductive aldol coupling (Scheme 4).[163] Upon exposure to substoichiometric quantities of $RhCl_3 \cdot 3H_2O$ in combination with Me_3SiH as terminal reductant, methyl methacrylate (and related α,β-unsaturated esters) undergoes reductive coupling to both aldehyde and ketone partners. Aldol products that incorporate contiguous fully substituted carbon centers are formed in good yields at ambient temperature at exceptionally low catalyst loading. The silyl ketene acetal derived from methyl methacrylate could be detected in crude reaction mixtures, and attempted reductive coupling of methyl vinyl ketone to acetone instead resulted in enol silane formation. These data are consistent with intervention of catalytic mechanism **B** (Scheme 3). Using the rhodium catalyst derived from $Rh_4(CO)_{12}$ and $MePh_2P$, Matsuda reports enone-aldehyde reductive couplings mediated by Et_2MeSiH.[164] Modest levels of *syn*-diastereoselectivity are observed for certain reaction products. Participation of β,β-disubstituted enone pronucleophiles is a notable feature of this catalytic system. Like Revis' catalytic system, enol silanes are detected as byproducts. For the processes developed by both Revis and Matsuda, exposure of preformed silyl enol ethers to the carbonyl electrophile under the reaction conditions does not result C-C coupling. These data implicate rhodium enolates as reactive intermediates in the C-C bond forming event, and that Mukaiyama aldol pathways are not operative.

Rhodium-catalyzed reductive aldol cyclizations were first reported by Motherwell (Scheme 5).[165,166] Diastereoselectivity in these processes is catalyst-dependent. Cyclizations catalyzed by Wilkinson's complex, $RhCl(PPh_3)_3$, display a modest preference for formation of the *cis*-diastereomer. For cyclizations catalyzed by $RhH(PPh_3)_4$, a more pronounced preference for the *anti*-diastereomer is observed. The reaction is restricted to aldehyde electrophiles, as attempted cyclization onto a tethered ketone catalyzed results in olefin isomerization-enone hydrosilylation to form the indicated enol silane. The observed

divergence in diastereoselectivity may reflect intervention of distinct catalytic pathways. For example, cyclizations catalyzed by $RhCl(PPh_3)_3$ vs $RhH(PPh_3)_4$ may occur through catalytic cycles **B** and **D** (Scheme 3), respectively; the latter involving a low-valent rhodium hydride. These different catalytic cycles might, in turn, possess different kinetic preferences for formation (*E*)- vs (*Z*)-enolates, which would be anticipated to undergo stereospecific addition.[33–36]

The first diastereo- and enantioselective reductive aldol couplings were developed by Morken (Scheme 6).[167–169] Using an arrayed catalyst screening method, 192 independent catalytic systems were evaluated, which revealed a strong interdependence of reaction variables.[167] Based on this approach, conditions for the diastereoselective reductive coupling of methyl acrylate and benzaldehyde were identified. Using the catalyst assembled from $[Rh(cod)Cl]_2$ and Me-DuPhos in combination with Cl_2MeSiH as terminal reductant, the aldol was obtained in good yield with exceptional *syn*-diastereoselectivity. Good levels of *syn*-diastereoselectivity are persevered upon application of these conditions to alternate reactants, but use of enolizable aldehydes results in lower isolated yields. Although these reactions employ a chiral ligand, racemic products are obtained. As subsequently determined, the reductant, Cl_2MeSiH, promotes formation of silyl ketene acetals that spontaneously participate in carbonyl addition.[169] Use of Et_2MeSiH as reductant prevents such racemic background reactions, enabling enantioselective aldol addition of phenyl acrylate, albeit with lower levels of diastereocontrol.[168] Under these conditions, but in the absence of aldehyde, less than 5% of the silyl ketene acetal was detected after 24 hours. Additionally, exposure of preformed silyl ketene acetal to aldehyde under these conditions in the absence of the acrylate led to the formation of the reductive aldol product in < 5% yield. Reactions employing $PhMe_2SiD$ as reductant result in partial deuteration at the former acrylate β-position with complete regiocontrol, consistent with reversible acrylate hydrometalation.

The preceding enantioselective aldol additions of phenyl acrylate are accompanied by oxidative esterification side-products, which form with identical levels of diastereo- and enantioselectivity.[170] Studies into the reaction mechanism led to several significant observations. Very little of the rhodium precatalyst entered the catalytic cycle, instead pooling as the chloro-bridged dimer, $[Rh(BINAP)Cl]_2$. Moreover, upon exposure to hydrosilane, the dimer $[Rh(BINAP)Cl]_2$ was converted to a species with NMR spectral characteristics consistent with the corresponding hydride-bridged dimer, $[Rh(BINAP)H]_2$. To facilitate formation of the rhodium(I) hydride and, therefrom, entry into catalytic cycle **B** (Scheme 3), it was posited that cationic rhodium(I) precatalysts would be beneficial. Indeed, the authors found that using precatalyst (*R*)-$[Rh(cod)BINAP]BF_4$ an expansion of reaction scope to encompass enal electrophiles could be realized (Scheme 6). Alternatively, by simply using a greater excess silane, the reaction of β-substituted acrylate pronucleophiles could be achieved.[170,172] In further studies, the authors demonstrate that comparable yields and selectivities are obtained in the formation of the silyl-protected aldol adducts upon use of $^{i}PrMe_2SiH$ as reductant (not shown).[171]

In 2005, Nishiyama disclosed a remarkably efficient Rh(phebox) catalyst for asymmetric silane-mediated reductive aldol addition (Scheme 7).[173] Using *tert*-butyl acrylate as

pronucleophile, uniformly high *anti*-diastereo- and enantioselectivities were observed across diverse aldehyde electrophiles. The level of enantiomeric enrichment is highly dependent upon the choice of silane, suggesting the silyl group is present during the enantiodetermining event, which is consistent with catalytic cycle **B** (Scheme 3). Although attempts to modify the structure of the phebox ligand did not avail significant expansion of scope (not shown),[175,176] it was subsequently shown that ketones are competent electrophilic partners in reactions of β-substituted acrylate pronucleophiles catalyzed by the parent Rh(phebox) complex.[177] High levels of stereoselectivity were observed in reductive aldol additions to the chiral α-stereogenic aldehyde, 2-phenyl propionaladehyde, when the enantiofacial bias of the catalyst matches the Felkin-Anh preference the aldehyde.[179] Finally, cyclic enones were shown to be effective pronucleophiles.[180] These transformations are conducted at 50°C with slow addition of hydrosilane. *anti*-Diastereo- and enantioselective aldol addition is postulated to occur through a chair-like transition state[37] by way of the (*E*)-enolate in accord with the indicated stereochemical model.

In 2005, Willis developed a variant of the catalytic reductive aldol reaction wherein β-sulfido-aldehydes serve dually as carbonyl electrophiles and reductants.[171] As initially observed by Bendorff,[311] the β-sulfide directs aldehyde C-H oxidative addition to form a chelated acylrhodium hydride. Enone hydrometalation provides a rhodium enolate. Carbonyl addition to a second β-sulfido-aldehyde provides an aldolate, which upon C-O reductive elimination delivers the *O*-acyl aldol with concomitant catalyst regeneration. Thus, oxidative esterification balances reductive aldol addition. The authors later demonstrated that crossed three-component reductive aldol addition could be achieved upon use of *tert*- butyl glyoxalate as the electrophilic partner.[178] Although these reactions proceed in excellent yield, the lack of diastereo- and enantiocontrol diminishes their preparative utility (Scheme 8).

In 2002, Matsuda reported the first rhodium-catalyzed reductive Mannich reaction (Scheme 9).[230] Exposure of methyl acrylate to *N*-tosyl or *N*-phenyl imines in the presence of Et_2MeSiH and substoichiometric quantities of $[Rh(cod)\{P(OPh)_3\}_2]OTf$ led to good yields of the Mannich products, however, modest levels of diastereoselectivity were observed. A Rh(phebox)-catalyzed reductive Mannich reaction of *tert*-butyl acrylate and *N*-phenyl imines mediated by Et_2MeSiH was subsequently reported by Nishiyama (Scheme 9).[233] Good yields were accompanied by uniformly good levels of *anti*-diastereoselectivity. Finally, using Et_2Zn as terminal reductant, Ando developed a reductive Mannich reaction of methyl acrylate with *N*-benzyl or *N*-*p*-methoxyphenyl imines (Scheme 9).[236] In this process, *anti*-diastereoselective imine addition delivers a zinc amides that undergoes cyclization to furnish *cis*-β- lactams in good to excellent yields and high levels of relative stereocontrol. The authors applied this method to the synthesis of the β-lactam cholesterol absorption inhibitor (±)-ezetimib (not shown).[237]

2.2.2 Reductant = Hydrogen—Hydroformylation, the prototypical C-C bond forming hydrogenation, is a longstanding method for industrial chemical manufacture.[312–317] As described in the review literature,[154,273,277,278,318,319] the Krische laboratory developed the first hydrogen-mediated reductive couplings beyond carbon monoxide, including reductive aldol additions.[181–189] Using cationic rhodium catalysts, hydrogenation of enone-aldehydes

promotes *syn*-diastereoselective aldol cyclization to form 5- and 6-membered rings (Scheme 10).[181–183] Enones bearing tethered ketones also undergo aldol cyclization with complete levels of *syn*-diastereoselectivity, however, variable quantities of competing enone hydrogenation are observed (indicated parenthetically).[182] In related cyclizations of enones bearing tethered 1,3-diketones, bicyclic ring systems that incorporate three contiguous stereocenters are formed and competing enone hydrogenation is not observed.[182] The aldol addition of aldehyde enolates to ketones represents a particularly challenging transformation due to the reversibility of carbonyl addition.[11,320] Rhodium-catalyzed hydrogenation of enal-ketones delivers the aldol adducts in good yield with a preference for the *syn*-diastereomer, but competitive enal hydrogenation is again evident.[183]

Initially developed intermolecular variants of the hydrogen-mediated reductive aldol reaction gave the desired products as diastereomeric mixtures (not shown).[181] It was later found that cationic rhodium complexes modified by tri-2-furylphosphine[321,322] catalyzed intermolecular hydrogen-mediated reductive aldol addition of methyl vinyl ketone or ethyl vinyl ketone with excellent levels of *syn*-diastereoselectivity (Scheme 11).[185] Notably, diverse reducible functional groups (alkynes, alkenes, benzylic ethers, nitroaryl and aromatic bromides) were tolerated under the reductive coupling conditions. Additionally, more highly functionalized enone pronucleophiles, such as crotyl vinyl ketone, were found to undergo chemoselective aldol reductive coupling at the less substituted vinyl moiety with good levels of *syn*-diastereoselectivity and without competing hydrogenation of the crotyl substructure.[186] Substrate-directed asymmetric induction is achieved in intermolecular hydrogen-mediated reductive aldol additions of vinyl ketones to *N*-Boc-α-aminoaldehydes.[187] Complete levels of *syn*-diastereoselectivity are accompanied by complete levels of *anti*-Felkin-Anh control due to intramolecular NH-O hydrogen-bonding in the low dielectric reaction medium. As determined by HPLC analysis, enantiomeric purity of the configurationally labile α-aminoaldehydes is fully preserved under the essentially neutral hydrogenation conditions. Acrolein and higher enals participate in hydrogenative aldol coupling with α-ketoaldehydes.[184] The resulting β-hydroxy-γ-ketoaldehydes are unstable, but are amenable to condensation with hydrazine to furnish 3,5-disubstituted pyridazines in good yield (not shown).

Highly diastereo- and enantioselective intermolecular hydrogen-mediated reductive aldol additions required the design of a chiral congener of tri-2-furylphosphine ligand; a formidable task as use of chelating phosphine ligands led to catalytically inactive rhodium complexes. Ultimately, a benzothiophene-substituted TADDOL-like phosphonite ligand was identified through modular ligand design, in which the *P*-aryl, ketal and carbinol substituents of the TADDOL-like scaffold were independently varied to illuminate key structure-selectivity trends. The ligand **AP-I** (“AbbasPhos-I”), which combines all three optimal substructures, provided the highest yields and stereoselectivities. Using the preformed cationic rhodium phosphonite complex, [Rh(cod)(**AP-I**)$_2$]OTf, hydrogenation of commercially available methyl vinyl ketone or ethyl vinyl ketone in the presence of aliphatic aldehydes provided the aldol adducts with excellent control of relative and absolute stereochemistry (Scheme 12).[188] The reactions are operationally facile and are conducted at 0 °C simply using balloons of hydrogen gas. A stunning application of the asymmetric

intermolecular hydrogen-mediated reductive aldol reaction is found in the total synthesis of the actin-binding marine polyketide swinholide A, a macrodiolide bearing 30 stereogenic centers (Scheme 13).[188] Hydrogenative aldol addition occurs chemoselectively in the presence of alkene and diene functional groups with good levels of catalyst-directed diastereoselectivity.

Regarding the mechanism of the hydrogen-mediated reductive aldol reaction, cationic rhodium-catalysts are required, as neutral rhodium complexes promote simple enone hydrogenation. Additionally, basic additives such as lithium carbonate incur a small but significant increase in isolated yield (ca 20%). The acidity of cationic rhodium hydrides[323] along with the improvement in yield upon introduction of substoichiometric base suggests heterolytic hydrogen activation ($H_2 + Rh^I\text{-}X \rightarrow Rh^I\text{-}H + HX$)[308–310] and entry into catalytic cycles involving low valent rhodium monohydrides, that is, catalytic cycle **D** (Scheme 3). Here, *syn*-diastereoselectivity would require enone hydrometalation to form the (*Z*)-rhodium enolate as the major isomer. An alternate interpretation is based on the following observations. Unlike neutral rhodium(I) complexes,[283–285] hydrogen oxidative addition is often turn-over-limiting for cationic rhodium(I) complexes.[286–289] Cationic rhodium(I) complexes also have an additional vacant coordination site, which facilitates simultaneous coordination of both enone and aldehyde reactants. These effects may conspire to promote enone-aldehyde oxidative coupling to form rhodium(III) oxametalacycles[303] as in catalytic cycle **C** (Scheme 3). To gain insight into the reaction mechanism, the intermolecular reductive coupling of methyl vinyl ketone was conducted under an atmosphere of elemental deuterium (Scheme 14).[185] Precisely one deuterium atom was incorporated into the aldol product exclusively at the former enone β-position. While this result alone cannot differentiate catalytic cycles **C** and **D**, alkene hydrometalation is often reversible and typically does not occur with complete regioselectivity, suggesting oxidative coupling pathways may be operative. The rhodium complex [Rh(cod)(**AP-I**)$_2$]OTf has been characterized single crystal X-ray diffraction analysis. A related model to account for diastereo- and enantiodetermining oxidative coupling is herewith proposed (Scheme 14).

Related hydrogen-mediated reductive Mannich-type reactions of enone and vinyl azine pronucleophiles have been developed (Scheme 15).[232,238] Rhodium-catalyzed hydrogenation of methyl vinyl ketone or ethyl vinyl ketone in the presence of electron deficient *N*-(*o*-nitrophenylsulfonyl)imines delivers reductive Mannich-type products with good levels of *syn*-diastereoselectivity.[232] *N*-Arylimines also participate in reductive coupling, but lower levels of *syn*-diastereoselectivity are evident. Similarly, hydrogenation of 2-vinyl azines in the presence of *N*-arylsulfonyl imines at ambient temperature and pressure employing cationic rhodium catalysts results in regioselective reductive coupling to furnish branched products of imine addition.[238] Under an atmosphere of elemental deuterium, the reductive coupling product incorporates a single deuterium atom exclusively at the former β-position of the vinyl moiety, which is consistent with vinyl azine-imine oxidative coupling to furnish a cationic aza-rhodacyclopentane, as described in catalytic mechanism **C** (Scheme 3).

2.3. Cobalt

The first cobalt catalysts for reductive aldol coupling were described by Mukaiyama in 1989.[190] A cobalt(II) precatalyst modified by dipivaloylmethane (dpm) was used in combination with phenylsilane as reductant (Scheme 16). Diverse pronucleophiles participate in the reductive coupling, including α,β-unsaturated nitriles, amides and esters. The aldol adducts are formed in good yield, but as diastereomeric mixtures. Related aldol cyclizations occur with complete levels of *syn*-diastereoselectivity,[191] which may be explained on the basis of the indicated stereochemical model, which involves aldol addition by way of the (*Z*)-cobalt enolate through a closed transition structure.[37] Unlike the intermolecular reactions, attempted aldol cycloreduction of α,β-unsaturated nitriles, amides and esters resulted in simple conjugate reduction.

Investigations into the reaction mechanism reveal silane-dependent partitioning of hydrometalative vs anion radical pathways (Scheme 17).[192] Aldol cyclization mediated by d_3-phenylsilane results in incorporation of a single deuterium at the former enone β-position as a 1:1 epimeric mixture, inferring rapid isomerization of the kinetic cobalt enolate in advance of carbonyl addition. For bis(enone) substrates, the silane source was found to influence competing Michael cycloreduction and [2 + 2] cycloaddition manifolds.[192,324] Tetrahedral d^7-metal complexes such as $Co(dpm)_2$ are paramagnetic and participate in single electron oxidative addition.[325] Co(II) complexes are also subject to disproportionation.[326] As illustrated in equations **A** and **B** (Scheme 16), these reaction manifolds enable access to cobalt(I) complexes, which exist in equilibrium with the corresponding cobalt(III) silyl hydrides. Whereas use of $PhSiH_3$, for which oxidative addition occurs readily, triggers hydrometalation *en route* to products of reductive cyclization, use of $PhMeSiH_2$ stabilizes cobalt(I) to promote catalytic anion radical [2 + 2] cycloaddition. Intervention of anion radical intermediates is corroborated by [2 + 2]cycloadditions induced via cathodic reduction[327] or single electron transfer from arene anion radicals.[328]

In a powerful extension of scope, the laboratory of Lam reports cobalt-catalyzed reductive aldol additions of α,β-unsaturated amides to ketone electrophiles mediated by Et_2Zn (Scheme 17).[193–195] The authors initial report describes aldol cyclizations to form 5- and 6-membered rings.[193] Excellent levels of *syn*-diastereoselectivity were observed. Intermolecular reactions were developed subsequently.[194] Here, acrylamides as well as fumaric amides undergo *syn*-diastereoselective aldol addition to ketones. Notably, the fumaric amides deliver aldol adducts as single regioisomers. Attempted enantioselective reactions using chiral ligands led to racemic products, suggesting aldol addition occurs through the (*Z*)-zinc(II) enolate. Hence, to induce asymmetry an *N*-acryloyloxazolidine pronucleophile is employed.[195] The mechanism for zinc(II) enolate formation is based on related Lewis acid-assisted oxidative additions of transition metals to enones to form oxy-π-allylmetal species.[329–333] Specifically, β-hydride elimination from the indicated ethyl substituted oxy-π-allylcobalt intermediate followed by C-H reductive elimination delivers the zinc(II) enolate (Scheme 18). The ethylzinc(II) enolates that arise via cobalt-catalyzed conjugate reduction of acryloylmorpholine can also be captured via imine addition to furnish Mannich products with good levels of *anti*-diastereoselectivity (Scheme 19).[235]

2.4. Iridium

Highly *syn*-diastereo- and enantioselective iridium-catalyzed reductive aldol couplings were reported by Morken using an Ir(pybox) catalyst and Et_2MeSiH as terminal reductant (Scheme 20).[196] Inductively activated aldehydes that incorporate adjacent alkoxy groups are required as the parent aliphatic aldehydes do not participate in coupling. Closely related Ir(phebox) complexes investigated by Nishiyama catalyze *anti*-diastereo- and enantioselective reductive aldol reactions of *tert*-butyl acrylate and benzaldehyde, representing a ligand-dependent inversion in diastereoselectivity.[175] Excellent yields and stereoselectivities are observed at relatively low loadings of the catalyst (1 mol%) (Scheme 20).

As described by Morken, iridium-catalyzed reductive couplings of pentafluorophenyl acrylates with *N*-aryl imines mediated by Et_2MeSiH provide Mannich products, which spontaneously cyclize to deliver β-lactams (Scheme 21).[231] Competing hydrosilylation of alkene and alkyne functional groups is not observed. A linear Hammett correlation involving both the imine *N*-aryl moiety and the acrylate aryloxy group implicate rate-determining cyclization. Interestingly, whereas Ando's rhodium-catalyzed reductive Mannich reactions deliver the *cis*-β-lactams (Scheme 9),[237] the iridium-catalyzed reactions display a pronounced preference for the corresponding *trans*-isomers. This divergence in diastereoselectivity may be attributed to intervention of zinc(II) vs iridium(III) enolates, respectively.

2.5. Ruthenium

Despite enormous progress in the area of ruthenium-catalyzed carbonyl reductive coupling,[275,334–336] true reductive aldol couplings have not been reported. However, closely related transformations have been described by Ryu, who reports a 2-propanol-mediated reductive homo-coupling of enals catalyzed by $RuHCl(CO)(PPh_3)_3$ (Scheme 22).[197] This transformation involves tandem reductive aldol addition-redox isomerization-aldehyde reduction and exploits 2-propanol as the terminal reductant. The catalytic mechanism is initiated by enal hydroruthenation to furnish a ruthenium(II) enolate. Aldehyde addition provides an aldolate, which upon internal redox isomerization delivers a transient β-ketoaldehyde. 2-Propanol-mediated reduction of the formyl group provides the reaction product. Related redox-neutral cross-couplings have been described wherein alcohols serve dually as reductants and aldehyde proelectrophiles (Scheme 22).[199]

2.6. Palladium

In 1998, a palladium-catalyzed reductive aldol coupling was reported by Kiyooka (Scheme 23).[200] The reaction employs tetrakis(triphenylphosphine)palladium as precatalyst and Cl_3SiH as reductant. Using *N,N*-dimethyl acrylamide as pronucleophiles, the aldol product is generated in good yield but with modest *anti*-diastereoselectivity. The corresponding reaction of *tert*-butyl acrylate occurs in low yield and modest *syn*-diastereoselectivity. The reaction mechanism is postulated to involve oxidative addition of the trichlorosilane to palladium(0), followed by hydropalladation of the α,β-unsaturated compound. However, given the fact that Cl_3SiH functions as a reductant in the presence of Lewis base (*vide infra*, Section 2.11.), it is possible that palladium is not required for the reported transformations.

2.7. Nickel

Triethylborane-mediated reductive aldol additions catalyzed by nickel were developed in the laboratory of Montgomery (Scheme 24).[201] Surprisingly, sterically unencumbered aryl iodides are required for initiation of the catalytic cycle. Specifically, oxidative addition of iodobenzene to nickel(0) with subsequent coordination of acrylate and triethylborane triggers formation of an ethyl(iodo)nickel complex and a β-aryl boron enolate (as evinced by conjugate addition-aldol addition byproducts). Entry into the catalytic cycle occurs from the ethyl(iodo)nickel complex, which upon elimination of ethylene forms a nickel hydride. Simultaneous coordination of acrylate and triethylborane results in acrylate hydrometalation, likely by way of an oxy-allylnickel(II) intermediate,[329–333] to form a boron enolate with regeneration of the key ethyl(iodo)nickel complex to close the catalytic cycle. The boron enolate undergoes spontaneous aldol addition with good levels of *syn*-diastereoselectivity. Corroborating the authors mechanistic hypothesis, nickel(II) precatalysts promote an alternate reaction pathway that involves ethyl transfer to the acrylate followed by aldol addition.

The Lam laboratory reports highly diastereoselective nickel-catalyzed reductive aldol cyclizations onto tethered ketones mediated by Et_2Zn (Scheme 25).[202] Esters and amides undergo cycloreduction to form lactone and lactam products, respectively. The mechanism was probed by deuterium labelling studies, but these were inconclusive (not shown). However, when the ketone electrophile is tethered to the α,β-unsaturated carbonyl through the β-carbon the indicated homoaldol adduct is obtained. This result suggests intervention of catalytic cycle **C** (Scheme 3), wherein oxametalacycles formation occurs by of oxy-π-allylnickel intermediates.[329–333] The nickel-catalyzed reductive aldol cyclization was used by the Lam laboratory to complete the formal synthesis of salinosporamide A (Scheme 25).[203]

2.8. Platinum

Platinum complexes modified by $SnCl_2$ are effective catalysts for alkene hydrogenation.[337–339] Jang and coworkers have demonstrated that the $PtCl_2$-$SnCl_2$ catalyst system promotes inter- and intramolecular hydrogen-mediated reductive aldol reactions (Scheme 26).[204] Addition occurs with good to complete levels of *syn*-diastereoselectivity for intermolecular couplings and corresponding cycloreductions, respectively. Reactions mediated by triethylsilane also were explored but lower efficiencies were observed (not shown). Under a deuterium atmosphere, incomplete incorporation of ^2H at the former enone β-position is evident, corroborating reversible enone hydrometalation in advance of C-C coupling. A monohydride mechanism involving $LnPtD(SnCl_3)$ was proposed (see Scheme 3, Cycle **D**).

2.9. Copper

Reductive aldol cyclizations promoted by stoichiometric quantities of Stryker's reagent, $[Ph_3PCuH]_6$, have been described.[205–207] Additionally, Stryker's reagent was reported to catalyze hydrosilane-mediated conjugate reduction of enones to form enol silanes that engage in aldol reactions with carbonyl electrophiles.[135–136] While true reductive aldol reactions catalyzed by Stryker's reagent remain undeveloped, related ynone-ketone

cycloreductions catalyzed by Stryker's reagent and mediated by hydrosilane have been reported by Chui (Scheme 27).[207]

The first copper-catalyzed reductive aldol reaction was reported by Maruoka in 1999.[208] The reaction mechanism is believed to involve copper(I) chloride initiated enone hydrostannation to form a tin enolate. The reaction does not proceed in the presence of galvinoxyl (5 mol%), which implicates a catalytic mechanism involving radical species. The authors speculate that copper serves a dual role in catalyzing tin enolate formation and subsequent Mukaiyama aldol addition. This process is applicable to the addition of vinyl ketone pronucleophiles to aliphatic, α,β-unsaturated or aromatic aldehydes. Good isolated yields are accompanied by modest levels of *syn*-diastereoselectivity (Scheme 28).

Copper-catalyzed reductive aldol cyclizations mediated by silane were reported by Lam (Scheme 29).[209] Upon exposure of keto-enones to 1,1,3,3-tetramethylhydroxysiloxane (TMDS) in the presence of copper catalysts modified by MeO-BIPHEP, β-hydroxylactone formation occurs with complete *syn*-diastereoselectivity and moderate enantioselectivity.[209] In related work, reductive cyclization of α,β-unsaturated keto-amides was found to provide 4-hydroxypiperdin-2-ones with high levels of substrate-directed asymmetric induction.[183] The authors propose a mechanism akin to catalytic cycle **D** (Scheme 3), in which $Cu(OAc)_2 \bullet H_2O$ is converted to a copper(I) monohydride complex, which hydrometallates the α,β-unsaturated ester or amide to form a copper enolate. Intramolecular ketone addition delivers a copper aldolate, which upon σ-bond metathesis with siloxane[304–306] forms the aldol product with regeneration of the copper(I) monohydride.

An impressive diastereo- and enantioselective intermolecular reductive aldol coupling of acrylate pronucleophiles to unactivated ketones was reported by Riant (Scheme 30).[211] Using a copper complex derived from $[CuF(PPh_3)_3]\cdot 2MeOH$ and a "TANIAPHOS" ligand in combination with phenylsilane as reductant, exceptional levels of *anti*-diastereo- and enantioselectivity are observed. Whereas corresponding aldehyde additions conducted under these conditions exhibit modest levels of diastereoselectivity and uneven levels of enantioselectivity (not shown),[212,215] related cyclizations of enone-diones provide bicyclic aldol adducts that incorporate 3-contiguous stereogenic centers with excellent control of relative and absolute stereochemistry.[217] Copper-catalyzed acrylate-ketone reductive aldol coupling using $[CuF(PPh_3)_3]\cdot 2MeOH$ as precatalyst has been explored further by Fukuzawa[218] and Li;[219] however, improved selectivities were not observed (not shown). Later, Li reported high yielding reductive aldol reactions of dimethyl maleate with acetophenones that deliver racemic lactone products as diastereomeric mixtures (not shown).[220]

Shibasaki and Kanai explored the intermolecular reductive aldol coupling of acrylates, β-substituted acrylates and allenic esters using $[CuF(PPh_3)_3]\bullet 2EtOH$ as precatalyst and triethoxysilane as the stoichiometric reductant, which displayed modest levels of relative and absolute stereocontrol (not shown).[213] However, in subsequent work using copper catalysts modified by a "TANIAPHOS" ligand and pinacolborane as reductant, enhanced stereoselectivities were observed in reductive aldol couplings of allenic esters to acetophenone (Scheme 31).[214] Furthermore, using (*R*)-DTBM-SEGPHOS as ligand in

combination with Cy_3P as an additive, the same reactants form products of vinylogous reductive aldol addition with high levels of enantiocontrol and complete alkene (Z)-stereoselectivity (Scheme 31). As in the preceding examples (Schemes 29 and 30), these processes are postulated to proceed by way of copper(I) monohydrides through catalytic cycle **D** (Scheme 3).

Lipshutz reports a copper-catalyzed reductive aldol cyclization of β,β-disubstituted enone pronucleophiles using a copper catalyst modified by a "JOSIPHOS" ligand (Scheme 32).[216] In this process, enantiodetermining enone reduction triggers aldol cyclization to form products that embody 3-contiguous stereogenic centers with excellent levels of diastereo- and enantioselectivity. As the initially formed stereocenter guides the stereochemistry of carbonyl addition, the reactions are stereospecific with (*E*)- and (*Z*) enones providing enantiomeric products under otherwise identical conditions. Specifically, pseudo-equatorial disposition of the methyl-bearing stereocenter that arises via conjugate reduction enforces the indicated chair-like conformation from which carbonyl addition occurs by way of the (*Z*)-enolate.

In 2008, Shibasaki and Kanai reported copper-catalyzed reductive Mannich reactions of acrylate pronucleophiles with *N*-diphenylphosphinoyl ketimines mediated by pinacol borane (Scheme 33).[234] Using a CuOAc-PPh_3 catalyst, the Mannich products are generated in good yield with excellent diastereocontrol for ketimines bearing aromatic, aliphatic and vinyl substituents. In an initial evaluation of chiral ligands using borane reductants, significant levels of enantioselectivity proved to be elusive. However, using $(EtO)_3SiH$ as reductant highly diastereo- and enantioselective copper-catalyzed reductive Mannich reactions could be achieved.

Based on the concept of using azaarenes as activating groups,[238,340] Lam developed copper-catalyzed reductive aldol reactions of vinyl-substituted heteroaromatic pronucleophiles with ketones (Scheme 34).[239] The absolute stereochemistry of the indicated isoquinoline-containing product is opposite to that of the pyrimidine-containing product, even though the same enantiomer of chiral ligand was employed used. The authors developed related diastereo- and enantioselective reductive coupling of vinylazaarenes with *N*-Boc aldimines mediated by 1,1,3,3-tetramethylhydroxysiloxane (TMDS). The Mannich-type products are generated with good levels of *anti*-diastereo- and enantioselectivity.

2.10. Zinc

Very recently, a zinc-catalyzed acrylate-ketone reductive aldol coupling was reported by Mlynarski (Scheme 35).[221] Using the catalyst derived from $Zn(OAc)_2$ and the indicated chiral diamine ligand, good yields of aldol product were obtained. Although modest stereoselectivities were observed, this catalyst system merits further investigation due to its cost-effectiveness. The reducing agent, $(EtO)_3SiH$, readily forms ate-complexes with Lewis basic compounds, and control experiments conducted in the absence of metal salts were not disclosed. As described in the review literature,[341] the proposed intervention of zinc vs silicon hydride intermediates is unclear.

2.11. Indium

Following reports of stoichiometric $InBr_3$-Bu_3SnH promoted reductive aldol additions by Baba and Shibata,[222] catalytic processes were developed employing hydrosilane as reductant (Scheme 36).[223] This catalyst system is applicable to the *syn*-diastereoselective coupling of enone pronucleophiles with aldehydes. The authors propose that the catalytic cycle is initiated via transmetallation between $InBr_3$ and Et_3SiH to form $HInBr_2$ and Et_3SiBr, enabling entry to a monohydride-based catalytic cycle (see Scheme 6, Cycle **D**). *syn*-Diastereoselectivity is believed to arise through addition of the (*Z*)-indium enolate, which is formed upon hydrometalation of the enone *s-cis*-conformer through a 6-centered transition structure,[133,134] followed by stereospecific carbonyl addition through a Zimmerman-Traxler type transition structure.[37] A contemporaneous study by Hosomi and Miura utilizes $PhSiH_3$ as reductant for intermolecular indium-catalyzed reductive aldol coupling and, as shown, corresponding reductive cyclizations.[224] In subsequent work, Shibata conducted intermolecular indium-catalyzed enone-ketone reductive aldol couplings that proceed with high levels of *syn*-diastereoselectivity.[225] Remarkably, the latter process is applicable to sensitive α-bromoketones.

2.12. Organocatalyzed Reactions

Beyond metal-catalyzed processes, significant progress on organocatalytic reductive aldol additions has been made.[226–229] Lewis basic catalysts in combination with Cl_3SiH as reductant have proven particularly effective, as initially illustrated by Nakajima and Sugiura (Scheme 37).[226] Specifically, using substoichiometric quantities $Ph_3P{=}O$, enone-aldehyde reductive coupling occurs in good yield but with low levels of diastereocontrol. Enone reduction from the *s-cis*-conformer was postulated to occur through the indicated boat-like transition structure. In subsequent work, the same authors disclosed highly *syn*-diastereo- and enantioselective reductive aldol reactions using (S)-BINAPO as catalyst.[227] Asymmetric additions to aromatic and α,β-unsaturated aldehydes were described. Continued studies by Nakajima and Kotani demonstrate that tertiary amines can serve as reductants in *syn*-diastereo- and enantioselective reductive aldol reactions.[228] These processes likely involve hydride transfer from the amine to Cl_3SiOTf by virtue of the so-called *tert*-amino effect; a topic that has recently been reviewed.[342] Schindler recently reported a variant of the organocatalyzed reductive aldol reaction mediated by Cl_3SiH that exploits α,α-disubstituted pronucleophiles.[229] This process delivers aldol adducts bearing quaternary carbon stereocenters. The authors propose a boat-like transition structure to account for relative stereochemistry. Diastereoselectivity was dependent on the steric demand of the aldehyde with pivaldehyde and, as illustrated, *ortho*-substituted benzaldehydes providing the highest levels of relative stereocontrol. A secondary amine-catalyzed tandem conjugate reduction-Mannich addition mediated by the Hantzsch ester has been described, but this method is a step-wise process in which the imine is added to the reaction mixture after the enal is reduced (not shown).[343]

3. Conclusion and Outlook

Chemical synthesis in the 20th century to the present day has largely been reliant on the use of non-native structural elements to manage issues of reactivity and selectivity. More ideal

chemical synthesis requires direct deployment of basic chemical feedstocks in atom-efficient transformations for which issues of isomer-selectivity and functional group compatibility are catalyst controlled.[242] While concepts pertaining to efficiency in chemical synthesis are longstanding[344,345] and perhaps self-evident, the frequency with which they are discussed far exceeds the instances in which they are realized. Nevertheless, progress on step- and atom-efficient complex molecule synthesis has been made.[346,347] In this context, the aldol reaction, which itself may be viewed as a bellwether for organic chemistry as a field, continues to pose unmet challenges in efficiency and selectivity. The reductive aldol reaction, discovered just over 30 years ago, addresses many of these unresolved issues: (a) the regiospecific nature of the reductive aldol reaction enables formation of aldol isomers that are otherwise inaccessible; (b) highly diastereo- and enantioselective additions to ketone electrophiles is possible; (c) the parent acrylate and enone pronucleophiles are inexpensive chemical feedstocks; and (d) in the case of hydrogen-mediated reductive aldol couplings, [181–189] diastereo- and enantioselective reactions occur in the absence of stoichiometric byproducts. Many future challenges remain. For example, the majority of reductive aldol reactions employ hydrosilanes as reductants, which are relatively expensive and deliver adducts that incorporate silyl ether moieties. Adapting these catalytic systems to more cost-effective, less mass-intensive reductants, such as formate, carbon monoxide, 2-propanol or hydrogen, and the use of inexpensive base-metal catalysts, would increase the suitability of these methods *vis-a-vis* large-volume chemical manufacture. It is the authors' hope that the chemistry and concepts put forth in this and other monographs[242,276,277,279,280] will accelerate progress toward these goals and, more broadly, further shift the paradigm for C-C bond formation away from premetalated reagents toward processes that directly exploit abundant, inexpensive and renewable feedstocks.

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Biographies

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), ACS Award for Creative Work in Synthetic Organic Chemistry (2020).

Cole C. Meyer obtained a B.S. in chemistry with honors from the University of California at Los Angeles (2018), where he conducted research under the tutelage of Professor Patrick G. Harran and received the Dean's Prize Medal of Excellence. In Fall 2018, he entered the doctoral degree program at the University of Texas at Austin in the laboratory of Professor Michael J. Krische, where he is developing enantioselective metal-catalyzed carbonyl reductive couplings of π-unsaturated feedstocks.

Eliezer Ortiz obtained a B.S. in biochemistry with honors from the University of Texas at San Antonio (2019), where he conducted research under the instruction of Professor Doug E. Frantz and received the Dr. Thyagarajan award for excellence in organic chemistry. After spending a summer as a Postbaccalaureate Research Fellow at UTSA, he entered the doctoral degree program at the University of Texas at Austin in the laboratory of Professor Michael J. Krische, in the Fall of 2019, where he is developing enantioselective metal-catalyzed carbonyl reductive couplings of π-unsaturated feedstocks.

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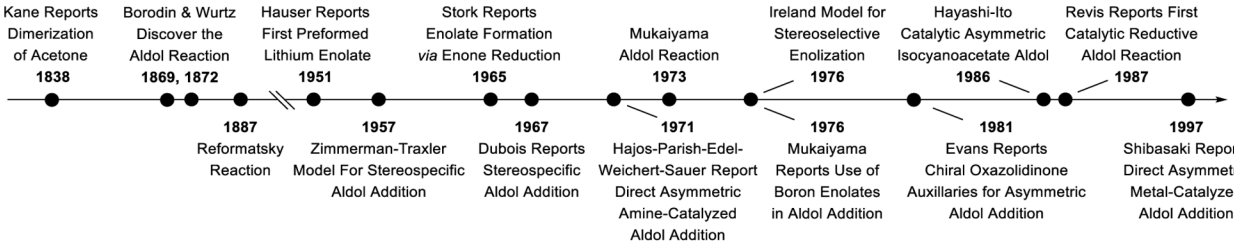


Figure 1.
Selected milestones in aldol addition and enolization chemistry.

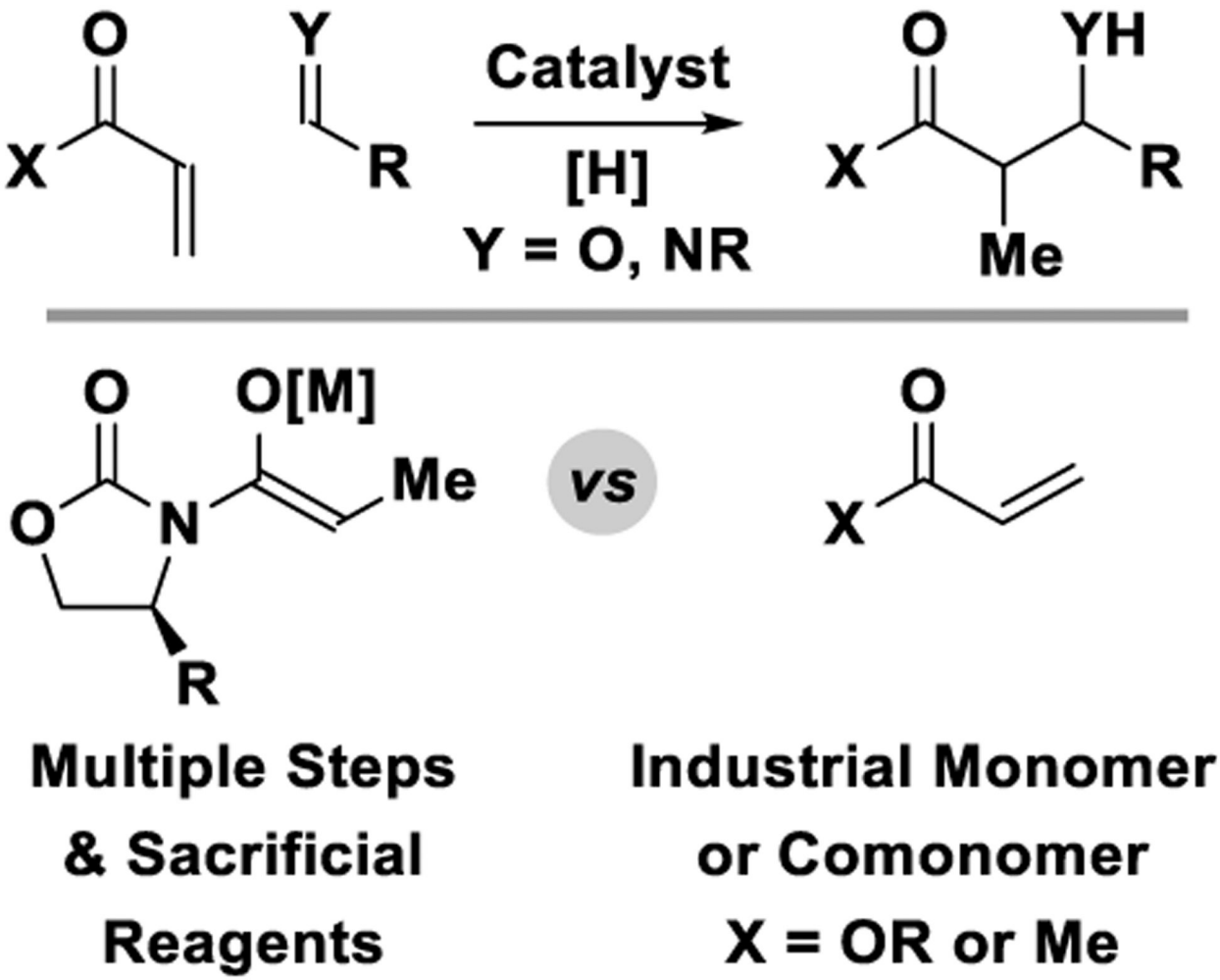
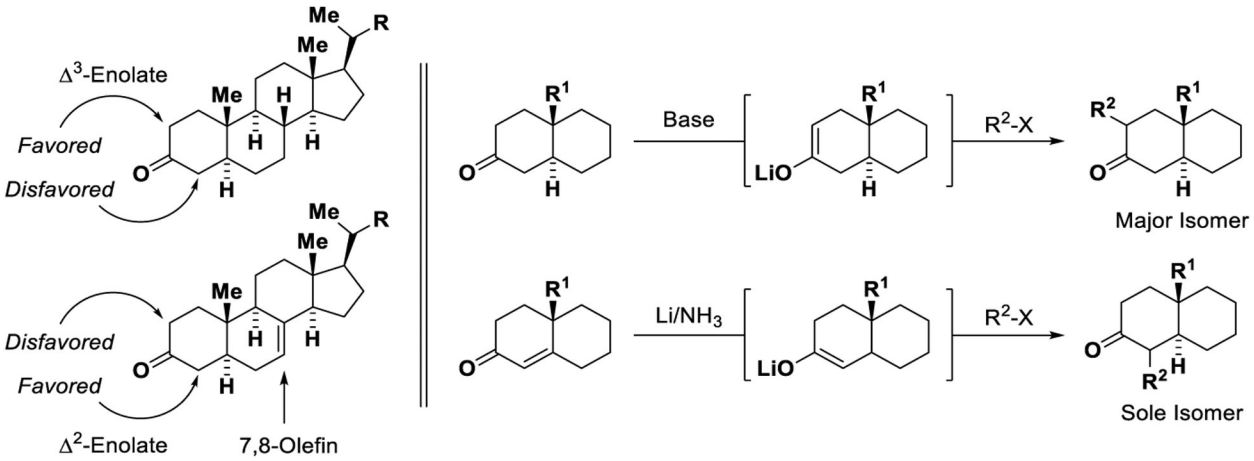
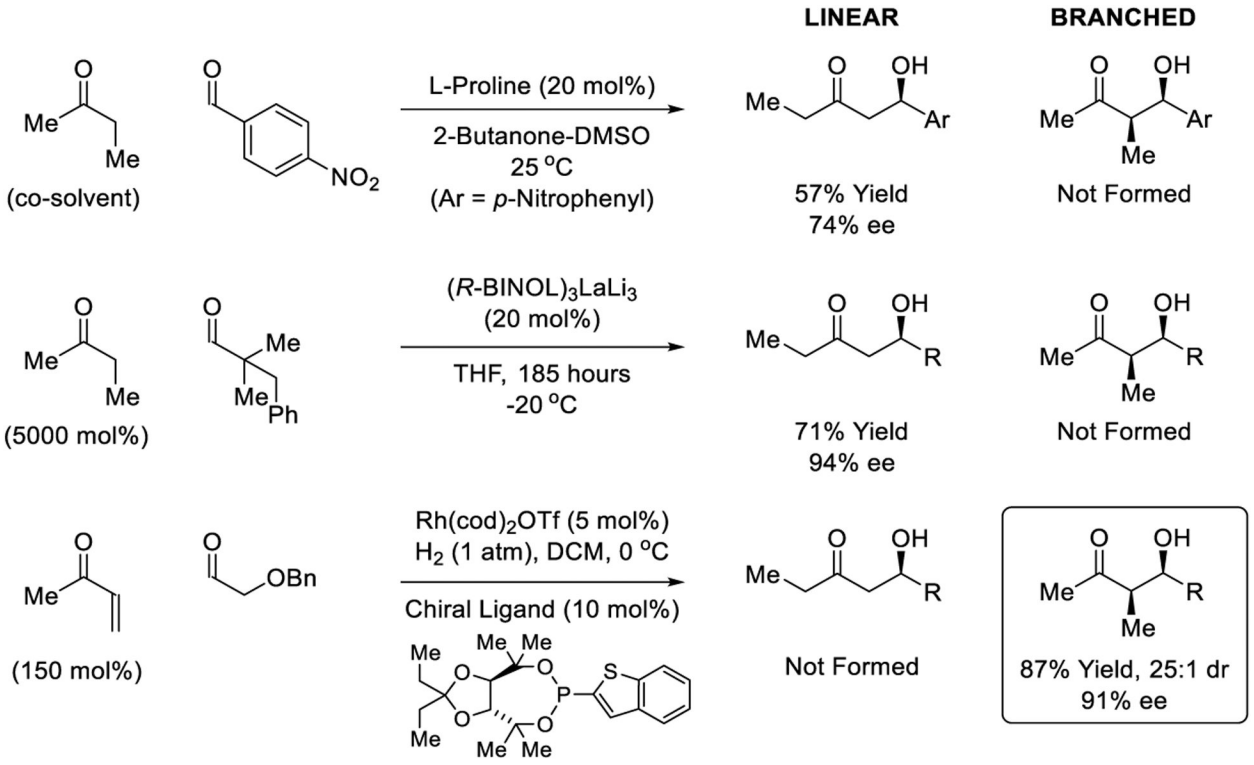


Figure 2.
Catalytic reductive aldol and Mannich additions using abundant feedstock pronucleophiles.



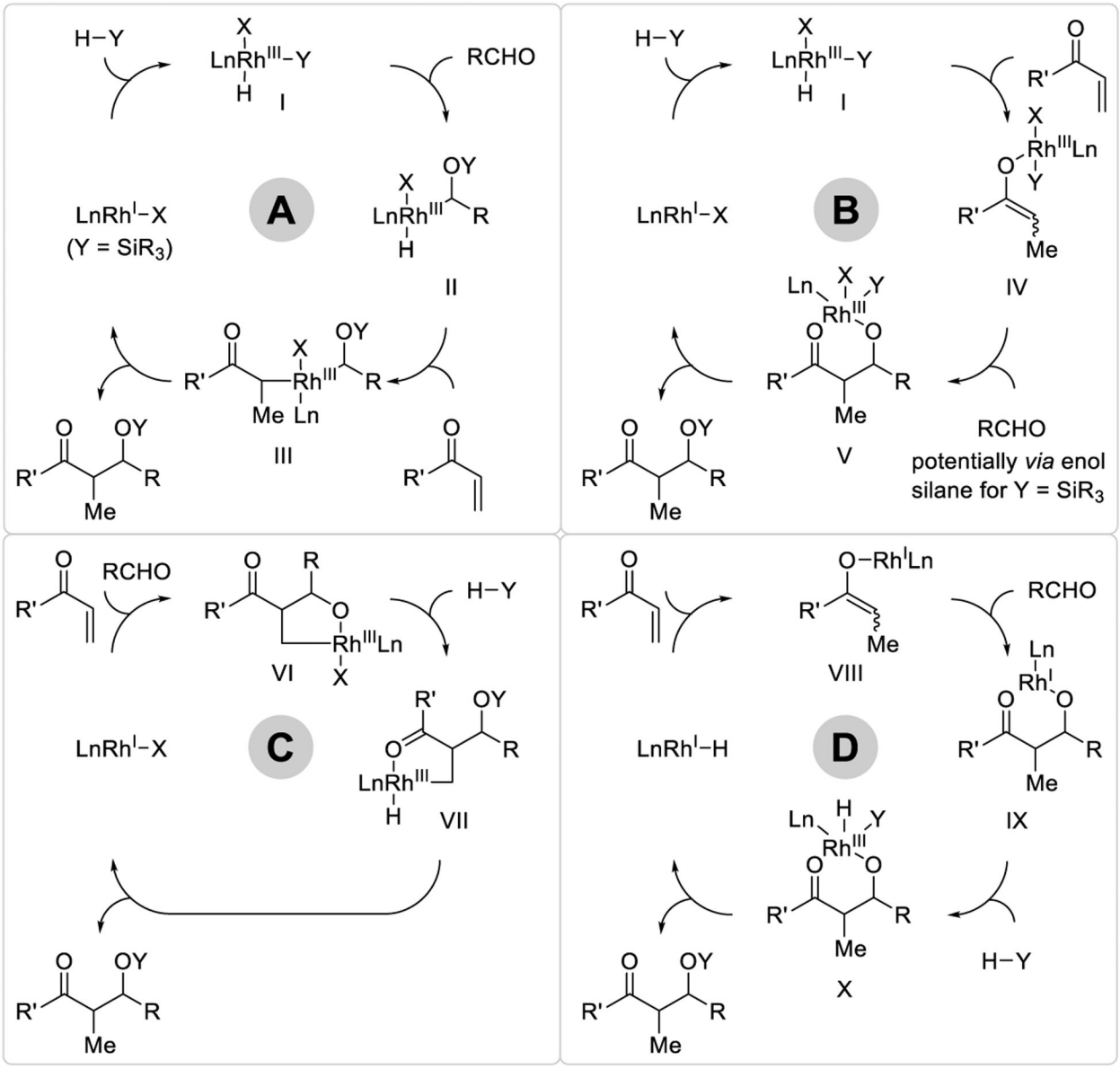
Scheme 1.

Classic studies highlighting the challenge of regioselective enolization.



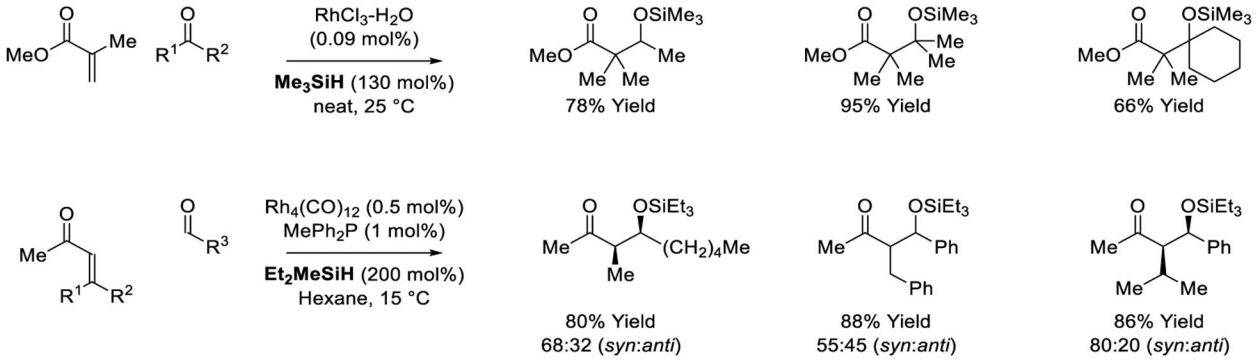
Scheme 2.

Catalytic reductive coupling enables regiospecific formation of branched aldol isomers.



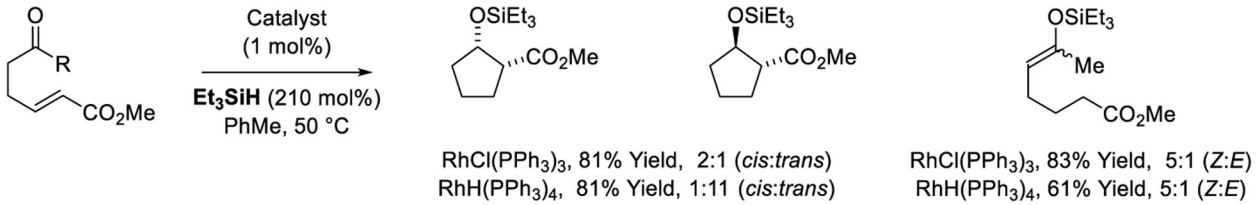
Scheme 3.

General mechanisms for metal-catalyzed reductive aldol addition using silane as terminal reductant.



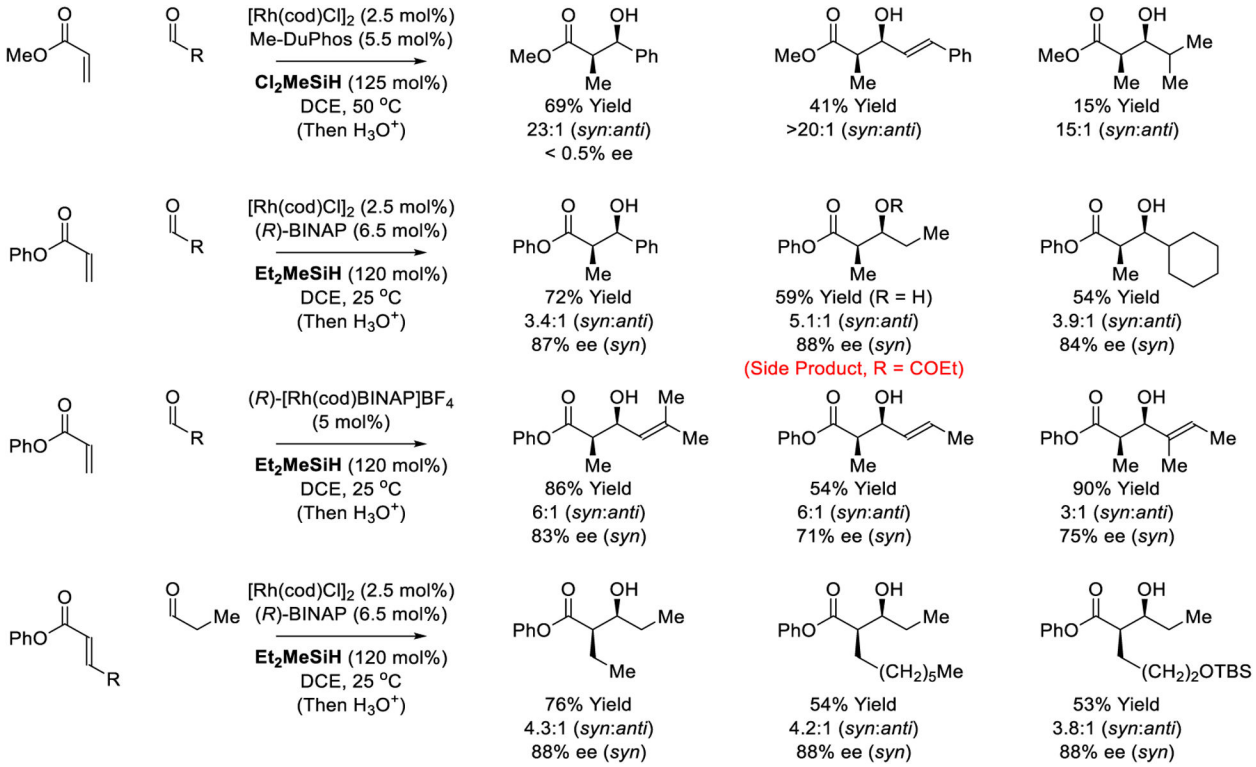
Scheme 4.

Rhodium-catalyzed reductive aldol reactions reported by Revis and Matsuda.



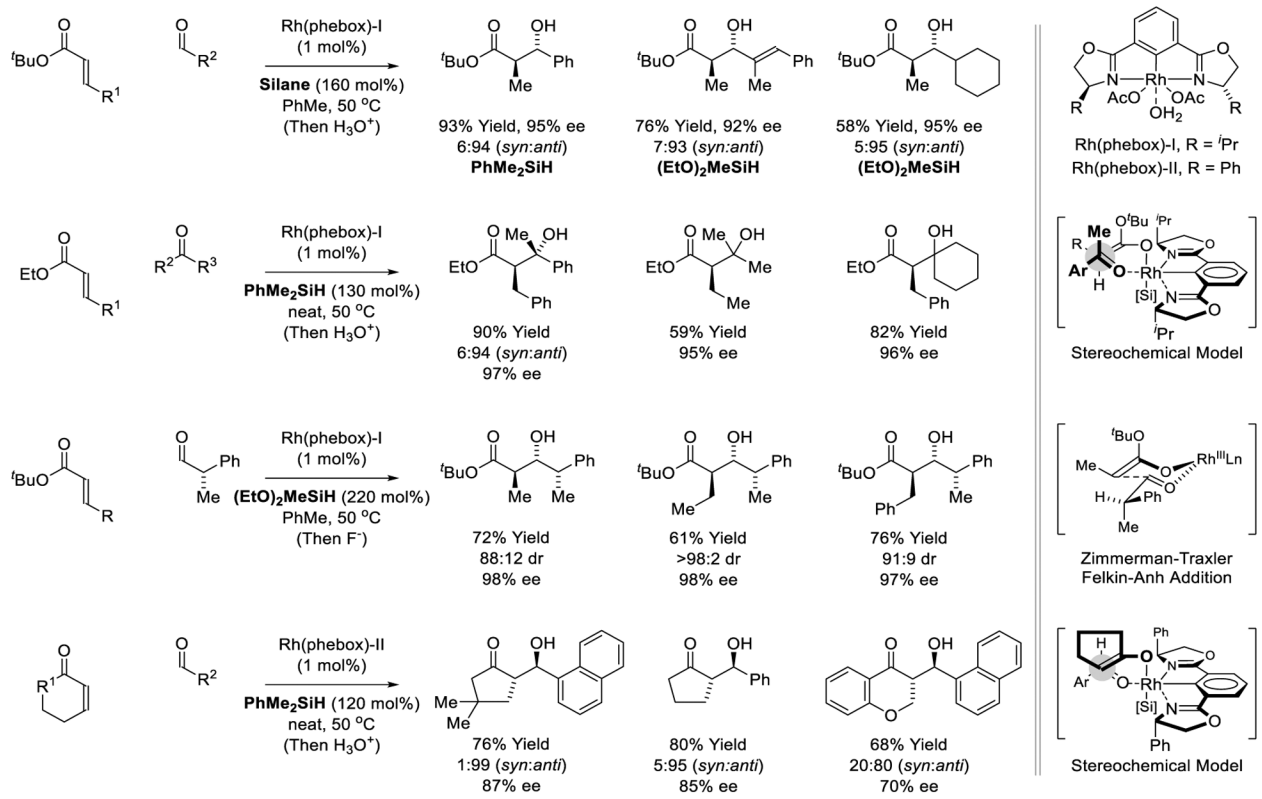
Scheme 5.

Rhodium-catalyzed reductive aldol cyclizations reported by Motherwell.



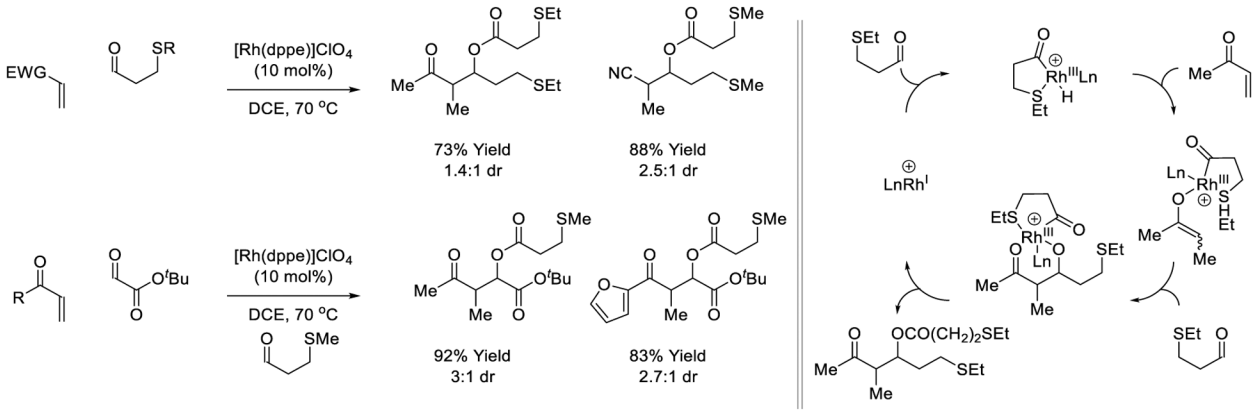
Scheme 6.

Diastereo- and enantioselective rhodium-catalyzed reductive aldol reactions reported by Morken.



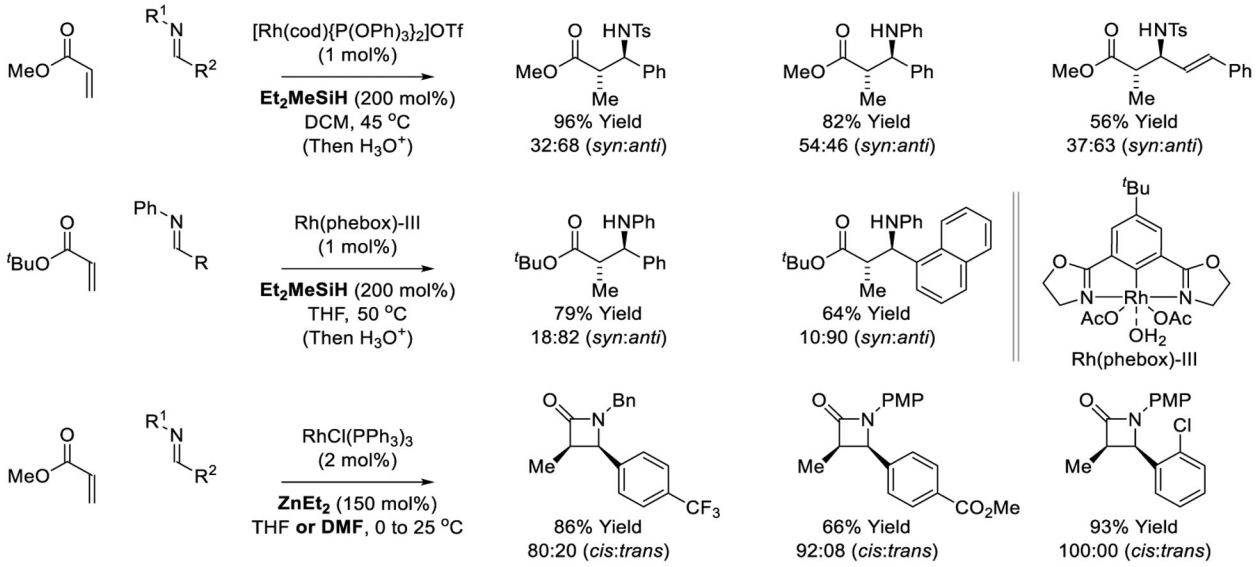
Scheme 7.

Diastereo- and enantioselective Rh(phebox)-catalyzed reductive aldol reactions reported by Nishiyama.



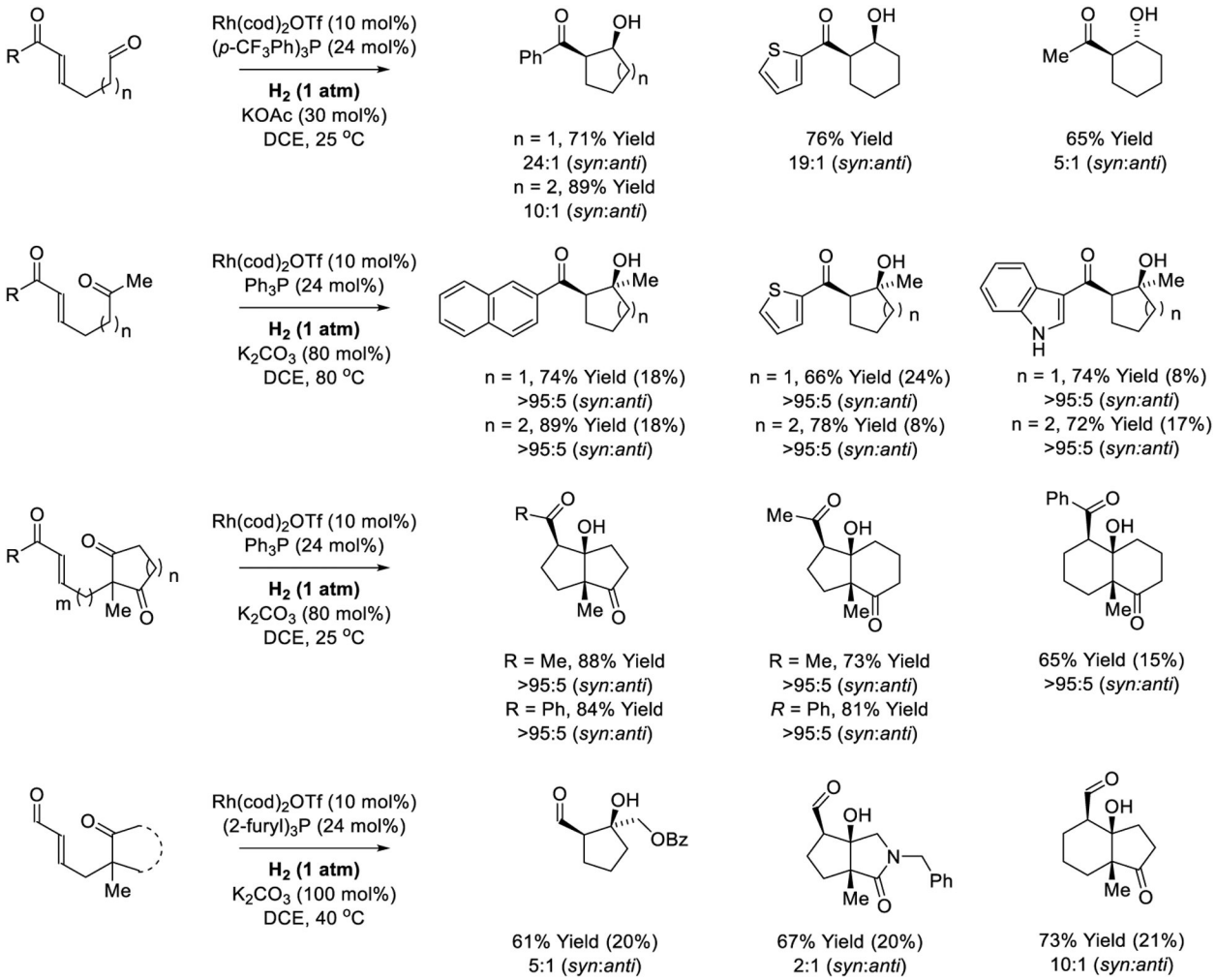
Scheme 8.

Rhodium-catalyzed reductive aldol reactions reported by Willis.



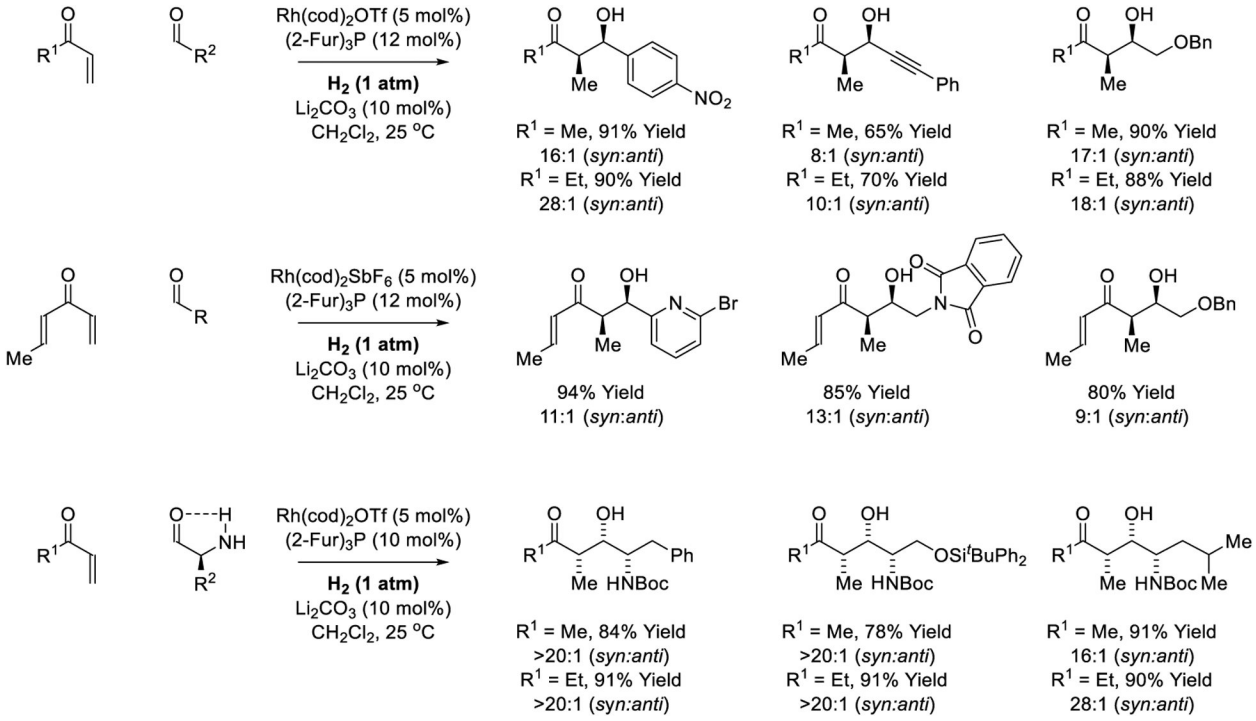
Scheme 9.

Rhodium-catalyzed reductive Mannich reactions reported by Matsuda, Nishiyama and Ando.



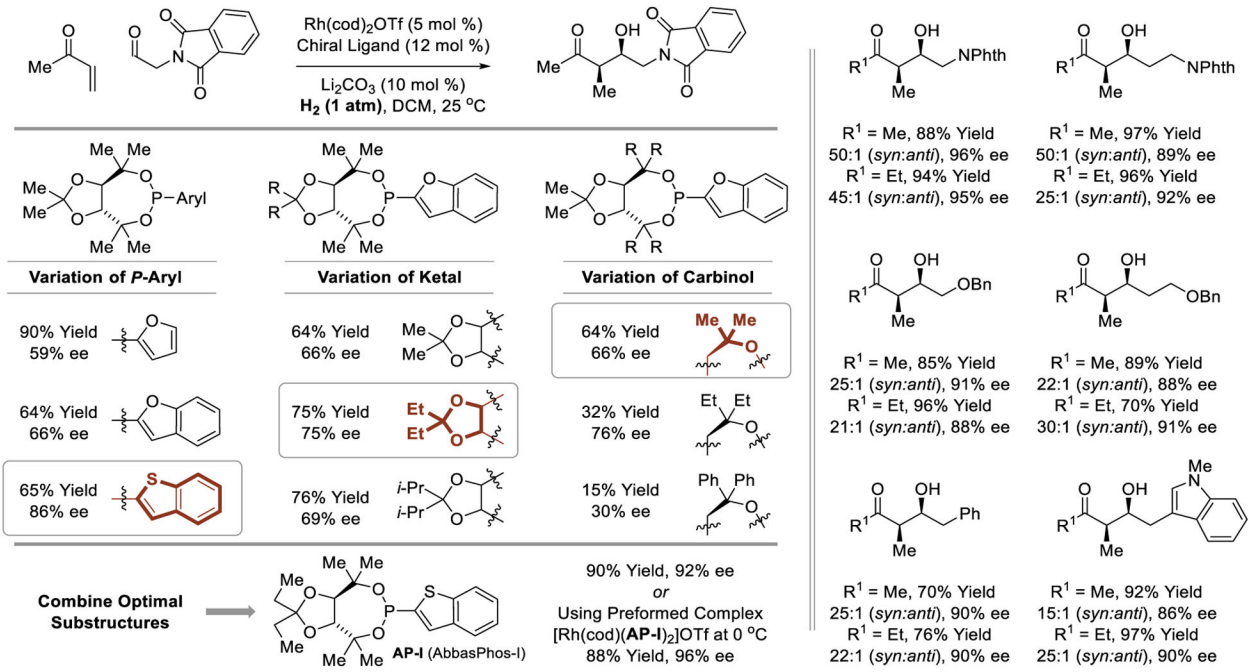
Scheme 10.

Reductive aldol cyclizations via rhodium-catalyzed hydrogenation reported by Krische.



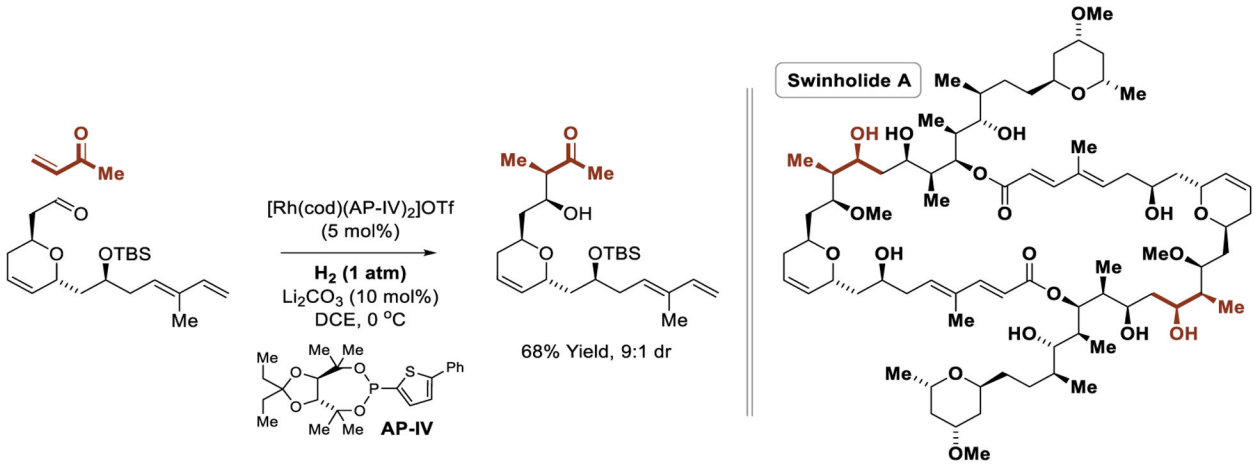
Scheme 11.

syn-Diastereoselective reductive aldol reactions via rhodium-catalyzed hydrogenation reported by Krische.



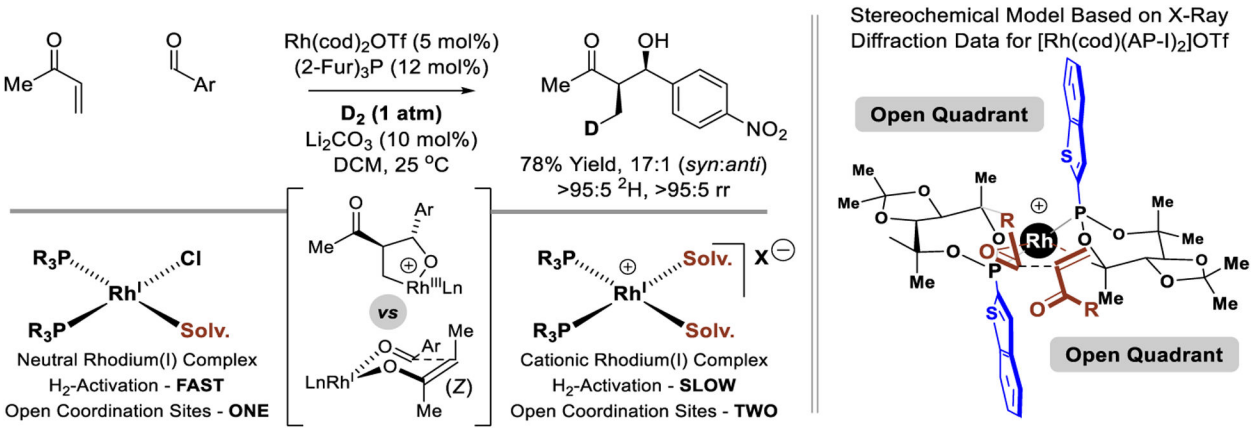
Scheme 12.

syn-Diastereo- and enantioselective reductive aldol reactions via rhodium-catalyzed hydrogenation reported by Krische.



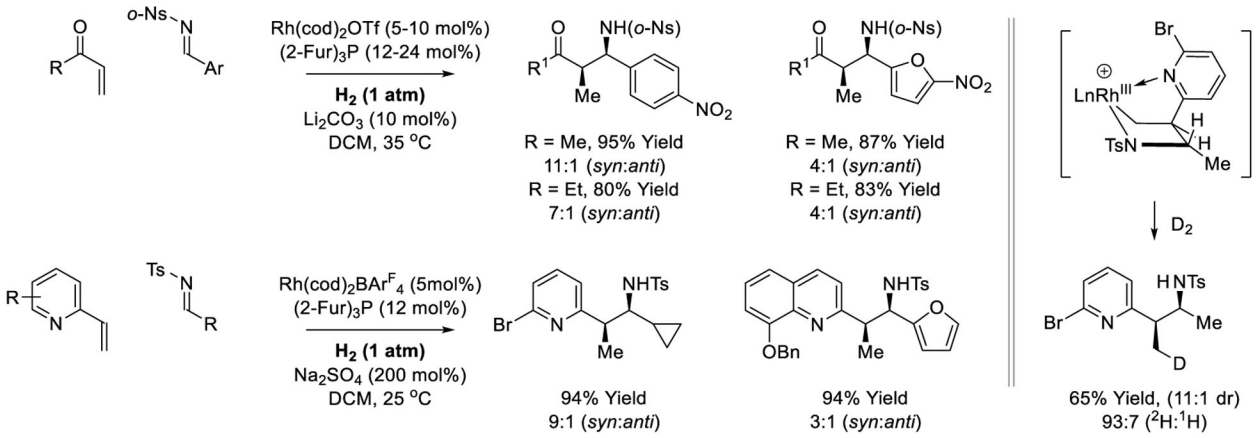
Scheme 13.

Application of the asymmetric intermolecular hydrogen-mediated reductive aldol reaction in Krische's total synthesis of swinholide A.



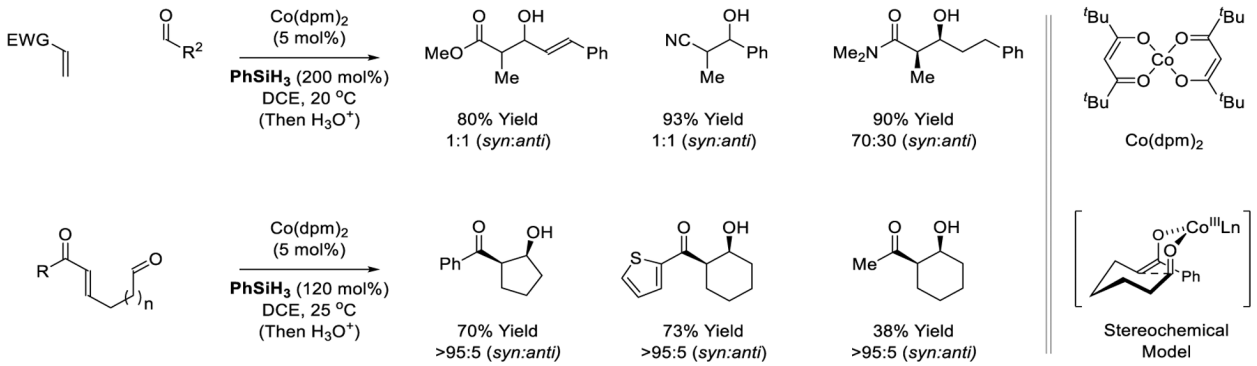
Scheme 14.

Deuterium labelling study and stereochemical model for *syn*-diastereo- and enantioselective reductive aldol reactions via rhodium-catalyzed hydrogenation.



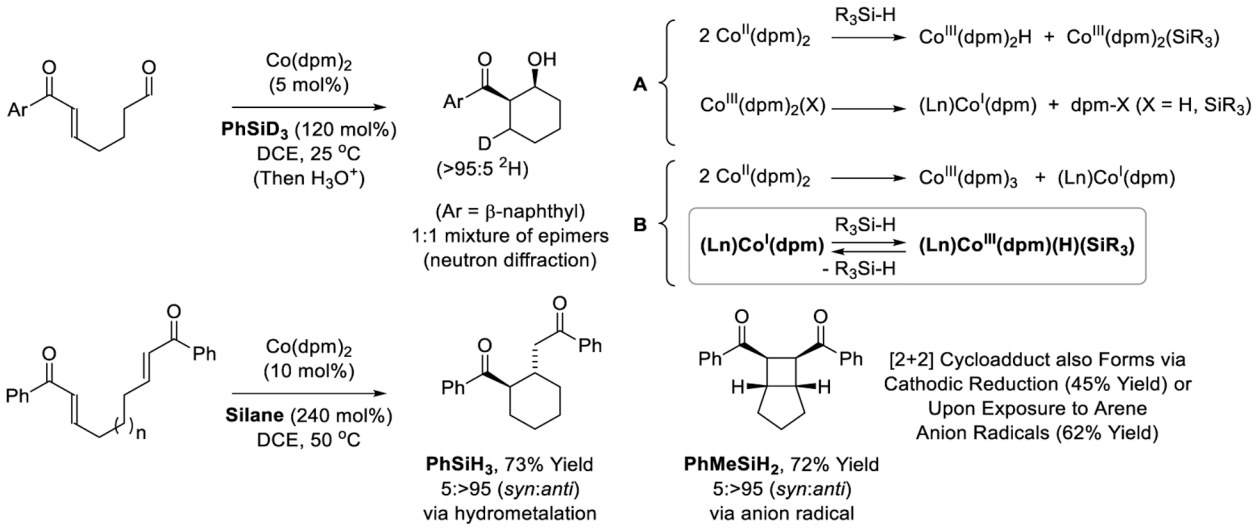
Scheme 15.

Reductive Mannich-type reactions via rhodium-catalyzed hydrogenation reported by Krische.



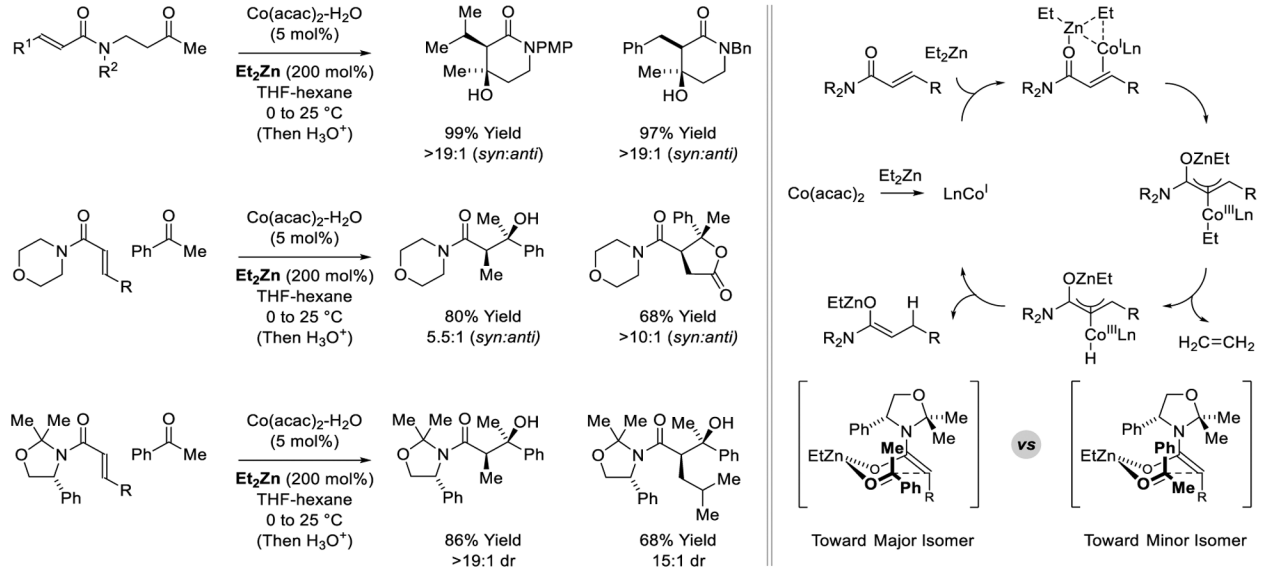
Scheme 16.

Inter- and intramolecular cobalt-catalyzed reductive aldol reactions reported by Mukaiyama and Krische, respectively.



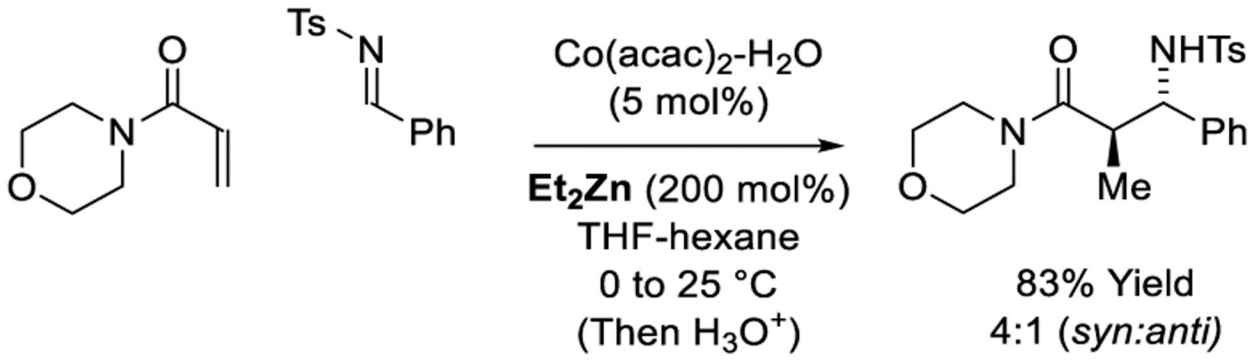
Scheme 17.

Silane-dependent partitioning of hydrometalative vs anion radical pathways in silane mediated reactions of cobalt(II) diketonates.

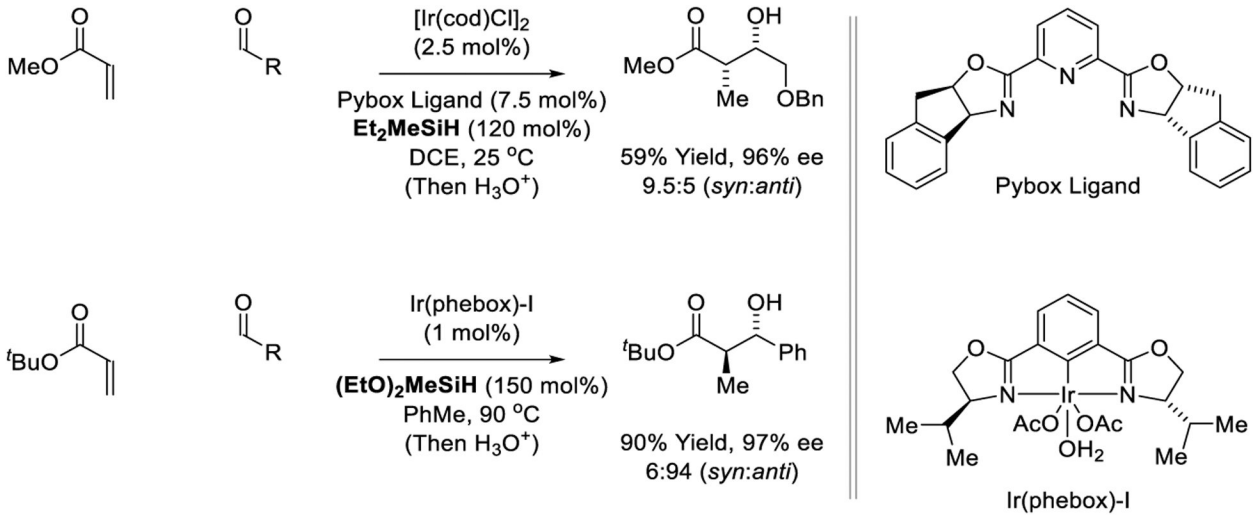


Scheme 18.

Cobalt-catalyzed reductive aldol reactions reported by Lam.

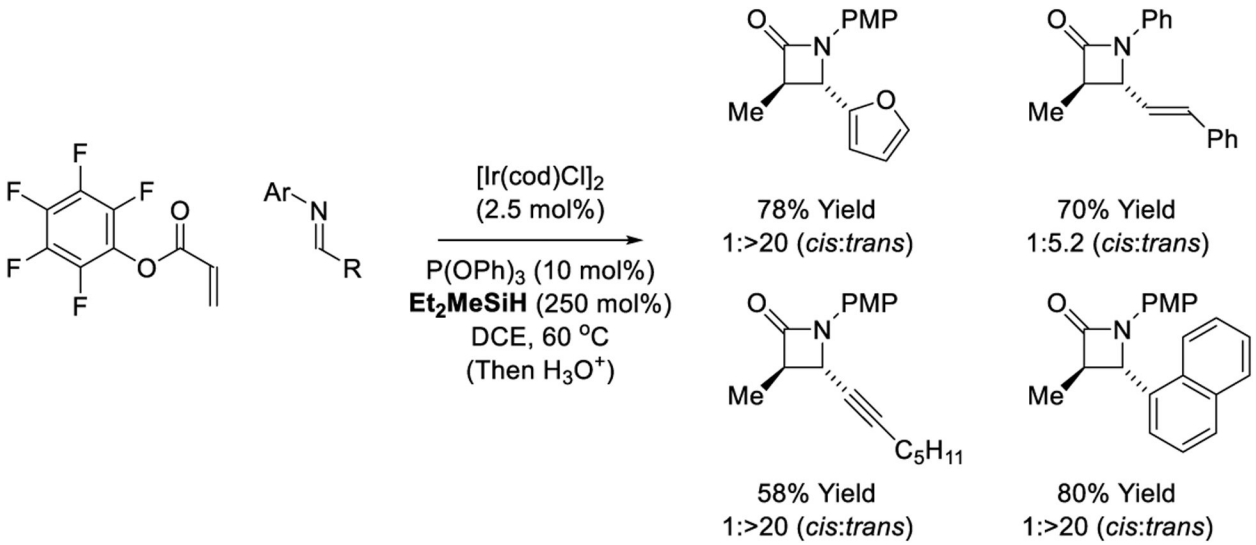


Scheme 19.
Cobalt-catalyzed reductive Mannich reaction reported by Lam.



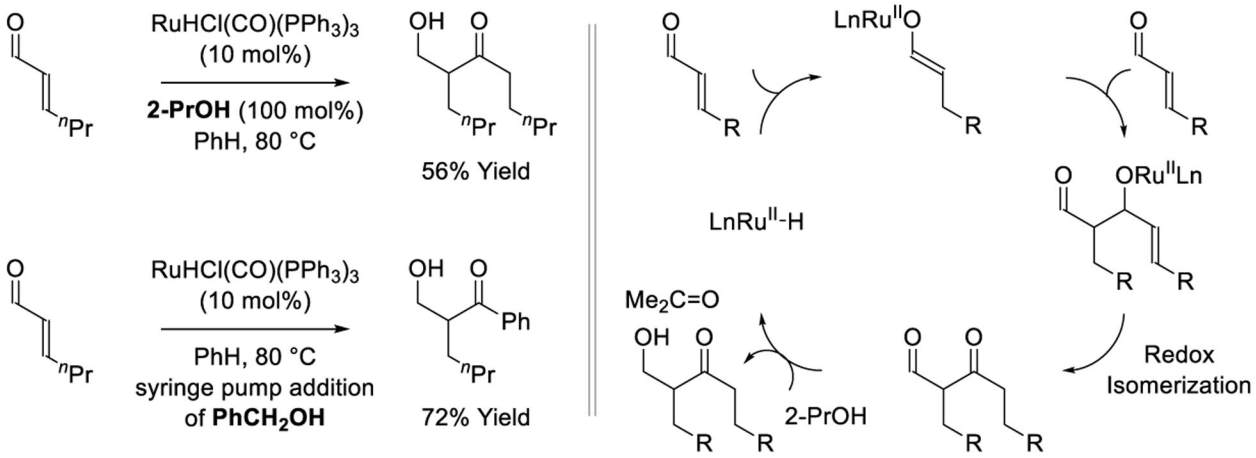
Scheme 20.

Diastereo- and enantioselective iridium-catalyzed reductive aldol reactions reported by Morken and Nishiyama.



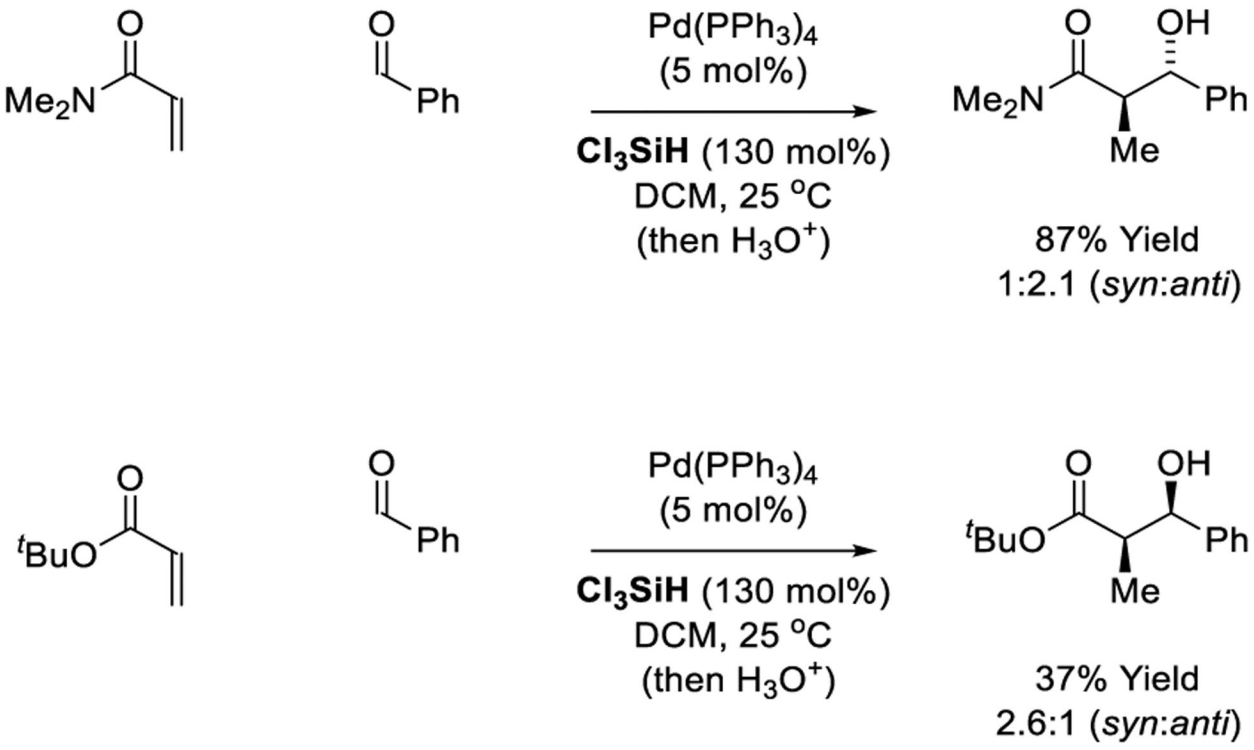
Scheme 21.

Diastereoselective iridium-catalyzed reductive Mannich-type reactions reported by Morken.

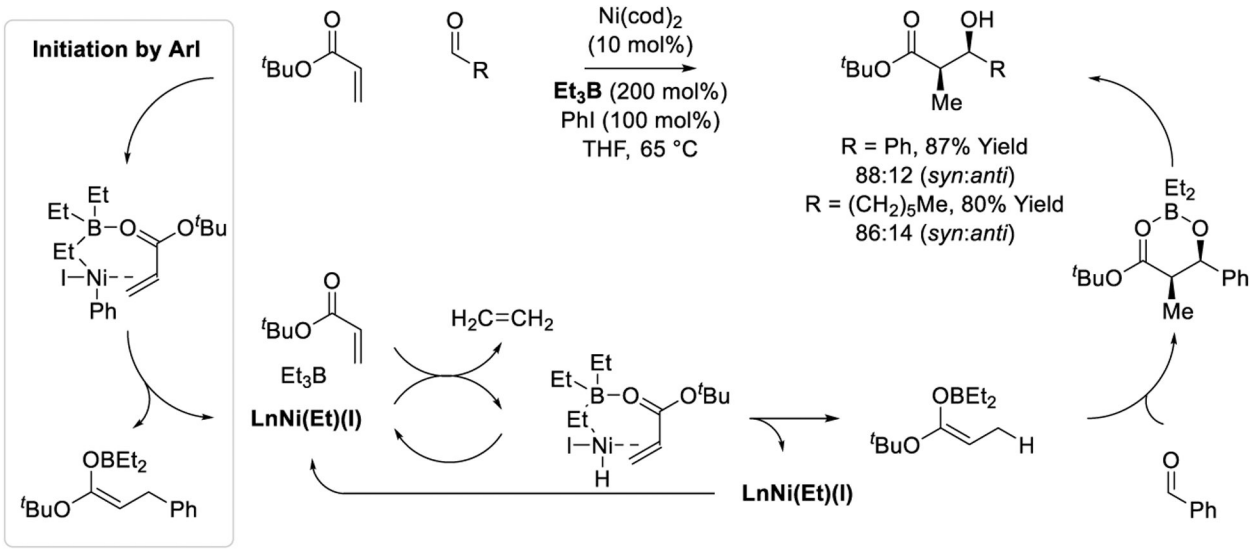


Scheme 22.

Ruthenium-catalyzed reductive aldol-type reactions reported by Ryu.

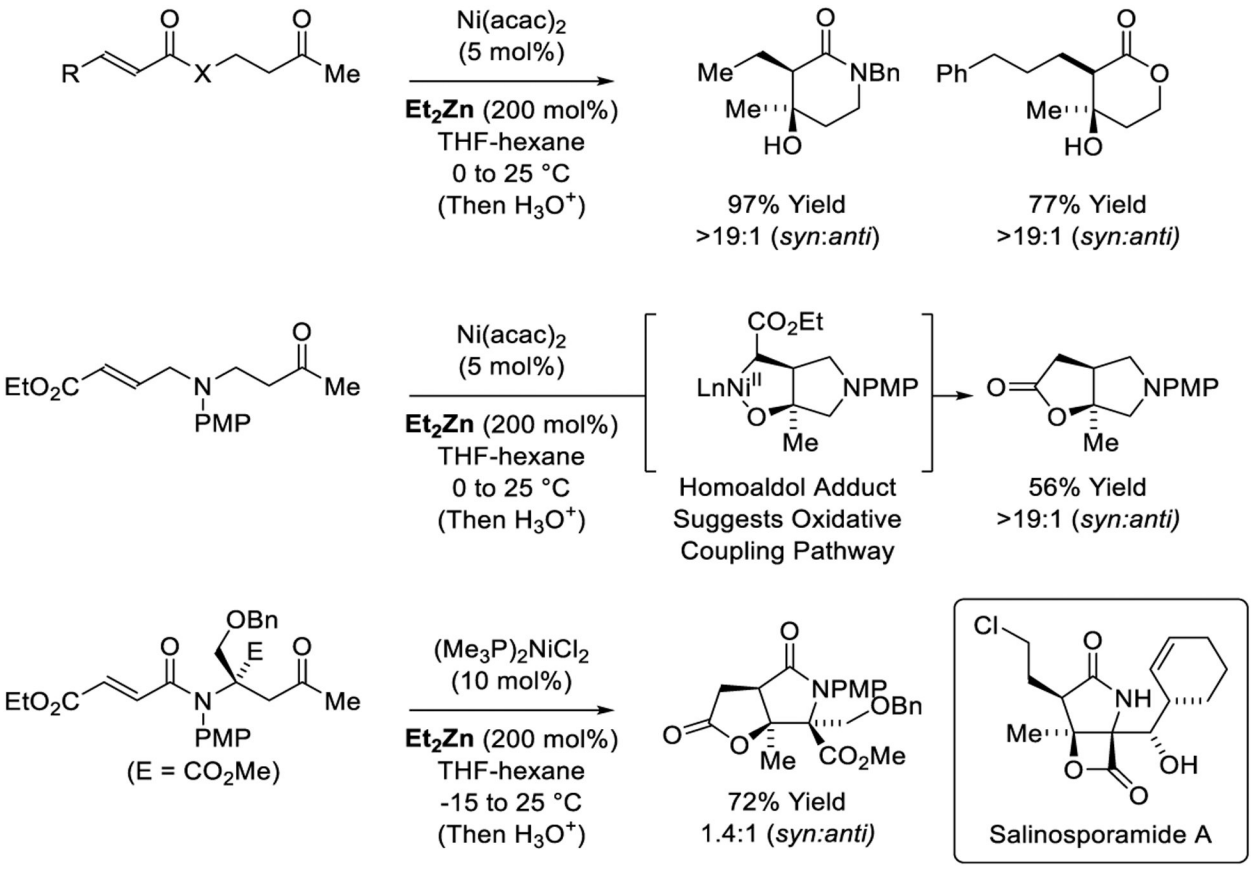


Scheme 23.
Palladium-catalyzed reductive aldol reactions reported by Kiyooka.



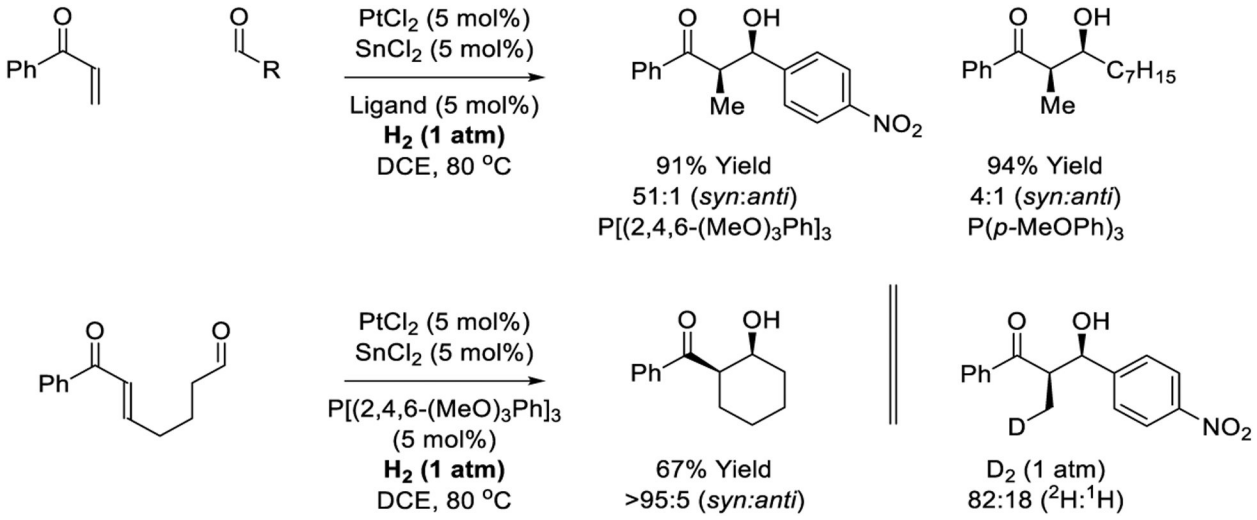
Scheme 24.

Nickel-catalyzed reductive aldol reactions reported by Montgomery.



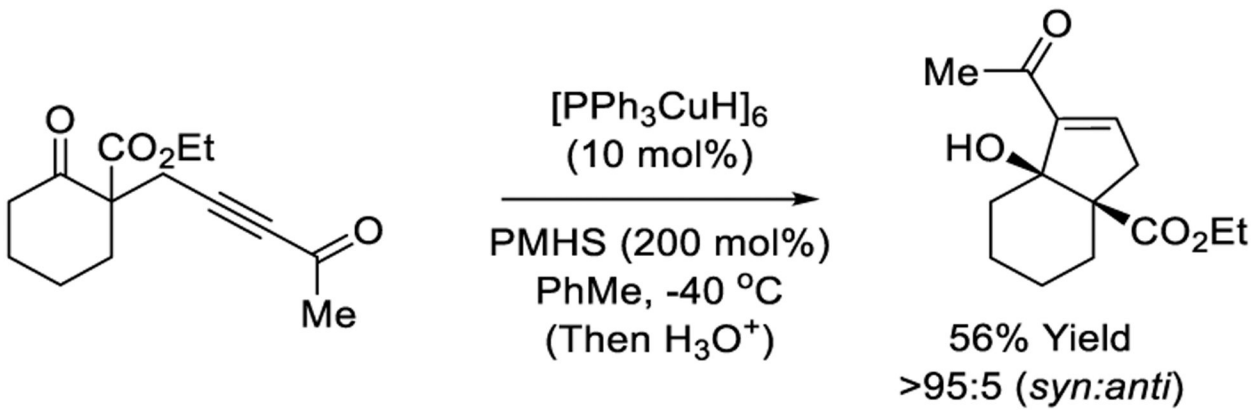
Scheme 25.

Nickel-catalyzed reductive aldol cyclizations reported by Lam.

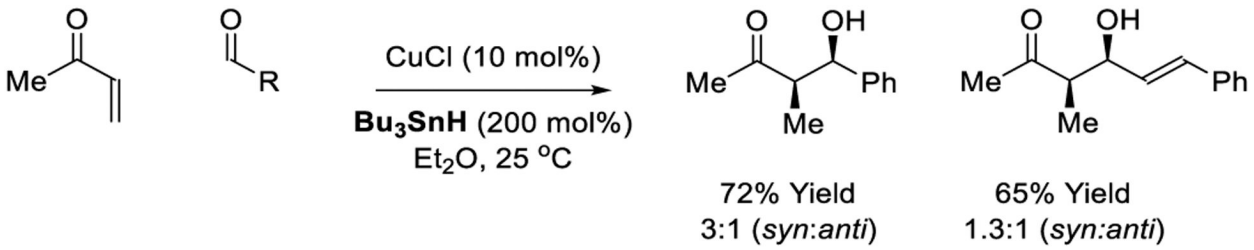


Scheme 26.

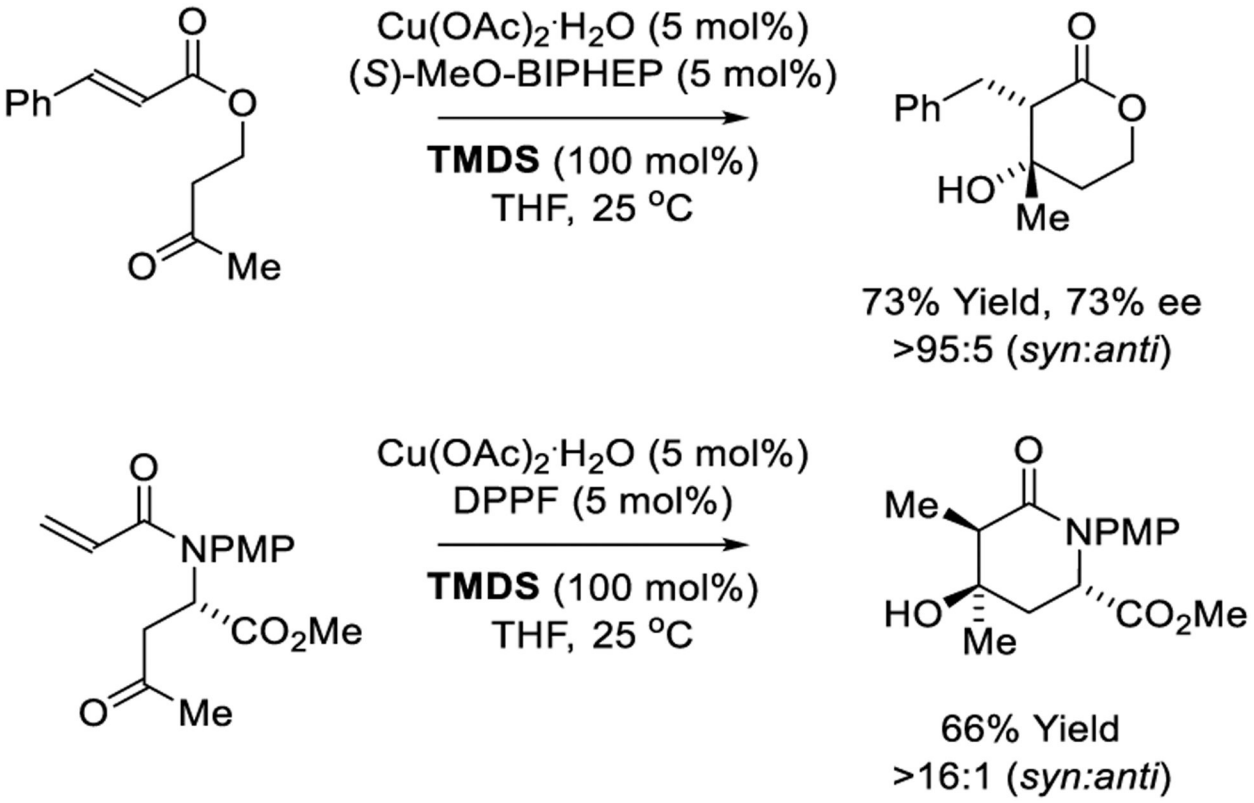
Inter- and intramolecular platinum-catalyzed reductive aldol reactions reported by Jang.



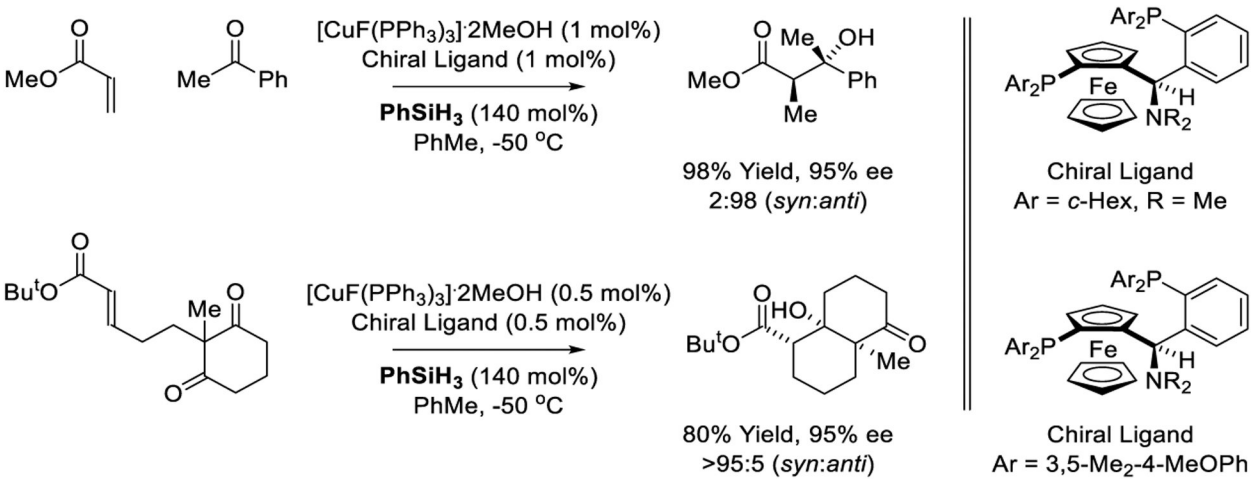
Scheme 27.
Copper-catalyzed reductive aldol cyclization of acetylenic ketones reported by Chui.



Scheme 28.
Copper-catalyzed reductive aldol reactions reported by Maruoka.

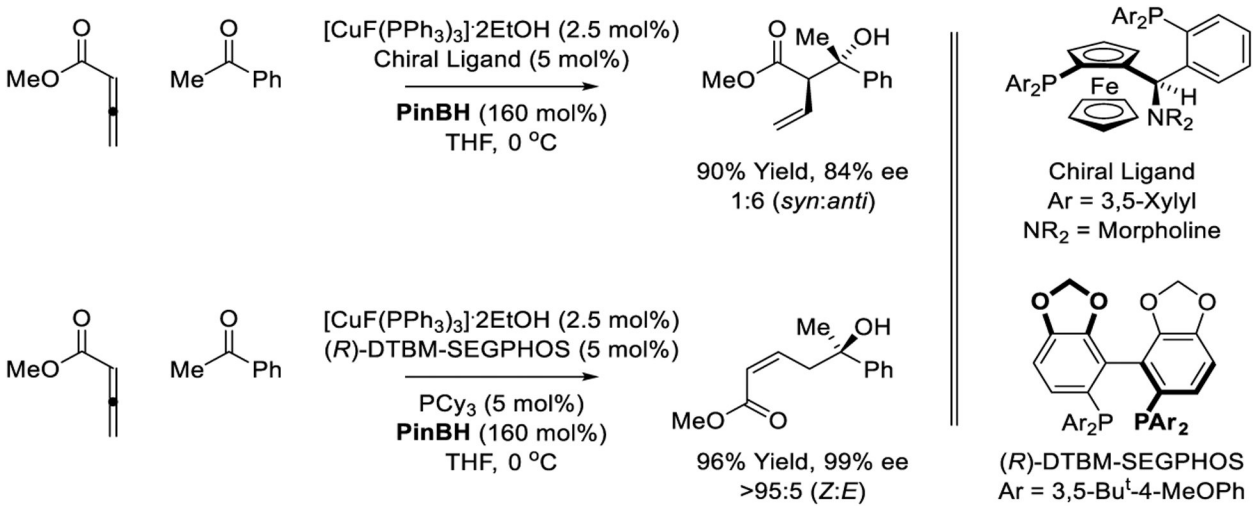


Scheme 29.
Copper-catalyzed reductive aldol cyclizations reported by Lam.



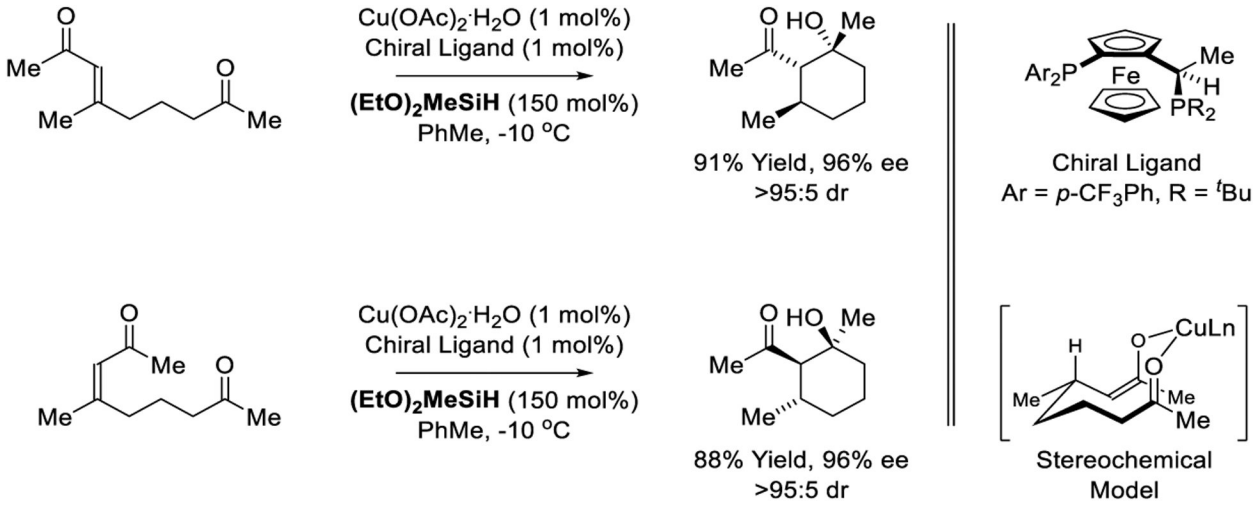
Scheme 30.

Inter- and intramolecular copper-catalyzed reductive aldol reactions reported by Riant.



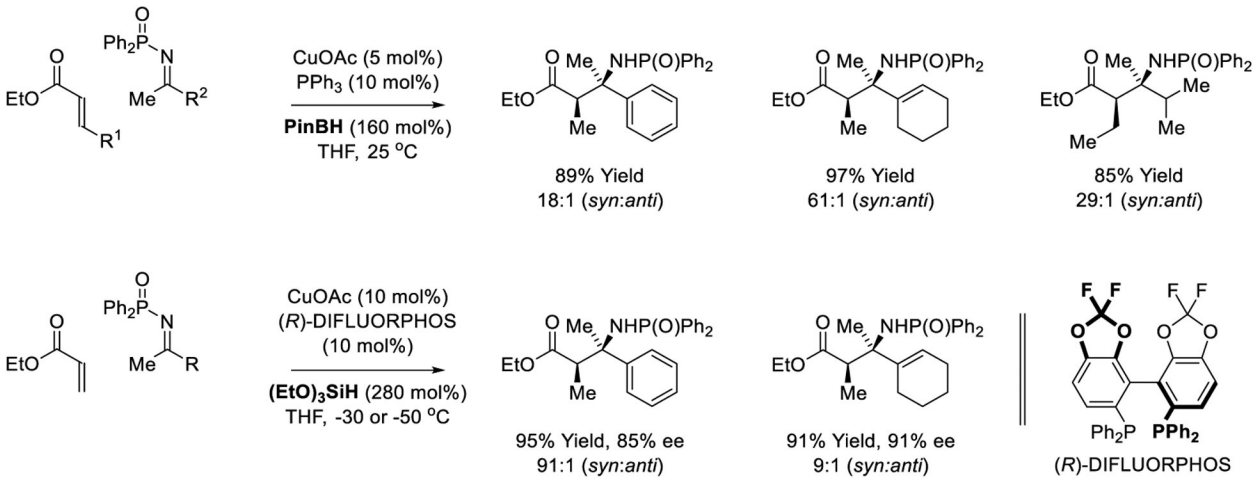
Scheme 31.

Copper-catalyzed reductive aldol reactions reported by Shibasaki and Kanai.



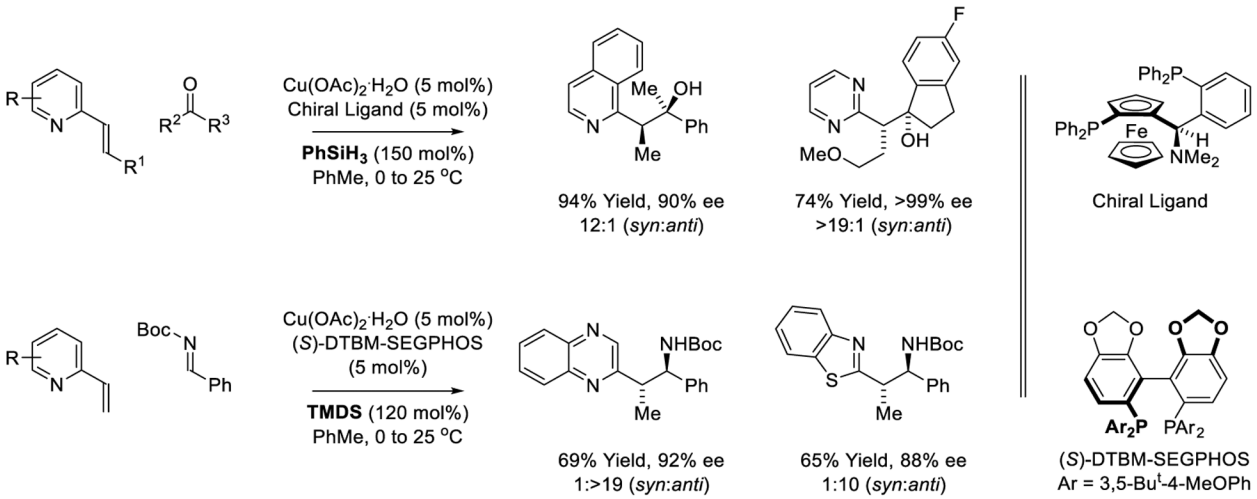
Scheme 32.

Copper-catalyzed reductive aldol cyclizations reported by Lipshutz.



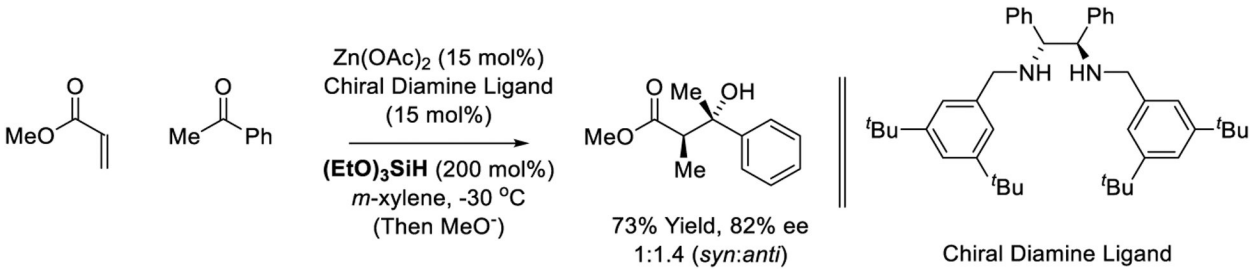
Scheme 33.

Copper-catalyzed reductive Mannich reactions reported by Shibasaki and Kanai.



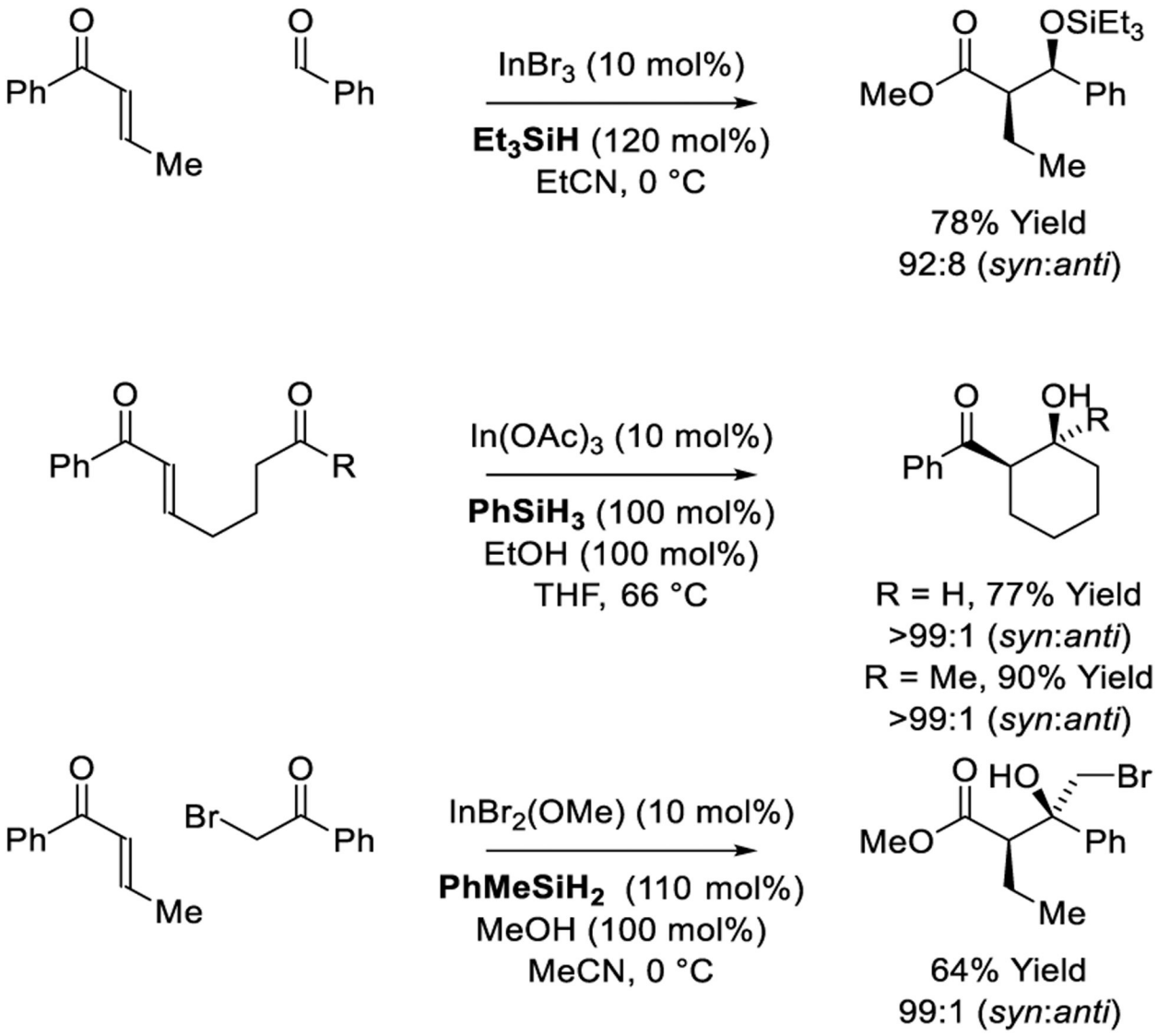
Scheme 34.

Copper-catalyzed reductive aldol and Mannich-type reactions of vinyl-substituted heteroaromatic pronucleophiles reported by Lam.



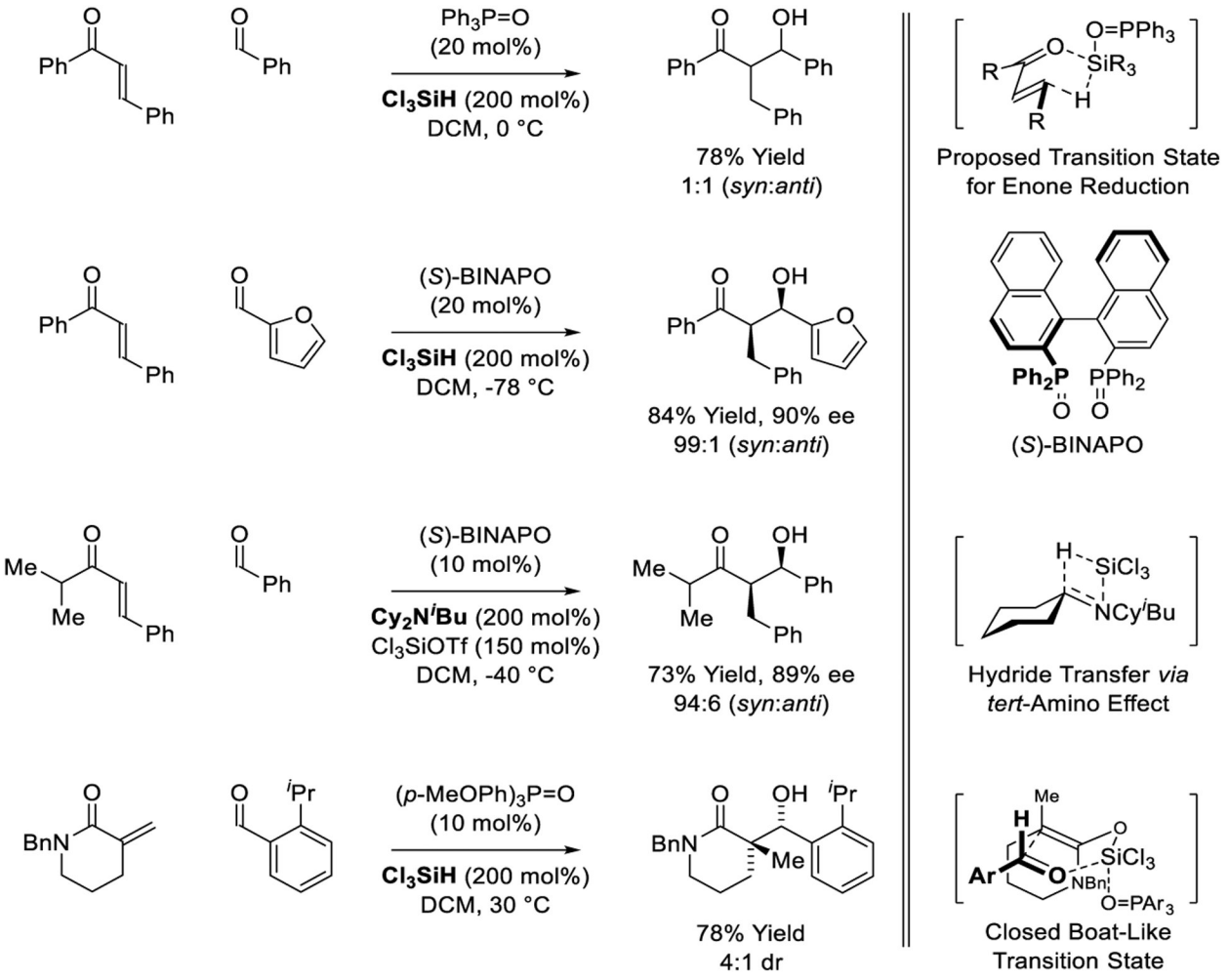
Scheme 35.

Zinc-catalyzed reductive aldol reaction reported by Mlynarski.



Scheme 36.

Inter- and intramolecular indium-catalyzed reductive aldol reactions reported by Baba, Shibata, Hosomi and Miura.



Scheme 37.

Organocatalyzed reductive aldol reactions reported by Nakajima, Sugiura, Kotani and Schindler.