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# Catalytic Enantioselective Carbonyl Allylation and Propargylation *via* Alcohol Mediated Hydrogen Transfer: Merging the Chemistry of Grignard and Sabatier

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## Conspectus

Merging the characteristics of transfer hydrogenation and carbonyl addition, we have developed a new class of catalytic enantioselective C-C bond formations. In these processes, hydrogen transfer between alcohols and π-unsaturated reactants generates carbonyl-organometal pairs that combine to deliver products of addition. Based on this mechanistic paradigm, lower alcohols are converted directly to higher alcohols in the absence of premetalated reagents or discrete alcohol-to-carbonyl redox reactions. In certain cases, due to a pronounced kinetic preference for primary *vs* secondary alcohol dehydrogenation, diols and higher polyols are found to engage in catalytic stereo- and site-selective C-C bond formation - a capability that further enhances efficiency by enabling skeletal construction events without extraneous manipulations devoted to the installation and removal of protecting groups. While this Account focuses on redox-neutral couplings of alcohols, corresponding aldehyde reductive couplings mediated by 2-propanol were developed in parallel for most catalytic transformations reported herein. Mechanistically, two distinct classes of alcohol C-H functionalizations have emerged, which are distinguished by the mode of pronucleophile activation; specifically, processes wherein alcohol oxidation is balanced by (a) π-bond hydrometalation or (b) C-X bond reductive cleavage. Each pathway offers access to allylmetal or allenylmetal intermediates and, therefrom, enantiomerically enriched homoallylic or homopropargylic alcohol products, respectively. In the broadest terms, carbonyl addition mediated by premetalated reagents has played a central role in synthetic organic chemistry for well over a century, however, the requisite organometallic reagents pose issues of safety, require multistep syntheses and generate stoichiometric quantities of metallic byproducts. The concepts and catalytic processes described in this Account, conceived and developed wholly within the author's laboratory, signal a departure from the use of stoichiometric organometallic reagents in carbonyl addition. Rather, they reimagine carbonyl addition as a hydrogen auto-transfer process or cross-coupling in which alcohol reactants, by virtue of their native reducing ability, drive generation of transient organometallic nucleophiles and, in doing so, serve dually as carbonyl proelectrophiles. The catalytic allylative and propargylative transformations developed thus far display capabilities far beyond their classical counterparts and their application to the total synthesis of type I

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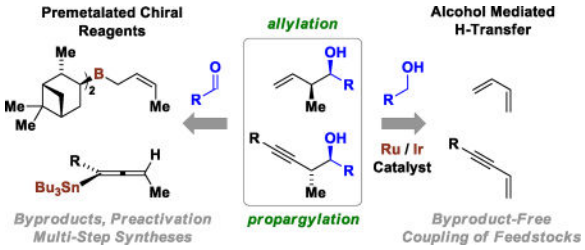
polyketide natural products have evoked a step-change in efficiency. More importantly, the present data suggest that diverse transformations traditionally reliant on premetalated reagents may now be conducted catalytically without stoichiometric metals. This Account provides the reader and potential practitioner with a catalog of enantioselective alcohol-mediated carbonyl additions – a user's guide, 10-year retrospective, and foundation for future work in this emerging area of catalytic C-C bond formation.

## Graphical abstract




## I. Introduction

In 1912, Victor Grignard[1] and Paul Sabatier[2] jointly received the Nobel Prize - Grignard for the development of reagents that transformed the field of carbonyl addition and Sabatier for catalytic hydrogenation, which is practiced across all segments of the chemical industry. Their pioneering chemistry has opened vast volumes of chemical space, demonstrating that new reactivity is the most fundamental and far reaching basis for innovation in the field of chemical synthesis. Merging the characteristics of carbonyl addition and catalytic hydrogenation, we have developed a broad, new family of catalytic C-C couplings that are mechanistically distinct, representing the first use of an alcohol's native reducing ability to generate transient carbonyl-organometal pairs.[3] Unlike classical carbonyl addition, which relies on the use of premetalated reagents, or metal catalyzed reductive C-C coupling, which often utilizes stoichiometric metallic reductants, the "redox-triggered carbonyl additions" we have introduced bypass the requirement of stoichiometric metals (Scheme 1).

The hydrogen transfer-mediated carbonyl additions we report deliver products of formal alcohol C-H functionalization and, hence, may be distinguished from related "borrowing hydrogen" chemistry that promotes formal alcohol substitution (Scheme 2).[4] Both processes are redox-neutral, which is significant as alcohol oxidation is often problematic on scale.[5] Already, dehydrogenative methods such as alcohol amination are finding broad use at the process level.[6] To our knowledge, the only other methods available for direct alcohol C-H functionalization are radical mediated transformations,[7] for which enantioselective variants remain elusive. This review will focus on enantioselective metal catalyzed methods for the conversion of lower alcohols to higher alcohols – a unique class of C-C bond formations discovered and developed solely within our laboratory.[3]

## II. Catalytic Enantioselective Alcohol C-H Functionalization

### II.A Cyclometalated π-Allyliridium *C,O*-Benzoate Catalysts

Using cyclometalated π-allyliridium *C,O*-benzoate complexes, diverse enantioselective alcohol C-H functionalizations were developed (Scheme 3-B).[8–22] As illustrated in the catalytic mechanism (Scheme 3-A), the internal carboxylate of the *ortho*-*C,O*-benzoate moiety maintains neutrality of the π-allyliridium intermediate and, hence, nucleophilic character. Dehydrogenation of the secondary alcohol products is prevented by internal chelation of the homoallylic olefin. Mechanistic studies[8b] corroborate the indicated catalytic mechanism wherein carbonyl addition represents the turnover limiting event. These processes embody an inversion of polarity (umpolung) with respect to π-allyl species evident in related allylic substitutions catalyzed by iridium[23] and represent a departure from the longstanding (1978)[24] use of chiral allylmetal reagents in carbonyl addition.[25] The requisite π-allyliridium *C,O*-benzoate complexes are chromatographically stable and are readily prepared through the combination of $[Ir(cod)Cl]_2$, allyl acetate, 4-substituted-3-nitro-benzoic acids and assorted axially chiral chelating phosphine ligands.[12b]

The ability to exploit alcohols as carbonyl equivalents enables transformations that are not possible *via* classical carbanion chemistry. For example, whereas malondialdehyde is highly intractable and has not been reported to participate in asymmetric addition, the corresponding 1,3-propane diols are robust compounds that readily engage in two-directional allylation and crotylation *via* successive generation and capture of transient mono-aldehydes. These reaction products, which represent acetate and propionate-based triketide building blocks,[3d,h] previously required numerous steps to prepare.[26] These compounds are now generated in a single manipulation and, due to Horeau's principle,[27] are formed as single enantiomers. As shown, the catalyst may be generated *in situ* or one may utilize the chromatographically isolated π-allyliridium *C,O*-benzoate complex (Scheme 4).

Due to a kinetic preference for primary alcohol dehydrogenation,[28] the site-selective allylation of 1,3-diols is readily achieved in the absence of protecting groups[29] with high levels of catalyst-directed diastereoselectivity (Scheme 5-A).[3g,8f,g] As illustrated in reactions of (*S*)-butanediol, this capability not only applies to the parent allylations.[8f,g] High levels of catalyst-directed diastereoselectivity also are evident in *tert*-(hydroxy)-prenylations mediated by isoprene oxide (Scheme 5-B)[18] and (α-aminomethyl)allylations mediated by *N*-(*p*-nitrophenylsulfonyl) protected vinyl aziridines (Scheme 5-C).[19] As evident upon application of this methodology to the total synthesis of natural product, the ability to directly engage diols and higher polyols in C-C coupling without discrete redox reactions or protecting groups has enabled a step-change in efficiency. For more detailed discussion, the reader is directed to the review literature.[3d,h] The use of excess allyl donor in these processes is not required, but led to slightly higher yields. As shown in catalytic C-C couplings of methanol (*vide infra*), the allyl donor can be used as the limiting reagent.

### II.B Non-Cyclometalated Iridium and Rhodium Catalysts

Cyclometalated π-allyliridium *C,O*-benzoate complexes are not required for asymmetric alcohol mediated carbonyl addition. Using the chiral iridium catalyst generated from

$[Ir(cod)Cl]_2$ and (*R*)-DM-SEGPHOS, 1,3-enynes exchange hydrogen with primary alcohols to generate allenyliridium-aldehyde pairs that combine to form enantiomerically enriched products of carbonyl *anti*-(α-methyl)propargylation (Scheme 6-A).[30] In this process, the axial chirality of DM-SEGPHOS is transmitted to the axial chirality of the allenyliridium intermediate and, ultimately, the central chirality of the product. Similarly, silyl-terminated propargyl chlorides react with primary alcohols in the presence of the cationic iridium complex {Ir(cod)[(*R*)-SEGPHOS]}OTf to form enantiomerically enriched homopropargyl alcohols (Scheme 6-B).[31] The chiral rhodium catalyst generated from $[Rh(cod)Cl]_2$ and (*R*)-BINAP overcomes the requirement of terminally substituted propargyl donors, allowing use of propargyl chloride itself (Scheme 6-C).[32] However, to achieve high levels of asymmetric induction, match-mismatch effects between the catalyst and an enantiomerically enriched chiral α-stereogenic amino alcohol are required. Collectively, these methods provide an alternative to the longstanding use of preformed chiral allenylmetal reagents in carbonyl propargylation.[33]

Using the chiral iridium catalyst generated from $[Ir(cod)Cl]_2$ and (*R*)-PhanePhos,[34] methanol reacts with 2-substituted dienes to form primary homoallylic alcohols bearing all-carbon quaternary centers (Scheme 7-A).[35] Mechanistic studies corroborate a Curtin-Hammett scenario in which methanol dehydrogenation triggers rapid, reversible diene hydrometalation to provide a rapidly equilibrating mixture of regio- and stereoisomeric allyliridium-formaldehyde pairs. Selection of predominantly one isomer from this dynamic mixture results in completely regioselective and highly enantioselective hydrohydroxymethylation. Following the development of racemic allene hydrohydroxyalkylations catalyzed by iridium[36] and ruthenium,[37] iridium-PhanePhos complexes were found to catalyze the coupling of methanol with allenes to form $CF_3$-bearing all-carbon quaternary centers with complete levels of regioselectivity and high levels of enantioselectivity (Scheme 7-B).[38]

The chiral iridium complex generated from $[Ir(cod)Cl]_2$ and (*R*)-$H_8$-BINAP catalyzes the enantioselective C-C bond formation between the propargyl ether, $TIPSOCH_2C{\equiv}CH$, and primary alcohols. The resulting γ-hydroxy enol silanes are formed with uniformly high levels of enantioselectivity and complete levels of alkene (*Z*)-stereoselectivity.[39] Deuterium labeling studies corroborated a novel catalytic mechanism involving a 1,2-hydride shift that converts a metal bound alkyne to a vinyl carbene, which upon protonation delivers a nucleophilic π-allyliridium complex (Scheme 8).

### II.C Ruthenium Catalysts

Initially developed couplings of butadiene, an abundant petrochemical feedstock, were not stereocontrolled.[40] However, in the presence of a ruthenium catalyst modified by DM-SEGPHOS, alcohols react with 2-trialkylsilyl-butadienes to form branched products of hydrohydroxyalkylation (Scheme 9-A).[41] The silyl moiety is essential in terms of defining the geometry of the transient allylruthenium intermediate and enforcing high levels of diastereoselectivity. To direct relative and absolute stereochemistry in reactions of butadiene, use of a ruthenium catalyst modified by a chiral phosphate counterion derived from H8-BINOL is required.[42] The anion is installed through the acid-base reaction of $H_2Ru(CO)$

$(PPh_3)_3$ with the indicated chiral phosphoric acid, precluding the more common (yet less atom-efficient) use of silver phosphate salts and metal halides. With the chiral phosphate counterion as the exclusive chiral inducing element, primary benzylic alcohols react with butadiene to form branched products of hydrohydroxyalkylation with good levels of *anti*-diastereoselectivity and enantioselectivity (Scheme 9-B). To access the corresponding enantiomerically enriched *syn*-diastereomers, use of the ruthenium catalyst generated *in situ* from $H_2Ru(CO)(PPh_3)_3$, (*S*)-SEGPHOS and the indicated TADDOL-derived phosphoric acid is required (Scheme 9-C).[43] Our collective studies suggest the s-*cis*-conformer of butadiene selectively undergoes hydrometalation to form the (*Z*)-σ-crotylruthenium intermediate. The more Lewis basic TADDOL-derived phosphate counterion preserves the kinetic selectivity of diene hydrometalation by diminishing the degree of coordinative unsaturation and, hence, retarding the rate of (*E*/*Z*)-isomerization with respect to the rate of carbonyl addition. Computational studies implicate intervention of a formyl hydrogen bond between the transient aldehyde and the phosphate oxo-moiety that stabilizes the transition state for carbonyl addition involving the (*Z*)-σ-crotylruthenium intermediate.[44]

In the ruthenium catalyzed coupling of primary alcohols with alkynes, seemingly minor changes to the reaction conditions or structural features of the reactants can promote strikingly different mechanistic pathways. For example, racemic allylic alcohols[45] and (*Z*)-homoallylic alcohols[46] are formed through mechanisms that involve alkyne-carbonyl oxidative coupling (not shown). Oxidative coupling is suppressed by exogenous iodide and careful selection of phosphine ligand, allowing hydrometalative pathways to dominate. Thus, in the presence of iodide, chiral ruthenium(II) complexes modified by Josiphos ligands were found to catalyze the reaction of alkynes with primary alcohols to form homoallylic alcohols with excellent control of regio-, diastereo- and enantioselectivity (Scheme 10-A).[47] Deuterium labelling studies corroborate a mechanism involving two discrete catalytic events: alkyne-to-allene isomerization followed by allene-alcohol C-C coupling. Remarkably, under identical conditions, the indicated TIPS-protected propargyl ether reacts with primary alcohol to furnish products of siloxy-crotylation.[48] However, deuterium labelling studies implicate a profoundly different mechanism involving hydride shift enabled π-allyl formation (Scheme 10-B).

As first demonstrated in reactions to form racemic products,[49] hydrogen transfer from primary alcohols to 1,3-enynes delivers allenylruthenium-aldehyde pairs that combine to form products of carbonyl propargylation. Subsequently, it was found that the chiral ruthenium complex derived from $(TFA)_2Ru(CO)(PPh_3)_2$ and (*R*)-BINAP catalyzes the C-C coupling of primary alcohols with the commercially available 1,3-enyne, $TMSC{\equiv}CC(Me){=}CH_2$, to form *gem*-dimethyl substituted secondary homopropargyl alcohols with high levels of enantioselectivity (Scheme 11).[50]

## III. Conclusion

The use of stoichiometric carbanions in carbonyl addition represents a cornerstone of chemical synthesis. However, the use of premetalated reagents mandates the generation of stoichiometric quantities of metallic byproducts. The studies summarized herein establish an alternative approach to carbonyl addition in the *absence* of stoichiometric metals that instead

exploits the native reducing ability of alcohols to drive generation of transient organometallics. The direct conversion of lower alcohols to higher alcohols via hydrogen exchange with π-unsaturated pronucleophiles is redox-economic.[51] The ability to perform such transformations in a stereo- and site-selective fashion further enhances efficiency by precluding the use of chiral auxiliaries and protecting groups. More broadly, these transformations raise the possibility that diverse reactions traditionally employing stoichiometric carbanions may now be conducted catalytically in the absence of stoichiometric metals via alcohol-mediated hydrogen transfer. It is the authors hope that the novel reactivity summarized in this monograph will accelerate progress toward this goal.

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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 been recognized by 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).

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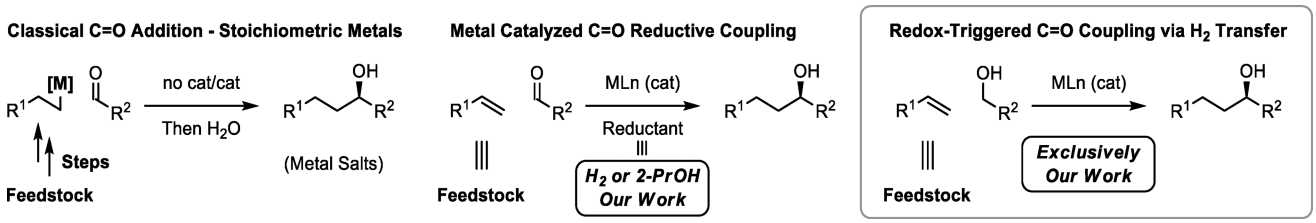
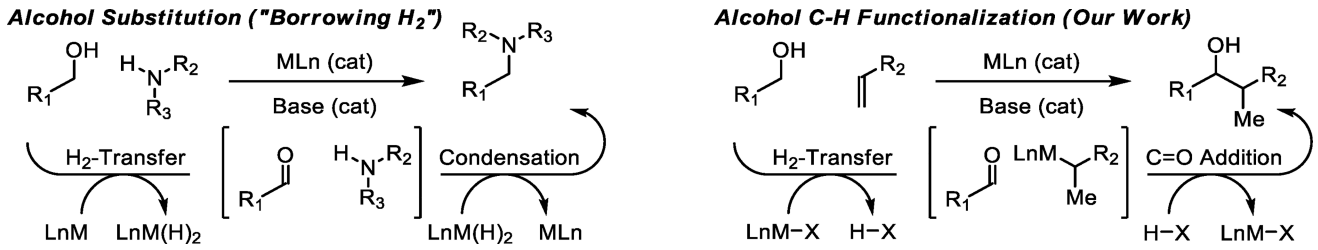


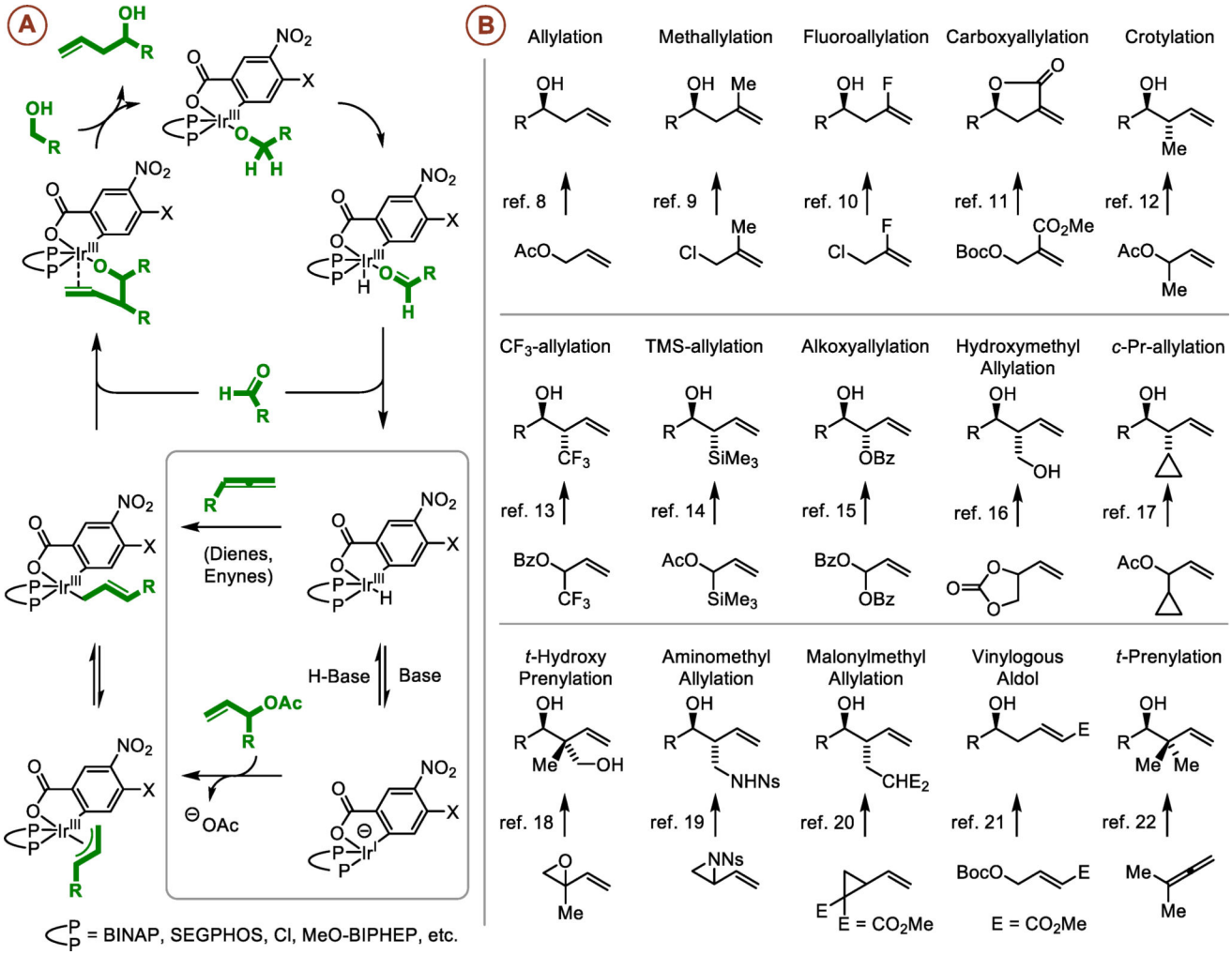

**Scheme 1.**

Evolution of C=O addition chemistry beyond stoichiometric metals.



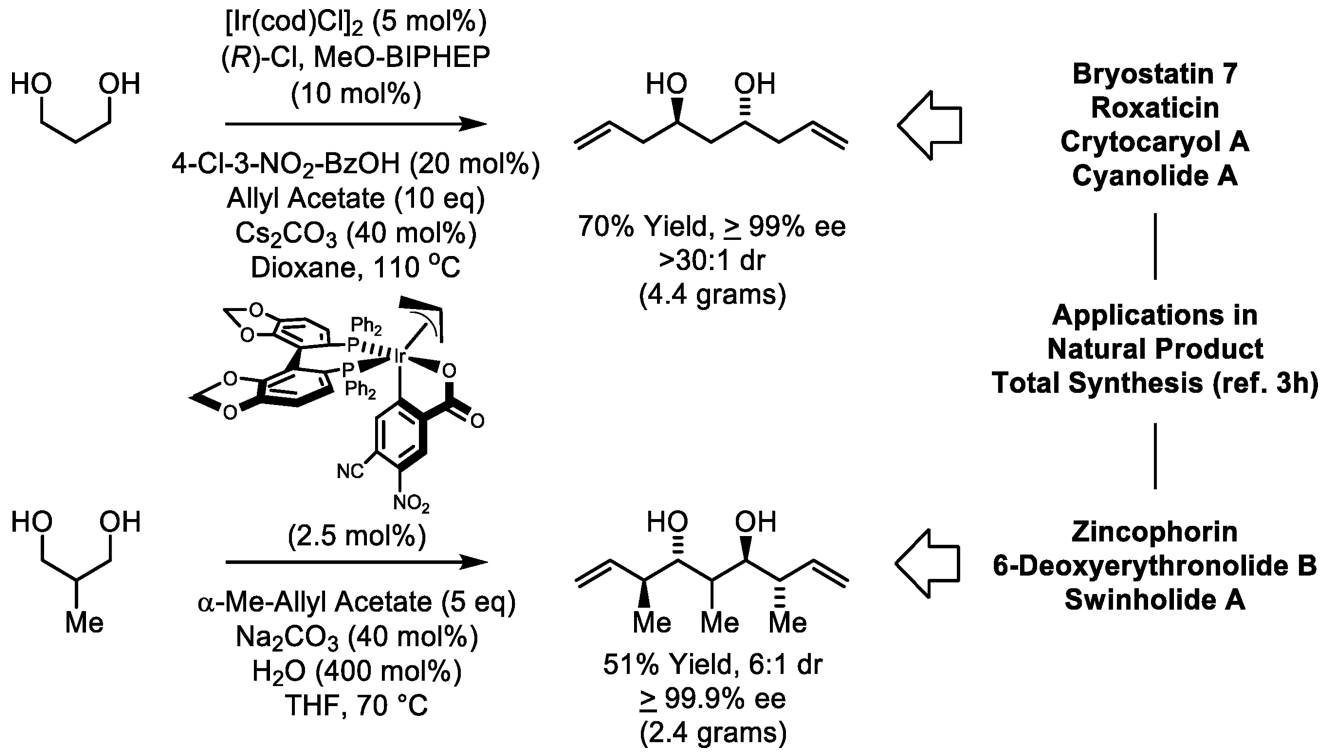

**Scheme 2.**

Alcohol substitution *vs* alcohol C-H functionalization.

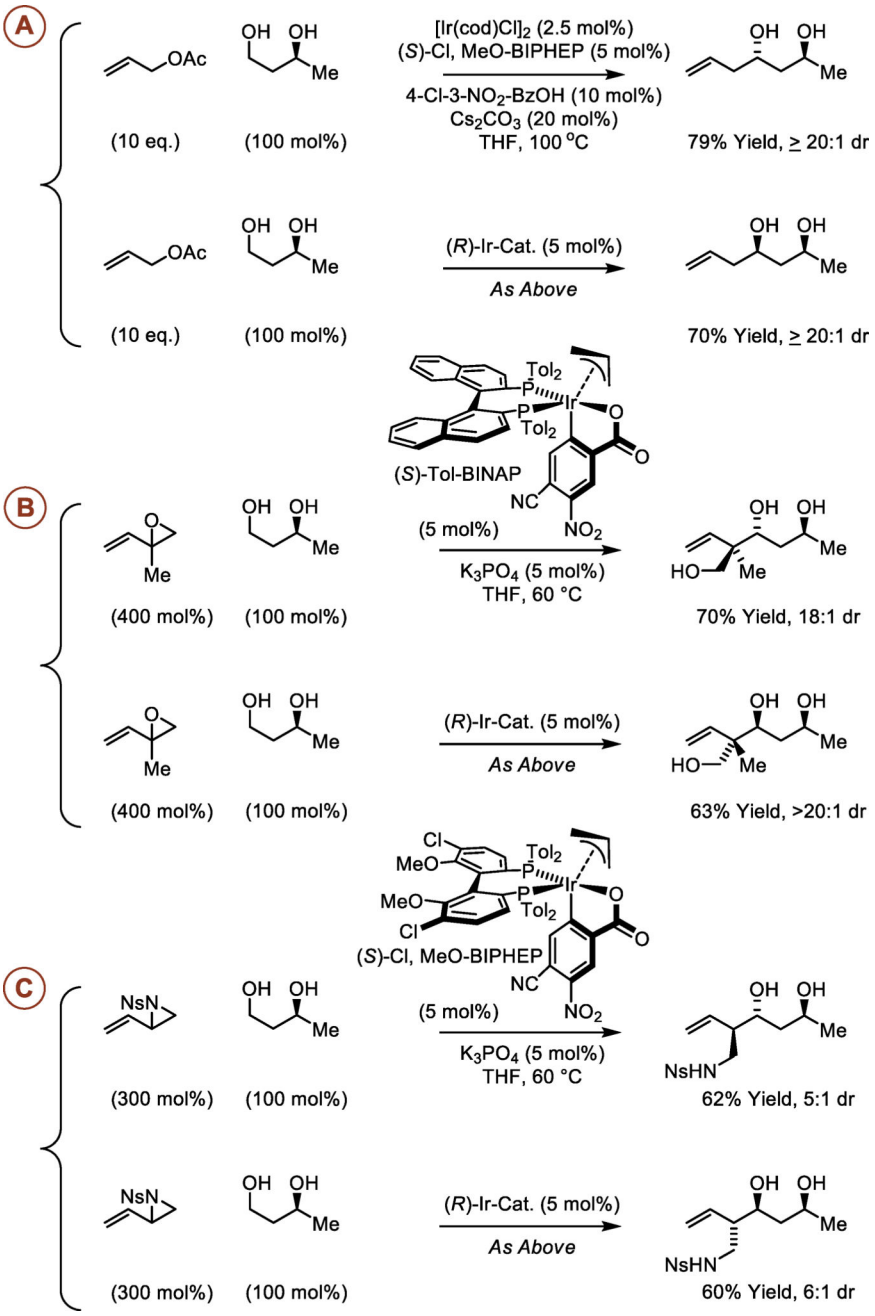



**Scheme 3.**

A. General catalytic mechanism. B. Survey of enantioselective (generally >90% ee) alcohol C-H allylations *via* iridium catalyzed hydrogen transfer.

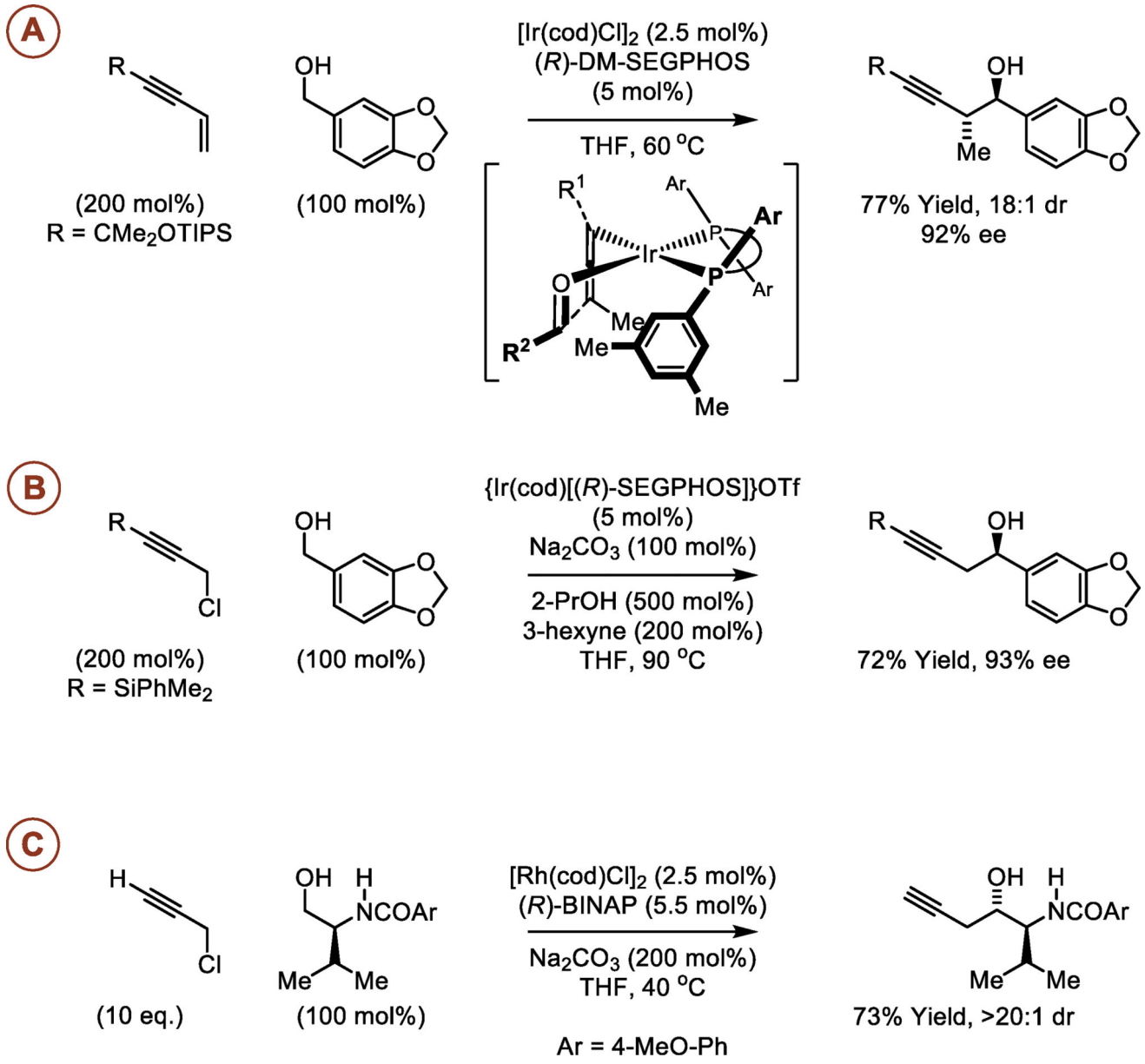



**Scheme 4.**
Enantioselective two-directional allylation and crotylation of 1,3-propane diols.



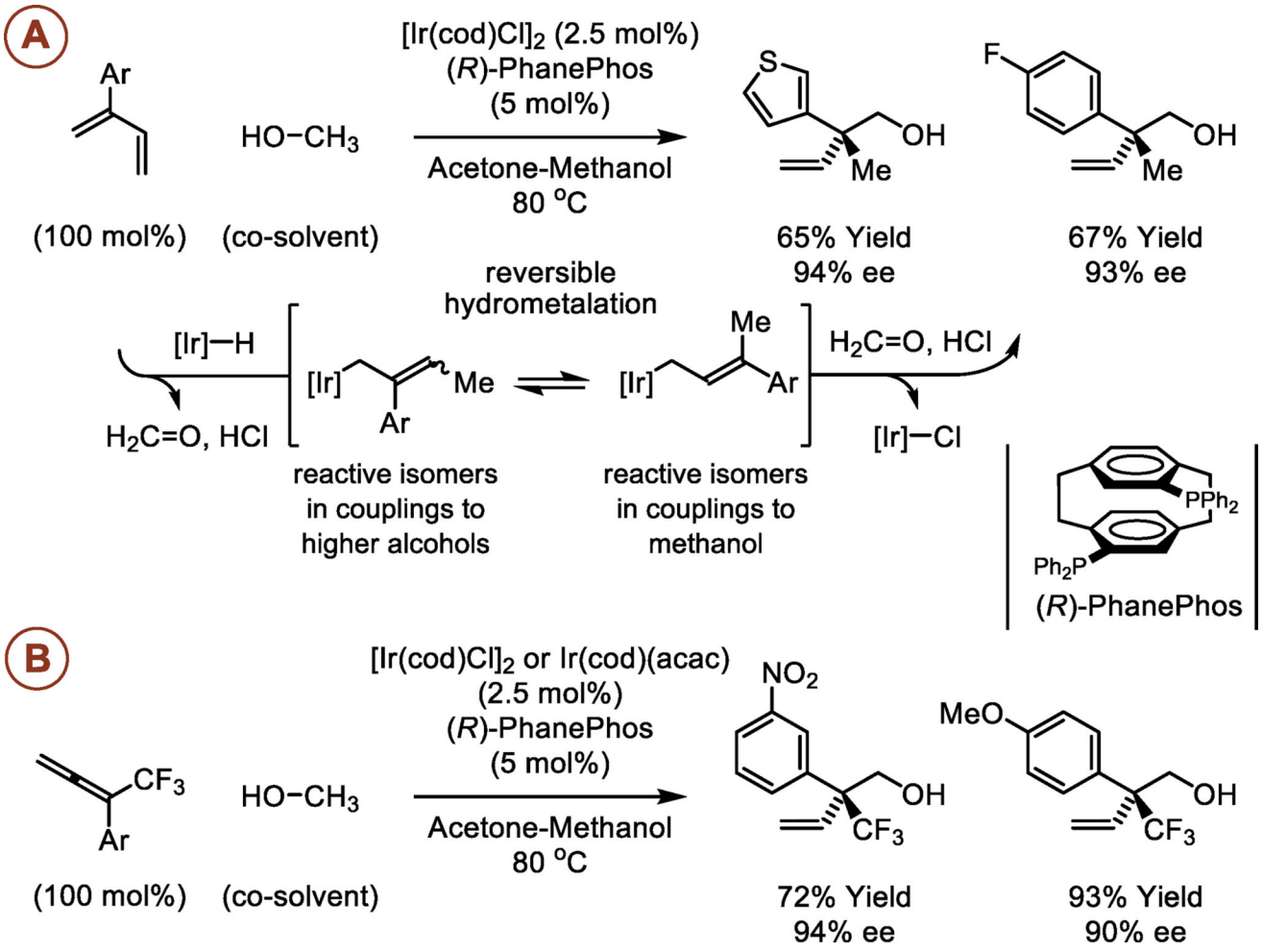

**Scheme 5.**

Site-selective carbinol C-H functionalization of (*S*)-butanediol with catalyst-directed diastereoselectivity: A. allylation, B. *tert*-(hydroxy)- prenylation, C. (α-aminomethyl)allylation.



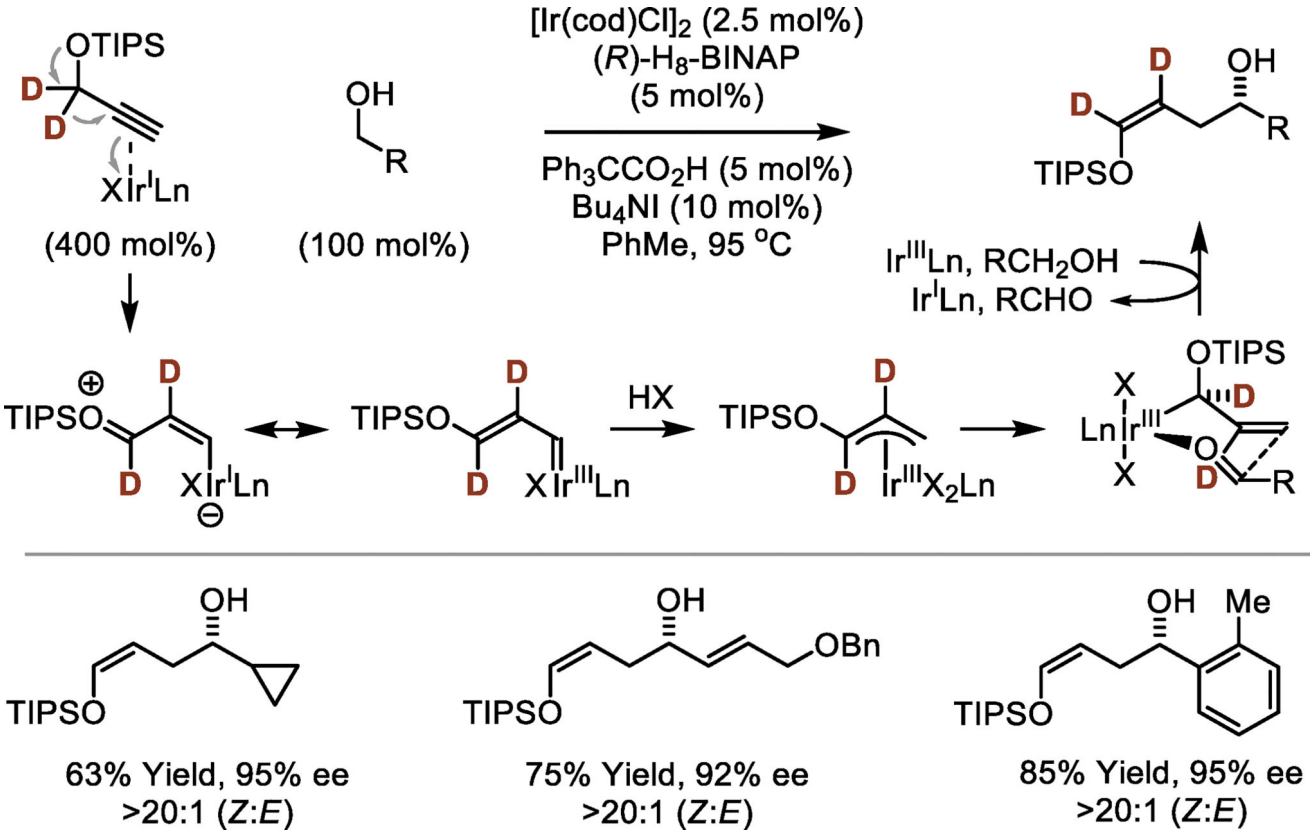

**Scheme 6.**

Enantioselective carbonyl propargylation *via* hydrogen auto-transfer: A. Iridium catalyzed coupling of enyne pronucleophiles, B. Iridium catalyzed coupling of silyl-terminated propargyl chlorides, C. Rhodium catalyzed coupling of unsubstituted propargyl chloride.




**Scheme 7.**

Enantioselective iridium catalyzed coupling of methanol to form quaternary carbon stereocenters: A. Reactions of 1,3-dienes and B. Reactions $CF_3$-allenes.

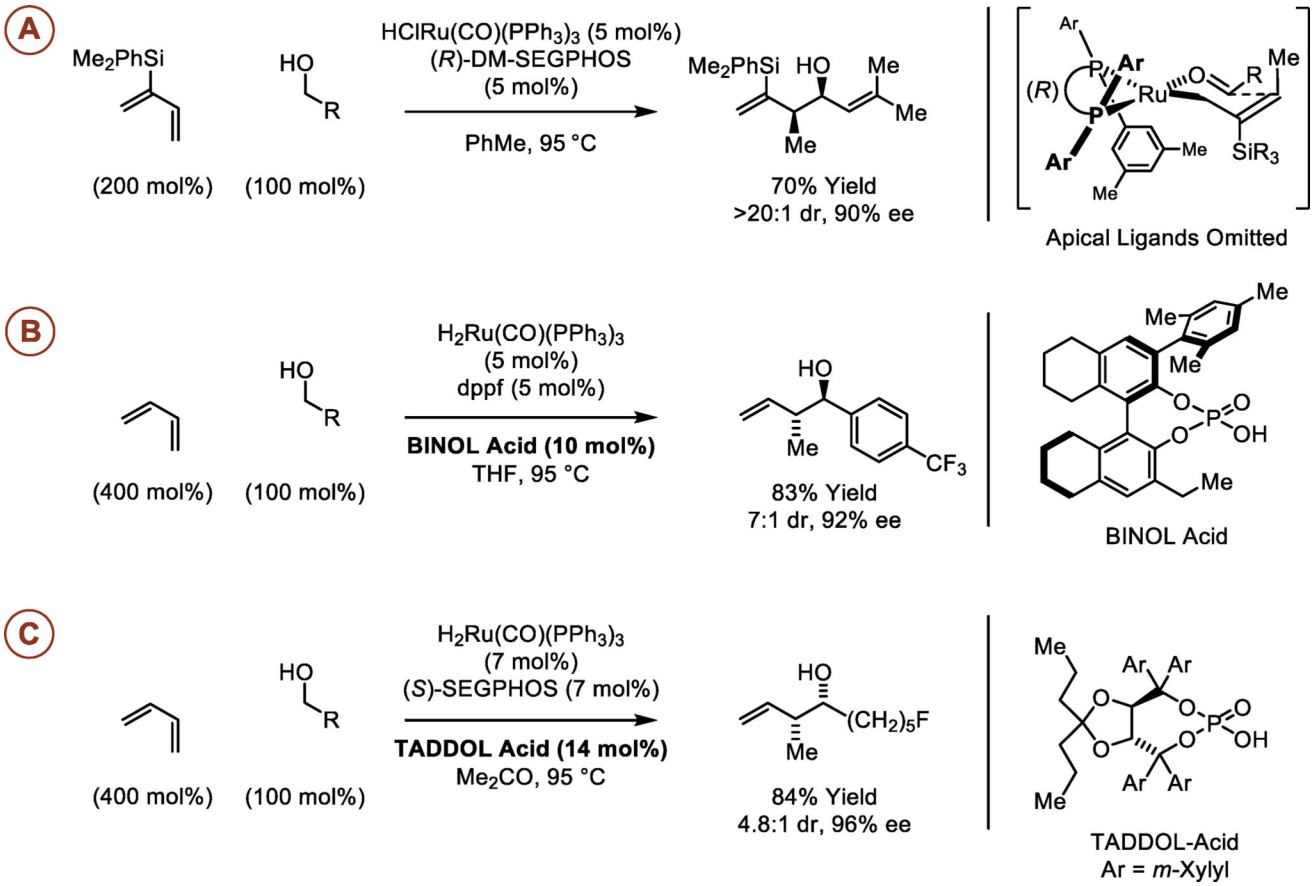






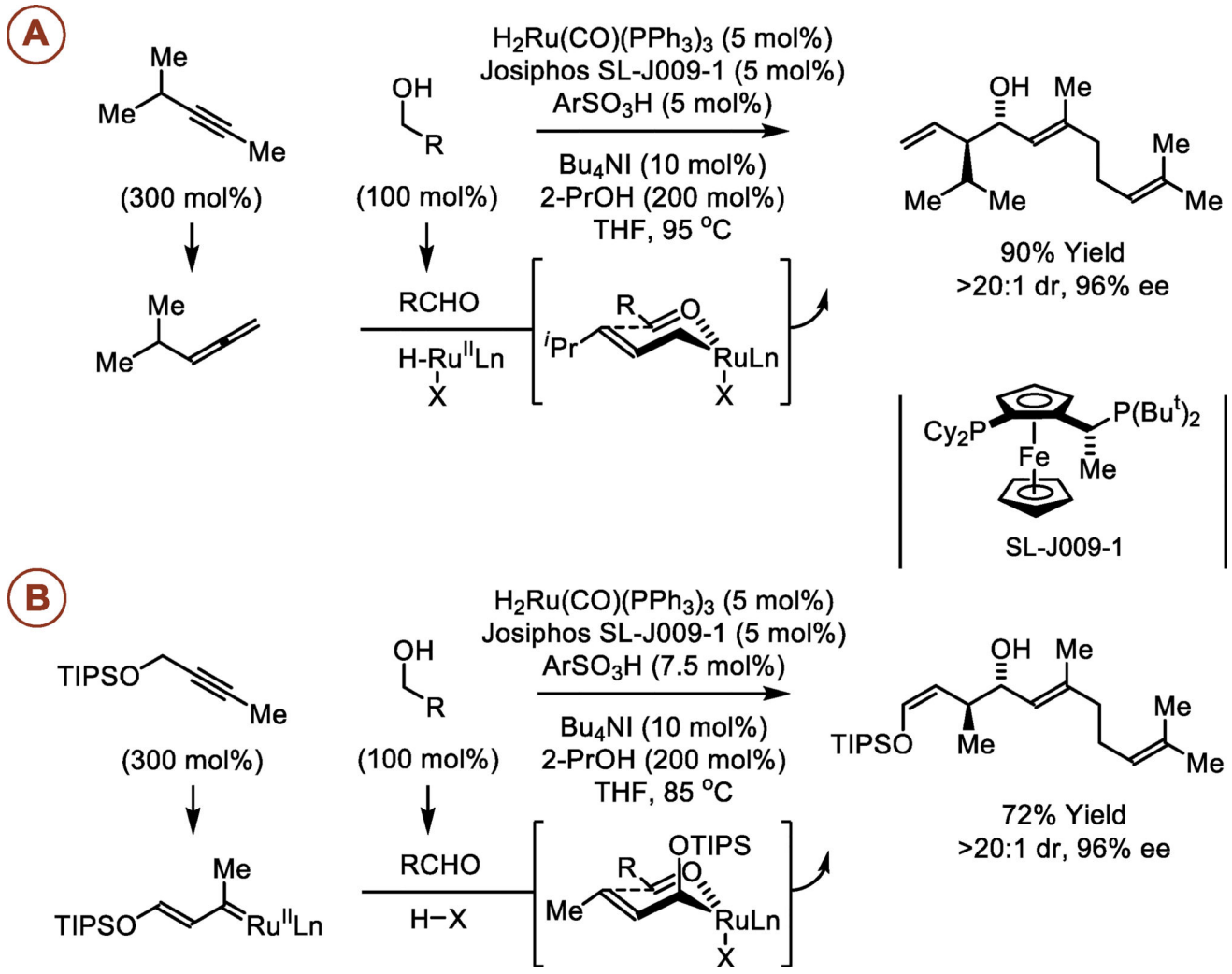
**Scheme 8.**

Enantioselective iridium catalyzed carbonyl (*Z*)-siloxyallylation *via* hydride shift enabled π-allyl formation.



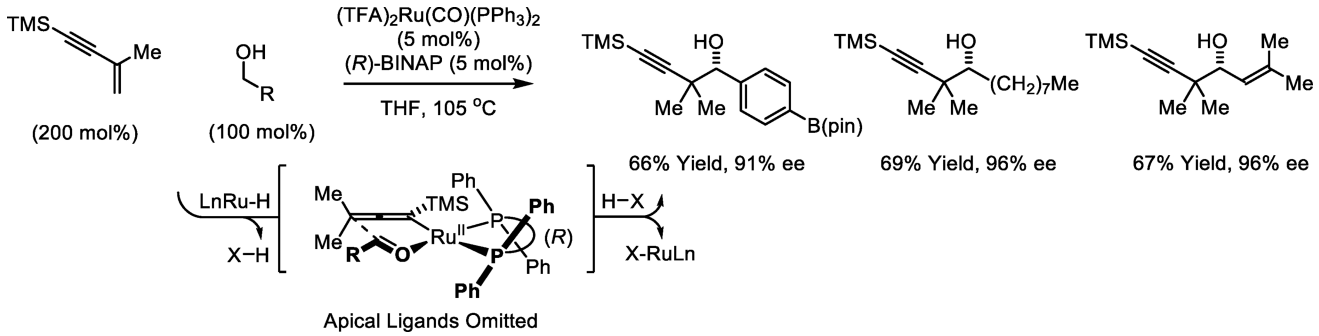

**Scheme 9.**

Diastereo- and enantioselective ruthenium catalyzed coupling of primary alcohols with 1,3-dienes: A. *syn*-Diastereoselective reaction of 2-trialkylsilyl-butadienes, B. *anti*-Diastereoselective reaction of butadiene, C. *syn*-Diastereoselective reaction of butadiene.




**Scheme 10.**

Alkynes as latent allylmetal nucleophiles in enantioselective ruthenium catalyzed couplings with primary alcohols: A. π-Allyl formation *via* tandem alkyne-to-allene isomerization-allene hydrometalation. B. π-Allyl formation *via* 1,2-hydride shift followed by vinyl carbene protonation.




**Scheme 11.**

Enantioselective ruthenium catalyzed coupling of primary alcohols with 1,3-enynes.