Catalytic Enantioselective Carbonyl Propargylation Beyond Preformed Carbanions: Reductive Coupling and Hydrogen Auto-Transfer

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Graphical Abstract

Chiral metal complexes catalyze enantioselective carbonyl propargylation via reductive coupling or as hydrogen auto-transfer processes, in which reactant alcohols serve dually as reductant and carbonyl proelectrophile. Unlike classical propargylation protocols, which rely on allenylmetal reagents or metallic reductants (e.g. NHK reactions), reductive protocols for carbonyl propargylation can occur in the absence of stoichiometric metals, precluding generation of metallic byproducts. Propargylations of this type exploit both enyne and propargyl halide pronucleophiles.
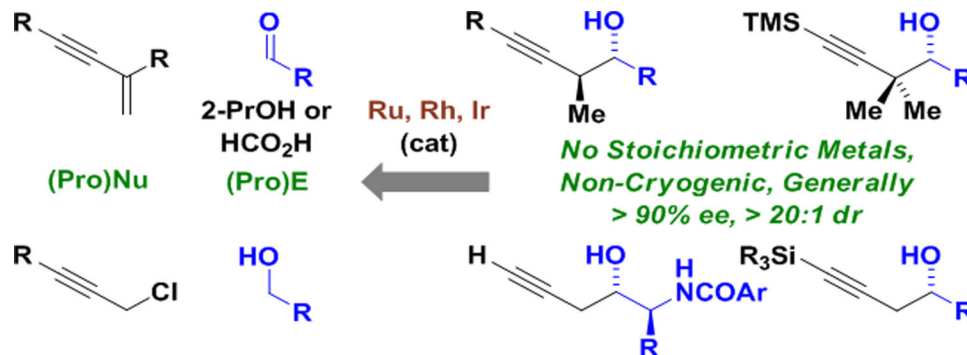
Keywords

Propargylation; Iridium; ruthenium; rhodium; enantioselective; dehydrogenation; hydrogen transfer

I. Introduction and Historical Perspective

Carbonyl propargylations represent a distinctive and useful subset of carbonyl addition reactions.[1] In the first reported carbonyl propargylations described by Prévost (1950) and

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Wotiz (1950), Grignard reagents derived from propargyl bromide were observed to form mixtures of β-acetylenic and α-allenic carbinols or carboxylic acids upon reaction with acetaldehyde or carbon dioxide, respectively.[2a,b] Chodkiewicz (1969) later demonstrated relative stereocontrol in aldehyde additions of this type.[2c] In a major advance, preformed allenylmetal reagents based on boron, tin and silicon were developed by Favre and Gaudemar (1966),[2d,e] Lequam and Guillerm (1973)[2f] and Danheiser (1980),[2g] respectively, and were shown to provide homopropargyl alcohols upon reaction with carbonyl electrophiles. Carbonyl propargylations through propargyl halide reductive coupling under Nozaki-Hiyama conditions were reported by Place, Delbecq and Gore (1978).[2h] Shortly thereafter, Mukaiyama (1981) showed that stannous chloride promoted aldehyde-propargyl halide reductive coupling.[2i] Finally, using a tartrate-modified allenylboron reagent, the first enantioselective carbonyl propargylations were reported by Yamamoto (1982).[3a]

Following Yamamoto's seminal contribution,[3a] numerous methods for enantioselective carbonyl propargylation were developed (Scheme 1).[3–12] The majority of these methods exploit chiral allenylmetal reagents based on boron.[3] However, related reagents based on aluminum,[5] tin,[6] silicon[8] and zinc[10] also have been developed. While effective, these methods require stoichiometric chiral modifiers. Chiral catalysts for the asymmetric addition of achiral allenyl- or propargylmetal reagents (B,[4] Sn,[7] Si[9]) to carbonyl electrophiles overcome this limitation, but these protocols still require hydrolytically unstable premetalated reagents that are prepared through multi-step sequences. A conceptually more appealing strategy for carbonyl propargylation involves the direct catalytic enantioselective reductive coupling of propargyl halides with carbonyl compounds, as realized under Nozaki-Hiyama-Kishi conditions.[11] However, the use of stoichiometric chromium(II) chloride as terminal reductant is far from ideal. More recently, in a significant departure from prior art, propargyl halide reductive couplings were accomplished using 2-propanol as terminal reductant and 1,3-enynes were introduced as pronucleophiles.[12] Furthermore, catalytic enantioselective propargylations have been achieved using alcohols *dually* as reductant and carbonyl proelectrophile, that is, *via* hydrogen auto-transfer.[12,13] Notably, the coupling of alcohols with enyne pronucleophiles[12a-c,f] enables completely atom-efficient carbonyl propargylation. In this monograph, we provide a concise overview of this emergent class of asymmetric alcohol-mediated carbonyl additions.
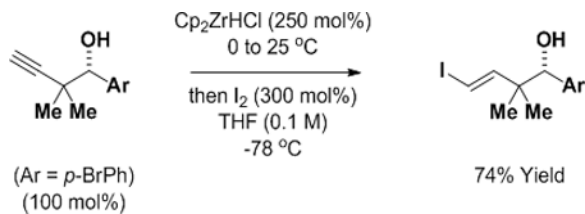
I. Enyne Pronucleophiles

The reductive coupling of carbonyl compounds with conjugated enynes using rhodium[14,15] and nickel catalysts[16] occurs at the acetylenic terminus of the enyne to provide products of carbonyl dienylation. In these processes, alkyne-carbonyl oxidative coupling to form an oxa-metalacyclopentene intermediate is the regio-determining event.[17] In 2008, ruthenium complexes were found to catalyze 2-propanol-mediated enyne-carbonyl reductive couplings.[12a] Remarkably, an alternate regioselectivity was observed wherein C-C coupling occurs at the interior vinylic position of the enyne. Furthermore, for the ruthenium-catalyzed reactions, carbonyl addition could be conducted from the alcohol oxidation level of the reactant via hydrogen auto-transfer. Mechanistic studies corroborate pathways involving enyne hydroruthenation to form nucleophilic allenylruthenium intermediates.[18] These processes, which represent the first examples of transfer hydrogenative carbonyl

propargylation, set the stage for the development of diverse diastereo- and enantioselective transformations of this type (Scheme 2).[12]
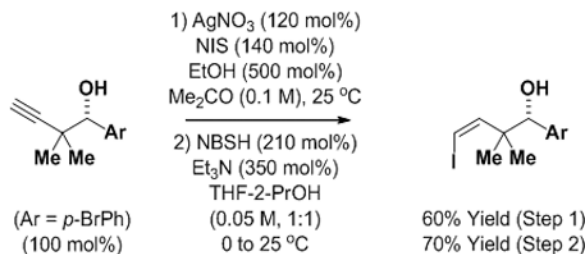
Enforcing relative and absolute stereocontrol in alcohol-mediated carbonyl propargylations catalyzed by ruthenium initially proved to be challenging.[12b] For 1,3-enynes with unsubstituted vinyl moieties ($RC≡CCH=CH_2$), the transient allenylruthenium nucleophiles that arise upon enyne hydroruthenation are axially chiral. Hence, to achieve high levels of enantiomeric enrichment, the transfer of chirality in both enyne hydroruthenation and carbonyl addition events must occur with high levels of fidelity. In contrast, the commercially available 1,3-enyne, $TMSC≡CC(Me)=CH_2$, delivers an allenylruthenium intermediate that is not axially chiral, mitigating erosion of asymmetry in the transmission of chirality from catalyst to product. Thus, through the action of the chiral ruthenium complex formed *in situ* from $(TFA)_2Ru(CO)(PPh_3)_2$ and (*R*)-BINAP, enyne-mediated carbonyl propargylation is achieved with uniformly high levels of enantioselectivity from aliphatic, allylic and benzylic alcohol reactants (Scheme 3).[12f] In the presence of 2-propanol under otherwise identical conditions, corresponding reductive couplings of aldehyde reactants are conducted with roughly equivalent yields and enantioselectivities (not shown).

The catalytic cycle for enyne-mediated propargylation is initiated by substitution of trifluoroacetate with benzyl alcohol to form the ruthenium alkoxide **I** (Scheme 4). β-Hydride elimination delivers the ruthenium hydride **II** with concomitant release of benzaldehyde.[19] Enyne hydrometalation provides the σ-propargyl complex **III**, which isomerizes to the σ-allenyl complex **IV**.[18] Aldehyde coordination, as in complex **V**, followed by carbonyl addition forms the homopropargyl ruthenium alkoxide **VI**. Trifluoroacetic acid-mediated protonolysis of alkoxide **VI** releases the homopropargyl alcohol and regenerates the catalyst to close the catalytic cycle. Alternatively, product may be released through direct exchange of alkoxide **VI** with benzyl alcohol to regenerate ruthenium alkoxide **I**. This interpretation of the catalytic mechanism is consistent with the results of deuterium labeling. Deuterium is mostly retained at the carbinol position ($H_c = 87\%\,^2H$), suggesting hydrogen transfer between the enyne and primary alcohol shows little if any reversibility, and that the homopropargyl alcohol is resistant to dehydrogenation, which would diminish enantioselectivity. Adventitious water likely contributes to incomplete transfer of deuterium.[20]
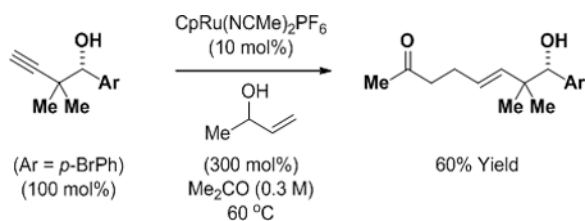
To illustrate the utility of the products obtained upon ruthenium-catalyzed enyne-mediated propargylation, the indicated homopropargyl alcohol derived from *p*-bromobenzyl alcohol was converted to a range of value-added products (eq. 1–3). Hydrozirconation of the homopropargyl alcohol followed by exposure to iodine provides the *trans*-vinyl iodide in good yield (eq. 1).[21] Conversion of the homopropargyl alcohol to the acetylenic iodide[22] followed by diimide reduction using 2-nitrobenzenesulfonylhydrazide (NBSH)[23] delivers the isomeric *cis*-vinyl iodide (eq. 2). Lastly, exposure of the homopropargyl alcohol to 3-buten-2-ol in the presence of a cationic Cp-ruthenium(II) catalyst (Cp = cyclopentadienyl) results in formation of the indicated γ,δ-unsaturated ketone (eq. 3).[24]

Cp$_2$ZrHCl (250 mol%)
0 to 25 °C
then I$_2$ (300 mol%)
THF (0.1 M)
-78 °C

(Ar = *p*-BrPh)
(100 mol%)

74% Yield

(eq. 1)

1) AgNO$_3$ (120 mol%)
NIS (140 mol%)
EtOH (500 mol%)
Me$_2$CO (0.1 M), 25 °C

2) NBSH (210 mol%)
Et$_3$N (350 mol%)
THF-2-PrOH
(0.05 M, 1:1)
0 to 25 °C

(Ar = *p*-BrPh)
(100 mol%)

60% Yield (Step 1)
70% Yield (Step 2)

(eq. 2)

CpRu(NCMe)$_2$PF$_6$
(10 mol%)

(300 mol%)
Me$_2$CO (0.3 M)
60 °C

(Ar = *p*-BrPh)
(100 mol%)

60% Yield

(eq. 3)

In parallel studies, it was found that iridium complexes are also competent catalysts for enyne-mediated propargylation (Scheme 5).[12c] In the presence of an iridium catalyst modified by (*R*)-DM-SEGPHOS or (*R*)-SEGPHOS, the indicated enyne derived from 2-methyl-3-butyn-2-ol (47 USD/Kg) undergoes formic acid-mediated hydrometalation to form aldehyde-allenyliridium pairs, which deliver products of carbonyl *anti*-(α-methyl)propargylation. Aromatic aldehydes, enals and aliphatic aldehydes all participate in propargylation with uniformly high levels of *anti*-diastereo- and enantioselectivity. In the absence of formic acid but under otherwise identical conditions, benzylic, allylic and aliphatic alcohols undergo propargylation via hydrogen auto-transfer. For reactions conducted from the alcohol oxidation level, lower yields were evident in certain cases but *anti*-diastereo- and enantioselectivities were consistently higher. The indicated stereochemical model, which invokes intervention of a square planar allenyliridium species, is inspired by the structure of a related η^1-allenylplatinum(II) complex, *trans*-Pt(PPh$_3$)$_2$(Br) (η^1-CH=C=CH$_2$), for which the allenyl moiety lies roughly perpendicular to the square coordination plane.[25] Finally, the products of propargylation are easily deprotected to reveal

the terminal alkyne in a "one-pot" procedure (eq. 4). Specifically, the propargylation products are initially exposed to TBAF (tetra-*n*-butylammonium fluoride) in THF at room temperature to cleave the silyl ether. Toluene and NaOH are subsequently added and the reaction mixture is heated to promote elimination of acetone.
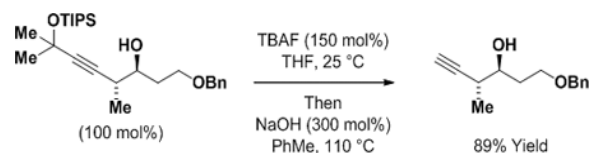
(eq. 4)

In a significant extension of these earlier studies, Buchwald recently developed enantioselective copper(I)-catalyzed enyne-carbonyl reductive couplings mediated by silane that are applicable to ketones (Scheme 6).[26] Using a copper complex modified by (*S*,*S*)-Ph-BPE, a wide range of ketones were converted to tertiary homopropargyl alcohols with high levels of *syn*-diastereo- and enantioselectivity. The authors demonstrate that the reaction could be run efficiently on 50 mmol scale with catalyst loadings as low as 0.2 mol% (not shown). Corresponding ketone propargylations from the alcohol oxidative level via hydrogen auto-transfer remain an unmet challenge that would bypass use of exogenous silane reductant.

II. Propargyl Chlorides as Pronucleophiles

The ability to balance alcohol dehydrogenation with C-X (X = OAc, halide, etc.) reductive cleavage[13] suggested the feasibility of catalytic propargylations wherein alcohol oxidation is used to generate allenylmetal intermediates from propargyl chlorides – a process akin to NHK-type propargylations,[11] but using alcohols rather than chromium(II) chloride as terminal reductant. In an initial step toward this objective, it was found that chiral iridium complexes modified by (*R*)-SEGPHOS catalyze enantioselective 2-propanol mediated propargylations of aryl aldehydes and related hydrogen auto-transfer processes of benzylic alcohols (Scheme 7).[12d] Trialkylsilyl substitution was required at the acetylenic terminus. The use of 3-hexyne as an additive improved conversion by mitigating over-reduction of the resulting homopropargyl alcohol products. Attempted propargylation of aliphatic aldehydes were significantly less efficient under these conditions. Remarkably, ether products obtained via *O*-propargylation were not observed.

Efforts toward the development of conditions enabling direct use of the unsubstituted propargyl chloride, HC≡CCH$_2$Cl, in alcohol-mediated carbonyl propargylation were sought. Eventually, it was discovered that neutral rhodium catalysts modified by *rac*-BINAP were effective in such transformations (Scheme 8). Diverse benzylic, allylic and aliphatic alcohols were converted to the homopropargyl alcohols. These transformations could also be conducted from the aldehyde oxidation level under the conditions of 2-propanol-mediated reductive coupling (not shown). Because the use of optically pure BINAP only led to moderate levels of enantiomeric enrichment (40–55% ee), match-mismatch effects in the *C*-

propargylation of chiral α-stereogenic amino alcohols were explored. As we hoped, products of asymmetric *C*-propargylation could be formed with high levels of stereocontrol (Scheme 8).[12e] Diastereoselectivities were found to increase with increasing size of the α-substituent. The collective data suggest intervention of an intramolecular NH-O hydrogen bond at the stage of the transient α-amino aldehyde accentuates diastereofacial bias in the carbonyl addition event. Again, ether products obtained via *O*-propargylation were not observed.

III. Summary and Outlook

Carbonyl addition ranks among the most fundamental methods for C-C bond formation and has played a central role in the field of chemical synthesis since its very inception. Classical methods for carbonyl addition rely on the use of premetalated reagents, which can be hazardous and give rise to stoichiometric quantities of metallic byproducts. Here, as shown in the specific context of carbonyl propargylation, metal catalyzed reductive coupling offers an alternative to preformed carbanions, allowing carbonyl addition to be achieved using safe, inexpensive reductants with low molecular weights. More broadly, these studies contribute to a growing body of green catalytic C-C couplings that exploit the native reducing ability of alcohol reactants.[13]

Acknowledgments

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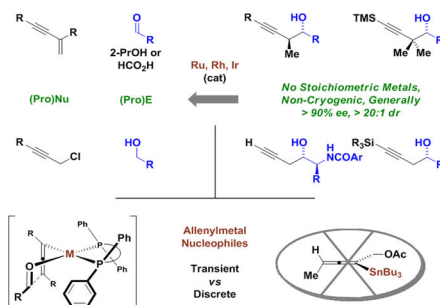
Biographies

Professor Michael J. Krische (B.S. UC Berkeley; PhD Stanford University) holds the Robert A. Welch Chair in Science at the University of Texas at Austin. 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 work has been recognized by numerous awards, including the NSF-CAREER Award (2000), Cottrell Scholar Award (2002), Eli Lilly Granteeship (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), Royal Society of Chemistry, Pedlar Award (2015).

Professor Sang Kook Woo received a B.S. in chemistry from Yeungnam University and a Ph.D. in organic chemistry from Seoul National University under the supervision of Professor Eun Lee. He carried out postdoctoral research at the University of Texas at Austin under the supervision of Professor Michael J. Krische, where he has contributed catalytic enantioselective carbonyl propargylation and total synthesis of polyketide natural products. In 2013, he joined the faculty at University of Ulsan as an assistant professor of chemistry, and was promoted to associate professor in 2018. His research is focused on the development of synthetic methods and the synthesis of biologically active compounds.

Brett Ambler received a B.A. in chemistry from St. Olaf College and a Ph.D. in Medicinal Chemistry from The University of Kansas under the supervision of Professor Ryan Altman. During his doctoral studies, he developed copper-catalyzed decarboxylative trifluoromethylation reactions. Dr. Ambler is presently an ACS postdoctoral fellow in the laboratory of Professor Michael J. Krische, where he has contributed to the development synthetic methods for the construction of antiproliferative polyketide natural products.

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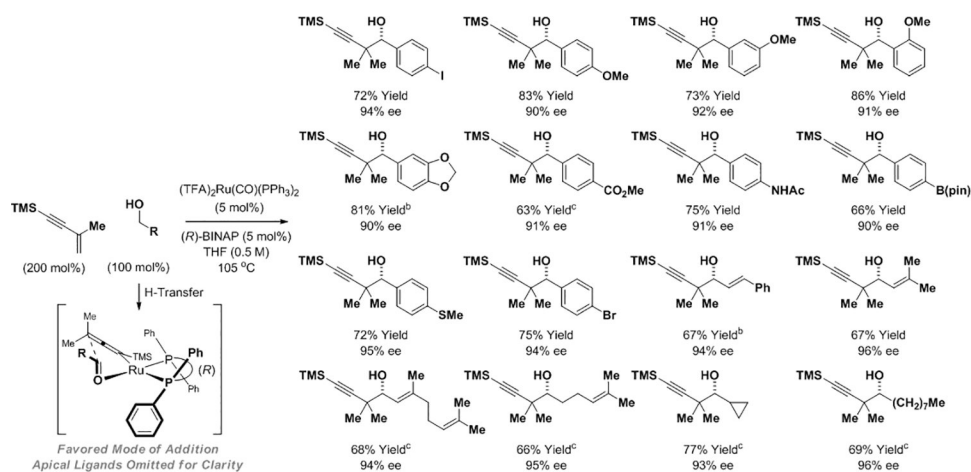[26]. Yang Y, Perry IB, Lu G, Liu P, Buchwald SL, Science 2016, 353, 144. [PubMed: 27284169]
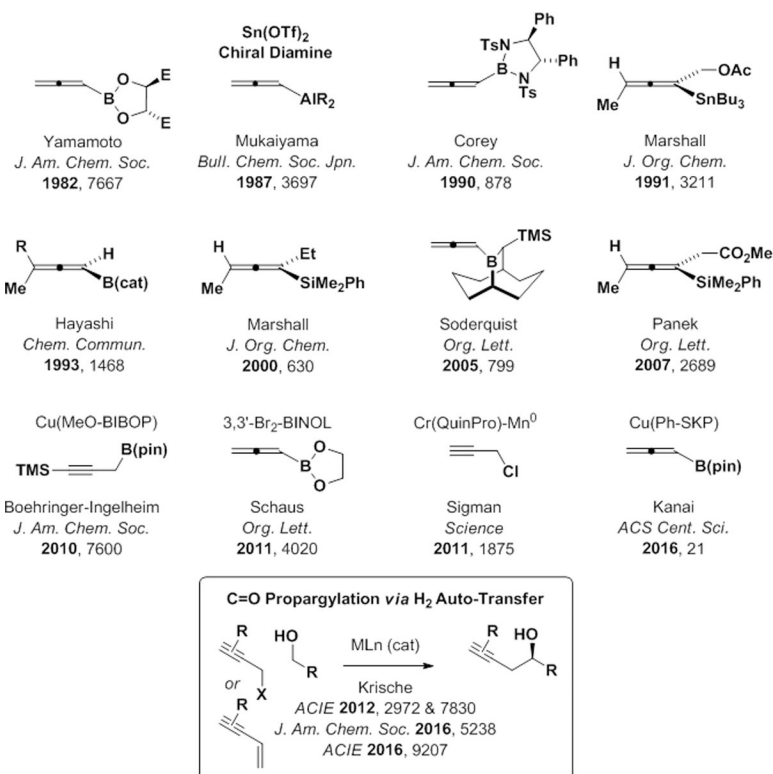
Scheme 1.
Selected milestones in enantioselective carbonyl propargylation.
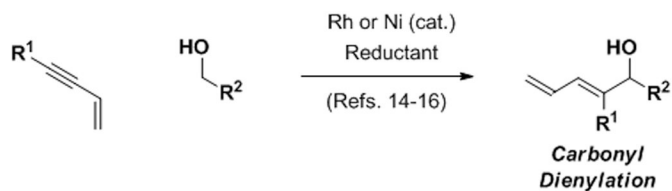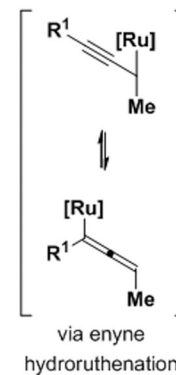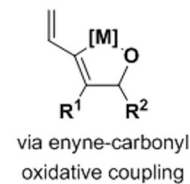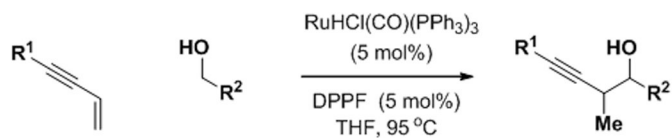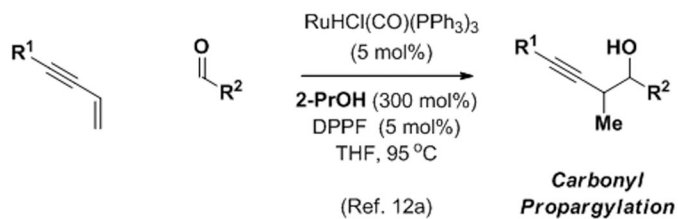
Scheme 2.
Divergent regioselectivity in enyne-carbonyl reductive coupling and discovery of enyne-mediated carbonyl propargylation.[a]
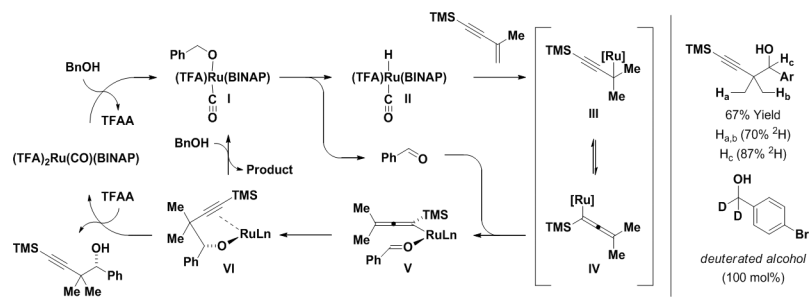
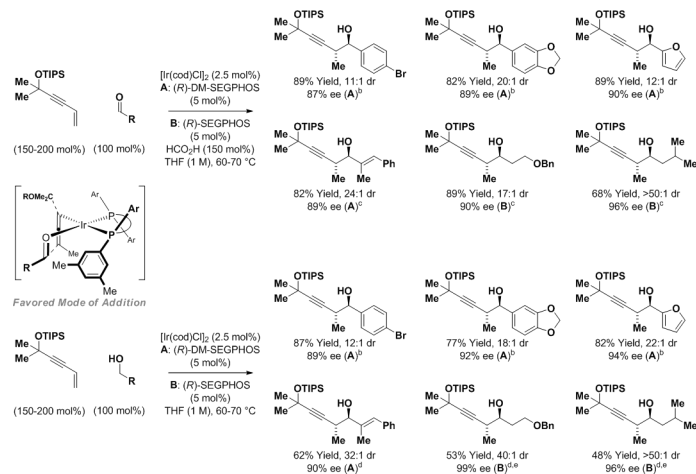[a]DPPF = 1,1'-*bis*(diphenylphosphino)ferrocene.

Scheme 3.

Enantioselective ruthenium catalyzed carbonyl propargylation via hydrogen auto-transfer using enyne pronucleophiles.[a]

[a]BINAP = 2,2′-*bis*-(diphenylphosphino)-1,1′-binaphthalene. TFA = trifluoroacetate. TMS = trimethylsilyl. Yields are of material isolated by silica gel chromatography. Enantioselectivities determined by stationary phase HPLC analysis.[b]95 °C.[c]120 °C.
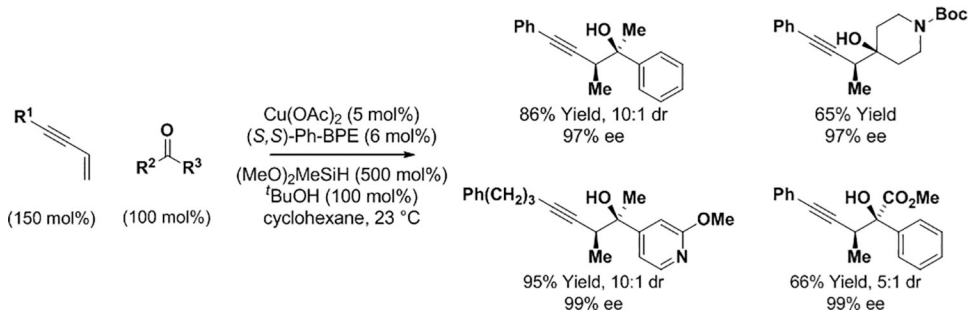
Scheme 4.
General catalytic mechanism and deuterium labeling studies.
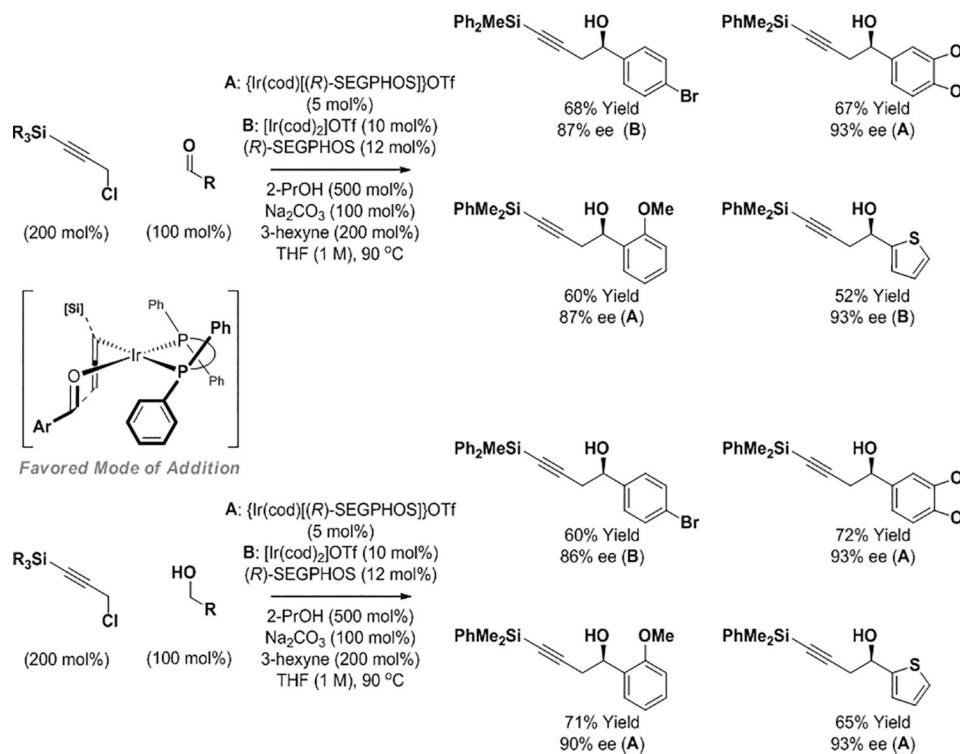
Scheme 5.

anti-Diastereo- and enantioselective iridium-catalyzed carbonyl propargylation via formic acid-mediated reductive coupling and hydrogen auto-transfer using enyne pronucleophiles.[a]
[a]DM-SEGPHOS = 5,5′−*bis*-[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole. SEGPHOS = 5,5′-*bis*-(diphenylphosphino)-4,4′-bi-1,3-benzodioxole. cod = cycloocta-1,5-diene. TIPS = triisopropylsilyl. Yields are of material isolated by silica gel chromatography. Enantioselectivities determined by stationary phase HPLC analysis.[b]MeCN (200 mol %).[c]Na$_2$SO$_4$ (100 mol%).[d]PhCF$_3$ (1 M) was used as solvent, HCO$_2$H (50 mol %).[e][Ir(cod)Cl]$_2$ (5 mol%), (*R*)-SEGPHOS (10 mol%).
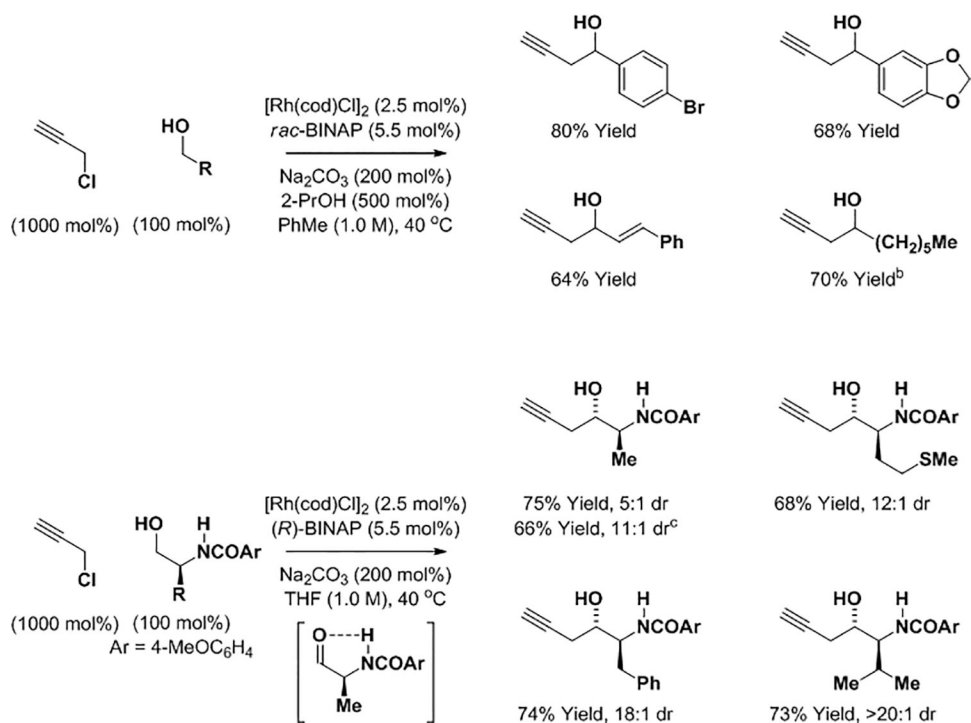
Scheme 6.

syn-Diastereo- and enantioselective copper-catalyzed carbonyl propargylation via silane-mediated reductive coupling and hydrogen auto-transfer using enyne pronucleophiles.[a]

[a](*S,S*)-Ph-BPE = 1,2-Bis[(*2S,5S*)-2,5-diphenylphospholano]ethane. Yields are of material isolated by silica gel chromatography. Enantioselectivities determined by stationary phase HPLC analysis.[a]DM-SEGPHOS = 5,5′−*bis*-[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole. SEGPHOS = 5,5′-*bis*-(diphenylphosphino)-4,4′-bi-1,3-benzodioxole. cod = cycloocta-1,5-diene. TIPS = triisopropylsilyl. Yields are of material isolated by silica gel chromatography. Enantioselectivities determined by stationary phase HPLC analysis.

Scheme 7.

Enantioselective iridium-catalyzed carbonyl propargylation via 2-propanol mediated reductive coupling and hydrogen auto-transfer using propargyl chloride pronucleophiles.[a]

[a]SEGPHOS = 5,5′-*bis*-(diphenylphosphino)-4,4′-bi-1,3-benzodioxole. OTf = trifluoromethanesulfonate. Yields are of material isolated by silica gel chromatography. Enantioselectivities determined by stationary phase HPLC analysis.

Scheme 8.
Rhodium catalyzed propargylation of alcohols via hydrogen auto-transfer using propargyl chloride.[a]

[a]Yields are of material isolated by silica gel chromatography.[b]2-PrOH was omitted.[c]Toluene (1.0 M).