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Ruthenium Catalyzed Transfer Hydrogenation for C-C Bond Formation: Hydrohydroxyalkylation and Hydroaminoalkylation *via* Reactant Redox Pairs

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I. Catalytic Hydrogenation – A Brief Historical Perspective

The first metal catalyzed additions of elemental hydrogen to π-unsaturated reactants were reported by James F. Boyce of the Nathaniel Kellogg Fairbank Soap Company in connection with the processing of vegetable oils.[1] Subsequently, Paul Sabatier of the University of Toulouse developed general protocols for the hydrogenation of alkenes employing heterogeneous nickel catalysts.[2] Foreshadowing the merger hydrogenation and carbonyl addition described in the present account, Paul Sabatier and Victor Grignard jointly received the Nobel Prize in Chemistry in 1912.[3] Following Sabatier's pioneering work, numerous noble metal catalysts for heterogeneous hydrogenation emerged. Among these, the platinum oxide catalyst developed by Roger Adams in 1922 is still one of the most active and readily prepared catalysts for heterogeneous hydrogenation.[4]

The first examples of homogeneous hydrogenation were reported by Melvin Calvin at the University of California at Berkeley in 1938.[5] Calvin showed that under one atmosphere of hydrogen, copper acetate catalyzed the reduction of 1,4-benzoquinone to 1,4-hydroquinone in quinoline solution at 100 °C. It was not until 1961 that Halpern's group at the University of British Columbia performed the first homogeneous hydrogenation of an olefin.[6] In Halpern's system, ruthenium catalysts were used to reduce activated alkenes such as maleic acid. In 1962, Vaska subsequently found that $IrCl(CO)(PPh_3)_2$ reacts reversibly with elemental hydrogen to form isolable dihydrides.[7] This result solidified the conceptual foundation of catalytic hydrogenation by establishing hydrogen "oxidative addition" as a key mechanistic feature.

Finally, in 1965, Wilkinson's group at Imperial College reported the homogeneous hydrogenation of unactivated alkenes and alkynes catalyzed by $RhCl(PPh_3)_3$.[8,9] This finding ultimately led William S. Knowles of Monsanto Company in St. Louis to discover the first enantioselective hydrogenation in 1968.[10] Knowles' discovery was made possible by Horner and Mislow's disclosure of methods for the preparation of nonracemic *P*-stereogenic phosphines.[11,12] In Knowles' initially reported asymmetric hydrogenation, a maximum enantiomeric excess of 15% was obtained. Subsequent work by Kagan in 1971 using chiral

bis(phosphines) derived from tartaric acid (i.e. “DIOP”) gave up to 72% enantiomeric excess.[13] Using a *P*-stereogenic *bis*(phosphine) known as DiPAMP, chemists at Monsanto performed the first industrial catalytic asymmetric synthesis for the production of *L*-DOPA, a treatment for Parkinson’s disease. Lastly, in 1980 Ryoji Noyori reported the synthesis of BINAP and demonstrated the broad utility of this ligand in asymmetric hydrogenation.[14,15]

The purpose of this review is to provide a comprehensive summary of ruthenium catalyzed C-C couplings induced *via* alcohol-mediated transfer hydrogenation.[16–20] These studies build on several important milestones in the area of ruthenium catalyzed hydrogenation and transfer hydrogenation (Scheme 1). In 1971, one decade beyond the seminal work of Halpern on ruthenium catalyzed hydrogenation,[6] transfer hydrogenations employing ruthenium catalysts were described.[21] The ruthenium catalyzed acceptorless dehydrogenation of alcohols was reported by Robinson in 1977,[22] and ruthenium catalyzed oxidative esterifications were reported by Shvo in 1981.[23,24] These studies were followed by the first highly enantioselective ruthenium catalyzed hydrogenations and transfer hydrogenations, reported by Noyori in 1986 and 1995, respectively.[25,26] As documented in this account, ruthenium catalyzed transfer hydrogenation now serves as the basis for C-C bond constructions that directly convert lower alcohols to higher alcohols.[16–20] This body of work was preceded by studies on metal catalyzed carbonyl reductive couplings mediated by elemental hydrogen, as initially described in 2002 by the present author,[27] and as documented in the review literature.[28,29]

II. Conversion of Primary Alcohols to Secondary Alcohols

In 2007, our laboratory reported the first transfer hydrogenative couplings of alcohols with π-unsaturated reactants using iridium-based catalysts.[30] In 2008, the first ruthenium catalyzed reactions of this type were developed (Scheme 2). Specifically, it was found that exposure of alcohols to 1,3-dienes in the presence of catalysts derived from $HClRu(CO)(PPh_3)_3$ and various phosphine ligands resulting in hydrogen transfer to furnish aldehyde-allylruthenium pairs that combine to form homoallylic alcohols as single regioisomers.[31] The coupling of isoprene to d_2-benzyl alcohol results in transfer of a benzylic deuteride to the allylic methyl (19% ^2H) and allylic methine (32% ^2H). These data are consistent with reversible hydrometalation of the less substituted olefin to form a secondary σ-allyl. Conversion to the more stable primary σ-allyl haptomer occurs in advance of carbonyl addition, which proceeds through the indicated closed six-centered transition state with allylic inversion to deliver the product of carbonyl allylation.

Remarkably, while the primary alcohol reactants readily dehydrogenate, the secondary homoallylic alcohol products resist further oxidation due to chelation of homoallylic olefin to ruthenium to generate a coordinatively saturated complex. Indeed, in the coupling of isoprene to d_2-benzyl alcohol, deuterium is completely retained at the carbinol position, suggesting the product is completely unreactive toward alcohol dehydrogenation. However, the ruthenium catalyst $(F_3CCO_2)(H)Ru(CO)(PPh_3)_2$, which is generated *in situ* through the acid base reaction of $H_2Ru(CO)(PPh_3)_3$ and F_3CCO_2H, possesses a higher degree of coordinative unsaturation, enabling β-hydride elimination at the stage of the homoallylic ruthenium alkoxide to form the β,γ-unsaturated enones (Scheme 2).[32] Notably, both

transformations, diene hydrohydroxyalkylation or hydroacylation, may be conducted from the alcohol or aldehyde (not shown) oxidation level of the reactant.[31,32]

Initial studies aimed at directing relative and absolute stereochemistry in alcohol mediated diene hydrohydroxyalkylation relied on the use of 2-trialkylsilyl-butadienes.[33] Hydrometalation of 2-trialkylsilyl-substituted dienes gives rise to crotylmetal species that exist as single geometrical isomers due to allylic strain.[34–36] In the event, using the chiral ruthenium catalyst generated *in situ* from $HClRu(CO)(PPh_3)_3$ and (*R*)-DM-SEGPHOS, the indicated 2-trialkylsilyl-butadiene couples with reactant alcohols to furnish the branched products of hydrohydroxyalkylation with complete *syn*-diastereoselectivity and uniformly high levels of enantioselectivity (Scheme 3).

Direct diastereo- and enantioselective hydrohydroxyalkylations of butadiene, an abundant petrochemical feedstock, required use of a ruthenium catalyst modified by a chiral phosphate counterion derived from H_8-BINOL. The anion is attached to the metal center through the acid-base reaction of $H_2Ru(CO)(PPh_3)_3$ with the indicated chiral phosphoric acid. With the chiral counterion as the sole chiral inducing element, primary benzylic alcohols hydrohydroxyalkylate butadiene with good levels of *anti*-diastereo- and enantioselectivity (Scheme 3).[37]

The corresponding *syn*-diastereomers are formed upon use of the ruthenium catalyst generated *in situ* from $RuH_2(CO)(PPh_3)_3$, (*S*)-SEGPHOS and the indicated TADDOL-derived phosphoric acid (Scheme 3).[38] It is postulated that the s-*cis*-conformer of butadiene hydrometalates to form a (*Z*)-σ-crotylruthenium intermediate. The relatively Lewis basic TADDOL-derived phosphate counterion preserves the kinetic selectivity of diene hydrometalation by attenuating the degree of coordinative unsaturation, decelerating isomerization to the (*E*)-σ-crotylruthenium haptomer with respect to carbonyl addition. Additionally, computational studies suggest a formyl hydrogen bond between the transient aldehyde and the phosphate oxo-moiety assists in stabilizing the (*Z*)-σ-crotylruthenium intermediate.[36]

A divergence in regioselectivity is observed upon use of neutral *vs* cationic ruthenium complexes in alcohol-mediated hydrohydroxyalkylations of 2-substituted dienes. For example, in 2-propanol mediated reductive couplings of 2-substituted dienes with paraformaldehyde (Scheme 4),[39–41] neutral ruthenium complexes favor coupling at the C3 position,[40] whereas ruthenium catalysts with greater cationic character favor coupling at the C2 position, resulting in formation of an all-carbon quaternary center.[39] An erosion in C2-regioselectivity is observed when cationic ruthenium catalysts are applied in reactions of higher carbonyl partners with 2-substituted dienes, as illustrated in couplings with ethanol (Scheme 4).[42]

The collective data, including deuterium labeling experiments,[39,40] are consistent with the following mechanistic interpretation (Scheme 5). Hydroruthenation to form allylruthenium complex **A** is kinetically preferred. For neutral ruthenium catalysts, hydrometalation is less reversible and strongly favors formation of allylruthenium complex **A**. Hence, formation of C3-coupling products is preferred. For cationic ruthenium complexes, hydrometalation

becomes highly reversible, enabling access to both allylruthenium complex **A** and allylruthenium complex **B**. It now appears that a Curtin-Hammett scenario is operative. For small aldehyde partners (R^1 = H), the transition state leading to C2-adducts is lower in energy. However, as the aldehyde increases in size (R^1 = Me), the formation of a more congested C-C bond raises the energy of the transition state for formation of C3-adducts, eroding regioselectivity.

Hydrogen transfer from primary alcohols to allenes represents an alternate means of accessing allylruthenium-carbonyl pairs that deliver products of hydrohydroxyalkylation (Scheme 6).[43–47] Interestingly, whereas 2-propanol-mediated reductive couplings of 1,1-disubstituted allenes display poor levels of diastereoselectivity,[43] related redox-neutral couplings with primary alcohols delivers branched homoallylic allylic alcohols bearing all-carbon quaternary centers with good to complete control of relative stereochemistry.[45] In reactions conducted from the alcohol oxidation level, diastereoselectivities are highly concentration dependent. At lower concentrations higher diastereoselectivities are observed. These data suggest a Curtin-Hammett scenario wherein turn-over limiting carbonyl addition preferentially consumes the (*E*)-σ-allylruthenium haptomer *via* stereospecific carbonyl addition from an equilibrating mixture of transient (*Z*)- and (*E*)-σ-allylruthenium isomers. At lower concentration, the (*E*)-isomer can be replenished *via* isomerization of the (*Z*)-σ-allylruthenium isomer. These conditions have been applied to the coupling of allenes with fluorinated alcohols (not shown).[47]

In the case of *mono*-substituted allenes, the steric demand of an appropriately defined substituent can direct exclusive formation of (*E*)-σ-allylruthenium intermediates that participate in stereospecific carbonyl addition to deliver single diastereomers. For example, hydrogen transfer from primary alcohols to allenamides provides geometrically defined (amino)allylruthenium-aldehyde pairs that combine to form vicinal *anti*-aminoalcohols as single diastereomers (Scheme 6).[45] Identical products are accessible as single diastereomers *via* 2-propanol-mediated reductive coupling allenamides and aldehydes (not shown).[44]

Isomerization of alkynes to allenes under the conditions of ruthenium catalyzed hydrohydroxyalkylation enables transformations that are otherwise inaccessible, including the conversion of primary alcohols to (*Z*)-homoallylic secondary alcohols (Scheme 7).[48] Isomerization is promoted through the use of cationic ruthenium catalysts generated through the acid-base reaction of $H_2Ru(CO)(PPh_3)_3$ and 2,4,6-$(2\text{-}Pr)_3PhSO_3H$. As corroborated by deuterium labelling studies, the cationic ruthenium complex appears to exist in equilibrium with zero-valent species that promote isomerization *via* propargyl C-H oxidative addition. Allene-aldehyde oxidative coupling mediated by ruthenium(0) then forms an oxaruthenacycle, which upon transfer hydrogenolysis delivers the (*Z*)-homoallylic alcohols with good to complete levels of stereocontrol. Oxidative coupling pathways are suppressed upon introduction of iodide ion and a chelating phosphine ligand, the Josiphos ligands SL-J009-1 or SL-J002-1, yet alkyne-to-allene isomerization pathways persist. Under these conditions, the transient allenes accept hydrogen from primary alcohols to form chiral allylruthenium-aldehyde pairs that deliver enantiomerically enriched branched homoallylic alcohols as single diastereomers.[49] In this way, alkynes serve as chiral allylmetal equivalents.[50–57]

A third mechanism for the coupling of primary alcohols with alkynes becomes operative when these conditions are applied to the propargyl ether, MeC≡CCH$_2$OTIPS (TIPS = triisopropylsilyl) (Scheme 8).[58] Unlike closely related ruthenium catalyzed alkyne-alcohol C-C couplings, deuterium labeling studies corroborate a novel 1,2-hydride shift mechanism that converts metal-bound alkynes to vinyl carbenes that protonate to form siloxy-π-allylruthenium nucleophiles in the absence of intervening allenes. Due to the negative inductive effect of the siloxy moiety, carbonyl addition occurs through a closed transition structure from the σ-allylruthenium haptomer where ruthenium resides at the oxygen-bearing carbon. Using a Josiphos (SL-J009-1) modified ruthenium(II) catalyst, the resulting products of siloxy-crotylation form as single regioisomers with complete levels of *anti*-diastereoselectivity and high levels of enantioselectivity. Although mixtures of enol geometrical isomers are produced, the (*Z*)- and (*E*)-selectivity is inconsequential as fluoride assisted cleavage of the enol in the presence of NaBH$_4$ converts both isomers to the same 1,4-diol.

Remarkably, a fourth mechanism for the coupling of primary alcohols with alkynes is evident in couplings that form allylic alcohols[59] or conjugated enones (Scheme 9).[60] These processes are catalyzed by (TFA)$_2$Ru(CO)(PPh$_3$)$_2$ in the absence of added phosphine ligand. It is postulated that coordinative unsaturation, the presence of a π-acidic carbonyl ligand and the reducing environment provided by 2-propanol promote equilibration between ruthenium(II) and ruthenium(0) complexes. Thus, while the experimental data cannot exclude hydrometalative pathways involving vinylruthenium-aldehyde pairs, another possible mechanism involves ruthenium(0)-mediated alkyne-carbonyl oxidative coupling to form a ruthenacyclopentene that suffers alcohol-mediated transfer hydrogenolysis to release the allylic alcohol and regenerate the zero valent catalyst. Under more forcing conditions (higher temperatures, longer reaction times) and in the absence of 2-propanol, the initially formed allylic alcohols undergo further dehydrogenation to form the conjugated enones. Resubjection of the allylic alcohols to the reaction conditions results in formation of the enone, suggesting β-hydride elimination may not occur at the stage of the intermediate ruthenacycle.

Hydrogen transfer from primary alcohols to 1,3-enynes delivers allenylruthenium-aldehyde pairs that combine to form products of carbonyl propargylation (Scheme 10).[61–63] Initially developed conditions provided products of α-methyl-propargylation as diastereomeric mixtures.[61] Identical products of propargylation are generated upon 2-propanol mediated 1,3-enyne-aldehyde reductive coupling.[62] In subsequent work, it was found that *anti*-diastereoselectivity improves upon use of sterically demanding reactants.[63] More recently, the chiral ruthenium complex formed *in situ* from (TFA)$_2$Ru(CO)(PPh$_3$)$_2$ and (*R*)-BINAP was found to catalyze the C-C coupling of primary alcohols with the 1,3-enyne, TMSC≡CC(Me)=CH$_2$, to form secondary homopropargyl alcohols bearing *gem*-dimethyl groups. These conditions deliver products of C-C coupling with uniformly high levels of enantioselectivity and are applicable to aliphatic, allylic and benzylic alcohols. One may view these protocols as an alternative to the use of stoichiometric allenylmetal reagents in carbonyl propargylation.[64,65]

III. Conversion of Secondary Alcohols to Tertiary Alcohols

In 2012, it was found that ruthenium(0) complexes catalyze the C-C coupling of activated secondary alcohols with feedstock dienes such isoprene and myrcene to furnish products of carbinol C-H prenylation and geranylation, respectively (Scheme 11).[66–68] Mechanistic studies corroborate a catalytic mechanism involving diene-carbonyl oxidative coupling to form an oxaruthenacycle. The transfer of hydrogen from the secondary alcohol reactant mediates transfer hydrogenolysis to release the products of C-C coupling and regenerate the activated ketone to close the catalytic cycle. The regioselectivity of C-C bond formation for the diene C4-position is unique among diene-carbonyl reductive couplings.[41,69] Beyond α-hydroxy esters,[66] these conditions are applicable to 3-hydroxy-2-oxindoles[67] and secondary alcohols substituted by certain heteroaromatic moieties.[68] In the latter case, the putative oxaruthenacycle intermediate was isolated, characterized and reversible metalacycle formation was demonstrated through experiments involving diene exchange.

The transient 1,2-dicarbonyl motifs required for oxidative coupling are also accessible from vicinal diols. For example, in the presence of the ruthenium(0) catalyst derived from $Ru_3(CO)_{12}$ and PCy_3, vicinal diols and alkynes react to form α-hydroxy β,γ-unsaturated ketones as single geometrical isomers (Scheme 12).[70] Here, it was found that carboxylic acid cocatalysts dramatically increase rate and conversion. A catalytic mechanism that accounts for the effect of the carboxylic acid cocatalysts is as follows. A mononuclear ruthenium(0) complex[71] promotes alkyne-dione oxidative coupling to form the indicated oxaruthenacycle.[72,73] Direct protonation of the oxaruthenacycle by the diol or ketol is postulated to be slow compared to protonolytic cleavage of the oxaruthenacycle by the carboxylic acid. The resulting ruthenium carboxylate exchanges with the diol or ketol to form a ruthenium alkoxide, which upon β-hydride elimination releases the ketol or dione, respectively, and a vinylruthenium hydride. C-H Reductive elimination furnishes the product of C-C coupling and returns ruthenium to its zero-valent form. Conventional diol-alkyne transfer hydrogenation provides the initial quantities of dione required for entry into the catalytic cycle.[23,24,74]

Intermolecular catalytic reductive couplings of α-olefins with unactivated aldehydes and ketones remains an unmet challenge.[75–77] In a significant step toward this goal, it was found that ruthenium(0) catalysts promote the transfer hydrogenative C-C coupling of 3-hydroxy-2-oxindoles with α-olefins, including feedstocks such as ethylene, propylene and styrene, to furnish the branched adducts as single regio- and diastereomers. In the absence of carboxylic acid cocatalyst, only trace quantities of product were formed (Scheme 13).[78]

IV. Transfer Hydrogenative Cycloaddition

Intermolecular hydrogen transfer reactions that result in the formation of rings represent a new class of metal catalyzed cycloadditions.[79,80] Ruthenium catalyzed C-C bond forming transfer hydrogenation contributes a new dimension to this emerging area. Using a ruthenium(0) catalyst, diols react with acrylates to form spiro-γ-butyrolactones (Scheme 14).[81] Ethyl 2-(hydroxymethyl)acrylate reacts with diols by way of transient oxaruthenacycles that engage in E1cB elimination to furnish α-methylene-spiro-γ-

butyrolactones.[81] As illustrated in couplings with 3-hydroxy-2-oxindoles, β-substituted acrylic esters provides spiro-γ-butyrolactones as single diastereomers.[81] Remarkably, the cycloadditions may be conducted in oxidative, redox-neutral or reductive modes using diols, ketols or diones, respectively, as reactants. To illustrate, ethyl acrylate reacts with hydrobenzoin, benzoin or benzil to form an identical γ-lactone. For the latter reaction involving benzyl, 2-propanol (300 mol%) is employed as terminal reductant (Scheme 15).

In the presence of a ruthenium(0) catalyst, vicinal diols transfer hydrogen to conjugated dienes to furnish diones that engage in diene-carbonyl oxidative coupling. The resulting oxaruthenacycles incorporate an allylruthenium moiety that engages the pendant ketone in intramolecular allylruthenation to form products of formal [4+2] cycloaddition as single diastereomers (Scheme 16).[82,83] The cycloadducts are readily transformed to the 9–12 membered 1,6-diketones upon exposure to iodosobenzene diacetate.[83] Alternatively, the cycloadducts can be dehydrated to form products of benzannulation.[84] Two-directional benzannulation is especially powerful. For example, exposure of the indicated pyracylene-based tetraol to butadiene in the presence of the ruthenium(0) catalyst delivers the double [4+2] cycloadduct, which is directly dehydrated to form the indeno[1,2,3-*cd*]-fluoranthene in a single “one-pot” operation.

Exposure of 3,4-benzannulated 1,5-diynes (benzo-endiynes) to α-ketols in the presence of ruthenium(0) catalysts derived from $Ru_3(CO)_{12}$ and RuPhos results in successive redox-triggered C-C coupling to generate products of [4+2] cycloaddition (Scheme 17).[85] Here, redox-neutral couplings using α-ketols are essential, as diols require a sacrificial hydrogen acceptor, which contributes to partial reduction of the diyne reactant. Regioselective cycloaddition is achieved using nonsymmetric diynes with alkyne termini substituted by *n*-propyl and *t*-butyl groups. This strategy for cycloaddition has been extended to the reaction of *ortho*-acetylenic benzaldehydes with α-ketols. Using ruthenium(0) catalysts modified by CyJohnPhos, the indicated products of [4+2] cycloaddition form as single regio- and diastereomers.[86] This methodology enables convergent construction of ring systems characteristic of type II polyketides, specifically those of the angucycline class.[87–89]

V. Hydroaminoalkylation

Since the initial discovery of metal catalyzed hydroaminoalkylation Maspero[90] and Nugent[91] in the early 1980’s, significant advances in the field of hydroaminoalkylation using early transition metal catalysts have been made. In contrast, the development of corresponding late transition metal catalyzed amine C-H functionalizations has proven challenging.[92–94] Indeed, with the exception of the present authors work,[95–99] all other late transition metal catalyzed hydroaminoalkylations require pyridyl directing groups in combination with mono-olefin reactants.[100–108] In a significant departure from prior art, it was found that ruthenium catalyzed hydrogen transfer from 4-aminobutanol to 1-substituted-1,3-dienes results in the generation of dihydropyrrole-allylruthenium pairs, which combine to form products of hydroaminoalkylation with good to complete control of *anti*-diastereoselectivity (Scheme 18).[95] As corroborated by deuterium labeling experiments, kinetically preferred hydrometalation of the terminal olefin of the 1-substituted-1,3-diene delivers a 1,1-disubstituted π-allylruthenium complex that isomerizes to the more stable

monosubstituted π-allylruthenium complex. Imine addition then occurs with allylic inversion through a closed transition structure. Using a carboxylic acid cocatalyst, pyrrolidine itself can be engaged in direct ruthenium catalyzed diene hydroaminoalkylations. Finally, 2-propanol mediated reductive coupling of butadiene with the dihydropyrrole trimer provides the identical product of diene hydroaminoalkylation. All three reaction types proceed through a common set of reactive intermediates, as shown in the indicated stereochemical model.

Carbonylative hydroaminomethylation (hydroformylation-reductive amination)[109–115] has only been reported for mono-olefin reactants, as hydroformylation of dienes and allenes suffers from poor regioselectivity and "over-hydroformylation" to form dialdehyde products. In contrast, 2-propanol-mediated reductive couplings of allenes or dienes with formaldimines (generated *in situ* from saturated 1,3,5-triazines) are efficient and selective processes.[95–98] Specifically, ruthenium catalyzed transfer hydrogenation of allenes in the presence of 1,3,5-*tris*(4-methoxyphenyl)-hexahydro-1,3,5-triazine provides products of hydroaminomethylation as single regioisomers.[96] Under similar conditions, butadiene and related 2-substituted dienes engage in regioselective reductive C-C coupling to furnish products of hydroaminomethylation.[97] Here, higher temperatures (140 °C) are required to supress the competing aza-Diels-Alder reaction of formaldimine. Regioselective 2-propanol mediated reductive coupling of dienes with iminoacetates also have been described (not shown).[98]

Whereas ruthenium(II) catalysts promote hydroaminoalkylation through hydrometalative pathways, ruthenium(0) catalysts derived from $Ru_3(CO)_{12}$ and triphos enable catalytic mechanism involving diene-imine oxidative coupling (Scheme 20).[99] Presently, transformations of this type are restricted to the hydroaminoalkylation of isoprene with aryl substituted hydantoins. The catalytic mechanism involves hydrogenolytic cleavage of the azaruthenacyclopentane intermediate through hydrogen transfer from the hydantoin reactant, which releases product and regenerates the requisite imine for oxidative coupling.

VI. Conclusion and Outlook

Since the seminal work of Sabatier and Grignard, hydrogenation and carbonyl addition have found longstanding use as methods for chemical synthesis. Merging the chemistry of transfer hydrogenation and carbonyl or imine addition, we have developed a broad, new family of reductive and redox-neutral hydrohydroxyalkylations and hydroaminomethylations – processes in which the transfer or redistribution of hydrogen is accompanied by C-C bond formation. We have just begun to exploit the potential of this novel reactivity mode, yet already one may see that carbonyl additions traditionally employing stoichiometric organometallic reagents can now be conducted catalytically *via* hydrogen transfer. Perhaps most importantly, this new reactivity has enabled transformations that have no counterpart in the current lexicon of synthetic methods.

Acknowledgments

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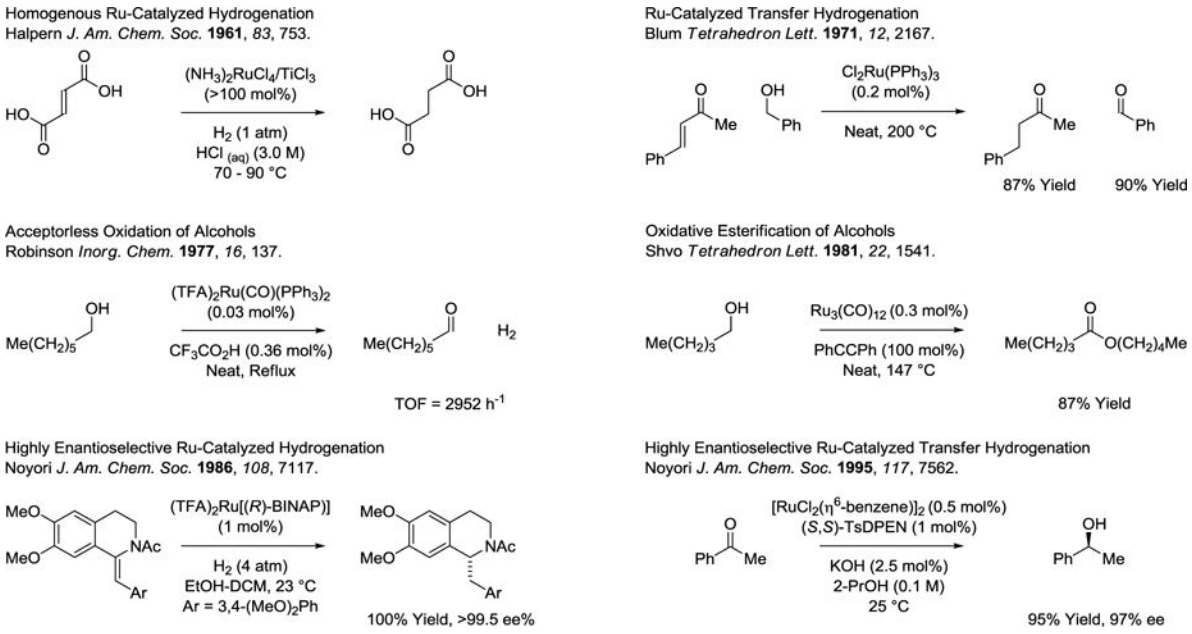
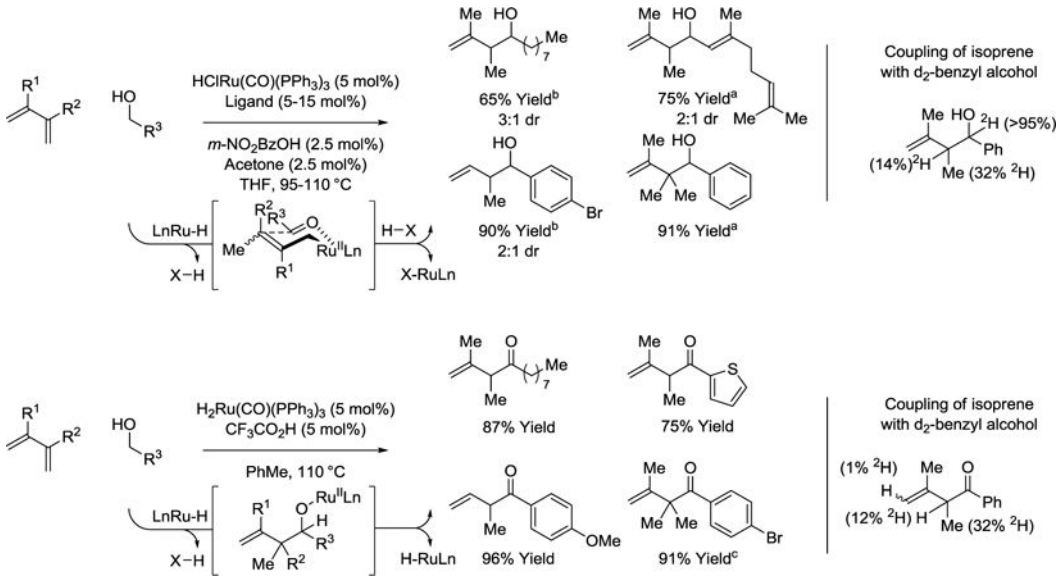


Scheme 1.

Selected milestones in homogeneous ruthenium catalyzed hydrogenation and transfer hydrogenation.[a]

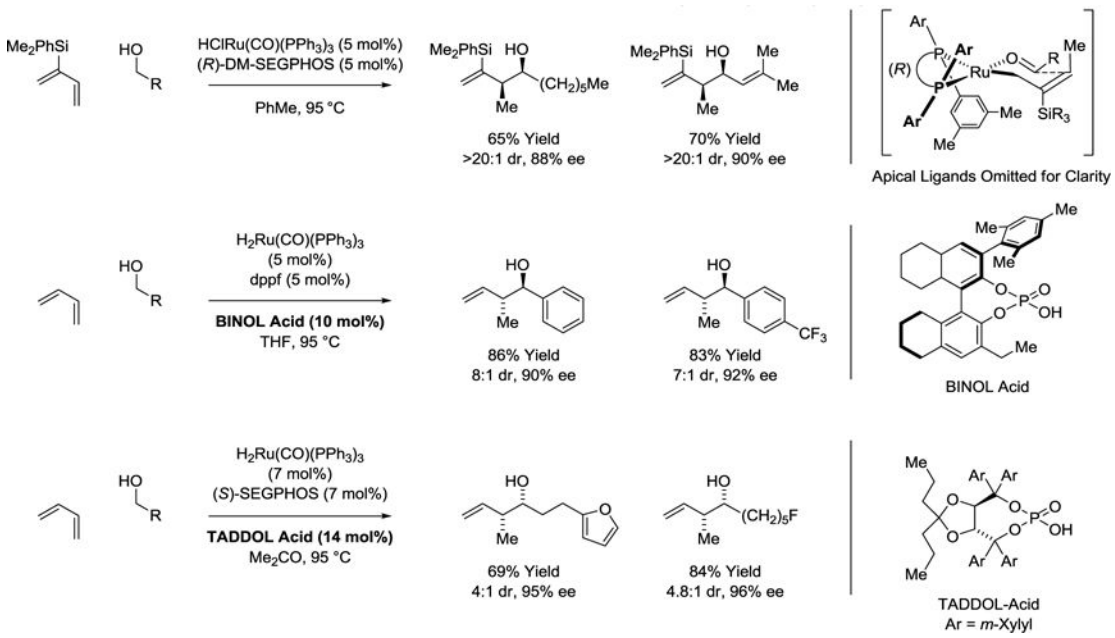
[a]BINAP = 2,2′-*bis*-(diphenylphosphino)-1,1′-binaphthalene. TsDPEN = *N*-*p*-Tosyl-1,2-diphenylethylenediamine.



Scheme 2.

Ruthenium catalyzed C-C coupling of primary alcohols with 1,3-dienes to form homoallylic alcohols or β,γ-enones.[a]

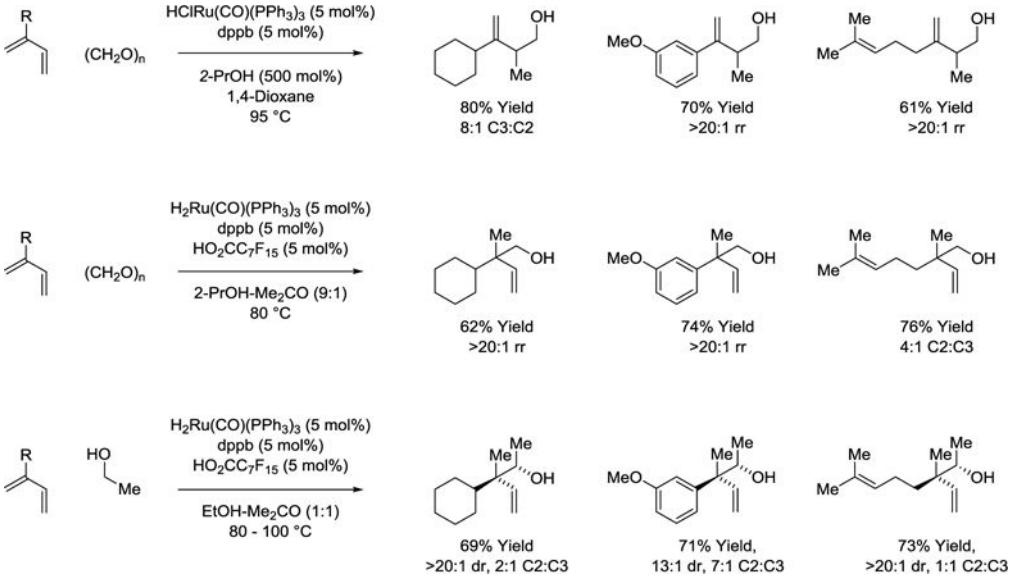
Yields are of material isolated by flash chromatography on silica gel. [a]Ligand = (*p*-MeOPh)$_3$P, [b]Ligand = *rac*-BINAP, 2,2′-*bis*-(diphenylphosphino)-1,1′-binaphthalene. [c]120 °C.



Scheme 3.

Diastereo- and enantioselective alcohol mediated hydrohydroxyalkylation of butadienes.[a]

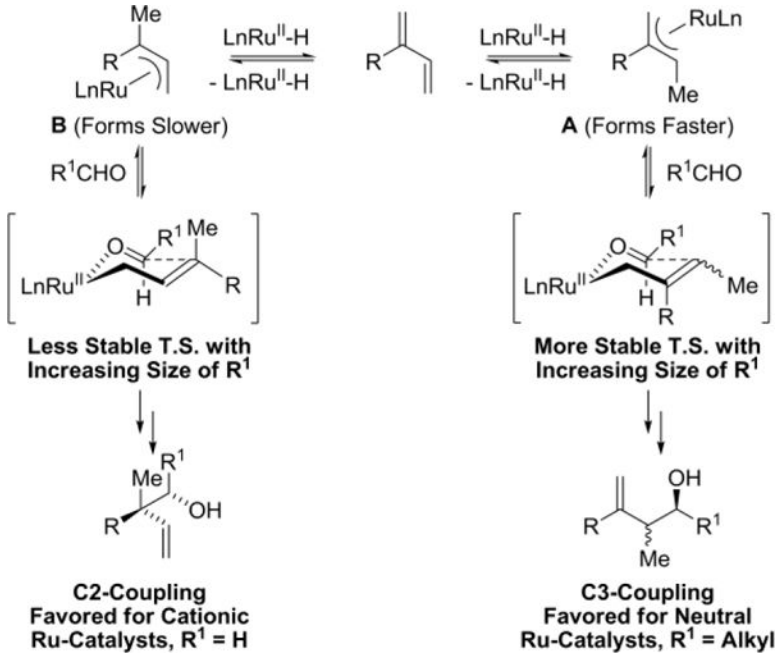
[a]Yields are of material isolated by flash chromatography on silica gel. Diastereoselectivity was determined through ^{1}H NMR analysis of crude reaction mixtures. Enantiomeric excess was determined by chiral stationary phase HPLC analysis. DM-SEGPHOS = 5,5′−*bis*-[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole. dppf = 1,1-*bis*-(diphenylphosphino)ferrocene. SEGPHOS = 5,5′-*bis*-(diphenylphosphino)-4,4′-bi-1,3-benzodioxole



Scheme 4.

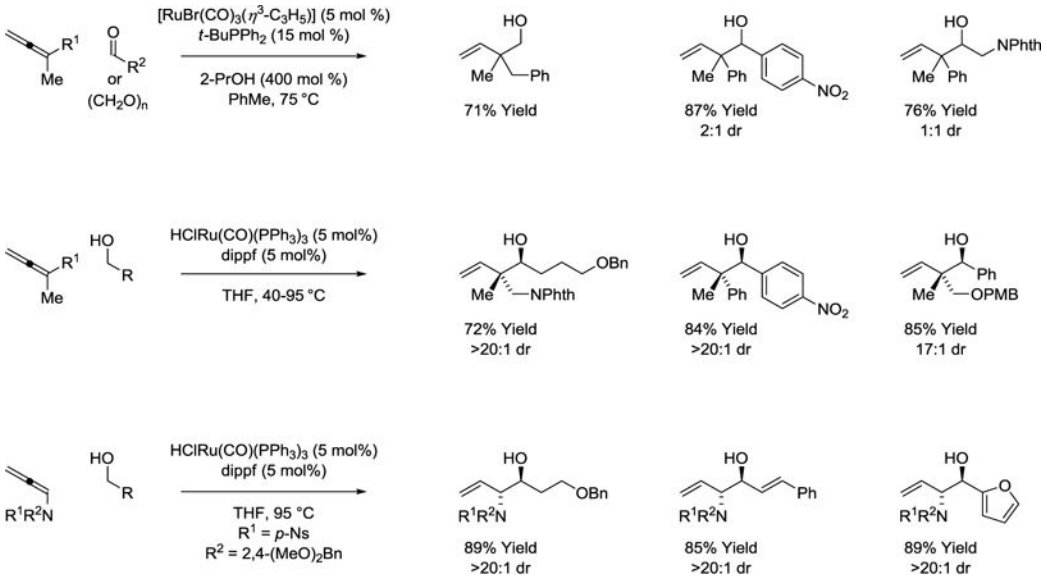
Divergent regioselectivity in 2-propanol mediated reductive couplings of dienes with paraformaldehyde and redox neutral couplings of ethanol.[a]

[a]Yields are of material isolated by flash chromatography on silica gel. Diastereoselectivity was determined through ^{1}H NMR analysis of crude reaction mixtures. dppb = *bis*-(diphenylphosphino)butane.



Scheme 5.

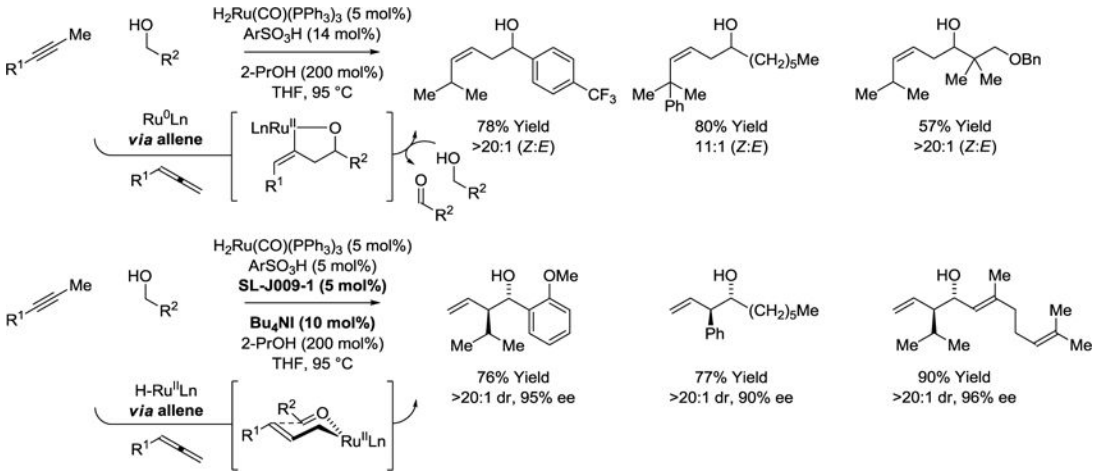
Divergent regioselectivity in the hydrohydroxyalkylation of 2-substituted dienes.



Scheme 6.

Alcohol-mediated hydrohydroxyalkylation of allenes.[a]

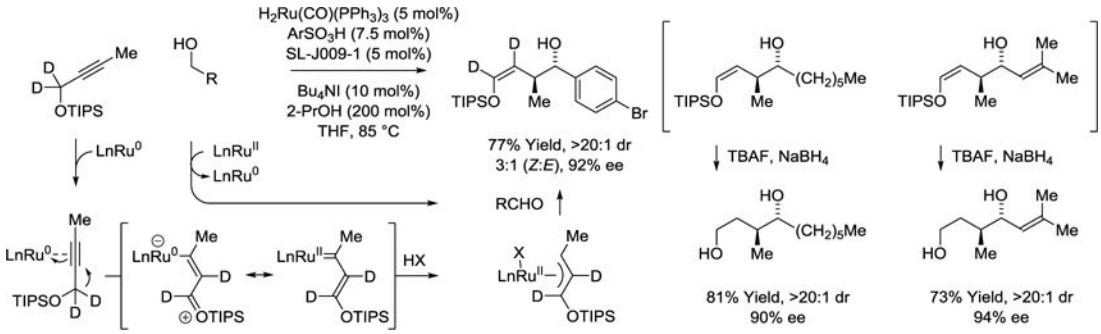
[a]Yields are of material isolated by flash chromatography on silica gel. Diastereoselectivity was determined through ^{1}H NMR analysis of crude reaction mixtures. dippf = *bis*-(diisopropylphosphino)ferrocene



Scheme 7.

Alkynes as latent allenes in alcohol-mediated hydrohydroxyalkylation to form linear or branched homoallylic alcohols.[a]

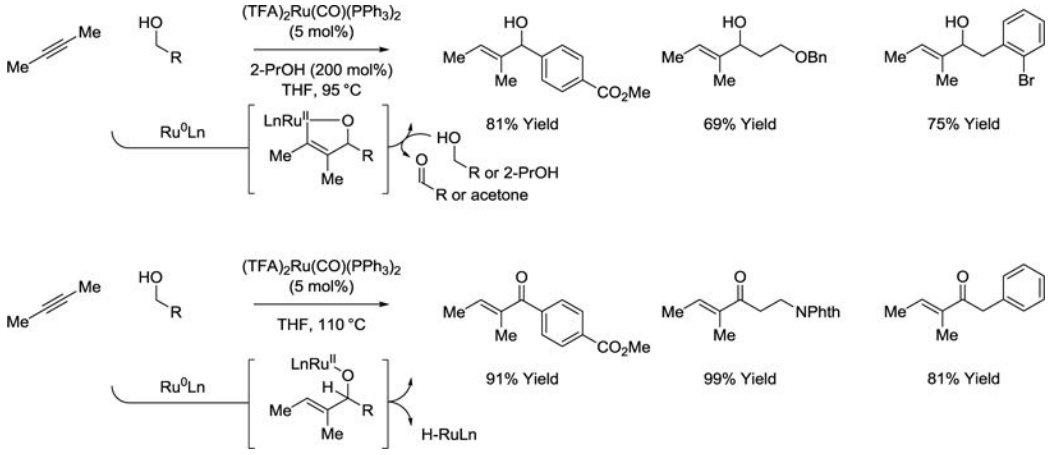
[a]Yields are of material isolated by flash chromatography on silica gel. Diastereoselectivity was determined through ^{1}H NMR analysis of crude reaction mixtures. Enantiomeric excess was determined by chiral stationary phase HPLC analysis. SL-J009-1 = (*R*)-1-[(SP)-2-(dicyclohexylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine. Ar = 2,4,6-triisopropylphenyl.



Scheme 8.

anti-Diastereo- and enantioselective siloxy-crotylation in the transfer hydrogenative coupling of primary alcohols with alkynes *via* hydride-shift enabled π-allyl formation.[a]

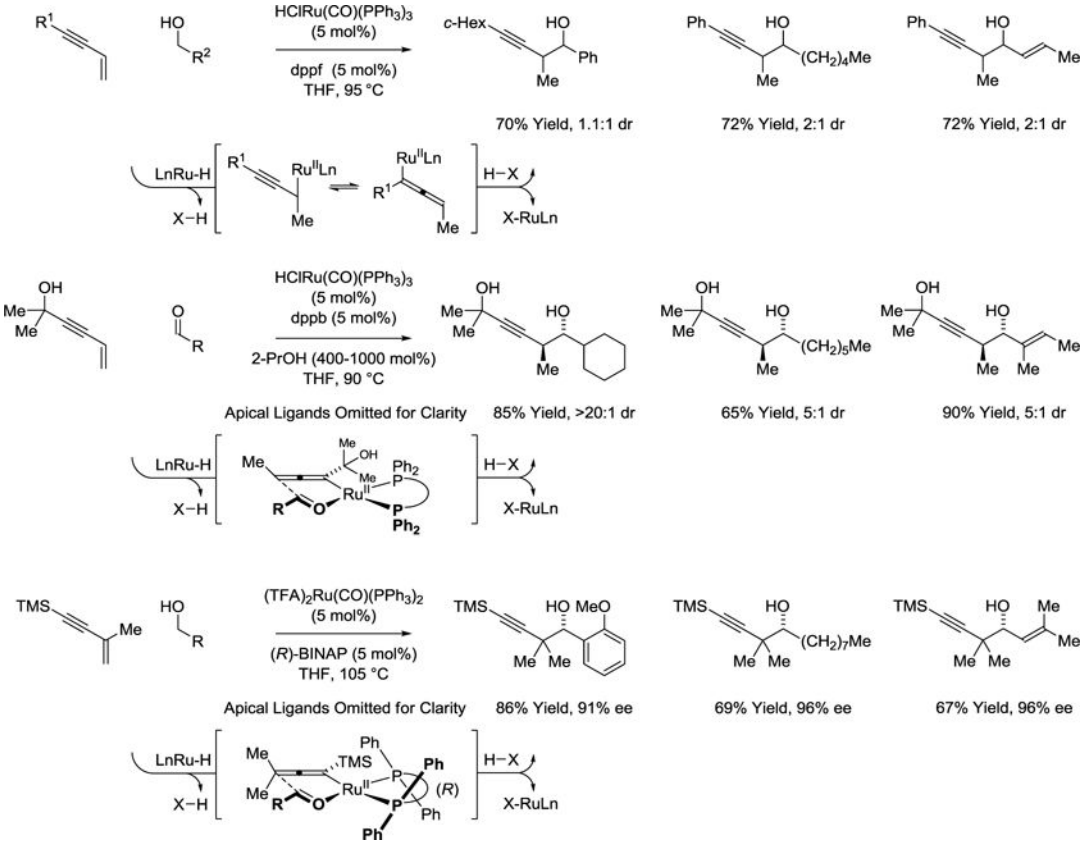
[a]Yields are of material isolated by flash chromatography on silica gel. Diastereoselectivity was determined through ^{1}H NMR analysis of crude reaction mixtures. Enantiomeric excess was determined by chiral stationary phase HPLC analysis. SL-J009-1 = (*R*)-1-[(SP)-2-(dicyclohexylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine.



Scheme 9.

Transfer hydrogenative couplings of 2-butyne to form allylic alcohols and conjugated enones.[a]

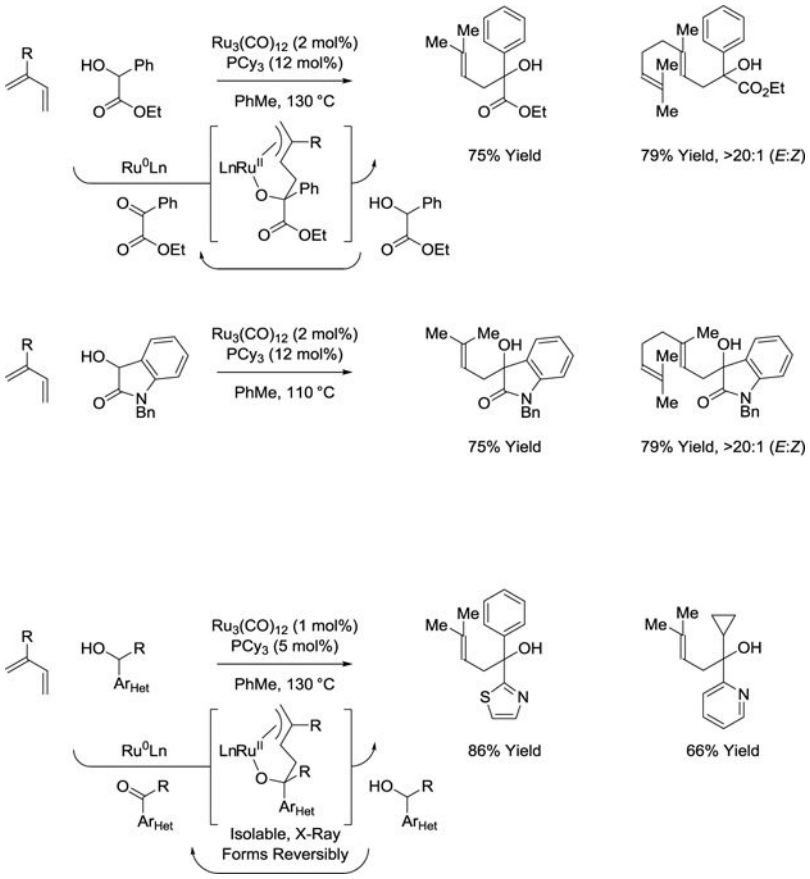
[a]Yields are of material isolated by flash chromatography on silica gel.



Scheme 10.

Carbonyl propargylation via 1,3-enyne hydrohydroxyalkylation.[a]

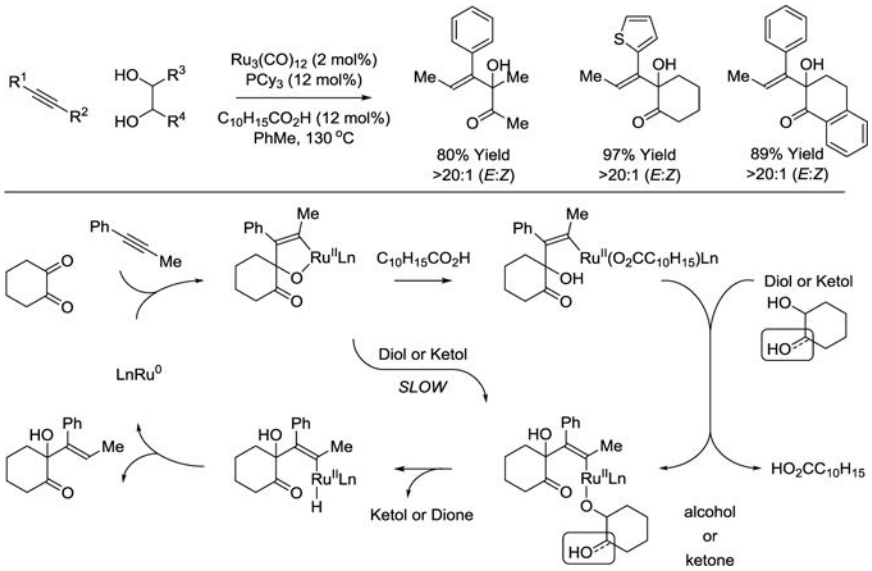
[a]Yields are of material isolated by flash chromatography on silica gel. Diastereoselectivity was determined through ^{1}H NMR analysis of crude reaction mixtures. Enantiomeric excess was determined by chiral stationary phase HPLC analysis. dppb = *bis*-(diphenylphosphino)butane. dppf = 1,1-*bis*-(diphenylphosphino)ferrocene. BINAP = 2,2′-*bis*-(diphenylphosphino)-1,1′-binaphthalene.



Scheme 11.

Conversion of secondary to tertiary alcohols *via* ruthenium(0) catalyzed C-C bond forming transfer hydrogenation with conjugated dienes.[a]

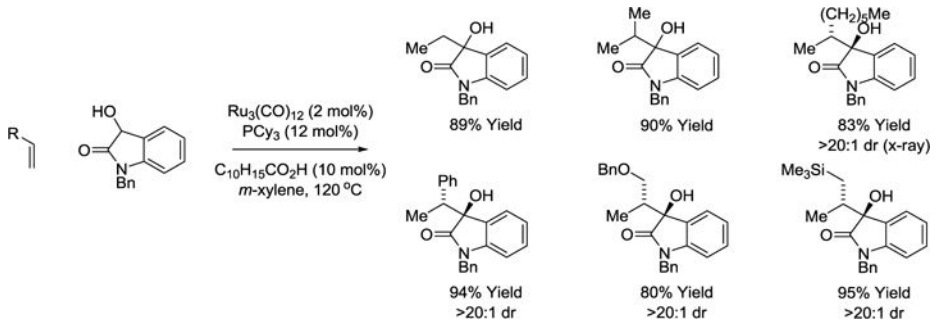
[a]Yields are of material isolated by flash chromatography on silica gel. PCy_3 = tricyclohexylphosphine.



Scheme 12.

Ruthenium(0) catalyzed C-C coupling of diols with alkynes *via* transfer hydrogenation.[a]

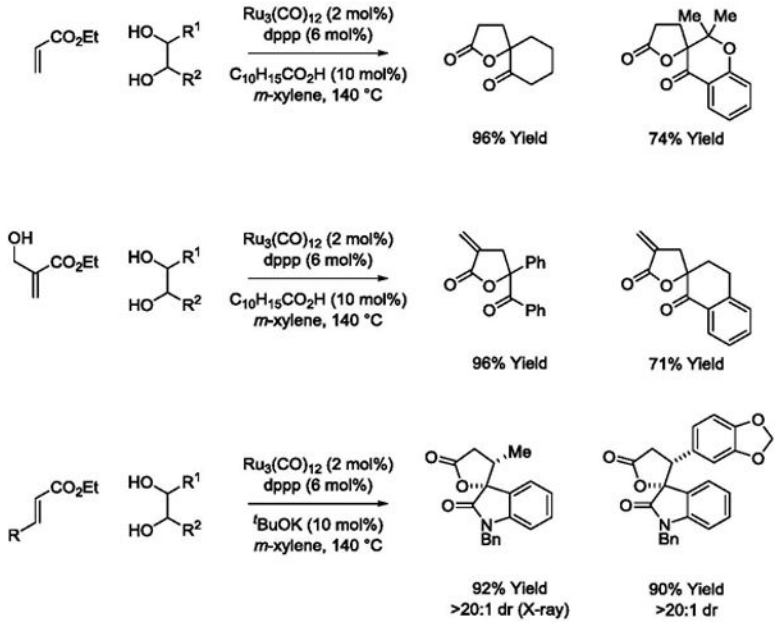
[a]Yields are of material isolated by flash chromatography on silica gel. $C_{10}H_{15}CO_2H$ = 1-adamantanecarboxylic acid. PCy_3 = tricyclohexylphosphine.



Scheme 13.

Ruthenium(0) catalyzed C-C coupling of diols with α-olefins *via* transfer hydrogenation.[a]

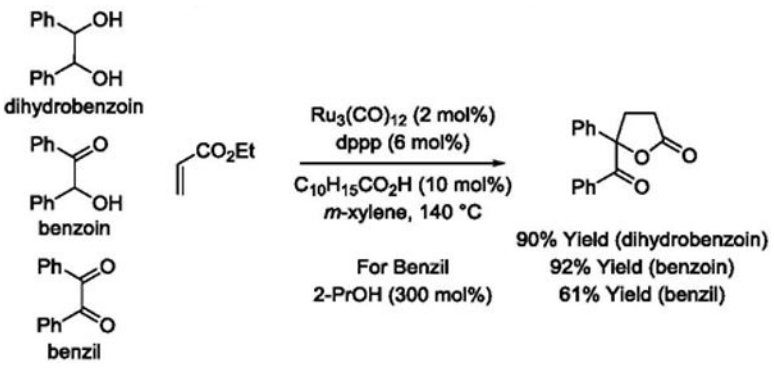
[a]Yields are of material isolated by flash chromatography on silica gel. $C_{10}H_{15}CO_2H$ = 1-adamantanecarboxylic acid. PCy_3 = tricyclohexylphosphine.



Scheme 14.

Ruthenium(0) catalyzed C-C coupling of acrylic esters with diols and α-hydroxycarbonyl compounds *via* transfer hydrogenation.[a]

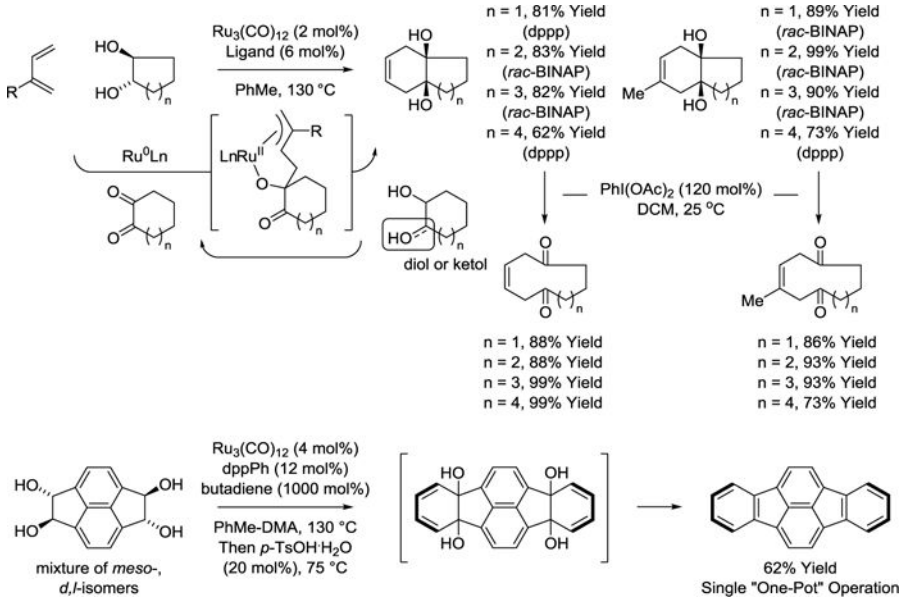
[a]Yields are of material isolated by flash chromatography on silica gel. $C_{10}H_{15}CO_2H$ = 1-adamantanecarboxylic acid. dppp = *bis*-(diphenylphosphino)propane.



Scheme 15.

Redox level-independent cycloaddition to form a γ-lactone.[a]

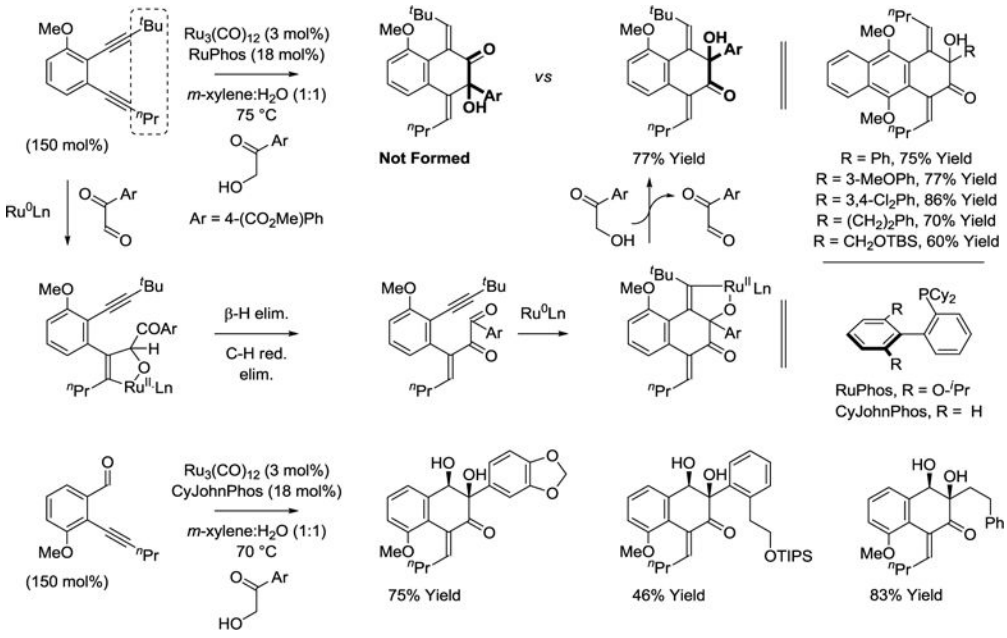
[a]Yields are of material isolated by flash chromatography on silica gel. $C_{10}H_{15}CO_2H$ = 1-adamantanecarboxylic acid. dppp = *bis*-(diphenylphosphino)propane.



Scheme 16.

Transfer hydrogenative diene-diol [4+2] cycloaddition.[a]

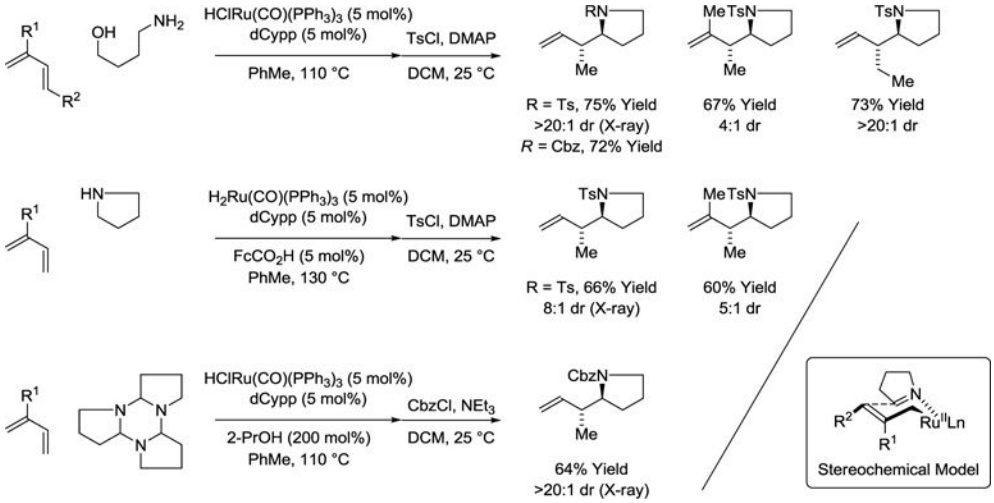
[a]Yields are of material isolated by flash chromatography on silica gel. dppp = *bis*-(diphenylphosphino)propane. BINAP = 2,2′-*bis*-(diphenylphosphino)-1,1′-binaphthalene. dppPh = *bis*-(1,2-diphenylphosphino)benzene.



Scheme 17.

Transfer hydrogenative cycloaddition of α-ketols with benzannulated 1,5-diynes or *ortho*-acetylenic benzaldehydes.[a]

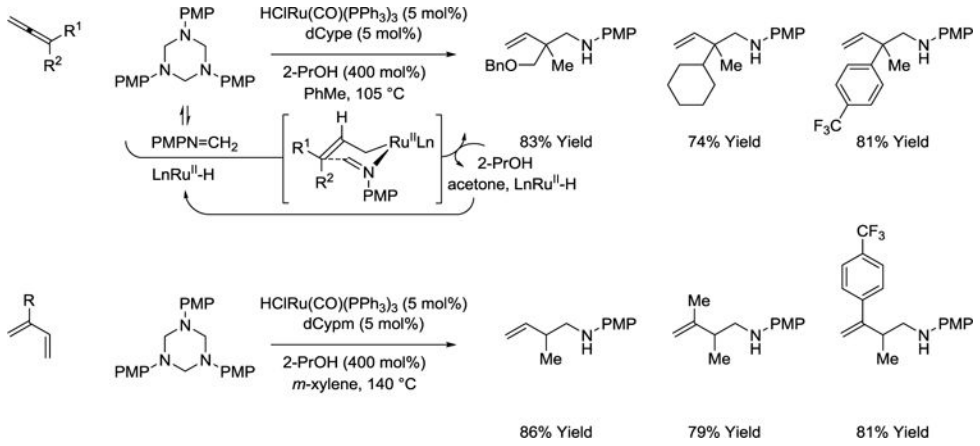
[a]Yields are of material isolated by flash chromatography on silica gel.



Scheme 18.

Transfer hydrogenative imine addition and hydroaminoalkylation.[a]

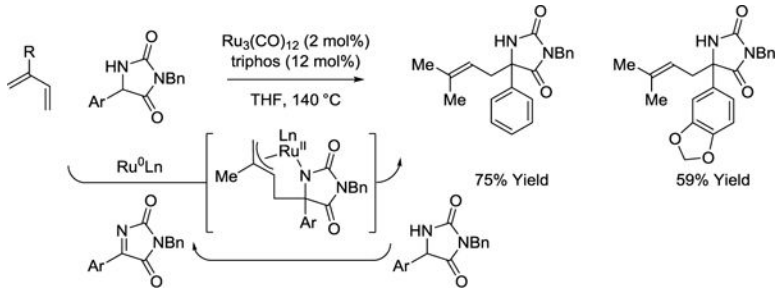
[a]Yields are of material isolated by flash chromatography on silica gel. $FcCO_2H$ = ferrocene carboxylic acid. dCypp = *bis*-(dicyclohexylphosphino)propane.



Scheme 19.

Regioselective hydroaminomethylation of allenes and dienes *via* 2-propanol mediated reductive coupling with formaldimines.[a]

[a]Yields are of material isolated by flash chromatography on silica gel. dCypm = *bis*-(dicyclohexylphosphino)methane. dCype = *bis*-(dicyclohexylphosphino)ethane.



Scheme 20.

Regioselective ruthenium(0) catalyzed hydroaminoalkylation of isoprene with hydantoins.[a]

[a]Yields are of material isolated by flash chromatography on silica gel. triphos = *bis*-(diphenylphosphinoethyl)phenylphosphine.