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Paraformaldehyde and Methanol as C_1 Feedstocks in Metal-Catalyzed C–C Couplings of π-Unsaturated Reactants: Beyond Hydroformylation

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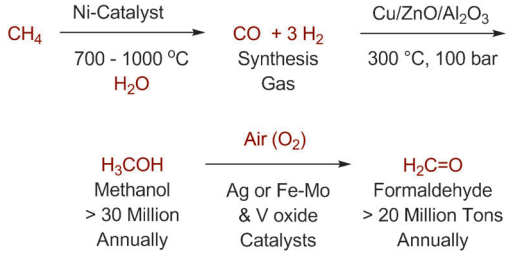
industrial chemistry · iridium · metal catalysis · nickel · ruthenium · transfer hydrogenation

Ruthenium-catalyzed reductive couplings of paraformaldehyde with dienes, alkynes, and allenes provide access to products of hydrohydroxymethylation that cannot be formed selectively under the conditions of hydroformylation. In certain cases, the regioselectivity of the C–C coupling can be inverted by using nickel catalysts. With iridium catalysts, methanol engages in redox-neutral regioselective hydrohydroxymethylations.

1. Introduction

Since its discovery in 1938 by Roelen,[1] hydroformylation, the byproduct-free synthesis of aldehydes from α-olefins and synthesis gas (CO/H_2), has grown to become one of the largest-volume applications of homogeneous metal catalysis.[2] While progress in this area continues, attempts to extend hydroformylation and tandem hydroformylation–hydrogenation[3] beyond α-olefins to 1,3-dienes,[4] allenes,[5] and alkynes[6] have proven challenging owing to incomplete regioselectivity or "over-hydroformylation" to form dialdehyde products. Methanol and paraformaldehyde are highly tractable compounds derived from synthesis gas and manufactured on enormous scale (Scheme 1). As certain metal catalysts were recently shown to promote reductive C–C couplings of π-unsaturated reactants with aldehydes using alcohols as the hydrogen source,[7] we undertook a collaborative effort to apply this technology to develop hydrohydroxymethylations wherein paraformaldehyde or methanol serve as C_1 feedstocks. Towards this end, highly regioselective metal-catalyzed reductive couplings of paraformaldehyde with 1,3-dienes,[8] allenes,[9,10] and alkynes[11] were developed (Scheme 2). As described in this Minireview, these processes deliver products that cannot be formed in a selective manner by conventional hydroformylation. Furthermore, in many cases, complete inversion of the regioselectivity can be enforced in reactions of dienes[8] and alkynes[11] through careful tailoring of the catalytic system. Finally, the first examples of methanol-mediated hydrohydroxymethylation reactions have been demonstrated with allenes.[10]



Scheme 1. Production of synthesis gas, methanol, and paraformaldehyde from methane.

2. Diene Hydrohydroxymethylation

The regioselective reductive coupling of paraformaldehyde with 2-substituted dienes at the C1, C2, and C3 positions is achieved using metal catalysts based on nickel, cationic ruthenium, and neutral ruthenium, respectively (Scheme 3). In 2008, one of the authors developed a neutral ruthenium catalyst for the reductive C–C coupling of 2-substituted 1,3-dienes with aldehydes and the corresponding redox-neutral C–C coupling of dienes with alcohols.[12] Under these

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conditions, hydroruthenation of the monosubstituted olefin generates a nucleophilic π-allylruthenium intermediate **B**, which reacts with the carbonyl partner through the primary σ-allylruthenium haptomer in a six-centered transition structure to furnish the C3 coupling product (Scheme 4). These catalytic conditions were transferable to the reductive coupling of 2-substituted 1,3-dienes with paraformaldehyde (Scheme 3).[8b] As corroborated by isotopic labeling studies, neutral ruthenium catalysts promote hydrometalation to form 1,2-disubstituted π-allylruthenium isomers, which deliver C3 coupling products. In contrast, cationic ruthenium catalysts hydrometalate reversibly at all diene positions, enabling access to the regioisomeric 1,1-disubstituted allylruthenium intermediates **A**, which undergo formaldehyde addition to furnish C2 coupling products that incorporate all-carbon quaternary centers (Schemes 3 and 4).[8a] The use of cationic ruthenium(II) catalysts in couplings of 2-substituted 1,3-dienes with higher aldehydes results in significant erosion of the C2 regioselectivity,[14] suggesting that a Curtin–Hammett-type scenario is in effect. Such cationic ruthenium complexes are readily generated through the acid–base reaction of $[RuH_2(CO)(PPh_3)_3]$ and $HO_2CC_7F_{15}$ in the presence of DPPB.[13] In the ruthenium-catalyzed reactions to form the C3 and C2 coupling products, isopropanol and paraformaldehyde both contribute as terminal reductants, the latter resulting in the conversion of the reaction product into small quantities of the formate ester, which are cleaved upon isolation.

The use of paraformaldehyde as both carbonyl electrophile and terminal reductant was achieved in nickel(0)-catalyzed reductive couplings of 2-substituted dienes, which display C1 regioselectivity (Scheme 3).[8b] A catalytic mechanism involving a diene–aldehyde oxidative coupling was invoked in earlier work by Tamaru to account for the C1 regioselectivity in the nickel(0)-catalyzed reductive coupling of 2-substituted dienes with higher aldehydes using silanes, boranes, and organozinc reagents as the terminal reductants.[15,16] In related mechanistic studies by Ogoshi,[17a] the stoichiometric reaction of nickel(0) with 2-substituted dienes and aldehydes provided isolable metallacycles. Here, metallacycle formation was demonstrated to be reversible, and it was shown that for the formation of the C1 adducts, oxidative coupling was kinetically preferred. Such oxidative pathways appear to be operative in the corresponding diene–paraformaldehyde reductive couplings, where the observed C1 regioselectivity would suggest a kinetically controlled process (Scheme 5).

Based on the preceding mechanistic analysis, 2-substituents on the diene that are capable of weakening the newly formed C–C bond of the C1 adduct might enable equilibration between π-allyl **A** and π-allyl **B**, potentially providing

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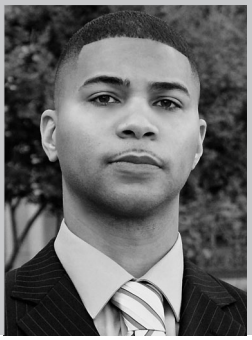
Professor Bernhard Breit is a graduate of the University of Kaiserslautern (Diploma, Dr. rer. nat.). After postdoctoral studies at Stanford University he joined the faculty at the University of Marburg for his habilitation and was then appointed Professor of Organic Chemistry at the University of Heidelberg. He is presently a Professor of Organic Chemistry at the Albert-Ludwigs-Universität in Freiburg. Professor Breit's research in organic synthesis and catalysis encompasses pioneering studies on supramolecular concepts in homogeneous catalysis and the development of atom-economic carbon–carbon and carbon–heteroatom bond forming reactions.



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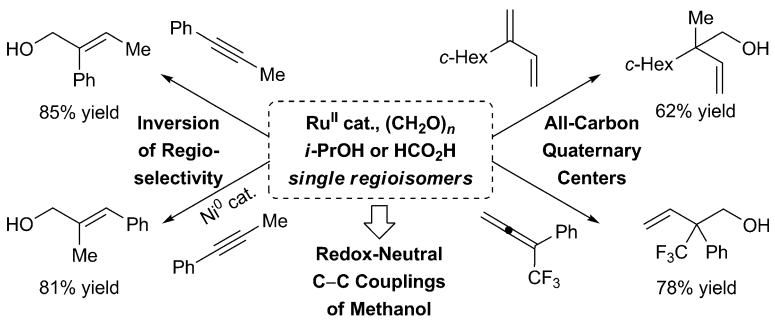
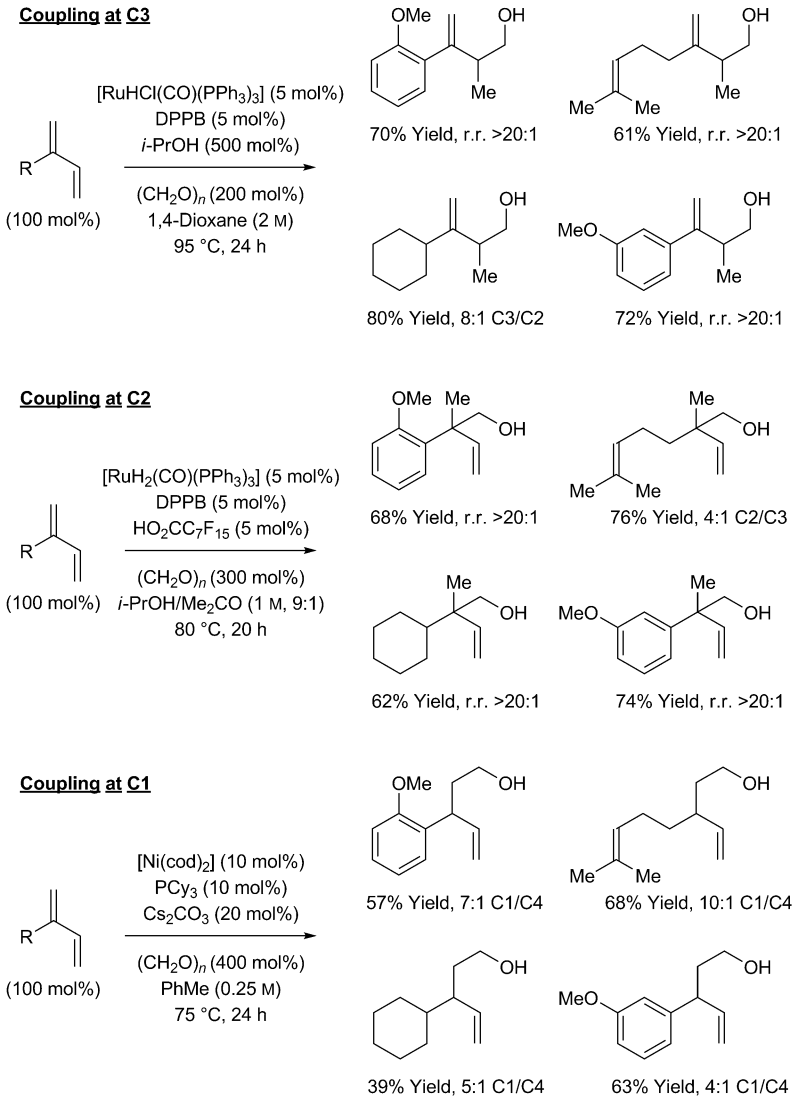
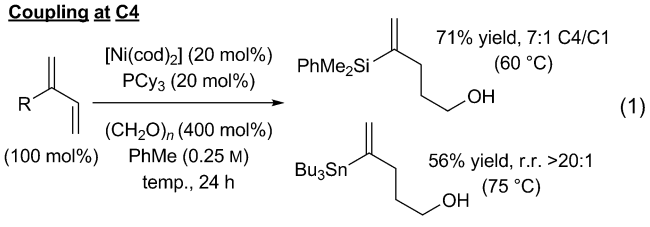


Scheme 2. Paraformaldehyde and methanol as C_1 feedstocks in metal-catalyzed couplings to π-unsaturated reactants. *c*-Hex = cyclohexyl.



Scheme 3. Regiodivergent ruthenium- and nickel-catalyzed reductive couplings of 2-substituted 1,3-dienes to paraformaldehyde. Cited yields are of material isolated by column chromatography on silica gel. cod = 1,5-cyclooctadiene, Cy = cyclohexyl, DPPB = 1,4-diphenylphosphinobutane, r.r. = regioselectivity ratio.

access to the C4 adducts (Scheme 5). Trialkylsilyl or trialkylstannyl substituents at the diene 2-position serve this purpose owing to hyperconjugation of the C–Si or C–Sn σ-bond with the σ-antibonding orbital of the newly formed C–C bond at the C1 position. In agreement with this interpretation, exposure of the indicated 2-dimethyl(phenyl)silyl- and 2-tributylstannyl-substituted butadienes to paraformaldehyde under the conditions of nickel(0) catalysis provides the C4 adducts as the major reaction products [Eq. (1)].[8b]



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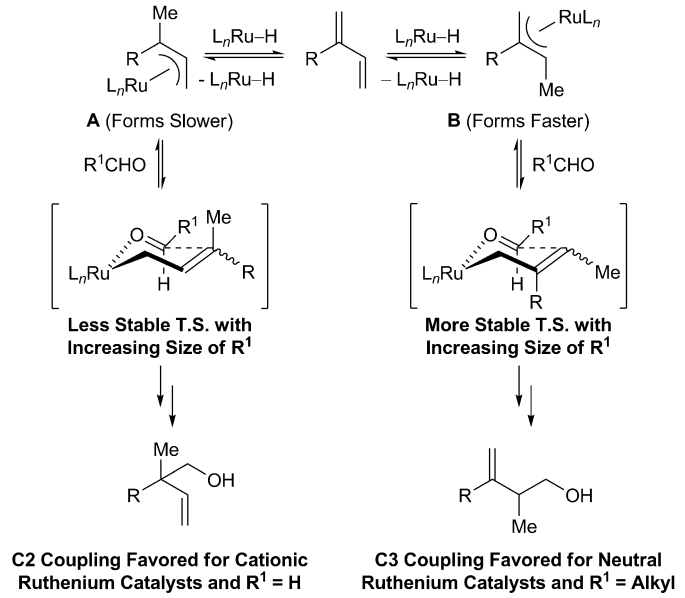
3. Alkyne Hydrohydroxymethylation

As described in several reviews,[18] numerous catalytic systems for alkyne–carbonyl reductive couplings exist, but they require terminal reductants that are metallic, pyrophoric, or mass-intensive (e.g., ZnR_2, BEt_3, $HSiR_3$). Recently reported catalytic alkyne–carbonyl reductive couplings under the conditions of hydrogenation[19,20] or alcohol-mediated transfer hydrogenation[21] overcome this limitation. Conditions for the regioselective ruthenium-catalyzed reductive coupling of nonsymmetric alkynes to *para*-nitrobenzaldehyde with formic acid as the terminal reductant were previously established.[21a] These conditions were applied successfully to



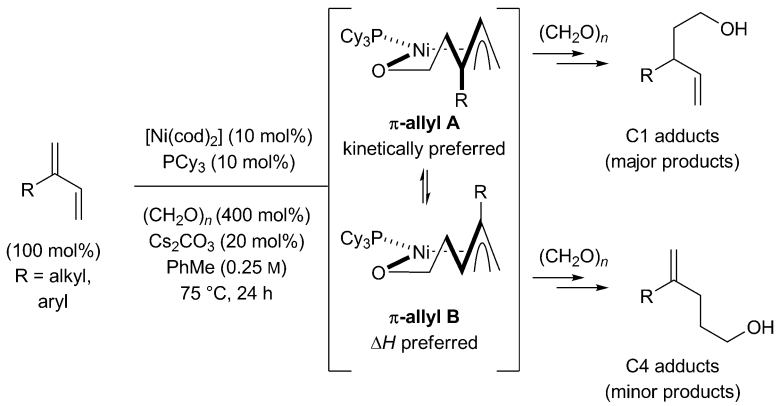
Scheme 4. C2 versus C3 regioselectivity in the ruthenium-catalyzed reductive coupling of 2-substituted dienes with paraformaldehyde.

reductive couplings of nonsymmetric alkynes with paraformaldehyde, which furnished primary allylic alcohols with good to complete levels of regioselectivity (Scheme 6).[11] Remarkably, under the conditions of the nickel-catalyzed reductive coupling, the isomeric allylic alcohols are formed with good to complete levels of regioselectivity (Scheme 6). As observed in related diene reductive couplings, deuterium labeling studies reveal that paraformaldehyde serves as both the electrophile and the terminal reductant for both the ruthenium- and nickel-catalyzed reductive couplings. Consequently, the reaction products are generated as formate esters, which are hydrolyzed in the course of isolation. Whereas in the nickel-catalyzed reactions exogenous reductants are not required, for the ruthenium-catalyzed transformations, formic acid is needed to enforce complete conversion.

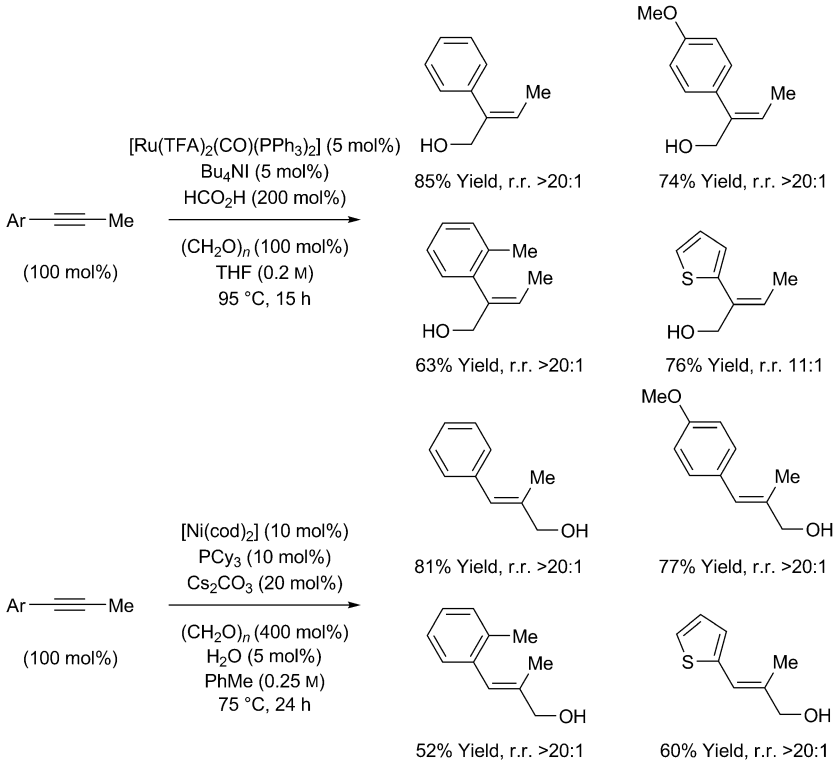
The complementary regioselectivities observed in the ruthenium- and nickel-catalyzed alkyne–paraformaldehyde reductive couplings appear to reflect the partitioning of hydrometalative and oxidative coupling pathways. It has been reported that ethanol and $[Ru(TFA)_2(CO)(PPh_3)_2]$ react to form acetaldehyde and $[RuH(TFA)(CO)(PPh_3)_2]$, and that $[RuH(TFA)(CO)(PPh_3)_2]$ generated under these conditions will hydrometalate alkynes to form vinylruthenium complexes.[22] These stoichiometric processes support the feasibility of hydrometalative pathways in ruthenium-catalyzed alkyne–paraformaldehyde reductive couplings (Scheme 7). The stoichiometric reaction of $[Ni(cod)_2]$ with butyne and benzaldehyde in the presence of PCy_3 delivers isolable nickeladihydrofurans, which were characterized by single-crystal X-ray diffraction analysis.[17b] These data support the feasibility of oxidative coupling pathways in nickel-catalyzed alkyne–paraformaldehyde reductive couplings (Scheme 7).

4. Allene Hydrohydroxymethylation

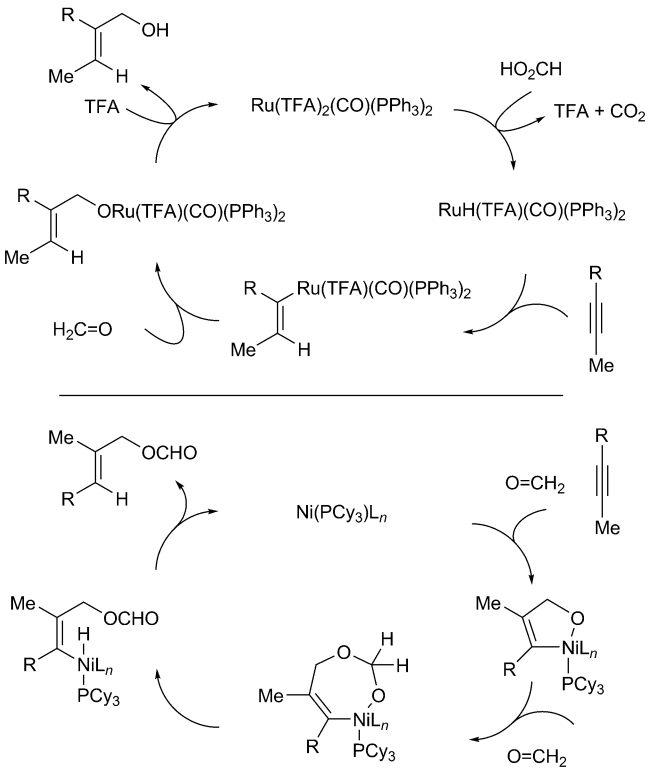
Nickel-catalyzed reductive couplings of allenes with aldehydes were accomplished using silanes, boranes, and organozinc reagents as the terminal reductants.[23] More recently, allene–aldehyde reductive couplings were achieved under the conditions of iridium-[24] and ruthenium-catalyzed[25] hydrogenation[24a] or transfer hydrogenation.[24b,c,25] In the presence of a ruthenium catalyst and isopropanol as the terminal reductant, 1,1-disubstituted allenes and paraformaldehyde engage in reductive couplings with complete levels of branch regioselectivity to provide the primary neopentyl alcohols.[9a] These conditions were adapted to the use of CF_3-substituted allenes, enabling the generation of CF_3-bearing all-carbon quaternary stereocenters (Scheme 8).[9b] The direct use of methanol as both terminal reductant and formaldehyde precursor would allow for byproduct-free hydrohydroxymethylations of π-unsaturated reactants. Remarkably, using the indicated cyclometalated π-allyliridium *C*,*O*-benzoate complex, redox-neutral C–C couplings of methanol with 1,1-disubstituted allenes occur in good yield with complete levels of branch regioselectivity.[10] This process is the first example



Scheme 5. Formation of C1 versus C4 regioisomers in the nickel-catalyzed reductive coupling of 2-substituted dienes with paraformaldehyde.



Scheme 6. Regiodivergent ruthenium- and nickel-catalyzed reductive couplings of alkynes to paraformaldehyde. Cited yields are of material isolated by column chromatography on silica gel. TFA = trifluoroacetate.



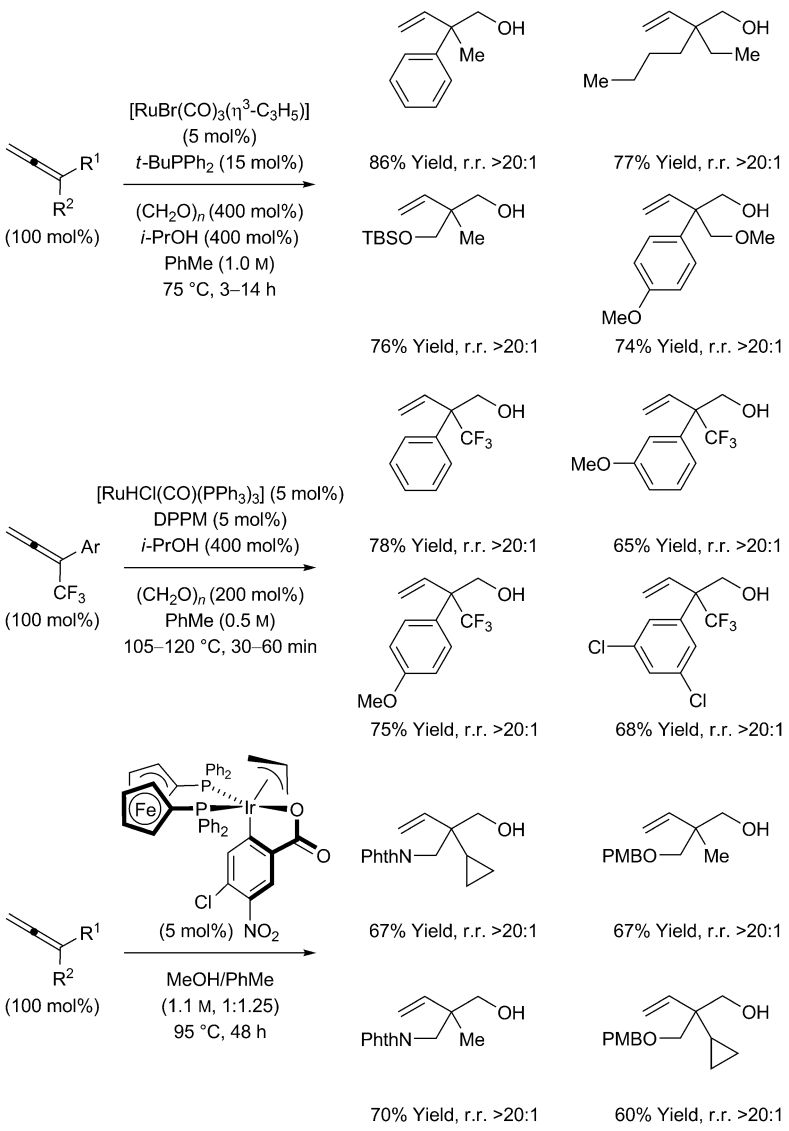
Scheme 7. Complementary regioselectivity in the ruthenium- and nickel-catalyzed alkyne–paraformaldehyde reductive couplings by partitioning of the hydrometalative and oxidative coupling pathways.

of the direct conversion of methanol into higher alcohols under the conditions of homogeneous catalysis (Scheme 8).

The proposed mechanism for the direct C–C coupling of methanol with 1,1-disubstituted allenes reveals the origins of the branch regioselectivity (Scheme 9). Entry into the catalytic cycle occurs upon methanolysis of the π-allyliridium precatalyst. The resulting iridium methoxide undergoes β-hydride elimination to furnish formaldehyde and an iridium hydride. Allene hydrometalation delivers an allyliridium complex that reacts with formaldehyde by way of the primary σ-allyl haptomer through a closed six-centered transition structure. Methanolysis of the resulting homoallylic iridium alkoxide closes the catalytic cycle. Notably, further oxidation of the coupling product is disabled by coordination of the homoallylic olefin to the iridium center. Hydrometalative mechanisms appear to be operative in the ruthenium-catalyzed reductive couplings of 1,1-disubstituted allenes with paraformaldehyde, which also display complete branch regioselectivity, as corroborated by stoichiometric reactions of $[HXRu(CO)(PR_3)_3]$ (X = Cl, Br) with 1,1-disubstituted allenes or dienes to form π-allylruthenium complexes.[26]

5. Summary and Outlook

While the hydroformylation of terminal alkenes employing synthesis gas as a C_1 feedstock is a well-established industrial process and a reliable transformation in organic synthesis, it is of limited value for other substrate classes, such



Scheme 8. Regioselective ruthenium-catalyzed reductive couplings of 1,1-disubstituted allenes with paraformaldehyde and related redox-neutral iridium-catalyzed C–C couplings with methanol. Cited yields are of material isolated by column chromatography on silica gel. DPPM = methylenebis[(diphenyl)phosphine].

as 1,3-dienes, alkynes, and allenes, owing to the incomplete control of the chemo- and regioselectivity. We have demonstrated that in these cases, the use of alternative C_1 sources, such as formaldehyde and methanol, in the presence of suitable ruthenium, nickel, or iridium catalysts can overcome the limitations evident in hydroformylation. Specifically, 2-substituted 1,3-dienes can be coupled in a site-selective manner at each of the four carbon atoms depending on the catalyst employed to furnish products of hydrohydroxymethylation. Similarly, nonsymmetric alkynes could be transformed into the C1-elongated trisubstituted allylic alcohols in a regiodivergent manner employing either ruthenium or nickel catalysts. For 1,1-disubstituted allenes, paraformaldehyde or methanol can serve as the C_1 source in hydrohydroxymethylations that furnish all-carbon quaternary centers. Although process optimization is yet required to enhance catalytic efficiency, these new transformations offer a potential alternative to the hydroformylation of π-unsaturated reactants beyond α-olefins, and in certain cases represent the only catalytic methods available to accomplish these particular C_1 homologations.

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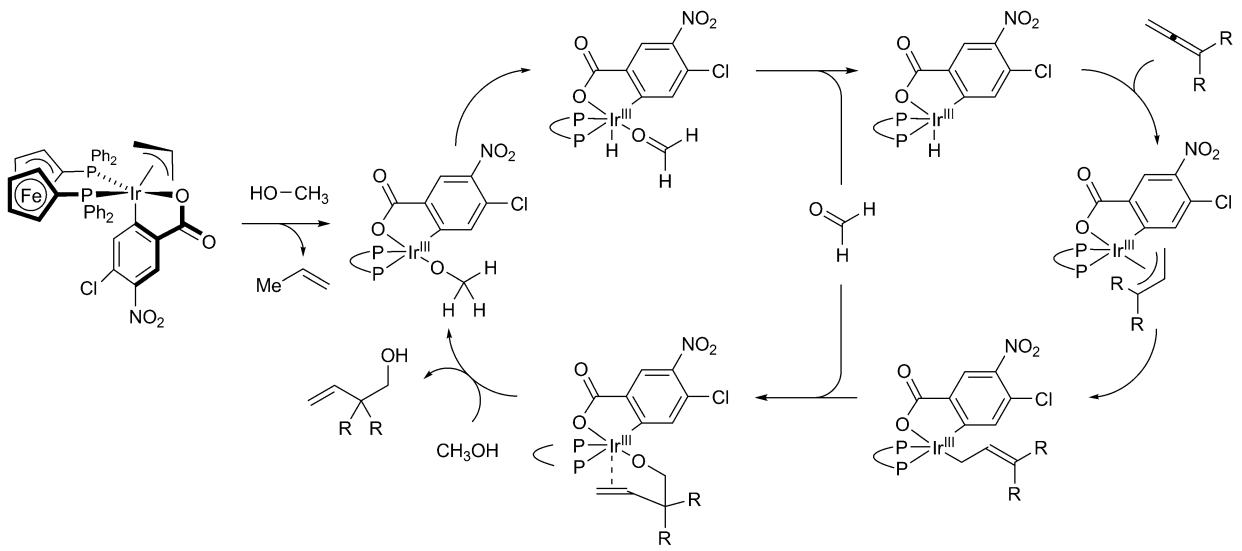

Scheme 9. General catalytic mechanism for the iridium-catalyzed C–C coupling of methanol with 1,1-disubstituted allenes.

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