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Hydrogen-Mediated C−C Bond Formation: A Broad New Concept in Catalytic C−C Coupling[1]

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1. Introduction

Hydrogenation ranks among the most powerful catalytic methods employed industrially, accounting for over half of the chiral compounds made by man not produced via physical or enzymatic resolution.[2] This fact portends an equally powerful approach to reductive C−C bond formations mediated by hydrogen: catalytic couplings achieved simply through the exposure of two or more molecules to gaseous hydrogen in the presence of a metallic catalyst. Whereas classical methods for the addition of *C*-nucleophiles to carbonyl compounds generally require stoichiometric preformation of moisture-sensitive organometallics, "*C−C bond forming hydrogenation*" enables direct coupling of diverse π-unsaturated reactants under neutral conditions with complete atom economy. In this Perspective, we describe the first systematic efforts toward the development of hydrogen-mediated C−C couplings beyond alkene hydroformylation, transformations that add a new dimension to catalytic hydrogenation, one of chemistry's oldest and most broadly utilized processes (Scheme 1).

II. Green Chemistry from the Smallest of Molecules

The goals of synthetic efficiency inherent to the design of cost-effective transformations have long been embraced by chemists and represent an inevitable consequence of a fiscal, as well as artistic, natural selection process.[3] Hence, while the field of Green Chemistry is relatively new, many of its central tenets (atom-economy,[4] step-economy, and the "ideal synthesis"[5]) are longstanding and can be appreciated by all chemists. The emergence and ever-increasing focus on Green Chemistry largely stems from recognition of the urgent need to devise environmentally sustainable means of manipulating limited resources in the face of a rapidly growing consumer population. For the Green Chemist, "*Quod me nutrit me destruit*" is not a statement—it is a challenge.

In the quest for Green Chemistry, "selective pressure" suggests we look to high volume processes, where slight improvement in efficiency confers substantial economic advantage. Indeed, upon consideration of the "E-factor" for various segments of the chemical industry (the waste generated per kilogram of product), a strong inverse correlation between process volume and waste generation is observed, with waste production most problematic for the fine chemical and pharmaceutical industrial segments.[6] These data also reveal an important opportunity for innovation: waste production generally increases with increasing complexity of the molecular target.

For the fine chemical and pharmaceutical industrial segments, a significant cause of excessive waste production resides in the use of classical stoichiometric transformations that produce molar equivalents of chemical byproducts. Such shortcomings are potentially overcome through the development of corresponding catalytic processes, especially those for which a high proportion of the reactant atoms are incorporated into the product, so-called "atom economical" processes.[4] With that said, in complex molecule synthesis, the value of a late-stage intermediate easily can exceed the cost of a reagent or product separation, undermining the motivation to implement green alternatives. Further, the selectivity issues posed by highly functionalized molecules often challenge the limits of known methodology, mandating highly specialized reaction conditions and leaving only suboptimal processes as an option. Clearly, there is a persistent need to expand the repertoire of selective, atom economical processes that generate complex products from basic chemical feedstocks. Hydrogen-mediated C−C bond formation may assist in addressing this need.

For the Organic Chemist, hydrogenation is typically associated with the reduction of C═X (X = C, N, O) π-bonds. The first heterogeneous catalysts for reactions of this type were developed by Paul Sabatier at the University of Toulouse in the late 1890s.[7] It was not until the 1960s that the first catalysts for the homogeneous alkene hydrogenation were developed,[8] largely owing to seminal contributions by Jack Halpern[9] and Geoffrey Wilkinson.[10] Catalytic hydrogenation continued to evolve to encompass enantioselective variants—the work of Knowles,[11] Kagan,[12] and Noyori.[13] Clean, cost-effective, and powerful, asymmetric hydrogenation is presently the most broadly utilized catalytic enantioselective process employed industrially.[2] Yet catalytic hydrogenation extends far beyond the reduction of olefins, imines, and carbonyl compounds. The very first catalytic hydrogenation, the platinum-catalyzed reaction of hydrogen with atmospheric oxygen, was described nearly two centuries ago. In 1823, at a time when fire was still created with flint and tinder, Döbereiner used this process to devise a household lighter.[14] The "Döbereiner lighter" instantly captured international attention and served as a prototype for legion

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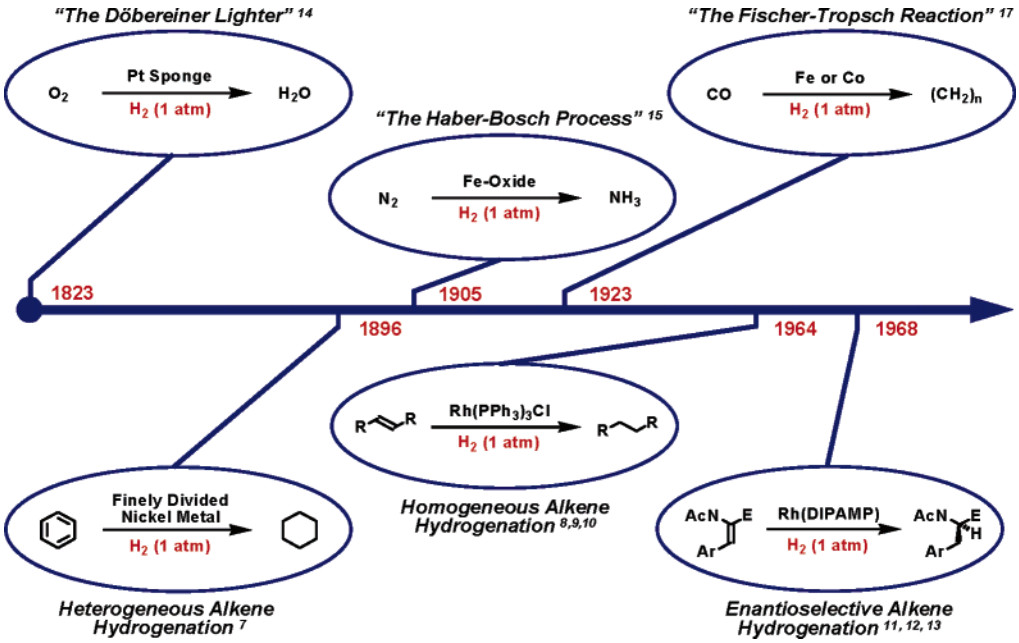
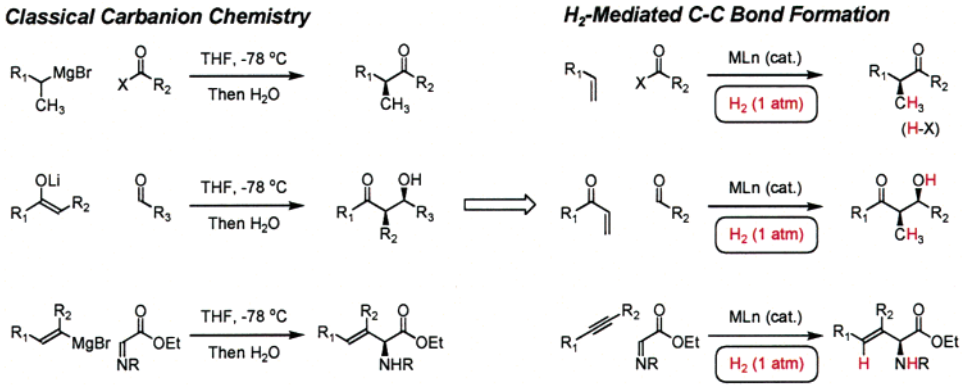


FIGURE 1. Selected milestones in catalytic hydrogenation.

SCHEME 1. Hydrogen-Mediated C−C Bond Formation: Catalytic Couplings beyond Alkene Hydroformylation



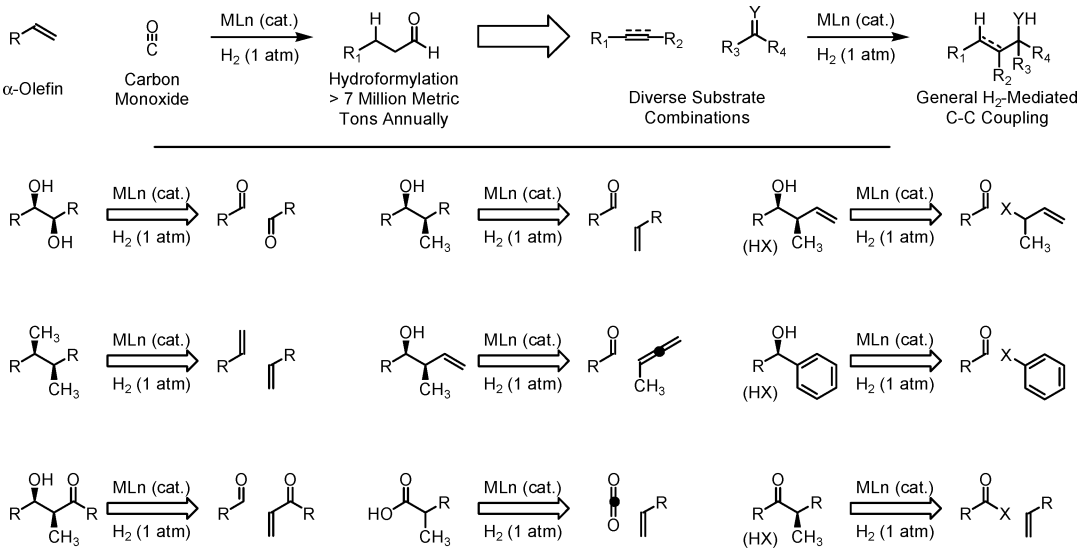
devices used for the self-ignition of coal-gas burners. The catalytic hydrogenation of atmospheric nitrogen to produce ammonia, reported by Haber in 1905,[15] continues to have massive socioeconomic impact.[16] Though developed in connection with the German military effort in WWI, the "Haber−Bosch process" provided cost-effective routes to nitrogenous fertilizer, increasing worldwide food production to unprecedented levels. Presently, over 100 million metric tons of ammonia are produced annually through the Haber−Bosch process. The "Fischer−Tropsch process," discovered in 1923[17] and broadly implemented in WWII, involves the production of liquid fuel via catalytic reductive polymerization of carbon monoxide mediated by hydrogen. In 1944, Germany produced over 6.5 million tons of synthetic petroleum using this process.[18] The rising cost of crude oil has rekindled interested in Fischer−Tropsch chemistry, stimulating development of improved catalytic systems.[19] Finally, in 1938, studies of the Fischer−Tropsch reaction by Otto Roelen led to the discovery of alkene hydroformylation: the "oxo-synthesis."[20] Hydroformylation employs basic feedstocks as reactants (α-olefins, carbon monoxide and hydrogen), combining them with complete atom economy under catalytic conditions—true green chemistry. The efficiency and cost-effectiveness of hydroformylation is made evident by the fact that it accounts for the production of over 7 million metric tons of aldehyde annually, making it the largest volume application of homogeneous metal catalysis (Figure 1).[21]

III. Breaking Dogma: Hydrogen-Mediated C−C Couplings beyond Hydroformylation

Given the impact of alkene hydroformylation, it is surprising that systematic efforts toward the development of related hydrogenative C−C couplings were absent from the literature.[22,23] The prevailing paradigm that "hydrogenation is a method for the reduction of C=X π-bonds" likely contributed to the perception of hydroformylation as an anomalous reaction specific to carbon monoxide. In contrast, we looked upon hydroformylation as the prototypical hydrogen-mediated C−C bond formation; a starting point en route to a broad family of completely atom-economical C−C couplings eminently suited to large volume application (Scheme 2).

Virtually all organic molecules incorporate hydrogen in their structure and, hence, may be envisioned to derive via hydrogenative coupling of unsaturated precursor fragments. When one begins to apply hydrogenation in this way, numerous possibilities unfold in terms of how one may "deconstruct" a given

SCHEME 2. Retrosyntheses of Pervasive Structural Motifs via C−C Bond-Forming Hydrogenation with an Eye toward Basic Feedstocks: Future Challenges for Hydrogenative C−C Coupling



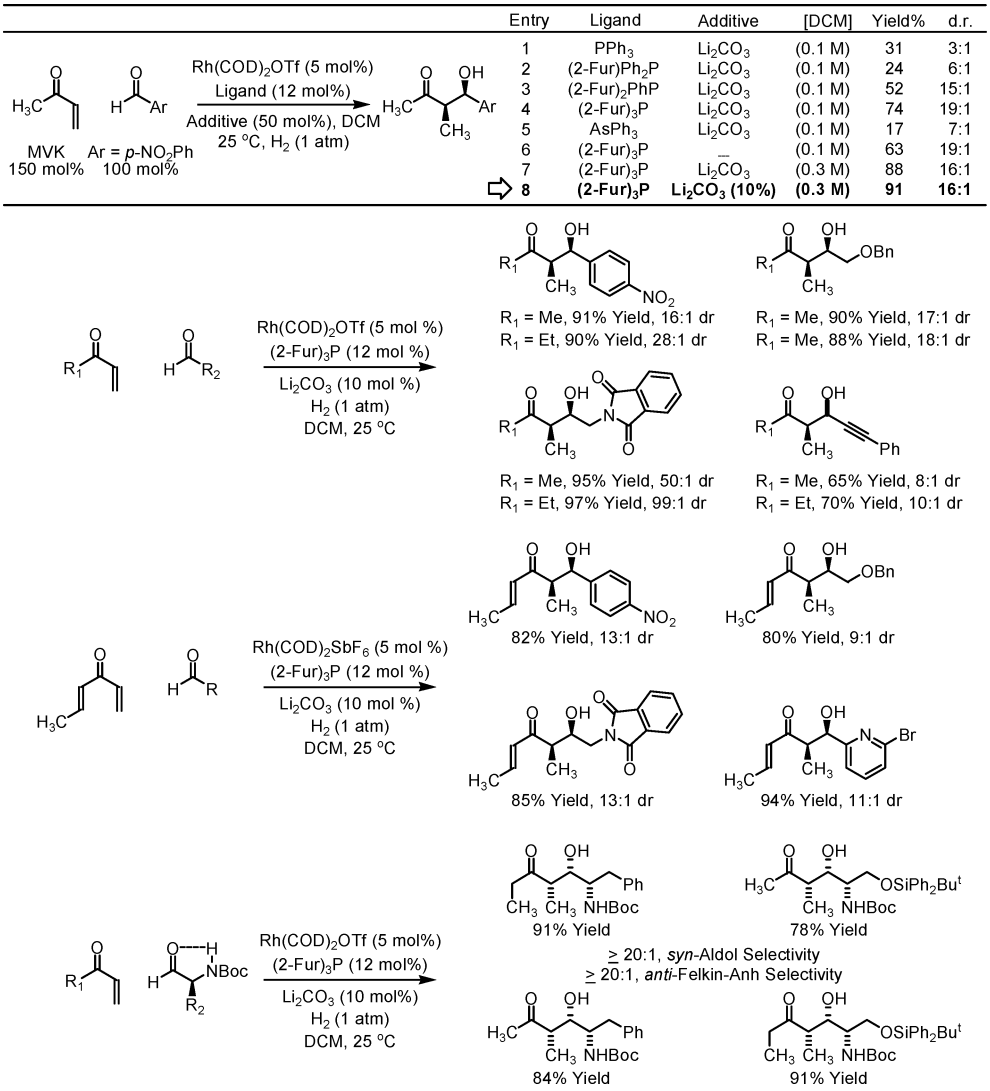
molecule. An intuitive example involves the retrosynthesis of a vicinal diol, which evokes a hydrogen-mediated pinacol coupling. Retrosynthetic analysis of the corresponding vicinal dimethyl motif is not as intuitive. Yet if one divides the molecule into two more highly oxidized fragments, a very simple transformation emerges: the hydrodimerization of an α-olefin. As demonstrated by the reductive aldol couplings and related aldehyde-α-olefin couplings, such retrosynthetic thinking is easily applied to polypropionate substructures. Similarly, carbonyl allylations and crotylations, transformations typically achieved using allylboranes or allylsilanes, may be envisioned to arise by way of hydrogen-mediated allene−aldehyde coupling, and arylpropionic acids, an important class of analgesics (ibuprofen, naproxen), are potentially generated via hydrogenation of vinylarenes in liquid CO_2. *σ*-Bond activation also gives rise to an abundance of opportunities, including hydrogenative variants of such commonly employed transformations as the Grignard reaction and the Nozaki−Hiyama−Kishi reaction. As borne out by the transformations described in this account, catalytic hydrogenation shows great promise as a method of C−C coupling, and we have only tapped into a fraction of its potential. There are many exciting opportunities for future investigations in this emerging field of research (Scheme 2).

III.a. Hydrogen-Mediated Reductive Aldol Coupling. Our first indication that organometallic intermediates arising transiently in the course of catalytic hydrogenation may be intercepted and rerouted to products of C−C bond formation stems from studies of the reductive aldol reaction.[24−27] Whereas hydrogenation of enones in the presence of aldehydes using neutral rhodium(I) complexes promotes conventional enone hydrogenation, cationic rhodium(I) complexes catalyze reductive aldol coupling, with increased isolated yields obtained upon use of mild basic additives. Moreover, upon use of tri-2-furylphosphine as ligand,[28] the observed levels of *syn*-diastereoselection, which are obtained at ambient temperature, exceed those observed in reactions of lithium enolates conducted at −78 °C.[24b] Such high *syn*-diastereoselectivity suggests a kinetically controlled process[29] and may be accounted for on the basis of a mechanism involving stereospecific *Z*(*O*)-enolate formation by way of internal hydride delivery to the enone *s-cis* conformer through a 6-centered transition structure[30] with subsequent addition of the *Z*(*O*)-enolate to the aldehyde through a Zimmerman−Traxler-type transition structure.[31] These coupling are applicable to commercially available methyl and ethyl vinyl ketone (MVK and EVK)[24b] or divinyl ketones such as crotyl vinyl ketone (CVK).[24c] Remarkably, functional groups generally considered to be "hydrogen-labile" (alkynes, alkenes, benzylic ethers, and nitroarenes) remain intact under the conditions of hydrogen-mediated coupling (Scheme 3).

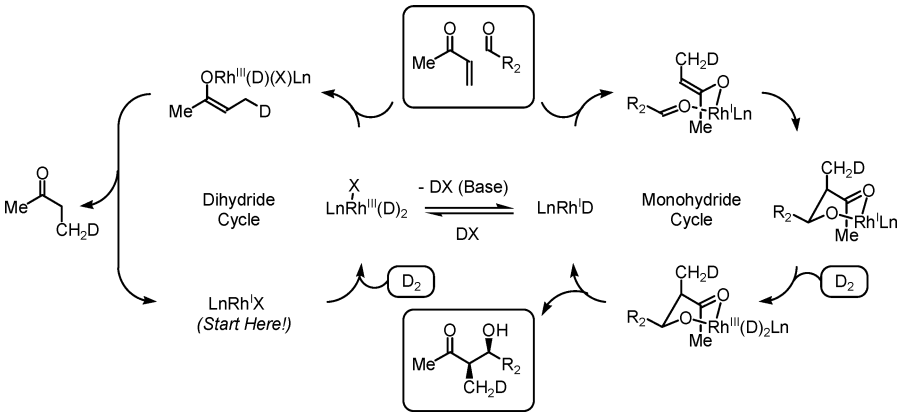
Hydrogen-mediated aldol coupling occurs under essentially neutral conditions in a low dielectric medium at ambient temperature—conditions conducive to the formation of hydrogen bonds. Hydrogenation of MVK and EVK in the presence of *N*-Boc-α-aminoaldehydes at ambient temperature results in the formation of aldol stereotriads that embody high levels of *syn*-aldol diastereoselectivity accompanied by high levels of *anti*-Felkin−Anh control.[24d] The collective data are consistent with a catalytic mechanism involving addition of the Z(*O*)-rhodium enolate to the sterically less encumbered aldehyde *π*-face of an intramolecularly hydrogen-bonded chelate. Deletion of the intramolecular hydrogen bond, as in the case of *N*-methyl-*N*-Boc-L-leucinal, inverts stereoselectivity to furnish the Felkin−Anh product. As revealed by HPLC analysis, optical purity of the stereochemically labile α-aminoaldehydes is preserved under the essentially neutral conditions of hydrogen-mediated aldol coupling (Scheme 3).

The influence of basic additives vis à vis partitioning of aldol coupling and 1,4-reduction manifolds may derive, in turn, from partitioning homolytic versus heterolytic hydrogen activation pathways. Whereas neutral rhodium(I) complexes are known to induce *homolytic* hydrogen activation,[32] related cationic complexes used in combination with basic additives promote *heterolytic* hydrogen activation ($H_2 + M-X \rightarrow M-H + HX$)[33] due to the enhanced acidity of the resulting dihydrides.[34] Hence, basic additives may disable direct enolate−hydrogen-reductive elimination manifolds through deprotonation of the (hydrido)-rhodium intermediates $LnRh^{III}X(H)_2$ or (enolato)$Rh^{III}X(H)Ln$, simultaneously inducing entry into a monohydride-based catalytic cycle that avoids regeneration of such intermediates. Consistent with this interpretation, reductive coupling of MVK and *p*-nitrobenzaldehyde performed under an atmosphere of elemental deuterium provides an aldol adduct incorporating a

SCHEME 3. *Syn*-Diasteroselective Hydrogen-Mediated Aldol Coupling Employing Cationic Rhodium Catalysts Ligated by Tri-2-furylphosphine



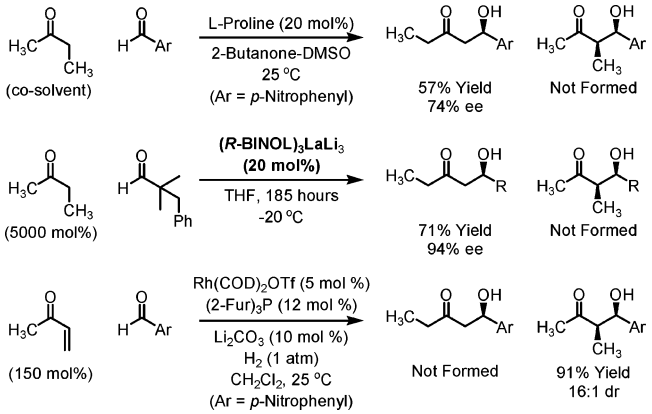
SCHEME 4. Plausible Mechanism Accounting for the Partitioning of Carbonyl Addition and 1,4-Reduction Products in Response to Basic Additives, as Corroborated by Deuterium Labeling



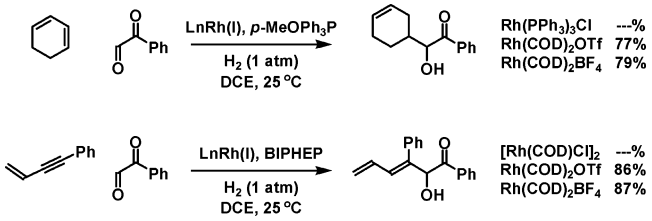
single deuterium atom at the former enone β-position.[24b] Deuterium incorporation at the α-carbon is not observed, excluding Morita−Baylis−Hillman pathways en route to aldol product. Incorporation of a single deuterium atom suggests irreversible enone hydrometalation (Scheme 4).

Enantioselective variants of the hydrogen-mediated aldol coupling will require chirally modified derivatives of tri-2-furylphosphine.[28c] An asymmetric variant of the hydrogen-mediated aldol coupling would offer a regiochemical complement to corresponding "direct" organocatalytic aldol additions involving ketone pronucleophiles. For example, direct aldol couplings of 2-butanone catalyzed by L-proline furnish linear

SCHEME 5. Regioselectivities in Direct Aldol Couplings of 2-Butanone Complement Those Observed in Corresponding Hydrogen-Mediated Reductive Aldol Couplings of MVK



SCHEME 6. Selected Results from a Broad Assay for Hydrogen-Mediated C−C Coupling Involving Hydrogenation of π-Unsaturated Compounds in the Presence of Various Electrophiles



adducts.[35,36] Similarly, direct aldol couplings of 2-butanone using the heterobimetallic catalyst $LaLi_3$−tris(binaphthoxide) (LLB) provide linear aldol products.[37] Under the conditions of hydrogenation, one may exploit the enone moiety of MVK as a regiochemical control element, directing generation of the more substituted enolate isomer. In this way, one gains access to the branched products of aldol addition desired for polypropionate synthesis (Scheme 5).[24b]

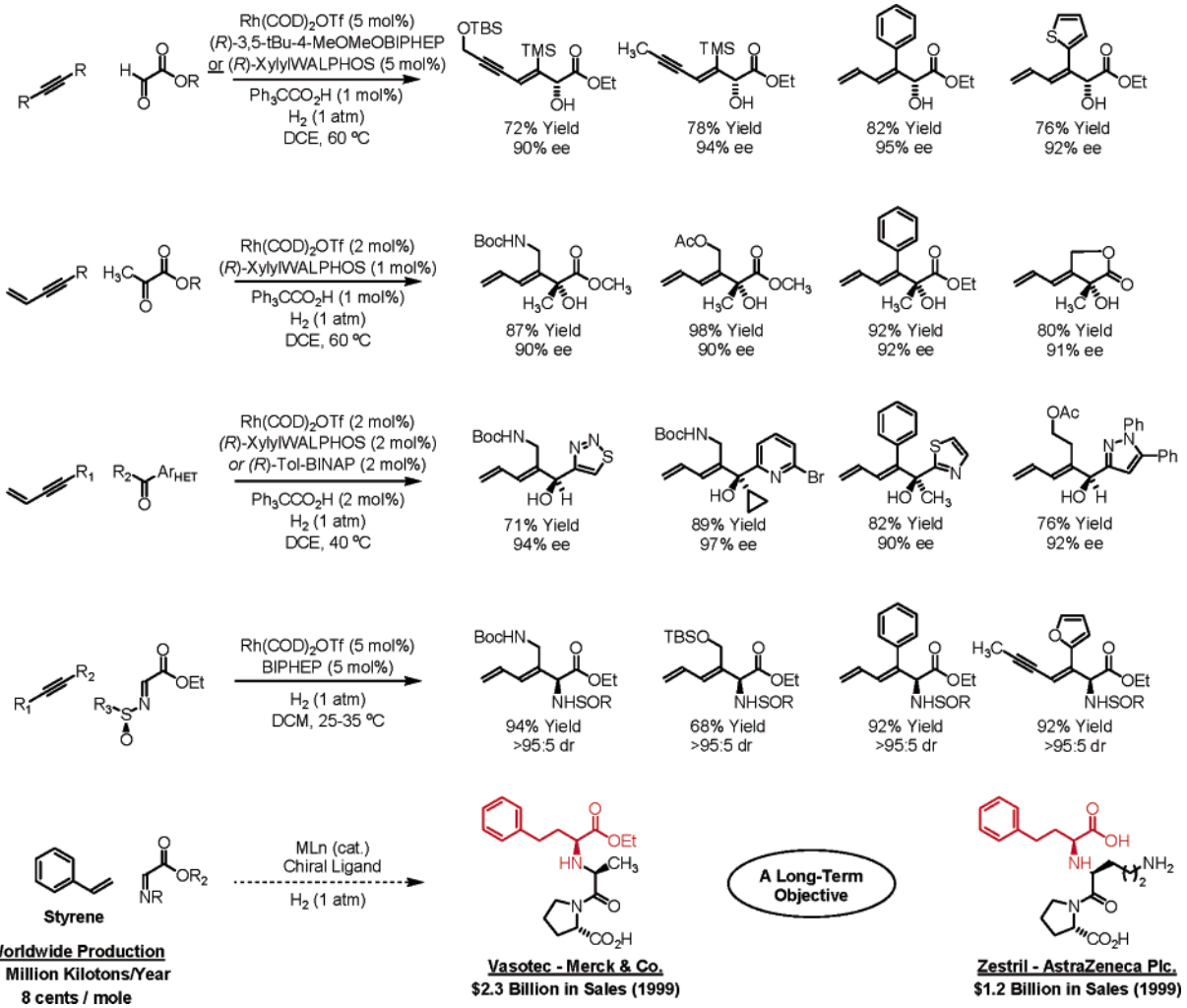
III.b. Hydrogen-Mediated Alkyne−Carbonyl Coupling. Inspired by the results obtained in the hydrogen-mediated vinyl ketone−aldehyde couplings, a broad assay was performed in which diverse π-unsaturated compounds were hydrogenated in the presence of assorted electrophiles. Gratifyingly, it was found that hydrogenation of conjugated alkenes and alkynes in the presence of the highly reactive vicinal dicarbonyl compound phenyl glyoxal furnish products of reductive C−C coupling.[38,39] Like the reductive aldol reaction, cationic rhodium precatalysts are required. However, in contrast to the enone−aldehyde couplings, basic additives do not effect partitioning of partitioning of C−C coupling and conventional hydrogenation manifolds. Rather, in certain cases (vide supra), acidic additives improve rate and conversion (Scheme 6).

These preliminary findings stimulated efforts toward related transformations involving glyoxalates, pyruvates, and iminoacetates. Such couplings would enable direct access to α-hydroxy acids and α-amino acids, respectively. In the event, hydrogenation of conjugated alkynes in the presence of ethyl glyoxalate using chirally modified cationic rhodium catalysts smoothly delivers the anticipated α-hydroxy esters with exceptional levels of asymmetric induction.[40] Attempted couplings to ethyl pyruvate, however, were problematic at first. Through an assay of additives, it was found that pyruvate couplings performed in the presence of substoichiometric quantities of Brønsted acid exhibit enhanced rate and conversion. Indeed, using triphenylacetic acid (1 mol %) as Brønsted acid co-catalyst, the corresponding α-hydroxy esters are produced in excellent yields and enantioselectivities.[41] Furthermore, under nearly identical conditions, isoelectronic heterocyclic aldehydes and ketones are converted to optically enriched heteroaryl-substituted secondary and tertiary alcohols.[42] Finally, iminoacetates in the form of sulfinylimines serve as precursors to novel nonproteogenic amino acid esters.[43] In all cases, the π-unsaturated products are not subject to over-reduction under the conditions of hydrogenative C−C coupling. Presumably, upon consumption of the electrophile, the limiting reagent, excess alkyne nonproductively coordinates the catalyst, retarding the rate of further conventional hydrogenation. These results represent an important step toward the ultimate goal of developing catalysts applicable to the hydrogenative coupling of basic feedstocks such as α-olefins and styrenes (Scheme 7).

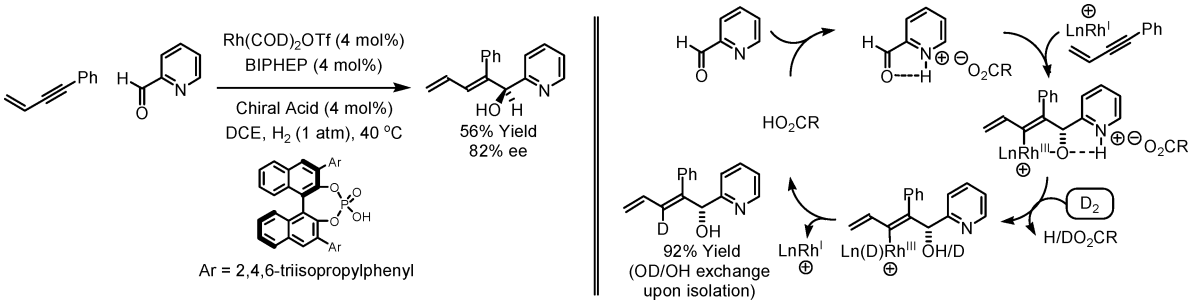
Our collective studies suggest that reactions of alkynes and carbonyl compounds are initiated by oxidative coupling to generate cationic oxarhodacyclopentenes, which hydrogenolytically cleave via σ-bond metathesis to deliver product and regenerate catalyst. One conceivable role of the Brønsted acid co-catalyst involves substrate protonation or hydrogen bond formation, which should lower the substrate LUMO to facilitate oxidative coupling. This hypotheses is consistent with results observed in the reductive coupling 1-phenylbut-3-en-1-yne to 2-pyridinecarboxaldehyde performed using an achiral rhodium catalyst in the presence of a chiral phosphoric acid derived from BINOL.[42,44] Substantial levels of optical enrichment are observed (82% ee), suggesting intervention of the chiral Brønsted acid co-catalyst in the enantiodetermining C−C coupling event, as well as acceleration of the C−C coupling event by virtue of the LUMO lowering effect of substrate protonation or hydrogen bonding (Scheme 8).

In analogous experiments involving pyruvates, chiral Brønsted acid co-catalysts do not provide optically enriched product. Nevertheless, an increase in rate and conversion in response to the Brønsted acid co-catalyst is clearly evident. Because pyruvate is less basic than pyridine-2-carboxaldehyde, protonation likely occurs subsequent to the C−C coupling event. We speculate that protonolytic cleavage of the intermediate oxarhodacyclopentene may accelerate σ-bond metathesis with hydrogen as follows. Recent computational studies by Musashi and Sakaki suggest that 4-centered transition structures for hydrogenolysis of Rh−O bonds are higher in energy than those occurring by way of 6-centered transition structures involving rhodium carboxylates.[45] Protonolysis of the oxarhodacyclopentene circumvents the 4-centered transition structure for σ-bond metathesis (**A**), as required for direct hydrogenolysis of the putative oxametallacyclic intermediate. The resulting rhodium carboxylate may now hydrogenolytically cleave through the 6-centered transition structure (**C**). The initial protonolysis of the oxarhodacyclopentene itself may occur through a 6-centered transition structure (**B**). ESI-mass spectrometric analyses of reactions performed in the presence and absence of the Brønsted acid co-catalyst reveal that the most abundant ions, as assigned on the basis of their *m*/*z* values, match the molecular weights of the purported oxarhodacyclopentadienes for both glyoxalate and pyruvate couplings. These data are consistent with the notion that the oxarhodacyclopentadiene is the catalyst resting state

SCHEME 7. Asymmetric Hydrogenative Coupling of Conjugated Alkynes to Activated Carbonyl Compounds and Imines: A Step toward Hydrogenative Reactions Involving α-Olefins and Styrenes



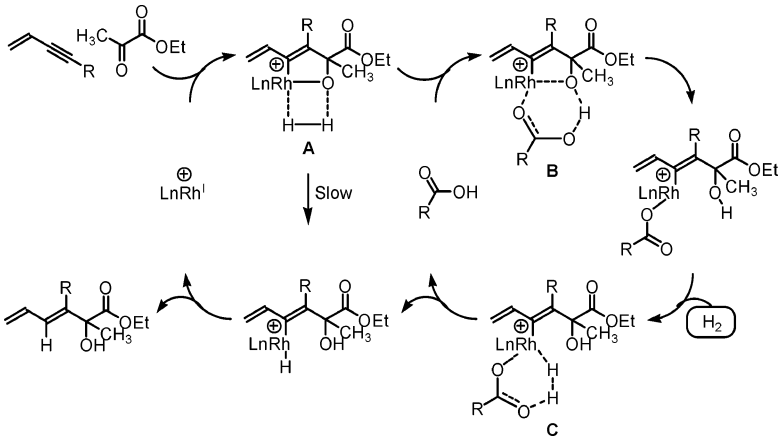
SCHEME 8. Plausible Catalytic Mechanism for Coupling of 1,3-Enynes to Pyridine-2-carboxaldehyde As Supported by the Effect of a Chiral Brønsted Acid Catalyst and Deuterium Labeling



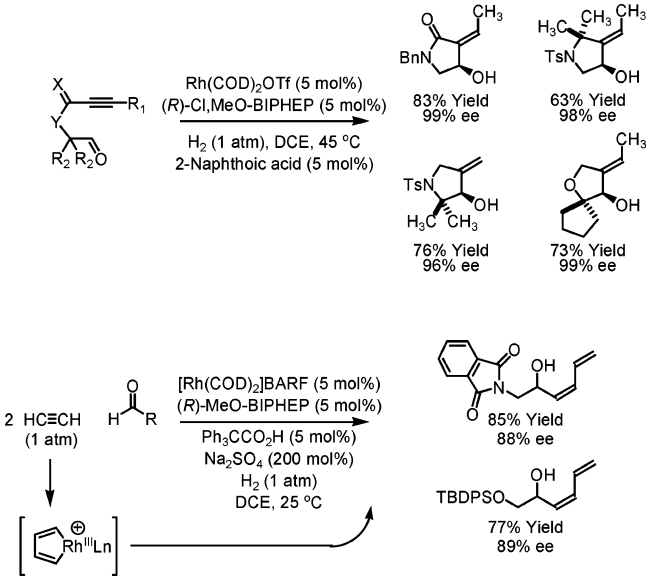
and that hydrogenolysis of the oxarhodacyclopentadiene is the slow step in the catalytic mechanism (Scheme 9).

There remains the question of whether catalytic hydrogenation may be applied to the reductive coupling of simple nonconjugated alkynes and unactivated aldehydes, which would represent an important step toward the ultimate goal of developing hydrogenative couplings applicable to basic chemical feedstocks. To explore this question, intramolecular reductive couplings of this type were explored.[46] It was found that catalytic hydrogenation of acetylenic aldehydes using chirally modified rhodium catalysts furnishes a range of cyclic allylic alcohols in highly optically enriched form. Again, Brønsted acid co-catalysts were found to enhance rate and conversion. Of greater interest, acetylene couples to diverse aldehydes and α-ketoesters under hydrogenation conditions to furnish products of *Z*-butadienylation.[47] Isotopic labeling and ESI-mass spectrometric analysis corroborate an unprecedented catalytic mechanism involving carbonyl insertion into a cationic rhodacyclopentadiene intermediate derived via oxidative dimerization of acetylene. Hydrogenolytic cleavage of the resulting oxarhodacycloheptadiene via σ bond metathesis provides the product of carbonyl addition

SCHEME 9. Potential Role of Brønsted Acid Co-catalyst As Supported by Computational Studies[45]



SCHEME 10. Hydrogenative Coupling of Simple Nonconjugated Alkynes to Unactivated Aldehydes



and cationic rhodium(I) to close the catalytic cycle (Scheme 10).

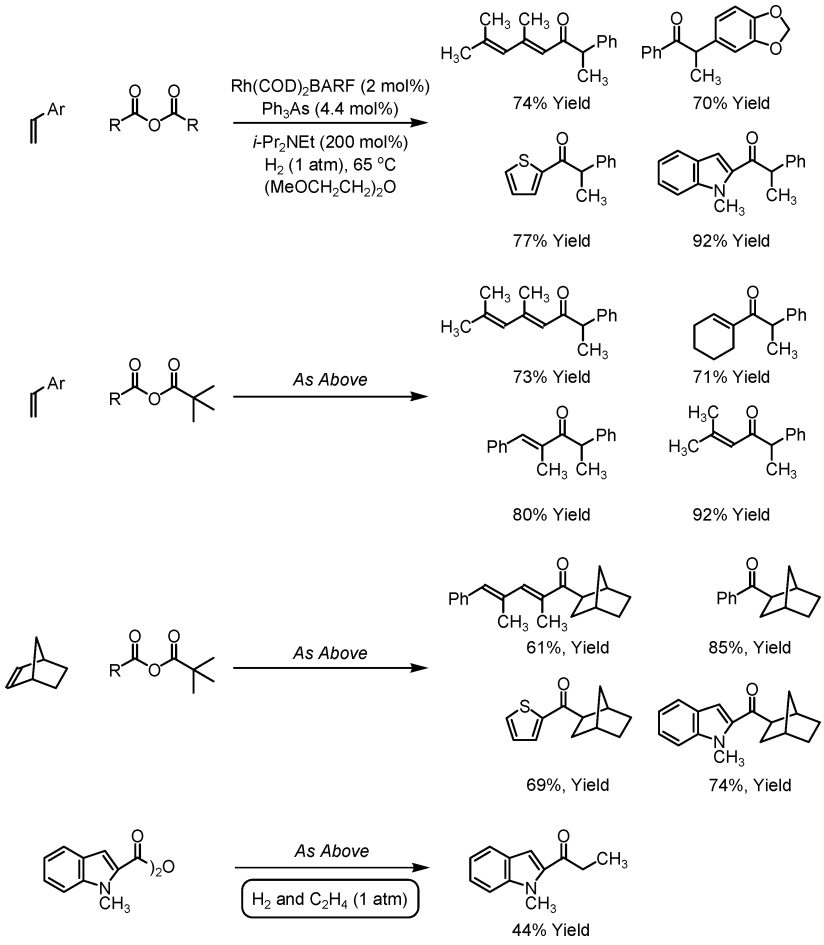
III.c. Hydrogen-Mediated Alkene−Anhydride Coupling (Hydroacylation). Guided by the prospect of developing catalytic processes applicable to basic feedstocks, the hydrogen-mediated coupling of carboxylic anhydrides to α-olefins was explored. It was found that upon hydrogenation of styrene (annual worldwide production 81 million kilotons)[48] in the presence of aromatic and α,*β*-unsaturated carboxylic anhydrides using cationic rhodium catalysts ligated by triphenylarsine, branched products of hydroacylation are obtained as single regioisomers.[49] These results are significant as intermolecular hydroacylation using aldehydes as acyl donors is inefficient due to competitive aldehyde decarbonylation.[50] To suppress aldehyde decarbonylation, aldehydes possessing adjacent sites of coordination are required (salicyladehydes and *β*-sulfidoaldehydes) or conventional aldehydes may be converted to the corresponding (*N*-2-pyridyl)aldimines, which are then used as acyl donors. Hence, the hydrogen-mediated coupling of carboxylic anhydrides to vinyl arenes represents the first efficient examples of direct intermolecular hydroacylation.

In terms of scope, aromatic and α,*β*-unsaturated acyl donors provide good to excellent yields of hydroacylation product. Aliphatic anhydrides, such as acetic anhydride, couple to styrene in 27% yield with a 9:1 (branched/linear) regioisomeric ratio. Symmetric anhydrides perform well, but their use is acceptable only in the case of inexpensive commercially available materials. For more precious carboxylic acids, couplings to mixed anhydrides derived from pivalic acid may be performed. As for the alkene partner, styrenes, vinylarenes and norbornene perform well. Of greater interest, ethylene participates in the coupling. Simply using a balloon containing roughly equal volumes of hydrogen and ethylene gas, the indicated 2-carboxyindole anhydride (chosen due to low volatility of the product) is converted to the corresponding ethyl ketone in an unoptimized 44% isolated yield (Scheme 11).

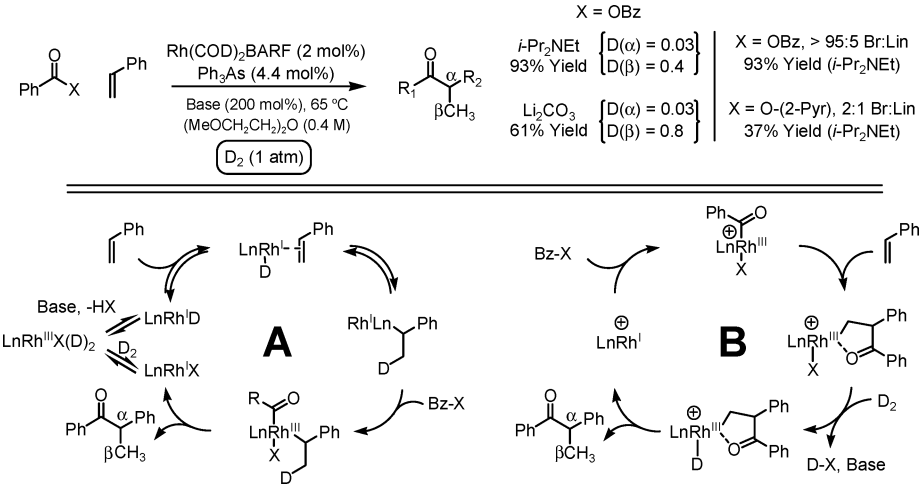
The reaction mechanism has been probed through isotopic labeling, and two catalytic cycles appear plausible. In catalytic mechanism **A**,[49b] heterolytic hydrogen activation is followed by insertion of styrene and formal acyl substitution to provide the product of hydroacylation. In mechanism **B**,[49a] anhydride oxidative addition[51] is followed by insertion of styrene and hydrogenolytic cleavage of the resulting alkylrhodium intermediate. In the coupling of benzoic anhydride and styrene mediated by deuterium, incorporation of deuterium is observed primarily at the *β*-position. However, the extent of incorporation is base dependent. Using *i*-Pr_2NEt or Li_2CO_3 as base, 0.4 and 0.8 deuterium atoms are incorporated, respectively, suggesting incomplete deuterium incorporation, in part, may result from dehydrogenation of *i*-Pr_2NEt. Reversible hydrometalation of styrene through mechanism **A** also may account for incomplete deuterium incorporation. However, this should increase the extent of deuterium incorporation at the α-position of the product, which is not observed. Further mechanistic evaluation of this transformation is in progress and will be disclosed in due course (Scheme 12).

IV. Future Challenges. Catalytic hydrogenation has stood the test of time due its inherent efficiency, atom economy and cost-effectiveness. Yet despite the enormous socioeconomic impact of hydrogenation, we have only tapped into a fraction of its potential as a method of C−C coupling. The prototypical hydrogen-mediated C−C bond formations, the Fischer−Tropsch reaction and alkene hydroformylation, are practiced on enormous scale. Hydrogenative C−C couplings that extend beyond carbon monoxide coupling have only begun to emerge, but promise to add a new dimension to one of chemistry's oldest and most broadly utilized catalytic transformations.

SCHEME 11. Hydrogen-Mediated Coupling of Carboxylic Anhydrides to Styrene, Vinylarenes, Norbornene, and Ethylene



SCHEME 12. Hydrogen-Mediated Coupling of Styrene to Carboxylic Anhydrides



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