Top Curr Chem (2007) 279: 77–104
DOI 10.1007/128_2007_122

Published online: 21 April 2007

Catalytic Reductive Coupling of Alkenes and Alkynes to Carbonyl Compounds and Imines Mediated by Hydrogen

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Abstract Catalytic transformations mediated by hydrogen or "hydrogenations" encompass a diverse range of environmentally benign processes, including large volume transformations of enormous socioeconomic impact, such as the Haber–Bosch process and the reduction of olefinic feedstocks. Despite considerable progress across diverse areas of catalytic hydrogenation, reductive C – C bond formations mediated by hydrogen have, until recently, been restricted to the incorporation of carbon monoxide, as illustrated by the Fischer–Tropsch reaction and alkene hydroformylation. In this account, the emerging family of hydrogen-mediated C – C bond formations beyond carbon monoxide coupling is reviewed. This new type of hydrogenation enables direct coupling of diverse π-unsaturated reactants to carbonyl compounds and imines under neutral condition with complete atom economy.

Keywords Atom economy · Cross-coupling · Green Chemistry · Hydrogenation · Iridium · Reductive coupling · Rhodium

1 Hydrogenation – The Proteus of Catalytic Transformations

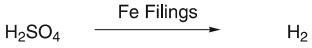
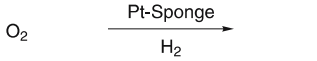
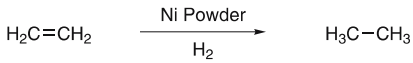
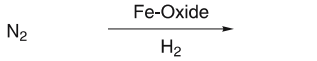
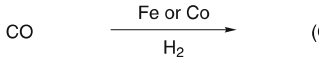
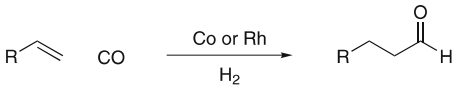
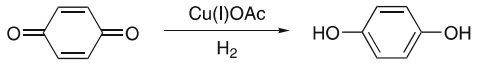
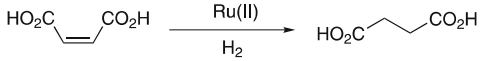
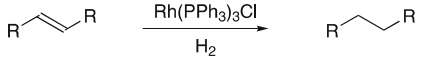
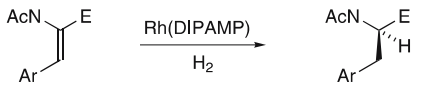
Hydrogen is the most abundant element in the universe, constituting roughly 75% of the universe's normal mass and 90% of the atoms present in the universe. Elemental hydrogen was first described by the legendary Swiss alchemist Paracelsus (1493–1541), and later in 1671 by Robert Boyle, but was

not recognized as a discrete substance until 1766, when in a paper entitled "*On factitious airs*" Henry Cavendish recorded the density of "inflammable air" that is generated upon the mixing of acids with mercury and which produces water when burned. Cavendish characterized many important properties of hydrogen, but incorrectly believed that hydrogen emanated from mercury. Although Cavendish is usually credited with the discovery of hydrogen, it should be noted that his work is articulated in terms of the phlogiston theory. Indeed, Cavendish believed that his "inflammable air" was phlogiston in its pure form. Antoine Lavoisier reproduced the experiments of Cavendish involving the combustion of hydrogen to form water and, further, regenerated hydrogen and oxygen through the decomposition of water. These experiments demonstrated that water is not an element, but is a compound of hydrogen and oxygen, which led Lavoisier to designate hydrogen as an element. In 1783, the very year hydrogen first was used in balloon ascents, Lavoisier gave this new element its name from the ancient Greek words *hydro*: "water" and *genes*: "forming".

Catalytic transformations mediated by hydrogen, termed "hydrogenations", are among the earliest reported metal-catalyzed reactions [1]. The first catalytic hydrogenation appears to be the platinum-catalyzed reaction of hydrogen with atmospheric oxygen, described nearly two centuries ago. In 1823, at a time when fire was created using flint and tinder, Döbereiner devised a household lighter based on this process [2, 3]. The "Döbereiner lighter" instantly captured worldwide attention and served as a prototype for legion devices used for the self-ignition of coal-gas burners. The catalytic hydrogenation of atmospheric nitrogen to produce ammonia, reported by Haber in 1905 [4], continues to have massive socioeconomic impact [5]. 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. At present, over 100 million metric tons of ammonia are produced annually through the Haber–Bosch process. The Fischer–Tropsch process, discovered in 1923 [6, 7] 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 [8, 9]. The rising cost of crude oil has rekindled interest in Fischer–Tropsch chemistry, stimulating development of improved catalytic systems [10]. Finally, in 1938, further studies of the Fischer–Tropsch reaction led by Otto Roelen resulted in the discovery of alkene hydroformylation, also known as the "oxo-synthesis" [11]. Presently, over 7 million metric tons of aldehyde are produced annually via hydroformylation, making it the largest volume application of homogeneous metal catalysis [12, 13].

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

Table 1 Twelve milestones in catalytic hydrogenation

1500s	Paracelsus (1493–1541) and Boyle (1671) describe gas generation upon mixing acid and metal filings	
1766	Henry Cavendish (1731–1810) isolates and characterizes "inflammable air", which he believes to be phlogiston	
1783	Lavoisier coins the name "hydrogen" and recognizes hydrogen as an element	
1823	Döbereiner reports the first catalytic hydrogenation: the Pt-catalyzed combustion of hydrogen in air [2, 3]	
1897	Sabatier reports the first heterogeneous catalytic hydrogenation of an organic molecule [14–17]	
1905	The catalytic hydrogenation of atmospheric nitrogen to produce ammonia is reported by Haber [3]	
1923	The catalytic hydrogenation of carbon monoxide to produce petroleum is reported by Fischer and Tropsch [5, 6]	
1938	Hydroformylation, the prototypical hydrogenative C – C coupling, is reported by Roelen [11]	
1938	Calvin reports the first homogeneous hydrogenation of an organic molecule [18, 19]	
1961	Halpern reports the first homogeneous hydrogenation of an activated alkene [20, 21]	
1964	Wilkinson reports the first homogeneous hydrogenation of an unactivated alkene [22–24]	
1968	Knowles reports the first enantioselective homogeneous hydrogenation of an alkene [25, 26]	

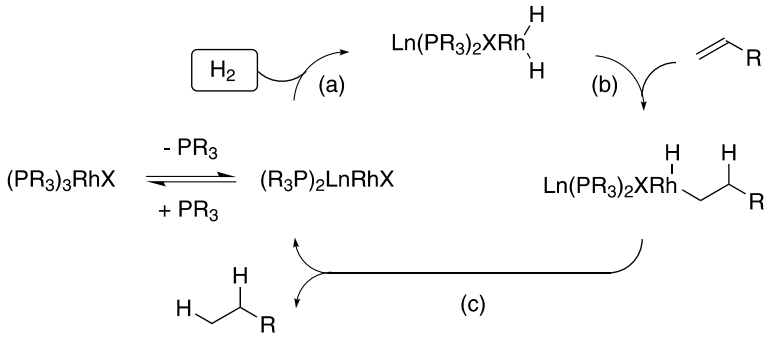
reactions of this type were developed by Paul Sabatier at the University of Toulouse in the late 1890s [14–17]. It was not until the 1960s that the first catalysts for the homogeneous alkene hydrogenation were developed [18, 19], largely owing to seminal contributions by Jack Halpern [20, 21] and Geoffrey Wilkinson [22–24]. Catalytic hydrogenation continued to evolve to encompass enantioselective variants, in large part due to the pioneering efforts of Knowles [25, 26], Kagan [27], and Noyori [28]. Clean, cost-effective and powerful, asymmetric hydrogenation is presently the most broadly utilized catalytic enantioselective process employed industrially, accounting for over half of the chiral compounds made by man not produced via physical or enzymatic resolution [29–31] (Table 1).

2
Hydrogenative C–C Bond Formations beyond Hydroformylation

The profound impact of hydrogenation portends an equally powerful approach to reductive C – C bond formations mediated by hydrogen: completely atom economical C – C couplings wherein two or more unsaturated molecules combine to furnish a single, more complex product simply through their exposure to gaseous hydrogen in the presence of a metal catalyst. However, since the discovery of the Fischer–Tropsch reaction and alkene hydroformylation, processes restricted to the incorporation of carbon monoxide, the field of hydrogen-mediated C – C bond formation has lain fallow. It is likely that the broad perception of hydrogenation as a method for the reduction of C = X π-bonds caused hydroformylation to be viewed as an anomalous reaction specific to carbon monoxide, impeding development of related hydrogenative couplings. Indeed, withstanding recent studies described in this account, systematic efforts toward the development of hydrogen-mediated C – C couplings beyond hydroformylation have been absent from the literature [32–35].

Among catalysts for alkene hydrogenation, those based upon rhodium have been studied in greatest detail. Through analysis of the mechanism of "conventional hydrogenation" catalyzed by *neutral* and *cationic* rhodium complexes, general strategies for intercepting the organometallic intermediates arising transiently in the course of catalytic hydrogenation may be formulated. For both the neutral and cationic rhodium catalysts, the dihydride based catalytic cycle involves three fundamental steps: (a) hydrogen oxidative addition, (b) substrate hydrometallation, and (c) C – H reductive elimination (Scheme 1).

The mechanism of alkene hydrogenation catalyzed by the neutral rhodium complex $RhCl(PPh_3)_3$ (Wilkinson's catalyst) has been characterized in detail by Halpern [36–38]. The hydrogen oxidative addition step involves initial dissociation of PPh_3, which enhances the rate of hydrogen activation by a factor



Scheme 1 Fundamental steps in Rh-catalyzed alkene hydrogenation involving a dihydride-based mechanism

of 1×10^4. The hydrogen oxidative addition step is reversible, as established by the equilibration of *para*-enriched hydrogen. Alkene hydrometallation is turnover-limiting, and the rapid nature of the subsequent C – H activation event renders the hydrometallation event irreversible. It should be emphasized that small changes in ligand or substrate are known to change the dominant reaction mechanism. Halpern elegantly demonstrates that none of the spectroscopically detectable species are actual participants in the catalytic cycle.

For cationic rhodium complexes, the mechanism for the hydrogenation of dehydroamino acid esters (i.e., α-amidocinnamates) has been characterized in detail [39–44]. For chirally modified catalysts, substrate coordination provides diastereomeric substrate complexes. The minor diastereomer activates hydrogen more quickly than the major diastereomer. Initially, it was presumed that substrate remains bound to rhodium during the hydrogen oxidative addition event. More recent studies suggest dissociation of substrate from the minor isomer occurs in advance of hydrogen oxidative addition [45]. Unlike the hydrogenations catalyzed by neutral rhodium complexes, the cationic systems irreversibly activate hydrogen in a turnover-limiting oxidative addition. At reduced temperatures (– 40 °C), the rate-determining step changes to C – H reductive elimination.

The hydrogenation of simple alkenes using cationic rhodium precatalysts has been studied by Osborn and Schrock [46–48]. Although kinetic analyses were not performed, their collective studies suggest that both monohydride- and dihydride-based catalytic cycles operate, and may be partitioned by virtue of an acid–base reaction involving deprotonation of a cationic rhodium(III) dihydride to furnish a neutral rhodium(I) monohydride (Eq. 1). This aspect of the mechanism finds precedent in the stoichiometric deprotonation of cationic rhodium(III) dihydrides to furnish neutral rhodium(I) monohydrides (Eq. 2). The net transformation ($H_2 + M – X \rightarrow M – H + HX$) is equivalent to a formal *heterolytic* activation of elemental

$$[RhH_2(PPhMe_2)_3S_x]^{\oplus} \rightleftharpoons [RhH(PPhMe_2)_3S_x] + H^{\oplus}$$

Cationic Dihydride — Neutral Monohydride

Equation 1

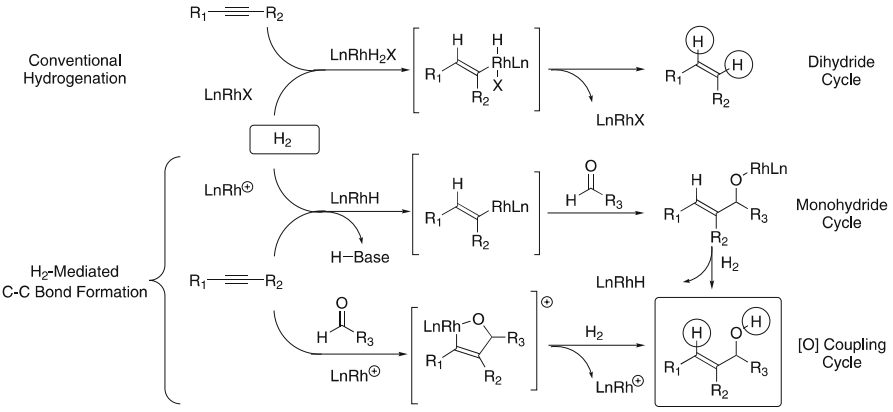
$$[Rh(NBD)(PPh_3)_2]^{\oplus} \xrightarrow[2)\ NEt_3]{1)\ 3\ PPh_3,\ H_2} RhH(PPh_3)_4 \qquad 80\%\ \text{Yield}$$

Equation 2

hydrogen [49, 50]. Cationic complexes are better at promoting heterolytic hydrogen activation, as the resulting dihydrides are more acidic than the neutral complexes [51].

Based upon the preceding data, the capture of reactive intermediate in catalytic hydrogenations catalyzed by cationic rhodium complexes appeared feasible. The cationic complexes are capable of promoting heterolytic hydrogen activation and entry into monohydride-based catalytic cycles. Substrate hydrometallation from the monohydride furnishes organometallic species that do not possess hydride ligands, thus disabling direct C – H reductive elimination manifolds, extending the lifetime of the resulting organometallic species to facilitate their capture. Further, because cationic rhodium complexes are slow to activate hydrogen, oxidative coupling of the reactants may precede hydrogen activation en route to products of C – C bond formation. The veracity of this analysis is supported by the transformations described herein, which uniformly require cationic rhodium precatalysts (Scheme 2).

In this account, the first systematic efforts toward hydrogen-mediated C – C couplings beyond alkene hydroformylation are described [52–54].



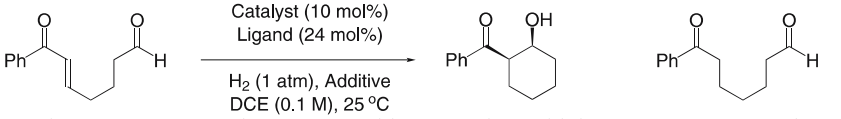
Scheme 2 General strategies for hydrogenative C – C coupling predicated on the mechanism of conventional Rh-catalyzed alkene hydrogenation

Whereas classical methods for the addition of *C*-nucleophiles to carbonyl compounds often require stoichiometric use of moisture-sensitive organometallic reagents, "C – C bond forming hydrogenation" enables direct C – C coupling of π-unsaturated reactants under neutral conditions with complete atom economy, thus taking catalytic hydrogenation in a powerful new direction. To date, we have only tapped into a fraction of the potential of catalytic hydrogenation to serve as a method of C – C bond formation. Just as the prototypical hydrogen-mediated C – C couplings, the Fischer–Tropsch reaction and alkene hydroformylation, are practiced on enormous scale. Hydrogenative couplings that extend beyond carbon monoxide coupling promise to add a new dimension to one of chemistry's oldest and most broadly utilized catalytic transformations.

2.1 Vinyl Ketone–C=X (X=O, NR) Coupling (Reductive Aldol and Mannich Additions)

Following seminal studies by Revis (1987) [55], the catalytic reductive coupling of α,β-unsaturated carbonyl compounds and aldehydes to form aldol products, termed the "reductive aldol reaction", has been the subject of intensive investigation. To date, catalysts for reductive aldol coupling based on rhodium [55–71], cobalt [72–75], iridium [76], palladium [73], copper [74–80], and indium have been described, which include highly diastereo- [57, 65, 66, 69–71, 73–75, 80–85] and enantioselective [58, 61, 62, 64, 76, 81–83] variants. Through studies of the rhodium-catalyzed reductive aldol reaction [65], it was found that organometallic intermediates arising transiently in catalytic hydrogenation may be diverted to products of C – C bond formation. Specifically, whereas catalytic hydrogenation of the indicated phenyl-substituted mono-enone mono-aldehyde using the neutral rhodium(I) catalyst $Rh(PPh_3)_3Cl$ furnishes the expected product of conventional hydrogenation, use of a rhodium salt that embodies increased cationic character, $Rh^I(COD)_2OTf/Ph_3P$, provides nearly equal proportions of the conventional hydrogenation and *syn*-aldol cyclization products. Finally, when $Rh^I(COD)_2OTf$ is used in conjunction with a more electron-deficient ligand and substoichiometric quantities of a mild basic additive, potassium acetate, formation of aldol product is increased to the point that conventional hydrogenation manifolds are virtually excluded. Reexposure of the conjugate reduction product to the reaction conditions does not produce the aldol product. Additionally, in the absence of hydrogen, Morita–Baylis–Hillman products are not observed, suggesting that tandem phosphine-catalyzed cyclization-conjugate reduction pathways en route to the aldol cyclization product are not operative. The observance of *syn*-aldol adducts suggests intermediacy of the *Z*-enolate and a closed Zimmerman–Traxler type of transition structure (Table 2) [86].

Table 2 Hydrogenative aldol cyclization is promoted through the use of cationic Rh pre-catalysts and substoichiometric quantities of mild basic additives [a]

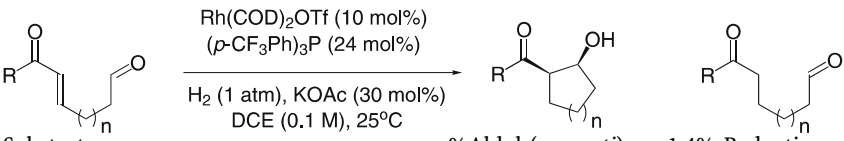


Catalyst	Ligand	Additive (mol%)	Aldol (*syn*:*anti*)	1,4%-Reduction
$Rh(PPh_3)Cl$	–	–	1 (99 : 1)	57
$Rh(COD)_2OTf$	PPh_3	–	21 (99 : 1)	25
$Rh(COD)_2OTf$	PPh_3	KOAc (30)	59 (58 : 1)	21
$Rh(COD)_2OTf$	$(p\text{-}CF_3Ph)_3P$	–	57 (14 : 1)	22
$Rh(COD)_2OTf$	**$(p\text{-}CF_3Ph)_3P$**	**KOAc (30)**	**89 (10 : 1)**	**0.1**

[a] As product ratios were found to vary with surface area to volume ratio of the reaction mixture, all transformations were conducted on 1.48 mmol scale in 50 mL round bottomed flasks

Under these conditions, the cycloreduction of aromatic, heteroaromatic and aliphatic enone substrates to form five- and six-membered ring products may be achieved (Table 3) [65]. Interestingly, the cycloreduction of substrates incorporating aryl-substituted enones yields aldol products with good levels of *syn*-diastereoselectivity, yet for substrates incorporating aliphatic enones, *anti*-diastereoselectivity is observed. These results are consistent with the generally accepted notion that *Z*-enolate formation is preferred for large

Table 3 Rh-catalyzed hydrogenative aldol cyclization of aldo-enones [a]



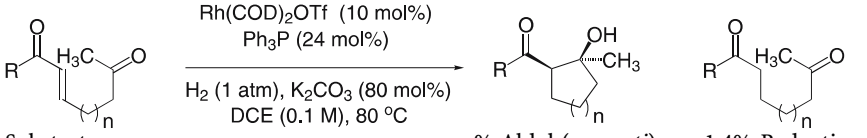
Substrate	%Aldol (*syn*:*anti*)	1,4%-Reduction
$n = 2$, R = Ph	89 (10 : 1)	0.1
$n = 2$, R = *p*-MeOPh	74 (5 : 1)	3
$n = 2$, R = 2-Naphthyl	90 (10 : 1)	1
$n = 2$, R = 2-Thiophenyl	76 (19 : 1)	2
$n = 2$, R = 2-Furyl	70 (6 : 1)	10
$n = 1$, R = Ph	71 (24 : 1)	1
$n = 2$, R = CH_3	65 (1 : 5)	–

[a] As product ratios were found to vary with surface area to volume ratio of the reaction mixture, all transformations were conducted on 1.48 mmol scale in 50 mL round bottomed flasks

acyl residues due to $A_{1,3}$-strain [87–90]. However, as demonstrated by the hydrogen-mediated cyclization of keto-enones [66], if the aldol addition event is rendered reversible, as is typically the case in enolate additions to ketones [87–90], the thermodynamically favored *syn*-aldol cyclization products are uniformly preferred (Tables 4 and 5).

Although a mechanism involving enone-aldehyde oxidative coupling cannot be excluded, the pronounced effect of basic additives on partitioning of the aldolization and 1,4-reduction manifolds suggests a monohydride catalytic cycle (Scheme 2). Basic additives may mediate deprotonation of the (hydrido)rhodium intermediates $LnRh^{III}(OTf)(H)_2$ or (enolato)Rh^{III}(OTf)(H)Ln, simultaneously disabling direct enolate-hydrogen reductive elimination and inducing entry into the monohydride catalytic cycle, which itself avoids regeneration of such intermediates. Consistent with this interpretation, hydrogenative aldol cyclization under an atmosphere of deuterium results in deuterium incorporation exclusively at the former enone β-position [66]. Deuterium incorporation at the α-position is not observed. Interestingly, the indicated distribution of deuterated products supports reversible enone hydrometallation in the case of ketone acceptors, where reversible aldol addition is anticipated (Scheme 3).

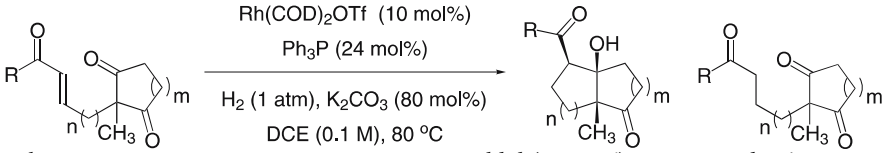
Table 4 Rh-catalyzed hydrogenative aldol cyclization of keto-enones[a]



Substrate	% Aldol (*syn*:*anti*)	1,4%-Reduction
n = 1, R = Ph	75 (> 95 : 5)	8
n = 1, R = 2-Naphthyl	74 (> 95 : 5)	18
n = 1, R = 2-Thienyl	66 (> 95 : 5)	24
n = 1, R = 2-Furyl	70 (> 95 : 5)	24
n = 1, R = 2-(*N*-Methyl)pyrrolyl	75 (> 95 : 5)	11
n = 1, R = 3-Indolyl	74 (> 95 : 5)	8
n = 2, R = Ph	72 (> 95 : 5)	20
n = 2, R = 2-Naphthyl	78 (> 95 : 5)	18
n = 2, R = 2-Thienyl	78 (> 95 : 5)	8
n = 2, R = 2-Furyl	83 (> 95 : 5)	8
n = 2, R = 2-(*N*-Methyl)pyrrolyl	82 (> 95 : 5)	12
n = 2, R = 3-Indolyl	72 (> 95 : 5)	17

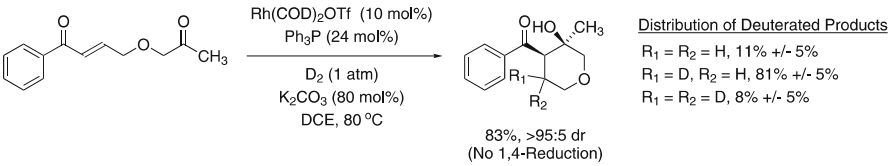
[a] As product ratios were found to vary with surface to volume ratio of the reaction mixture, all transformations were conducted on 0.46 mmol scale in 13 × 100 mm test tubes at 80 °C. Reactions performed at 25 °C gave similar results but with diminished reproducibility

Table 5 Rh-catalyzed hydrogenative aldol cyclization of 1,3-diketone-enones[a]



Substrate	% Aldol (*syn*:*anti*)	1,4%-Reduction
n = 1, m = 1, R = Ph	84 (> 95 : 5)	> 1
n = 1, m = 1, R = CH_3	88 (> 95 : 5)	> 1
n = 1, m = 2, R = Ph	86 (> 95 : 5)	> 1
n = 2, m = 1, R = Ph	81 (> 95 : 5)	> 1
n = 2, m = 1, R = CH_3	73 (> 95 : 5)	> 1
n = 2, m = 2, R = Ph	65 (> 95 : 5)	15

[a] As product ratios were found to vary with surface to volume ratio of the reaction mixture, all transformations were conducted on 0.46 mmol scale in 13 × 100 mm test tubes at 80 °C. Reactions performed at 25 °C gave similar results but with diminished reproducibility



Scheme 3 Rh-catalyzed hydrogenative aldol cyclization of a keto-enone under an atmosphere of deuterium

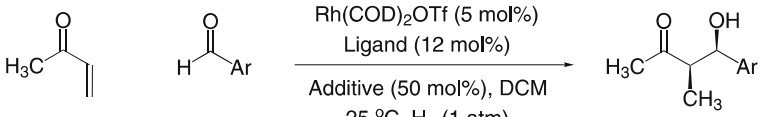
Intermolecular hydrogenative aldol coupling using triphenylphosphine ligated rhodium catalysts provides aldol products in good yield, but with poor levels of diastereoselection [65]. A progressive increase in diastereoselectivity is achieved upon sequential replacement of the ligand phenyl residues for 2-furyl residues (Ph_3P, $FurPh_2P$, Fur_2PhP, Fur_3P) [69]. Indeed, for reactions employing tri-2-furylphosphine [91–93] ligated rhodium catalysts, the observed levels of *syn*-diastereoselectivity for reactions performed at ambient temperature exceed those observed in corresponding aldol additions of lithium enolates conducted at – 78 °C [69]. These high levels of *syn*-diastereoselectivity suggest kinetic control at the stages of both enolization and aldol addition. The *anti*-aldol diastereomers are thermodynamically preferred. Hence, high *syn*-diastereoselectivity suggests kinetic control at the stages of both enolization and aldol addition. For detailed descriptions, see literature cited in [86].

Rhodium hydride addition to the enone *s-cis* conformer through a six-centered transition structure accounts for stereospecific *Z*(*O*)-enolate forma-

tion. Enones constrained in the *s-trans* configuration, such as cyclohexenone, do not participate in hydrogen-mediated reductive aldol coupling. Addition of the resulting *Z*(*O*)-enolate to the aldehyde through a Zimmerman–Traxler type transition structure stereospecifically delivers the *syn*-aldol stereoisomer [86]. To preserve high levels of *syn*-diastereoselectivity, both enolization and aldol addition should be irreversible or exhibit high levels of kinetic stereospecificity (Table 6).

Under optimum conditions employing the tri-2-furylphosphine ligated rhodium catalyst, commercially available methyl and ethyl vinyl ketone (MVK and EVK) [69] and divinyl ketones such as crotyl vinyl ketone (CVK) [70] engage in highly diastereoselective hydrogenative aldol coupling to a diverse collection of aldehydes. The hydrogenative coupling conditions are highly chemoselective, as underscored by the fact that functional groups generally considered to be "hydrogen-labile" (alkynes, alkenes, benzylic ethers, and nitroarenes) remain intact. Because hydrogen-mediated aldol coupling occurs under essentially neutral conditions in a low dielectric media at ambient temperature, substrate hydrogen bonds may be exploited as stereochemical control elements. For example, hydrogenation of MVK and EVK in the presence of *N*-Boc-α-aminoaldehydes enables formation of aldol stereotriads that embody high levels of *syn*-aldol diastereoselectivity accompanied by high levels of *anti*-Felkin-Anh control [71]. The collective data are consistent with a catalytic mechanism involving addition of the *Z*(*O*)-

Table 6 Highly *syn*-diastereoselective intermolecular Rh-catalyzed hydrogenative aldol coupling of vinyl ketones through the tri-2-furylphosphine effect[a]

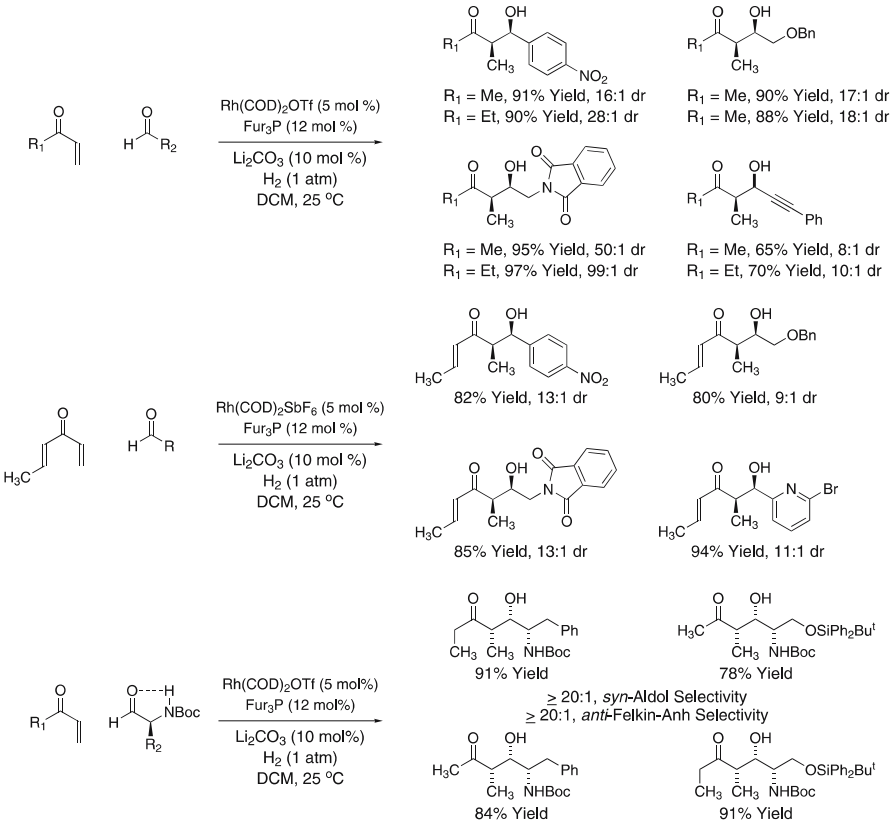


MVK 150 mol% | Ar = *p*-NO_2Ph 100 mol%

Ligand	Additive	DCM	Yield %	Dr
PPh_3	Li_2CO_3	(0.1 M)	31	3 : 1
$FurPh_2P$	Li_2CO_3	(0.1 M)	24	6 : 1
Fur_2PhP	Li_2CO_3	(0.1 M)	52	15 : 1
Fur_3P	Li_2CO_3	(0.1 M)	74	19 : 1
$AsPh_3$	Li_2CO_3	(0.1 M)	17	7 : 1
Fur_3P	–	(0.1 M)	63	19 : 1
Fur_3P	Li_2CO_3	(0.3 M)	88	16 : 1
Fur_3P	**Li_2CO_3**	**(0.1 M)**	**91**	**16 : 1**

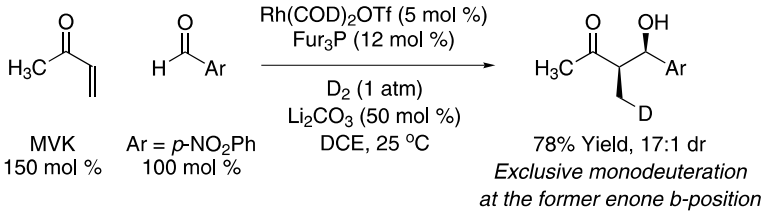
[a] As product ratios were found to vary with surface to volume ratio of the reaction mixture, all transformations were conducted on 0.66 mmol scale in 13 × 100 mm test tubes

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. Notably, optical integrity of the stereochemically labile α-aminoaldehydes is preserved under the conditions of hydrogen-mediated aldol coupling, as revealed by HPLC analysis (Scheme 4).



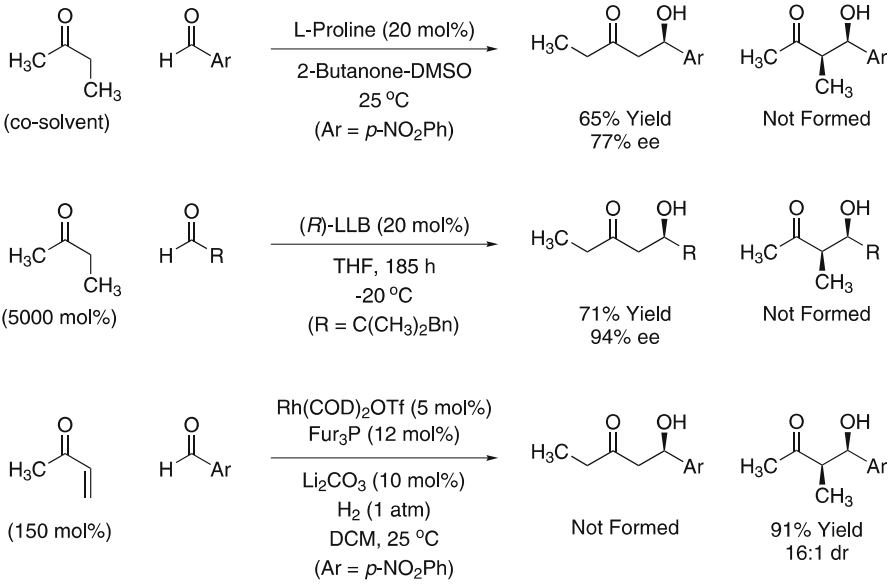
Scheme 4 *syn*-Diastereoselective intermolecular hydrogen-mediated aldol coupling employing cationic Rh catalysts ligated by tri-2-furylphosphine

Diastereoselective reductive coupling of MVK and *p*-nitrobenzaldehyde performed under an atmosphere of elemental deuterium provides an aldol adduct incorporating a single deuterium atom at the former enone β-position [69]. Deuterium incorporation at the α-carbon is not observed, excluding Morita–Baylis–Hillman pathways en route to product. Incorporation of a single deuterium atom suggests irreversible enone hydrometallation (Scheme 5).



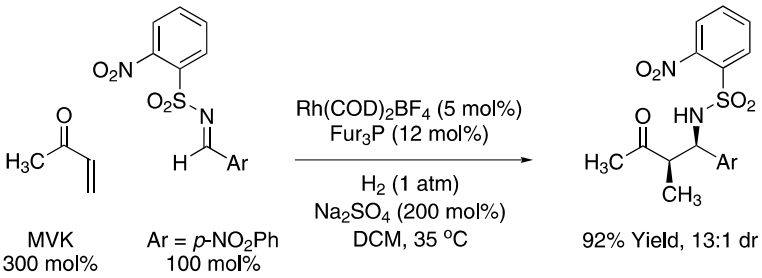
Scheme 5 Intermolecular Rh-catalyzed hydrogenative aldol coupling under an atmosphere of deuterium

While much progress in the area of hydrogen-mediated reductive aldol coupling has been made, many challenges remain. For example, an enantioselective variant of the hydrogen-mediated aldol coupling would require the design of a chirally modified monophosphine bearing 2-furyl residues. An asymmetric hydrogen-mediated aldol coupling would offer a regiochemical complement to corresponding "direct" asymmetric aldol additions. Direct aldol couplings of 2-butanone catalyzed by L-proline furnish linear adducts [94, 95]. Similarly, direct aldol couplings of 2-butanone promoted by the heterobimetallic catalyst $LaLi_3$-tris(binaphthoxide) (LLB) provide linear aldol products [96]. Under the conditions of hydrogenative coupling, the enone moiety of MVK may be exploited a regiochemical control element, directing formation of the branched aldol addition product desired for polypropionate synthesis (Scheme 6) [69].



Scheme 6 Complementary regioselectivities in direct aldol couplings of 2-butanone and corresponding hydrogen-mediated reductive aldol couplings of MVK

Reductive Mannich couplings of α,β-unsaturated carbonyl compounds mediated by silane [97, 98] and the Hantzsch ester [99] support the feasibility of corresponding hydrogen-mediated transformations. In the event, hydrogenation of MVK in the presence of *N*-sulfonylimines using a tri-2-furylphosphine ligated rhodium catalyst provides the desired Mannich addition products with good levels of *syn*-diastereoselectivity (Garner and Krische, unpublished results) (Scheme 7). As product ratios were found to vary with surface-to-volume ratio of the reaction mixture, this transformation was conducted on 0.46 mmol scale in a 13 × 100 mm test tube.

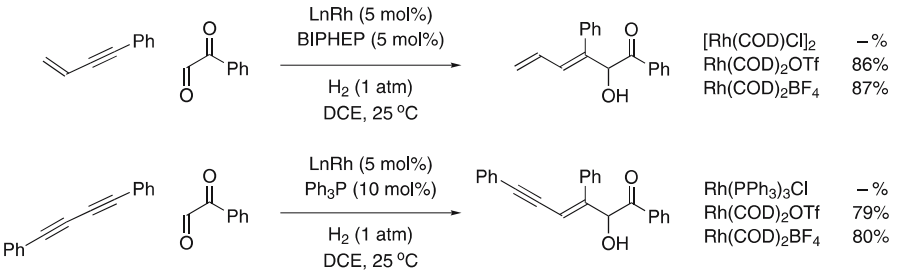


Scheme 7 *syn*-Diastereoselective intermolecular hydrogen-mediated Mannich coupling employing cationic Rh catalysts ligated by tri-2-furylphosphine

2.2 Alkyne–C=X (X=O, NR) Coupling (Reductive Carbonyl-Ene Additions)

The feasibility of hydrogenative aldol coupling prompted efforts toward the discovery of related C – C bond forming hydrogenations. A broad assay was performed in which various π-unsaturated compounds were hydrogenated in the presence of diverse carbonyl electrophiles. It was found that hydrogenation of conjugated alkenes and alkynes in the presence of phenyl glyoxal, a highly reactive vicinal dicarbonyl compound, gives rise to products of formal reductive carbonyl–ene-type coupling [100, 101]. As for the hydrogenative aldol couplings, cationic rhodium precatalysts are required. However, basic additives do not enhance the efficiency of C – C coupling. Rather, acidic additives improve rate and conversion for certain substrate combinations (vide supra) (Scheme 8).

Based on these preliminary findings, related couplings to pyruvates and iminoacetates were explored as a means of accessing α-hydroxy acids and α-amino acids, respectively. It was found that hydrogenation of 1,3-enynes in the presence of pyruvates using chirally modified cationic rhodium catalysts delivers optically enriched α-hydroxy esters [102]. However, chemical yields were found to improve upon aging of the solvent 1,2-dichloroethane (DCE), which led to the hypothesis that adventitious HCl may promote re-

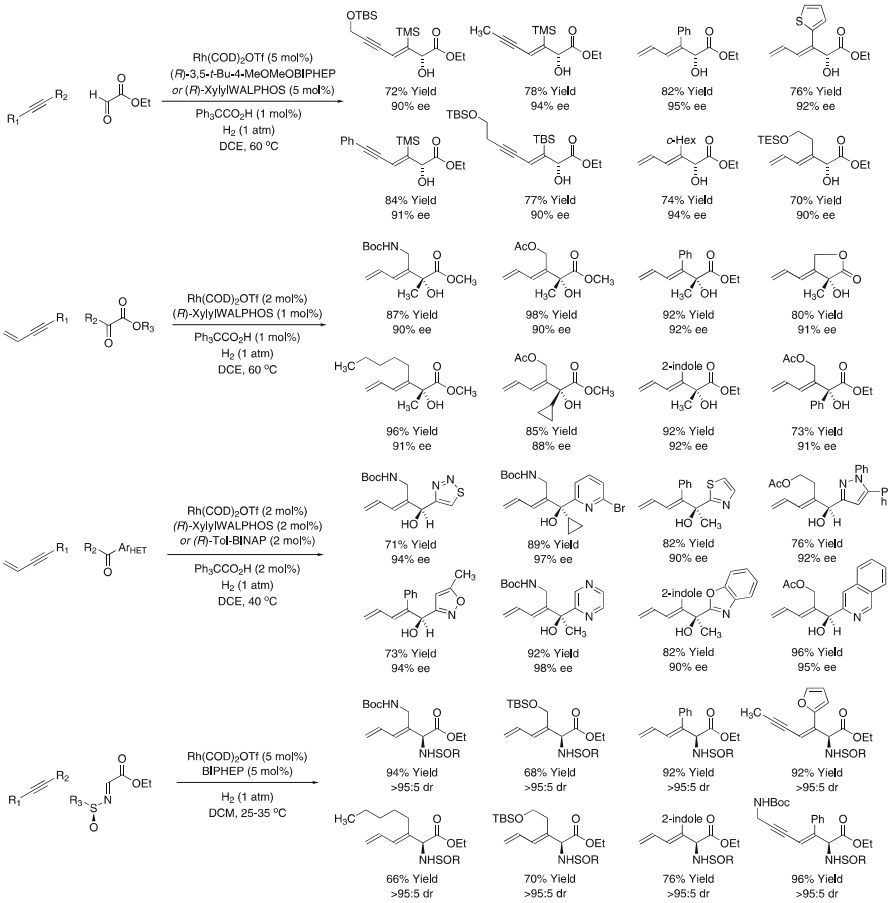


Scheme 8 Selected results from a broad assay for hydrogen-mediated C – C bond formations

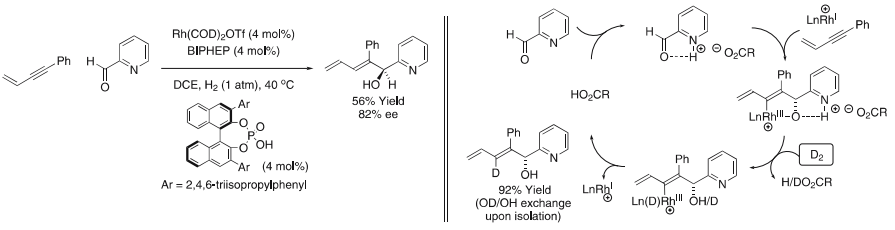
ductive coupling. Using freshly distilled DCE, an assay of Brønsted acid additives reveals that reactions performed in the presence of substoichiometric quantities of triphenylacetic acid (1 mol %) exhibit enhanced rate and conversion. Through the use of a Brønsted acid co-catalyst, highly enantioselective hydrogenative couplings of conjugated alkynes to pyruvates [102] and glyoxalates [103](Hong and Krische, unpublished results) are achieved. Brønsted acid co-catalysts also facilitate couplings to heterocyclic aromatic aldehydes and ketones that are isoelectronic with respect to the vicinal dicarbonyl motif, thus providing access to optically enriched heteroaryl-substituted secondary and tertiary alcohols [104]. Finally, hydrogenation of 1,3-enynes in the presence of optically enriched ethyl (*N*-sulfinyl)iminoacetates furnishes novel nonproteogenic amino acid esters (Scheme 9) [105].

The fact that the reductive aldol and alkyne–vicinal dicarbonyl couplings both require cationic rhodium precatalysts belies substantial differences in mechanism. Rather than a hydrometallative mechanism, the collective data suggest that hydrogenative additions of alkynes to carbonyl compounds proceed via oxidative coupling to furnish cationic oxarhodacyclopentenes, which then hydrogenolytically cleave via σ-bond metathesis to deliver product and regenerate the catalyst (Scheme 2). To gain insight into the role of the Brønsted acid co-catalyst, the reductive coupling of a 1,3-enyne to 2-pyridinecarboxaldehyde was performed using an achiral rhodium catalyst in the presence of a chiral Brønsted acid co-catalyst derived from BINOL [106–108]. The coupling product was produced in highly optically enriched form (82% ee) [104], strongly suggesting that C – C coupling is accelerated by the LUMO lowering effect of substrate protonation and/or hydrogen bonding and that the Brønsted acid co-catalyst is associated with 2-pyridinecarboxaldehyde during the stereogenic C – C bond forming event (Scheme 10).

Chiral Brønsted acid co-catalysts do not promote formation of optically enriched products in analogous couplings to pyruvates, although increased rate and conversion in response to the Brønsted acid co-catalyst is unmistakably apparent. For pyruvates, protonation likely occurs subsequent to the C – C



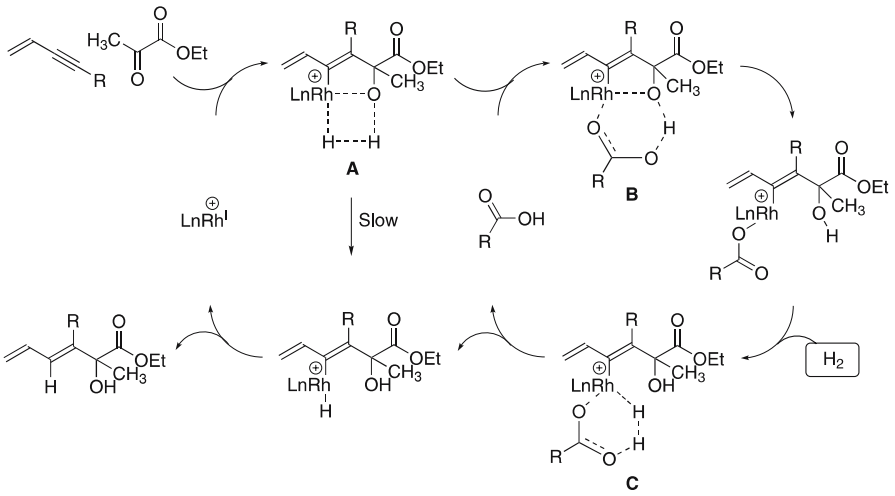
Scheme 9 Asymmetric hydrogen-mediated coupling of conjugated alkynes to carbonyl compounds and imines



Scheme 10 Plausible catalytic mechanism for alkyne–carbonyl coupling as supported by the effect of chiral Brønsted acid catalyst and deuterium-labeling

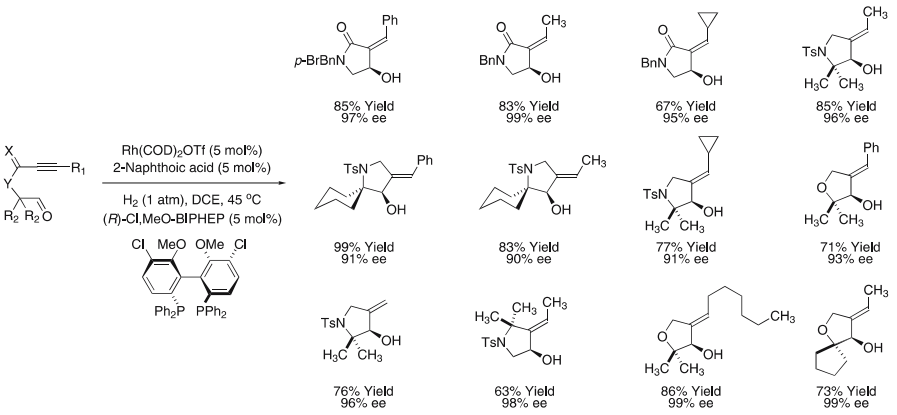
coupling event, effecting cleavage of the intermediate oxarhodacyclopentene. Indeed, computational studies suggest that four-centered transition structures for hydrogenolysis of Rh – O bonds are higher in energy than those

occurring by way of six-centered transition structures involving rhodium carboxylates [109]. Protonolysis of the oxarhodacyclopentene, which itself may occur through a six-centered transition structure (**B**, Scheme 11), circumvents direct hydrogenolysis of the putative oxametallacyclic intermediate via σ-bond metathesis through a four-centered transition structure (**A**). Hydrogenolysis of the resulting rhodium carboxylate through the six-centered transition structure (**C**) completes the "co-catalytic cycle". 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 and that hydrogenolysis of the oxarhodacyclopentadiene is the slow step in the catalytic mechanism (Scheme 11).



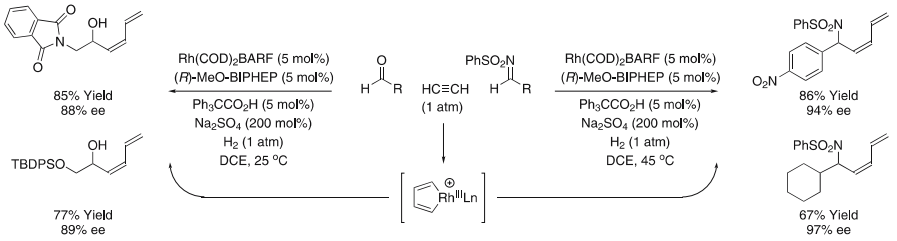
Scheme 11 Plausible role of Brønsted acid co-catalyst as supported by computational studies

Catalytic hydrogenation is eminently suited to large volume applications. Hence, the development of hydrogenative C – C couplings applicable to basic feedstocks and commodity chemicals represents an important research objective. To assess the feasibility of performing hydrogenative couplings of commercially available nonconjugated alkynes to simple unactivated aldehydes, intramolecular reductive couplings of this type were examined [110]. In the event, catalytic hydrogenation of acetylenic aldehydes using chirally modified rhodium catalysts delivers the desired products of reductive carbocyclization with uniformly high levels of optical enrichment. Brønsted acid co-catalysts again were found to enhance reaction rate and conversion (Scheme 12).



Scheme 12 Reductive cyclization of acetylenic aldehydes via Rh-catalyzed asymmetric hydrogenation

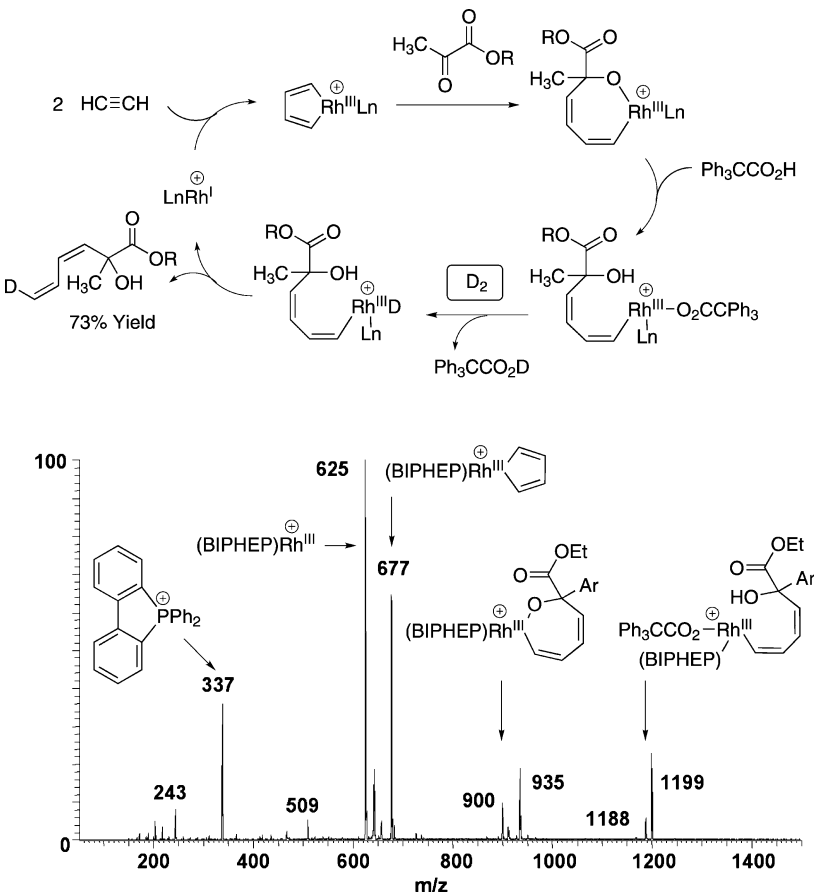
Given the preceding results, intermolecular hydrogenative couplings of commercially available nonconjugated alkynes and simple unactivated aldehydes were explored. It was found that hydrogenation of gaseous acetylene (2 cents/mol, annual US production > 500 metric kilotons) [111] in the presence of diverse aldehydes generates products of *Z*-butadienylation, which appear as single alkene geometrical isomers [112]. More recently, corresponding couplings to aldimines have been achieved (Skucas et al., unpublished results). For both aldehyde and imine couplings, the use of chirally modified rhodium catalysts enables formation of highly optically enriched allylic alcohols and allylic amines, respectively (Scheme 13).



Scheme 13 Enantioselective carbonyl (*Z*)-dienylation via reductive coupling of acetylene to aldehydes and imines mediated by hydrogen

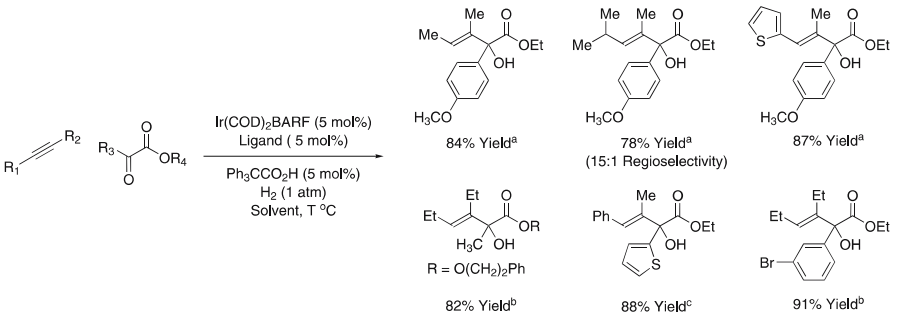
As corroborated by deuterium labeling studies, the catalytic mechanism likely involves oxidative dimerization of acetylene to form a rhodacyclopentadiene [113] followed by carbonyl insertion [114, 115]. Protonolytic cleavage of the resulting oxarhodacycloheptadiene by the Brønsted acid co-catalyst gives rise to a vinyl rhodium carboxylate, which upon hydrogenolysis through a six-centered transition structure and subsequent C – H reductive elimina-

tion delivers the product of *Z*-butadienylation. The veracity of this interpretation is supported by direct ESI-mass spectrometric analyses of reaction mixture aliquots diluted 5000-fold in methanol [116, 117]. All postulated reactive intermediates are observed, withstanding the proposed vinyl rhodium hydride, which should have a very short lifetime due to the generally rapid nature of C – H reductive elimination. Of particular interest is the ion of m/z 677 which matches the molecular weight of the rhodacyclopentadiene, and the ions matching the molecular weights of the oxarhodacycloheptadiene (m/z 900) and the intermediate obtained upon protonolytic cleavage of the oxarhodacycloheptadiene by triphenylacetic acid (m/z 1188). These data provide further support for the key role of Brønsted acid co-catalysts in hydrogenative C – C coupling (Scheme 14).



Scheme 14 *Top*: Plausible catalytic cycle as supported by deuterium labeling. *Bottom*: ESI mass spectrum of a reaction mixture aliquot diluted 5000-fold in methanol from the hydrogen-mediated coupling of gaseous acetylene to an α-ketoester (Ar = *p*-NO_2Ph)

Under the conditions of rhodium catalysis, simple nonconjugated alkyl substituted alkynes failed to provide satisfactory yields of carbonyl coupling product. The collective work on hydrogenative alkyne–carbonyl coupling suggests that alkyne–carbonyl oxidative coupling is facilitated by the formation of metal–alkyne complexes that embody a high degree of metallacyclopropene character by virtue of π-backbonding in accordance with the Dewar–Chatt–Duncanson model [118–120]. Iridium(I) complexes are stronger π-donors than rhodium [121–123] due to relativistic effects associated with the lanthanide contraction [124]. Hence, cationic iridium complexes were assayed for their ability to promote the hydrogenative C – C coupling of substituted nonconjugated alkynes to various carbonyl compounds. As anticipated, iridium-catalyzed hydrogenation of commercially available alkyl-substituted alkynes, 3-hexyne and 1-phenylpropyne, results in reductive C – C coupling to afford the corresponding β,γ-unsaturated α-hydroxyesters in excellent yield, with complete control of olefin geometry and, in most cases, excellent regiocontrol (Scheme 15) [125].

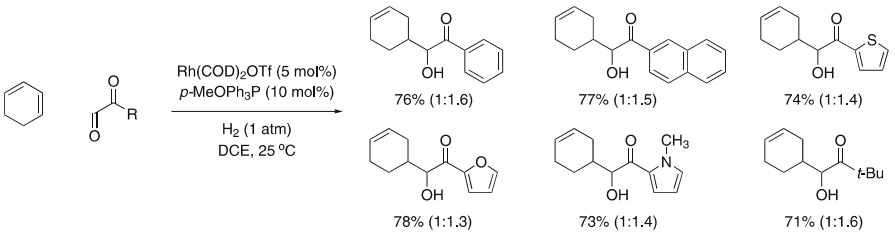


Scheme 15 Iridium-catalyzed hydrogen-mediated coupling of alkyl-substituted alkynes to activated ketones and aldehydes. Conditions: *a* ligand = BIPHEP, solvent = toluene, T = 80 °C; *b* ligand = DPPF, solvent = toluene, T = 60 °C; *c* ligand = BIPHEP, solvent = DCE, T = 80 °C

2.3 Alkene–C=X (X=O, NR) Coupling (Reductive Carbonyl-Ene and Reductive Hydroacylation)

The reductive coupling of α-olefins to simple aliphatic aldehydes to afford branched regioisomers would represent a powerful method for the generation of polypropionate substructures. With this goal in mind, the hydrogenative coupling of various alkenes to carbonyl compounds was explored. Remarkably, it was found that hydrogenation of conjugated alkenes in the presence of phenyl glyoxal provides products of formal reductive carbonyl-ene type coupling. Optimal results were obtained in connection with the use of 1,3-cyclohexadiene as the nucleophilic partner, as formation of regioisomeric

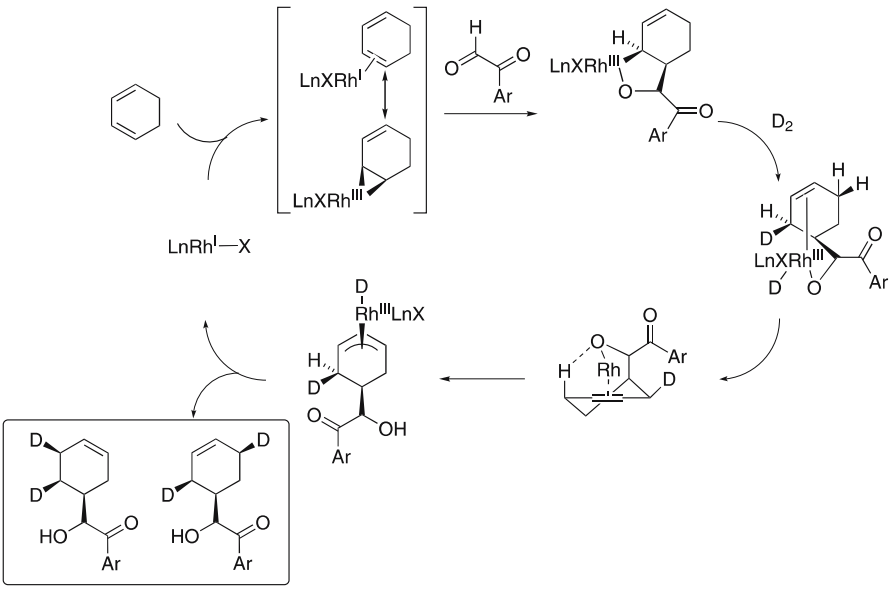
products are avoided and the *s-cis* configuration of 1,3-cyclohexadiene appears to facilitate coupling [126]. Again, cationic rhodium complexes catalyze C – C coupling, whereas neutral rhodium complexes promote conventional hydrogenation. Under optimum conditions, 1,3-cyclohexadiene was found to couple to a range of α-ketoaldehydes (Scheme 16).



Scheme 16 Hydrogen-mediated coupling of 1,3-cyclohexadiene to α-ketoaldehydes

Reductive coupling of 1,3-cyclohexadiene with 2-naphthyl glyoxal under an atmosphere of deuterium generates coupling products that incorporate precisely two deuterium atoms as an equimolar distribution of 1,2- and 1,4-regioisomers. A relative stereochemical assignment of the deuterated adducts is currently underway. This result may be understood on the basis of a mechanism involving diene–glyoxal oxidative coupling. Specifically, diene–glyoxal oxidative coupling furnishes an oxarhodacycle, which then reacts with deuterium via σ bond metathesis to afford a rhodium alkoxide. Abstraction of an allylic hydrogen provides a rhodium π-allyl complex, which upon C – D reductive elimination delivers the dideuterated products as an equimolar distribution of regioisomers. When the diene–glyoxal coupling is performed under an atmosphere of hydrogen deuteride (HD) as the terminal reductant, the coupling product incorporates a single molecule of deuterium distributed over the same three carbons found when deuterium (D_2) is used as reductant. These data disqualify the initially disclosed hydrometallative mechanism, and strongly support the aforementioned mechanism involving diene–carbonyl oxidative coupling (Scheme 17).

The structural homology of conjugated dienes and styrene suggests the feasibility of analogous styrene–glyoxal couplings. However, under standard conditions using both rhodium- and iridium-based catalysts products of hydrogenative C – C coupling were not observed. It is possible that the LUMO of styrene is too high in energy to enable activation of the vinyl residue in the form of the π-complex, which, as previously discussed, appears to facilitate oxidative coupling to carbonyl partners. An alternate strategy involves activation of the electrophilic partner. For example, oxidative addition of rhodium(I) to carboxylic anhydrides affords acylrhodium(III)carboxylates [127], which may be induced to engage in olefin insertion. Indeed, using a neutral rhodium(I) source with triphenylphosphite as ligand, Miura reports that hydrogenation

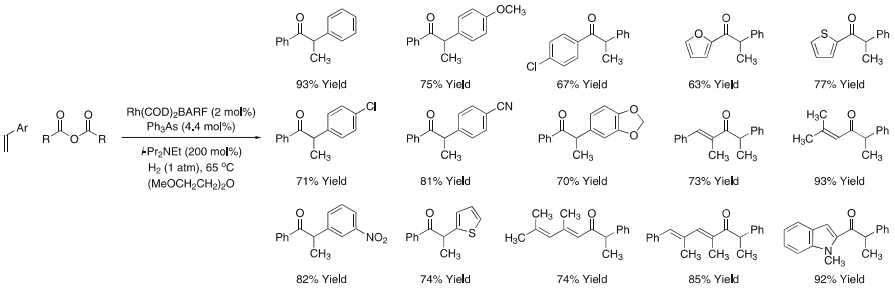


Scheme 17 A plausible catalytic mechanism for the hydrogen-mediated coupling of 1,3-cyclohexadiene to α-ketoaldehydes as corroborated by deuterium labeling

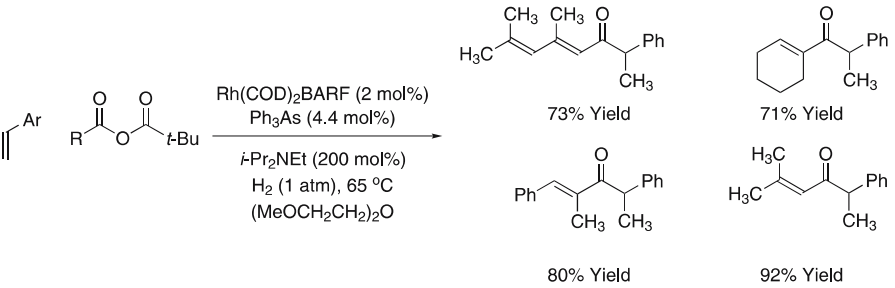
of styrene in the presence of benzoic anhydride furnishes a mixture of linear and branched hydroacylation products in modest yield [33]. Subsequent studies reveal that cationic rhodium catalysts ligated by triphenylarsine catalyze formation of branched hydroacylation products as single regioisomers in good to excellent yield using aromatic and α,β-unsaturated anhydrides as acyl donors [128]. These results are significant in view of the fact that intermolecular hydroacylation using aldehydes as acyl donors is notoriously inefficient due to competitive aldehyde decarbonylation. Consequently, to suppress aldehyde decarbonylation, aldehydes possessing adjacent sites of coordination are required (salicyladehydes and β-sulfido-aldehydes) or conventional aldehydes may be converted to the corresponding (*N*-2-pyridyl)aldimines, which are then used as acyl donors (Scheme 18) [129–141].

A potential liability associated with such reductive hydroacylations resides in the fact that only one acyl residue of the symmetric anhydride is incorporated into the coupling product. For more precious carboxylic acids, selective acyl transfer from mixed anhydrides is possible. Mixed anhydrides derived from pivalic acid are especially convenient, as they may be isolated chromatographically in most cases. In practice, mixed anhydrides of this type enable completely branch-selective hydroacylation with selective delivery of the aromatic and α,β-unsaturated acyl donors (Scheme 19).

In terms of scope, activated alkenes beyond vinyl arenes, such as norbornene, couple effectively to aromatic and α,β-unsaturated anhydrides, in-

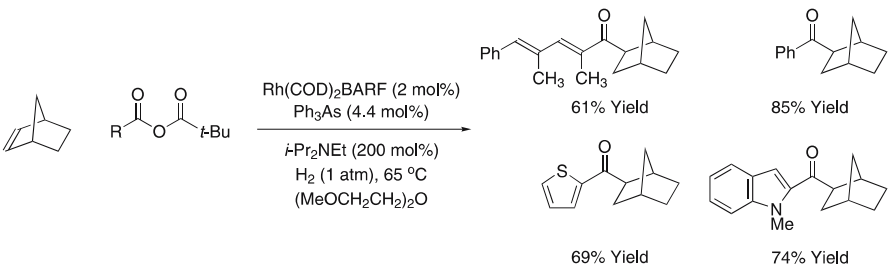


Scheme 18 Branch-selective hydroacylation via hydrogen-mediated coupling of vinyl arenes to carboxylic anhydrides

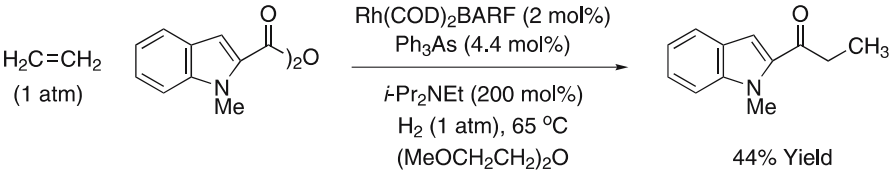


Scheme 19 Selective acyl transfer in reductive hydroacylations involving mixed carboxylic anhydrides derived from pivalic acid

cluding mixed anhydrides derived from pivalic acid (Scheme 20). Of greater interest, hydrogenation of ethylene in the presence of carboxylic anhydrides delivers the corresponding ethyl ketones. For example, 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 21). Several challenges remain. Terminal alkenes such



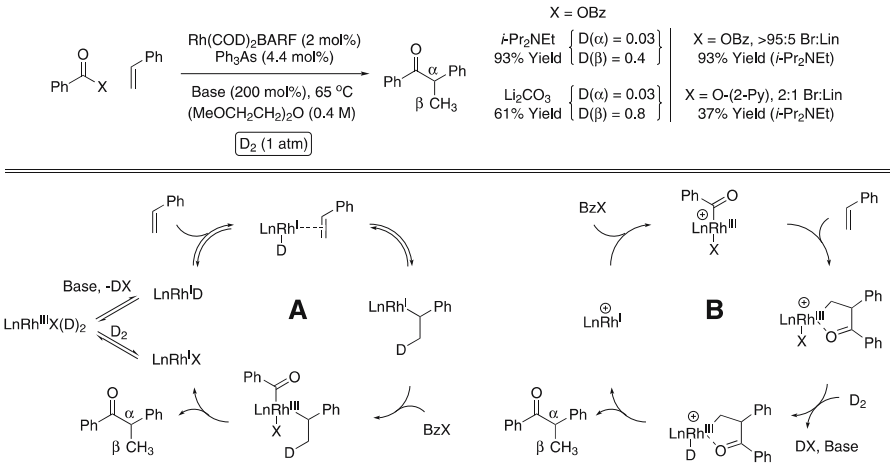
Scheme 20 Reductive hydroacylation of norbornene employing mixed carboxylic anhydrides derived from pivalic acid



Scheme 21 Hydrogenative coupling of ethylene to a carboxylic anhydride to form an ethyl ketone

as 4-phenyl-1-butene couple to benzoic anhydride in only 34% yield with a 1 : 2.5 ratio of branched to linear regioisomers, respectively, under optimum conditions employing cationic rhodium catalysts ligated by triphenylarsine. Additionally, aliphatic ahydrides such as acetic anhydride couple to styrene in only 27% yield with a 9 : 1 ratio of branched to linear regioisomers.

In terms of mechanism, the results of isotopic labeling suggest two possible catalytic cycles. In catalytic mechanism **A** (Scheme 22) [33], heterolytic hydrogen activation with subsequent hydrometallation of styrene delivers an organorhodium intermediate that engages in formal acyl substitution to provide the hydroacylation product. In mechanism **B** [128], anhydride oxidative addition is followed by insertion of styrene and hydrogenolysis of the resulting alkyl-rhodium intermediate. In the couplings mediated by deuterium, incorporation of deuterium takes place mainly at the β-position. However, the degree of deuterium incorporation is base-dependant. Using *i*-Pr_2NEt or Li_2CO_3 as base, 0.4 and 0.8 deuterium atoms are incorporated, respectively, suggesting that incomplete deuterium incorporation may arise via dehydro-



Scheme 22 Deconvoluting the catalytic mechanism in the hydrogen-mediated coupling of styrene to carboxylic anhydrides

genation of *i*-Pr_2NEt. Reversible hydrometallation 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 underway (Scheme 22).

3 Future Challenges

Over half a century ago, seminal studies by Fischer, Tropsch and Roelen led to the prototypical hydrogen-mediated C – C bond formations. Such processes, which involve coupling to carbon monoxide, continue to rank among the largest volume metal-catalyzed reactions known [6, 7, 11]. Only recently has it been discovered that catalytic hydrogenation may induce reductive C – C bond formation between π-unsaturated reactants and conventional electrophilic partners in the form of carbonyl compounds and imines. These data suggest countless possibilities in terms of the innovative methodologies and diverse applications that will arise in the future. As catalysts for water splitting improve and hydrogen production no longer depends upon the availability of petroleum, a nonrenewable resource, the environmental and economic advantages of hydrogen-mediated transformations will be even greater.

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