Catalytic C−C Bond Formation via Capture of Hydrogenation Intermediates

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ABSTRACT

Although catalytic hydrogenation has been practiced for over a century, use of hydrogen as a terminal reductant in catalytic C−C bond formation has been restricted to processes involving migratory insertion of carbon monoxide, e.g., alkene hydroformylation and related Fischer−Tropsch-type reactions. In an effort to develop hydrogenation as a new method for catalytic cross-coupling, a catalytic system enabling capture of hydrogenation intermediates was recently developed in our lab. These results support the feasibility of developing a broad new family of hydrogen-mediated C−C bond formations.

1. Introduction

Elemental hydrogen is the cleanest and most cost-effective chemical reductant available to humankind. Despite the fact that catalytic hydrogenation has been practiced routinely for over a century,[1−3] use of hydrogen as a terminal reductant in catalytic C−C bond formation has been restricted to processes involving migratory insertion of carbon monoxide, e.g., alkene hydroformylation and related Fischer−Tropsch-type reactions.[4,5] Recently, a catalytic system enabling capture of the organometallic intermediates that appear transiently in the course of catalytic hydrogenation was developed in our lab. These results establish catalytic hydrogenation as a powerful and mechanistically novel means of catalytic C−C bond formation and support the feasibility of developing a broad new class of catalytic hydrogen-mediated C−C bond formations. Here, a concise overview of these studies is presented (Scheme 1).

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Michael J. Krische received his B.S. degree in Chemistry from the University of California at Berkeley under the tutelage of Professor H. Rapoport as a Presidents Undergraduate Fellow, whereupon he was granted a Fulbright Fellowship for study in Europe. Dr. Krische received his Ph.D. degree in Chemistry from Stanford University for studies performed with Professor B. M. Trost as a Peter Veatch Fellow and then pursued postdoctoral studies with Jean-Marie Lehn at the Université Louis Pasteur as an NIH Postdoctoral Fellow, where he was granted the title of Maître de Conference, Collége de France. Dr. Krische joined the faculty at the University of Texas at Austin in Fall 1999, where he established a program of research combining the topics of catalytic reaction development, asymmetric synthesis, self-assembly, and materials chemistry. Selected honors and awards include the Camille Dreyfus Teacher Scholar Award (2003), the Alfred P. Sloan Research Fellowship (2003), the Cottrell Scholar Award (2002), the Frasch Foundation Award in Chemistry (2002), the Eli Lilly Grantee for Untenured Faculty (2002), and the National Science Foundation-CAREER Award (2000).

2. Background

Recently, catalytic reductive methods for carbon−carbon bond formation have emerged as the subject of intensive research.[6−10] Catalytic systems for the hydrometallative reductive coupling of alkenes,[6] alkynes,[7] enones,[8] and dienes[9,10] to carbonyl partners has been achieved using silanes, alanes, and boranes as terminal reductants. While use of such terminal reductants mandates generation of stoichiometric byproducts, it was recognized that use of *elemental hydrogen* would enable such transformations to proceed with complete levels of atom economy.[11] Moreover, the ultimate objective of coupling basic chemical feedstocks, e.g., α-olefins and carbonyl compounds, under hydrogenation conditions would represent a technology of profound economic interest. Indeed, it has been estimated that 20% of the United States gross national product (GNP) derives from catalysis.[12]

The principal challenge associated with hydrogen-mediated C−C bond formation involves circumventing conventional hydrogenation pathways. It was speculated that such nonproductive hydrogenation manifolds would be attenuated through *heterolytic* activation of elemental hydrogen ($H_2 + M-X \rightarrow M-H + HX$),[13] which enables monohydride based catalytic cycles for which direct alkyl−hydrogen reductive elimination pathways are disabled. Here, the lifetime of the organometallic intermediates initially obtained upon hydrometalation should be extended, which should facilitate their capture (Scheme 2).

Among catalysts applicable to the heterolytic activation of hydrogen, those based on rhodium are especially well studied. Whereas homolytic activation of hydrogen is observed in conjunction with the use of neutral Rh(I) complexes (e.g., Wilkinson's catalyst),[14,15] the use of cationic Rh(I) complexes in conjunction with basic additives is found to induce heterolytic activation pathways.[16] The ability of cationic rhodium complexes to promote heterolytic activation of hydrogen owes to the enhanced acidity of the dihydrides that results upon oxidative addition.[17] Thus, heterolytic activation of hydrogen is believed to occur through a two-stage process involving hydrogen oxidative addition followed by base-induced H−X reductive elimination (Figure 1).[18]

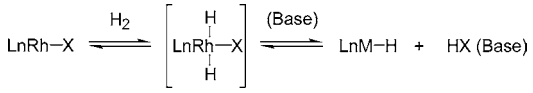

FIGURE 1. Heterolytic activation of hydrogen.

The veracity of this analysis is borne out by the development of a Rh-based catalyst system for hydrogen-mediated C−C bond formation that is applicable to the condensation of diverse organic fragments. The following hydrogen-mediated reductive couplings have been achieved: (1) the intra- and intermolecular reductive coupling of enone and enal pronucleophiles with aldehyde

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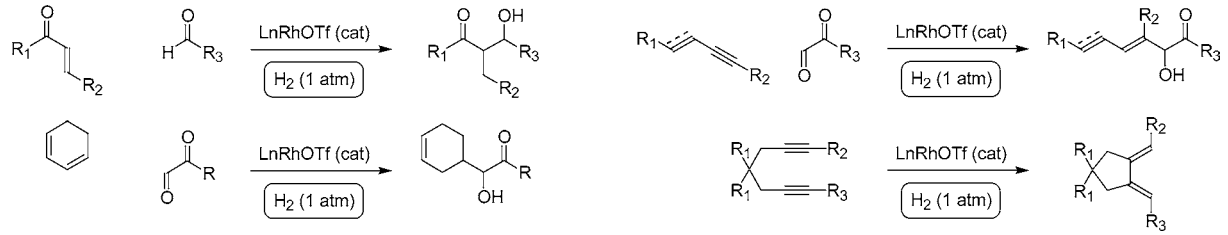
Scheme 1. Catalytic Hydrogen-Mediated C−C Bond Formation



Scheme 2. Heterolytic Activation of Hydrogen Disables Direct Alkyl−Hydrogen Reductive Elimination Pathways

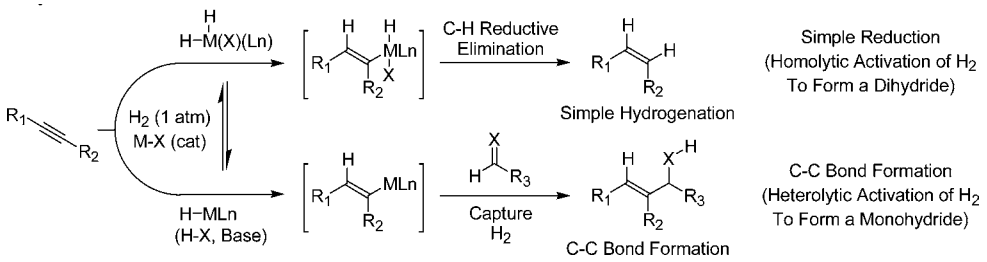
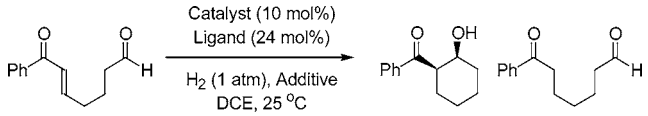


Table 1. Partitioning of Aldolization and 1,4-Reduction Pathways Depends Critically on the Use of Cationic Rh Complexes and Mild Basic Additives



catalyst	ligand	additive (mol %)	yield aldol (syn:anti)	yield 1,4-reduction
$Rh(PPh_3)_3Cl$			1% (99:1)	95%
$Rh(COD)_2OTf$	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%

and ketone partners,[19] (2) the intermolecular reductive coupling of 1,3-cyclohexadiene with α-keto aldehydes,[20] (3) the intermolecular reductive coupling of 1,3-enynes and 1,3-diynes with α-keto aldehydes,[21] and (4) the reductive cyclization of 1,6-diynes (Scheme 1).[22]

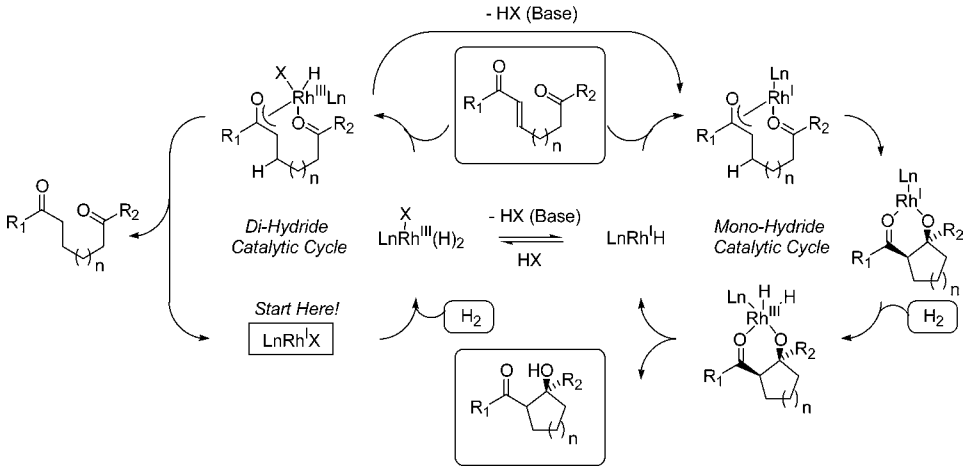
3. Catalytic Hydrogen-Mediated Reductive Aldol Condensation

Optimization studies pertaining to the Rh-catalyzed aldol cycloreduction under hydrogenation conditions support the bifurcated catalytic mechanism depicted in Scheme 2.[19a] Catalytic hydrogenation of the indicated enone−aldehyde using the neutral complex $Rh(PPh_3)_3Cl$ provides only trace quantities of the aldol product, along with substantial quantities of simple 1,4-reduction. In contrast, rhodium salts that embody increased cationic character, such as $Rh^I(COD)_2OTf$, provide nearly equal proportions of aldol and 1,4-reduction products. Finally, when $Rh^I(COD)_2OTf$ is used in conjunction with substoichiometric quantities of the mildly basic additive potassium acetate, the proportion of aldol product is increased such that simple 1,4-reduction manifolds are nearly fully suppressed (Table 1). A series of control experiments was performed. Exposure of the simple 1,4-reduction product to the reaction conditions does not result in aldolization. Conversely, reexposure of the aldol product to the reaction conditions does not result in retroaldolization. Finally, exposure of the substrate to standard reaction conditions in the *absence* of hydrogen does not afford products of Morita−Baylis−Hillman cyclization. The observed *syn*-diastereoselectivity suggests intermediacy of a *Z*-enolate and a Zimmerman−Traxler-type transition state.

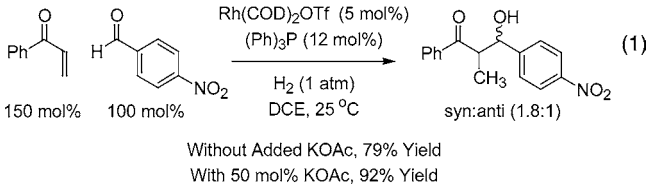
The pronounced effect of basic additives on partitioning of the aldolization and 1,4-reduction manifolds suggests enolate−hydrogen reductive elimination pathways are disabled through deprotonation of the (hydrido)metal intermediates $LnRh^{III}X(H)_2$ or (enolato)$Rh^{III}X(H)Ln$. Thus, as observed by Osborn and Schrock,[16] deprotonation changes the catalytic mechanism from a dihydride-based cycle to a monohydride-based cycle. In the former case, 1,4-reduction products would predominate, while in the latter case aldolization should be promoted (Scheme 3).

Competitive 1,4-reduction does not preclude intermolecular condensation. Hydrogenation of phenyl vinyl ketone with *p*-nitrobenzaldehyde requires only a slight excess of the enone. The addition of potassium acetate significantly increases the yield of aldol product, lending further credence to the notion that productive mono-

Scheme 3. Use of Elemental Hydrogen as Terminal Reductant for Catalytic Aldol Cycloreduction. Formal Heterolytic Activation of Hydrogen Mitigates Competitive 1,4-Reduction Manifolds by Enabling Monohydride Pathways

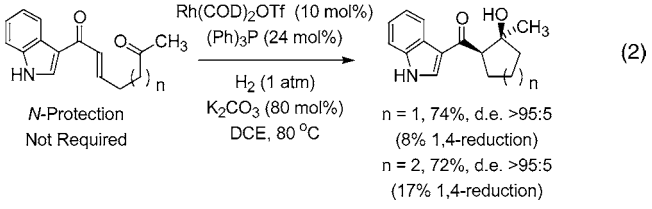


hydride pathways are assisted through the use of mild basic additives (eq 1).[19a]



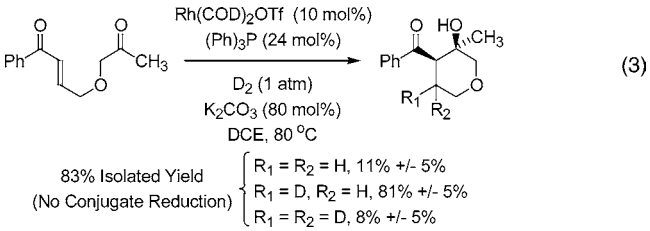
(1)

An especially challenging variant of the aldol reaction involves the use of ketones as electrophilic partners. Aldolizations onto ketone acceptors are inherently less exergonic than corresponding aldehyde additions. As aldolization may be driven by chelation,[23,24] intramolecular condensation to form a robust transition-metal aldolate should favorably bias the enolate−aldolate equilibria. Indeed, catalytic hydrogenation of keto−enone substrates results in formation of five- and six-membered ring aldol products with >95:5 *syn*-diastereoselectivity under exceptionally mild conditions.[19b] As demonstrated by the catalytic aldol cycloreduction of indole-substituted keto−enones, the low basicity of the transition-metal-complexed intermediates circumvents the need to protect acidic residues (eq 2).



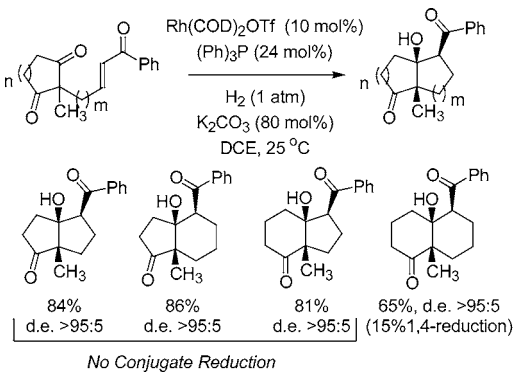
(2)

Reductive aldolization performed under an atmosphere of elemental deuterium results in the incorporation of deuterium at the β-position exclusively. In addition to monodeuterated material (81% composition), doubly-deuterated (8% composition) and nondeuterated materials (11% composition) are observed. These data suggest that hydrometalation is reversible in the case of keto−enone substrates. Consistent with the mechanism depicted in Scheme 3, deuterium is not incorporated at the α-position of the aldol product (eq 3).



(3)

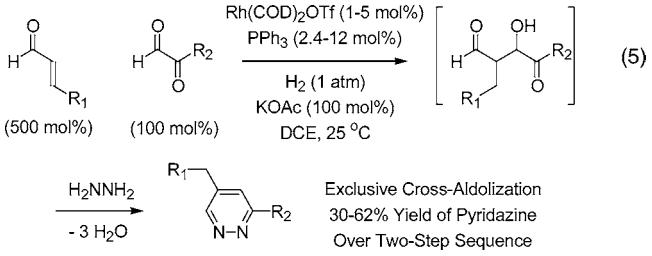
For the cycloreduction of keto−enones, competitive 1,4-reduction in response to reduced reactivity of the electrophilic partner is generally observed. Diones are more susceptible to addition in virtue of inductive effects and relief of dipole−dipole interactions. Accordingly, catalytic hydrogenation of dione-containing substrates affords the corresponding aldol products in good yield and with excellent *syn*-diastereoselectivity. Simple 1,4-reduction only accompanies formation of the strained *cis*-decalone ring system (eq 4).[19b]



(4)

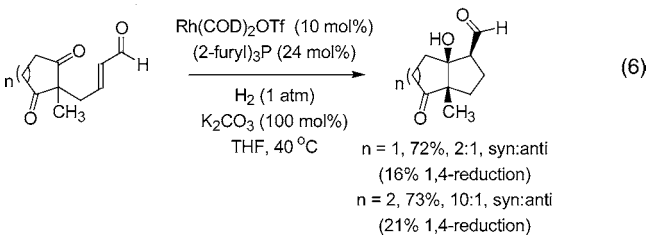
The use of metalloaldehyde enolates vis-à-vis aldol condensation typically suffers from polyaldolization, product dehydration, and competitive Tishchenko-type processes.[25] While catalytic cross-aldolization of aldehyde donors has been achieved through amine catalysis and the use of aldehyde-derived enol silanes,[26] the actual use of metalloaldehyde enolates in this capacity is unknown.

Under hydrogenation conditions, enals serve as metalloaldehyde enolate precursors, participating in cross-aldolization with α-keto aldehydes.[19c] The resulting β-hydroxy-γ-keto aldehydes are highly unstable but may be trapped in situ through the addition of methanolic hydrazine to afford 3,5-disubsituted pyridazines (eq 5).



(5)

The addition of metalloaldehyde enolates to ketones represents an even more elusive variant of the aldol reaction. A single stoichiometric variant of this transformation is known.[27] Under catalytic hydrogenation conditions, the intramolecular addition of metalloaldehyde enolates to ketones proceeds well, though aldolization is accompanied by competitive 1,4-reduction (eq 6).[19d]

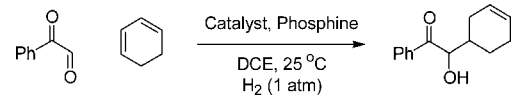


(6)

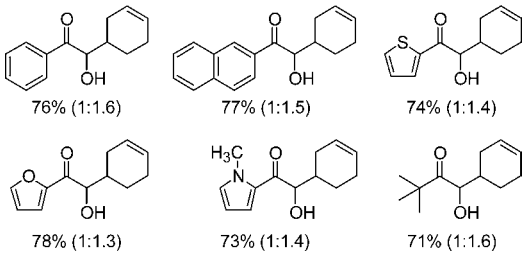
4. Catalytic Hydrogen-Mediated Reductive Coupling of Cyclohexadiene and α-Keto Aldehydes

The capability of enolate generation via catalytic enone hydrogenation suggests other π-unsaturated precursors may be subject to nucleophilic activation under hydrogenation conditions. Given the structural homology of enones and dienes, the reductive condensation of 1,3-cyclohexadiene and phenyl glyoxal was examined under hydrogenation conditions.[20] Optimization studies again reveal the requirement of cationic rhodium catalysts. Whereas hydrogenation of 1,3-cyclohexadiene and phenyl glyoxal using Wilkinson's catalyst provides products of simple reduction, a 61% yield of reductive coupling product is obtained using $Rh(COD)_2OTf$ with PPh_3 as ligand. When $(p\text{-}CH_3OPh)_3P$ is employed as ligand, the yield of coupling product increases to 77%. Related cationic complexes, such as $Rh(COD)_2BF_4$, exhibit similar efficiencies when used in conjunction with $(p\text{-}CH_3OPh)_3P$. Under optimized conditions, the catalytic reductive coupling of 1,3-cyclohexadiene with diverse α-keto aldehydes was examined. Aryl, heteroaryl, and aliphatic α-keto aldehydes provide reductive coupling products in good yield. Notably, basic additives are not required, perhaps due to scavenging of triflic acid by excess 1,3-cyclohexadiene (Table 2).

Table 2. Catalytic Reductive Condensation of 1,3-Cyclohexadiene with Alkyl, Aryl, and Heteroaryl α-Keto Aldehydes

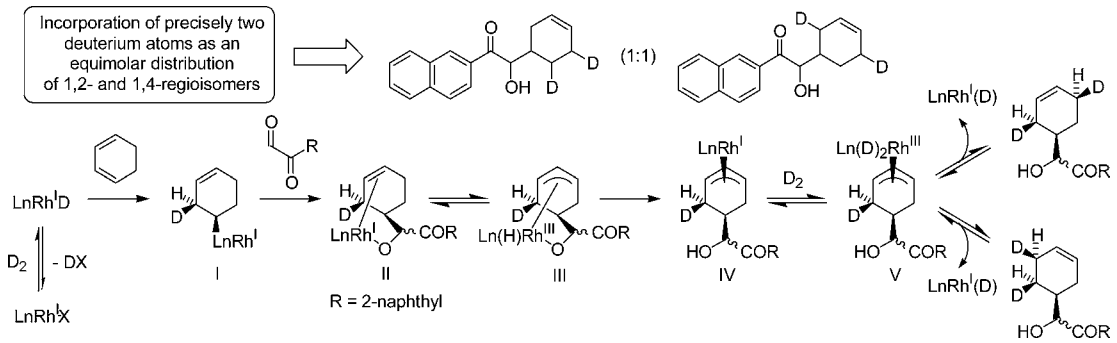


entry	catalyst (mol%)	ligand (mol%)	yield
1	$Rh(PPh_3)_3Cl$ (10%)		
2	$Rh(COD)_2OTf$ (10%)	Ph_3P (20%)	61%
3	$Rh(COD)_2OTf$ (10%)	$(p\text{-}CF_3Ph)_3P$ (20%)	24%
4	$Rh(COD)_2OTf$ (10%)	$(p\text{-}CH_3OPh)_3$ P (20%)	77%
5	$Rh(COD)_2BF_4$ (10%)	$(p\text{-}CH_3OPh)_3$ P (20%)	79%
6	$Rh(COD)_2OTf$ (5%)	$(p\text{-}CH_3OPh)_3$ P (10%)	76%



Deuterium-labeling studies reveal that the reductive coupling of 1,3-cyclohexadiene with α-keto aldehydes occurs through a mechanism very different than that postulated for related enone−aldehyde couplings. Reductive condensation of 1,3-cyclohexadiene with 2-naphthyl glyoxal under an atmosphere of D_2(g) results in the incorporation of precisely two deuterium atoms as an equimolar distribution of 1,2- and 1,4-regioisomers. A mechanism consistent with the results of deuterium

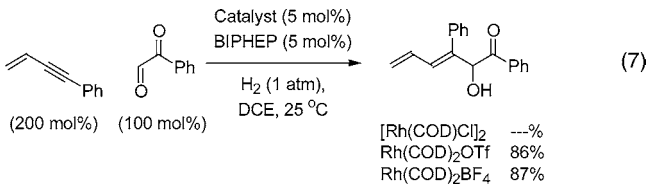
Scheme 4. Plausible Catalytic Mechanism for the Reductive Coupling of 1,3-Cyclohexadiene and 2-Naphthyl Glyoxal under an Atmosphere of D_2(g)



labeling is presented in Scheme 4. Diene deuteriometalation affords the homoallyl rhodium intermediate **I**, which is followed by glyoxal addition to afford rhodium alkoxide **II**. The indicated regiochemistry of C−C bond formation is consistent with that observed by Loh in the nickel-catalyzed reductive coupling of 1,3-cyclohexadiene with aldehydes.[10e] Additionally, as observed by Mori, the presence of excess 1,3-cyclohexadiene induces 1,4-regiochemistry in nickel-promoted diene−aldehyde cyclizations.[9b] Allylic C−H insertion gives the π-allyl **III**, which upon O−H reductive elimination gives intermediate **IV**. Similar allylic C−H insertions are observed in metal-catalyzed alkene isomerization.[28] Finally, oxidative addition of elemental deuterium, to give dideuteride **V**, followed by C−D reductive elimination completes the catalytic cycle. The intermediacy of π-allyls **III**−**V** is required to account for the incorporation of precisely two deuterium atoms as an equimolar distribution of 1,2- and 1,4-regioisomers.

5. Catalytic Hydrogen-Mediated Reductive Coupling of 1,3-Enynes and 1,3-Diynes with α-Keto Aldehydes

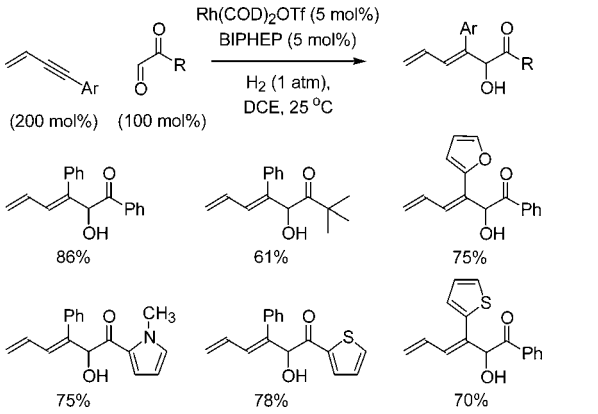
Pursuant to the design of efficient conditions for the catalytic reductive coupling of 1,3-cyclohexadiene and α-keto aldehydes, related 1,3-enyne-α-keto aldehyde condensations were explored. Conditions optimized for the aforementioned diene-α-keto aldehyde couplings, which employ Ph_3P as ligand, were ineffective at promoting the condensation of 1-phenyl but-3-en-1-yne and phenyl glyoxal. Under otherwise identical conditions, use of bidentate ligands such as BIPHEP provide the products of reductive coupling in excellent yield. Again, reductive coupling fails upon use of neutral Rh(I) sources, such as $[Rh(COD)Cl]_2$ (eq 7).



(7)

Under optimized conditions, the 1,3-enyne-α-keto aldehyde condensation proceeds smoothly to afford diene-containing products as single regio- and stereoisomers. Products of over-reduction are not observed (Table 3).

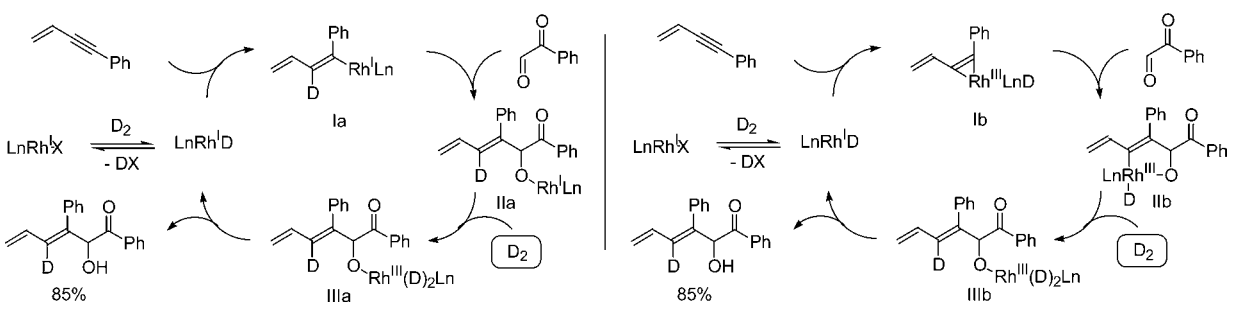
Table 3. Catalytic reductive condensation of 1,3-Enynes with Alkyl, Aryl, and Heteroaryl α-Keto Aldehydes



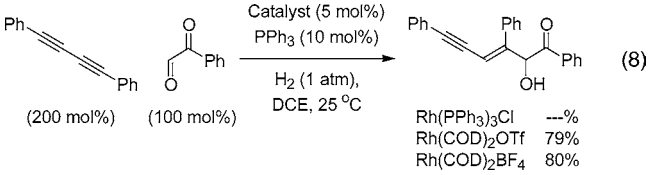
Catalytic reductive condensation of 1-phenyl but-3-en-1-yne with phenyl glyoxal conducted under an atmosphere of D_2(g) provides the monodeuterated product in 85% yield. Two catalytic mechanisms are consistent with this result: (a) direct alkyne deuterio-metalation to afford the vinyl rhodium intermediate **Ia** followed by carbonyl addition and hydrogenolytic cleavage of the resulting Rh(I)−alkoxide **IIa** or (b) nucleophilic activation of the alkyne through coordination of low-valent rhodium in accordance with the Dewar−Chatt−Duncanson model,[29] followed by carbonyl insertion, C−H reductive elimination of the resulting (hydrido)Rh(III)−oxametallocyclopentene **IIb**, and, finally, hydrogenolytic cleavage of Rh(I) from the bound organic fragment. In the former case, C−H bond formation precedes C−C bond formation. In the latter case, the converse is true. At this stage, the carbonyl insertion mechanism, which may be viewed as an oxidative coupling of alkyne and aldehyde moieties, better accounts for the regiochemistry of reductive coupling (vide supra) and is favored on this basis (Scheme 5).

The ability to regioselectively condense 1,3-enynes and α-keto aldehydes under hydrogenation conditions without over-reduction of the diene products suggests the feasibility of condensing 1,3-diynes and α-keto aldehydes. Indeed, 1,3-diynes participate in highly regio- and stereoselective reductive couplings to aryl, heteroaryl, and aliphatic glyoxals under catalytic hydrogenation conditions.[21b] Unlike the corresponding reaction of 1,3-enynes, both mono- and bis(phosphines) may serve as ligands. As for all hydrogen-mediated C−C bond formations developed in

Scheme 5. Catalytic Reductive Condensation of 1-Phenyl but-3-en-1-yne with Phenyl Glyoxal Conducted under an Atmosphere of D_2(g). (Left) Proposed Hydrometallative Mechanism. (Right) Proposed Carbonyl Insertion Mechanism

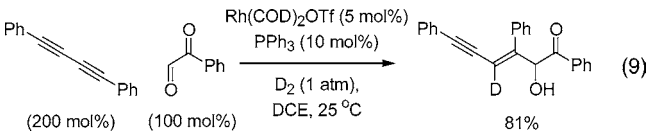


our lab, cationic Rh(I) catalysts are required. Remarkably, formation of the highly unsaturated 1,3-enyne products is not accompanied by over-reduction (eq 8).



(8)

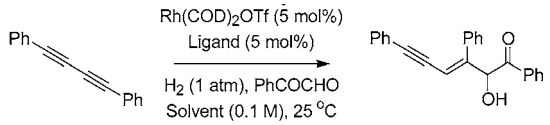
Again, to gain insight into the catalytic mechanism, reductive condensation was performed under an atmosphere of D_2. The indicated monodeuterated product is obtained in 81% isolated yield (eq 9). This result is consistent with the aforementioned catalytic mechanisms outlined in Scheme 5.



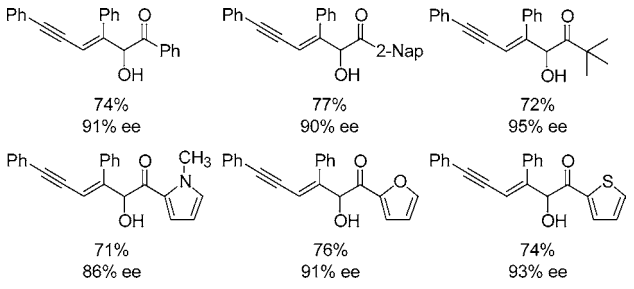
(9)

A highly enantioselective variant of this transformation is achieved through the use of the commercially available chiral bis(phosphine) ligand (*R*)-Cl,MeO-BIPHEP. Optimization studies pertaining to the enantioselective transformation reveal that high levels of asymmetric induction are critically dependent upon the dihedral angle of the diphenylphosphino moieties of the ligand. Under optimized conditions, condensation products are produced in 71−77% yield and 86−95% enantiomeric excess. Notably, highly enantioselective C−C bond formation is achieved at ambient temperature and pressure (Table 4).

Table 4. Enantioselective Catalytic Reductive Condensation of 1,3-Diynes with Alkyl, Aryl, and Heteroaryl α-Keto Aldehydes

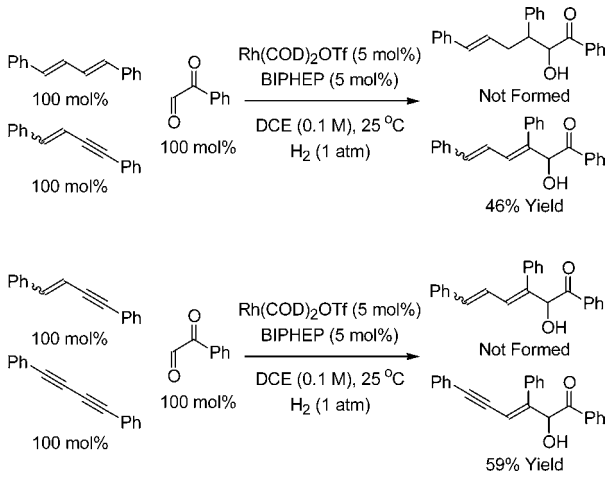


entry	ligand	solvent	yield	e.e.
1	(*R*)-BINAP	DCE	72%	47%
2	(*R*)-Phanepho s	DCE	79%	67%
3	(*R*)-Cl-OMe-BIPHEP	DCE	74%	76%
4	(*R*)-Cl-OMe-BIPHEP	EtOH	69%	80%
5	(*R*)-Cl-OMe-BIPHEP	THF	67%	82%
6	(*R*)-Cl-OMe-BIPHEP	PhH	74%	91%



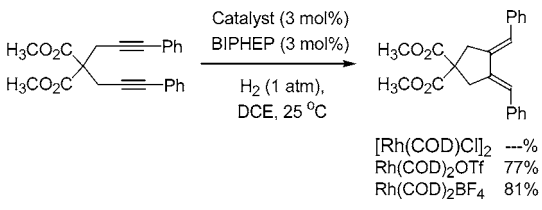
To gain insight into the origins of chemo- and regioselectivity observed for the intermolecular reductive coupling of 1,3-enynes and 1,3-diynes with α-keto aldehydes, a series of competition experiments were performed. Catalytic hydrogenation of phenyl glyoxal in the presence of equimolar quantities of 1,4-diphenylbutadiene and 1,4-diphenylbut-3-en-1-yne results in coupling to the more highly unsaturated enyne partner. Similarly, catalytic hydrogenation of phenyl glyoxal in the presence of equimolar quantities of 1,4-diphenylbut-3-en-1-yne and 1,4-diphenylbutadiyne results in coupling to the more highly unsaturated diyne partner. Chemoselective coupling to the more highly unsaturated pronucleophile suggests preferential coordination of the most π-acidic reacting partner by low-valent rhodium, as explained by the Dewar−Chatt−Duncanson model for alkyne coordination (Scheme 6).[29]

Scheme 6. Competition Experiments Reveal Coupling to the Strongest π-Acid



6. Catalytic Hydrogen-Mediated Reductive Cyclization of 1,6-Diynes

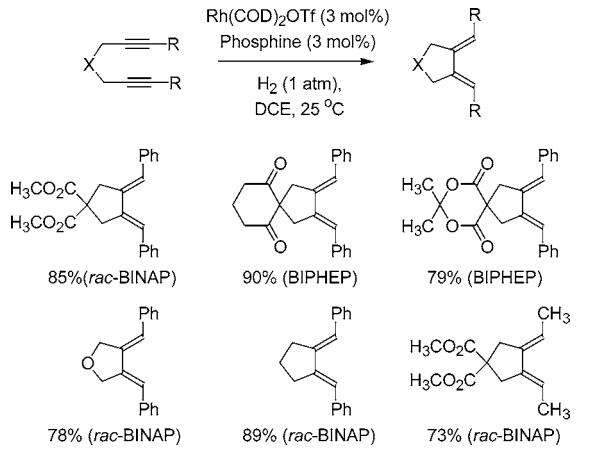
The catalytic C−C bond-forming hydrogenations described thus far operate through interception of hydrogenation intermediates by the addition or insertion of C−O π-bonds. Related transformations involving migratory insertion of C−C π-bonds are also feasible, as demonstrated by the hydrogen-mediated reductive cyclization of 1,6-diynes to afford 1,2-dialkylidenecycloalkane products.[22,30] Consistent with the requirements for heterolytic activation of hydrogen, cationic Rh(I) catalysts are required (eq 10).



(10)

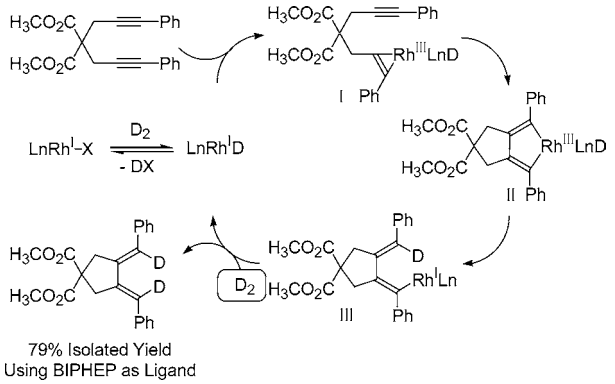
Under optimized conditions, reductive cyclization proceeds smoothly across a range of 1,6-diynes. Notably, conformationally predisposed substrates possessing geminal substitution in the tether are not required for efficient reductive cyclization (Table 5).

Table 5. Catalytic Reductive Cyclization of Assorted 1,6-Diynes



To further probe the mechanism of this transformation, reductive diyne cyclization was performed under an atmosphere of elemental deuterium. The reductive cyclization product, which incorporates two deuterium atoms, was obtained in 79% yield. These data are consistent with a catalytic mechanism involving alkyne insertion to a preexisting rhodium−alkyne complex **I** to afford a rhodacyclopentadiene intermediate **II**. The formation of this metallocyclic intermediate is equivalent to an oxidative cyclization of the diyne. Carbon−deuterium reductive elimination provides the indicated vinyl rhodium species **III**, which upon hydrogenolytic cleavage of the vinylic carbon−rhodium bond liberates the product of reductive cyclization along with LnRh(I)D to close the catalytic cycle (Scheme 7).

Scheme 7. Catalytic Mechanism for the Reductive Cyclization 1,6-Diynes Mediated by Deuterium



7. Conclusion

Since the discovery of catalytic hydrogenation over a century ago, the interception of hydrogenation intermediates has been restricted to processes involving migratory insertion of carbon monoxide. The present results suggest that low-valent rhodium monohydrides obtained through the heterolytic activation of hydrogen give rise to organometallic intermediates that are susceptible to capture through oxidative coupling via C−O π-insertion and C−C π-insertion. In this way, complex organic fragments may be condensed under mild conditions. Future studies will be devoted to expanding the scope of this new reaction type through the development of improved second-generation catalyst systems with the goal of achieving the catalytic coupling of unactivated alkenes and alkynes to simple carbonyl partners.

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