Catalytic Hydrogen-Mediated Cross-Coupling of Enones and Carbonyl Compounds: Aldol Condensation by Hydrogenation

Hye-Young Jang[a] and Michael J. Krische*[a]

Keywords: Hydrogenation / Rhodium catalysis / Aldol reaction / Cross-coupling / Transition metal enolate

Catalytic hydrogenation of enones and enals in the presence of aldehyde and ketone partners results in the formation of aldol products. A key feature of such hydrogen-mediated C–C bond formations relates to the heterolytic activation of elemental hydrogen by cationic rhodium(I) complexes, that enables monohydride-based catalytic cycles for which direct alkyl-hydrogen reductive elimination pathways are disabled. Here, a concise overview of catalytic hydrogen-mediated aldol condensation is presented.

1. Introduction

Although catalytic hydrogenation has been practiced routinely for over a century,[1−3] hydrogen-mediated C−C bond formation is presently restricted to catalytic processes involving migratory insertion of carbon monoxide, for example alkene hydroformylation and related Fischer−Tropsch-type reactions.[4,5] With the ultimate objective of developing catalytic hydrogenation as a general cross-coupling methodology, the capture of hydrogenation intermediates has been the topic of intensive investigation in our group. These studies have led to the discovery of several hydrogen-mediated reductive couplings: (1) the intra- and intermolecular reductive coupling of enone and enal pronucleophiles with aldehyde and ketone partners,[6] (2) the intermolecular reductive coupling of 1,3-cyclohexadiene with α-oxo aldehydes,[7] (3) the intermolecular reductive coupling of 1,3-enynes and 1,3-diynes with α-oxo aldehydes,[8] and (4) the reductive cyclization of 1,6-diynes and 1,6-enynes (Scheme 1).[9]

Here, an overview of catalytic hydrogen-mediated enone-aldehyde and enone-ketone couplings is presented. Related studies pertaining to the catalytic hydrometallative reductive coupling of alkenes,[10] alkynes,[11] enones,[6,12] and dienes[13,14] to carbonyl partners with silanes, alanes, and boranes as terminal reductants is not discussed. These results represent the first examples of enolate generation by enone hydrogenation, as well as the first use of elemental

Hye-Young Jang received her B.S. and M. S. degrees in Chemistry from Seoul National University and is currently a doctoral candidate at the University of Texas at Austin.

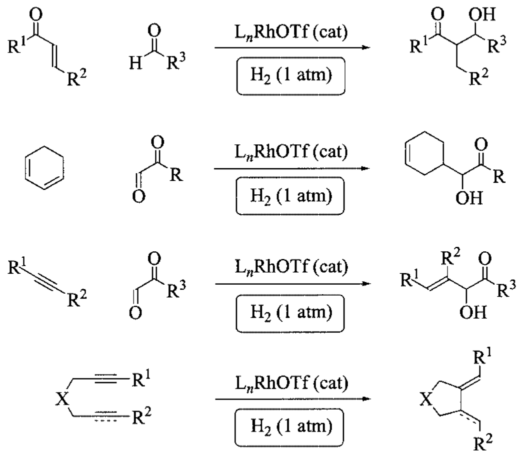
Michael J. Krische received a B.S. in Chemistry from the University of California at Berkeley under the tutelage of Professor H. Rapoport as a Presidents Undergraduate Fellow, whereupon he was granted a Fulbright Fellowship for study in Europe. Dr. Krische received his Ph.D. in Chemistry from Stanford University for studies performed with Professor B. M. Trost as a Peter Veatch Fellow, and then pursued post-doctoral studies with Jean-Marie Lehn at the Université Louis Pasteur (Strasbourg) as an NIH Post-Doctoral Fellow where he was granted the title of Maître de Conference, Collège de France. Dr. Krische joined the faculty at the University of Texas at Austin in Fall 1999, where he has established a program of research combining the topics 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).

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

---

[a] Department of Chemistry and Biochemistry, University of Texas at Austin,
1 University Station A5300, Austin, Texas 78712, USA
Fax: (internat.) + 1-512-471-6835
E-mail: mkrische@mail.utexas.edu

DOI: 10.1002/ejoc.200400270

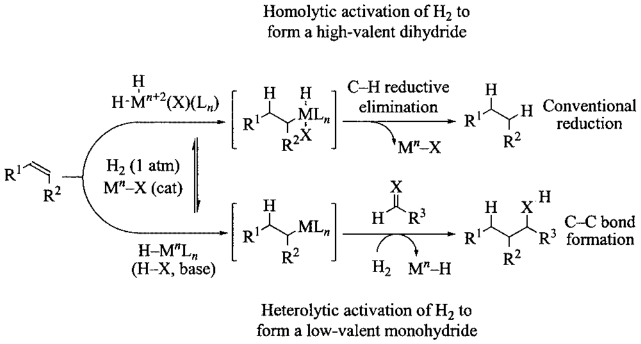


Scheme 1. New catalytic hydrogen-mediated C−C bond formations

hydrogen as a terminal reductant in metal-catalyzed cross coupling (that do not involve insertion of carbon monoxide).

2. Heterolytic Activation of Hydrogen − The Key to Atom-Economical Cross-Coupling

It was recognized that use of elemental hydrogen as a terminal reductant in catalytic C−C bond formation would enable completely atom-economical transformations.[15] However, the use of hydrogen in this capacity would require that conventional hydrogenation pathways be rendered inoperative. It was speculated that such "non-C−C bond-forming" hydrogenation manifolds would be attenuated through heterolytic activation of elemental hydrogen (H_2 + M−X → M−H + HX),[16] enabling monohydride-based catalytic cycles for which direct alkyl-hydrogen reductive elimination pathways are disabled. Here, the lifetime of the organometallic intermediates initially obtained upon hydrometallation should be extended, which, in turn, should facilitate their capture (Scheme 2).



Scheme 2. Disabling of direct alkyl-hydrogen reductive elimination pathways through heterolytic activation of hydrogen

The partitioning of homolytic and heterolytic hydrogen activation pathways using rhodium-based catalysts is especially well studied. In general, homolytic activation of hydrogen is achieved through the use of neutral Rh^I complexes (for example Wilkinson's catalyst),[17,18] while heterolytic activation of hydrogen is achieved through the use of cationic Rh^I complexes in conjunction with basic additives.[19] The ability of cationic rhodium complexes to promote heterolytic activation of hydrogen is due to the enhanced acidity of the dihydrides, that result upon oxidative addition.[20] Thus, heterolytic activation of hydrogen is believed to occur through a two-stage process involving hydrogen oxidative addition, followed by base-assisted H−X reductive elimination.[21] This latter event is likely to proceed through deprotonation of the cationic dihydridorhodium intermediate (Figure 1).

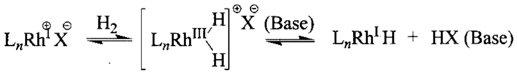
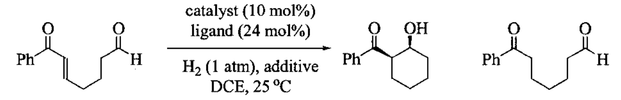


Figure 1. Heterolytic activation of hydrogen

3. Catalytic Hydrogen-Mediated Reductive Aldol Condensation

This mechanistic analysis is supported by optimization studies that involve the aldol cycloreduction of the indicated enone-aldehyde under hydrogenation conditions. Here, catalytic hydrogenation with the neutral rhodium complex [$Rh(PPh_3)_3Cl$], i.e. Wilkinson's catalyst, provides only trace quantities of the aldol product, along with substantial quantities of simple 1,4-reduction products. However, rhodium salts that have 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 products are almost completely suppressed (Table 1).

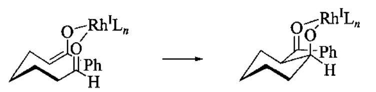
Table 1. Partitioning of aldolization and 1,4-reduction pathways[a]



Catalyst	Ligand	Additive (mol%)	Yield aldol (*syn*/*anti*)	Yield 1,4-reduction
$Rh(PPh_3)_3Cl$	–	–	1% (99:1)	95%
$Rh(COD)_2OTf$	Ph_3P	–	21% (99:1)	25%
$Rh(COD)_2OTf$	Ph_3P	KOAc (30%)	59% (58:1)	21%
$Rh(COD)_2OTf$	(p-$F_3CC_6H_4)_3P$	–	57% (14:1)	22%
$Rh(COD)_2OTf$	**(p-$F_3CC_6H_4)_3P$**	**KOAc (30%)**	**89% (10:1)**	**0.1%**

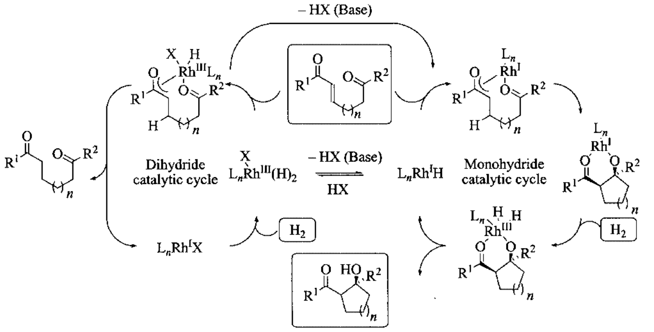
[a]As product ratios were found to vary with surface area to volume ratio of the reaction mixture, all transformations were conducted on a 1.48-mmol scale in 50-mL round-bottomed flasks.

Stereochemical model



(*Z*)-enolate, Zimmerman–Traxler-type transition state

The pronounced effect of basic additives on the partitioning of the aldolization and 1,4-reduction routes is consistent with the hypothesis that enolate-hydrogen reductive elimination pathways are disabled through deprotonation of the hydridometal intermediates, [LnRh^{III}X(H)$_2$] or [(enolato)Rh^{III}X(H)Ln]. Thus, as observed by Osborn,[19] deprotonation changes the catalytic mechanism from a dihydride-based cycle to a monohydride-based cycle. In the former case, 1,4-reduction products are expected to predominate, while in the latter case aldolization should be promoted due to the absence of (alkyl)(hydrido)metal intermediates (Scheme 3). To corroborate the proposed mechanism, a series of control experiments were performed. Exposure of the simple 1,4-reduction product to the reaction conditions does not lead to aldolization. Conversely, re-exposure of the aldol product to the reaction conditions does not lead to retro-aldolization. Finally, exposure of the substrate to standard reaction conditions in the absence of hydrogen does not afford Morita–Baylis–Hillman cyclization products.

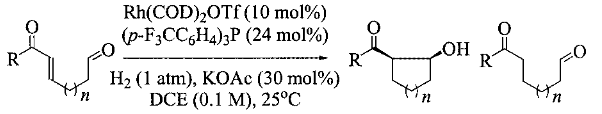


Scheme 3. Proposed catalytic mechanism for hydrogen-mediated reductive aldol condensation

These conditions proved to be general for the cycloreduction of aromatic, heteroaromatic, and aliphatic enone substrates to form five- and six-membered ring products. The cycloreduction of aromatic enone substrates yields *syn*-aldol products with good levels of diastereoselectivity. The observed *syn* diastereoselectivity suggests intermediacy of a (*Z*)-enolate and a Zimmerman–Traxler-type transition state. These results are consistent with the generally accepted notion that large acyl substituents preferentially give rise to (*Z*)-enolates due to $A_{1,3}$-strain (Table 1). Interestingly, α,β-unsaturated esters exclusively afford products of simple conjugate reduction, suggesting that for more electron-rich Rh^I-enolate intermediates, hydrogenolytic cleavage is faster than aldolization (Table 2).

Due to competitive conjugate reduction, the outcome of related intermolecular condensations is uncertain. To assess the feasibility of an intermolecular variant, the hydrogen-mediated reductive condensation of phenyl vinyl ketone and *p*-nitrobenzaldehyde was explored. Remarkably, addition of 10 mol % catalyst and 50 mol % KOAc to an equimolar solution of enone/aldehyde in dichloroethane (0.5 M) under 1 atm of hydrogen affords a 53% yield of the aldol product (Table 3, Entry 1). As competitive enone conjugate reduction accounts for the mass balance, the reaction was repeated using 1.5 equiv. of the enone; here, a 75% yield of the aldol product is obtained (Table 3, Entry 2). Under more dilute conditions (0.1 M), the yield increases to 85% (Table 3, Entry 3). When the amount of catalyst is reduced to 5 mol-%, the yield increases further to 92% (Table 3, Entry 4). Notably, the addition of potassium acetate significantly increases the yield of the aldol product, lending further credence to the notion that productive monohydride pathways are assisted through the use of mild basic additives (Table 3).

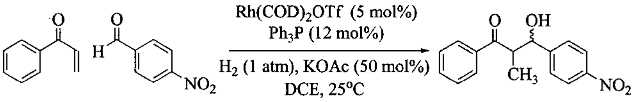
Table 2. Catalytic hydrogen-mediated aldol cycloreduction of enone-aldehydes[a]



Substrate	Aldol (*syn*/*anti*)	1,4-Reduction
$n = 2$, R = Ph	89% (10:1)	0.1%
$n = 2$, R = *p*-MeOC$_6$H$_4$	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 = Me	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 a 1.48-mmol scale in 50-mL round-bottomed flasks.

Table 3. Catalytic intermolecular hydrogen-mediated reductive aldol condensation[a]



Entry	Enone (mol%)	Catalyst (mol%)	Conc. (mol/L)	KOAc (mol%)	Yield
1	100	10	0.5	50	53%
2	150	10	0.5	50	75%
3	150	10	0.1	50	85%
4	**150**	**5**	**0.1**	**50**	**92%**
5	150	5	0.1	–	79%

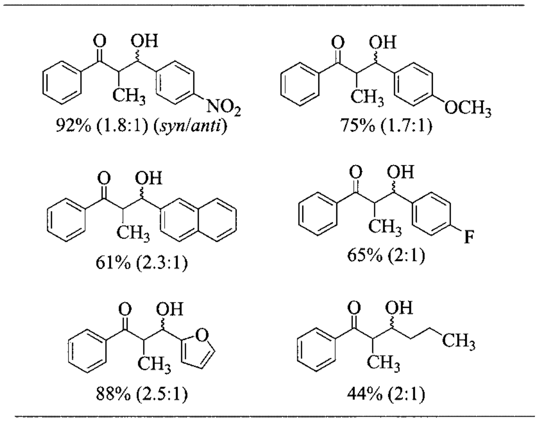
[a]As product ratios were found to vary with surface area to volume ratio of the reaction mixture, all transformations were conducted on a 1.48-mmol scale in 50-mL round-bottomed flasks.

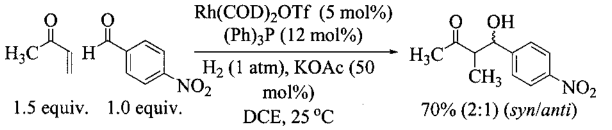
Under the optimum conditions identified for condensation of phenyl vinyl ketone and *p*-nitrobenzaldehyde, condensation with diverse electrophilic partners was explored. Aromatic and heteroaromatic aldehydes give good yields of the aldol product. Aliphatic aldehydes participate in the reaction, but their reduced electrophilicity exacerbates the problem of competitive conjugate reduction, leading to somewhat diminished yields (Table 4).

The response of the reaction to different nucleophilic partners was also briefly explored. Whereas ethyl acrylate exclusively provides 1,4-reduction products, methyl vinyl ketone reacts with *p*-nitrobenzaldehyde to give a 70% yield of the aldol product (Scheme 4).

An especially challenging variation of the aldol reaction involves the use of ketones as electrophilic partners. Aldolizations involving ketone acceptors are inherently less exergonic than corresponding aldehyde additions. As aldoliz-

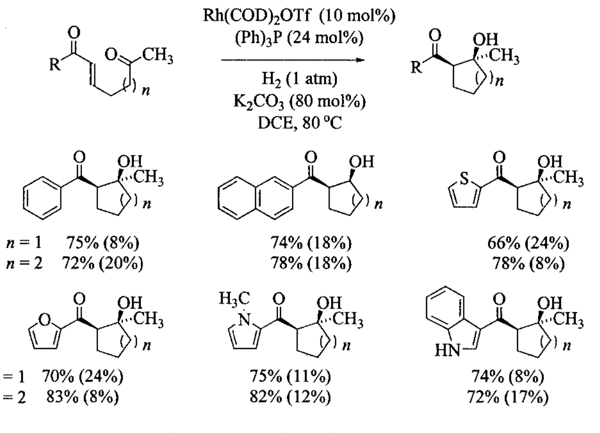
Table 4. Intermolecular catalytic hydrogen-mediated reductive aldol condensation of phenyl vinyl ketone





Scheme 4. Intermolecular catalytic hydrogen-mediated reductive aldol condensation of phenyl vinyl ketone

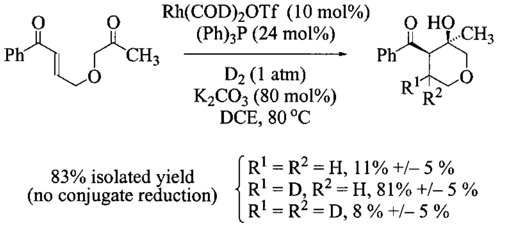
ation is driven by chelation,[22,23] intramolecular condensation to form a robust transition-metal aldolate should favorably bias the enolate-aldolate equilibria. Indeed, catalytic hydrogenation of keto-enone substrates results in formation of five- and six-membered ring aldol products with > 95:5 *syn* diastereoselectivity under exceptionally mild conditions.[6b] 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 (Scheme 5).



[a]As product ratios were found to vary with surface/volume ratio of the reaction mixture, all transformations were conducted on 1.48-mmol scale in 13 x 100 mm sealed test tubes. [b]Yields of 1,4-reduction products are indicated in parentheses.

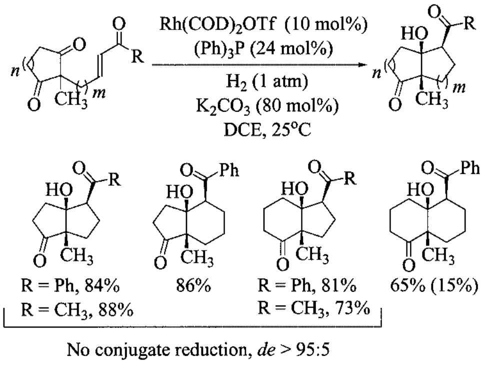
Scheme 5. Catalytic hydrogen-mediated reductive aldol condensation of keto-enones[a,b]

To gain further insight into the reaction mechanism, reductive aldolization of the indicated oxygen-tethered keto-enone was performed using elemental deuterium. Deuterium incorporation occurs exclusively at the β-position. In addition to monodeuterated material (81% composition), doubly deuterated (8% composition) and non-deuterated materials (11% composition) are observed. These data suggest that hydrometallation 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 (Scheme 6).



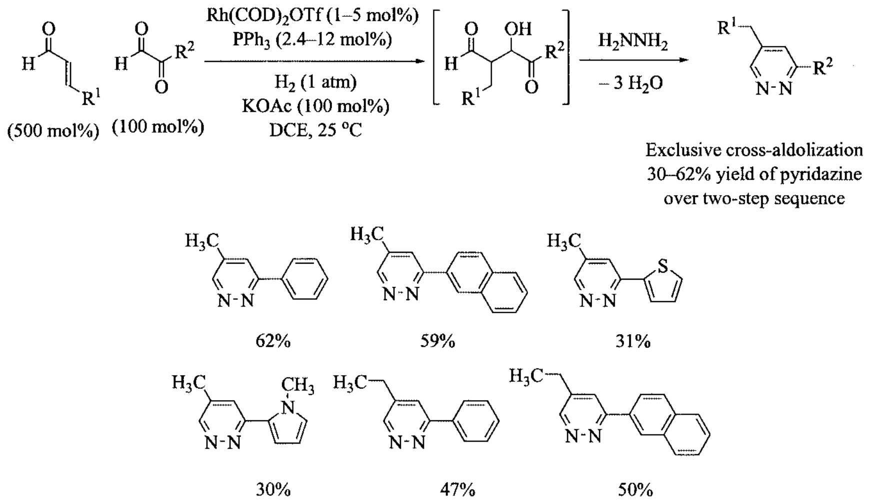
Scheme 6. Catalytic aldol cycloreduction under 1 atm to $D_2(g)$

For the cycloreduction of keto-enones, the competitive 1,4-reduction pathway, in response to the reduced reactivity of the electrophilic partner, is generally observed. Diones are more susceptible to addition due to inductive effects and the relief of dipole−dipole interactions. 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 (Scheme 7).[6b]



Scheme 7. Catalytic hydrogen-mediated reductive aldol condensation of enone-diones

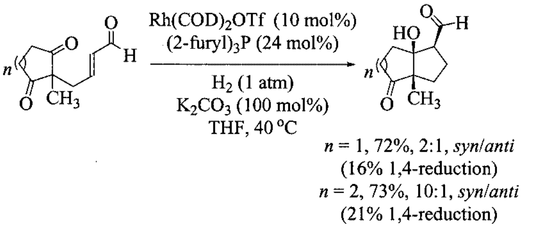
The use of metallo-aldehyde enolate nucleophiles in aldol condensation typically leads to polyaldolization, product dehydration, and competitive Tishchenko-type processes.[24] While catalytic cross-aldolization of aldehyde donors has been achieved through amine catalysis and with the use of aldehyde-derived silyl enol ethers,[25] the actual use of metallo-aldehyde enolates in this respect is unknown. Under hydrogenation conditions, enals serve as metallo-aldehyde enolate precursors and participate in cross-aldolization with α-oxo aldehydes.[6c] The resulting β-hydroxy-γ-



Scheme 8. Catalytic intermolecular addition of metallo-aldehyde enolates to α-oxo aldehydes

oxo aldehydes are highly unstable, but may be trapped in situ through the addition of methanolic hydrazine to afford 3,5-disubstituted pyridazines (Scheme 8).

The addition of metallo-aldehyde enolates to ketones represents an even more challenging variation of the aldol reaction. To the best of our knowledge, a single stoichiometric variation of this transformation is reported.[26] Under catalytic hydrogenation conditions, the intramolecular addition of metallo-aldehyde enolates to ketones proceeds well, although aldolization is accompanied by competitive 1,4-reduction.[6d] For such aldol reactions, a favorable enolate-aldolate equilibrium is presumably driven by the formation of a robust Rh−aldolate (Scheme 9).[23]



Scheme 9. Catalytic addition of metallo-aldehyde enolates to ketones

4. 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 rhodium monohydrides obtained through the heterolytic activation of hydrogen give rise to organometallic intermediates that can be captured through carbonyl addition, allowing a range of complex organic fragments to 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.

Acknowledgments

We acknowledge the Robert A. Welch Foundation (F-1466), the Alfred P. Sloan Foundation, the Camille and Henry Dreyfus Foundation, Eli Lilly and the UT Austin Center for Materials Chemistry (CMC) for partial support of this research.

---

[1] For the first example of catalytic homogeneous hydrogenation, see: M. Calvin, *Trans. Faraday Soc.* **1938**, *34*, 1181−1191.

[2] For early examples of catalytic heterogeneous hydrogenation, see: [2a] O. Loew, *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 289−290. [2b] P. Sabatier, J.-B. Senderens, *C. R. Acad. Sci. Paris* **1897**, *124*, 1358−1361.

[3] For the first practical heterogeneous catalyst system for hydrogenation at ambient temperature, see: V. Voorhees, R. Adams, *J. Am. Chem. Soc.* **1922**, *44*, 1397−1405.

[4] For recent reviews on alkene hydroformylation, see: [4a] B. Breit, *Acc. Chem. Res.* **2003**, *36*, 264−275. [4b] B. Breit, W. Seiche, *Synthesis* **2001**, 1−36.

[5] For reviews on the Fischer−Tropsch reaction, see: [5a] W. A. Herrmann, *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 117−130. [5b] C.-K. Rofer-Depoorter, *Chem. Rev.* **1981**, *81*, 447−474.

[6] [6a] H.-Y. Jang, R. R. Huddleston, M. J. Krische, *J. Am. Chem. Soc.* **2002**, *124*, 15156−15157. [6b] R. R. Huddleston, M. J. Krische, *Org. Lett.* **2003**, *5*, 1143−1146. [6c] G. A. Marriner, S. A. Garner, H.-Y. Jang, M. J. Krische, *J. Org. Chem.* **2004**, *69*, 1380−1382. [6d] P. K. Koech, M. J. Krische, *Org. Lett.* **2004**, *6*, 691−694.

[7] H.-Y. Jang, R. R. Huddleston, M. J. Krische, *Angew. Chem. Int. Ed.* **2003**, *42*, 4074−4077.

[8] [8a] H.-Y. Jang, R. R. Huddleston, M. J. Krische, *J. Am. Chem. Soc.* **2004**, *126*, 4664. [8b] R. R. Huddleston, H.-Y. Jang, M. J. Krische, *J. Am. Chem. Soc.* **2003**, *125*, 11488−11489.

[9] H.-Y. Jang, M. J. Krische, *J. Am. Chem. Soc.*, in press.

[10] For use of alkenes as nucleophilic partners in catalytic reductive couplings, see: [10a] N. M. Kablaoui, S. L. Buchwald, *J. Am. Chem. Soc.* **1995**, *117*, 6785−6786. [10b] W. E. Crowe, M. J. Rachita, *J. Am. Chem. Soc.* **1995**, *117*, 6787−6788. [10c] N. M. Kablaoui, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 3182−3191.

[11] For use of alkynes as nucleophilic partners in catalytic hydro-

metallative reductive couplings, see: [11a] X. Q. Tang, J. Montgomery, *J. Am. Chem. Soc.* **1999**, *121*, 6098–6099. [11b] W.-S. Huang, J. Chen, T. F. Jamison, *Org. Lett.* **2000**, *2*, 4221–4223. [11c] E. A. Colby, T. F. Jamison, *J. Org. Chem.* **2003**, *68*, 156–166. [11d] K. M. Miller, W.-S. Huang, T. F. Jamison, *J. Am. Chem. Soc.* **2003**, *125*, 3442–3443. [11e] K. Takai, S. Sakamoto, T. Isshiki, *Org. Lett.* **2003**, *5*, 653–655. [11f] G. M. Mahandru, G. Liu, J. Montgomery, *J. Am. Chem. Soc.* **2004**, *126*, 3698–3699. [11g] K. M. Miller, T. Luanphaisarnnont, C. Molinaro, T. F. Jamison, *J. Am. Chem. Soc.* **2004**, *126*, 4130–4131.

[12] For use of enones as nucleophilic partners in catalytic reductive couplings, see: [12a] A. Revis, T. K. Hilty, *Tetrahedron Lett.* **1987**, *28*, 4809–4812. [12b] S. Isayama, T. Mukaiyama, *Chem. Lett.* **1989**, 2005–2008. [12c] I. Matsuda, K. Takahashi, S. Sato, *Tetrahedron Lett.* **1990**, *31*, 5331–5334. [12d] S. Kiyooka, A. Shimizu, S. Torii, *Tetrahedron Lett.* **1998**, *39*, 5237–5238. [12e] T. Ooi, K. Doda, D. Sakai, K. Maruoka, *Tetrahedron Lett.* **1999**, *40*, 2133–2136. [12f] S. J. Taylor, J. P. Morken, *J. Am. Chem. Soc.* **1999**, *121*, 12202–12203. [12g] S. J. Taylor, M. O. Duffey, J. P. Morken,, *J. Am. Chem. Soc.* **2000**, *122*, 4528–4529. [12h] C.-X. Zhao, M. O. Duffey, S. J. Taylor, J. P. Morken, *Org. Lett.* **2001**, *3*, 1829–1831. [12i] T.-G. Baik, A. L. Luis, L.-C. Wang, M. J. Krische, *J. Am. Chem. Soc.* **2001**, *123*, 5112–5113. [12j] D. Emiabata-Smith, A. McKillop, C. Mills, W. B. Motherwell, A. J. Whitehead, *Synlett* **2001**, 1302–1304. [12k] L.-C. Wang, H.-Y. Jang, V. Lynch, M. J. Krische, *J. Am. Chem. Soc.* **2002**, *124*, 9448–9453. [12l] R. R. Huddleston, M. J. Krische, *J. Org. Chem.* **2003**, *68*, 11–14. [12m] M. Freira, A. J. Whitehead, D. A. Tocher, W. B. Motherwell, *Tetrahedron* **2004**, *60*, 2673–2692.

[13] For use of dienes as nucleophilic partners in intramolecular catalytic reductive couplings, see: [13a] Y. Sato, M. Takimoto, K. Hayashi, T. Katsuhara, K. Tagaki, M. Mori, *J. Am. Chem. Soc.* **1994**, *116*, 9771–9772. [13b] Y. Sato, Y. Takimoto, M. Mori, *Tetrahedron Lett.* **1996**, *37*, 887–890. [13c] Y. Sato, T. Takanashi, M. Hoshiba, M. Mori, *Tetrahedron Lett.* **1998**, *39*, 5579–5582. [13d] Y. Sato, N. Saito, M. Mori, *J. Am. Chem. Soc.* **2000**, *122*, 2371–2372. [13e] K. Shibata, M. Kimura, M. Shimizu, Y. Tamaru, *Org. Lett.* **2001**, *3*, 2181–2183.

[14] For use of dienes as nucleophilic partners in intermolecular catalytic reductive couplings, see: [14a] M. Kimura, A. Ezoe, K. Shibata, Y. Tamaru, *J. Am. Chem. Soc.* **1998**, *120*, 4033–4034. [14b] M. Kimura, H. Fujimatsu, A. Ezoe, K. Shibata, M. Shimizu, S. Matsumoto, Y. Tamaru, *Angew. Chem. Int. Ed.* **1999**, *38*, 397–400. [14c] M. Kimura, K. Shibata, Y. Koudahashi, Y. Tamaru, *Tetrahedron Lett.* **2000**, *41*, 6789–6793. [14d] M. Kimura, A. Ezoe, S. Tanaka, Y. Tamaru, *Angew. Chem. Int. Ed.* **2001**, *40*, 3600–3602. [14e] T.-P. Loh, H.-Y. Song, Y. Zhou, *Org. Lett.* **2002**, *4*, 2715–2117.

[15] For reviews on atom economy, see: [15a] B. M. Trost, *Science* **1991**, *254*, 1471–1477. [15b] B. M. Trost, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259–281.

[16] For reviews on the heterolytic activation of elemental hydrogen, see: [16a] P. J. Brothers, *Prog. Inorg. Chem.* **1981**, *28*, 1–61. [16b] G. Jeske, H. Lauke, H. Mauermann, H. Schumann, T. J. Marks, *J. Am. Chem. Soc.* **1985**, *107*, 8111–8118.

[17] [17a] C. A. Tolman, P. Z. Meakin, D. L. Lindner, J. P. Jesson, *J. Am. Chem. Soc.* **1974**, *96*, 2762–2774. [17b] J. Halpern, T. Okamoto, A. Zakhariev, *J. Mol. Catal.* **1977**, *2*, 65–68.

[18] For a review, see: L. Marko, *Pure Appl. Chem.* **1979**, *51*, 2211–2224.

[19] Monohydride formation by deprotonation of a dihydride intermediate is known for cationic Rh complexes: [19a] R. R. Schrock, J. A. Osborn, *J. Am. Chem. Soc.* **1976**, *98*, 2134–2143. [19b] R. R. Schrock, J. A. Osborn, *J. Am. Chem. Soc.* **1976**, *98*, 2143–2147. [19c] R. R. Schrock, J. A. Osborn, *J. Am. Chem. Soc.* **1976**, *98*, 4450–4455.

[20] For a review on the acidity of metal hydrides, see: J. R. Norton, in *Transition Metal Hydrides* (Ed.: A. Dedieu), VCH, New York, **1992**, p. 309–359.

[21] Direct heterolytic activation of hydrogen by $[RhCl(CO)(PPh_3)_2]$ has been suggested, but likely involves an intermediate dihydride: D. Evans, J. A. Osborn, G. Wilkinson, *J. Chem. Soc., A* **1968**, 3133–3142.

[22] E. M. Arnett, F. J. Fisher, M.A. Nichols, A. A. Ribeiro, *J. Am. Chem. Soc.* **1989**, *111*, 748–749.

[23] The failure of tris(dialkylamino)sulfonium enolates to react with aldehydes is attributed to unfavorable enolate-aldolate equilibria: [23a] R. Noyori, J. Sakata, M. Nishizawa, *J. Am. Chem. Soc.* **1980**, *102*, 1223–1225. [23b] R. Noyori, I. Nishida, J. Sakata, *J. Am. Chem. Soc.* **1981**, *103*, 2106–2108. [23c] R. Noyori, I. Nishida, J. Sakata, *J. Am. Chem. Soc.* **1983**, *105*, 1598–1608.

[24] [24a] C. H. Heathcock, in *Comprehensive Organic Synthesis: Additions to C–X Bonds, Part 2* (Eds.: B. M. Trost, I. Fleming, C. H. Heathcock), Pergamon Press, New York, **1991**, p. 181–238. [24b]B. Alcaide, P. Almendros, *Angew. Chem. Int. Ed.* **2003**, *42*, 858–860.

[25] [25a] S. Denmark, S. K. Ghosh, *Angew. Chem. Int. Ed.* **2001**, *40*, 4759–4762. [25b] A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799. [25c] C. Pidathala, L. Hoang, N. Vignola, B. List, *Angew. Chem. Int. Ed.* **2003**, *42*, 2785–2788.

[26] A method for the stoichiometric addition of metallo-aldehyde enolates to ketones has recently been reported: K. Yachi, H. Shinokubo, K. Oshima, *J. Am. Chem. Soc.* **1999**, *121*, 9465–9466.

Received April 20, 2004
Early View Article
Published Online July 6, 2004