J|A|C|S
COMMUNICATIONS

Published on Web 11/28/2002

Reductive Generation of Enolates from Enones Using Elemental Hydrogen: Catalytic C−C Bond Formation under Hydrogenative Conditions

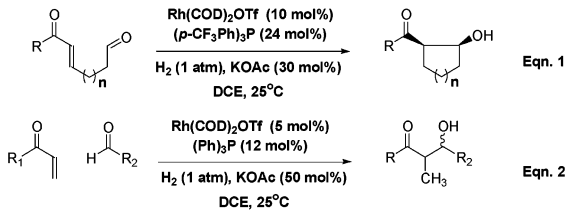
Hye-Young Jang, Ryan R. Huddleston, and Michael J. Krische*

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712

Received September 9, 2002

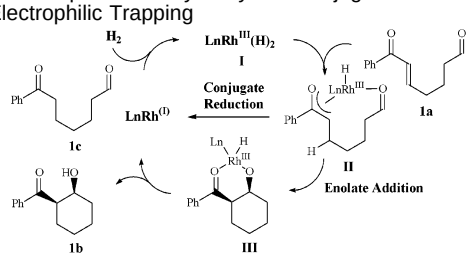
Enolates are among the most broadly utilized reactive intermediates in organic chemistry.[1] Despite the fundamental significance of enolate chemistry, there is a paucity of mechanistically distinct methods for enolate generation. Most often, enolate formation is accomplished through deprotonation of carbonyl compounds or activation of related enol derivatives. Seminal studies by Stork demonstrate that stoichiometric generation of enolates may be achieved via dissolving metal reduction of enones.[2] Subsequently, catalytic hydrometalative methods for the reductive generation of enolates and enol derivatives from α,β-unsaturated carbonyl compounds have emerged: catalytic enone 1,4-hydrosilation,[3] 1,4-hydroboration,[4] 1,4-hydroalumination,[5] and 1,4-hydrostannylation.[6,8e] The availability of catalytic methods for reductive enolate generation has enabled the development of an emerging family of catalytic C−C bond-forming processes.[7]

While the conjugate reduction of enones under hydrogenation conditions is well known,[8] to our knowledge, the reductive generation of enolates from enones under hydrogenative conditions is unknown and would represent a mild and atom economical means of enolate generation. Here, we report a catalytic protocol for the reductive generation of transition metal enolates using elemental hydrogen as terminal reductant. Transition metal enolates generated in this fashion are subject to electrophilic trapping by appendant or exogenous aldehyde partners, enabling catalytic C−C bond formation under hydrogenative conditions (eqs 1 and 2, respectively).



The generally accepted mechanism for Rh-catalyzed alkene hydrogenation involves three fundamental steps: (1) oxidative addition of LnRh(I) to elemental hydrogen, (2) alkene hydrometalation to afford LnRh(III)(alkyl)(hydrido) intermediates, and (3) alkyl-hydrogen reductive elimination to provide the saturated product along with LnRh(I) to complete the catalytic cycle.[9,10] Hypothetically, in the presence of an exogenous electrophile, trapping of the alkyl-rhodium intermediate might occur in competition with alkyl-hydrogen reductive elimination. Moreover, were the electrophilic trap appended to the nascent alkyl-rhodium intermediate, C−C bond formation may fully intercede the reductive elimination event. Predicated on this analysis, hydrogenative cycloreduction of monoenone monoaldehydes was deemed feasible. Enone hydrometalation should produce Rh-enolate **II**. Addition to the appendant aldehyde

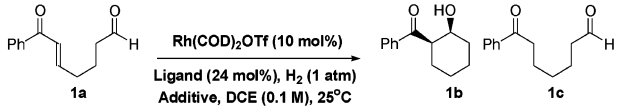
Scheme 1. Proposed Catalytic Cycle: Conjugate Reduction versus Electrophilic Trapping



should result in formation of Rh-aldolate **III**, which upon oxygen−hydrogen reductive elimination, should afford the aldol product along with LnRh(I) to complete the catalytic cycle (Scheme 1).

To explore the feasibility of catalytic C−C bond formation under hydrogenative conditions, solutions of phenyl-substituted monoenone monoaldehyde **1a** in dichloroethane (DCE, 0.1 M) were exposed to various Rh(I) sources under 1 atm of hydrogen. While the majority of Rh-catalysts screened produce products of 1,4-reduction, $Rh(COD)_2OTf/PPh_3$ gives roughly equal proportions of *syn*-aldol cycloreduction product **1b** and 1,4-reduction product **1c** (Table 1, entry 1). It was speculated that deprotonation of (hydrido)Rh species **I** or **II** would disable the 1,4-reduction manifold. Indeed, transformations conducted in the presence of potassium acetate produce **1b** in 59% yield, along with a 21% yield of 1,4-reduction product **1c** (Table 1, entry 2). Exposure of conjugate reduction product **1c** to identical conditions does not produce **1b**. Additionally, enone **1a** is unreactive toward triarylphosphine addition, thus excluding tandem Baylis−Hillman cyclization-conjugate reduction pathways en route to **1b**. It was speculated that enhanced Lewis acidity of the metal would promote coordination of the appendant aldehyde, in turn, promoting aldol cyclization. Accordingly, utilization of $(p\text{-}CF_3Ph)_3P$ as ligand, in the absence of base, results in a 53% yield of **1b**, along with a 22% yield of **1c** (Table 1, entry 3). Taking advantage of both potassium acetate and ligand electronic effects, we found that the yield of **1b** is increased to 89%, with only 0.1% 1,4-reduction (Table 1, entry 4). The latter conditions proved general

Table 1. Optimization of Rh-Catalyzed Hydrogenative Aldol Cycloreduction of **1a**[a]



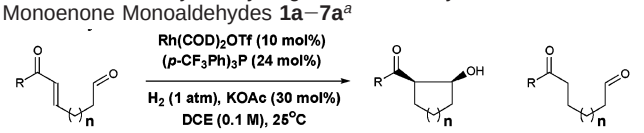
entry	ligand	additive (mol %)	yield[b] aldol (syn–anti)	yield[b] 1,4-reduction
1	PPh_3		21% (99:1)	25%
2	PPh_3	KOAc (30%)	59% (58:1)	21%
3	$(p\text{-}CF_3Ph)_3P$		57% (14:1)	22%
4	$(p\text{-}CF_3Ph)_3P$	KOAc (30%)	89% (10:1)	0.1%

[a] As product ratios were found to vary with surface-to-volume ratio of the reaction mixture, all transformations were conducted on a 1.48 mmol scale in 50 mL round-bottomed flasks. [b] Isolated yields after purification by silica gel chromatography.

* To whom correspondence should be addressed. E-mail: mkrische@mail.utexas.edu.

10.1021/ja021163l CCC: $22.00

Table 2. Rh-Catalyzed Hydrogenative Aldol Cycloreduction of Monoenone Monoaldehydes **1a**−**7a**[a]



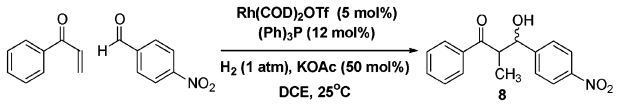
substrate	product (syn:anti)	1,4-reduction
1a, $n = 2$, R = Ph	**1b**, 89% (10:1)	**1c**, 0.1%
2a, $n = 2$, R = *p*-MeOPh	**2b**, 74% (5:1)	**2c**, 3%
3a, $n = 2$, R = 2-naphthyl	**3b**, 90% (10:1)	**3c**, 1%
4a, $n = 2$, R = 2-thiophenyl	**4b**, 76% (19:1)	**4c**, 2%
5a, $n = 2$, R = 2-furyl	**5b**, 70% (6:1)	**5c**, 10%
6a, $n = 1$, R = Ph	**6b**, 71% (24:1)	**6c**, 1%
7a, $n = 2$, R = CH_3	**7b**, 65% (1:5)	

[a] See Supporting Information for detailed experimental procedure.

for cycloreduction of aromatic, heteroaromatic, and aliphatic enone substrates to form five- and six-membered ring products (Table 2).

Competitive conjugate reduction rendered the outcome of intermolecular condensation uncertain. To assess the feasibility of an intermolecular variant, initial studies focused on the reductive condensation of phenyl vinyl ketone and *p*-nitrobenzaldehyde. Remarkably, addition of 10 mol % catalyst and 50 mol % KOAc to an equimolar solution of enone/aldehyde partners in dichloroethane (0.5 M) under 1 atm of hydrogen gave a 53% yield of the aldol product **8** (Table 3, entry 1). As competitive enone conjugate

Table 3. Optimization of the Intermolecular Rh-Catalyzed Hydrogenative Aldol Condensation



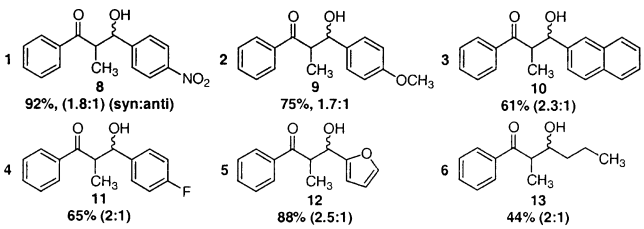
entry	enone (mol %)	catalysts (mol %)	conc. (mol/L)	KOAc (mol %)	yield[a]
1	100	10	0.5	50	53%
2	150	10	0.5	50	75%
3	150	10	0.1	50	85%
4	150	5	0.1	50	92%
5	150	5	0.5		79%

[a] Isolated yields after purification by silica gel chromatography.

reduction accounted for the mass balance, the reaction was repeated using 1.5 equiv of the enone. A 75% yield of the aldol **8** was obtained (Table 3, entry 2). Under more dilute conditions (0.1 M), the yield of **8** was increased to 85% (Table 3, entry 3). When the amount of catalyst was reduced to 5%, the yield of **8** increased further to 92% (Table 3, entry 4). Notably, omission of KOAc under these conditions gave a 79% yield of aldol product **8** (Table 3, entry 5). Exposure of propiophenone to the optimized conditions does not result in aldolization. Additionally, phenyl vinyl ketone does not engage in Baylis−Hillman chemistry under these conditions, excluding Baylis−Hillman-conjugate reduction pathways.

Under optimum conditions identified for condensation of phenyl vinyl ketone and *p*-nitrobenzaldehyde, variation of the electrophilic partner was explored. Conditions proved general for the catalytic

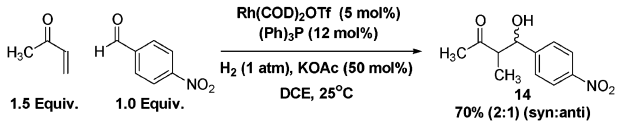
Table 4. Intermolecular Rh-Catalyzed Hydrogenative Aldol Condensation of Phenyl Vinyl Ketone and Various Aldehydes[a]



[a] See Supporting Information for detailed experimental procedure.

reductive aldol condensation of aromatic and heteroaromatic aldehyde partners (Table 4, entries 1−5). Aliphatic aldehydes participate in the reaction, but their reduced rate of reaction exacerbates the issue of competitive conjugate reduction, resulting in diminished yields (Table 4, entry 6).

Tolerance with respect to variation of the nucleophilic partner next was explored. Whereas ethyl acrylate exclusively provides products of 1,4-reduction, methyl vinyl ketone undergoes reaction with *p*-nitrobenzaldehyde to provide a 70% yield of the aldol product.



In summary, we report a catalytic C−C bond formation under hydrogenative conditions. The significance of these findings resides in the ability to regioselectivity generate and transform transition metal enolates under catalytic conditions that circumvent formation of stoichiometric byproducts. Future studies will focus on the development of related hydrogenative catalytic transformations predicated on the use of enones as latent enolates.

Acknowledgment. We acknowledge the Robert A. Welch Foundation (F-1466), the NSF-CAREER program (CHE0090441), the Herman Frasch Foundation (535-HF02), the NIH (RO1 GM65149-01), Eli Lilly Faculty Grantee Program, and the Research Corp. Cottrell Scholar Award (CS0927) for partial support of this research.

Supporting Information Available: Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For selected reviews on the generation and utilization of enolates, see: (a) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917. (b) Hughes, D. L. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. III, p 1273. (c) Evans, D. A. *Asymmetric Synth.* **1984**, *3*, 1. (d) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737.

(2) Stork, G.; Rosen, P.; Goldman, N. L. *J. Am. Chem. Soc.* **1961**, *83*, 2965. (b) Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J. *J. Am. Chem. Soc.* **1965**, *87*, 275.

(3) For selected examples of metal-catalyzed silane-mediated 1,4-reduction of α,β-unsaturated carbonyl compounds, see: (a) Speier, J. L.; Webster, J. A.; Barnes, G. H. *J. Am. Chem. Soc.* **1957**, *79*, 974. (b) Bourhis, R.; Frainnet, E.; Moulines, F. *J. Organomet. Chem.* **1977**, *141*, 157. (c) Barlow, A. P.; Boag, N. M.; Stone, G. A. *J. Organomet. Chem.* **1980**, *191*, 39. (d) Mahoney, W. S.; Stryker, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 8818. (e) Hilty, T. K.; Revis, A. *J. Org. Chem.* **1990**, *55*, 2972. (f) Johnson, C. R.; Raheja, R. K. *J. Org. Chem.* **1994**, *59*, 2287. (g) Vivian, R.; Papa, P.; Keith, J.; Lipshutz, B. H. *Tetrahedron Lett.* **1998**, *39*, 4627. (h) Apella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473. (i) Chrisman, W.; Nosson, K.; Papa, P.; Sclafani, J. A.; Vivian, R. W.; Keith, J. M.; Lipshutz, B. H. *Tetrahedron* **2000**, *56*, 2779.

(4) Evans, D. A.; Fu, G. C. *J. Org. Chem.* **1990**, *55*, 5678.

(5) (a) Tsuda, T.; Hayashi, T.; Satomi, H.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 537. (b) Ikeno, T.; Kimura, T.; Ohtsuka, Y.; Yamada, T. *Synlett* **1999**, 96.

(6) (a) Four, P.; Guibe, F. *Tetrahedron Lett.* **1982**, *23*, 1825. (b) Keinan, E.; Gleize, P. A. *Tetrahedron Lett.* **1982**, *23*, 477.

(7) For a review on the use of enones as latent enolates in catalysis, see: Huddleston, R. R.; Krische, M. J. *Synlett* **2003**, in press.

(8) For selected reviews on the conjugate reduction of enones via catalytic hydrogenation, see: (a) Keinan, E.; Greenspoon, N. Partial Reduction of Enones, Styrenes, and Related Systems. *Comprehensive Organic Synthesis*; Pergamon Press: New York, 1991. (b) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin: Menlo Park, CA, 1972. (c) James, B. R. *Homogeneous Hydrogenation*; Wiley-Interscience: New York, 1973. (d) Rylander, P. N. *Hydrogenation Methods*; Academic Press: London, 1985. (e) Rylander, P. N. *Catalytic Hydrogenation in Organic Synthesis*; Academic Press: New York, 1979. (f) Freifelder, M. *Catalytic Hydrogenation in Organic Synthesis*; Wiley-Interscience: New York, 1978.

(9) (a) Tolman, C. A.; Meakin, P. Z.; Lindner, D. L.; Jesson, J. P. *J. Am. Chem. Soc.* **1974**, *96*, 2762. (b) Halpern, J.; Okamoto, T.; Zakhariev, A. *J. Mol. Catal.* **1976**, *2*, 65.

(10) For a review, see: Marko, L. *Pure Appl. Chem.* **1979**, *51*, 2211.

JA021163L