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Enolate Generation under Hydrogenation Conditions: Catalytic Aldol Cycloreduction of Keto-Enones

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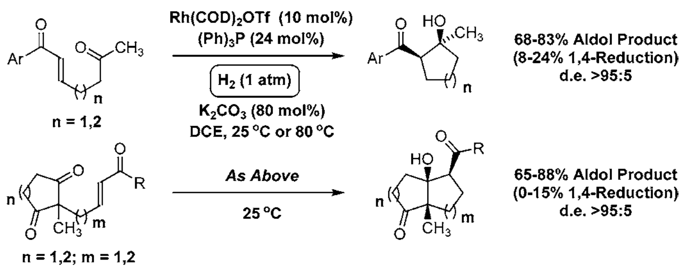
ABSTRACT



Formal heterolytic activation of elemental hydrogen under Rh catalysis enables the reductive generation of enolates from enones under hydrogenation conditions. Enolates generated in this fashion participate in catalytic C–C bond formation via carbonyl addition to aldehyde and, as demonstrated in this account, ketone partners. Notably, the use of appendant dione partners enables diastereoselective formation of cycloaldol products possessing 3-stereogenic centers, including 2-contiguous quaternary centers.

While the significance of metalloenolates as reactive intermediates in organic chemistry is universally appreciated, preparatively useful protocols for enolate generation are largely restricted to the deprotonation and derivatization of carbonyl compounds.[1] Recently, a method for the production and catalytic transformation of transition metal enolates via enone hydrogenation was disclosed by our lab.[2] This method effects regioselective enolate formation under mild conditions (ambient temperatures and pressures) and has led to the first completely atom economical catalytic reductive aldol process.[3,4] Applicability of this methodology vis-à-vis intra- and intermolecular condensation with aldehyde partners has been established.[2] The outcome of related condensations employing *ketone* partners was rendered uncertain, as competitive conjugate reduction in response to reduced reactivity of the electrophilic partner was anticipated. In this account, we report that catalytic intramolecular aldol cycloreduction under hydrogenative conditions proceeds readily with ketone partners to provide the corresponding five- and six-membered ring products.[5] Through the use of dione acceptors, 3-stereogenic centers, including 2-contiguous quaternary centers, are

(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. (e) Mekelburger, H. B.; Wilcox, C. S. In *Comprehensive Organic Synthesis;* Trost, B. M., Ed.; Permagon: New York, 1991; Vol. II, p 99.

(2) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 15156.

(3) For related catalytic reductive aldol processes, see: (a) Revis, A.; Hilty, T. K. *Tetrahedron Lett.* **1987**, *28*, 4809. (b) Matsuda, I.; Takahashi, K.; Sato, S. *Tetrahedron Lett.* **1990**, *31*, 5331. (c) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 2005. (d) Kiyooka, S.; Shimizu, A.; Torii, S. *Tetrahedron Lett.* **1998**, *39*, 5237. (e) Ooi, T.; Doda, K.; Sakai, D.; Maruoka, K. *Tetrahedron Lett.* **1999**, *40*, 2133. (f) Taylor, S. J.; Morken, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 12202. (g) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528. (h) Zhao, C.-X.; Duffey, M. O.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829. (i) Baik, T.-G.; Luiz, A. L.; Wang, L.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 5112. (j) Emiabata-Smith, D.; McKillop, A.; Mills, C.; Motherwell, W. B.; Whitehead, A. J. *Synlett* **2001**, 1302.

(4) For a review on the use of enones as latent enolates in catalysis, see: Huddleston, R. R.; Krische, M. J. *Synlett* **2003**, 12.

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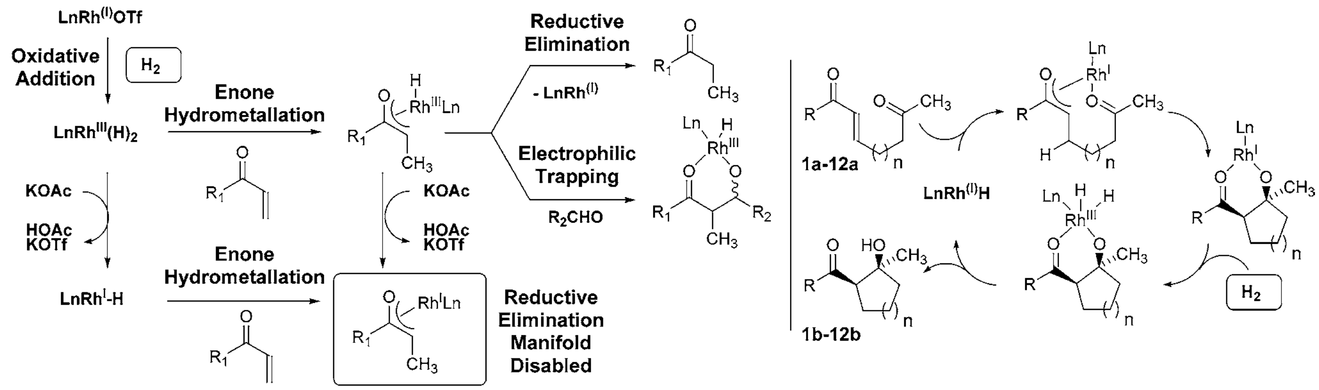
Scheme 1. Formal Heterolytic Activation of Elemental Hydrogen Mitigates Competitive Conjugate Reduction Manifolds by Enabling Monohydride-Based Catalytic Cycles.



formed with control of the relative stereochemistry in a completely atom economical fashion.

The principal challenge in using elemental hydrogen for reductive enolate generation involves circumventing 1,4-reduction.[6] To overcome this pitfall, it was speculated that hydrogenative enolate generation might be achieved upon formal heterolytic activation of elemental hydrogen to yield (monohydrido)metal intermediates.[7] Formal heterolytic activation of hydrogen may occur through tandem oxidative addition of hydrogen, followed by reductive elimination of HX, which may be assisted by base. Unlike the mechanism for alkene hydrogenation involving Wilkinson's catalyst,[8,9] cationic rhodium complexes appear to operate through formal heterolytic hydrogen activation pathways.[7,10,11] This is likely due to the enhanced acidity of cationic rhodium hydrides with respect to their neutral counterparts.[12] Predicated on this analysis, and given the established efficiency of aldol additions involving rhodium enolates,[13] aldol cycloreduction under hydrogenation conditions was studied using $(COD)_2$-$Rh^I(OTf)$ as a precatalyst. A mechanism was envisioned whereby enolate-hydrogen reductive elimination pathways are disabled through deprotonation of the (hydrido)metal intermediates $LnRh^{III}(H)_2$ or (enolato)Rh^{III}(H)Ln (Scheme 1).

To probe the viability of ketones as electrophilic partners, the cycloreduction of monoenone monoketone **1a** was explored. Exposure of **1a** to conditions related to those employed for intra- and intermolecular condensation with aldehyde partners resulted in formation of the desired aldol product, accompanied by substantial quantities of conjugate reduction product **1c**. While these reactions proceed readily at room temperature, decreased variation in the ratio of cycloreduction to conjugate reduction products was observed at higher temperatures, presumably due to an attendant decrease in the concentration of hydrogen in solution. Under these conditions, *syn*-**1b** was obtained in 72% isolated yield as a single diastereomer as determined by ^{1}H NMR analysis, along with a 20% isolated yield of conjugate reduction product **1c**. The structural assignment of **1b** was corroborated by single-crystal X-ray diffraction analysis.[5] For this and other transformations, a series of control experiments were routinely performed to ensure the cycloreductions proceed in accordance with the postulated mechanism. Exposure of conjugate reduction product **1c** to the reaction conditions does not produce **1b**. Conversely, aldol product **1b** does not undergo retro-aldolization upon exposure to the reaction conditions. Additionally, β-substituted enones are unreactive toward triarylphosphine addition, thus excluding tandem Morita−Baylis−Hillman cyclization−conjugate reduction pathways. These conditions proved to be general for the syn-

(5) Borane-mediated aldol cycloreduction of keto-enones was recently reported by our lab: Huddleston, R. R.; Cauble, D. F.; Krische, M. J. *J. Org. Chem.* **2003**, *68*, 11.

(6) 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. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Permagon: New York, 1991; Vol. III, p 523. (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.

(7) For a review on the heterolytic activation of elemental hydrogen, see: Brothers, P. J. *Prog. Inorg. Chem.* **1981**, *28*, 1.

(8) (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.

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

(10) Monohydride formation by deprotonation of a dihydride intermediate is known for cationic Rh complexes: (a) Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 2134. (b) Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 2143. (c) Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 4450.

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

(12) For a review, see: Norton, J. R. In *Transition Metal Hydrides*; Dedieu, A. Ed.; New York, 1992, Chapter 9.

(13) For a review, see: Burkhardt, E. R.; Doney, J. J.; Slough, G. A.; Stack, J. M.; Heathcock, C. H.; Bergman, R. G. *Pure Appl. Chem.* **1988**, *60*, 1.

(14) Procedure: To a 13 × 100 mm test tube charged with $Rh(COD)_2OTf$ (0.0462 mmol, 10 mol %) and Ph_3P (0.111 mmol, 24 mol %) was added DCE (0.185 M, 2.5 mL). The mixture was stirred for 10 min under an argon atmosphere, at which point the substrate (0.462 mmol, 100 mol %) and K_2CO_3 (0.37 mmol, 80 mol %) were added. The system was purged with hydrogen gas for 3 min, and the reaction was allowed to stir at 80 °C under 1 atm of hydrogen until complete consumption of the substrate. Yields represent averages of three runs. Cycloreductions to produce compounds **6b**, **12b**, and **13b**−**18b** were conducted at 25 °C.

selective aldol cycloreduction of aromatic and heteroaromatic enone substrates to form six-membered ring products. In all cases, formation of the cycloreduction product was accompanied by 8−20% isolated yield of the corresponding conjugate reduction product. 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 × 100 mm sealed test tubes (Figure 1).

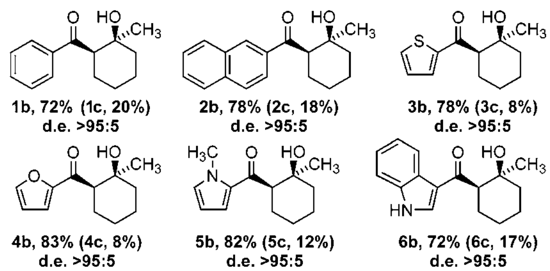


Figure 1. Catalytic hydrogenative cycloreduction of keto-enones: six-membered ring formation.[14]

The formation of five-membered rings also proceeds smoothly for both aromatic and heteroaromatic enone substrates under these conditions. Cycloreduction products **7b**−**12b** were obtained as single diastereomers, as determined by ^{1}H NMR analysis. Again, due to the reduced electrophilicity of the ketone acceptor, the formation of each cycloreduction product was accompanied by 8−24% isolated yield of the corresponding conjugate reduction product (Figure 2).

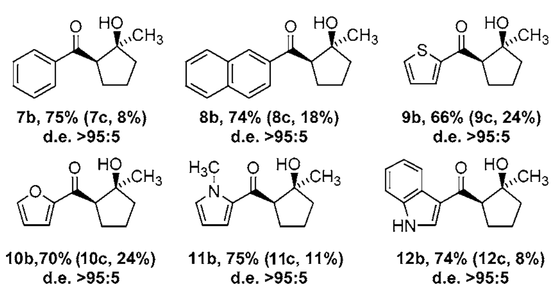
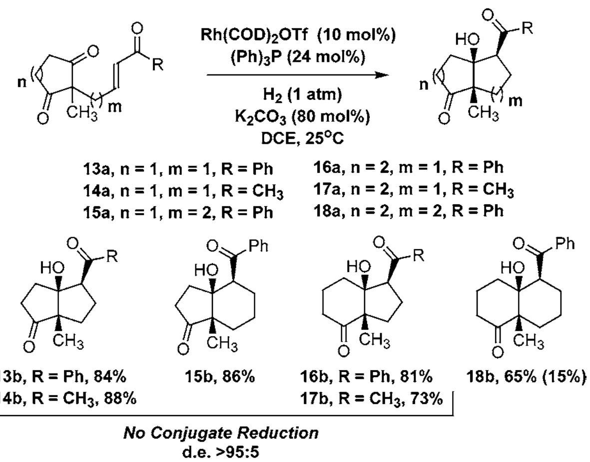


Figure 2. Catalytic hydrogenative cycloreduction of keto-enones: five-membered ring formation.[14]

The cycloreduction of monoenone monoketones **1a**−**12a** was accompanied by significant quantities of conjugation reduction (8−24%). Conjugate reduction pathways should be attenuated in the case of more reactive ketone electrophiles. Dione-containing substrates **13a**−**18a** should be more reactive by virtue of inductive effects and relief of dipole−dipole interactions. Indeed, exposure of enone-diones **13a**−**18a** to catalytic hydrogenation conditions at ambient temperature led to formation of the corresponding bicyclic aldol products **13b**−**18b** in >95:5 d.e. as determined by ^{1}H NMR. The structural assignment of **15b** was corroborated by single-crystal X-ray diffraction analysis. With the exception of substrate **18a**, which affords strained *cis*-decalone **18b**, 1,4-reduction products were not produced. This method enables diastereoselective formation of 3-contiguous stereogenic centers, including 2-contiguous quaternary centers (Scheme 2).

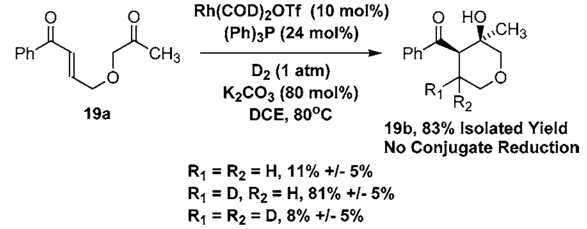
Scheme 2. Catalytic Hydrogenative Cycloreduction of Dione-enones[14]



To corroborate the mechanism proposed in Scheme 1 and further explore the effect of ketone electronics on the extent of conjugate reduction, the aldol cycloreduction of ether-containing substrate **19a** was explored under catalytic hydrogenation conditions employing molecular deuterium (98% isotopic purity). The *syn*-aldol cycloreduction product **19b** was obtained in 83% yield. Conjugate reduction was not observed. For **19b**, deuterium was exclusively incorporated at the β-position. In addition to monodeuterated material (81% composition), doubly deuterated (8% composition) and nondeuterated materials (11% composition) were also observed. These data suggest that enone hydrometalation is reversible, i.e., β-hydride elimination of the Rh-enolate occurs.

In summary, elemental hydrogen represents a clean and cost-effective reductant for the catalytic generation and transformation of rhodium-enolates. Unlike reductive C−C bond formations employing silane, borane, alane, and stan-

Scheme 3. Catalytic Cycloreduction Employing Elemental Deuterium



nane as terminal reductants, the use of elemental hydrogen circumvents formation of stoichiometric byproducts. Enolate nucleophiles generated under hydrogenation conditions readily participate in catalytic C−C bond formation via carbonyl addition to aldehyde and, as demonstrated in this account, ketone partners. Notably, the use of appendant dione partners enables diastereoselective formation of cycloaldol products possessing 3-stereogenic centers, including 2-contiguous quaternary centers. Future studies will be devoted to the development of related C−C bond formations induced through catalytic hydrogenation of alkene pronucleophiles.

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Supporting Information Available: Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS) and X-ray crystallographic data for **15b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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