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Catalytic Addition of Metallo-Aldehyde Enolates to Ketones: A New C–C Bond-Forming Hydrogenation

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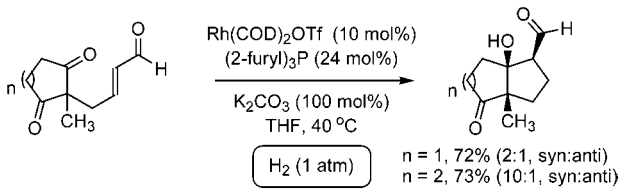
ABSTRACT



The first catalytic cross-aldolization of metallo-aldehyde enolates with ketone acceptors is enabled via hydrogenation of keto-enals with cationic rhodium catalysts. These results, in conjunction with prior studies involving the catalytic hydrogen-mediated reductive coupling of enones, dienes, and diynes with carbonyl acceptors, support the feasibility of developing a broad new class of catalytic C–C bond formations based on the electrophilic trapping of hydrogenation intermediates.

Recently, a method for the catalytic generation and aldolization of transition metal enolates via enone hydrogenation was disclosed from our lab.[1] Applicability of this methodology toward intra- and intermolecular condensation of aromatic and aliphatic enones with aldehyde partners has been established.[1a] Additionally, a more challenging variant of the aldol reaction, which employs ketones as electrophilic partners, proceeds readily under hydrogenation conditions to give cyclic aldol products in diastereomerically pure form.[1b] Finally, the generality of catalytic hydrogenation as a conceptually novel approach to reductive C−C bond formation is demonstrated by the capacity of diverse π-unsaturated partners, such as enones,[1] dienes,[2] and diynes,[3] to participate in catalytic hydrogen-mediated condensations with carbonyl partners.

To assess the limits of catalytic hydrogen-mediated C−C bond formation vis-à-vis aldol condensation, the catalytic hydrogenation−aldolization of enals was explored. Aldolizations that proceed through the intermediacy of metallo-aldehyde enolates are among the most challenging variants of the aldol reaction known.[4] Catalytic cross-aldolizations of this type have only been achieved through amine catalysis[5] and the use of enol silanes.[6] The catalytic addition of metallo-aldehyde enolates to ketones is, to our knowledge, unprecedented, as only a single stoichiometric variant of such an aldolization is reported.[7] In this account, we disclose that catalytic aldol cyclization of keto-enals proceeds readily under hydrogenation conditions to provide the corresponding

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(2) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4074.

(3) Huddleston, R. R.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 11488.

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(5) (a) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798. (b) Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 2785.

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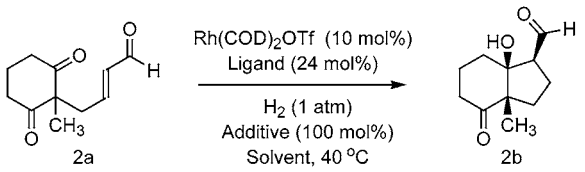
five- and six-membered ring products, along with modest quantities of simple 1,4-reduction products.

The primary issues limiting the utility of aldehyde enolates in cross-aldolizations with ketone partners involve polyaldolization along with a diminished thermodynamic driving force.[8] It was recognized that intramolecular aldolization should attenuate polyaldolization. Additionally, as aldolization is primarily driven by chelation,[9] intramolecular aldolization should also favorably bias the enolate−aldolate equilibria. Predicated on this analysis, catalytic hydrogenation−aldolization of keto-enal **2a** was attempted. Exposure of a solution of keto-enal **2a** in dichloroethane (DCE) at 40 °C to $Rh^{I}(COD)_2OTf$ under an atmosphere of hydrogen (1 atm) in the presence of triphenylphosphine and potassium acetate gave the aldol product **2b** in 23% yield, accompanied by a 50% yield of the product of simple conjugate reduction (Table 1, entry 1). The conjugate reduction manifold should

Table 1. Optimization of the Catalytic Aldol Cycloreduction of Keto-Enal **1a**[a]



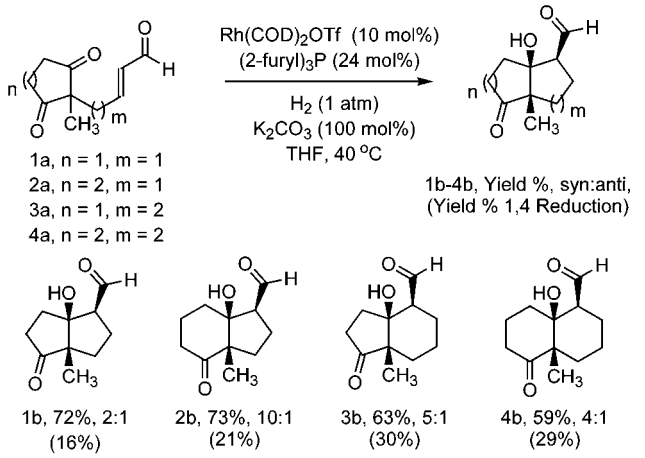
entry	ligand	additive	solvent (concn)	yield[b] (1,4-reduction)
1	Ph_3P	KOAc	DCE (0.1 M)	23% (50%)
2	Ph_3P	K_2CO_3	DCE (0.1 M)	40% (28%)
3	Ph_3P	K_2CO_3	DCE (0.05 M)	59% (29%)
4	Ph_3P	K_2CO_3	THF (0.05 M)	65% (32%)
5	$(p\text{-}CF_3Ph)_3P$	K_2CO_3	THF (0.05 M)	73% (22%)
6	$(2\text{-furyl})_3P$	K_2CO_3	THF (0.05 M)	73% (21%)

[a] Procedure: To a 25 mL round-bottomed flask charged with $Rh(COD)_2OTf$ (24 mg, 0.052 mmol, 10 mol %) and ligand (0.12 mmol, 24 mol %) was added solvent. The mixture was stirred for 10 min under an argon atmosphere, at which point **2a** (100 mg, 0.52 mmol, 100 mol %) and base (0.52 mmol, 100 mol %) were added. The system was purged with hydrogen gas and the reaction was allowed to stir at 40 °C under 1 atm of hydrogen until complete consumption of substrate. [b] Isolated yields after purification by silica gel chromatography.

be attenuated by base-assisted entry into the monohydride catalytic cycle (vide supra). Accordingly, substituting potassium carbonate for potassium acetate, the yield of **2b** is increased to 40% (Table 1, entry 2). Reactions performed at higher dilution provide **2b** in 59% yield (Table 1, entry 3). Under otherwise identical conditions, but in THF solvent, the yield of **2b** is increased to 65% (Table 1, entry 4). Finally, moving to more electron deficient phosphine ligands, **2b** is obtained in greater than 70% yield (Table 1, entries 5 and 6). To ensure the cycloreductions proceed in accordance with the postulated mechanism, several control experiments were performed. Exposure of the conjugate reduction product to the reaction conditions does not produce **2b**. Conversely, **2b** does not undergo retro-aldolization upon exposure to the reaction conditions. Enal **2a** is unreactive toward triarylphosphine addition, excluding tandem Morita−Baylis−Hillman cyclization−conjugate reduction pathways. Finally, upon omission of hydrogen, no reaction is observed. The structural assignment of **2b** was corroborated by single-crystal X-ray diffraction analysis of the corresponding carboxylic acid (Table 1).

Under these optimized conditions, the scope of the catalytic aldol cycloreduction of keto-enals was explored. As demonstrated by the catalytic cycloreduction of substrates **1a** and **2a**, five-membered-ring formation proceeds well to provide the bicyclic aldol products **1b** and **2b** in 72% and 73% yield, respectively. As illustrated by substrates **3a** and **4a**, cyclization to form six-membered rings occurs in slightly diminished yield due to increasing levels of conjugate reduction. Here, aldol products **3b** and **4b** are produced in 63% and 59% yields, respectively. The structural assignment of **4b** was corroborated by single-crystal X-ray diffraction analysis (Scheme 1).

Scheme 1. Catalytic Aldol Cycloreduction of Keto-Enals **1a**−**4a**

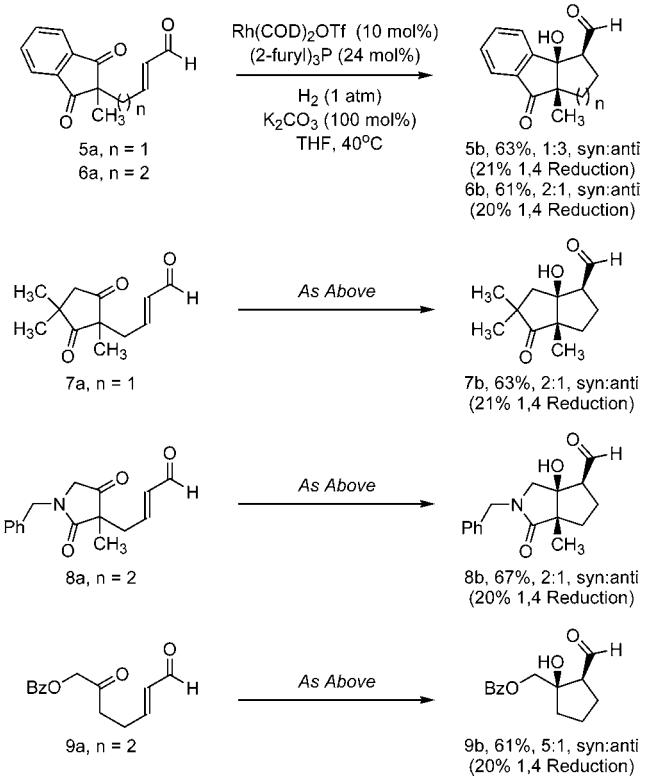


To further explore the scope of this new catalytic variant of the aldol reaction, a range of other substrates were subjected to conditions for hydrogenation−aldolization. As demonstrated by the cycloreduction of the indanedione containing substrates **5a** and **6a**, aromatic ketones are viable electrophilic partners. Keto-enals **7a** and **8a** highlight the chemoselectivity of aldolization with regard to the use of nonequivalent ketone acceptors. For **7a**, steric bias in the form of geminal dimethyl substitution induces addition to the less encumbered ketone partner. In the case of **8a**, addition to the ketone occurs smoothly in the presence of

(8) As reported in ref 7, ab initio calculation (RHF/6-31G) revealed that ΔH_f for the β-hydroxyaldehyde $(CH_3)_2C(OH)CH_2CHO$ derived from acetaldehyde and acetone is +21.155 kcal/mol, while ΔH_f for the isomeric β-hydroxyketone $CH_3CH(OH)CH_2COCH_3$ also derived from acetaldehyde and acetone is −10.455 kcal/mol.

(9) The failure of tris(dialkylamino)sulfonium enolates to react with aldehydes is attributed to unfavorable enolate−aldolate equilibria: Noyori, R.; Nishida, I.; Sakata, J.; Nishizawa, M. *J. Am. Chem. Soc.* **1980**, *102*, 1223.

Scheme 2. Catalytic Aldol Cycloreduction of Keto-Enals **5a−9a**



the *N*-benzyl amide. Notably, hydrogenolytic cleavage of the *N*-benzyl amide is not observed. As illustrated by the cycloreduction of enal ketone **9a**, addition to an appendant monoketone proceeds with levels of efficiency comparable to that of related 1,3-dione partners. In all cases, the formation of aldol products is accompanied by significant quantities of simple 1,4-reduction products. As resubmission of the aldol products to the reaction conditions does not result in retro-aldolization, the formation of 1,4-reduction products is attributed to a modest enolate−aldolate equilibrium ratio with kinetic trapping from the equilibrium mixture via oxygen−hydrogen reductive elimination. Finally, modest syn:anti ratios are consistent with the well-established lack of stereoselectivity inherent to aldol additions employing aldehyde enolates (Scheme 2).[10]

Mechanistically, we speculate that a key feature of these catalytic C−C bond-forming hydrogenations involves heterolytic activation of elemental hydrogen to yield (monohydrido)metal intermediates.[11] Heterolytic activation of hydrogen, which may be achieved through the deprotonation of cationic rhodium dihydrides,[12,13] enables monohydride-based catalytic cycles that circumvent direct enolate−hydrogen reductive elimination. The veracity of this analysis is now borne out by a large body of empirical data (Scheme 3).[1−3]

In summation, the first catalytic addition of metallo-aldehyde enolates to ketones is achieved through hydrogenation−aldolization. Future studies will be devoted to the development of related catalytic C−C bond-forming hydrogenations, including the hydrogen-mediated reductive coupling of simple alkenes to diverse electrophilic partners.

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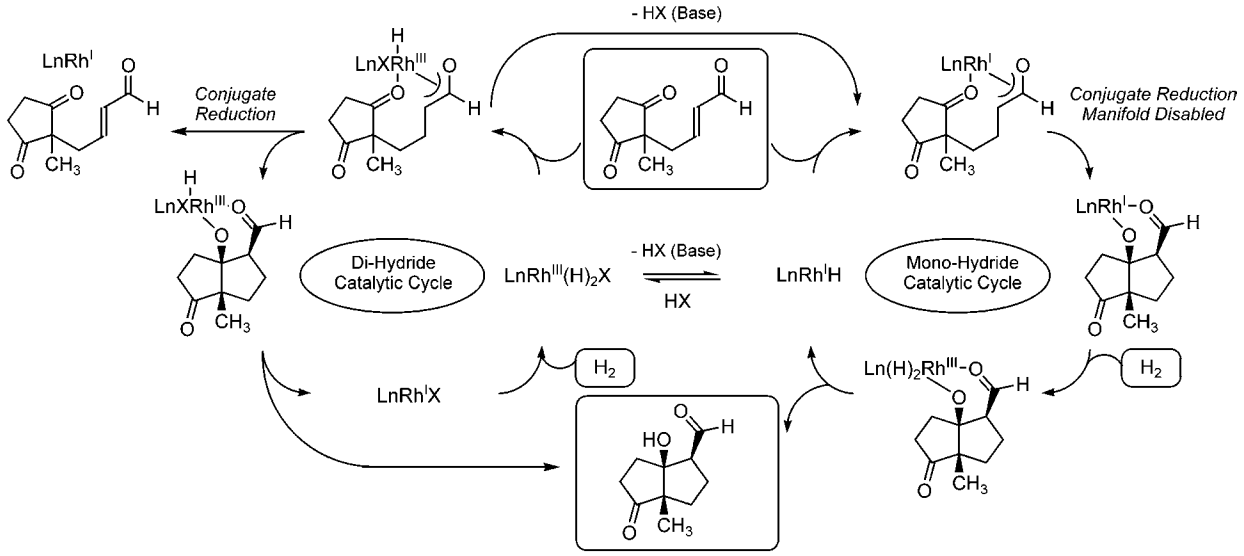
Scheme 3. A Possible Catalytic Mechanism for the Aldol Cycloreduction of Keto-Enals under Hydrogenation Conditions



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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, IR, and HRMS data for all new compounds and X-ray crystallographic data file in CIF format for the carboxylic acid derived from **2b** and the *cis*-decalone aldehyde **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Heathcock et al. reveal that the kinetic stereoselectivity in the addition of *both Z*- and *E*-lithium enolates of propanal to benzaldehyde gives 1:1 mixtures of *syn*- and *anti*-aldol products. Given that *Z*-lithium ketone enolates generally exhibit good levels of *syn*-diastereoselectivity in aldol additions, this result underscores the lack of stereoselectivity inherent to aldol additions employing aldehyde enolates: Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.

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

(12) Initiation of monohydride-based hydrogenation cycles via deprotonation of cationic Rh(III)-dihydrides is known: (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.

(13) For a review on the acidity of metal hydrides, see: Norton, J. R. In *Transition Metal Hydrides*; Dedieu, A., Ed.: VCH Publishers: New York, 1992; Chapter 9.