

## Diastereoselective Cobalt-Catalyzed Aldol and Michael Cycloreductions

Tae-Gon Baik, Ana Liza Luis, Long-Cheng Wang, and Michael J. Krische\*

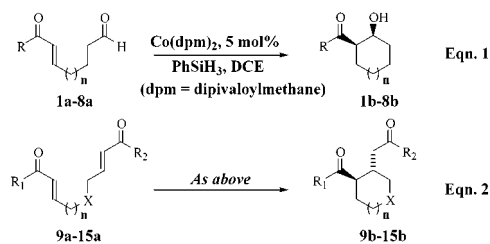
University of Texas at Austin  
Department of Chemistry and Biochemistry  
Austin, Texas 78712

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Many classes of chemical transformations exist for which catalytic variants have not been devised or require further development. The aldol and Michael reactions represent classical methods of carbon–carbon bond formation that have found extensive use in synthesis, yet the selectivity issues posed by these transformations have been answered only in part. In the case of the aldol reaction, the vast majority of catalytic asymmetric variants<sup>1</sup> involve the utilization of latent enolates, which must be preformed. More recently, direct catalytic asymmetric aldol condensations of unmodified aldehyde and ketone partners have been described.<sup>2</sup> Although a tremendous advance, current catalytic systems for the direct aldol reaction exhibit suboptimal diastereoselectivity and are restricted to symmetric ketone partners or those possessing a single set of acidic hydrogens. Methodologies for catalytic asymmetric Michael reaction are similarly restricted to the use of preformed enol derivatives or  $\beta$ -dicarbonyl nucleophiles.<sup>3,4</sup>

Catalytic enone hydrometallation represents a promising strategy for enolate generation, circumventing the utilization of preformed enol or enolate derivatives. Indeed, the metal-catalyzed reductive condensation of  $\alpha,\beta$ -unsaturated carbonyl compounds with aldehydes in the presence of a hydride donor, that is, a “reductive aldol” reaction, has been described.<sup>5</sup> There are, however, no accounts of analogous catalytic reductive Michael reactions. Additionally, despite a wealth of research on catalytic aldol and Michael processes, *intramolecular* transition metal-catalyzed variants have not been forthcoming.<sup>6,7</sup> In this account,

we report the first examples of catalytic aldol and Michael cycloreductions (eqs 1 and 2). These reactions exhibit high levels of *syn*- and *anti*-diastereoselectivity, respectively, and are viable for both five- and six-membered ring formations.



Catalytic aldol cycloreductions were first examined. The intermolecular reductive aldol reaction catalyzed by  $\text{Co}(\text{dpm})_2$  ( $\text{dpm}$  = dipivaloylmethane), which utilizes phenylsilane as the terminal reductant, exhibits poor diastereoselectivity.<sup>5d</sup> In the case of an *intramolecular* process, the geometrical requirements for bond formation would be more stringent, and hence, enhanced diastereoselectivities would be anticipated. Initial attempts at aldol cycloreduction bore out this notion. Addition of **2a** to a preformed solution containing 5 mol%  $\text{Co}(\text{dpm})_2$  and 120 mol% of phenylsilane in dichloroethane at 25 °C yielded the cyclization product **2b** in 87% yield with a *syn:anti* ratio of >99:1 as determined by HPLC analysis (Table 1, entry 2). These conditions proved quite general for five-, six- and seven-membered ring formation, albeit the latter in reduced yield (Table 1, entries 1–5). The heteroaromatic enones **6a** and **7a** also underwent cycloreduction in good yield (Table 1, entry 4). Aliphatic enone partners, however, gave diminished yields of the corresponding cyclized products (Table 1, entry 3). In all cases, irrespective of yield, only the *syn*-diastereomers of products **1b–8b** were observed. The capability of both five- and six-membered ring formations is significant, as related Ti-catalyzed cycloreductions of enals and enones only are viable for five-membered ring formation.<sup>8</sup>

Analogous Michael cycloreductions serve to illustrate the scope of this process with respect to variability of the electrophilic partner. Symmetrical bis-enones were initially examined. Upon exposure of bis-enone **10a** to similar conditions employed for the catalytic reductive aldol cyclization process, formation of the anticipated reductive Michael cyclization product **10b** was observed (Table 1, entry 7). Whereas products obtained from the reductive aldol cyclization exhibited *syn*-stereochemistry, *anti*-stereochemistry was observed exclusively for products obtained via reductive Michael cyclization. The formation of five- and six-membered rings occurs in good yield under these conditions (Table 1, entries 6–12). As evidenced by ether-linked substrate **11a**, heteroatoms are tolerated in the tether-connecting enones (Table 1, entry 8). Heteroaromatic enones, including 3-indolyl substituted bis-enone **15a** and 2-furyl substituted bis-enone **14a**, underwent cycloreduction in moderate yield. Michael cycloreductions of unsymmetrical bis-enones **12a** and **13a** reveal the capability of the catalyst to distinguish electronic differences between enones in the hydrometallation event. Thus, mixed bis-enone **12a**, containing phenyl- and methyl-substituents, exhibits a preference for hydrometallation of the phenyl-substituted enone over the methyl-substituted enone. The isomeric products **12b** and **12c** are obtained in a 3:1 ratio. In contrast, mixed enone **13a**, which contains phenyl- and 2-furyl-substituted enone moieties, yields a 1:1 mixture of isomeric products **13b** and **13c**. These results suggest that higher levels of chemoselectivity may be

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**Table 1.** Cobalt-Catalyzed Aldol and Michael Cycloreductions<sup>a</sup>

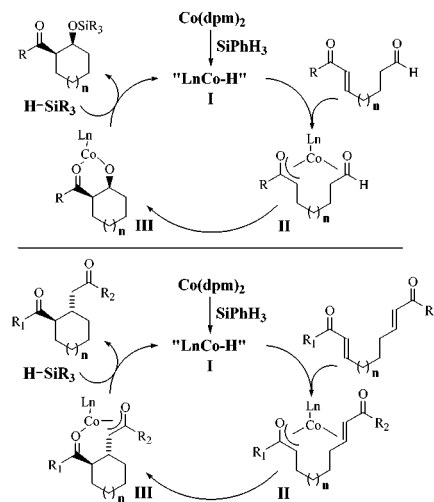
Entry	Substrate	Product	Temperature	PhSiH <sub>3</sub> (eq.)	Isolated Yield (%) (Average of 2 Runs)
1			25°C	1.2	70
2			25°C	1.2	87
	2a, R = Ph	2b, R = Ph	25°C	1.2	72
	3a, R = <i>p</i> -CF <sub>3</sub> Ph	3b, R = <i>p</i> -CF <sub>3</sub> Ph	25°C	1.2	68
	4a, R = 2-naphthyl	4b, R = 2-naphthyl	25°C	1.2	68
3			25°C	1.2	38
4			25°C	1.2	75
	6a, X = O	6b, X = O	25°C	1.2	73
	7a, X = S	7b, X = S	25°C	1.2	73
5			35°C	1.2	35
6			50°C	2.4	62
7			50°C	2.4	73
8			50°C	2.4	63
9			70°C	2.4	62
	12b, R <sub>1</sub> =Ph, R <sub>2</sub> =CH <sub>3</sub>				
	12c, R <sub>1</sub> =CH <sub>3</sub> , R <sub>2</sub> =Ph				
	12b:12c (3:1)				
10			50°C	2.4	54
	13b, R <sub>1</sub> =Ph, R <sub>2</sub> =2-furyl				
	13c, R <sub>1</sub> =2-furyl, R <sub>2</sub> =Ph				
	13b:13c (1:1)				
11			50°C	2.4	52
12			50°C	2.4	68

<sup>a</sup> Procedure: Co(dpm)<sub>2</sub> (5 mol %) was added to a solution of phenylsilane in dichloroethane (0.45 M with respect to substrate) at room temperature. After 30 min, the substrate was added as a 0.45 M solution in dichloroethane, and the reaction was allowed to stir at the indicated temperature until complete.

achieved in the Michael cycloreduction of unsymmetrical bis-enones, provided a sufficient electronic bias.

The Chalk–Harrod process is the widely accepted mechanism for olefin hydrosilylation where, after oxidative addition of the silane to the metal, hydride-olefin insertion occurs followed by alkyl-silicon reductive elimination to afford the product.<sup>10</sup> For metal diketonate complexes, it is likely that any silyl-metal species formed via oxidative addition of silane would reductively eliminate to give the silyl enol ether of the diketonate ligand,

representing a “formal”  $\sigma$ -bond metathesis. Mechanisms involving  $\sigma$ -bond metathesis have been proposed for the related titanium-catalyzed cycloreductions of 1,5-enones and 1,5-enals conducted in the presence of silane.<sup>8</sup> Although we have not yet engaged in detailed mechanistic studies, a plausible pathway for the catalytic aldol cycloreduction is depicted in Scheme 1. Thus, exposure of Co(dpm)<sub>2</sub> to phenylsilane generates hydrido-cobalt species **I** which, upon hydrometallation of the enone, yields cobalt enolate **II**. Subsequent addition to the appendant aldehyde, results in the formation of cobalt-alkoxide **III**.  $\sigma$ -Bond metathesis liberates the product to regenerate the hydrido-cobalt species **I** and complete the catalytic cycle (Scheme 1, top). An analogous catalytic cycle is postulated for the related Michael cycloreduction (Scheme 1, bottom). Notably, the use of catalytic Co(acac)<sub>2</sub> under these conditions gives a complex distribution of products, suggesting that at least one dpm ligand remains bound to the metal throughout the catalytic cycle.

**Scheme 1.** Top: Postulated Mechanism for the Cobalt-Catalyzed Aldol Cycloreduction; Bottom: Postulated Mechanism for the Cobalt-Catalyzed Michael Cycloreduction

In summary, we have developed highly diastereoselective aldol and Michael cycloreductions. A remarkable aspect of this hydrometallative approach to enolate generation lies in the ability to selectively direct the formation of ketone enolates in the presence of aliphatic aldehydes, which are more acidic, while at the same time circumventing competitive alkene and aldehyde hydrosilylation processes. The parallel development of both catalytic aldol and Michael cycloreductions serves to illustrate the broad scope of this hydrometallative approach to enolate generation. From a practical standpoint, the catalyst precursor, Co(dpm)<sub>2</sub> may be prepared in large scale, is easily isolated in pure form via sublimation, and may be handled in air. Further work is in progress to utilize this and related systems for other functional group interconversions including the development of enantioselective variants of the processes described herein.

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

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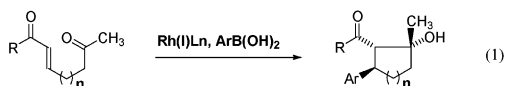
## Diastereo- and Enantioselective Catalytic Carbometallative Aldol Cycloreduction: Tandem Conjugate Addition–Aldol Cyclization

David F. Cauble, John D. Gipson, and Michael J. Krische\*

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

Received August 21, 2002; E-mail: mkrische@mail.utexas.edu

Enolate chemistry represents a methodological cornerstone of organic synthesis, encompassing numerous classical transformations, including the aldol reaction.<sup>1</sup> Owing to the fundamental role of enolate chemistry, considerable effort has been devoted to the development of increasingly effective protocols for the generation and utilization of enolate nucleophiles.<sup>2</sup> Recently, catalytic methods for the reductive generation of enolates from enones have been introduced, which, through variation of the electrophilic partner, have led to the inception of a rapidly growing family of catalytic transformations.<sup>3</sup> Such hydrometallative methods would be complemented by related catalytic carbometallative transformations. However, true carbometallative variants are uncommon,<sup>4</sup> as the majority of methods for catalytic conjugate addition–enolate-trapping require introduction of the electrophilic partner *subsequent* to carbometallative enolate generation.<sup>5,6</sup> As part of a program focused on the use of enones as latent enolates in catalysis,<sup>3,7</sup> and inspired by recent accounts of highly enantioselective Rh-catalyzed enone conjugate addition,<sup>8,9</sup> we herewith report a carbometallative variant of the catalytic aldol cycloreduction methodology previously reported from our lab,<sup>7a,c,d</sup> that is, a catalytic tandem conjugate addition–aldol cyclization. This methodology enables the formation of five- and six-membered ring products from aromatic and aliphatic mono-enone mono-ketone precursors. Notably, in a single manipulation, three contiguous stereogenic centers are created with high levels of relative and absolute stereochemical control (eq 1).

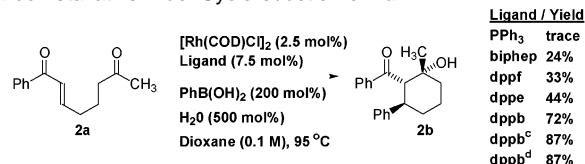


The design of a catalytic tandem conjugate addition–aldol cyclization reaction required consideration of several factors. As Rh-catalyzed conjugate addition is performed in aqueous organic media, trapping of the nascent Rh-enolate via carbonyl addition must be faster than enolate protonation. Furthermore, Rh-catalyzed addition of arylboronic acids to aldehydes is known to occur with great facility,<sup>10</sup> suggesting the chemoselectivity of aryl transfer could be problematic were aldehydes used as aldol partners. To address the former concern, reactions were performed with a minimum amount of water (5 equiv with respect to substrate). To address the latter concern, methyl ketones were utilized as the electrophilic aldol partner.

Initial efforts focused on establishing optimal conditions for the diastereoselective catalytic carbometallative aldol cycloreduction of mono-enone mono-ketone **2a**. Gratifyingly, upon an initial screen of achiral ligands, dppb was found to provide a 72% yield of the carbometallative cycloreduction product **2b** as a single diastereomer. Epimeric materials could not be detected by HPLC analysis. It was found that the yield of **2b** could be increased to 87% when the reactions were performed using triethylamine or potassium hydroxide as additives (Scheme 1).

Using these optimized conditions, the scope of the diastereoselective catalytic carbometallative aldol cycloreduction was inves-

### Scheme 1. Optimization of the Diastereoselective Carbometallative Aldol Cycloreduction of **2a**<sup>a</sup>



<sup>a</sup> (a) All reactions were performed on a 0.5 mmol scale. (b) Reactions were stopped after 18 h or upon complete consumption of **2a**. (c) Addition of TEA (1000 mol %). (d) Addition of KOH (10 mol %).

Table 1. Catalytic Diastereoselective Carbometallative Aldol Cycloreduction<sup>a</sup>

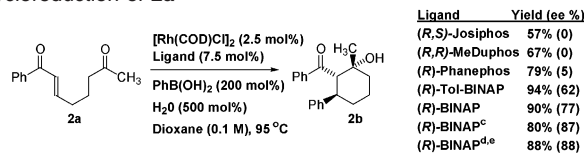
Entry	Substrate	Product	Isolated Yield
1			73% 87%
2			75% 45%
3			40% 70%
4			84%

<sup>a</sup> Procedure: See Supporting Information for a detailed experimental procedure.

tigated. This set of conditions, which makes use of phenylboronic acid, is effective for the formation of five- and six-membered ring products derived from aromatic and aliphatic mono-enone mono-ketone precursors (Table 1, entries 1 and 2). 2-Naphthylboronic acid also participates in the reaction (Table 1, entry 3). Finally, the high yielding carbometallative aldol cycloreduction of **5a** demonstrates the viability of substrates possessing heteroatoms in the tether connecting the aldol partners (Table 1, entry 4).  $\alpha,\beta$ -Unsaturated esters undergo conjugate addition when triethylamine is used as additive, but cyclization does not occur. All carbometallative aldol cycloreduction products were obtained with complete control of relative stereochemistry, as determined by HPLC analysis. The stereochemical assignment of both five- and six-membered ring products was corroborated by single-crystal X-ray diffraction analysis of **1b** and **2b**.

Having devised a general protocol for the diastereoselective carbometallative aldol cycloreduction of aromatic and aliphatic mono-enone mono-ketone precursors, we focused our efforts on

**Scheme 2.** Optimization of the Enantioselective Carbometallative Cycloreduction of **2a**<sup>a</sup>



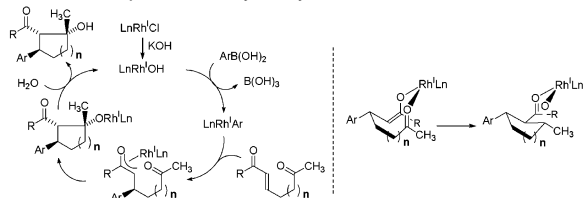
<sup>a</sup> (a) All reactions were performed on a 0.5 mmol scale. (b) Reactions were stopped after 18 h or upon complete consumption of **2a**. (c) Addition of TEA (1000 mol %). (d) Addition of KOH (10 mol %). (e) Rh(C<sub>2</sub>H<sub>4</sub>)<sub>2</sub>(acac) was used as catalyst precursor.

**Table 2.** Catalytic Enantioselective Carbometallative Aldol Cycloreduction<sup>a</sup>

Entry	Substrate	Product	Isolated Yield (ee%)
1			78% (77)
			88% (88)
2			88% (94)
			69% (95)

<sup>a</sup> Procedure: See Supporting Information for a detailed experimental procedure.

**Scheme 3.** Proposed Catalytic Cycle and Stereochemical Model



establishing optimal conditions for the enantioselective catalytic carbometallative aldol cycloreduction of substrate **2a**. A range of chiral ligands were screened (Scheme 2). In accordance with the results of Miyaura and Hayashi,<sup>9b</sup> BINAP was found to be the ligand of choice. Using the Rh–BINAP catalyst system, mono-enone mono-ketone **2a** was converted to the corresponding cyclized product **2b** in 88% chemical yield, >99% diastereomeric excess, and 88% enantiomeric excess as determined by chiral stationary phase HPLC analysis.

Using these optimized conditions, the scope of the enantioselective catalytic carbometallative aldol cycloreduction was investigated. This set of conditions, which makes use of phenylboronic acid, proved general for the formation of five- and six-membered ring products derived from aromatic and aliphatic mono-enone mono-ketone precursors (Table 2). The highest enantioselectivities are observed for methyl-substituted enone precursors **3a** and **4a**, which provide the cyclized products **3b** and **4b** in 94 and 95% enantiomeric excess, respectively (Table 2, entry 2).

A simplified mechanism for the carbometallative aldol cycloreduction of mono-enone mono-ketones, which is based on detailed mechanistic studies performed by Hayashi on the related Rh-catalyzed enone conjugate addition,<sup>9f</sup> is proposed above. A model accounting for the observed relative stereochemistry invokes the intermediacy of a *Z*-enolate and a Zimmerman–Traxler-type transition state (Scheme 3).

Motivated by the paucity of methods for catalytic aldol cyclization, diastereoselective catalytic hydrometallative aldol cycloreductions were developed by our lab.<sup>7a,c,d</sup> In this account, we report

a simple and effective method for the diastereo- and enantioselective catalytic carbometallative aldol cycloreduction of aromatic and aliphatic mono-enone mono-ketone precursors to yield five- and six-membered ring products. An attractive feature of this methodology resides in the ability to create three contiguous stereogenic centers, including a quaternary center, in a single manipulation with high levels of relative and absolute stereochemical control. Through variation of the electrophilic partner, it is our anticipation that this carbometallative methodology will stimulate further contributions to the rapidly growing family of catalytic reactions predicated on the use of enones as latent enolates.

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**Supporting Information Available:** Spectral data for all new compounds (<sup>1</sup>H NMR, <sup>13</sup>C NMR, IR, HRMS) (PDF). Crystallographic data for compounds **1b** and **2b** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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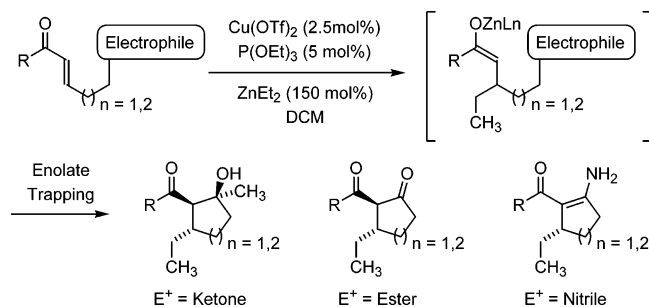
## Copper-Catalyzed Tandem Conjugate Addition–Electrophilic Trapping: Ketones, Esters, and Nitriles as Terminal Electrophiles

Kyriacos Agapiou, David F. Cauble, and Michael J. Krische\*

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

Received October 29, 2003; E-mail: mkrische@mail.utexas.edu

Tandem C–C bond formations are attractive methodological targets, as they enable rapid increases in molecular complexity.<sup>1,2</sup> Recently, we have explored conjugate addition–electrophilic trapping as a modular platform for catalytic reaction development.<sup>3–7</sup> Through variation of the nucleophilic initiator and electrophilic trap, a variety of catalytic conjugate addition–cyclizations are enabled: Co- and Rh-catalyzed conjugate reduction–aldol cyclizations,<sup>3,4</sup> related Co- and phosphine-catalyzed Michael cyclizations,<sup>3,5</sup> a two-component catalyst system for enone cycloallylation,<sup>6</sup> and finally, a diastereo- and enantioselective Rh-catalyzed conjugate addition–aldol cyclization have been developed.<sup>7</sup> To extend the latter reaction type, a study of Cu-catalyzed conjugate addition–electrophilic trapping was undertaken. Here, we report that exposure of enone substrates **1a–18a**, which possess appendant ketone, ester, and nitrile moieties, to organozinc reagents in the presence of catalytic Cu(OTf)<sub>2</sub>/P(OEt)<sub>3</sub> provides the cyclized products in good to excellent yields and diastereoselectivities. *These results represent the first use of ketones, esters and nitriles as terminal electrophiles in Cu-catalyzed conjugate addition–electrophilic trapping.*



Cu-catalyzed addition of organozinc reagents to  $\alpha,\beta$ -unsaturated carbonyl compounds has been the subject of intensive investigation.<sup>8</sup> Enantioselective variants of the parent transformation now encompass diverse  $\alpha,\beta$ -unsaturated substrates.<sup>9</sup> Moreover, trapping of the intermediate Zn-enolate has been achieved using aldehydes,<sup>10</sup> Pd- $\pi$ -allyls,<sup>10a,11</sup> halides and tosylates,<sup>12</sup> and oxocarbenium ions<sup>13</sup> (by way of acetal decomposition). While ketone aldols are observed as homocondensation side products in Cu-catalyzed conjugate addition,<sup>10d</sup> the deliberate use of ketones as electrophilic traps is reported to fail in the absence of strong Lewis acidic additives.<sup>13</sup> To our knowledge, the use of esters and nitriles as terminal electrophiles in Cu-catalyzed conjugate addition remains unexplored.

It was recognized that the limitations inherent to the use of such recalcitrant electrophiles *vis-à-vis* intermolecular condensation might be overcome in the case of the analogous intramolecular processes, because of a reduced entropy of activation. To assess the veracity of this analysis, keto-enone **2a** was subjected to conditions for Cu-catalyzed conjugate addition.

Gratifyingly, it was found that exposure of keto-enone **2a** to Et<sub>2</sub>Zn in the presence of Cu(OTf)<sub>2</sub> and triethyl phosphite gave the

**Table 1.** Cu-Catalyzed Tandem Conjugate Addition–Aldol Cyclization<sup>a</sup>

Entry	Substrate	Product <sup>b</sup>	Yield (%)	(d.r.) <sup>d</sup>
1			1b, R = CH <sub>3</sub> : 83% 1c, R = CH <sub>2</sub> CH <sub>3</sub> : 81% 1d, R = CH(CH <sub>3</sub> ) <sub>2</sub> : 76% <sup>c</sup> 1e, R = (CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub> : 91%	(>95:1) (>95:1) (>95:1) (>95:1)
2			98%	(>95:1)
3			77%	(3:1)
4			96%	(2.2:1)
5			99%	(>95:1)
6			99%	(10:1) <sup>e</sup>
7			96%	(2:1)
8			84%	(8:1)
9			94%	(>95:1)
10			78%	(3:1)

<sup>a</sup> See Supporting Information for detailed experimental procedures. <sup>b</sup> The structural assignment of **6b**, **8b–10b** is based on X-ray diffraction analysis. <sup>c</sup> Compound **1d** was prepared via Cu-catalyzed addition of the Grignard reagent as described in the Supporting Information. <sup>d</sup> Reflects ratio of *syn*-aldol to *anti*-aldol product. <sup>e</sup> Reflects ratio of *cis*-fused to *trans*-fused hydrindane.

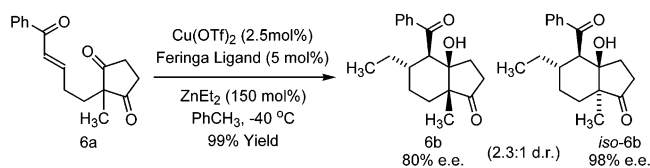
**Table 2.** Cu-Catalyzed Tandem Conjugate Addition–Dieckmann and Blaise Condensation<sup>a</sup>

Entry	Substrate	Product <sup>b</sup>	Yield (%)
1			93%
			88%
			88%
2			87%
3			90%
4			93%
5			84%
			91%
			87%
6			73% <sup>c</sup>
7			98%
8			85%

<sup>a</sup> See Supporting Information for detailed experimental procedures. <sup>b</sup> The structural assignment of **15b** is based on X-ray diffraction analysis. <sup>c</sup> The vinylogous amide **16b** spontaneously hydrolyzes in situ to afford  $\beta$ -diketone **12b**.

desired cyclization product **2b** in nearly quantitative yield and as a single diastereomer. Under these optimized conditions, Cu-catalyzed tandem conjugate addition–aldolization of keto-enone substrates **1a–10a** was demonstrated (Table 1). Inspired by these results and the established ability of zinc-enolates to condense with recalcitrant electrophiles such as nitriles,<sup>14</sup> related catalytic tandem conjugate addition–Dieckmann and Blaise cyclizations were explored. Upon application of standard reaction conditions to mono-enone mono-esters **11a–14a** and mono-enone mono-nitriles **15a–18a**, the corresponding cyclized products were obtained in excellent yield (Table 2). Finally, to demonstrate the feasibility of developing enantioselective variants of these tandem C–C bond formations, enone-dione **6a** was subjected to standard reaction conditions using Feringa's phosphoramidite ligand.<sup>8c</sup> While diastereoselectivity suffered, high levels of asymmetric induction were observed.

In summation, the use of ketones, esters, and nitriles as terminal electrophiles in Cu-catalyzed tandem conjugate addition–electro-



philic trapping has been demonstrated. Future studies will focus on the development of related catalytic tandem C–C bond forming transformations with attendant applications toward the total synthesis of complex natural products.

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

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

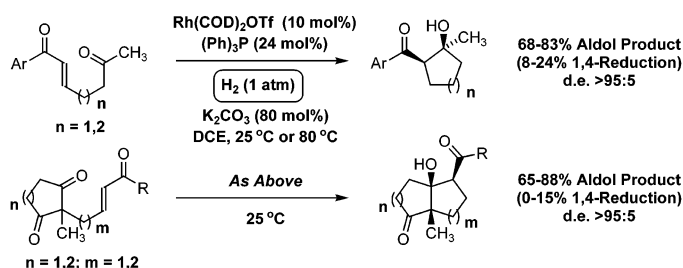
Ryan R. Huddleston and Michael J. Krische\*

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

mkrische@mail.utexas.edu

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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.<sup>1</sup> Recently, a method for the production and catalytic transformation of transition metal enolates via enone hydrogenation was disclosed by our lab.<sup>2</sup> 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.<sup>3,4</sup> Applicability of this methodology vis-à-vis intra- and intermolecular condensation with aldehyde partners has been

established.<sup>2</sup> 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.<sup>5</sup> Through the use of dione acceptors, 3-stereogenic centers, including 2-contiguous quaternary centers, are

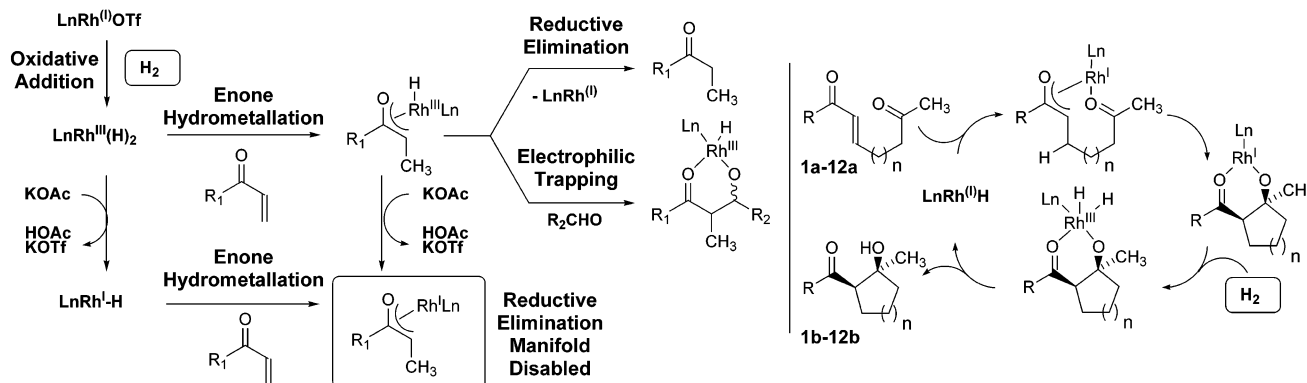
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**Scheme 1.** Formal Heterolytic Activation of Elemental Hydrogen Mitigates Competitive Conjugate Reduction Manifolds by Enabling Monohydride-Based Catalytic Cycles.



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.<sup>6</sup> 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.<sup>7</sup> 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,<sup>8,9</sup> cationic rhodium complexes appear to operate through formal heterolytic hydrogen activation pathways.<sup>7,10,11</sup> This is likely due to the enhanced acidity of cationic rhodium hydrides with respect to their neutral counterparts.<sup>12</sup> Predicated on this analysis, and given the established efficiency of aldol additions involving rhodium enolates,<sup>13</sup> aldol cycloreduction

under hydrogenation conditions was studied using (COD)<sub>2</sub>-Rh<sup>I</sup>(OTf) as a precatalyst. A mechanism was envisioned whereby enolate-hydrogen reductive elimination pathways are disabled through deprotonation of the (hydrido)metal intermediates LnRh<sup>III</sup>(H)<sub>2</sub> or (enolato)Rh<sup>III</sup>(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 <sup>1</sup>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.<sup>5</sup> 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*-

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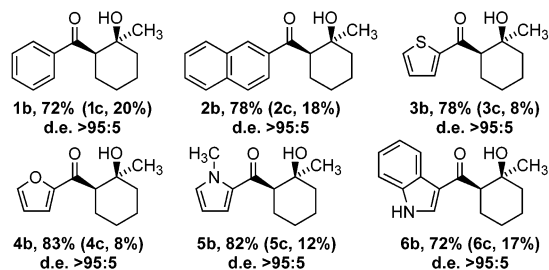
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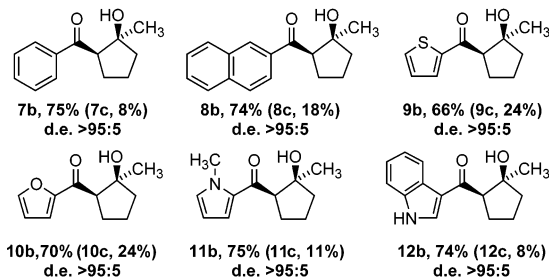
(14) Procedure: To a 13 × 100 mm test tube charged with Rh(COD)<sub>2</sub>OTf (0.0462 mmol, 10 mol %) and Ph<sub>3</sub>P (0.111 mmol, 24 mol %) was added DCE (0.185 M, 2.5 mL). The mixture was stirred for 10 min under an argon atmosphere, at which point the substrate (0.462 mmol, 100 mol %) and K<sub>2</sub>CO<sub>3</sub> (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  $13 \times 100$  mm sealed test tubes (Figure 1).



**Figure 1.** Catalytic hydrogenative cycloreduction of keto-enones: six-membered ring formation.<sup>14</sup>

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 <sup>1</sup>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).

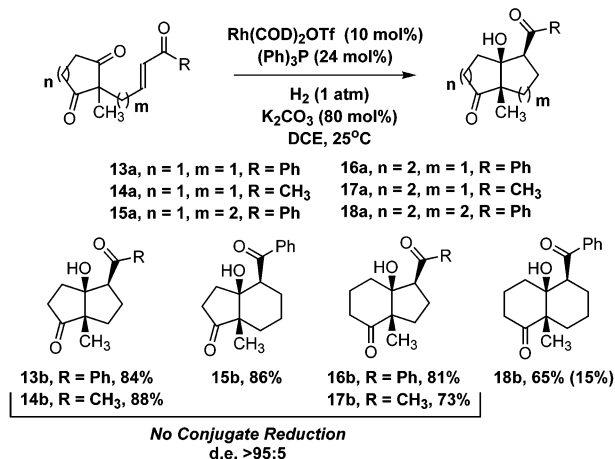


**Figure 2.** Catalytic hydrogenative cycloreduction of keto-enones: five-membered ring formation.<sup>14</sup>

The cycloreduction of monoene 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 <sup>1</sup>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).

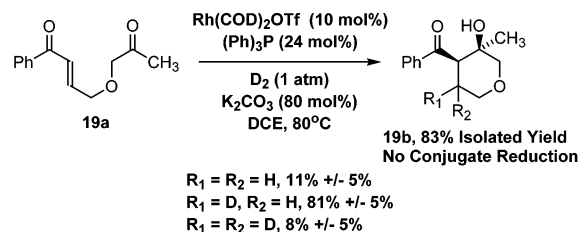
**Scheme 2.** Catalytic Hydrogenative Cycloreduction of Dione-enones<sup>14</sup>



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  $\beta$ -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 hydro-metalation is reversible, i.e.,  $\beta$ -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 ( $^1\text{H}$  NMR,  $^{13}\text{C}$  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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