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

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Enolate chemistry represents a methodological cornerstone of organic synthesis, encompassing numerous classical transformations, including the aldol reaction.[1] 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.[2] 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.[3] Such hydrometallative methods would be complemented by related catalytic carbometallative transformations. However, true carbometallative variants are uncommon,[4] as the majority of methods for catalytic conjugate addition−enolate-trapping require introduction of the electrophilic partner *subsequent* to carbometallative enolate generation.[5,6] As part of a program focused on the use of enones as latent enolates in catalysis,[3,7] and inspired by recent accounts of highly enantioselective Rh-catalyzed enone conjugate addition,[8,9] we herewith report a carbometallative variant of the catalytic aldol cycloreduction methodology previously reported from our lab,[7a,c,d] 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).
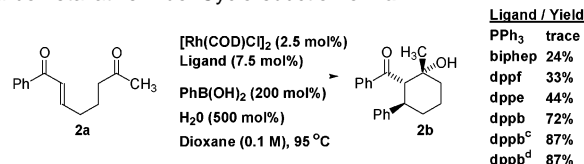

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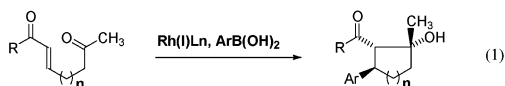
The design of a catalytic tandem conjugate addition−aldol cyclization reaction required consideration of several factors. As Rh-catalyzed conjugate addition is performed in aqueous organic media, trapping of the nascent Rh-enolate via carbonyl addition must be faster than enolate protonation. Furthermore, Rh-catalyzed addition of arylboronic acids to aldehydes is known to occur with great facility,[10] 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**[a]

[a] (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 %).

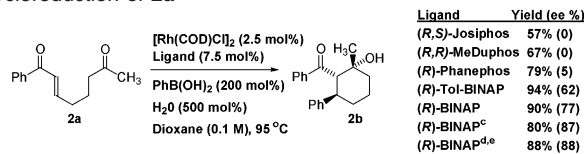**Table 1.** Catalytic Diastereoselective Carbometallative Aldol Cycloreduction[a]

[a] 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). α,β-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**[a]

| Ligand	Yield (ee %)
(R,S)-Josiphos	57% (0)
(R,R)-MeDuphos	67% (0)
(R)-Phanephos	79% (5)
(R)-Tol-BINAP	94% (62)
(R)-BINAP	90% (77)
(R)-BINAP[c]	80% (87)
(R)-BINAP[d,e]	88% (88)

[a] (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$_2$H$_4$)$_2$(acac) was used as catalyst precursor.

Table 2. Catalytic Enantioselective Carbometallative Aldol Cycloreduction[a]

Entry	Substrate	Product	Isolated Yield (ee%)
1	**1a**, n = 1 / **2a**, n = 2	**1b** / **2b**	78% (77) / 88% (88)
2	**3a**, n = 1 / **4a**, n = 2	**3b** / **4b**	88% (94) / 69% (95)

[a] Procedure: See Supporting Information for a detailed experimental procedure.

Scheme 3. Proposed Catalytic Cycle and Stereochemical Model
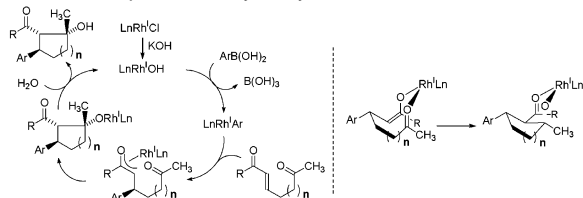
establishing optimal conditions for the enantioselective catalytic carbometallative aldol cycloreduction of substrate **2a**. A range of chiral ligands were screened (Scheme 2). In accordance with the results of Miyaura and Hayashi,[9b] BINAP was found to be the ligand of choice. Using the Rh−BINAP catalyst 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,[9f] 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.[7a,c,d] 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.

Supporting Information Available: Spectral data for all new compounds (^{1}H NMR, ^{13}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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