

Diastereoselective Cobalt-Catalyzed Aldol and Michael Cycloreductions

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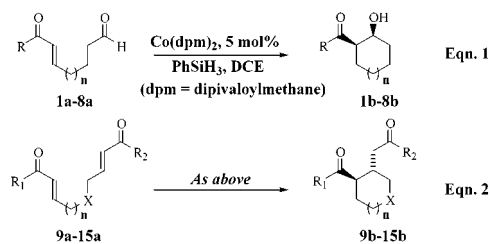
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Many classes of chemical transformations exist for which catalytic variants have not been devised or require further development. The aldol and Michael reactions represent classical methods of carbon–carbon bond formation that have found extensive 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 variants¹ 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.² 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 β -dicarbonyl nucleophiles.^{3,4}

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 α,β -unsaturated carbonyl compounds with aldehydes in the presence of a hydride donor, that is, a “reductive aldol” reaction, has been described.⁵ 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.^{6,7} 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 $\text{Co}(\text{dpm})_2$ (dpm = dipivaloylmethane), which utilizes phenylsilane as the terminal reductant, exhibits poor diastereoselectivity.^{5d} 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.⁸

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

(1) For reviews, see: (a) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1353. (b) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432. (c) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357. (d) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. III, p 1. (e) Braun, M. In *Stereoselective Synthesis, Methods of Organic Chemistry* (Houben-Weyl), ed. E21; Helmchen, G., Hoffman, R., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 3, p 1730.

(2) (a) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168. (b) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (c) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003. (d) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466.

(3) For a review, see: Yamaguchi, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. III, p 1121.

(4) For selected examples, see: (a) Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194. (b) Evans, D. A.; Willis, M. C.; Johnston, J. N. *Org. Lett.* **1999**, *1*, 865. (c) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994. (d) Zhang, F.-U.; Corey, E. J. *Org. Lett.* **2001**, *3*, 639.

(5) (a) Revis, A.; Hilty, T. K. *Tetrahedron Lett.* **1987**, *28*, 4809. (b) Matsuda, I.; Takahashi, K.; Sata, S. *Tetrahedron Lett.* **1990**, *31*, 5331. (c) Kiyooka, S.; Shimizu, A.; Torii, S. *Tetrahedron Lett.* **1998**, *39*, 5237. (d) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 2005. (e) Taylor, S. J.; Morken, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 12202. (f) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528.

(6) Asymmetric aldol cyclodehydrations have been catalyzed using antibodies and chiral amines: (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *Org. Lett.* **1999**, *1*, 59. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (c) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (d) Agami, C.; Platzer, N.; Sevestre, H. *Bull. Soc. Chim. Fr.* **1987**, *2*, 358.

(7) A radical-mediated aldol/Michael cycloreduction has been described: Suwa, T.; Nishino, K.; Miyatake, M.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **2000**, *41*, 3403.

(8) (a) Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 3182. (b) Crowe, W. E.; Rachita, M. *J. Am. Chem. Soc.* **1995**, *117*, 6787.

Table 1. Cobalt-Catalyzed Aldol and Michael Cycloreductions^a

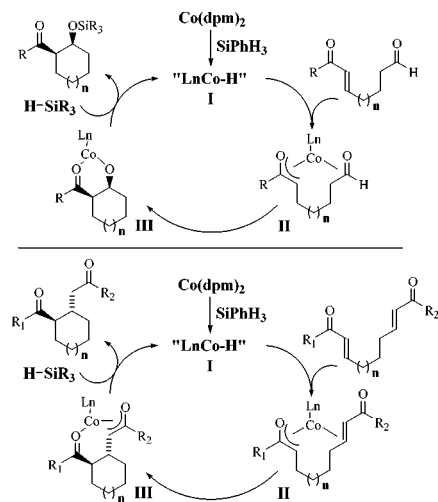
Entry	Substrate	Product	Temperature	PhSiH ₃ (eq.)	Isolated Yield (%) (Average of 2 Runs)
1			25°C	1.2	70
2			25°C	1.2	87
	2a, R = Ph	2b, R = Ph	25°C	1.2	72
	3a, R = <i>p</i> -CF ₃ Ph	3b, R = <i>p</i> -CF ₃ Ph	25°C	1.2	68
	4a, R = 2-naphthyl	4b, R = 2-naphthyl	25°C	1.2	68
3			25°C	1.2	38
4			25°C	1.2	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 ₁ =Ph, R ₂ =CH ₃				
	12c, R ₁ =CH ₃ , R ₂ =Ph				
	12b:12c (3:1)				
10			50°C	2.4	54
	13b, R ₁ =Ph, R ₂ =2-furyl				
	13c, R ₁ =2-furyl, R ₂ =Ph				
	13b:13c (1:1)				
11			50°C	2.4	52
12			50°C	2.4	68

^a Procedure: Co(dpm)₂ (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.¹⁰ 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” σ -bond metathesis. Mechanisms involving σ -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.⁸ 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)₂ 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**. σ -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)₂ 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)₂ may 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 (¹H NMR, ¹³C NMR, IR, HRMS). This material is available free of charge via the Internet at <http://pubs.acs.org>.

(9) (a) Chalk, A. J.; Harrod, J. F. *J. Am. Chem. Soc.* **1965**, *87*, 16. (b) This mechanism is the subject of debate: Bosnich, B. *Acc. Chem. Res.* **1998**, *31*, 667.