J|A|C|S
ARTICLES
Published on Web 07/23/2002

Diastereoselective Cycloreductions and Cycloadditions Catalyzed by $Co(dpm)_2$-Silane (dpm = 2,2,6,6-tetramethylheptane-3,5-dionate): Mechanism and Partitioning of Hydrometallative versus Anion Radical Pathways

Long-Cheng Wang,[†] Hye-Young Jang,[†] Yeonsuk Roh,[†] Vincent Lynch,[†] Arthur J. Schultz,[‡] Xiaoping Wang,[‡] and Michael J. Krische*,[†]

Contribution from the Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712, and Intense Pulsed Neutron Source, Argonne National Laboratory, Argonne, Illinois 60439-4814

Received February 13, 2002

Abstract: In the presence of phenylsilane and 5 mol % cobalt(II) bis(2,2,6,6-tetramethylheptane-3,5-dionate), aryl-substituted monoenone monoaldehydes and bis(enones) undergo reductive cyclization to afford *syn*-aldol and *anti*-Michael products, respectively. For both aldol and Michael cycloreductions, five- and six-membered ring formation occurs in good yield with high levels of diastereoselectivity. Cycloreduction of monoenone monoaldehyde **1a** in the presence of d^3-phenylsilane reveals incorporation of a single deuterium at the enone β-position as an equimolar mixture of epimers, inferring rapid isomerization of the kinetically formed cobalt enolate prior to cyclization. The deuterated product was characterized by single-crystal neutron diffraction analysis. For bis(enone) substrates, modulation of the silane source enables partitioning of the competitive Michael cycloreduction and [2 + 2] cycloaddition manifolds. A study of *para*-substituted acetophenone-derived bis(enones) reveals that substrate electronic features also direct partitioning of cycloreduction and cycloaddition manifolds. Further mechanistic insight is obtained through examination of the effects of enone geometry on product stereochemistry and electrochemical studies involving cathodic reduction of bis(enone) substrates. The collective experiments reveal competitive enone reduction pathways. Enone hydrometalation produces metallo-enolates en route to aldol and Michael cycloreduction products, that is, products derived from coupling at the α-position of the enone. Electron-transfer-mediated enone reduction produces metallo-oxy-π-allyls en route to [2 + 2] cycloadducts and, under Ni catalysis, homoaldol cycloreduction products, that is, products derived from coupling at the β-position of the enone. The convergent outcome of the metal-catalyzed and electrochemically induced transformations suggests the proposed oxy-π-allyl intermediates embody character consistent with the mesomeric metal-complexed anion radicals.

Introduction

The aldol and Michael reactions represent classical methods of stereogenic carbon−carbon bond formation whereby an enolate nucleophile undergoes addition to an electron-deficient π-unsaturated partner. To adequately address the issues of selectivity posed by these transformations, considerable effort has been applied toward the development of stereoselective catalytic processes that yield formal aldol and Michael products.[1,2] The ideal aldol or Michael reaction would involve the condensation of unmodified nucleophilic and electrophilic partners to yield adducts that embody control of both relative and absolute stereochemistry. For the aldol reaction, recently described enantioselective catalytic systems promoting the direct condensation of unmodified ketone and aldehyde partners are remarkable as they approach this ideal.[3] Nevertheless, current catalytic systems fail to address the fundamental issue of

* To whom correspondence should be addressed. E-mail: mkrische@mail.utexas.edu.
[†] University of Texas at Austin.
[‡] Argonne National Laboratory.

(1) For selected reviews on catalytic enantioselective aldol reactions, see: (a) Machajewski, T. D.; Wong, C.-H.; Lerner, R. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352. (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) For selected reviews on catalytic enantioselective Michael reactions, see: (a) Yamaguchi, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. III, p 1121. (b) Krause, N.; Hoffman-Röder, A. *Synthesis* **2001**, 171.

(3) For selected examples of direct catalytic enantioselective aldol reactions, see: (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. (e) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367.

10.1021/ja020223k CCC: $22.00

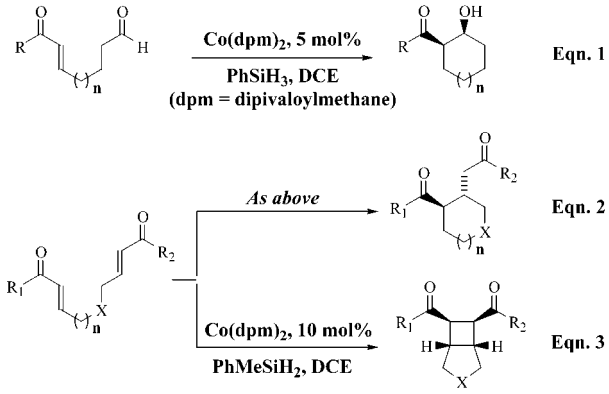
regioselective enolate formation and thus require symmetric ketone partners, ketones possessing a single set of acidic hydrogens or the use of hydroxy-directing groups. Enantioselective catalytic systems for direct Michael reaction exhibit similar restrictions in scope.[4,5]

An alternative strategy toward catalytic stereoselective aldol and Michael processes involves the use of latent enolates. Enol derivatives are most commonly employed in this capacity.[1,2] However, as for the direct enantioselective catalytic aldol and Michael reactions, regioselective enolate generation is again problematic vis-à-vis preparation of enol derivatives from unsymmetrical ketone precursors. Additionally, the chemical lability of enol derivatives detracts from their utility.

As demonstrated in seminal studies by Stork, nucleophilic activation of enones via conjugate reduction enables regioselective enolate formation from chemically robust precursors.[6] The development of selective catalytic systems for the nucleophilic activation of enones, which are suited to a range of electrophilic partners, constitutes a largely unresolved methodological challenge.[7] It was not until 1987 that the first catalytic enone-aldehyde coupling, or "reductive aldol" process, was described, which employed a Rh(III) precatalyst.[8a] A second Rh-based catalyst system was described in 1990.[8b] Transition metals other than rhodium catalyze the reductive aldol reaction. Co(II)-,[8c] Pd(0)-,[8d] and Cu(I)-based[8e] catalyst systems are known. The scope of the Rh-based catalyst system has been extended to include diastereoselective[8f] and enantioselective variants.[8g] Finally, an enantioselective Ir-based catalyst has been described.[8h] To the best of our knowledge, analogous catalytic reductive Michael processes are unknown, as existing methods for metal-catalyzed enone hydrodimerization primarily afford products of β,β-coupling.[9,10]

Despite a wealth of research on catalytic aldol and Michael processes, metal-catalyzed aldol and Michael cyclizations remain undeveloped.[11−13] Recently, a catalytic method for aldol and Michael cycloreduction was reported from our labs (Scheme 1, eqs 1 and 2, respectively).[14] These catalytic reactions exhibit exceptionally high levels of *syn*- and *anti*-diastereoselectivity, respectively, and are viable for both five- and six-membered ring formations. An ancillary study describes a related metal-catalyzed [2 + 2] cycloaddition whereby bis(enones) are transformed to diastereomerically pure bicyclo[3.2.0] ring systems (Scheme 1, eq 3).[15] In this account, studies pertaining to the mechanism and partitioning of these catalytic cycloreductions and cycloadditions are presented.

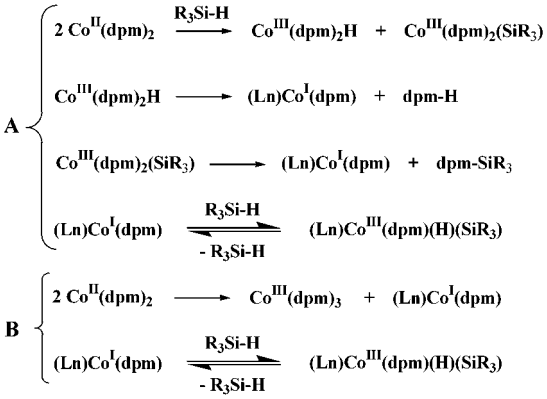
Scheme 1



Mechanism

The interaction of silane with $Co(dpm)_2$ is a key feature of the cycloreduction mechanism. Tetrahedral d^7-metal complexes such as $Co(dpm)_2$[16] are known to participate in single electron oxidative addition.[17] Disproportionation of Co(II) is also well documented.[18] Thus, formation of the hydrido-metal intermediates required for initiation of the catalytic cycle via enone hydrometalation may arise through (A) single electron oxidative addition of silane, with subsequent reductive elimination to produce Co(I), followed by two-electron oxidative addition to silane or (B) disproportionation followed by two-electron oxidative addition of silane to Co(I). The latter pathway is supported by HRMS analysis of $Co(dpm)_2$ in the presence and absence of $PhMeSiH_2$, which in the former case reveals an intense signal consistent with the mass of $Co(dpm)_3$. Direct oxidative addition of silane to Co(II) is unlikely as the resulting Co(IV) intermediate represents an unstable oxidation state (Scheme 2).[19]

Scheme 2



In principle, σ-bond metathesis of silane to $Co(dpm)_2$ may account for the formation of hydrido-metal intermediates. Mechanisms involving σ-bond metathesis have been proposed for the Ti-catalyzed cycloreduction of 1,5-enones and 1,5-enals

(4) For selected examples of direct catalytic enantioselective Michael reactions, see: (a) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 4251. (b) Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097. (c) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423. (d) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 4441.

(5) The majority of catalytic enantioselective Michael reactions require use of preformed enol derivatives or β-dicarbonyl nucleophiles: (a) Narasaka, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223. (b) Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194. (c) Zhang, F.-U.; Corey, E. J. *Org. Lett.* **2001**, *3*, 639. (d) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480.

(6) (a) Stork, G.; Rosen, P.; Goldman, N. L. *J. Am. Chem. Soc.* **1961**, *83*, 2965. (b) Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J. *J. Am. Chem. Soc.* **1965**, *87*, 275.

(7) For a review, see: Huddleston, R. R.; Krische, M. J. *Synlett* **2002**, in press.

(8) For 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.

(9) For a review on the metal-catalyzed dimerization of electron-deficient alkenes, see: Tembe, G. L.; Bandyopadhyay, A. R.; Ganeshpure, P. A.; Satish, S. *Catal. Rev.-Sci. Eng.* **1996**, *38*, 299.

(10) For examples of cobalt-catalyzed acrylate and enone hydrodimerization, see: (a) Kanai, H.; Okada, M. *Chem. Lett.* **1975**, 167. (b) Kanai, H.; Ishii, K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1015. (c) Kanai, H. *J. Mol. Catal.* **1981**, *12*, 231.

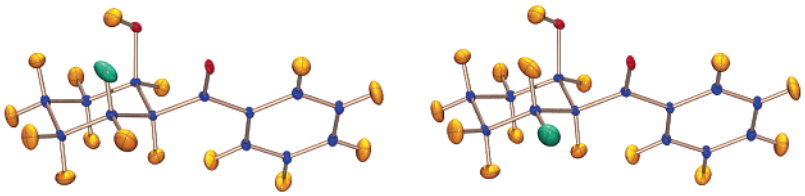


Figure 1. Structure of deuterio-**1b** determined by single-crystal neutron diffraction. The two equimolar epimers are disordered on the same crystallographic site. Atoms are drawn at their 50% probability level. Left: *syn*,*syn*-epimer. Right: *syn*,*anti*-epimer. Atom colors: H, orange; D, green; C, blue; O, red.[30]

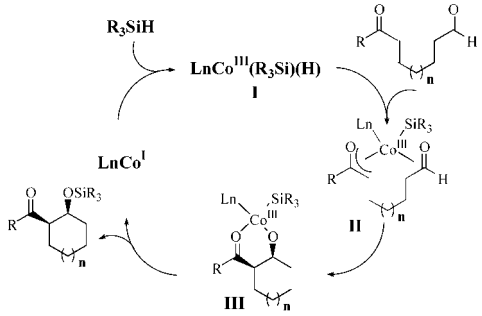
Table 1. Site Occupancies of H and D Atoms at the β-Position As Determined by Neutron Diffraction of Monocrystalline Deuterio-**1b**[30]

atom	occupancy	total occupancy	total H/D ratio	site H/D ratio	D syn/anti ratio
H-syn	0.476(6)	0.988(9)	0.976(9)	0.908(9) (syn)	0.518(8) (syn)
H-anti	0.512(6)				
D-syn	0.524(6)	1.012(9)		1.049(9) (anti)	0.482(8) (anti)
D-anti	0.488(6)				

conducted in the presence of silane.[20,21] This mechanistic motif is well recognized for catalytic reactions of early transition metals, actinides, and lanthanides.[22] More recently, σ-bond metathesis pathways have been proposed for catalytic reactions of late transition metals with silanes and boranes.[23]

Given the preceding discussion, a catalytic mechanism predicated on a Co(I)−Co(III) cycle is proposed as a working model (Scheme 3). Oxidative addition of silane to LnCo(I) affords hydrido-cobalt species **I**. Hydrometalation of the enone provides cobalt enolate **II**, which undergoes carbonyl addition to the appendant aldehyde to provide cobalt-alkoxide **III**. Oxygen−silicon reductive elimination liberates the aldol product in the form of the silyl ether and regenerates LnCo(I) to complete the catalytic cycle. An analogous catalytic cycle is envisioned for the related Michael cycloreduction. Evolution of elemental hydrogen is observed throughout the reaction suggesting competitive dehydrogenative coupling of silane.[24] The proposed mechanism bears similarity to the Chalk−Harrod process,[25] which (although subject to debate[26]) is the commonly accepted mechanism for alkene hydrosilylation.

Scheme 3

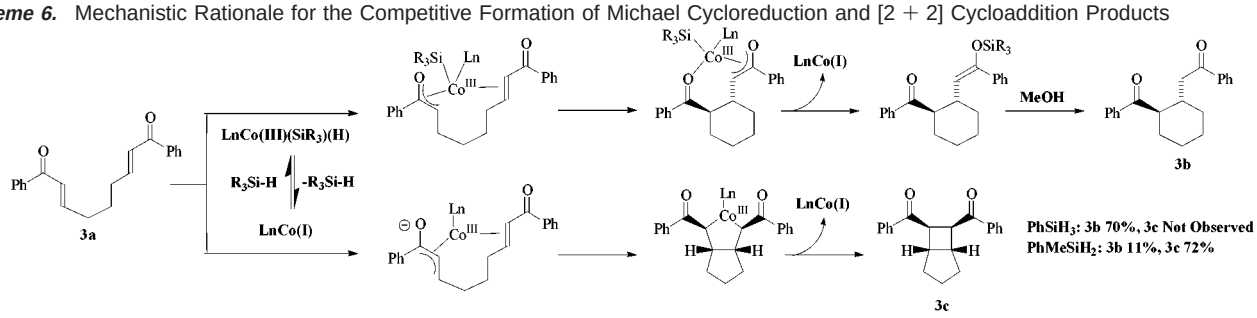


A related mechanistic possibility involves oxygen−silicon reductive elimination at the stage of the cobalt enolate **II** followed by condensation of the resulting silyl enol ether with the appendant aldehyde. This pathway is observed for the intermolecular Rh-catalyzed reductive aldol reaction utilizing dichloromethylsilane as terminal reductant.[8h] Here, the intermediate enol silane was isolated and exposed to benzaldehyde in the absence of catalyst to provide the *syn*-aldol product.[27] For the cycloreductions reported herein, this pathway is unlikely. While the spontaneous aldol condensation of trichlorosilyl enol ethers and related ketene acetals has been reported,[28] aliphatic enol silanes covalently appended to aldehydes and capable of five-membered ring formation do not spontaneously react.[29]

Deuterium labeling studies employing d^3-phenylsilane support the proposed mechanism. Exposure of **1a** to d^3-phenylsilane under standard conditions results in the formation of the monodeuterated aldol cycloreduction product deuterio-**1b** as an equimolar mixture of stereoisomers (Figure 1). The stereochemical assignment deuterio-**1b** was established by ^{1}H NMR analysis and single-crystal neutron diffraction analysis, the latter enabling a precise assessment of the site occupancy of deuterium

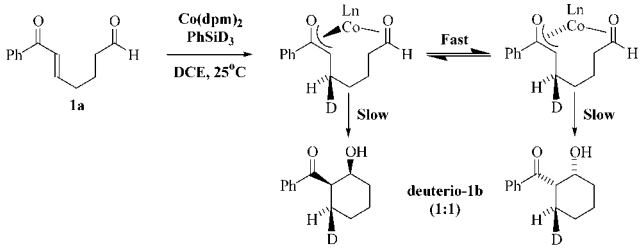
(11) Aldol cyclizations have been catalyzed by antibodies and chiral amines: (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *Org. Lett.* **1999**, *1*, 59. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (c) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (d) Agami, C.; Platzer, N.; Sevestre, H. *Bull. Soc. Chim. Fr.* **1987**, *2*, 358. (e) Eder, U.; Weichert, R.; Sauer, G. German Patent DE 2014757, Oct. 7, 1971.
(12) Hydride-mediated aldol and Michael cycloreductions have been described: Suwa, T.; Nishino, K.; Miyatake, M.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **2000**, *41*, 3403.
(13) An intramolecular Mukaiyama−Michael addition has been reported: Jung, M. E.; McCombs, C. A.; Takeda, Y.; Pan, Y.-G. *J. Am. Chem. Soc.* **1981**, *103*, 6677.
(14) Baik, T.-G.; Luiz, A. L.; Wang, L.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 5112.
(15) Baik, T.-G.; Luiz, A. L.; Wang, L.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 6716.
(16) $Co(dpm)_2$ was characterized by single-crystal X-ray diffraction. See Supporting Information for crystallographic data.
(17) Halpern, J. *Acc. Chem. Res.* **1970**, *3*, 386.
(18) Socol, S. M.; Verkade, J. G. *Inorg. Chem.* **1986**, *25*, 2658.
(19) Topich, J.; Halpern, J. *Inorg. Chem.* **1979**, *18*, 1339.
(20) (a) Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6785. (b) Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 3182.
(21) (a) Crowe, W. E.; Rachita, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 6787. (b) Crowe, W. E.; Vu, A. T. *J. Am. Chem. Soc.* **1996**, *118*, 1557.
(22) For reviews, see: (a) Folga, E.; Woo, T.; Ziegler, T. In *Theoretical Aspects of Homogeneous Catalysis*; van Leeuwen, P. W. N. M., Morokuma, K., van Lenthe, J. H., Eds.; Kluwer: Dordrecht, The Netherlands, 1995; p 115 and references therein. (b) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154. (c) Crabtree, R. H. *Chem. Rev.* **1995**, *95*, 987. (d) Jones, W. D. In *Selective Hydrocarbon Activation*; Davies, J. A., Watson, P. L., Greenberg, A., Liebman, J. F., Eds.; Wiley-VCH: Weinheim, Germany, 1990; pp 113−148.
(23) (a) Hartwig, J. F.; Bhandari, S.; Rablen, P. R. *J. Am. Chem. Soc.* **1994**, *116*, 1839. (b) Milet, A.; Dedieu, A.; Kapteijn, G.; van Koten, G. *Inorg. Chem.* **1997**, *36*, 3223. (c) LaPointe, A. M.; Rix, F. C.; Brookhart, M. *J. Am. Chem. Soc.* **1997**, *119*, 906. (d) Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797.
(24) Rosenberg, L.; Davis, C. W.; Yao, J. *J. Am. Chem. Soc.* **2001**, *123*, 5120 and references therein.
(25) Chalk, A. J.; Harrod, J. F. *J. Am. Chem. Soc.* **1965**, *87*, 16.
(26) (a) Chatani, N.; Kodama, T.; Kajikawa, Y.; Murakami, H.; Kakiuchi, F.; Ikeda, S.-I.; Murai, S. *Chem. Lett.* **2000**, 14. (b) Brookhart, M.; Grant, B. E. *J. Am. Chem. Soc.* **1993**, *115*, 2151. (c) Bosnich, B. *Acc. Chem. Res.* **1998**, *31*, 667 and references therein.
(27) Zhao, C.-X.; Bass, J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 2839.
(28) Denmark, S. E.; Wong, K. T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333.
(29) (a) Enda, J.; Kuwajima, I. *J. Am. Chem. Soc.* **1985**, *107*, 5495. (b) Enda, J.; Matsutani, T.; Kuwajima, I. *Tetrahedron Lett.* **1984**, *25*, 5307.

Scheme 6. Mechanistic Rationale for the Competitive Formation of Michael Cycloreduction and [2 + 2] Cycloaddition Products



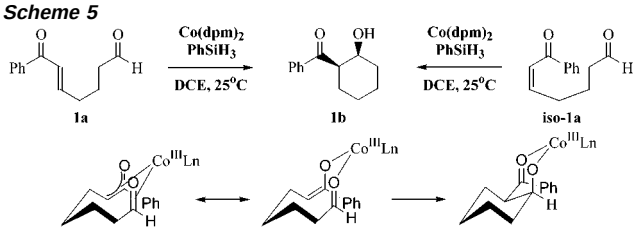
at the β-position (Table 1).[30] Related deuterium labeling studies on the Mn(dpm)$_3$-phenylsilane catalyst system for enone conjugate reduction also reveal incorporation of a single deuterium at the β-position.[31] The formation of deuterio-**1b** as a 1:1 mixture of epimers suggests π-facial interconversion of the kinetically formed metallo-enolate is faster than aldehyde addition. Both isomerization and aldehyde addition are likely to occur through the η^1-haptomer of the enolate, as supported by related studies involving Ni(II)-enolates (Scheme 4).[32a]

Scheme 4



Also consistent with the proposed mechanism (Scheme 3), the stereochemical outcome of the aldol cycloreduction is independent of alkene geometry.[32] Both *trans*- and *cis*-configured enones **1a** and iso-**1a** provide the *syn*-aldol cycloreduction product. The observed *syn*-diastereoselectivity is accounted for on the basis of a Zimmerman−Traxler type transition state.[33] Coordination of the reacting partners in the form of their higher haptomers results in chelates of normal ring size. *Z*-Enolate formation is preferred on a steric basis, that is, allylic 1,2 strain.[34] A similar stereochemical model has been proposed for related hydride-mediated aldol and Michael cycloreductions (Scheme 5).[12]

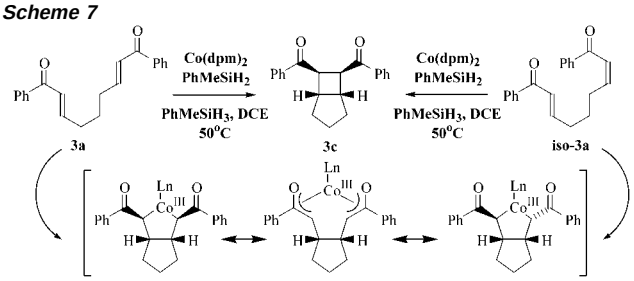
Scheme 5



Competitive α- and β-Coupling Manifolds. Upon exposure of bis(enone) **3a** to the Co(dpm)$_2$-silane catalyst system, both α- and β-coupled products are observed. Here, α-coupling is represented by the formation of Michael cycloreduction product **3b**, whereas β-coupling is represented by the formation of [2 + 2] cycloadduct **3c**. As previously demonstrated, these competitive reaction manifolds may be partitioned as a function of silane; phenylsilane promotes the Michael cycloreduction pathway, while methylphenylsilane promotes the [2 + 2] cycloaddition pathway.[15] A mechanistic rationale for the partitioning of the cycloreduction and cycloaddition pathways is proposed in Scheme 6. In the presence of phenylsilane, facile oxidative addition promotes the hydrometallative pathway en route to Michael cycloreduction product **3b**. However, in the presence of methylphenylsilane, oxidative addition to the secondary silicon center is retarded presumably due to crowding of the incipient adduct, stabilizing LnCo(I) and promoting [2 + 2] cycloaddition via intermediacy of a Co(III)-oxy-π-allyl.

The convergent stereochemical outcome observed for the cycloaddition of **3a** and iso-**3a** is consistent with the mechanism outlined in Scheme 6. The proposed mechanism for cycloaddition invokes the intermediacy of a bis(Co(III)-enolate). As suggested by the deuterium labeling experiment performed on monoenone aldehyde **1a**, Co(III)-enolates are subject to rapid π-facial interconversion. Equilibration of the intermediate bis(Co-enolate) should favor the isomer in which the benzoyl substituents reside on the convex face of the metallobicyclo ring system. Reductive elimination then provides the cyclobutane product that embodies a *cis*-stereochemical relationship between the benzoyl moieties (Scheme 7). The *cis*-stereochemistry of cycloadducts such as **3c** does not represent the thermodynamically preferred configuration. As previously described, exposure of **3c** to either Brønsted or Lewis acid catalysts at 30 °C results in clean conversion to the corresponding *trans*-derivative.[15]

Scheme 7

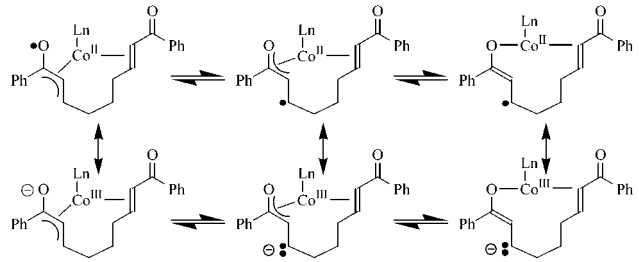


Co(II)-complexed anion radicals and Co(III)-oxy-π-allyls may be viewed as mesomeric forms that result upon one-electron versus two-electron reduction of the enone precursor, respectively. As demonstrated by electrochemical studies performed in collaboration with Bauld, cathodic reduction of bis(enones) **3a** and **8a** affords the very same [2 + 2] cycloadducts obtained under Co-catalysis.[15,35] These electrochemical studies establish

(30) See Supporting Information for detailed data pertaining to the structural assignment of deuterio-**2b** by ^{1}H NMR and neutron diffraction.
(31) Magnus, P.; Waring, M. J.; Scott, D. A. *Tetrahedron Lett.* **2000**, *41*, 9731.
(32) The stereochemical outcome of the Ni-catalyzed [2 + 2 + 2] cycloaddition is also independent of enone geometry: (a) Amarasinghe, K. K. D.; Chowdhury, S. K.; Heeg, M. J.; Montgomery, J. *Organometallics* **2001**, *20*, 370. (b) Seo, J.; Chui, H. M. P.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 476.
(33) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.
(34) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841 and references therein.

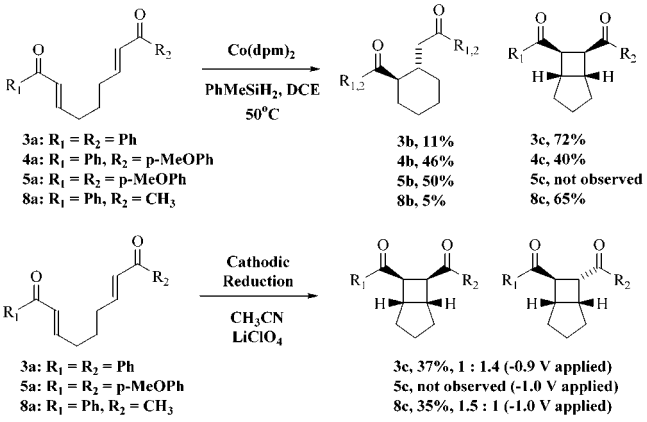
the plausibility of Co(II)-complexed anion radicals as reactive intermediates in the Co-catalyzed [2 + 2] cycloaddition. They do not provide sufficient basis to exclude the intermediacy of oxy-π-allyls. The reactive intermediates en route to β-coupled products are perhaps best described as oxy-π-allyls that possess anion radical character (Scheme 8).

Scheme 8



To further evaluate the plausibility of intermediates possessing anion radical character, the electrochemically promoted[35] and Co-catalyzed cycloadditions of several electronically biased, sterically unbiased bis(enone) substrates were compared. A parallel outcome of the metal-catalyzed and electrochemically promoted transformations would lend credence to mechanisms involving reactive intermediates that embody anion radical character (Scheme 9). For the Co-catalyzed process, cycloaddition predominates for phenyl-substituted bis(enone) **3a**. In contrast, bis(enone) **4a**, which bears a single *para*-methoxy substituent, yields roughly equal proportions of cycloreduction and cycloaddition products.[36] Cycloreduction represents the exclusive reaction pathway for bis(enone) **5a**, which incorporates two *para*-methoxy substituents. These results suggest that cycloaddition is disfavored for electron-rich enones because of their diminished susceptibility to reduction. As borne out by CV studies, the parent benzoyl-based enone reduces more easily than the corresponding anisoyl derivative (peak reduction potentials of -1.20 and -1.30 V, respectively).[35] Finally, only a single aroyl moiety should be required for anion radical formation. Accordingly, mixed bis(enone) **8a**, which incorporates a single benzoyl moiety, smoothly undergoes cycloaddition (Scheme 9).

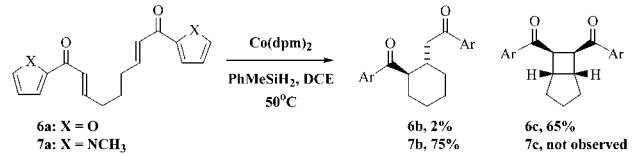
Scheme 9



The trends observed for the electrochemically promoted cycloadditions bear striking similarities to the analogous reactions performed under Co-catalysis. Under cathodic reduction and cobalt catalysis, bis(benzoyl) derivative **3a** yields [2 + 2] cycloadducts, whereas bis(anisoyl) derivative **5a** does not. Additionally, as demonstrated by the electrochemically promoted cycloaddition of mixed bis(enone) **8a**, only a single benzoyl moiety is required for both the electrochemically promoted and the metal-catalyzed transformations.

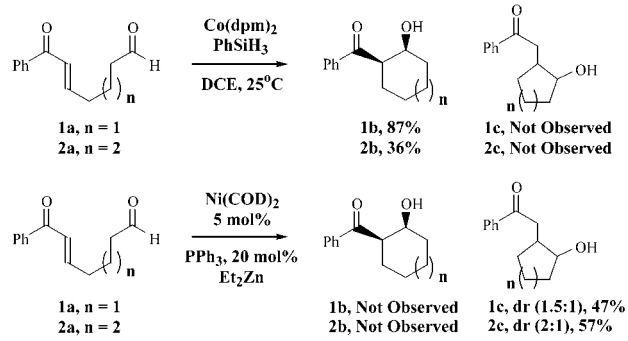
Thus, for the Co-catalyzed transformations, the requirement of aroyl-substituted enones and the observed effects of enone electronics on partitioning of the reaction manifolds likely relate to the susceptibility of a given enone moiety to reduction by LnCo(I). For bis(enones) that are more easily reduced, cycloaddition predominates. Upon introduction of electron-donating groups, electron-transfer-mediated reduction is disfavored, enabling competitive hydrometallative pathways. The results obtained for heteroaromatic bis(enones) **6a** and **7a** are consistent with this interpretation. Cycloaddition predominates for 2-furyl substituted bis(enone) **6a**, while under identical conditions cycloreduction is exclusively observed for 2-(*N*-methylpyrrolyl) substituted bis(enone) **7a** (Scheme 10).

Scheme 10



On the basis of the observance of competitive α- and β-coupling manifolds for bis(enone) substrates **3a**−**8a**, analogous α- and β-coupling pathways would be anticipated for monoenone monoaldehydes **1a** and **2a**. Under Co-catalysis, aldol cycloreduction products **1b** and **2b** are observed, that is, products of "α-coupling". Under Ni-catalysis, the very same substrates provide products of homoaldol cycloreduction, that is, "β-coupling" products (Scheme 11).[37] The homoaldol cycloreduction products **1c** and **2c** obtained under Ni-catalysis may derive from transition metal-complexed anion radical intermediates. The mesomerically related Ni(II)-trimethylsilyloxy-π-allyls, obtained upon enal reduction in the presence of chlorotrimethylsilane, have been isolated and characterized via single-crystal X-ray diffraction.[38] Anion radical pathways are further supported by reports of electrochemically induced homoaldol cycloreductions.[39]

Scheme 11



(35) Roh, Y.-S.; Jang, H.-Y.; Lynch, V.; Bauld, N. L.; Krische, M. J. *Org. Lett.* **2002**, *4*, 611.
(36) Compound **4b** was obtained as a 1:1.2 ratio of constitutional isomers.
(37) Montgomery, J.; Oblinger, E.; Savchenko, A. V. *J. Am. Chem. Soc.* **1997**, *119*, 4911.
(38) (a) Johnson, J. R.; Tully, P. S.; Mackenzie, P. B.; Sabat, M. *J. Am. Chem. Soc.* **1991**, *113*, 6172. (b) Grisso, B. A.; Johnson, J. R.; Mackenzie, P. B. *J. Am. Chem. Soc.* **1992**, *114*, 5160.

Conclusion

The most significant aspect of these studies resides in the observance of competitive enone reduction manifolds and the inference of reactive intermediates possessing anion radical character. Whereas enone hydrometalation enables catalytic aldol and Michael cycloreduction pathways (i.e., products derived from coupling at the β-position of the enone), electron transfer results in the formation of [2 + 2] cycloadducts and, under Ni-catalysis, homoaldol products (i.e., products derived from coupling at the β-position of the enone). The viability of anion radical pathways is underscored by the observance of identical [2 + 2] cycloadducts and related homoaldol products for both metal-catalyzed and electrochemically induced transformations.[35,39] Thus, for the formulation of mechanistic hypotheses accounting for the observance of β-coupling products from enone substrates obtained in the presence of low valent metals, it should be obligatory to consider the intermediacy of transition metal anion radicals in addition to metallo-oxy-π-allyls.

Many mechanistic questions remain regarding these transformations. For the Co-catalyzed cycloreductions, the superior performance of aromatic versus aliphatic enone partners is not wholly understood. In addition to electronic effects, aroyl residues may facilitate hydrometalation by stabilizing the enone *S-cis*-conformation. Additionally, it is possible that enone hydrometalation does not occur through the canonical *syn*-addition of a metal hydride. Hydrogen atom abstraction of the metallo-anion radical at the β-position of the enone is also plausible and would yield formal products of hydrometalation. Beyond addressing such questions, future studies are aimed at developing catalyst systems of enhanced substrate scope, enantioselective catalytic systems, and the discovery of related catalytic functional group interconversions.

Acknowledgment. Acknowledgment is made to the Robert A. Welch Foundation (F-1466), the NSF-CAREER program, the Herman Frasch Foundation (535-HF02), the NIH (RO1 GM65149-01), donors of the Petroleum Research Fund administered by the ACS (34974-G1), and the Research Corporation Cottrell Scholar Award (CS0927) for partial support of this research. The work at Argonne National Laboratory was supported by the U.S. Department of Energy, Basic Energy Sciences-Materials Sciences, under contract no. W-31-109-ENG-38.

Supporting Information Available: Experimental procedures and spectral data (^{1}H NMR, ^{13}C NMR, IR, and HRMS) for all new compounds. 2-Dimensional NMR spectra pertaining to deuterio-**1b**. X-ray crystallographic data for **1b** and Co(dpm)$_2$. Neutron diffraction data for deuterio-**2b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA020223K

(39) Little, R. D.; Fox, D. P.; Van Hijfte, L.; Dannecker, R.; Sowell, G.; Wolin, R. L.; Moens, L.; Baizer, M. M. *J. Org. Chem.* **1988**, *53*, 2287.