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Generation of (*E*)-Silylketene Acetals in a Rhodium-DuPhos Catalyzed Two-Step Reductive Aldol Reaction

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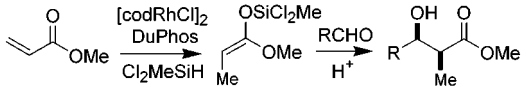
ABSTRACT



Mechanistic studies employing in situ NMR analysis implicate intermediate silicon enolates as reactive intermediates in the Rh-DuPhos catalyzed two-step reductive aldol reaction with Cl_2MeSiH. These enolates undergo noncatalyzed reaction with a variety of aldehydes to give the derived *syn*-aldol adduct in high yields and diastereoselection.

The aldol reaction is a well-developed and reliable process for the stereoselective synthesis of β-hydroxy carbonyl compounds.[1] While ligand-based, auxiliary-based,[2] and catalyst-based[3] asymmetric inductions have proven to be reliable routes to homochiral aldol adducts, until recently these methods have required stoichiometric preformation of a metal or silicon enolate.[4] The reductive aldol reaction (see eq 1, Scheme 1) avoids such a requirement as the metal enolate is presumably formed in situ by conjugate reduction of an unsaturated carbonyl.[5] We have begun to explore the reductive aldol reaction as an alternative to traditional aldol processes with the notion that this mode of bond formation might provide stereoselectivity patterns that are complementary to current aldol processes.[6] In this communication, we describe our studies on the Rh-DuPhos catalyzed reductive aldol reaction with Cl_2MeSiH, which have allowed us to introduce a practical method for the efficient and highly selective preparation of *erythro*-aldol adducts derived from simple esters.[7]

(1) For leading references on stereoselective aldol reactions, see: (a) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. (b) Heathcock, C. H. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 1.6, p 181. (c) Kim, B. M.; Williams, S. F.; Masamune, S. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 1.7, p 239. (d) Paterson, I. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 2, Chapter 1.9, p 301. (e) Heathcock, C. H. In *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: New York, 1984; Vol. 5B, p 177. (f) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.

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(3) For reviews on catalyst-based asymmetric induction, see: (a) Arya, P.; Qin, H. P. *Tetrahedron* **2000**, *56*, 917. (b) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1353. (c) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357.

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(5) (a) Revis, A.; Hilty, T. K. *Tetrahedron Lett.* **1987**, *28*, 4809. (b) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989** 2005. (c) Matsuda, I.; Takahashi, K.; Sato, S. *Tetrahedron Lett.* **1990**, *31*, 5331. (d) Kiyooka, S.; Shimizu, A.; Torii, S. *Tetrahedron Lett.* **1998**, *39*, 5237. For a recent intramolecular version of this reaction, see: Baik, T. G.-; Luis, A. L.; Wang, L. C.-; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 5112.

(6) (a) Taylor, S. J.; Morken, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 12202. (b) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528. (c) Zhao, C.-X.; Duffey, M. O.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829.

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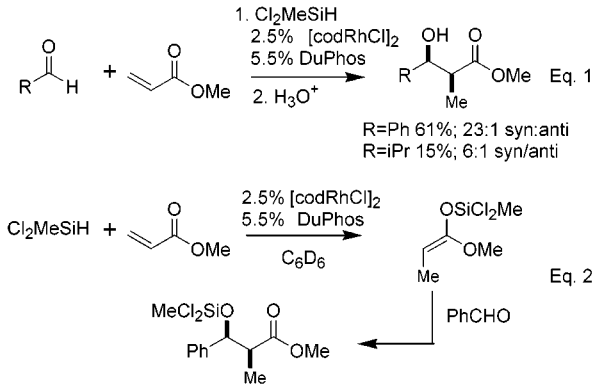
We recently reported that an efficient *syn*-selective reductive aldol reaction of aromatic aldehydes may be catalyzed by the combination of $[(cod)RhCl]_2$ and nonracemic DuPhos (see eq 1).[6a] Reactions with aliphatic aldehydes occurred with diminished product yields, and with both aromatic and aliphatic substrates, the reaction products are racemic. In an effort to design metal−ligand complexes that provide the high *syn* selectivity observed with the DuPhos ligand but are also able to provide enantiomerically pure adducts in high yields, we have investigated this reaction in further detail.

As depicted in Scheme 1, treatment of benzaldehyde,

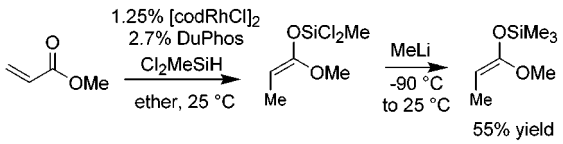
Scheme 1



methyl acrylate, and Cl_2MeSiH with Rh-DuPhos (herein taken to mean the catalyst prepared in situ from $[(cod)RhCl]_2$ and DuPhos[8]) provides the reductive aldol adduct in 60% yield and 23:1 diastereoselection (eq 1). Using ^1H NMR spectroscopy to identify relevant reaction intermediates, we examined the Rh-DuPhos catalyzed reaction between methyl acrylate and Cl_2MeSiH. One hour after addition of the silane and acrylate to the catalyst in C_6D_6, the reagents were completely converted to a new compound that is spectroscopically consistent with a single stereoisomer of the derived silylketene acetal (eq 2).[9] Subsequent introduction of benzaldehyde led to rapid disappearance (20 min at room temperature) of the silyl ketene acetal and formation of a single stereoisomer of the reductive aldol adduct. To determine whether the Rh-DuPhos catalyst was required for reaction between the putative silyl ketene acetal and the aldehyde, we carried out a second experiment where the intermediate silyl ketene acetal was vacuum-distilled away from the metal complex. Addition of benzaldehyde to the metal-free and phosphine-free silyl ketene acetal provided the aldol adduct in high stereoselection. These observations suggest that the role of the Rh-DuPhos complex in the reductive aldol reaction is to catalyze formation of the silicon enolate and that the chiral catalyst is not involved in the aldol addition step.[10] Notably, Denmark has observed analogous noncatalyzed aldol additions when enoxytrichlorosilanes, trichlorosilyl ketene acetals, and dichloromethylsilyl ketene acetals are treated with aldehydes.[11]

To establish the geometry of the silyl ketene acetal formed by the Rh-DuPhos catalyzed hydrosilation of methyl acrylate, the putative dichloromethylsilyl ketene acetal was generated in ether and treated with 2 equiv of methyllithium at −90 °C followed by warming to room temperature (Scheme 2).

Scheme 2



After isolation of the reaction product, comparison of the ^1H and ^{13}C NMR with literature data[12] revealed that the derived trimethylsilyl ketene acetal is in the *E* configuration exclusively; the *Z* isomer could not be detected nor could the C-silyl derivative.[13] This observation is noteworthy in light of the *Z* selectivity for the $ClRh(PPh_3)_3$-catalyzed reduction of α,β-unsaturated esters with either *t*-$BuMe_2SiH$ or catecholborane.[14]

Cyclic acrylate **1** was used as a probe to assess the influence of acrylate conformation on silyl ketene acetal geometry. Treatment of **1** with Cl_2MeSiH and the Rh-DuPhos catalyst for 12 h followed by addition of benzaldehyde and quench with HCl afforded the lactone-opened aldol adduct in 32% yield. X-ray analysis of the reaction product indicated that the *syn* stereoisomer is formed.[15] This observation implies that the *s-trans* isomer of acrylate can lead to the (*E*)-silylketene acetal in the Rh-DuPhos catalyzed reduction of acrylates and that the subsequent aldol reaction likely proceeds through a boatlike transition state (i.e., **2**, Scheme

(8) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Organometallics* **1990**, *9*, 2653. Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125.

(9) Pt-catalyzed reduction of methyl acrylate to the derived dichloromethylsilyl enolate has been reported; however, the reaction product was only characterized by refractive index measurements. See: Petrov, A. D.; Sadykh-Zade, S. I.; Filatova, E. I. *Zh. Obshch. Khim.* **1959**, *29*, 2936.

(10) For transition metal catalyzed hydrosilation of unsaturated esters, see: (a) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473. (b) Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. *Tetrahedron Lett.* **1998**, *39*, 4627. (c) Ito, H.; Ishizuka, T.; Arimoto, K.; Miura, K.; Hosomi, A. *Tetrahedron Lett.* **1997**, *38*, 8887. (d) Zheng, G. Z.; Chan, T. H. *Organometallics* **1995**, *14*, 70. (e) Doyle, M. P.; Devora, G. A.; Nefedov, A. O.; High, K. G. *Organometallics* **1992**, *11*, 549. (f) Keinan, E.; Perez, D. *J. Org. Chem.* **1987**, *52*, 2576. (g) Takeshita, K.; Seki, Y.; Kawamoto, K.; Murai, S.; Sonoda, N. *J. Org. Chem.* **1987**, *52*, 4864. (h) Keinan, E.; Greenspoon, N. *J. Am. Chem. Soc.* **1986**, *108*, 7314.

(11) (a) Denmark, S. E.; Wong, K. T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333. (b) Denmark, S. E.; Winter, S. B. D. *Synlett* **1997**, 1087. (c) For a related reaction of silylenol triflates, see: Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1993**, *58*, 2647.

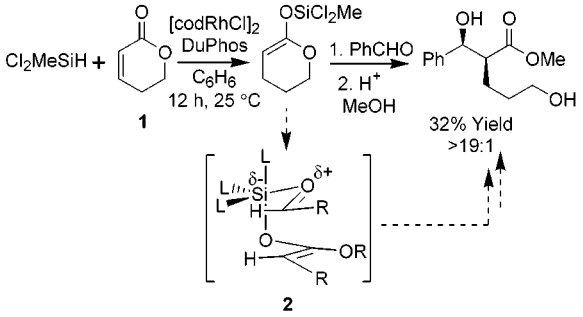
(12) (a) Mikami, K.; Matsumoto, S.; Ishida, A.; Takamuku, S.; Suenobu, T.; Fukuzumi, S. *J. Am. Chem. Soc.* **1995**, *117*, 11134. (b) Emde, H.; Simchen, G. *Synthesis* **1977**, 867.

(13) Yield of reaction product was determined by ^1H NMR versus an internal standard. Attempted purification resulted in substantial decomposition. Attempts to methylate the dichloromethylsilyl ketene acetal generated in benzene provided complex product mixtures.

(14) (a) Slougui, N.; Rousseau, G. *Synth. Commun.* **1987**, *17*, 1. (b) Evans, D. A.; Fu, G. C. *J. Org. Chem.* **1990**, *55*, 5678.

(15) Details of the X-ray analysis can be found in the Supporting Information. Coordinates have been deposited at the Cambridge Crystal Data Center under accession number CCDC 1681361.

Scheme 3



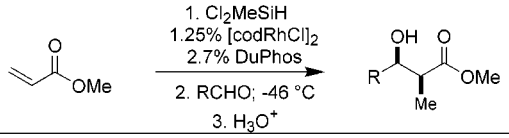
3) involving a pentacoordinate silicate as observed for the enoxytrichlorosilanes.[16,17]

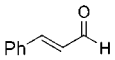
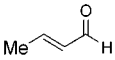
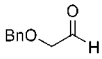
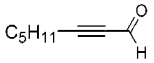
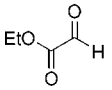
Although the observations described above do not appear to bode well for eventual development of an enantioselective reductive aldol reaction using chiral rhodium-phosphine complexes and Cl_2MeSiH, these studies delineate a procedure for simple and high-yielding diastereoselective aldol reactions. Suspecting that competitive carbonyl hydrosilation accounted for low yields in the single-pot reductive aldol reactions of aliphatic aldehydes, we attempted the two-step process with these problematic substrates. In the optimal procedure, Cl_2MeSiH and methyl acrylate are allowed to react with 2.5 mol % of the Rh-DuPhos catalyst at room temperature in ether for 1 h. The aldehyde (0.5 equiv) is then added to a precooled (−46 °C) solution of the derived silylketene acetal, and the reaction is allowed to proceed for 4 h. As shown in Table 1, a range of functionality is tolerated in the aldehyde, and yields are significantly higher than in the single-step process. For instance, isobutyraldehyde provides reductive aldol adduct in 15% isolated yield (6:1 *syn*:*anti*) in the single-step process; however, the two-step procedure provides the same adduct in 89% yield and in a 9:1 stereoisomer ratio. Notably, alkoxy aldehydes, ynals, and enals react with high *syn* selectivity, as do aliphatic, aromatic, and α,*β*-unsaturated aldehydes.

(16) The correlation between *E*-enolate and syn aldol adduct implies either a closed boatlike transition state or an open transition state. In anology to reactions involving Lewis acidic Si, Zr, Ti, and Sn enolates, which are postulated to proceed through boatlike transtition states, we expect that reactions of dichloromethylsilyl enolates require precoordination of the aldehyde to the enolate and that a closed boatlike transition state results. See: (a) Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* **1980**, *21*, 3975. (b) Shenvi, S.; Stille, J. K. *Tetrahedron Lett.* **1982**, *23*, 627. (c) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 3343. (d) Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* **1985**, *18*, 181. (e) Murphy, P. J.; Procter, G.; Russell, A. T. *Tetrahedron Lett.* **1987**, *28*, 2037. (f) Myers, A. G.; Widdowson, K. L.; Kukkola, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 2765. (g) Myers, A. G.; Kephart, S. E.; Chen, H. *J. Am. Chem. Soc.* **1992**, *114*, 7922. (h) Denmark, S. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 5136. (i) Denmark, S. E.; Wong, K. T.-; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333. (j) Denmark, S. E.; Stavenger, R. A.; Wong, K. T.-; Su, X. *J. Am. Chem. Soc.* **1999**, *121*, 4982.

(17) For computational evidence that suggests boat transition structures are preferred for reactions proceeding through pentavalent silicates, see: Denmark, S. E.; Griedel, B. D.; Coe, D. M.; Schnute, M. E. *J. Am. Chem. Soc.* **1994**, *116*, 7026. For similar computational conclusions with enol borates, see: (a) Gennari, C.; Todeshini, R.; Beretta, M. G.; Favini, G.; Scolastico, C. *J. Org. Chem.* **1986**, *51*, 612. (b) Hoffmann, R. W.; Ditrich, K.; Froech, S. *Tetrahedron* **1985**, *41*, 5517. (c) Li, Y.; Paddon-Row: N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481. (d) Li, Y.; Paddon-Row: N.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3684.

Table 1. Two-Step Rh-DuPhos Catalyzed Reductive Aldol Reaction[a]



Entry	RCHO	Yield[b]	Syn:Anti[c]
1		94	>60:1
2		95	13:1
3		98	>20:1
4		89	9:1
5		71	10:1
6		80	>20:1
7		91	>20:1
8		84	>20:1
9		83	>20:1

[a] All reactions were carried out at −46 °C for 4 h. [b] Yields refer to isolated material after column chromatography. [c] Ratios determined by GC analysis for entry 1 and ^1H NMR for entries 2−9.

In conclusion, we have documented the intermediacy of silicon enolates in Rh-DuPhos catalyzed two-step reductive aldol reactions employing dichloromethylsilane as reducing agent. While these studies do not necessarily implicate silicon enolates in the Rh-DuPhos catalyzed single-step process, their intermediacy is most consistent with our experiments; the observation that the single-step process catalyzed by enantiomerically pure Rh-DuPhos complex affords racemic (<0.5% ee) product appears to exonerate the transition metal from the stereochemistry-determining step. While the reaction mechanism suggested by these studies appears to preclude development of an enantioselective Rh-DuPhos catalyzed reductive aldol reaction, the two-step reductive aldol reaction process does appear to be useful for simple diastereoselective propionate aldol reactions. Current studies in regards to relative stereoinduction with chiral aldehydes are in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and compound characterization for reactions products. This material is available free of charge via the Internet at http://pubs.acs.org.

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