Rhodium-Catalyzed Enantioselective Reductive Aldol Reaction

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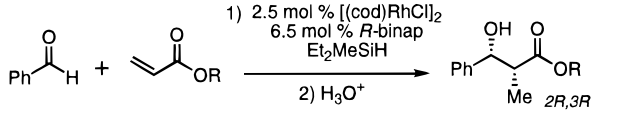
Catalytic enantioselective carbon−carbon coupling reactions, particularly those that form $C(sp^3)-C(sp^3)$ bonds from readily available prochiral substrates, are useful tools for the synthesis of natural products and commodity chemicals. Such a mode of bond formation is available for the asymmetric synthesis of β-hydroxy carbonyls through catalytic enantioselective aldol processes.[1,2] With the exception of reports by Nelson,[3] Shibasaki,[4] and Watanabe,[5] methods for the catalytic asymmetric synthesis of β-oxygenated carbonyls derive reactivity from latent enolates which must be prepared, in advance, in a stoichiometric fashion.[6] We recently reported a diastereoselective catalytic reductive aldol reaction that may provide an alternative to such Mukaiyama aldol processes.[7−9] The reductive aldol reaction does not require preformation of metal enolates or silyl enol ethers; catalytic condensation between an activated alkene, an aldehyde, and a silane directly furnishes protected propionate products. Challenges to the development of effective reductive aldol catalysts include reaction stereoselection and also product selectivity; late transition metal-catalyzed condensations between aldehydes and silanes (carbonyl hydrosilation[10]) and between acrylates and silanes (alkene hydrosilation[11]) are well-known processes and are potential competing reaction pathways. Herein we report the first asymmetric catalytic reductive aldol reaction; a complex derived from [(cod)RhCl]$_2$ and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)[12] effects catalytic diastereoselective and enantioselective reductive aldol reaction between acrylate esters and aldehydes with good to excellent levels of enantioselectivity.[13]

Table 1. Rh-Catalyzed Asymmetric Reductive Aldol Reaction with Varied Acrylate Component[a]



entry	R	syn:anti[b]	ee syn (config[c])	ee anti (config)	% yield
1	Me	1.7:1	91 (2*R*,3*R*)	88 (2*R*,3*S*)	37
2	*t*-Bu	1.4:1	58 (nd)	38 (nd)	21
3	Ph	3.4:1	87 (2*R*,3*R*)	34 (nd)	72

[a] All reactions were carried out at room temperature for 24 h in dichloroethane solvent using the procedure described in the text. [b] Stereoisomer ratios determined by chiral GC analysis of the unpurified esters. [c] Absolute configuration established by comparison to reported optical rotation for entry 1 and by independent synthesis for entry 3.

Our initial studies with 192 independent catalyst systems identified [(cod)RhCl]$_2$-*R*-BINAP-Et$_2$MeSiH as one catalyst system able to effect room-temperature catalytic enantioselective reductive aldol reaction between methyl acrylate and benzaldehyde. While enantioselectivity in the initial microscale assay was low (20% enantiomeric excess), it was noted that reaction in the presence of ligand was less efficient than the reaction with metal salt alone (4% relative yield versus 16% relative yield, data not shown). We surmised that during the microscale reaction, inefficient complexation of the ligand to the metal might leave uncomplexed metal salt available to effect relatively rapid and nonselective transformation. Upon scale-up in the presence of excess *R*-BINAP (1.3:1 ligand/metal; 2.5 mol % [(cod)RhCl]$_2$) the catalytic reductive aldol reaction between methyl acrylate, benzaldehyde, and diethylmethylsilane occurs to provide a diastereomeric mixture (1.7:1 syn:anti) of β-hydroxy esters in good enantiomeric excess (91% ee syn; 88% ee anti, 37% yield; see Table 1, entry 1).[14] Notably, loss of diastereoselection occurs from lack of stereocontrol in bond formation to the prochiral carbonyl; the sense and level of stereoselection at C_α is maintained with good fidelity.

The impact of acrylate and aldehyde structure on stereoselection was examined with the following experimental procedure: Under a dry and oxygen-free nitrogen atmosphere, 2.5 mol % [(cod)-RhCl]$_2$ was stirred with 6.5 mol % *R*-BINAP in dichloroethane at room temperature for 1 h. Diethylmethylsilane was then added and the mixture stirred for an additional 30 min. After addition of carbonyl substrates, the reaction was allowed to proceed for

(1) For an excellent review on enantioselective aldol reactions with latent enolates see: Nelson, S. G. *Tetrahedron Asymmetry* **1998**, *9*, 357.

(2) For recent lead references on catalytic asymmetric aldol reactions using latent enolates, see: (a) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T.; Su, X. *J. Am. Chem. Soc.* **1999**, *121*, 4982. (b) Evans, D. A.; Kozlowski, M. C.; Murray, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669. (c) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686. (d) Fujimura, O. *J. Am. Chem. Soc.* **1998**, *120*, 10032. (e) Kruger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837. (f) Evans, D. A.; MacMillan, D. W. M.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859. (g) Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363. (h) Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649. (i) Uotsu, K.; Sasai, H.; Shibasaki, M. *Tetrahedron Asymmetry* **1995**, *6*, 71. (j) Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 2648. (k) Mikami, K.; Matsuka, S. *J. Am. Chem. Soc.* **1994**, *116*, 4077.

(3) Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742.

(4) (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871. (b) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168.

(5) Nakagawa, M.; Nakao, H.; Watanabe, K.-I. *Chem. Lett.* **1985**, 391.

(6) For relevant methods involving catalytic enantioselective functionalization of unmodified carbonyls or their equivalent see: (a) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. (b) Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, *119*, 6452. (c) Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. *J. Am. Chem. Soc.* **1999**, *121*, 10215.

(7) Taylor, S. J.; Morken, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 12202.

(8) (a) Revis, A.; Hilty, T. K. *Tetrahedron Lett.* **1987**, *28*, 4809. (b) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 2005. (c) Kiyooka, S.; Shimizu, A.; Torii, S. *Tetrahedron Lett.* **1998**, *39*, 5237. For a reductive aldol reaction with unsaturated ketones, see: Matsuda, I.; Takahashi, K.; Sato, S. *Tetrahedron Lett.* **1990**, *31*, 5331.

(9) Catalytic enantioselective tandem conjugate addition−aldol reaction involving enones has been reported, see: Barrett, A. G. M.; Makimura, A. *J. Chem. Soc., Chem. Commun.* **1995**, 1755.

(10) For transition metal-catalyzed hydrosilation of carbonyls, see: Ojima, I. *Catalytic Asymmetric Synthesis*; VCH Publishers: New York, 1993; Chapter 6.

(11) 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.* **1987**, *109*, 7314.

(12) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932.

(13) For Rh(I)-BINAP catalyzed conjugate addition of boronic esters to unsaturated carbonyls, see: Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579.

(14) Along with an increase in enantioselectivity in the presence of excess ligand, the reaction in a flask also provides an increase in reaction yield compared to reaction in a microtitre plate. We attribute this disparity to the fact that reaction in the plate was unstirred; unstirred reactions in a flask reproducibly provide <10% product yield.

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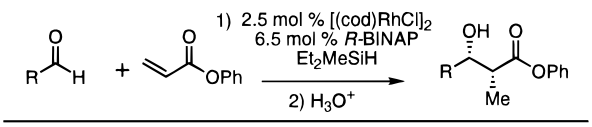
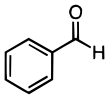
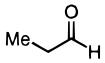
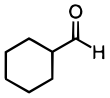
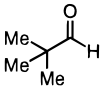
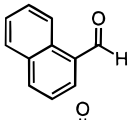
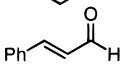
Table 2. Rh-Catalyzed Asymmetric Reductive Aldol Reaction with Varied Aldehyde Component[a]



entry	RCHO	% yield[b]	*syn*:*anti*[c]	e.e. syn (anti)[d]
1		72	3.4:1	87 (34)
2		59	5.1:1	88 (7)
3		54	3.9:1	84 (48)
4		48	1.8:1	45 (>99)
5		82	3.8:1	80 (13)
6		0	-	-

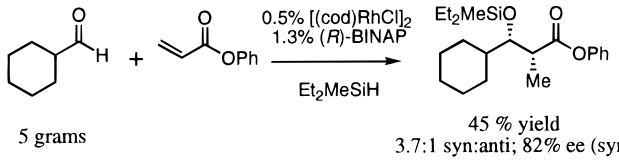
[a] All reactions were carried out at room temperature for 24 h in dichloroethane solvent using the procedure described in the text. [b] Percent yield is of isolated material after silica gel chromatography. Satisfactory elemental analysis was obtained for all reaction products. [c] Stereochemical ratios were determined by chiral GC or HPLC analysis, see Supporting Information for details. [d] Configuration of syn reaction products was determined by comparison to reported optical rotation or by synthesis of authentic enantiomers.

24 h at room temperature before being subjected to aqueous acidic (4 M HCl) workup. Examination of the data in Table 1 reveals a substantial dependence of stereoselectivity on acrylate structure; whereas reaction with methyl acrylate provides product in good enantiopurity, reaction with *tert*-butyl acrylate exhibits diminished absolute stereoselection (Table 1, entries 1 and 2). Electronic effects in the acrylate component appear to be important as phenyl acrylate, with a steric size between that of *tert*-butyl acrylate and methyl acrylate, reacts with high enantioselectivity, modest diastereoselectivity and in the highest yield.

As shown in Table 2, catalytic reductive aldol reaction with both aromatic and nonaromatic aldehydes proceeds in an enantioselective fashion with phenyl acrylate and diethylmethylsilane. In contrast to our previously reported catalyst system ([(cod)-$RhCl]_2$-DuPhos-Cl_2MeSiH) where low yields were obtained with aliphatic aldehydes bearing an α-hydrogen, with $[(cod)RhCl]_2$-BINAP-Et_2MeSiH aliphatic aldehydes give useful product yields and, except for pivaldehyde, react with good enantioselectivity. Also in contrast to our earlier report, enals (entry 6) give no reductive aldol product and return the unsaturated aldehyde and acrylate unaffected. In all cases, the syn diastereomer is favored and the major enantiomer of the syn isomer has the *R* configuration at C-2. Notably, in these reactions a decrease in both diastereomer ratio and syn enantiomer ratio is accompanied by an increase in anti enantiomer ratio as substrate size is increased (entries 2−4).

The catalytic reductive aldol reaction is attractive because it allows preparation of aldol adducts via operationally simple, room temperature condensation between inexpensive commercially available substrates. The "scale-up" experiment described in Scheme 1 exemplifies the ease with which larger scale reactions may be performed. At 0.9 M substrate concentration, cyclohexanecarboxaldehyde (5 g) was subjected to the reductive aldol reaction conditions with 0.5 mol % $[(cod)RhCl]_2$ and *R*-BINAP ligand. After aqueous nonacidic workup, the silyl-protected aldol adduct was isolated in 45% yield as a 3.7:1 mixture of syn:anti diastereomers in good enantiomeric excess (82% ee syn).

Scheme 1



Preliminary mechanistic experiments indicate that the silane hydrogen is transferred to the acrylate β-carbon: when the reductive aldol reaction in Table 2, entry 1, is carried out with phenyldimethylsilyldeuteride in place of diethylmethylsilane, ^{13}C NMR analysis shows partial deuteration of the C2 methyl group.[15,16] Experiments also suggest that the $[(cod)RhCl]_2$-(*R*)-BINAP catalyzed reductive aldol reaction does not proceed by initial conversion of the silane and acrylate to a silyl ketene acetal; treatment of phenyl acrylate with diethylmethylsilane in the presence of the $[(cod)RhCl]_2$-(*R*)-BINAP catalyst provides <5% silylketene acetal after 24 h. It is also of note that <5% reductive aldol adduct is formed from independently prepared silylketene acetal and benzaldehyde under the catalytic reaction conditions. While these experiments suggest that silicon enolates are not involved, the intermediacy of a rhodium enolate may not be ruled out. At present we expect that after oxidative addition of silane to rhodium, the reaction is likely to proceed either by insertion of the aldehyde into a Rh−Si bond followed by insertion of the acrylate into the resulting Rh−C bond or by insertion of the acrylate into a Rh−H bond followed by aldol addition of the derived rhodium enolate to the aldehyde.[17] Ongoing mechanistic studies are addressing this issue and will be the subject of a forthcoming report.

While propionate synthesis with the current catalytic reductive aldol reaction does not yet rival the high diastereo- and enantioselectivity (>20:1 d.r., >97% ee) often observed[2] in direct catalytic asymmetric addition of silyl enol ethers to carbonyls, we expect improvements may be gained by fine-tuning the acrylate ester substituent and the silane component. As a note in proof, initial studies reveal that enantioselective transformation is not limited to use of diethylmethylsilane.[15] That a variety of silanes might be employed and retained as protecting groups for the β-hydroxyl should also prove useful for propionate synthesis.

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Supporting Information Available: Characterization data for all compounds (Tables 1 and 2) and experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) $[(cod)RhCl]_2$-(*R*)-BINAP catalyzed reductive aldol reaction with benzaldehyde, phenyl acrylate, and dimethylphenylsilane provides 60% yield of the 2*R*,3*R* adduct with 3.9:1 syn:anti selectivity and 89% ee.

(16) Incomplete deuteration requires a pathway involving exchange of hydrogen atoms. Accordingly, treatment of phenyl acrylate with phenyldimethylsilyldeuteride, in the presence of $[(cod)RhCl]_2$-(*R*)-BINAP, results in nonselective deuterium incorporation at the β-carbon of the acrylate.

(17) Neither mechanism is without precedent: the first scenario is analogous to that proposed by Wright for Rh-catalyzed silylformylation of aldehydes (Wright, M. E.; Cochran, B. B. *J. Am. Chem. Soc.* **1993**, *115*, 2059) and, as required by the second, rhodium enolates are known to undergo aldol addition reactions (Slough, G. A.; Bergman, R. G.; Heatchcock, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 938).