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Investigation of the Rh-Catalyzed Asymmetric Reductive Aldol Reaction. Expanded Scope Based on Reaction Analysis

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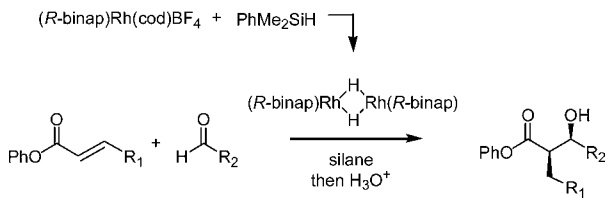
ABSTRACT



A series of experiments are described that suggest that the Rh-catalyzed reductive aldol reaction proceeds by addition of a Rh(I) hydride, generated in situ, to the reacting acrylate followed by a stereochemistry-controlling aldol addition reaction. On the basis of this hypothesis, reaction conditions are engineered that allow for increased substrate scope.

As part of a program focused on the catalytic asymmetric transformation of simple organic molecules into value-added products, we have been investigating the late transition-metal-catalyzed reductive aldol reaction between aldehydes and unsaturated esters. This transformation, first demonstrated by Revis and later by Mukaiyama, Kiyooka, and Murai, provides access to aldol adducts in a mild and catalytic fashion.[1] Development of an asymmetric reductive aldol reaction is complicated by the fact that group 9 and group 10 catalysts, which are effective for the reaction itself, also exhibit reactivity in carbonyl and acrylate hydrosilylation. Thus, our initial work on the introduction of an asymmetric version of the Rh-catalyzed reaction was facilitated by the aid of high-throughput screening. We expected that subsequent design of improved reaction conditions and engineering of new reaction pathways would be facilitated by a more detailed understanding of this reaction. Of particular concern is the nature of the transition metal complex that is involved in the C−C bond-forming step and whether it is a Rh(I) or Rh(III) complex. In this communication, we describe a series of experiments that suggest a plausible mechanism for the Rh-catalyzed asymmetric reductive aldol reaction and provide a working hypothesis that allows for expansion of the substrate scope.

The asymmetric reductive aldol reaction may be accomplished in an enantioselective manner with $[(cod)RhCl]_2$/binap as the precatalyst and with Et_2MeSiH as the reductant. Early experiments indicated that the reaction produces silyl-protected aldol adducts from phenyl acrylate and aliphatic aldehydes and that these may be hydrolyzed during workup to afford the derived β-hydroxy ester.[2] An informative observation on the nature of the asymmetric reductive aldol

(1) (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 an excellent recent review of this area, see: Huddleston, R. R.; Krische, M. J. *Synlett* **2003**, 12.

(2) (a) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528. For an iridium-catalyzed asymmetric reductive aldol reaction, see: (b) Zhao, C. X.; Duffey, M. O.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829.

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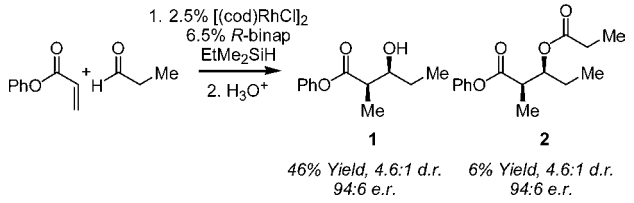
reaction arises from analysis of minor reaction products and is shown in Scheme 1. Analysis of the reaction mixture after

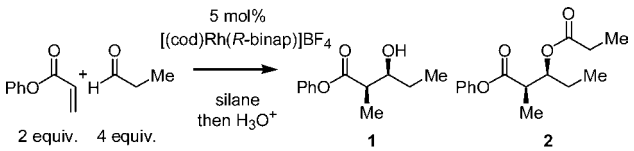
Scheme 1



hydrolytic workup reveals that, in addition to the major product **1**, a second aldol-type reaction product is formed in which the β-hydroxyl group is acylated (**2**, Scheme 1). Control experiments indicate that **2** does not likely arise from the silyl ether of **1** under the reaction conditions; inclusion of the silylated benzaldehyde reductive aldol adduct, in a reductive aldol reaction with propionaldehyde, does not lead to acylation of the benzaldehyde adduct. Significant to our mechanistic hypothesis, both aldol adducts **1** and **2** are formed with the same level of stereoselectivity and the product ratio is dependent on reagent concentration: doubling the aldehyde concentration and halving the silane concentration results in a 1:1 ratio of **1**:**2**.

Reductive aldol reactions with (*R*-binap)Rh(cod)BF_4 (**3**) provide the acylated aldol adduct **2** in a similar manner as reactions with the neutral catalyst; however, hydrosilylation of the acrylate predominates when an equimolar ratio of silane, acrylate, and aldehyde are employed. When a 4:2:1 ratio of aldehyde:acrylate:silane was employed with the cationic catalyst, then **2** is the dominant reaction product with either $PhMe_2SiH$ or Et_2MeSiH. As shown in Scheme 2, the

Scheme 2

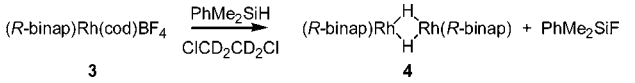


Et_2MeSiH	23%y; 91:9 e.r.	42%y; 91:9 e.r.
$PhMe_2SiH$	18%y; 90:10 e.r.	48%y; 90:10 e.r.
(EtO)Me_2SiH	not formed	29%y; 89:11 e.r.

ratio of **1** to **2** appears to be dependent on the structure of the silane, and with (EtO)Me_2SiH, only the acylation adduct is observed. Significantly, in each experiment the syn diastereomer of compound **2** is produced in the same level of enantioselection as is the syn diastereomer of **1**. Additionally, the enantioselection appears to be relatively insensitive to significant changes in silane structure (enantiomer ratio varies from ~89:11 to 91:9 for $PhMe_2SiH$, (EtO)Me_2SiH, and Et_2MeSiH). Collectively, these observations suggest that **1** and **2** may arise from the same catalytic intermediate and that the organosilane may not be involved in the stereochemistry-controlling step of the cycle.

In an effort to learn more about the nature of transition metal species generated under the reaction conditions, (*R*-binap)Rh(cod)BF_4 (**3**, Scheme 3) was subjected to each of

Scheme 3



the reaction components in concentrations reflective of reaction conditions ([binapRhCl]$_2$ shows little detectable reaction with any of the reaction components). While neither acrylate nor aldehyde was reactive with the precatalyst, reaction with $PhMe_2SiH$ provides free cyclooctadiene and a single new C_2-symmetric species **4** (Scheme 3) in about 20% conversion after 30 min. $\{^1H\}^{31}P$ NMR (doublet, 38.6 ppm, $J = 147$ Hz), ^1H NMR (broad overlapping triplet of quintets, -8.2 ppm, $J_{Rh-H} = 17$ Hz, $J_{P-H} = 17$ Hz), and $\{^{31}P\}^1H$ NMR spectra (triplet, -8.2 ppm, $J = 17$ Hz) are consistent with structure **4**, a dinuclear bridged Rh(I) hydride.[3] In addition to **4**, ^{19}F NMR indicates that $PhMe_2SiF$ is also formed in this transformation.[4] While efforts to prepare **4** by ligand exchange with [(cod)RhH]$_4$ and by $NaEt_3BH$ addition to [(binap)RhCl]$_2$ were unsuccessful, **4** was detected in the reaction of **3** with (EtO)Me_2SiH. Under similar conditions, treatment of **3** with Et_2MeSiH did not lead to a detectable hydride-containing product. That **4** is a competent catalyst or precatalyst was determined by allowing conversion of **3** to **4** to reach completion prior to introduction of acrylate and aldehyde. This was accomplished by allowing **3** to react with 28 equiv of $PhMe_2SiH$ for 2 h at which point ^{31}P NMR showed >95% **4** relative to all other phosphorus-containing compounds. Upon introduction of acrylate and aldehyde, the reductive aldol adduct was generated at a slightly elevated rate and identical enantioselectivity relative to reactions initiated with **3**.

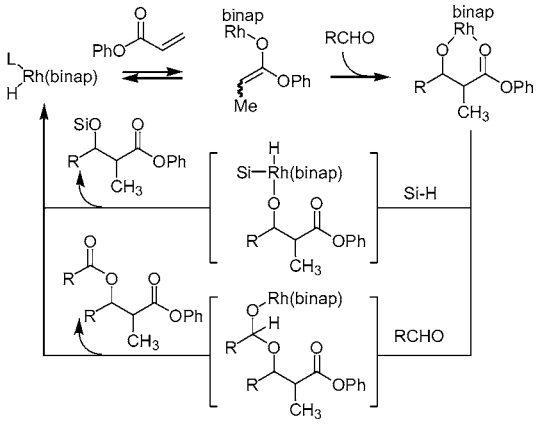
A mechanism that is consistent with the experimental observations is depicted in Scheme 4. We suspect that dissociation of the bridged dimer **4** provides a Rh(I) hydride that reacts with the acrylate to provide a Rh(I) enolate.[5] After

(3) For other dinuclear μ-H Rh(I) phosphine complexes, see: (a) Fryzuk, M. D.; Piers, W. E.; Einstein, F. W. B.; Jones, T. *Can. J. Chem.* **1989**, *67*, 883. (b) Fryzuk, M. D. *Organometallics* **1982**, *1*, 408. (c) Day, V. W.; Fredrich, M. F.; Reddy, G. S.; Sivak, A. J.; Pretzer, W. R.; Muetterties, E. L. *J. Am. Chem. Soc.* **1977**, *99*, 8091.

(4) Transformation of **3** to **4** likely proceeds by oxidative addition of silane followed by fluoride abstraction from BF_4, thereby generating a Rh(I) hydride, $PhMe_2SiF$, and BF_3. We have been unable to detect BF_3 by ^{19}F NMR, although, in the absence of Lewis bases, it can be anticipated that it would readily outgas from solution. For a discussion of fluoride abstraction with electrophilic complexes, see: Brookhart, M. S.; Grant, B.; Volpe, A. F., Jr. *Organometallics* **1992**, *11*, 3920.

(5) Such compounds are precedented in the literature and have been observed to exist as either O-bound enolates or oxo-π-allylmetal complexes depending on the ligand environment. (a) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052. (b) Slough, G. A.; Hayashi, R.; Ashbaugh, J. R.; Shamblin, S. L.; Aukamp, A. M. *Organometallics* **1994**, *13*, 890. (c) Slough, G. A.; Bergman, R. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 938.

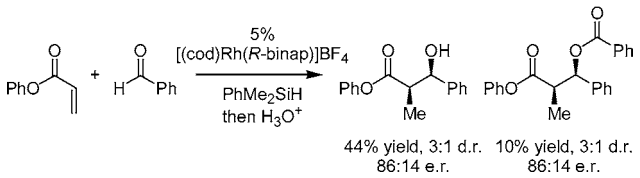
Scheme 4



the enolate participates in an aldol reaction with the aldehyde,[6] a bifurcation in the reaction pathway might then provide the silylated adduct (by oxidative addition/reductive elimination with silane) or the acylated adduct (by addition/elimination with the aldehyde[7]) in identical levels of stereoselectivity. The lack of dependence of enantioselection on silane structure and the dependence of the product ratio (**1**:**2)** on silane structure and concentration are accommodated by the proposed mechanism where Rh(I) enolates are involved and the organosilane is not involved in the C−C bond-forming step.[8]

As expected on the basis of the mechanism proposed in Scheme 4, other aldehyde substrates lead to differing ratios of acylation:silylation products. For instance, benzaldehyde provides a 4:1 ratio of silylation:acylation products (Scheme 5). Consistent with the observations described above, both

Scheme 5



reaction products obtained from benzaldehyde were obtained in similar levels of enantioselection.

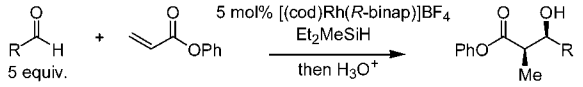
The experiments described above indicate that [(cod)Rh(binap)]BF_4 is converted to the putative reactive hydride with higher efficiency than the neutral catalyst and that Et_2MeSiH

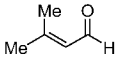
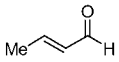
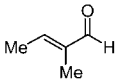
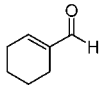
(6) (a) Yoshida, K.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 10984. (b) See ref 5c.

(7) For Tishchenko reactions with Rh(I) alkoxides, see: (a) Krug, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 1674.(b) Slough, G. A.; Ashbaugh, J. R.; Zannoni, L. A. *Organometallics* **1994**, *13*, 3587.

(8) NMR analysis of the catalyst during the course of the reaction is not informative, as **3** and **4** are the predominant detectable species. Kinetic analysis would clearly assist our understanding of the reaction mechanism; however, interpretation of these experiments is hampered by competitive silylation and hydrosilylation of the acrylate at increased silane concentration.

Table 1. Asymmetric Reductive Aldol Reaction with Unsaturated Aldehyde Substrates[a]

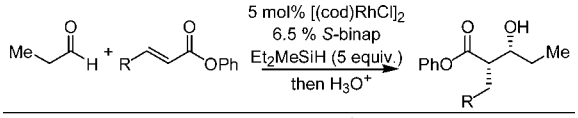


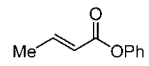
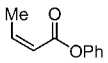
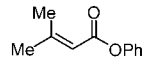
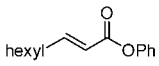
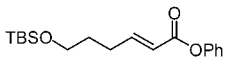
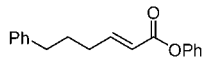
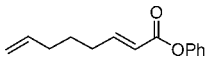
entry	RCHO	% yield[b]	*syn*:*anti*	% ee syn
1		86	6:1	83
2		54	6:1	71
3		90	3:1	75
4		73	7:1	81

[a] Conditions: 1.0 M aldehyde, 0.2 M phenyl acrylate, 0.35 M Et_2MeSiH, room temp, 12 h. [b] Isolated yield of purified material. Percent yield based on acrylate.

provides optimal yields of the silylated adduct. We therefore decided to employ this combination of catalyst and reducing agent with α,β-unsaturated aldehydes since these substrates

Table 2. Asymmetric Reductive Aldol Reaction with Crotonate Derivatives[a]



entry	acrylate	% yield[b]	*syn*:*anti*	% ee syn
1		76	4.3:1	88
2		52	3.9:1	88
3		0	—	—
4		54	4.2:1	88
5		53	3.8:1	88
6		49	3.9:1	93
7		30(85)[c]	4.4:1	n.d.

[a] Conditions: 0.5 M aldehyde, 0.6 M phenyl acrylate, 2.5 M Et_2MeSiH, room temp, 48 h. [b] Isolated yield of purified material. [c] Number in parentheses is yield based on recovered starting material.

do not participate in reductive aldol reactions when [(cod)-RhCl]$_2$/binap is used as the catalyst. With 1 equiv each of aldehyde, acrylate, and silane, low conversion was observed; however, the reaction was highly selective for the silylated product. Since α,β-unsaturated aldehydes provide only the silylated reductive aldol adduct and not the acylated adduct, higher concentrations of these aldehydes were employed, thereby maximizing catalyst turnover, while avoiding formation of the acylated adduct. Under these reaction conditions, previously unreactive unsaturated aldehydes participate in reductive aldol reactions providing acceptable reaction yields and modest levels of stereoinduction (Table 1).

Reductive aldol reactions with phenyl crotonate in place of phenyl acrylate proceed with lower reaction yields (15% combined yield of acylated and silylated products, 1:1 ratio, data not shown) when the neutral catalyst is used. As mentioned above, it appears that with the neutral catalyst derived from [(cod)RhCl]$_2$ and binap, only a small amount of catalyst enters the catalytic cycle such that [binapRhCl]$_2$ is the sole species observed by ^{31}P NMR. To increase the amount of putative reactive hydride and to favor the silylation pathway in reactions with crotonate derivatives, these reductive aldol reactions were conducted with an increased concentration of silane.[9] As observed in Table 2, with 5 equiv of Et$_2$MeSiH and reaction for 48 h, reductive aldol adducts can be isolated in moderate yields and with selectivity that mirrors that of the acrylate derivatives. The geometry of the acrylate does not have a significant impact on reaction stereoselectivity, and both (*E*)- and (*Z*)-configured crotonates provide the same level of stereoinduction. Reactions with trisubstituted acrylates do not proceed; however, arenes, silyl ethers and alkenes could be accommodated in the reacting substrate.

In conclusion, stereochemical analysis of reaction products from diverging reaction pathways suggests a plausible common catalytic intermediate in the Rh(I)/binap-catalyzed reductive aldol reaction. This observation, combined with other data, suggests that the catalytic cycle may be composed primarily of Rh(I) intermediates and that an aldol addition of a Rh(I) enolate to aldehyde substrates is the stereochemistry-controlling step of the reaction.[10]

Acknowledgment. We thank NIGMS (GM064451), Astra-Zeneca, Bristol-Myers Squib, DuPont, GlaxoSmithKline, and the David and Lucile Packard Foundation for financial support.

Supporting Information Available: Characterization data for all new compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Unlike reactions of acrylates, reactions of crotonates exhibit lower enantioselection when **3** is used as a catalyst (40% ee, 97% yield for entry 1, Table 2).

(10) An elegant approach to catalytic intra- and intermolecular reductive aldol reactions with molecular hydrogen as a reductant was reported recently. These reactions may proceed through a Rh(I) or Rh(III) hydride. See: (a) Huddleston, R. R.; Krische, M. J. *Org. Lett.* **2003**, *5*, 1143. (b) Jang, H. Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 15156.