

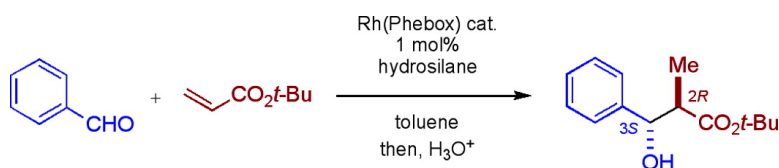
Communication

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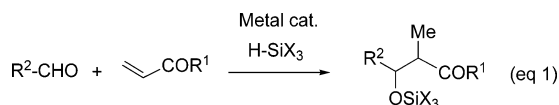
High Performance of Rh(Phebox) Catalysts in Asymmetric Reductive Aldol Reaction: High Anti-Selectivity

Hisao Nishiyama,* Takushi Shiomi, Yasunori Tsuchiya, and Isamu Matsuda

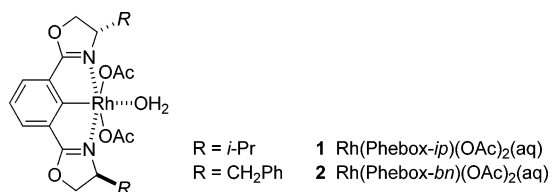
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Reductive aldol reaction (RA) of α,β -unsaturated esters or enones with aldehydes promoted by a catalytic amount of certain transition-metal complexes and stoichiometric hydrosilanes is one of the most promising aldol reaction alternatives, offering an advantage of in situ generation of enolates as nucleophilic condensation counterparts (eq 1).^{1–3} An impressive extension has been demonstrated by Morken et al. with chiral phosphine–rhodium or nitrogen-based ligand–iridium catalysts attaining asymmetric induction accompanied with syn-diastereoselectivity.⁴ RA is, nevertheless, still a developing reaction paradigm of C–C bond formation in terms of efficiency, control of stereochemistry, and asymmetric induction, for example, loading amounts of unsaturated carbonyls and silanes toward substrate aldehydes, or lower to moderate yields depending on substrates. We disclose here a reasonable protocol producing aldol compounds, β -hydroxyesters, with our chiral rhodium catalysts.



We have so far reported chiral 2,6-bis(2-oxazolonyl)phenyl skeleton (abbreviated as Phebox) as a C_2 -symmetric N–C–N ligand and its transition metal complexes, which exhibit high potentiality as Lewis acids in asymmetric reactions.⁵ Very recently, we have found that Rh(Phebox) complexes act as efficient catalysts for the asymmetric conjugate reduction of α,β -unsaturated esters with several hydrosilanes.⁶ On the basis of this finding, we have reasoned that a chiral Rh–Phebox catalyst could promote the asymmetric RA reaction.



The reaction was carried out at 50 °C as a standard condition by dropwise addition of hydrosilane into a mixture of benzaldehyde (1.0 mmol), *tert*-butyl acrylate (1.5 mmol), and the catalyst **1** (1 mol %) in toluene. The reaction was completed within 0.5–1.0 h to form the corresponding aldol–silyl ethers, which were treated under an acid condition (aq HCl) to give the mixture of **3anti** and **3syn** (Scheme 1). Alkoxyhydrosilanes **S1**, **S2**, and **S3** smoothly promoted the reduction–condensation process to give high yields of 87–93% (Table 1). The anti-isomer, **3anti**, was selectively obtained in the ratio of 94:6–95:5 with high enantioselectivity up to 94% (runs 1–4). Under the same condition, the catalyst loading could be reduced to 0.1 mol % to keep the efficiency (run 3).

Scheme 1

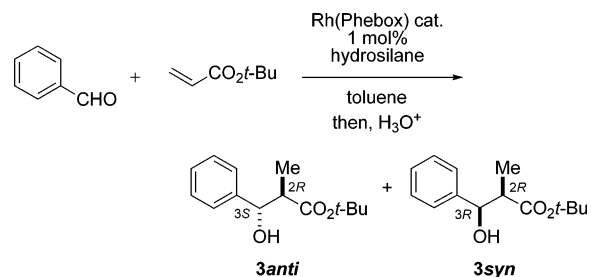


Table 1. Asymmetric Reductive Aldol Reaction of *tert*-Butyl Acrylate and Benzaldehyde with Rh(Phebox) Catalysts^a

run	catalyst	silane	temp/time (°C/h)	yield of 3 (%)	%ee		
					anti:syn	anti	syn
1	1	S1	50/0.5	93	94:6	94	2
2	1	S2	50/0.5	91	95:5	91	11
3 ^b	1	S2	50/0.5	91	95:5	92	4
4	1	S3	50/0.5	87	94:6	88	4
5	1	S4	60/3.0	89	93:7	93	7
6	1	S5	50/0.5	93	94:6	95	5
7	1	S6	50/5.0	95	93:7	96	34
8	2	S1	50/0.5	92	95:5	95	65
9	2	S2	50/1.0	98	98:2	94	57
10	2	S5	50/0.5	93	94:6	96	54

^a Benzaldehyde (1.0 mmol), catalyst (0.01 mmol), *tert*-butyl acrylate (1.5 mmol), silane (1.6 mmol), toluene (3 mL). **S1**, (EtO)₂MeSiH; **S2**, (EtO)₂MeSiH; **S3**, (EtO)₃SiH; **S4**, Et₂MeSiH; **S5**, Me₂PhSiH; **S6**, MePh₂SiH.
^b Catalyst (0.001 mmol, 0.1 mol %).

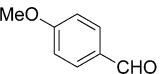
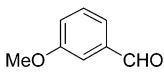
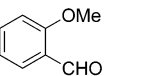
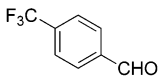
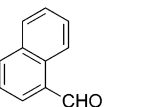
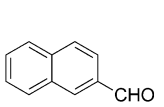
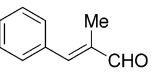
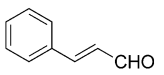
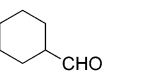
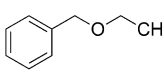
Alkylhydrosilanes **S4**, **S5**, and **S6** similarly worked to give 93–96% ee (runs 5–7). Compared to the isopropyl complex **1**, the benzyl **2** was slightly effective to give 98% of anti-selectivity (runs 8–10). Other reaction profiles are as follows: enantiomeric excess of the syn-product proved to be lower in all cases in 2–65%. At 20 °C, the aldol reaction did not take place. The catalysts could be recovered as the chloride complex, Rh(Phebox-*R*)Cl₂(H₂O), by elution with ethyl acetate from silica gel residue after chromatographic separation of the aldol products.⁷

Aromatic aldehydes **4–9** were subjected to the reaction to also give high anti-selectivity up to 98% and high enantioselectivity up to 96% ee (Table 2). Although the cinnamaldehydes **10** and **11** and the aliphatic aldehydes **12** and **13** resulted in lower yields under the same condition, their stereoselectivity could be improved by changing the loading of acrylate or by choice of the hydrosilanes.

The reaction of *tert*-butyl crotonate **14** efficiently gave *anti*-**15** in 97% ee (93% yield, anti:syn = 93:7) with the catalyst **1** and the silane **S5** under the same condition for run 1 of Table 1. Methyl methacrylate **16** resulted in 61 and 55% ee for **17**.

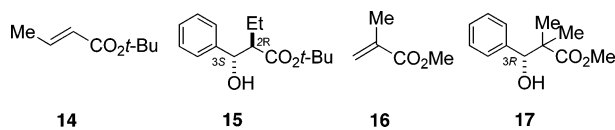
To clarify the mechanism, several experiments were carried out as follows: in the absence of an acceptor benzaldehyde, the conjugate reduction of methyl acrylate with Me₂PhSiH **S5** and the

Table 2. Asymmetric Reductive Aldol Reaction of Several Aldehydes and *tert*-Butyl Acrylate with Rh(Phebox) Catalysts^a[catalyst/silane:
yield of aldols (%), ratio of *anti*:*syn*, %*ee* of *anti* and *syn*]

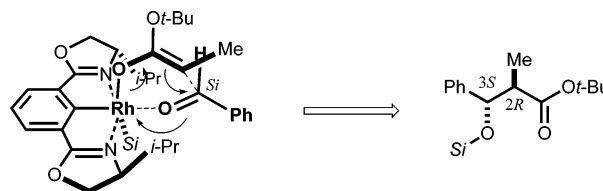
	4		5
[1/S1: 94%, 93:7, 94, 1] [1/S2: 82%, 94:6, 93, 1] [1/S5: 90%, 92:8, 95, 2] [2/S2: 98%, 94:6, 94, 42]		[1/S2: 92%, 93:7, 92, 28] [1/S5: 96%, 93:7, 96, 15] [2/S2: 99%, 91:9, 93, 64]	
	6		7
[1/S2: 84%, 92:8, 87, 5] [1/S5: 95%, 87:13, 93, 27]		[1/S2: 93%, 92:8, 89, 34] [1/S5: 95%, 87:13, 93, 27]	
	8		9
[1/S1: 93%, 95:5, 95, 13] [1/S2: 95%, 98:2, 95, 23] [1/S5: 92%, 81:19, 90, 0] [2/S2: 97%, 98:2, 96, -]		[1/S2: 92%, 93:7, 93, 17] [1/S5: 93%, 93:7, 96, 5]	
	10		11
[1/S2: 76%, 93:7, 92, 52] ^b [1/S5: 78%, 68:32, 55, 8] ^b		[1/S2: 56%, 81:19, 93, 79] ^b [1/S5: 32%, 90:10, 72, 58] ^b	
	12		13
[1/S1: 70%, 87:13, 93, 12] [1/S2: 58%, 95:5, 95, 5] [1/S5: no aldol] [2/S2: 72%, 86:14, 93, 57]		[1/S2: 75%, 72:28, 93, 77] [2/S2: 81%, 59:41, 91, 87]	

^a Aldehyde (1.0 mmol), catalyst (0.01 mmol), *tert*-butyl acrylate (1.5 mmol), silane (1.6 mmol), toluene (3 mL), 50 °C, 0.5–1.0 h. ^b *tert*-Butyl acrylate (2.0 mmol), silane (2.1 mmol).

catalyst **1** smoothly proceeded at 50 °C for 1 h to form a mixture of the corresponding *Z*:*E* silylketene acetal, which was analyzed by ¹H NMR; *Z*:*E* = 5:95.⁸ To the reaction mixture was then added



benzaldehyde. However, the aldol reaction did not proceed at 50 °C for 5 h. This fact intensively suggests that the aldol reaction takes place on the rhodium metal. The intermediary species may be Rh–O–enolate as demonstrated by Bergman–Heathcock⁹ or Rh–oxa– π -allyl as proven by Hayashi.¹⁰ While, with (EtO)₂MeSiH (**S2**) the reaction of the generated silylketene acetal and benzaldehyde proceeded at 50 °C for 5 h to give the aldol products in 68% with high *syn*-selectivity (**3anti**:**3syn** = 5:95); the intermediate silylketene acetal (*Z*:*E* = 39:61) was detected by NMR.⁸ The major *syn*-product proved to be racemic. Thus, the background aldol reaction was observed in the case of the alkoxyisilane, probably because of Lewis acidity of the incorporated alkoxyisilyl moiety.¹¹ However, it does not influence enantioselectivity of the *anti*-aldol, very fortunately. It is thought that the starting Rh^{III}(Phebox) complex can be reduced with hydrosilane via Rh^I(Phebox) species to form the H–Rh^{III}(Phebox) species, which reacts with α,β -unsaturated ester to give Rh^{III}–enolate. Benzaldehyde is, in turn, captured on



chair-like transition state

Figure 1. Hypothetical stereochemical course of the reaction.

one vacant site of the enolate complex. A final step is the release of aldol products in the reductive elimination process, regenerating the Rh^I(Phebox) species. Judging from the stereochemical outcome of *anti*-(**2R,3S**), a chairlike transition state of Zimmerman–Traxler-type can be hypothesized involving the Rh(*E*)-enolate species, which attacks the *si* face of the coordinating benzaldehyde (Figure 1).¹² Experimental study of the mechanistic detail is now underway.

In conclusion, we have thus found a new efficient catalytic system for the highly *anti*-selective and enantioselective reductive aldol reaction of acrylates and aldehydes with hydrosilanes.

Supporting Information Available: Experimental details and analysis. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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