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# Intermolecular Antiselective and Enantioselective Reductive Coupling of Enones and Aromatic Aldehydes with Chiral Rh(Phebox) Catalysts

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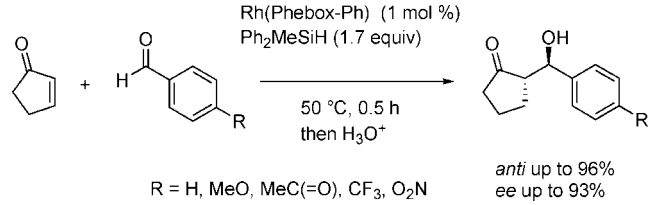
## ABSTRACT




**The intermolecular reductive coupling reaction of cyclopent-2-enone and aromatic aldehydes was realized by chiral rhodium−(bisoxazolinyl)phenyl catalysts, Rh(Phebox-Ph)(OAc)$_2$(H$_2$O), with diphenymethylsilane as a hydride donor to give the corresponding *β*-hydroxyketones in high *anti*-selectivity (up to 96%) with high enantioselectivity (up to 93%).**

Catalytic reductive coupling reactions enabled on conjugate reduction of α,*β*-unsaturated carbonyl compounds followed by aldol-type coupling reaction toward aldehydes or ketones as acceptors have been recognized as a versatile synthetic method of *β*-hydroxycarbonyl compounds.[1] In 1990, Matsuda et al. first reported $Rh_4(CO)_{12}$/phosphine-catalyzed direct coupling of α,*β*-unsaturated linear and cyclic ketones toward hexanal or benzaldehyde in the presence of diethylmethylsilane as a hydride donor to give the corresponding aldol products in the range of moderate to high yields with moderate *syn*-selectivity of 10−66%.[2] Recently, several intermolecular direct couplings of enones toward aldehydes using copper,[3] indium,[4] and rhodium catalysts[5] have been reported to show synthetic versatility with high *syn* stereoselectivity. Krische et al. reported the coupling reaction between vinyl ketones and aldehydes under hydrogenation condition with $[Rh(COD)_2]OTf/(2\text{-furyl})_3P$ catalyst to attain high diastereoselectivity up to 99:1 of *syn*:*anti*, and extended the reaction to synthesis of α,*β*,*γ*-stereotriads with optically active α-amino aldehydes.[6−8] In terms of enantioselective reductive coupling, Krische et al. reported intermolecular hydrogenative aldol coupling of vinyl ketones catalyzed by $[Rh(COD)_2]OTf$/phosphonite to find high diastereoselectivity to 50:1 and enantioselectivity of 96%.[9] As for the intra-

(1) (a) Jang, H.-Y.; Krische, M. J. *Acc. Chem. Res.* **2004**, *37*, 653. (b) Chiu, P. *Synthesis* **2004**, 2210. (c) Nishiyama, H.; Shiomi, T. Metal Catalyzed Reductive C-C Bond Formation. In *Topics in Current Chemistry*; Krische, M. J., Ed.; Springer-Verlag: Berlin/Heidelberg, Germany, 2007; Vol. 279, p 105. (d) Iida, H.; Krische, M. J. Metal Catalyzed Reductive C-C Bond Formation. In *Topics in Current Chemistry*; Krische, M. J., Ed.; Springer-Verlag: Berlin/Heidelberg, Germany, 2007; Vol. 279, p 77. (e) Han, S. B.; Hassan, A.; Krische, M. J. *Synthesis* **2008**, 2669.

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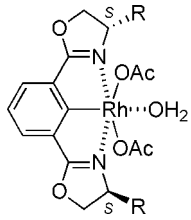
molecular coupling, Lipshutz succeeded with enantioselective coupling of enone−ketone substrates with copper−hydride species combined with chiral bis-phosphines.[10] In this trend, the enantioselective intermolecular reductive coupling is still an important class of carbon−carbon coupling reactions to obtain the corresponding aldol products directly from enone substrates. We have, therefore, challenged the subject using our catalytic system.

So far, we have demonstrated enantioselective reductive coupling of α,β-unsaturated esters with aldehydes or ketones as acceptors catalyzed by chiral rhodium(bisoxazolinylphenyl) complexes, Rh(Phebox), to show high potential for *anti*-selectivity and high enantioselectivity.[11,12] We have therefore intended to execute the coupling with enones and aldehydes catalyzed by Rh(Phebox-R) and hydrosilanes.

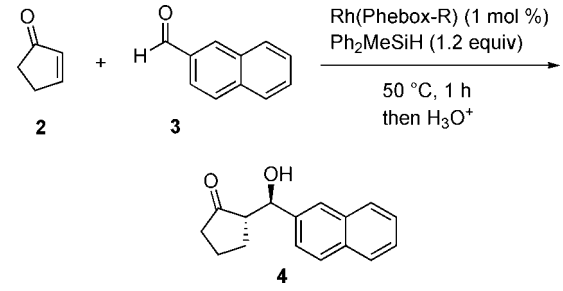



Rh(Phebox-R)

**1a** R = *i*-Pr
**1b** R = *s*-Bu
**1c** R = *i*-Bu
**1d** R = Bn
**1e** R = Ph

We selected cyclopent-2-enone (**2**) and 2-naphthaldehyde (**3**) as coupling partners to give β-hydroxyketone **4** with Rh(Phebox) acetates **1a**−**e** and diphenylmethylsilane as a hydride donor (Table 1, entries 1−5). The mixture of **2** and **3** (1:1 mol ratio) was treated in THF at 50 °C in the presence of 1 mol % of the catalyst and 1.2 equiv of the hydrosilane. After hydrolysis, the corresponding β-hydroxyketone **4** was obtained in 71−83% yields with high *anti*-selectivity up to 94%. Use of Rh(Phebox-Ph) **1e** resulted in 86% ee (entry 5). In place of THF, toluene was employed to show a slight increase of diastereoselectivity (entry 6). The excess of aldehyde **3** apparently enabled an increase in the product yield (entry 7). Surprisingly, acetone was tolerated as a solvent to provide a high yield of 85% with similar diastereoselectivity and 87% ee (entry 8). Ethyl acetate also could be used as a solvent (entry 9). In place of diphenylmethylsilane, use of phenyldimethylsilane and diethoxymethylsilane, unfortunately, resulted in lower yields, respectively (entries 10 and 11).

**Table 1.** Enantioselective Reductive Coupling of Cyclopent-2-enone and 2-Naphthaldehyde with Rh(Phebox-R) Catalysts and $Ph_2MeSiH$[a]




| entry | cat. | solvent | yield (%) | dr *anti*:*syn* | ee (%) *anti*/*syn* |
|---|---|---|---|---|---|
| 1 | **1a** | THF | 72 | 93:7 | 68/−19 |
| 2 | **1b** | THF | 71 | 86:14 | 72/25 |
| 3 | **1c** | THF | 83 | 89:11 | 82/−58 |
| 4 | **1d** | THF | 71 | 88:12 | 84/−27 |
| 5 | **1e** | THF | 76 | 94:6 | 86/60 |
| 6 | **1e** | $C_6H_5CH_3$ | 79 | 96:4 | 86/65 |
| 7[b] | **1e** | $C_6H_5CH_3$ | 95 | 93:7 | 85/69 |
| 8 | **1e** | $CH_3COCH_3$ | 85 | 93:7 | 87/72 |
| 9 | **1e** | $CH_3CO_2C_2H_5$ | 77 | 94:6 | 85/67 |
| 10[c] | **1e** | THF | 63 | 93:7 | 81/60 |
| 11[d] | **1e** | THF | 44 | 92:8 | 84/62 |

[a] **2** (1.0 mmol), **3** (1.0 mmol), cat. **1** (0.01 mmol), $Ph_2MeSiH$ (1.2 mmol), solvent (1.0 mL). [b] **3** (1.5 mmol), $Ph_2MeSiH$ (1.7 mmol), yield based on **2**. The isolated yield was corrected by $^1H$ NMR, because the product included naphthalen-2-ylmethanol. [c] $PhMe_2SiH$ (1.2 mmol) was used. [d] $(EtO)_2MeSiH$ (1.2 mmol) was used.

Next, several aromatic aldehydes **5a**−**i** were subjected to the reductive coupling with cyclopent-2-enone (**2**) under the optimized condition with the catalyst **1e** (1.0 mol%) and $Ph_2MeSiH$ (1.7 equiv) similar to entry 7 of Table 1 to give the aldol products in 49−90% yields (Table 2). 1-Naphthaldehyde (**5a**) gave rise to an increase of ee up to 90% for *anti*-diastereomer compared to that of 2-naphthaldehyde (**3**) (entry 1). The aldehydes bearing electron-withdrawing groups kept ee values in the 90−93% range (entries 3−5). It is noteworthy that the acetyl group survived during the reduction and the aldol reaction to give 62% yield with 90% ee for *anti*. The 4-methoxy group decreased ee to 65% (entry 6), whereas teh 3-methoxy substituent improved the yield and the stereoselectivities (entry 8). On the other hand, 3-acetylbenzaldehyde resulted in a lower yield (entry 7).

In place of cyclopent-2-enone, several cyclic enones **7**, **9**, and **11** (Scheme 1) were subjected to the coupling with 1-naphthaldehyde (**5a**) selected as an acceptor under the similar condition to entry 1 of Table 2. 4,4-Dimethylcyclopentenone **7** gave almost complete *anti*-selectivity with 87% ee, while 2-cyclohexenone (**9**) drastically decreased the yield to 31%. The conjugate reduction of 2-cylcohexenone predominately proceeded to form cyclopentanone. It was

(7) For other metal-catalyzed reductive coupling reactions of enones see the following: [Cu and tinhydride]: (a) Ooi, T.; Doda, K.; Sakai, D.; Maruoka, K. *Tetrahedon Lett.* **1999**, *40*, 2133[Pt]: (b) Lee, H.; Jang, M.-S.; Hong, J.-T.; Jang, H.-Y. *Tetrahedron Lett.* **2008**, *49*, 5785[L-Selectride]: (c) Ghosh, A. K.; Kass, J.; Anderson, D. D.; Xu, X.; Marian, C. *Org. Lett.* **2008**, *10*, 4811. [Ru]: (d) Fukuyama, T.; Doi, T.; Minamino, S.; Omura, S.; Ryu, I. *Angew. Chem., Int. Ed.* **2007**, *46*, 5559.

(8) For organo-Lewis base-catalyzed reductive aldol coupling of enones with trichlorosilane as reducing agent, see: Sugiura, M.; Sato, N.; Kotani, S.; Nakajima, M. *Chem. Commun.* **2008**, 4309.

(9) Bee, C.; Han, S.-B.; Hassan, A.; Iida, H.; Krische, H.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 2746.

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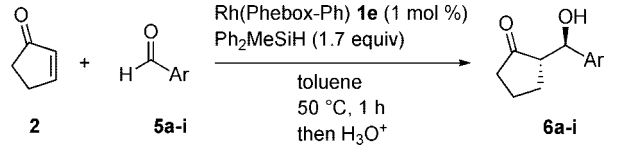
(12) For the preparation method for Rh(Phebox) acetates, see: Kanazawa, Y.; Tsuchiya, Y.; Kobayashi, K.; Shiomi, T.; Ito, J.; Kikuchi, M.; Yamamoto, Y.; Nishiyama, H. *Chem. Eur. J.* **2006**, *12*, 63.

**Table 2.** Enantioselective Reductive Coupling of Cyclopent-2-enone and Aromatic Aldehydes **5** with Rh(Phebox-Ph) Catalysts and $Ph_2MeSiH$[a]

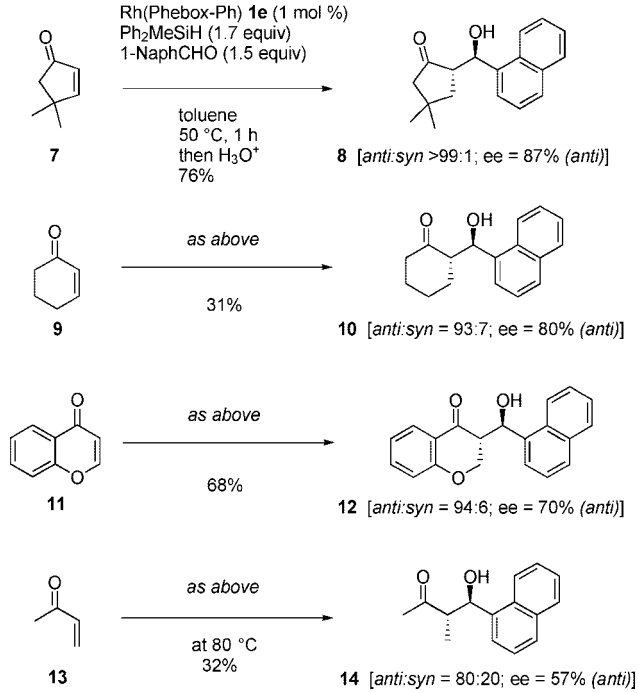



| entry | | aldehyde | yield of **6** (%) | dr *anti*:*syn* | ee (%) *anti*/*syn* |
|---|---|---|---|---|---|
| 1 | **5a** | 1-NaphCHO | 90 | 94:6 | 90/85 |
| 2 | **5b** | $C_6H_5CHO$ | 80 | 95:5 | 85/64 |
| 3 | **5c** | $4\text{-}CH_3COC_6H_4CHO$ | 62 | 85:15 | 90/73 |
| 4 | **5d** | $4\text{-}CF_3C_6H_4CHO$ | 70 | 79:21 | 91/84 |
| 5 | **5e** | $4\text{-}NO_2C_6H_4CHO$ | 68 | 70:30 | 93/85 |
| 6[b] | **5f** | $4\text{-}MeOC_6H_4CHO$ | 72 | 88:12 | 65/24 |
| 7[c] | **5g** | $3\text{-}CH_3COC_6H_4CHO$ | 49 | 79:21 | 82/78 |
| 8 | **5h** | $3\text{-}CH_3OC_6H_4CHO$ | 81 | 93:7 | 87/69 |
| 9 | **5i** | $2\text{-}CH_3OC_6H_4CHO$ | 68 | 94:6 | 68/75 |

[a] **2** (1.0 mmol), **5** (1.5 mmol), cat. **1e** (0.01 mmol), $Ph_2MeSiH$ (1.7 mmol), toluene (1.0 mL). [b] 2 h. [c] At 80 °C.

assumed that the intermediate enolate could not smoothly be captured by the aldehyde. On the other hand, a chromenone derivative **11** with excellent *anti*-selectivity of 94% gave a moderate yield with 60% and 70% ee. However, methyl vinyl ketone (**13**) as a linear enone resulted in a low yield with 57% ee of *anti*.

**Scheme 1.** Enantioselective Reductive Coupling of Several Enones and 1-Naphtaldehyde (**5a**) with Rh(Phebox-Ph) Catalyst and $Ph_2MeSiH$




Thus, we have demonstrated enantioselective reductive coupling with several enones and aromatic aldehydes.[13] We observed high *anti*-selectivity for most of the cases and high enantioselectivity of *anti*-products over 90% ee for some cases. However, the yields drastically chagned depending on the enones.

The absolute configuration of the *anti*-products **6b**-*anti* and **6e**-*anti* was confirmed by comparison with those reported in the literature.[14] Both *anti*-products were found to have 2*S*,1′*R*, and for **6b**-*syn*, 2*S*,1′*S*. On the basis of *anti*-selectivity and the absolute configuration, a cyclic transition state was postulated as illustrated in Figure 1. The Re-face of the enolate carbon atom may attack the Re-face of the aldehyde carbon atom to form 2*S*,1′*R* stereochemistry via cyclic transition state on the rhodium active site. One of a little bulky phenyl substituent on the oxazoline rings could appropriately control enolate formation derived from cyclopent-2-enone to give high stereoselectivities rather than those with the isopropyl or *sec*-butyl group of other catalysts.

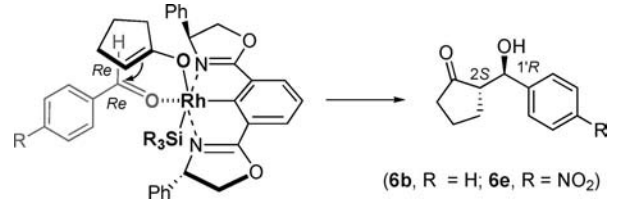



**Figure 1.** Hypothetical transition state giving *anti*-stereoselectivity and 2*S*,1′*R* absolute configurtion.

To confirm the coupling reaction mechanism, after the conjugate reduction of the enone **2** under the condition

(13) The reaction of cyclopent-2-one with $PhCH_2CH_2CHO$ as an acceptor resulted in formation of a trace of the corresponding aldol at 80 °C under the same condition of Table 2.

(14) For **6b**: (a) Ishihara, K.; Kondo, S.; Yamamoto, H. *J. Org. Chem.* **2000**, *65*, 9125. For **6e**: (b) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 734.

(15) Typical procedure: Table 1, entry 7: $Rh(Phebox\text{-}Ph)(OAc)_2(H_2O)$ (**1e**) (6.1 mg, 0.01 mmol) was placed in a 10 mL flask. Under an argon atmosphere, cyclopent-2-enone (**2**) (82.2 mg, 1.0 mmol), 2-naphtaldehyde (**3**) (235 mg, 1.50 mmol), and toluene (1.0 mL) were added. Methyldiphenylsilane (337 mg, 1.7 mmol) was slowly added at 50 °C by syringe, and the mixture was stirred for 1 h. The reaction was monitored by TLC examination; $R_f$ ca. 0.6 for the silyl ether of the aldol product (eluent: EtOAc/hexane = 1:3). To the mixture was added EtOH (1 mL) and aq HCl (1 mL, 4 N) at 0 °C, and the mixture was stirred at room temperature for 2 h; TLC, $R_f$ ca. 0.6 for the aldol product **4** (eluent: EtOAc/hexane = 1:1). The mixture was treated with aq $NaHCO_3$ (ca. 10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with saturated brine (5 mL) and then dried over $MgSO_4$. After concentration, the residue was purified by silica gel column chromatography with EtOAc/hexane as eluent to give the aldol product **4** in 95% yield (0.95 mmol, 229 mg, corrected by $^1H$ NMR because of contamination of naphthalen-2-ylmethanol) as a white yellowish oil. $^1H$ NMR: for *anti*, $\delta$ 1.52−1.79 (m, 3H), 1.95 (m, 1H), 2.30 (m, 1H), 2.41−2.64 (m, 2H), 4.69 (s, 1H, O*H*), 4.88 (d, $J$ = 9.3 Hz, 1H, C*H*OH), 7.45−7.52 (m, 3H), 7.78−7.86 (m, 4H); for *syn*, $\delta$ 5.47 (m, 1H, C*H*OH) ppm. $^{13}C$ NMR $\delta$ 20.8, 27.3, 39.0, 55.5, 75.5, 124.2, 125.6, 125.9, 126.1, 127.6 (×2), 128.0, 128.3, 133.1, 138.7, 222.7 ppm. IR (neat) $\nu$ 3460 (broad, O−H), 1717 (C=O) $cm^{-1}$. EI-HRMS $[M^+]$ *m*/*z*, found 240.1153, calcd ($C_{16}H_{16}O_2$) 240.1150. Chromatography DAICEL CHIRALCEL OD-H; eluent hexane/2-propanol (90:10) (1.0 mL/min); retention time 27.8 min (*syn*, minor), 33.7 min (*syn*, major), 44.5 min (*anti*, minor), 48.3 min (*anti*, major).

described for entry 7 of Table 1, the aldehyde **3** was added to the mixture. However, the coupling product **4** was not formed. Therefore, it is assumed that the intermediate rhodium enolate directly attacks the enone to form rhodium aldolate, which releases the coupling product.[15]

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**Supporting Information Available:** Examples of the reactions and spectroscopic data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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