Intermolecular Asymmetric Reductive Aldol Reaction of Ketones as Acceptors Promoted by Chiral Rh(Phebox) Catalyst

Takushi Shiomi and Hisao Nishiyama*

Department of Applied Chemistry, Graduate School of Engineering, Nagoya University Chikusa, Nagoya, 464-8603, Japan

hnishi@apchem.nagoya-u.ac.jp

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R = Me, Et, i-Pr, Bn, t-Bu, Ph

up to 98% ee

The conjugate reduction of cinnamates with hydrosilane and chiral Rh(Phebox-ip) catalyst in the presence of excess acetone is shown to provide the corresponding intermolecular reductive aldol product in extremely high enantioselectivity (up to 98%). Several cinnamates and crotonate substrates and several ketone acceptors were also examined.

The reaction sequence of conjugate reduction of α,β unsaturated carbonyl groups and subsequent aldol reaction toward carbonyl functions as acceptors is commonly defined as the reductive-aldol reaction, which is promoted by certain metal-hydride species and organocatalytic hydride sources in situ prepared.¹ The initial reduction step generates intermediate enolate species, which attack carbonyl groups to give the corresponding aldol products. It is highly advantageous in synthesis to be able to generate the corresponding enolates from carbonyl compounds without the need to use stoichiometric amounts of strong bases. Moreover, use of chiral ligands can realize asymmetric induction at the α - and β -carbon centers of product aldols. Given the scope of acceptors, aldehydes are commonly used in both intermolecular and intramolecular aldol reactions.²⁻⁴ However, there are a few examples with ketones as acceptors giving ester derivatives bearing β -tertiary alcohols.⁵ Recently, Lam's group reported an intramolecular reductive aldol of ω -keto- α , β -unsaturated esters producing five- and sixmembered β -hydroxylactones with enantioselection to 83%

using a chiral bis-phosphine/Cu(OAc)₂ catalyst.⁶ In intermolecular reactions, Riant's group achieved the coupling of methyl acrylate and acetophenone derivatives with a diastereomer ratio of up to 92:8 and 95% ee for the erythro product with a chiral ferrocenyl-phosphine/[CuF(PPh₃)₃]. 2MeOH catalyst,⁷ and Shibasaki's group found the coupling of cinnamate and diethyl ketone with tol-BINAP/[CuF-

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(PPh₃)₃]•2EtOH catalyst giving 82% ee.^{8a} Very recently, Shibasaki's group has accomplished the highly enantioselective reductive aldol reaction of allenic esters to ketones in up to 99% ee.^{8b} Thus, reductive aldol reactions with ketones are still developing and have room for improvement for substrate scope, yields, and enantioselectivity.

We have developed a highly enantioselective reductive aldol reaction with acrylates using aldehydes as acceptors by chiral rhodium—bis(oxazolinylphenyl) catalysts, Rh-(Phebox), which show several excellent profiles such as exceptional *anti*-selectivity, lower catalyst loading (<1 mol %), and catalyst recoverability.⁹ We have, therefore, taken on a difficult and significant challenge using ketones as acceptors.



Rh(Phebox-*ip*)

The reaction was carried out at 50 °C by addition of Me₂-PhSiH (1.6–3.0 equiv) into a mixture of ethyl cinnamate **1** (1.5–3.0 equiv) and acetone (1.0 mmol, yield based on acetone) in toluene solvent (2 mL) with the catalyst Rh-(Phebox-*ip*) (1 mol %) (Table 1, entries 1 and 2). The reactions finished within 0.5 h and resulted in enantioselectivities of 93–94%, but the yields of the aldol product **2** were disappointingly very low, where the conjugate reduction of the cinnamate predominately proceeded to produce the

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	Rh(Phebox- <i>ip</i>) cat. hydrosilane MeCOMe	Me. C_6H_5	
✓ CO₂Et	then H ₃ O ⁺	Me CO ₂ Et	

entry	hydrosilane	1/hydrosilane/acetone (mmol) (mL, acetone)	yield (%)	ee (%)
1	Me_2PhSiH	$1.5/1.6/1.0^{a}$	29	94
2		$3.0/3.0/1.0^{a}$	23	93
3^b		$1.5/1.6/1.0^{b}$	71	92
4^c		1.0/1.3/2.7 (0.2 mL)	78	95
5^c		1.0/1.3/6.8 (0.5 mL)	72	95
6^c		1.0/1.3/13.6 (1.0 mL)	60	96
7^c	$MePh_2SiH$	1.0/1.3/2.7 (0.2 mL)	83	97
8^c	${ m Et_2MeSiH}$	1.0/1.3/2.7 (0.2 mL)	33	95
9^c	$(EtO)_2MeSiH$	1.0/1.3/2.7 (0.2 mL)	19	91
10^{c}	TMDS^d	1.0/1.3/2.7 (0.2 mL)	54	94

^{*a*} Rh(Phebox-*ip*) cat. (0.01 mmol, 1 mol %), toluene (2.0 mL) as a solvent, 50 °C, 0.5 h, yield based on acetone. ^{*b*} No toluene. ^{*c*} No toluene, yield based on **1**. ^{*d*} TMDS: tetramethyldisiloxane.

dihydrocinnamate. After several trials, concentrated conditions with no solvent were found to improve the yield to 71% (entry 3). Eventually, based on the optimization of the quantity of acetone toward the cinnamate (1.0 mmol) (entries 4–6), 2.7–13.6 equiv of acetone (0.2–1.0 mL) operated well to give 60–78% yields with 95–96% ee. MePh₂SiH, among other hydrosilanes, attained the highest ee of 97% with a yield of 83% (entry 7), whereas alkyl- and alkoxysilanes resulted in lower yields (entries 8–10).

Table 2. Asymmetric Reductive Aldol Reaction of Several Cinnamates and Acetone^a

<i>p</i> -X−C ₆ H R = Me, X = H,	H ₄ , <i>i-</i> Pr, Bn CF ₃ , Cl, 3	CO ₂ R , <i>t-</i> Bu, Ph OMe	Rh(Phebo MePh MeCC	x- <i>ip</i>) cat. ₂SiH DMe 	Me Me OH	C ₆ H₄- <i>p</i> -X ₹ CO ₂ R
entry	3	R	Х	4	yield (%)	ee (%)
1	3a	Me	Н	4a	83	96
2	3b	i-Pr	н	4b	82	98
3	3c	Bn	Η	4c	82	96
4	3 d	t-Bu	Н	4d	36	97
5^b	3e	Ph	Н	4e	28	<1
6	3f	\mathbf{Et}	CF_3	4f	64	97
7	3g	\mathbf{Et}	Cl	4g	62	97
8	3h	\mathbf{Et}	OMe	4h	81	96

 a Rh(Phebox-ip) cat. (0.01 mmol, 1 mol %), no solvent, acetone (0.2 mL, 2.7 mmol), **3** (1.0 mmol), silane (1.3 mmol), 50 °C, 0.5 h, yield based on **3**. b Acetone (0.4 mL).

⁽³⁾ Cu and In catalysts (nonasymmetric): [Cu]: (a) Ooi, T.; Doda, K.; Sakai, D.; Maruoka, K. *Tetrahedron Lett.* **1999**, *40*, 2133–2163. (b) Chiu, P.; Leung, S. K. *Chem. Commun.* **2004**, 2308–2309. Review: (c) Chiu, P. *Synthesis* **2004**, 2210–2215. [In]: (d) Shibata, I.; Kato, H.; Shida, T.; Yasuda, M.; Baba, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 711–714. (e) Miura, K.; Yamada, Y.; Tomita, M.; Hosomi, A. *Synlett* **2004**, 1985–1989.

Next, substituted cinnamates 3a-h were subjected to the reductive aldol reaction under the optimized condition with MePh₂SiH similar to entry 7 of Table 1 to give the corresponding aldol products 4a-h in up to 83% yield and with enantioselectivities up to 98% (Table 2). Methyl, isopropyl, and benzyl cinnamates gave similarly high yields and enantioselectivities of 96–98% (entries 1–3), whereas bulky *tert*-butyl and phenyl esters (4d and 4e) influenced the reaction to provide lower yields (36% and 28%, respectively) (entries 4 and 5). The *tert*-butyl ester 4d kept the high enantioselectivity of 97% (entry 4), but the phenyl ester 4e resulted in a racemic mixture (entry 5). The electron-withdrawing *p*-CF₃ and *p*-Cl substituents on the cinnamates decreased the product yields compared to that of the *p*-MeO group (entries 6–8).

Cyclohexanone was employed as an acceptor to give 5 in 96% ee and 82% yield (Table 3, entry 1). Surprisingly,

 Table 3.
 Asymmetric Reductive Aldol Reaction of Ethyl

 Cinnamate and Other Ketones^a
 Image: Compared and Co



 a Rh(Phebox-ip) cat. (0.01 mmol, 1 mol %), no solvent, ketone (3.0 mmol), 1 (1.0 mmol), MePh₂SiH (1.3 mmol), 50 °C, 0.5 h, yield based on 1.

diethyl ketone reacted with diminished yield (entry 2). The reasons why the aldol reaction was prevented in this case could not be identified. The active site of the catalyst may not be able to supply a sufficient space for the ethyl ketone skeleton. On the other hand, ethyl methyl ketone and acetophenone were subjected to the reaction to produce the aldols in good to excellent yields (entries 3 and 4). Ethyl methyl ketone gave a lower diastereoselectivity of 59:41. However, both isomers have high enantiomeric excesses of up to 96% (entry 3). When acetophenone was employed as an acceptor, a diastereoselectivity of 96:4 was obtained to give the adduct 8 in 90% yield with 97% ee for the major isomer (entry 4). In this context, Riant et al. reported similarly high diastereoselectivity (92:8) and enantioselectivity (95% ee) for the erythro isomer.⁷ On the basis of our previous finding on the asymmetric reductive coupling

of acrylates and aldehydes, 9a the relative configuration of major diastereomer of **8** is assumed as an *erythro* form of (2*R*,3*S*).

In place of cinnamate, benzyl acrylate and crotonate were subjected to the reaction with acetone under the same conditions of entry 7 of Table 1 (Scheme 1). Although the



reaction with acrylate **9** resulted in 57% ee in a yield of 20% of **11**, benzyl crotonate **10** fortunately increased the percent ee up to 95% in 76% yield of **12**.

On the basis of the absolute configuration of the product **2**, the intermediate *E*- or *Z*-enolate derived from the conjugate reduction of ethyl cinnamates attacks from the *Si*-face carbon atom to acetone to generate *R*-absolute configuration at the α -position of the aldol products.

In conclusion, we have successfully accomplished the challenging intermolecular reductive aldol reaction of ketones as acceptors with cinnamates and crotonate under optimal concentrated condition to attain good to high yields and an extremely high level of enantioselectivity. This process can provide a new synthetic access to optically active β -hydroxy dihydrocinnamates and related esters by one-pot coupling of readily available α , β -unsaturated esters and ketones.¹⁰

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⁽¹⁰⁾ Typical procedure: Table 1, entry 7: the rhodium complex, Rh-(Phebox-ip)(OAc)₂(H₂O) (5.4 mg, 0.01 mmol), was placed in a 10 mL flask. Under an argon atmosphere, ethyl cinnamate (176 mg, 1.0 mmol) and acetone (0.20 mL) were added. Methyldiphenylsilane (258 mg, 1.3 mmol) was slowly added at 50 °C by syringe, and the mixture was stirred for 0.5 h. The reaction was monitored by TLC examination; R_f ca. 0.8 for the silyl ether of the aldol product (eluent: EtOAc/hexane = 1:2). To the mixture was added EtOH (1 mL) and aq HCl (1 mL, 4 N) at 0 °C, then the mixture was stirred at room temperature for 4 h; TLC, R_f ca. 0.4 for the aldol product 2 (eluent: EtOAc/hexane = 1:2). The mixture was treated with aq NaHCO₃ (ca. 15 mL) and extracted with EtOAc (3 \times 5 mL). The combined organic layer was washed with saturated brine (5 mL), then dried over Na₂SO₄. After concentration, the residue was purified by silica gel column chromatography with EtOAc/hexane as eluent to give the aldol product 2 in 83 % yield (196 mg, 0.83 mmol) as a colorless oil. ¹H NMR: δ 0.99 (t, J =7.2 Hz, 3H), 1.31 (s, 3H), 1.34 (s, 3H), 2.69 (dd, J = 9.0, 6.3 Hz, 1H), 3.00 (m, 2H), 3.02 (s, 1H), 3.95 (q, J = 7.2 Hz, 2H), 7.12–7.30 (m, 5H) ppm. ¹³C NMR: δ 14.1, 26.9, 29.2, 33.9, 57.8, 60.35, 71.0, 126.0, 128.0, pp 128.6, 138.9, 174.9 pp m. IR (neat): ν 3458 (broad, O–H), 1720 (C=O) cm⁻¹. EI-HRMS: [M⁺ – (H₂O)] m/z found 218.1300, calcd (C₁₄H₁₈O₂) 218.1307. [α]²⁸_D +58.7 (*c* 1.0, CHCl₃). Chromatography: DAICEL CHIRALPAK AS-H; eluent: hexane/2-propanol (99:1) (0.5 mL/min); retention time: 22.3 min (minor), 26.3 min (major); 97% ee. Determination of absolute configuration, see the Supporting Information.

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Supporting Information Available: Typical exrimental procedures 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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