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Asymmetric, Regioselective Direct Aldol Coupling of Enones and Aldehydes with Chiral Rhodium(bis-oxazolinylphenyl) Catalysts

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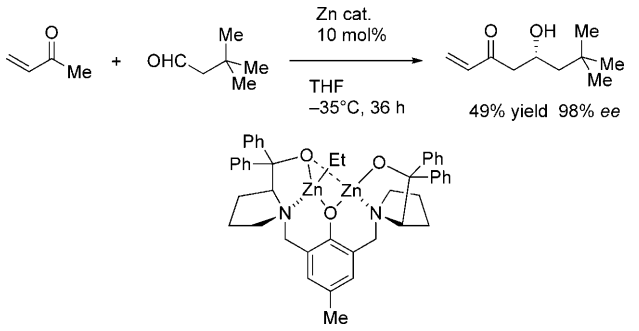
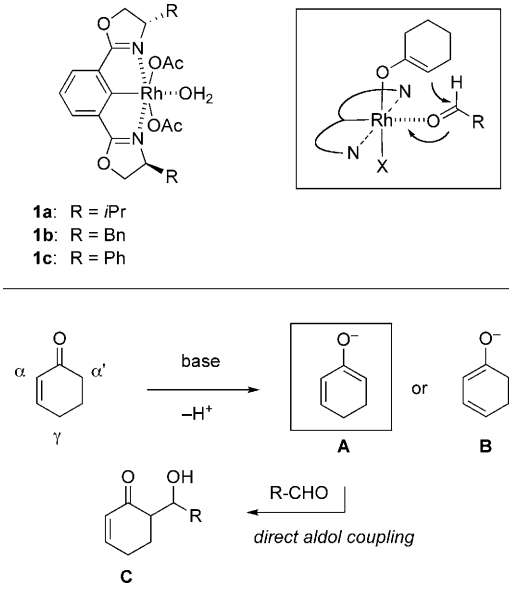
The asymmetric direct aldol coupling reactions of ketones as enolate sources have been extensively developed by the use of chiral organocatalysts via in situ generated enamine species to provide optically active β-hydroxyketones efficiently.[1] However, among the candidate ketone substrates, acyclic and cyclic enones as enolate sources have rarely been applied because of problems of instability, as well as the ability for enones to act as reactive acceptors in conjugate additions, the possibility of retro-aldol equilibrium, or β-hydroxy elimination from the aldol products. It is clearly of importance that the vinylogous unsaturated aldol products derived from enones possess high potential to serve as useful components for organic synthesis. In 2005, Trost et al. first disclosed a potent catalyst based on a dinuclear Zn complex for the asymmetric direct aldol coupling of substituted aliphatic aldehydes with methyl vinyl ketone (MVK) as an enolate source with up to 98% enantiomeric excess (*ee*) (Scheme 1).[2] Nevertheless, there is still a challenge in terms of the scope of the substrate ketones. On the other hand, in terms of similar vinylogous aldol couplings, versatile methods that use silyl-protected dienolates have been successfully developed to give multifunctional unsaturated compounds.[3] In addition, the regioselective direct aldol coupling of enones is thought to be a promising approach to the synthesis of the corresponding unsaturated aldol products.

We have demonstrated that rhodium(bis-oxazolinylphenyl) ([Rh(Phebox)]) acetate complexes catalyze the asymmetric direct aldol reactions of cyclohexanone and aldehydes. We hypothesized that the [Rh(Phebox)] complex acts as a Lewis acid and a Brønsted base to form a rhodium–enolate species (Scheme 2).[4,5] On the basis of our findings, we envisioned the possibility of regioselective formation of dienolate **A** (Scheme 2) by activation of Cα′–H, which leads exclusively to the formation of the unsaturated aldol product



Scheme 1. Dinuclear zinc catalyst for asymmetric direct aldol coupling of MVK reported by Trost et al.



Scheme 2. [Rh(Phebox)] complexes, aldol reaction, and regioselective formation of dienolates.

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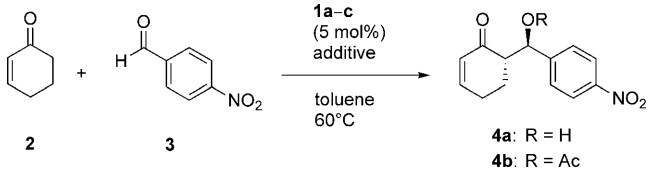
C as opposed to the formation of dienolate **B** by the activation of Cγ–H.

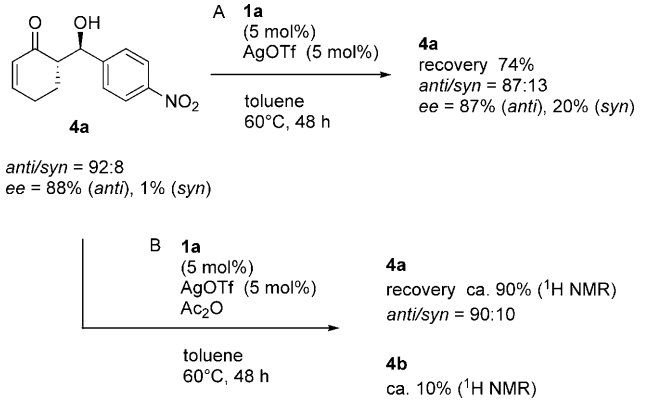
In an initial trial, we selected cyclohex-2-eneone (**2**) as the enolate source and the electron-deficient aldehyde 4-nitrobenzaldehyde (**3**) as the coupling partner. The coupling was performed in the presence of **1a** (5 mol%) in toluene at 60°C for 72 h (Table 1).[6] The coupling product was observed in 26% yield with a moderate *anti* selectivity of 78% and a good *ee* value of 72% (Table 1, entry 1). Addition of AgOTf (OTf = trifluoromethanesulfonate) enhanced the catalytic reactivity to slightly increase the yield to 34% with 93% *anti* selectivity and 91% *ee* for the *anti* product (Table 1, entry 2). The yield was increased to 73% by conducting the reaction at a higher temperature (80°C), however, the stereoselectivity decreased a little (Table 1, entry 3). A catalyst loading of 10 mol% increased the *ee* value to 92% (Table 1, entry 4). Interestingly, the addition of TfOH in place of AgOTf worked similarly well (Table 1, entry 5). Although THF and *t*BuOH were used as solvents, the coupling reactions resulted in lower yields (Table 1, entries 6 and 7). Carrying out the reaction in the presence of extra acetate ion by the addition of AgOAc was not effective (Table 1, entry 8). The yields remained moderate, approximately 60–70%, therefore, it was strongly presumed that the retro-aldol reaction was in equilibrium. Therefore, we examined the treatment of **4a** in the presence of the catalyst **1a** and AgOTf at 60°C for 48 h and indeed observed the retro-aldol reaction by the recovery of **4a** in 74% yield with a slight decrease in the diastereomeric ratio (Scheme 3, method A). Hence, we attempted to trap the aldol product in situ by acetylation with acetic anhydride. Addition of acetic anhydride (3 equiv relative to **3**), under the conditions detailed in entry 2, produced the corresponding acetylated product **4b** in 80% yield with the highest *anti* selectivity thus far of 97% and with 93% *ee* for the *anti* diastereomer (Table 1, entry 9). Increased reaction time, addition of five equivalents of acetic anhydride, or five equivalents of the enone **2** did not increase the yield (Table 1, entries 10–12). In place of the isopropyl catalyst **1a**, the benzyl (**1b**) and phenyl (**1c**) derivatives did not give better results (Table 1, entries 13 and 14).

Table 1. Asymmetric, regioselective direct aldol coupling of **2** and **3** catalyzed by [Rh(Phebox)] complexes.[a]



	Additive	Solvent	Product	Yield [%]	Ratio *anti*/*syn*	*ee* [%] *anti*	*ee* [%] *syn*
1	–	toluene	**4a**	26	78:22	72	16
2	AgOTf	toluene	**4a**	34	93:7	91	16
3[b]	AgOTf	toluene	**4a**	73	91:9	86	25
4[c]	AgOTf	toluene	**4a**	63	95:5	92	35
5	HOTf	toluene	**4a**	58	87:13	90	37
6	AgOTf	THF	**4a**	21	91:9	82	−22
7	AgOTf	*t*BuOH	**4a**	41	93:7	77	13
8	AgOAc	toluene	**4a**	48	64:36	58	5
9[d]	AgOTf/Ac_2O	toluene	**4b**	80	97:3	93	–
10[e]	AgOTf/Ac_2O	toluene	**4b**	74	96:4	93	–
11[f]	AgOTf/Ac_2O	toluene	**4b**	74	95:5	92	–
12[g]	AgOTf/Ac_2O	toluene	**4b**	72	92:8	93	–
13[h]	AgOTf/Ac_2O	toluene	**4b**	29	82:16	73	6
14[i]	AgOTf/Ac_2O	toluene	**4b**	59	93:7	63	9

[a] **1a** (5 mol%, 0.025 mmol), additive (AgOTf, HOTf, or AgOAc, 0.025 mmol), **2** (5.0 mmol), **3** (0.50 mmol), solvent (0.5 mL), 60°C, 72 h. [b] 80°C, 72 h. [c] Rh cat. (10 mol%), AgOTf (10 mol%), scale: 0.25 mmol of **3**. [d] Ac_2O (1.5 mmol). [e] Ac_2O (1.5 mmol), 60°C, 192 h. [f] Ac_2O (2.5 mmol). [g] **2** (2.5 mmol). [h] **1b** (5 mol%), Ac_2O (1.5 mmol). [i] **1c** (5 mol%), Ac_2O (2.5 mmol).



Scheme 3. Retro-aldol reaction and acetylation of **4a** under different reaction conditions.

Next, we examined the acetylation of the aldol product **4a** under the coupling conditions at 60°C (Scheme 3, method B). However, only 10% of the acetylated product **4b** was obtained. This fact evidently shows that most of the acetylation in the reaction media occurs on the in situ formed rhodium–aldolate species.

Under the standard conditions (Table 1, entries 2 and 9), the direct coupling of **2** and cyclopent-2-enone with some aromatic aldehydes containing electron-withdrawing aromatic substituents were examined (Scheme 4). In the presence of acetic anhydride, the product yields of **5b**, **6b**, **7b**, and **8b** were improved, to between 55 and 66%, relative to those without acetic anhydride. The highest enantioselectivities of 93 and 94% were obtained for **5b** and **6b**, respectively, and were accompanied with high *anti* selectivity up to 97%. The reaction of benzaldehyde and 2-naphthaldehyde, aldehydes without an electron-withdrawing group, resulted in approximately 30% yields of **9b** and **10b** with good stereoselectivity. The reaction with 3-methylcyclohex-2-enone gave a mixture of β-hydroxy and acetoxy products. Therefore, the crude products were treated with acetic anhydride and pyridine to give **11b** in 40% yield with 89% *anti* selectivity and 85% *ee*. The use of cyclopent-2-enone as an enolate source increased the yields to approximately 50–70%. However, to our surprise, the acetylation did not proceed smoothly in the

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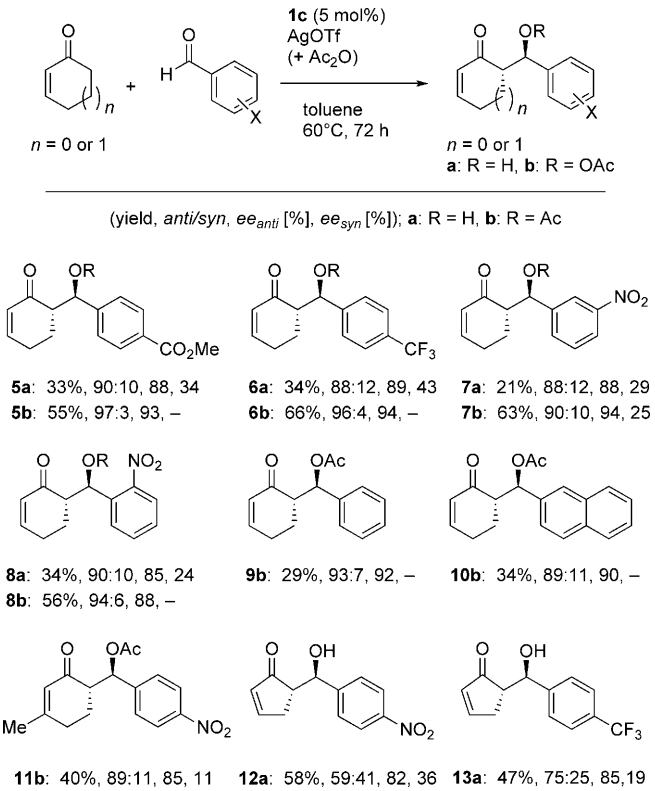
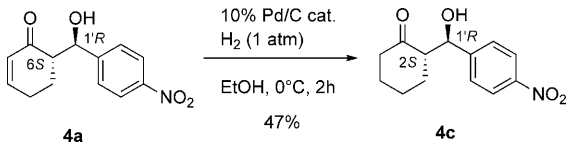


Scheme 4. Asymmetric, regioselective direct aldol coupling of **2** and cyclopent-2-enone with various aldehydes catalyzed by **1c**.

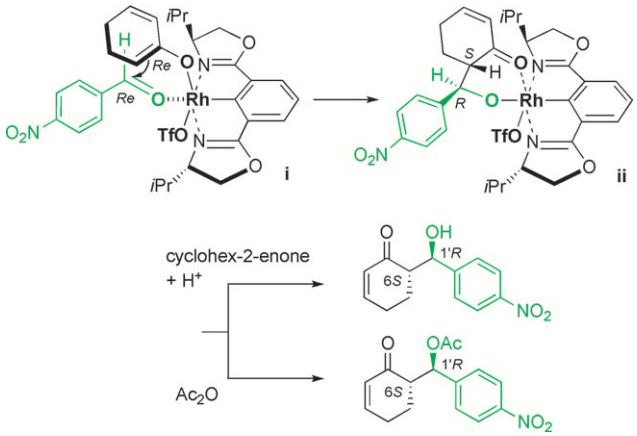
presence of acetic anhydride. It is thought that the corresponding intermediate rhodium–aldolate derived from cyclopent-2-enone could not be efficiently captured by acetic anhydride to release the product.

The absolute configuration 6*S*,1′*R* of product **4a** was unambiguously confirmed by hydrogenation with Pd-C/hydrogen to give the β-hydroxyketone **4c**, the absolute configuration of which, 2*S*,1′*R*, was already determined (Scheme 5).



Scheme 5. Determination of the absolute configuration of **4a**.

On the basis of the absolute configuration, the transition-state model was proposed as follows: attack from the *Re* face of the intermediate dienolate (Scheme 6, **i**) to the *Re* face of the aldehyde forms the rhodium aldolate (Scheme 6, **ii**), which then releases the aldol or acetylation product. We think that in the case of cyclopent-2-enone, which does not result in formation of the acetylated product, the release of the aldol product may be very quick and is therefore not acetylated. We also examined linear enones, such as MVK and benzalacetone, but we obtained very low yields.



Scheme 6. Proposed transition-state model for the coupling reaction.

In summary, we have developed a new asymmetric, regioselective direct aldol coupling reaction using chiral rhodium(bis-oxazolinylphenyl) catalysts. Although the yields are still moderate, this is an important synthetic approach to access challenging aldol products and the corresponding acetylated products. We think that the development of transition-metal catalysts that can act as Lewis acid and Brønsted base catalysts is progressing, and as such, we are exploring the reaction further.

Experimental Section

Typical procedure for the direct aldol coupling of 2 and 3 with acetic anhydride (Table 1, entry 9): The rhodium complex **1a** (13.5 mg, 0.025 mmol, 5.0 mol% relative to aldehyde **3**), compound **3** (75.6 mg, 0.50 mmol), and silver trifluoromethanesulfonate (6.4 mg, 0.025 mmol) were placed in a flask. Under an argon atmosphere, toluene (0.5 mL), compound **2** (481 mg, 5.0 mmol, 10 equiv relative to aldehyde **3**) and acetic anhydride (153 mg, 1.5 mmol, 3 equiv relative to aldehyde) were added. The mixture was stirred at 60 °C for 72 h. The reaction was monitored by TLC; $R_f = 0.24$ (ethyl acetate/hexane = 1:2). The reaction mixture was directly introduced onto a silica-gel column and eluted with ethyl acetate/hexane (1:5) to give the desired acetate product **4b** as a pale yellow oil (80%, 115 mg, 0.40 mmol). The diastereomeric ratio (97:3) was determined by ^{1}H NMR spectroscopy. ^{1}H NMR (300 MHz, $CDCl_3$): *anti*: $\delta = 1.48$ (m, 1H), 2.08 (m, 1H), 2.14 (s, 3H), 2.40 (m, 2H), 3.00 (m, 1H), 5.95 (d, $J = 10.2$ Hz, 1H; C*H*=C), 6.50 (d, $J = 5.2$ Hz, 1H; C*H*OAc), 6.93 (m, 1H), 7.54 (d, $J = 7.8$ Hz, 2H), 8.16 ppm (d, $J = 7.8$ Hz, 2H); *syn*: 6.08 (m, 1H; C*H*=C), 6.53 ppm (d, $J = 3.6$ Hz, 1H; C*H*OAc); ^{13}C NMR (75 MHz, $CDCl_3$): *anti*: $\delta = 21.4$, 24.2, 25.6, 51.6, 72.8, 123.4, 128.0, 129.6, 145.0, 147.4, 149.8, 169.4, 196.6 ppm; IR (neat), $\nu = 3487$, 1742, 1676, 1518, 1345 cm^{-1}; HRMS (FAB): *m/z*: calcd for $C_{15}H_{16}NO_5$: 290.1028 [*M*+H]; found: 290.1030; the *ee* was determined by HPLC: Daicel Chiralpak AD-H; hexane/2-propanol (90:10, 1.0 mL min^{-1}); retention times: 22.5 (*anti*, major), 25.2 (*anti*, minor), 36.8 (*syn*, major), 60.4 min (*syn*, minor); 93% *ee* for the *anti* product.

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Keywords: aldol reaction · asymmetric catalysis · dienolates · enones · rhodium

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