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Diastereoselective reductive Mannich-type coupling of acrylates and aldimines with Rh(Phebox) catalyst

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Abstract—The conjugate reduction of α,β-unsaturated esters such as acrylates, crotonate, and cinnamates followed by Mannich-type coupling toward aldimines was efficiently promoted by rhodium-bis(oxazolinyl)phenyl catalyst and alkoxyhydrosilanes to show high *anti*-selectivity up to 99.
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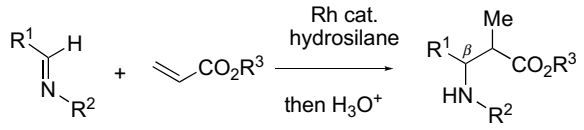
Mannich reaction is an important and preparative C–C bond forming reaction of enolized carbonyl compounds and imines to produce β-amino-substituted carbonyl derivatives.[1] Especially, adoption of ketene silylacetals as nucleophiles can provide β-amino esters, which are raw materials essential to β-amino acids and β-lactams. As an attractive alternative method, Matsuda et al. reported rhodium-catalyzed approach to Mannich-products with α,β-unsaturated esters and hydrosilane (Scheme 1).[2] In the catalytic reaction, however, the issue of diastereoselectivity, *syn*:*anti*, has remained unsolved; *anti*-selectivity up to 68%. In this context, Isayama demonstrated cobalt catalyzed coupling of crotonate and *N*-methylimine to attain *syn*-selectivity.[3] In addition, Morken demonstrated iridium catalyst for coupling between trifluorophenyl acrylate and aldimines to produce β-lactams in trans-selectivity.[4]

As we have recently found highly diastereoselective (*anti*-selective) and enantioselective reductive aldol coupling



Scheme 1.

reactions of α,β-unsaturated esters toward aldehydes or ketones using chiral rhodium-bis(oxazolinylphenyl) [Rh(Phebox)] catalysts and hydrosilanes, we have strongly intrigued to challenge this issue.[5] We disclose here a new efficient protocol producing β-amino esters with high *anti*-diastereoselectivity.

The reaction of imine **2** and *tert*-butyl acrylate in THF was carried out at 50 °C with 2–5 mol % of Rh(Phebox) catalyst **1**[6] to furnish a mixture of diastereomers in 76–79% yields (Scheme 2) (Table 1, entries 1 and 2). Diastereoselectivity resulted in high *anti*-selectivity (18:82). Methyl acrylate decreased the *anti*-selectivity (entry 3), and use of other alkoxyhydrosilanes decreased the yields (entries 4 and 5). Other solvents were examined to decrease catalytic efficiency (entries 6–9).

In turn, substituted imines **4** were subjected to the coupling reaction with *tert*-butyl acrylate under the same condition in entry 1 of Table 1 (Scheme 3 and Table 2). The reaction smoothly took place to give good to excellent yields (65–73%) and high *anti*-selectivity up to 83% for the case of *p*-MeO substituted imine **4a** (entry 1). Substituents at *p*-position of the imines **4d–f** weakly influenced the diastereoselectivity (entries 4–6). The reaction with the imines derived from α-naphthoaldehyde and β-naphthoaldehyde gave the corresponding coupling products **6** and **7** in moderate yields, respectively. Aminoester **6** showed high *anti*-selectivity of 90%.

Next, we employed a crotonate and cinnamates as enolate sources (Scheme 4 and Table 3). Eventually, crotonate **8a** selectively provided product **9a** in 80%

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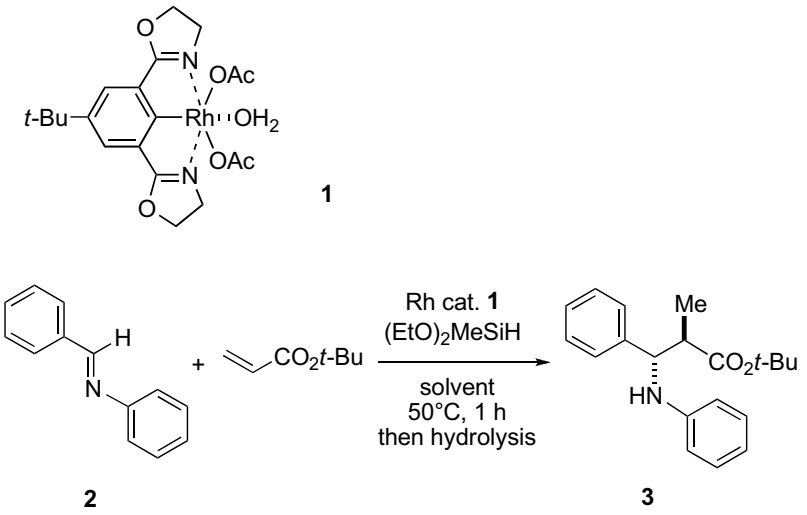
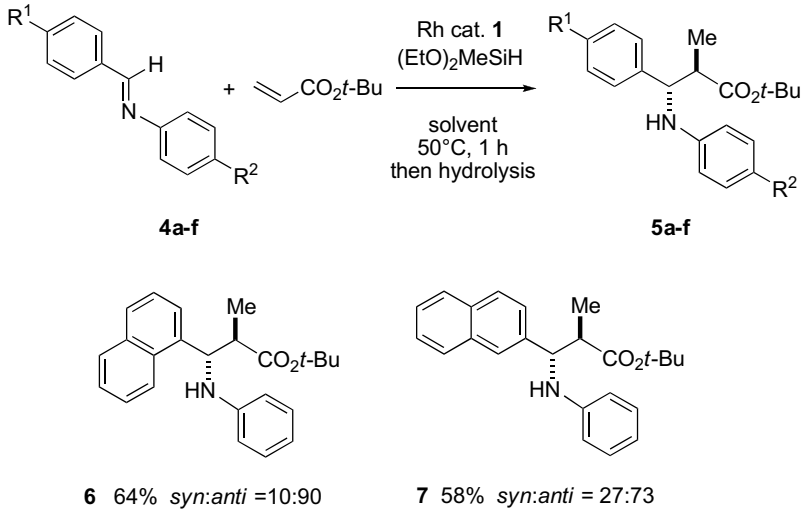


Scheme 2.

Table 1. Reductive Mannich-type coupling of imine **2** and *tert*-butyl acrylate[a]

Entry	Hydrosilane	Solvent	Yield of **3** (%)	Ratio of *syn*:*anti*
1	$(EtO)_2MeSiH$	THF	79	18:82
2[b]	$(EtO)_2MeSiH$	THF	76	18:82
3[c]	$(EtO)_2MeSiH$	THF	75	27:73
4	$(EtO)Me_2SiH$	THF	74	24:76
5	$(EtO)_3SiH$	THF	69	19:81
6	$(EtO)_2MeSiH$	Toluene	68	20:80
7	$(EtO)_2MeSiH$	DME	71	20:80
8	$(EtO)_2MeSiH$	DMF	34	32:68
9	$(EtO)_2MeSiH$	CH_3CN	6	17:83

[a] Cat. **1** (0.005 mmol, 1 mol %), **2** (0.5 mmol), acrylate (1.0 mmol), hydrosilane (1.0 mmol), solvent (2.0 mL).
[b] Cat. **1** (2 mol %).
[c] Methyl acrylate (1.0 mmol) was used in place of *tert*-butyl acrylate.



Scheme 3.

yield with 14:86 of *syn*:*anti*. Surprisingly, ethyl and isopropyl cinnamates **8c** and **8d** exclusively gave the corresponding *anti*-products **9c** and **9d**, respectively, up to <1:>99 (entries 3 and 4).

As we thus found *anti*-selective Mannich-type coupling, we turned our attention to asymmetric coupling with chiral Rh(Phebox) catalyst **10**. However, we observed no asymmetric induction for the reaction of *p*-meth-

Table 2. Reductive Mannich-type coupling of other imines **4** and *tert*-butyl acrylate[a]

Entry	4	R^1	R^2	5	Yield of 5 (%)	Ratio of *syn*:*anti*
1	**4a**	Ph	*p*-MeO	**5a**	70	17:83
2	**4b**	Ph	*p*-Cl	**5b**	73	25:75
3	**4c**	Ph	*p*-CF_3	**5c**	70	36:64
4	**4d**	*p*-MeO	Ph	**5d**	65	22:78
5	**4e**	*p*-Cl	Ph	**5e**	76	29:71
6	**4f**	*p*-CF_3	Ph	**5f**	65	24:76

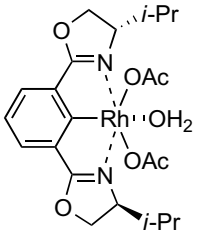
[a] Cat. **1** (0.005 mmol, 1 mol %), **4** (0.5 mmol), acrylate (1.0 mmol), $(EtO)_2MeSiH$ (1.0 mmol), THF (2.0 mL).

Table 3. Reductive Mannich-type coupling of imine **2** and crotonate and cinnamates[a]

Entry	R^1	R^2	9	Yield of 9 (%)	Ratio of *syn*:*anti*
1	Me	*t*-Bu	**9a**	80	14:86
2	Ph	Me	**9b**	84	20:80
3	Ph	Et	**9c**	71	<1:>99
4	Ph	*i*-Pr	**9d**	70	<1:>99

[a] Cat. **1** (0.005 mmol, 1 mol %), **8** (0.5 mmol), cinnamate (1.0 mmol), $(EtO)_2MeSiH$ (1.0 mmol), THF (2.0 mL).

oxy-imine **4a** and *tert*-butyl acrylate; 80% yield of **5a**, *syn*:*anti* = 12:88.



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In order to clarify the reaction route, we attempted a reaction in the absence of imine as an acceptor. First, the conjugate reduction of *tert*-butyl acrylate with $(EtO)_2MeSiH$ in the presence of catalyst **1** was carried out to form the intermediate silyl-enolate. Then, imine **2** was added into the mixture at 50 °C. We confirmed formation of the Mannich-type coupling product **3** in 66% with 18:82 of *syn*:*anti* ratio. This fact indicates that the coupling proceeds via reaction between imines and silyl-enolate not rhodium-enolate. Importantly, diethoxymethylsilyl moiety itself may act as a Lewis acid to promote the coupling with the imine and *E*(O)-silyl-enolate via cyclic transition state **TS** resulting in the high *anti*-selectivity (Fig. 1).[7]

In conclusion, we have found highly *anti*-selective reductive Mannich-type coupling (up to >99%) with Rh(Phebox) catalyst and diethoxymethylsilane as a hydrogen donor. We also propose the Mannich-type coupling induced sequentially by internal alkoxysilyl group. We are now strongly intrigued by the extension toward asymmetric coupling.[8]

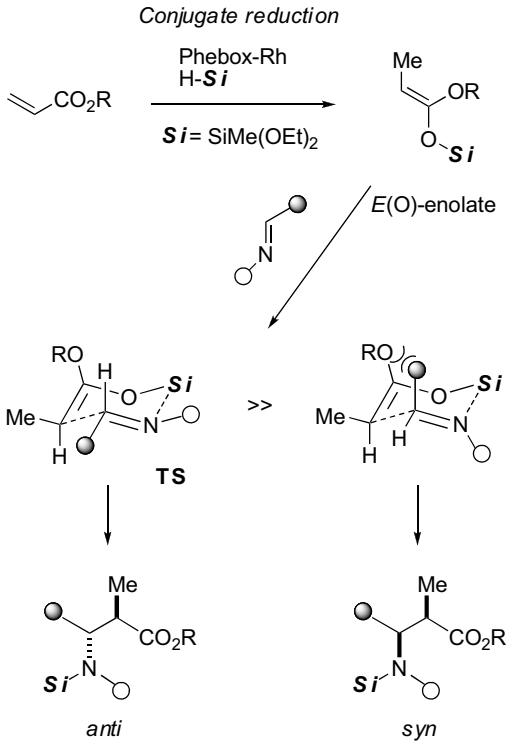

Figure 1. Hypothetical reaction route.

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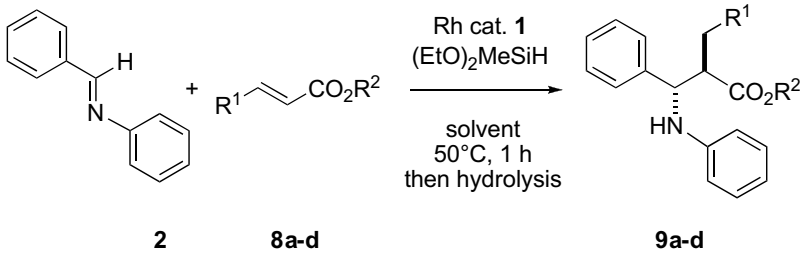

2 **8a-d** **9a-d**

Scheme 4.

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References and notes

1. (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Ind. Ed.* **1998**, *37*, 1045; (b) Kürti, L.; Cakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: Burlington, 2005; p 274.
2. Muraoka, T.; Kamiya, S.; Matsuda, I.; Itoh, K. *Chem. Commun.* **2002**, *1284*, and references cited therein.
3. Isayama, S. *J. Synth. Org. Chem. Jpn.* **1992**, *50*, 190.
4. Townes, J. A.; Evans, M. A.; Queffelec, J.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2002**, *4*, 2537.
5. (a) Nishiyama, H.; Shiomi, T.; Tsuchiya, Y.; Matsuda, I. *J. Am. Chem. Soc.* **2005**, *127*, 6972; (b) Shiomi, T.; Nishiyama, H. *Org. Lett.* **2007**, *9*, 1651.
6. Kanazawa, Y.; Nishiyama, H. *Synlett* **2006**, 3343.
7. For other reaction profiles: Me_2PhSiH gave a trace amount of the Mannich-type coupling product. The imine derived from *p*-toluenesulfonamide and benzaldehyde did not give the coupling product.
8. *Typical reaction (Table 1, entry 1):* To a solution of catalyst **1** (2.6 mg, 0.005 mmol) and aldimine **2** (91 mg, 0.50 mmol) in absolute THF (2.0 mL), *tert*-butyl acrylate (128 mg, 1.0 mmol) was added by syringe. At 50 °C, $(EtO)_2MeSiH$ was added to the mixture, which was stirred for 1 h. For work up, THF (1.0 mL), MeOH (1.0 mL), and aq HCl (4 N, 1.0 mL) were added at 0 °C. Then the mixture was extracted with ethyl acetate (3×5 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (2×5 mL), saturated brine (5 mL), and dried over $MgSO_4$. After concentration, the residue was purified by column chromatography with hexane/ethyl acetate (20:1) as eluent to give the desired product **3** in 79% (123 mg, 0.395 mmol). The *syn*:*anti* ratio was determined by ^1H NMR compared to the corresponding methyl ester reported by Matsuda et al., see Ref. 2; ^1H NMR ($CDCl_3$, 300 MHz) $\delta = 4.43$ (d, $J = 6.0$ Hz, 1H, NHC*H*) for *anti*, $\delta = 4.67$ (d, $J = 3.6$ Hz, 1H, NHC*H*) for *syn*. The *syn*:*anti* ratio of **5a** and **5b** were also compared to those reported by Matsuda et al.; **5a**, $\delta = 4.35$ (d, $J = 7.8$ Hz, 1H, NHC*H*) for *anti*, $\delta = 4.59$ (d, $J = 5.4$ Hz, 1H, NHC*H*) for *syn*; **5b**, $\delta = 4.35$ (d, $J = 7.5$ Hz, 1H, NHC*H*) for *anti*, $\delta = 4.63$ (d, $J = 5.0$ Hz, 1H, NHC*H*) for *syn*. The ratios of other products were similarly determined.