Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 7841–7844

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

Hisao Nishiyama,* Junji Ishikawa and Takushi Shiomi

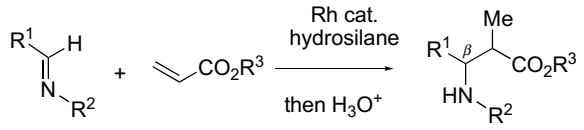
Department of Applied Chemistry, Graduate School of Engineering, Nagoya University, Chikusa, Nagoya 464-8603, Japan

Received 1 August 2007; accepted 31 August 2007
Available online 11 September 2007

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.

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.

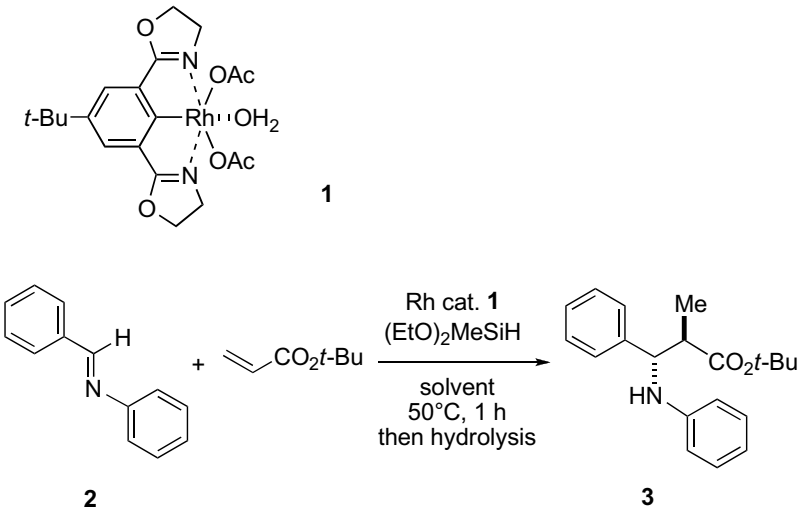
The reaction of imine **2** and *tert*-butyl acrylate in THF was carried out at 50 °C with 2–5 mol % of Rh(Phebox) catalyst **1**[6] to furnish a mixture of diastereomers in 76–79% yields (Scheme 2) (Table 1, entries 1 and 2). Diastereoselectivity resulted in high *anti*-selectivity (18:82). Methyl acrylate 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%

Keywords: Mannich reaction; Rhodium; Bisoxazoline; Conjugate reduction.
* Corresponding author. Fax: +81 52 789 3209; e-mail: hnishi@apchem.nagoya-u.ac.jp

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.08.135

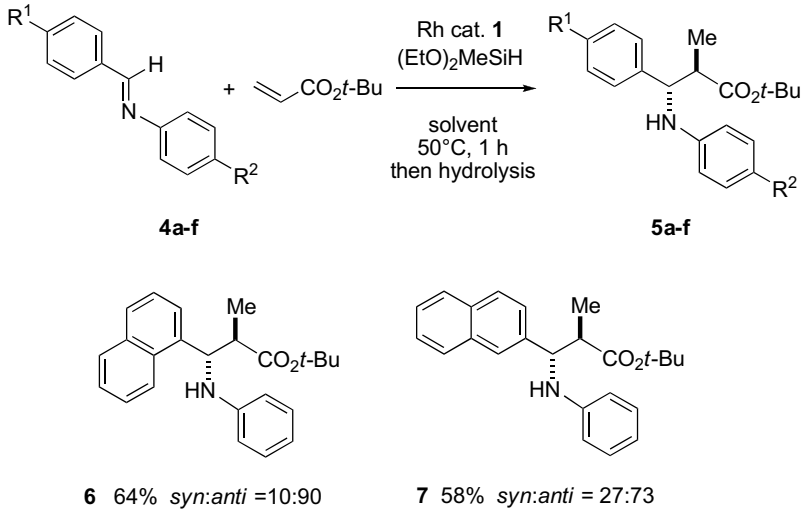


Scheme 2.

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-