Lewis Base-catalyzed Diastereoselective Mannich-type Reaction between Ketene Silyl Acetals and Chiral Sulfinimines

Eiki Takahashi,[†,††] Hidehiko Fujisawa,[†,††] Toshiharu Yanai,[†,††] and Teruaki Mukaiyama*[†,††]
[†]*Center for Basic Research, The Kitasato Institute (TCI), 6-15-5 Toshima, Kita-ku, Tokyo 114-0003*
[††]*Kitasato Institute for Life Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641*

(Received December 22, 2004; CL-041584)

Lewis base-catalyzed diastreoselective Mannich-type reaction between ketene silyl acetals and chiral sulfinimines proceeded smoothly to afford the corresponding β-amino carbonyl compounds in good to high yields with high selectivities.

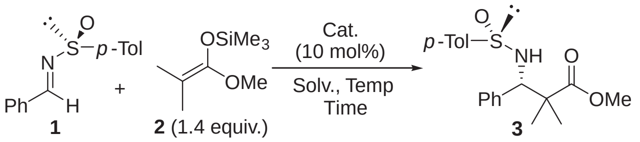
Mannich-type reaction of an aldimine with a ketene silyl acetal is one of the most important tools for the construction of β-amino carbonyl compounds.[1,2] It was recently shown from our laboratory that trimethylsilyl (TMS) enolate was activated successfully with Lewis bases such as the nitrogen and oxygen containing-anions generated from amides, imides, or carboxylic acids and they catalytically promoted aldol, Michael and Mannich-type[3] reactions. It was noted in our previous communication[3d] that ammonium carboxylate catalyzed Mannich-type reaction between TMS enolates and *N*-tosylaldimines proceeded smoothly to afford the corresponding Mannich-adducts in good to high yields with good to excellent *anti*-selectivities under metal-free conditions.

Recently, several reactions using a chiral sulfinimine were investigated, for the sulfinyl groups are recognized as excellent chiral auxiliaries; those chiral sulfinimines can be obtained easily from an aldehyde and a chiral sulfinamide[4] and those auxiliaries are removed under mild acidic conditions.

In this communication, we would like to report on diastereoselective Lewis base-catalyzed Mannich-type reaction between chiral sulfinimines and ketene silyl acetals.

In the first place, Lewis base-catalyzed Mannich-type reaction between chiral sulfinimines **1** and ketene silyl acetal **2** generated from methyl isobutyrate was tried in the presence of 10 mol % of lithium acetate (AcOLi) at room temperature to obtain the corresponding Mannich-adducts in good to high yields with moderate diastereoselectivities (75:25) (Table 1, Entry 2).[5] When the above reaction was tried at −45 °C, the selectivities increased up to 87:13 (Entry 3). It indicated that the reaction temperatures should be low in order to achieve high selectivities. Further, it was shown that the selectivities were improved when AcOK, AcOCs, or AcON*n*-Bu$_4$ was used (Entries 4, 5, and 7). The Mannich-adduct was afforded in good yield with highest diastereoselectivity when the reaction was carried out in the presence of AcON*n*-Bu$_4$ at −78 °C in THF (96:4) (Entry 12). In addition, a similar result was obtained even when 1 mol % of AcON*n*-Bu$_4$ was used (Entry 13). Thus, the ammonium carboxylate is quite efficient to promote the Lewis base-catalyzed Mannich-type reaction between chiral sulfinimine and ketene silyl acetal in THF.

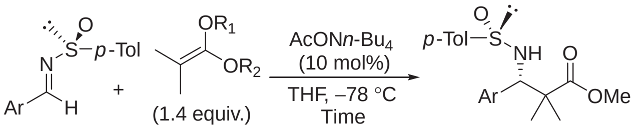
Table 1.



Entry	Cat.	Solv.	Temp /°C	Time /h	Yield[a] /%	major/ minor
1	—	DMF	rt	12	16	82:18
2	AcOLi	DMF	rt	6	88	75:25
3	AcOLi	DMF	−45	12	81	87:13
4	AcOK	DMF	−45	12	97	92:8
5	AcOCs	DMF	−45	12	quant.	92:8
6	PhCO$_2$Li	DMF	−45	12	quant.	85:15
7	AcON*n*-Bu$_4$	DMF	−45	12	quant.	89:11
8	AcON*n*-Bu$_4$	THF	−45	12	96	93:7
9	PhCO$_2$N*n*-Bu$_4$	DMF	−45	12	91	88:12
10	PhCO$_2$N*n*-Bu$_4$	THF	−45	24	96	94:6
11	PhCO$_2$N*n*-Bu$_4$	THF	−78	12	86	94:6
12	AcON*n*-Bu$_4$	THF	−78	12	quant.	96:4
13	AcON*n*-Bu$_4$	THF	−78	24	quant.[b]	96:4

[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]1 mol % of catalyst was used.

Table 2.

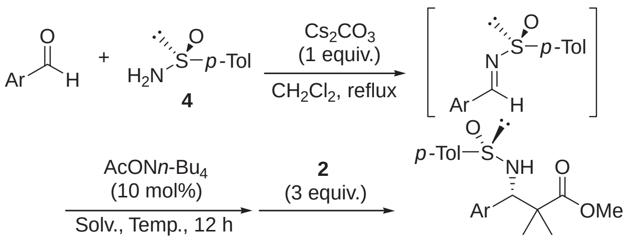


Entry	Ar	R$_1$	R$_2$	Time /h	Yield[a] /%	major /minor
1	*p*-MeC$_6$H$_4$	**2**		12	86	96:4
2	*p*-ClC$_6$H$_4$	**2**		12	quant.	93:7
3	*p*-BrC$_6$H$_4$	**2**		12	quant.	95:5
4	3-Pyridyl	**2**		12	quant.	93:7
5	*p*-Me$_2$NC$_6$H$_4$	**2**		24	89[b]	92:8
6	**1**	SiEt$_3$	Me	12	quant.	95:5
7	**1**	SiMe$_3$	Et	24	quant.	95:5
8	**1**	SiMe$_3$	*i*-Pr	24	88	96:4

[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]3 equiv. of silyl enolate were used.

Next, Lewis base-catalyzed Mannich-type reaction was examined by using various chiral sulfinimines and ketene silyl acetals (Table 2). When reactions of ketene silyl acetal **2** with various aldimines were tried by using 10 mol % of AcON*n*-Bu$_4$ in THF at −78 °C, they proceeded smoothly to afford the Mannich-adducts in good to high yields with excellent diastereoselectivities. Similarly, aromatic chiral sulfinimines having an

Table 3.



Entry	Ar	Solv.	Temp./°C	Yield[a]/%	major:minor
1	Ph	DMF	−60	quant.	90:10
2	Ph	THF	−78	quant.	94:6
3	Ph	THF	−78	98[b]	93:7
4	Ph	THF	−78	n.d.[c]	—:—
5	Ph	DMF	−60	quant.[c]	91:9
6	p-ClC_6H_5	THF	−78	90	91:9
7	p-BrC_6H_5	THF	−78	quant.	90:10
8	p-MeC_6H_5	THF	−78	quant.	95:5
9	3-Pyridyl	THF	−78	70	90:10

[a] Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b] $PhCO_2NBu_4$ was used instead of $AcONBu_4$. [c] Catalyst was not used in this reaction.

electron-withdrawing group, -donating group, or basic function such as pyridyl or dimethylamino group gave the adducts (Entries 1–5). In the case when reactions of the ketene silyl acetals generated from methyl, ethyl, or isopropyl isobutyrate with chiral sulfinimines **1** were tried in THF, they proceeded smoothly as well to afford the Mannich-adducts in good yields with high diastreoselectivities (Entries 6–8).

Recently, a convenient synthesis of chiral sulfinimine by treating an aldehyde and a chiral sulfinamide in the presence of cesium carbonate (Cs_2CO_3) was reported.[6] Then, three-component reaction of aldehyde, chiral sulfinamide and ketene silyl acetal **2** was tried according to the above procedure: that is, chiral sulfinimine in situ generated from aldehyde and chiral sulfinamide **4** reacted successively with TMS enolate in the presence of AcON*n*-Bu$_4$ to afford the desired adduct in one-pot (Table 3). The Mannich-adducts were afforded in quantitative yields with excellent diastereoselectivities when the reactions were carried out in THF at −78 °C (Entries 1–3). In addition, it was found that the above reaction proceeded in DMF also without further addition of the catalyst. This indicates that the remained Cs_2CO_3 or the formed $CsHCO_3$ also catalyzed this reaction. Further, one-pot Lewis base-catalyzed Mannich-type reactions were tried by using various aldehydes. Consequently, the reactions proceeded smoothly to afford the corresponding Mannich-adduct in good to high yields with good to excellent diastereoselectivities.

Thus, Lewis base-catalyzed Mannich-type reaction between chiral sulfinimines and ketene silyl acetals proceeded smoothly to afford β-amino esters with excellent diastereoselectivities in the presence of organic catalysts such as AcON*n*-Bu$_4$ and $PhCO_2$N*n*-Bu$_4$. This is the first example of the Lewis base-catalyzed Mannich-type reaction between chiral sulfinimines and silyl enolates that afforded the Mannich-adducts with high diastereoselectivities. From environmental point of view, these catalysts have great advantages for their low toxities and are disposable without special treatment.

This method is practically applicable for the synthesis of various β-amino esters. Further extension of this reaction is now in progress.

This study was supported in part by the Grant of the 21st Century COE Program from Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

References and Notes

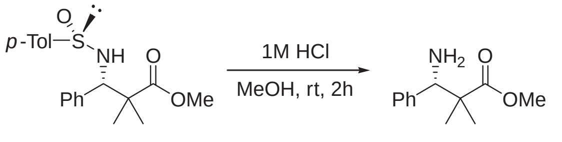
1 For recent reports relevant to Mannich-type reaction, see: a) H. Kunz and D. Schanzenbach, *Angew. Chem., Int. Ed.*, **28**, 1068 (1989). b) F. A. Davis, R. T. Reddy, and R. E. Reddy, *J. Org. Chem.*, **57**, 6387 (1992). c) M. Shimizu, K. Kume, and T. Fujisawa, *Tetrahedron Lett.*, **36**, 5227 (1995). d) F. A. Davis, R. E. Reddy, and J. M. Szewczyk, *J. Org. Chem.*, **60**, 7037 (1995). e) F. A. Davis, J. M. Szewczyk, and R. E. Reddy, *J. Org. Chem.*, **61**, 2222 (1996). f) K. Higashiyama, H. Kyo, and H. Takahashi, *Synlett*, **1998**, 489. g) T. P. Tang and J. A. Ellman, *J. Org. Chem.*, **64**, 12 (1999). h) R. Kawecki, *J. Org. Chem.*, **64**, 8724 (1999). i) P. Allef and H. Kunz, *Tetrahedron: Asymmetry*, **11**, 375 (2000). j) M. F. Jacobsen and T. Skrydstrup, *J. Org. Chem.*, **68**, 7112 (2003). k) A. Kennedy, A. Nelson, and A. Perry, *Synlett*, **2004**, 967. l) M. F. Jacobsen, L. Ionita, and T. Skrydstrup, *J. Org. Chem.*, **69**, 4793 (2004).

2 For recent reports relevant to asymmetric Mannich-type reaction, see: a) H. Fujieda, M. Kanai, T. Kambara, A. Iida, and K. Tomioka, *J. Am. Chem. Soc.*, **119**, 2060 (1997). b) H. Ishitani, M. Ueno, and S. Kobayashi, *J. Am. Chem. Soc.*, **119**, 7153 (1997). c) E. Hagiwara, A. Fujii, and M. Sodeoka, *J. Am. Chem. Soc.*, **120**, 2474 (1998). d) D. Ferraris, B. Young, T. Dudding, and T. Lectka, *J. Am. Chem. Soc.*, **120**, 4548 (1998). e) S. Kobayashi and H. Ishitani, *Chem. Rev.*, **99**, 1069 (1999). f) A. G. Wenzel and E. N. Jacobsen, *J. Am. Chem. Soc.*, **124**, 12964 (2002). g) S. Matsunaga, N. Kumagai, S. Harada, and M. Shibasaki, *J. Am. Chem. Soc.*, **125**, 4712 (2003). h) S. Kobayashi, R. Matsubara, Y. Nakamura, H. Kitagawa, and M. Sugiura, *J. Am. Chem. Soc.*, **125**, 6610 (2003). i) T. Akiyama, J. Itoh, K. Yokota, and K. Fuchibe, *Angew. Chem., Int. Ed.*, **43**, 1566 (2004).

3 For our reports relevant to Mannich-type reaction: a) H. Fujisawa, E. Takahashi, T. Nakagawa, and T. Mukaiyama, *Chem. Lett.*, **32**, 1036 (2003). b) E. Takahashi, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, **33**, 936 (2004). c) E. Takahashi, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, **33**, 1426 (2004). d) E. Takahashi, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, **34**, 84 (2005). e) E. Takahashi, H. Fujisawa, T. Yanai, and T. Mukaiyama, *Chem. Lett.*, **34**, 216 (2005).

4 For reports relevant to synthesis of chiral sulfinimines, see: a) F. A. Davis, R. E. Reddy, J. M. Szewczyk, G. V. Reddy, P. S. Portonovo, H. Zhang, D. Fanelli, R. T. Reddy, P. Zhou, and P. J. Carroll, *J. Org. Chem.*, **62**, 2555 (1997). b) F. A. Davis, Y. Z. Y. Andemichael, T. Fang, D. L. Fanelli, and H. Zhang, *J. Org. Chem.*, **64**, 1403 (1999).

5 Stereochemistry of **3** was confirmed by comparison with ^{1}H NMR data reported in Ref. 1h. Stereochemistries of other derivatives were also determined by ^{1}H NMR data. The ester **3** was led to the known β-aminoester **5** by removing its sulfinyl group with 1 M HCl. The absolute configuration of **5** was determined by comparison of optical rotation reported in the literature. {(*R*); $[\alpha]_D^{26} = +34.6$ (c = 0.17, 1 M HCl)}[1a], {(*S*); $[\alpha]_D^{23} = -32.8$ (c = 1.10, 1 M HCl)}[2b].



3 **5**

$[\alpha]_D^{23} = -30.6$
(c = 0.4, in 1M HCl)

6 S. Higashibayashi, H. Tohmiya, T. Mori, K. Hashimoto, and M. Nakata, *Synlett*, **2004**, 457.

Published on the web (Advance View) February 26, 2005; DOI 10.1246/cl.2005.468