Lewis Base-catalyzed *anti*-Selective Mannich-type Reaction between Trimethylsilyl Enolates and Aldimines

Eiki Takahashi,[†,††] Hidehiko Fujisawa,[†,††] 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*

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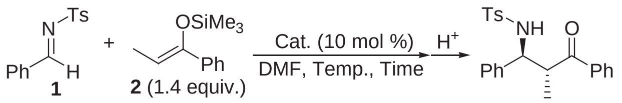
Potassium or ammonium carboxylates catalyzed Mannich-type reaction between trimethylsilyl enolates and aldimines proceeded smoothly to afford the corresponding β-amino carbonyl compounds in good to high yields with high anti selectivity.

Mannich-type reaction of aldimine with trimethylsilyl (TMS) enolate is one of the most important tools for the construction of β-amino carbonyl compounds.[1] In our continued investigation on the activation of TMS enolate with a Lewis base catalyst,[2–4] lithium carboxylates such as a lithium acetate (AcOLi) were found to be a quite useful catalyst since it was readily available, inexpensive, and could be used under mild conditions because of its weakly basic property. These carboxylates could be very useful reagents also from the environmental points of view because their toxicities are low and their disposal is easy. Then, in order to extend the synthetic utility of a Lewis base catalyst, diastereoselective Mannich-type reactions using several carboxylate anions were examined. In this communication, we would like to report on Lewis base-catalyzed *anti*-selective Mannich-type reaction between *N*-tosylaldimines and TMS enolates.

In our previous report, the diastereomeric ratio of *anti* isomer (*anti*:*syn* = 75:25) was obtained when the reaction of *N*-tosylaldimine **1** and TMS enolate **2** was carried out in the presence of 10 mol % of AcOLi at room temperature, and the selectivity further increased up to 84:16 when the above reaction mixture was treated at −20 °C (Table 1, Entries 1 and 2).[4]

In order to increase the *anti*-selectivity, it was considered to lower the temperature. Then, the above reaction was carried out at −45 °C and the corresponding Mannich-adduct was obtained with high *anti*-selectivity (*anti*:*syn* = 94:6) although the yield remained in 20% (Entry 3). To increase the activity of a Lewis base catalyst at low temperatures, the effect of counter cations of the catalyst was examined. It was then found that a potassium or ammonium ion was useful and the above reaction proceeded smoothly to afford the corresponding Mannich-adduct in good yield with excellent *anti*-selectivity. When $PhCO_2Nn$-Bu_4 was used, this reaction was accelerated particularly even in THF while the use of AcOK hardly promoted the reaction (Entries 6 and 12). The reaction afforded the adduct in quantitative yield with highest diastereoselectivity by using $PhCO_2Nn$-Bu_4 in DMF at −45 °C (Entry 8). It was considered that isomerization of Mannich-adducts in this reaction did not proceed because the ratio of the isomers was maintained throughout the reaction (Entries 8–11). Thus, it is noted that the organic ammonium salt catalyst is quite efficient to promote the Lewis base-catalyzed Mannich-type reaction.

Table 1.

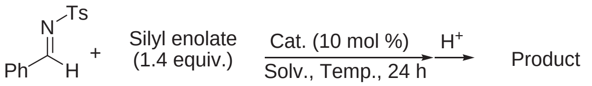


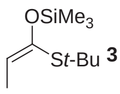
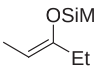
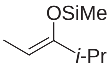
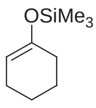
Entry	Cat.	Temp. /°C	Time /h	Yield[a] /%	*anti*:*syn*
1[b]	AcOLi	rt	3	quant.	75:25
2[b]	AcOLi	–20	24	quant.	84:16
3	AcOLi	–45	12	20	94:6
4	AcONa	–45	24	11	96:4
5	AcOK	–45	24	quant.	94:6
6[c]	AcOK	–45	12	NR	-
7	$AcONMe_4$	–45	12	93	92:8
8	$PhCO_2Nn$-Bu_4	–45	2	17	95:5
9	$PhCO_2Nn$-Bu_4	–45	6	38	96:4
10	$PhCO_2Nn$-Bu_4	–45	24	quant.	96:4
11	$PhCO_2Nn$-Bu_4	–45	48	quant.	96:4
12[c]	$PhCO_2Nn$-Bu_4	–45	24	34	93:7

[a]Yield was determined by ^1H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]See Ref. 2d). [c]THF was used instead of DMF.

Next, Lewis base-catalyzed *anti*-selective Mannich-type reaction was studied by using several silyl enolates (Table 2). It was found that the ratio of *anti*-selectivity was influenced by the structure of silyl enolates as well as the reaction conditions. The reactions of TMS enolate **3** with aldimine **1** were carried out by using 10 mol % of AcOK or $PhCO_2Nn$-Bu_4 in DMF. The reactions smoothly proceeded to afford the Mannich-adducts in high yields with moderate *anti*-selectivity either when AcOK or $PhCO_2Nn$-Bu_4 was employed in DMF. The ratio of *anti*-se-

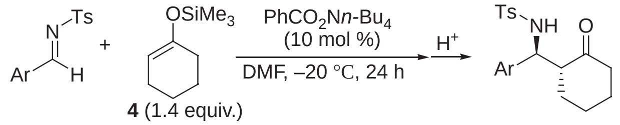
Table 2.



Entry	Silyl enolate	Cat.	Solv.	Temp. /°C	Yield[a] /%	*anti*:*syn*
1[b]	 **3**	AcOLi	DMF	–45	85[c]	76:24
2		AcOK	DMF	–45	quant.[d]	75:25
3		$PhCO_2Nn$-Bu_4	DMF	–45	93	76:24
4		$PhCO_2Nn$-Bu_4	THF	–45	98	90:10
5		$PhCO_2Nn$-Bu_4	DMF	–20	quant.	89:11
6		$PhCO_2Nn$-Bu_4	THF	–20	60	93:7
7		$PhCO_2Nn$-Bu_4	DMF	–20	75	86:14
8		$PhCO_2Nn$-Bu_4	THF	–20	9	91:9
9	 **4**	$PhCO_2Nn$-Bu_4	DMF	–20	98	>99:1
10		$PhCO_2Nn$-Bu_4	THF	–20	93	>99:1

[a]Yield was determined by ^1H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]See Ref. 2d). [c]Reaction time; 6 h. [d]Reaction time; 12 h.

Table 3.



Entry	Ar	Yield[a] /%	*anti*:*syn*
1	$\mathrm{4\text{-}ClC_6H_4}$	quant.	>99:1
2	$\mathrm{4\text{-}BrC_6H_4}$	93	>99:1
3	$\mathrm{4\text{-}NCC_6H_4}$	quant.[b]	>99:1
4	$\mathrm{4\text{-}NO_2C_6H_4}$	92	>99:1
5	$\mathrm{4\text{-}MeC_6H_4}$	98	>99:1
6	$\mathrm{4\text{-}MeOC_6H_4}$	quant.	>99:1
7	2-Naphthyl	97	>99:1
8	(*E*)-PhCHB2CH	quant.[b]	>99:1
9	$\mathrm{4\text{-}Me_2NC_6H_4}$	50[c]	98:2
10	4-Pyridyl	90	>99:1

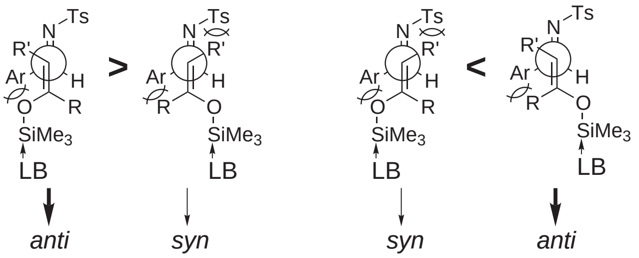
[a] Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b] 5 mol % catalyst was used. [c] Conditions; $\mathrm{PhCO_2N}$*n*-$\mathrm{Bu_4}$ (30 mol %), **4** (3.0 equiv.), 0 °C, 48 h.

lectivity increased up to 90:10, when $\mathrm{PhCO_2N}$*n*-$\mathrm{Bu_4}$ was used in THF. Excellent *anti*-selectivity was attained in the case when TMS enolate derived from cyclohexanone was used.

The reactions of TMS enolate **4** with various aldimines were further tried by using 10 mol % of $\mathrm{PhCO_2N}$*n*-$\mathrm{Bu_4}$ in DMF at −20 °C (Table 3). The Mannich-type reactions proceeded smoothly irrespective of the aromatic aldimines having an electron-withdrawing group or having an electron-donating group and afforded the Mannich-adducts in good to high yields with excellent *anti*-selectivities. When conjugated aldimine was used, only 1,2-addition took place to afford the desired Mannich adduct in good yield with excellent *anti*-selectivity (Entry 8).

When aldimines having a basic part such as dimethylamino- or pyridiyl-function within the same molecules were used, the corresponding β-amino esters were obtained in good to high yields with high *anti*-selectivities, respectively (Entries 9 and 10).

In this reaction, Mannich-adducts were obtained with *anti*-selectivities irrespective of the geometry of silyl enolates which indicatied the reaction to have proceeded via acyclic transition states. It was considered then that the *anti*-selectivity was achieved because of the steric hindrance caused by an interaction between Ts group of imine and a substituent R' of enolate which was stronger than Ar group of imine and R group of silyl enolate (Scheme 1).



Scheme 1.

Thus, ammonium carboxylate catalyzed Mannich-type reaction between TMS enolates and aldimines proceeded smoothly to afford the corresponding Mannich-adduct in good to high yields with good to excellent *anti*- selectivities without using any metal salts. This method is practically applicable for the synthesis of various β-amino esters. Further extension of this reaction is now in progress.

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References and Notes

1 For recent reports relevant to diastereoselective Mannich-type reaction: a) S. Matsunaga, T. Yoshida, H. Morimoto, N. Kumagai, and M. Shibasaki, *J. Am. Chem. Soc.*, **126**, 8777 (2004). b) T. Hamada, K. Manabe, and S. Kobayashi, *J. Am. Chem. Soc.*, **126**, 7768 (2004). c) T. Akiyama, J. Itoh, K. Yokota, and K. Fuchibe, *Angew. Chem., Int. Ed.*, **43**, 1566 (2004). d) K. Miura, K. Tamaki, T. Nakagawa, and A. Hosomi, *Angew. Chem., Int. Ed.*, **39**, 1958 (2000). e) S. Kobayashi and H. Ishitani, *Chem. Rev.*, **99**, 1069 (1999).

2 Aldol reaction: a) T. Nakagawa, H. Fujisawa, Y. Nagata, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **77**, 1555 (2004). b) T. Nakagawa, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, **33**, 92 (2004). c) T. Nakagawa, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, **32**, 696 (2003). d) T. Nakagawa, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, **32**, 462 (2003). e) T. Mukaiyama, H. Fujisawa, and T. Nakagawa, *Helv. Chim. Acta*, **85**, 4518 (2002). f) H. Fujisawa and T. Mukaiyama, *Chem. Lett.*, **2002**, 858. g) H. Fujisawa and T. Mukaiyama, *Chem. Lett.*, **2002**, 182. h) T. Mukaiyama, H. Fujisawa, and T. Nakagawa, *Adv. Synth. Catal.*, in press.

3 Michael reaction: a) T. Mukaiyama, T. Tozawa, and H. Fujisawa, *Chem. Lett.*, **33**, 1410 (2004). b) T. Nakagawa, H. Fujisawa, Y. Nagata, and T. Mukaiyama, *Chem. Lett.*, **33**, 1016 (2004). c) H. Fujisawa, T. Nakagawa, and T. Mukaiyama, *Chem. Lett.*, **32**, 56 (2003).

4 Mannich-type reaction: a) E. Takahashi, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, **33**, 1426 (2004). b) E. Takahashi, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, **33**, 936 (2004). c) H. Fujisawa, E. Takahashi, and T. Mukaiyama, *Chem. Lett.*, **32**, 1036 (2003).

5 General experimental procedure is as follows: To a stirred solution of $\mathrm{PhCO_2N}$*n*-$\mathrm{Bu_4}$ (0.02 mmol) in DMF (0.3 mL) were added successively a solution of silyl enolate (0.28 mmol) in DMF (0.6 mL) and a solution of aldimine (0.2 mmol) in DMF (0.6 mL) at −45 °C. After the mixture was further stirred for 24 h at the same temperature, and quenched with saturated aqueous $\mathrm{NH_4Cl}$. The mixture was extracted with AcOEt. Organic layer was washed with brine and dried over anhydrous sodium sulfate. After filtration and evaporation of the solvent, the crude product was purified by preparative TLC to give the corresponding Mannich adducts. Products and yields were as reported in the text.

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