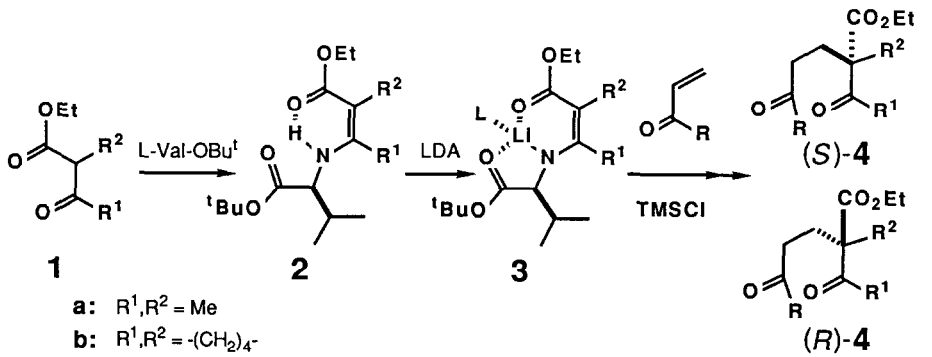
Tetrahedron Letters,Vol.28,No.52,pp 6637-6640,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

CHLOROTRIMETHYLSILANE PROMOTED ASYMMETRIC MICHAEL REACTION OF CHIRAL ENAMINES OF α-ALKYL β-KETO ESTERS

Kiyoshi Tomioka, Wonjun Seo, Kaori Ando, and Kenji Koga*
Faculty of Pharmaceutical Sciences, University of Tokyo,
Hongo, Bunkyo-ku, Tokyo 113, Japan

*Summary: By the promotion of chlorotrimethylsilane, asymmetric Michael reaction of the chiral enamines (**2**) of α-alkyl β-keto esters (**1**) with methyl vinyl ketone and ethyl acrylate proceeded to afford, after hydrolysis, either enantiomer of the corresponding adducts (**4**) in a good enantioselectivity.*

Previously, we have reported asymmetric Michael reaction of the chiral enamines, derived from L-valine *tert*-butyl ester and α-alkyl β-keto esters, with activated Michael acceptors such as alkylidene malonates, producing either enantiomer of the Michael adducts in high enantioselectivity.[1] However, the reactions attempted with non-activated Michael acceptors such as methyl vinyl ketone (MVK) and ethyl acrylate failed to afford products. To overcome these disadvantage of the reaction, exhaustive screening of the Lewis acids as activators was carried out.[2,3] We report here the chlorotrimethylsilane (TMSCl) promoted asymmetric Michael reaction of chiral enamines (**2**) of α-alkyl β-keto esters (**1**) with useful Michael acceptors, MVK and ethyl acrylate, producing either enantiomer (**4**) in a good enantioselectivity.



1 **2** **3**

a: R^1,R^2 = Me
b: R^1,R^2 = -$(CH_2)_4$-

The typical reaction procedure is exemplified in the reaction of **2a** with MVK in the presence of TMSCl (run 1 in Table III). A solution of the lithioenamine of **2a** (2 mmol) prepared according to the standard procedure[1] was added to a cooled (-100 °C) solution of MVK (3 mmol) and TMSCl (10 mmol) in tetrahydrofuran (THF) (10 ml) and the whole was stirred for 5 hr at -100 °C. Hydrolysis with 10% aq. HCl followed by extractive work up afforded (*R*)-**4a** (R=Me) (66% yield) in 87% enantiomeric excess (ee).[4,5] The absolute configuration and enantiomeric excess were determined by comparing the optical rotation with those of the reported[4] and further by the NMR analysis in the presence of $Eu(hfc)_3$.

As summarized in the Table I, among surveyed Lewis acids BF_3•Et_2O and TMSCl exhibited profound effects on both of the reaction yield and enantioselectivity (run 4, 8). It is essential to add

BF_3•Et_2O into the lithioenamine solution before the addition of MVK. On the other hand, the addition of lithioenamine solution to the mixture of MVK and TMSCl is necessary to obtain a practical yield.

Table I. Reaction of **2a** with MVK in the presence of Lewis acids in THF[a]

run	Lewis acid/eq	yield/%[b]	$[\alpha]_D^{22}$ °($CHCl_3$)[c]	ee/%	*R/S*
1	none	trace			
2[d]	LiCl/2	2	+5.0	52	*R*
3[d]	LiI/2	46	+2.2	23	*R*
4	BF_3•Et_2O/2	69	+2.3	23	*R*
5	$AlCl_3$/2	27	+1.8	18	*R*
6	$ZnCl_2$/2	28	-1.7	18	*S*
7[d]	$SnCl_4$/1	40	+2.4	24	*R*
8	TMSCl/5	65	+7.1	73	*R*

a) Reaction was carried out at -78 °C according to the typical procedure described in the text. b) Isolated yield. c) For the maximum optical rotation for **4a** (R=Me), see reference 4. d) *n*-BuLi was used as a base instead of lithium diisopropylamide (LDA).

Then we turned our focus to the optional control of diastereoface differentiation. As reported previously,[1] Michael reaction of **3** with *tert*-butyl methylenemalonate in THF solvent affords adducts, arising by the entry of Michael acceptors from the back face of **3**. On the other hand, in toluene solvent HMPA (hexamethylphosphoric triamide) works as a ligand (**3**, L=HMPA) for the lithium cation, allowing entry of the acceptor from the front face of **3**.[6]

As shown in runs 1~4 in Table II, the reaction of the cyclic enamine (**2b**) with MVK in the presence of BF_3•Et_2O, TMSOTf, or TMSCl in THF solvent afforded the expected (*R*)-**4b**.[7] In toluene solvent, effects of these Lewis acids on diastereoface differentiation were extremely dramatic. Thus, excess of BF_3•Et_2O over HMPA afforded (*R*)-**4b** (run 5), whereas excess of HMPA over BF_3•Et_2O failed to afford the product (run 6). A small excess of TMSOTf over HMPA also afforded (*R*)-**4b** (run 7). Fortunately, three molar excess of TMSCl over HMPA led to the formation of (*S*)-**4b** (run 8).

These data described above implies that TMSCl and HMPA are independently playing their roles as an activator of the Michael acceptor and as a ligand to the lithium cation, respectively, while BF_3•Et_2O and TMSOTf are also working as Lewis acids to Lewis base (HMPA), removing HMPA from coordination to the lithium cation.[8]

Based on the data obtained above, asymmetric Michael reaction of **2** with MVK and ethyl acrylate was carried out in the presence of five equivalents of TMSCl. As shown in Table III, either

enantiomer **4** could be prepared in good enantioselectivity from the same chiral enamines (**2**) simply by changing the solvent.[9)]

Table II. Reaction of **2b** with MVK in the presence of Lewis acids[a]

run	solvent-ligand/eq	Lewis acid/eq	yield/%	$[\alpha]_{577}^{22}$ °(CCl_4)[b]	ee/%	*R/S*
1	THF	none	trace			
2	THF	BF_3•Et_2O/2	90	+67.5	79	*R*
3	THF	TMSOTf/2.5	75	+65.0	77	*R*
4	THF	TMSCl/5	60	+47.1	55	*R*
5	toluene-HMPA/1	BF_3•Et_2O/2	54	+59.0	69	*R*
6	toluene-HMPA/4	BF_3•Et_2O/2	trace			
7	toluene-HMPA/2	TMSOTf/2.5	44	+34.1	40	*R*
8	toluene-HMPA/2	TMSCl/5	35	-40.5	48	*S*

a) See the footnote a) of the Table I. b) See reference 10).

Table III. Asymmetric Michael reaction of **2** promoted by TMSCl[a]

run	**2**	R	solvent-ligand/eq	temp/°C	yield/%	$[\alpha]_D^{22}$ °($CHCl_3$)	ee/%	*R/S*
1	**2a**	Me	THF	-100	66	+8.4[b]	87	*R*
2	**2a**	Me	toluene-HMPA/1	-95	38	-4.8[b]	50	*S*
3	**2b**	Me	THF	-100	67	+76.4[c]	90	*R*
4	**2b**	Me	toluene-HMPA/1	-95	48	-51.3[c]	60	*S*
5	**2a**	OEt	THF	-100	43	+9.0[d,e]	79	*R*
6	**2a**	OEt	toluene-HMPA/1	-95	16	-4.6[d,e]	41	*S*
7	**2b**	OEt	THF	-100	53	+43.4[d,f]	57	*R*
8	**2b**	OEt	toluene-HMPA/1	-95	23	-58.5[d,f]	77	*S*

a) Reaction was carried out using five equivalents of TMSCl at -95 or -100 °C according to the typical procedure described in the text. b) See reference 4. c) Taken at 22 °C using 577 nm in CCl_4. See reference 10). d) Absolute configuration and ee were determined by NMR analysis in the presence of $Eu(hfc)_3$ and by chemical correlation to the compound which was prepared from **2** and *tert*-butyl methylenemalonate (See reference 1). e) Taken at 23.5 °C. f) Taken at 25 °C.

References and Notes

1) K. Tomioka, K. Ando, K. Yasuda, and K. Koga, *Tetrahedron Lett.*, **27**, 715 (1986).
2) TMSCl : C. R. Johnson and T. J. Marren, *Tetrahedron Lett.*, **28**, 27 (1987); T. Yura, N. Iwasawa, and T. Mukaiyama, *Chemistry Lett.*, **1987**, 791; A. Alexakis, J. Berlan, Y. Besace, *Tetrahedron Lett.*, **27**, 1047 (1986); Y. Horiguchi, S. Matsuzawa, E. Nakamura, and I. Kuwajima, *Tetrahedron Lett.*, **27**, 4025 (1986); E. J. Corey and N. W. Boaz, *Tetrahedron Lett.*, **26**, 6015 (1985); C. Chuit, J. P. Foulon, and J. F. Normant, *Tetrahedron*, **36**, 2305 (1980).
3) BF_3• Et_2O : M. Zervos and L. Wartski, *Tetrahedron Lett.*, **27**, 2985 (1986); B. H. Lipshutz, D. A. Parker, J. A. Kozlowski, and S. L. Nguyen, *Tetrahedron Lett.*, **25**, 5959 (1984); Y. Yamamoto and K. Maruyama, *J. Am. Chem. Soc.*, **100**, 3240 (1978).
4) G. Frâter, U. Müller, and W. Günther, *Tetrahedron*, **40**, 1269 (1984).
5) Satisfactory analytical and spectroscopic data were obtained for **2** and **4**.
6) Optional control of diastereoface differentiation is general in the alkylation of the enamines (**3**). K. Tomioka, K. Ando, Y. Takemasa, and K. Koga, *J. Am. Chem. Soc.*, **106**, 2718 (1984); *Idem*, *Tetrahedron Lett.*, **25**, 5677 (1984). For the another type of Michael reaction of lithioenamines, see: K. Tomioka, K. Yasuda, and K. Koga, *Tetrahedron Lett.*, **27**, 4611 (1986); *Idem*, *J. Chem. Soc., Chem. Commun.*, **1987**, 1345.
7) The BF_3• Et_2O promoted reaction of lithioenamine (**3**) prepared by lithiation of **2** with *n*-BuLi instead of LDA afford (*R*)-**4** in a significantly decreased yield. TMSCl or TMSOTf promoted reaction afforded (*R*)-**4** in a comparable yield regardless to the lithiation procedure. The reason is not clear.
8) Involvement of TMS azaenolate as an active species is unlikely. Treatment of **3** with TMSCl at -78 °C for 3 hr followed by the addition of MVK afforded **4** in a significantly decreased yield.
9) The authors are grateful to Mr. K. Yasuda for his contribution in the early stage of the study.
10) The maximum optical rotation reported for **4b** (R=Me) is significantly different (G. Frâter, *Helv. Chim. Acta*, **63**, 1383 (1980); K. Hermann and H. Wynberg, *J. Org. Chem.*, **44**, 2238 (1979)). Therefore the rotation ($[\alpha]_{577}^{22}$ +85.0 °(CCl_4)) for optically pure (*R*)-**4b** (R=Me) was determined by NMR analysis in the presence of Eu(hfc)$_3$.

(Received in Japan 8 September 1987)