Chemoselective Activation of Aldimine in Preference to Aldehyde by the Combination of $BF_3{\bullet}OEt_2$ and Water: Novel Catalyst for the Mannich-type Reaction

Takahiko Akiyama,* Jun Takaya, and Hirotaka Kagoshima
Department of Chemistry, Faculty of Science, Gakushuin University, 1-5-1 Mejiro, Toshima-ku, Tokyo 171-8588

(Received June 16, 1999; CL-990515)

Reported herein are that catalytic amount of conventional Lewis acids activated aldimines in preference to aldehydes, and addition of water to $BF_3{\bullet}OEt_2$ accelerated the Mannich-type reaction significantly to afford β-amino carbonyl compounds in high yields.

Nucleophilic addition of carbon nucleophiles to imine constitutes a significant class of organic reactions.[1] Chemoselective nucleophilic addition to imine moiety in the presence of carbonyl moiety is important from the synthesis of multi-functional compounds. In general, aldimines are less reactive toward nucleophilic addition in comparison with aldehydes.[2] Furthermore, equal amount of activator is frequently required for the activation of aldimines. Thus, chemoselective addition toward imine group by means of catalytic amount of activator is not a trivial issue. Several chemoselective activators of imine moiety have been developed recently. For instance, Yamamoto and co-workers reported Pd(II) catalyzed chemoselective allylation of aldimines with allylstannanes.[3] Kobayashi and co-workers found that lanthanide or scandium triflate[4] mediated allylation and Mannich-type reactions proceeded smoothly toward aldimines in preference to aldehydes.[5,6] We have also reported that $Sc(OTf)_3$ catalyzed allylation with allylgermane took place highly chemoselectively toward aldimine in preference to aldehyde.[7]

Conventional Lewis acids, such as $BF_3{\bullet}OEt_2$ and $SnCl_4$, are reported to activate aldehydes in preference to aldimines whereas both Pd(II) and $Ln(OTf)_3$ activate aldimines highly chemoselectively.[3,6] I suspected that aldimine might well be activated more strongly even under the influence of conventional Lewis acid in consideration that Lewis basicity of nitrogen in aldimine is stronger than that of oxygen of aldehyde. In this communication, we document that conventional Lewis acids do activate aldimine chemoselectively with small loading. Furthermore, addition of water to $BF_3{\bullet}OEt_2$ increased the reactivity of aldimine significantly and Mannich-type addition of silyl enolates to aldimine proceeded highly chemoselectively in the presence of aldehydes to afford β-amino ketones in high yields.[8]

At the outset, Lewis acid mediated addition of 1-phenyl-1-trimethylsiloxyethene was studied in the presence of equal amount of benzylideneaniline and benzaldehyde in acetonitrile and the results are shown in Table 1. When $BF_3{\bullet}OEt_2$ or $SnCl_4$ was employed, dramatic changeover in chemoselectivity was observed by the loading of the Lewis acid used. Use of 1.0 equiv of $BF_3{\bullet}OEt_2$ led to the chemoselective reaction toward aldehyde, affording **2** preferentially (Entry 1), which is in accord with the previous reports.[3,6] In striking contrast, use of catalytic amount of $BF_3{\bullet}OEt_2$ resulted in the reversal of the chemoselectivity and addition to aldimine took place chemoselectively, affording the corresponding β-amino ketone (**1**) preferentially though the reaction did not come to completion (entry 2). The same effect of the loading of the Lewis acid was

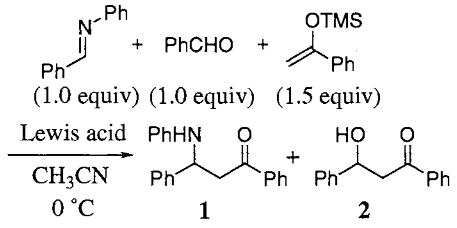


Table 1. Effect of the loading of the Lewis acid

Entry	Lewis acid	Equiv[a]	Reaction time	Yield of **1**/%	Yield of **2**/%
1	$BF_3{\bullet}OEt_2$	1.0	30 min	18	48
2	$BF_3{\bullet}OEt_2$	0.2	30 min	60	15
3	$SnCl_4$	1.0	1 h[b,c]	1	75
4	$SnCl_4$	0.2	30 min[b]	67	3
5	$Zn(OTf)_2$	1.0	1 h	83	0
6	$Zn(OTf)_2$	0.2	1 h	78	0
7	$Zr(OTf)_4$	1.0	30 min	81	0
8	$Zr(OTf)_4$	0.2	30 min	71	0

[a]Molar equivalent of Lewis acid. [b]CH_2Cl_2 was employed as a solvent. [c]The reaction temperature was −78 °C.

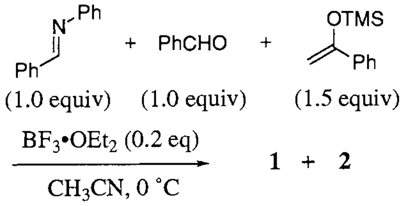


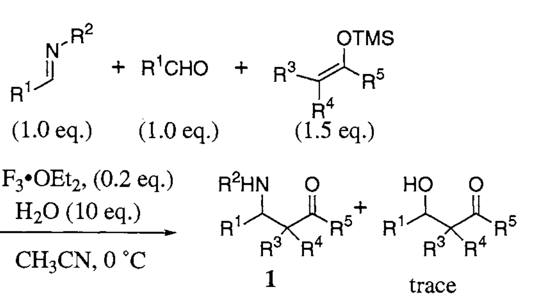
Table 2. Effect of the additive

Entry	Additive	Equiv[a]	Reaction time	Yield of **1**/%	Yield of **2**/%
1	H_2O	0.1	30 min	92	5
2	H_2O	1.0	1 h	98	1
3	H_2O	10	30 min	97	1
4	H_2O	50	17 h	92	0
5	H_2O[b]	0.1	30 min	69	12
6	H_2O[b]	1.0	30 min	75	11
7	CH_3OH	1.0	30 min	86	6
8	CH_3CO_2H	1.0	30 min	88	3
9	PhCOOH	1.0	30 min	90	8

[a]Molar equivalent of H_2O. [b]1.0 equiv of $BF_3{\bullet}OEt_2$ was employed.

observed with $SnCl_4$ (entries 3 and 4). Metal triflates, however, did not show such changeover in chemoselectivity (entries 5-8).

Although it turned out that use of catalytic amount of Lewis acid activated aldimines preferentially, the Mannich adduct was not obtained in moderate yield. Recently it was found that addition of Brønsted acid[8c,9] or water[10,11] to Lewis acid accelerated the reaction. We screened several protic acid and found that addition of a catalytic amount of water to $BF_3{\bullet}OEt_2$ accelerated the Mannich-type reaction significantly, affording the adduct (**1**) predominantly in high yield. Selected results are shown in Table 2. Interestingly, aldol reaction was completely suppressed.[12] Mannich-type reaction underwent even in the presence of 50 equiv of water (entry 4). When 1.0 equiv of $BF_3{\bullet}OEt_2$ was employed, addition of water led to the changeover in the chemoselectivity (entries 5 and 6). Not only water but also methanol, acetic acid, and benzoic acid turned out to be effective as additive for the activation of aldimines.[13]



1

Table 3. Results of the Mannich-type reaction

Entry	R^1	R^2	R^3	R^4	R^5	Yield of **1**/%
1	Ph	Ph	H	H	Ph	97
2	p-$NO_2C_6H_4$	Ph	H	H	Ph	84
3	p-$CH_3C_6H_4$	Ph	H	H	Ph	97
4	Ph	p-$MeOC_6H_4$	H	H	Ph	94
5	Ph	p-Ts	H	H	Ph	0
6	Ph	$PhCH_2$	H	H	Ph	0
7	Ph	Ph	H	Me	Ph	84
8	Ph	Ph	H	$-(CH_2)_4-$		72
9	Ph	Ph	Me	Me	OMe	79[a]

[a] Three equivalents of ketene silyl acetal was used.

Present Mannich-type reaction took place smoothly with other aromatic aldimines under the influence of 0.2 equiv of $BF_3{\bullet}OEt_2$ and 10 mol equiv of H_2O in CH_3CN at 0 °C and the results are shown in Table 3. For the substituents on nitrogen, aromatic ring is requisite and aldimines with *N*-*p*-Ts and benzyl moieties were not effective (entries 5 and 6). Not only other silyl enol ethers but also a ketene silyl enol ether, which was considered to be labile in aqueous conditions, also worked as a nucleophile to afford the corresponding β-amino ester in a good yield when 3.0 equiv of the ketene silyl acetal was employed.[14]

It is known that BF_3 forms dihydrates with water and the hydrates partially dissociate into ions in liquid phase.[15] We have quite recently reported that aqueous HBF_4 is an efficient catalyst in the Mannich-type reaction in aqueous media but HF is not so effective.[16] Thus, the active species may be strong Brønsted acid such as $H^+BF_3X^-$ generated from $BF_3{\bullet}OEt_2$ and HX.[15,17] Furthermore, present results clearly imply that strict anhydrous conditions are required for the Lewis acid catalyzed aldol reaction.

References and Notes

1 R. Bloch, *Chem. Rev.*, **98**, 1407 (1998).
2 M. Yamaguchi, in "Comprehensive Organic Synthesis," ed by B. M. Trost and I. Fleming, Pergamon Press, Oxford (1991), Vol. 1, p. 325.
3 H. Nakamura, N. Asao, and Y. Yamamoto, *J. Chem. Soc., Chem. Commun.*, **1995**, 1273; H. Nakamura, H. Iwama, and Y. Yamamoto, *J. Am. Chem. Soc.*, **118**, 6641 (1996).
4 S. Kobayashi, *Synlett*, **1994**, 689; S. Kobayashi, *Eur. J. Org. Chem*, 15 (1999); S. Kobayashi, *Chem. Soc. Rev.*, **28**, 1 (1999).
5 S. Kobayashi, *Eur. J. Org. Chem* **1999**, 15; S. Kobayashi, T. Busujima, and S. Nagayama, *Synlett*, **1999**, 545. See also references cited therein.
6 S. Kobayashi and S. Nagayama, *J. Org. Chem.*, **62**, 232 (1997); S. Kobayashi and S. Nagayama, *J. Am. Chem. Soc.*, **119**, 10049 (1997).
7 T. Akiyama and J. Iwai, *Synlett*, **1998**, 273.
8 Selected examples of Mannich-type reactions; a) I. Ojima, K. Yoshida, and S. Inaba, *Chem. Lett.*, **1977**, 429. b) M. Onaka, R. Ohno, N. Yanagiya, and Y. Izumi, *Synlett*, **1993**, 141. c) K. Ishihara, M. Miyata, K. Hattori, T. Tada, and H. Yamamoto, *J. Am. Chem. Soc.*, **116**, 10520 (1994). d) K. Ishihara, M. Funahashi, N. Hanaki, M. Miyata, and H. Yamamoto, *Synlett*, **1994**, 963. e) D. Ferraris, B. Young, T. Dudding, and T. Lectka, *J. Am. Chem. Soc.*, **120**, 4548 (1998). f) M. Arend, B. Westermann, and N. Risch, *Angew. Chem., Int. Ed. Engl.*, **37**, 1044 (1998). g) A. Fujii, E. Hagiwara, and M. Sodeoka, *J. Am. Chem. Soc.*, **121**, 5450 (1999).
9 H. C. Aspinall, N. Greeves, and E. G. McIver, *Tetrahedron Lett.*, **39**, 9283 (1998); K. Manabe and S. Kobayashi, *Tetrahedron Lett.*, **40**, 3773 (1999).
10 Activation of imines by the combination of Lewis acid and protic acid, see; K. M. Ryan, R. A. Reamer, R. P. Volante, and I. Shinkai, *Tetrahedron Lett.*, **28**, 2103 (1987).
11 S. Kobayashi and I. Hachiya, *J. Org. Chem.*, **59**, 3590 (1994); S. Otto, G. Boccaletti, and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, **120**, 4238 (1998); S. Kobayashi, S. Nagayama, and T. Busujima, *Chem. Lett.*, **1999**, 71.
12 Solvent effects were examined in the presence of 0.2 equiv of $BF_3{\bullet}OEt_2$ and 10 equiv of H_2O at 0 °C for 30 min. The yield of **1** was 89% in CH_3CN, and 48% in CH_2Cl_2. Formation of **2** was not observed in both cases.
13 The same effect of the addition of water to $SnCl_4$ was observed, but in that case HCl generated by decomposition of $SnCl_4$ with H_2O might be the reactive species.
14 When 1.5 equiv of ketene silyl acetal was employed, the adduct was obtained in 59% yield.
15 F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," 5th ed, John Wiley & Sons, New York (1986), p. 174.
16 T. Akiyama, J. Takaya, and H. Kagoshima, *Synlett*, **1999**, 1045.
17 It is known that a combination of Lewis acid and a Brønsted acid generates fairly strong acid. See; K. Tanabe and R. Noyori, "Super Strong acid and Super Strong Base," Kodansha-Scientific, Tokyo (1980).