



A highly stereo-divergent Mannich-type reaction catalyzed by Brønsted acid in aqueous media

Takahiko Akiyama,* Jun Takaya and Hirotaka Kagoshima

Department of Chemistry, Faculty of Science, Gakushuin University, 1-5-1, Mejiro, Toshima-ku, Tokyo 171-8588, Japan

Received 19 March 2001; revised 10 April 2001; accepted 13 April 2001

Abstract—*anti* And *syn* stereoselectivity on the HBF_4 -catalyzed Mannich-type reaction of ketene silyl acetal derived from α -oxy esters with aldimines were investigated. Whereas use of ketene silyl acetal derived from aryl ester in aqueous 2-propanol gave *anti* β -amino- α -siloxy ester with excellent stereoselectivity, use of ketene silyl acetal derived from methyl ester in water in the presence of sodium dodecyl sulfate gave the *syn* isomer preferentially. © 2001 Elsevier Science Ltd. All rights reserved.

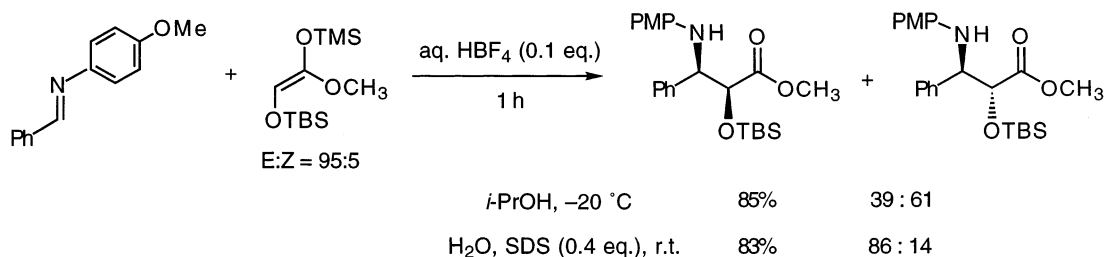
Lewis acid-catalyzed Mannich-type reactions of silyl enol ether with aldimine are important synthetic reactions for the preparation of β -amino carbonyl compounds, which are precursors of β -lactam and amino acids.¹ Numerous kinds of activators have been developed,^{2,3} and highly enantioselective Mannich-type reactions have been reported.⁴

Organic reactions in aqueous media have attracted much attention of synthetic organic chemists as an environmentally benign synthetic process.⁵ We have recently found that Mannich-type reactions took place smoothly under the influence of Brønsted acid, typically aq. HBF_4 , to afford the corresponding β -amino carbonyl compounds in high yields in aqueous organic solvents.⁶ Furthermore, the HBF_4 -catalyzed Mannich-type reaction took place smoothly in the presence of sodium dodecyl sulfate in water under organic solvent-free conditions.^{7,8} Aza-Diels–Alder reactions in aqueous media have been successfully achieved.⁹ Because there are quite a few reports that attained high diastereoselec-

tivity in the Mannich-type reactions of silyl enolates with aldimines,³ we investigated the stereoselectivity of the Brønsted acid-catalyzed Mannich-type reaction. We wish to report herein highly diastereoselective Mannich-type reaction catalyzed by Brønsted acid in aqueous media, wherein both *syn* and *anti* isomers were obtained highly stereoselectively by the proper choice of the solvent system and ketene silyl acetal.

At the outset, we found a changeover of the diastereoselectivity in the HBF_4 -catalyzed Mannich-type reaction of ketene silyl acetal derived from α -siloxy ester.¹⁰ Although the Mannich-type reaction in aqueous 2-propanol led to the preferential formation of the *anti* adduct, the reaction in water in the presence of a water-surfactant (SDS) furnished the *syn* adduct as a major product (Scheme 1).

After screening the substrates, we found that 1,2-bis-(*t*-butyldimethylsiloxy)-1-(2,4,6-trimethylphenoxy)ethene (**1**) showed excellent *anti* selectivity. The results of the



Scheme 1.

Keywords: Brønsted acid; diastereoselectivity; Mannich-type reactions; Schiff bases; water.

* Corresponding author. Fax: (+81)-3-5992-1029; e-mail: takahiko.akiyama@gakushuin.ac.jp

HBF₄-catalyzed Mannich-type reaction of **1** (*E*:*Z* = <1:>99) with aldimines derived from *p*-anisidine (Protocol A) are shown in Table 1. Aldimines derived from an aromatic aldehyde as well as an aliphatic aldehyde worked quite well to afford the corresponding β-amino-α-siloxy esters with excellent *anti* selectivity. Because aldimines are generally labile, it would be quite useful if the aldimine, generated in situ from aldehyde and amine, was allowed to react directly to furnish the Mannich-adducts.¹¹ Three-component synthesis starting from aldehyde and amine (Protocol B) proceeded smoothly to afford predominantly the *anti* adducts. An aliphatic aldehyde as well as an aromatic aldehyde worked well to afford the Mannich adducts with excellent diastereoselectivity (entries 2, 9, and 10).¹² Use of water–SDS system as a solvent in place of 2-propanol resulted in the lower yields with good *anti* selectivity (entry 11).

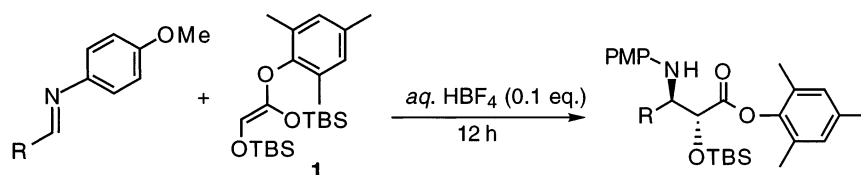
The Mannich-adducts thus obtained were readily transformed into β-lactams with retention of the stereochem-


istry (Scheme 2). The relative stereochemistry was unambiguously confirmed by *J*-values of the vicinal protons of the β-lactams.¹³

In contrast, 1-methoxy-1-trimethylsiloxy-2-triphenylsiloxyethene (**2**) exhibited high *syn* selectivity in the reaction with aldimine derived from *p*-anisidine. In this case, diastereoselectivity depended on the *N*-substituents of imines. An aldimine bearing a *p*-methoxyphenyl group exhibited the highest *syn* selectivity. Results of the *syn*-selective Mannich-type reaction of **2** (*E*:*Z* = 97:3) with aldimines are shown in Table 2.¹⁴ Aldimines derived from an aromatic aldehyde, an aliphatic aldehyde, an α,β-unsaturated aldehyde and a heteroaromatic aldehyde worked well to furnish the adducts with good to high *syn* diastereoselectivity. Interestingly, use of 2-propanol as a solvent significantly decreased the stereoselectivity (entry 8).

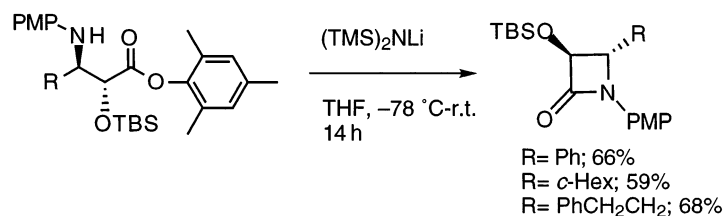
In conclusion, we have reported a highly diastereoselective Mannich-type reaction of ketene silyl acetal with

Table 1. *anti*-Selective Mannich-type reaction

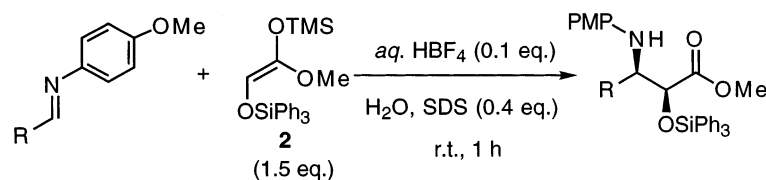




Entry	R	Protocol	Solvent	Temp. / °C	Yield / %	syn:anti
1	Ph	A	<i>i</i> -PrOH	0	92	1 : 99
2	Ph	B	<i>i</i> -PrOH	0	93	1 : 99
3	<i>p</i> -ClC ₆ H ₄	A	<i>i</i> -PrOH	r.t.	87	1 : 99
4	<i>p</i> -NO ₂ C ₆ H ₄	A	CH ₃ CN	r.t.	84	4 : 96
5	(<i>E</i>)-PhCH=CH	A	<i>i</i> -PrOH	r.t.	90	4 : 96
6		A	<i>i</i> -PrOH	r.t.	90	2 : 98
7	<i>c</i> -Hex	A	CH ₃ CN	–20	88	3 : 97
8	<i>i</i> Pr	A	CH ₃ CN	–20	64	2 : 98
9	<i>i</i> Pr	B	CH ₃ CN	–20	58	2 : 98
10	PhCH ₂ CH ₂	B	CH ₃ CN	–40	67	4 : 96
11	Ph	A	H ₂ O–SDS	r.t.	24	4 : 96

Protocol A: reaction with aldimine, Protocol B: three-component reaction.



Scheme 2. Formation of β-lactam.

Table 2. *syn*-Selective Mannich-type reaction

Entry	R	Yield / %	syn : anti
1	Ph	90	90 : 10
2	<i>p</i> -MeOC ₆ H ₄	88	92 : 8
3	<i>p</i> -ClC ₆ H ₄	72	89 : 11
4	(<i>E</i>)-PhCH=CH	62	95 : 5
5		93	83 : 17
6		56	89 : 11
7	<i>c</i> -Hex	99	85 : 15
8 ^{a)}	Ph	81	64 : 36

a) 2-Propanol was used as a solvent.

aldimines catalyzed by Brønsted acid in aqueous media, wherein both *syn* and *anti* isomers were obtained by the proper choice of the solvent and ketene silyl acetal.

Acknowledgements

Partial financial support from the Ministry of Education, Science and Culture of Japan (Grant-in-Aid for Scientific Research, #12640528) is deeply acknowledged.

References

- (a) Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p. 893; (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1045–1070.
- (a) Ojima, I.; Inaba, S.; Yoshida, K. *Tetrahedron Lett.* **1977**, 3643; (b) Pilli, R. A.; Russowsky, D. *J. Chem. Soc., Chem. Commun.* **1987**, 1053; (c) Guanti, G.; Narisano, E.; Banfi, L. *Tetrahedron Lett.* **1987**, *28*, 4331; (d) Mukaiyama, T.; Kashiwagi, K.; Matsui, S. *Chem. Lett.* **1989**, 1397; (e) Mukaiyama, T.; Akamatsu, H.; Han, J. S. *Chem. Lett.* **1990**, 889; (f) Onaka, M.; Ohno, R.; Yanagiya, N.; Izumi, Y. *Synlett* **1993**, 141–142; (g) Ishihara, K.; Funahashi, K.; Hanaki, N.; Miyata, M.; Yamamoto, H. *Synlett* **1994**, 963–964; (h) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520–10524.
- (a) Hattori, K.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 2785–2792; (b) Hayakawa, R.; Shimizu, M. *Chem. Lett.* **1999**, 591–592; (c) Miura, K.; Tamaki, K.; Nakagawa, T.; Hosomi, A. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1958–1960.
- (a) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153–7154; (b) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548–4549; (c) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474–2475; (d) Ferraris, D.; Dudding, T.; Young, B.; Drurry, III, W. J. D.; Lectka, T. *J. Org. Chem.* **1999**, *64*, 2168–2169; (e) Ferraris, D.; Young, B.; Dudding, T.; Drurry, III, W. J.; Lectka, T. *Tetrahedron* **1999**, *55*, 8869–8882; (f) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431–432; (g) Kobayashi, S.; Hasegawa, Y.; Ishitani, H. *Chem. Lett.* **1998**, 1131–1132; (h) Ishitani, H.; Kitazawa, T.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 2161–2164; (i) Tomioka, K.; Fujieda, H.; Hayashi, S.; Hussein, M.-A.; Kambara, T.; Nomura, Y.; Kanai, M.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1999**, 715–716; (j) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450–5458; (k) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180–8186; (l) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337.
- For reviews, see: (a) Reissig, H.-U. *Organic Synthesis Highlights*; VCH: Weinheim, 1991; pp. 71; (b) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023–2035; (c) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley: New York, 1997; (d) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994**, 741–760; (d) Li, C.-J. *Tetrahedron* **1996**, *52*, 5643–5668; (e) *Organic Reactions in Water*; Grieco, P., Ed.; Blackie Academic & Professional: London, 1998.
- (a) Akiyama, T.; Takaya, J.; Kagoshima, H. *Chem. Lett.* **1999**, 947–948; (b) Akiyama, T.; Takaya, J.; Kagoshima, H. *Synlett* **1999**, 1045–1048.

7. Akiyama, T.; Takaya, J.; Kagoshima, H. *Synlett* **1999**, 1426–1427.
8. For related work, see: Manabe, K.; Mori, Y.; Kobayashi, S. *Synlett* **1999**, 1401–1402.
9. Akiyama, T.; Takaya, J.; Kagoshima, H. *Tetrahedron Lett.* **1999**, *40*, 7831–7834.
10. Mannich-type reactions using ketene silyl acetal derived from α -oxy ester, see: Refs. 3a and 4f.
11. For recent examples of the three-component Mannich-type reactions, see: Kobayashi, S.; Ishitani, H. *J. Chem. Soc., Chem. Commun.* **1995**, 1379. Loh, T.-P.; Liung, S. B. K. W.; Tan, K.-L.; Wei, L.-L. *Tetrahedron* **2000**, *56*, 3227–3237. See also Refs. 6b, 7 and 8.
12. A typical experimental procedure for entry 2 of Table 1. To a solution of benzaldehyde (7.0 μ L, 0.069 mmol), *p*-anisidine (8.8 mg, 0.072 mmol), and **1** (65 μ L, 0.15 mmol) in 2-propanol (0.4 mL) was added 8.5% solution of HBF₄ in water (7.5 μ L, 0.0073 mM) at 0°C. After being stirred at this temperature for 12 h, the reaction was quenched by addition of satd NaHCO₃ and CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂ and the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated to dryness. Purification of the crude mixture by preparative TLC (SiO₂, hexane:ethyl acetate=10:1, v/v) gave a β -amino- α -siloxy ester in 93% yield. (*syn:anti*=1:99).
13. Vicinal coupling constants ($J_{3,4}$) of the β -lactams are 1.7 Hz.
14. A typical experimental procedure for entry 1 of Table 2. To a suspension of *N*-(benzylidene)-*p*-methoxyaniline (35.2 mg, 0.160 mM), sodium dodecyl sulfate (21.0 mg, 0.0728 mmol), and **2** (100 mg, 0.237 mmol) in water (1.0 mL) was added 8.5% solution of HBF₄ in water (17.0 μ L, 0.0165 mM) at room temperature. After being stirred at the temperature for 1 h, Dowex 1-X8 (100–200 mesh, Cl[−] form), CH₂Cl₂ and H₂O were added to quench the reaction, and the reaction mixture was further stirred at the temperature for 10 min. After removing the solid by filtration, the filtrate was extracted with CH₂Cl₂ and the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated to dryness. The crude material was purified by *p*-TLC (hexane:ethyl acetate=10:1, R_f =0.3) to afford a β -amino- α -siloxy ester in 90% yield. (*syn:anti*=90:10).