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Stereoselective Mannich-type reaction of chiral aldimines with 2-silyloxybutadienes by using trifluoromethanesulfonic acid

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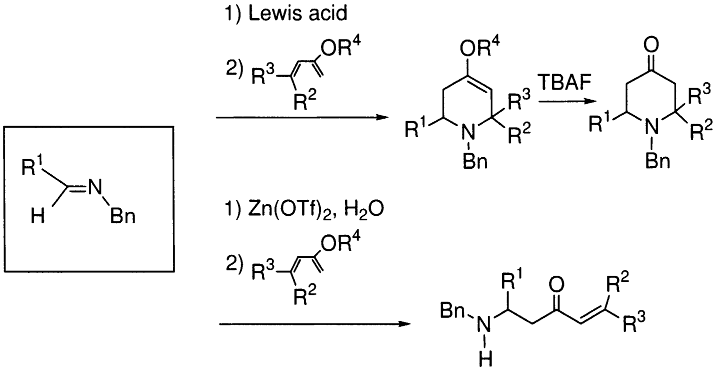
Abstract—Novel stereoselective Mannich-type reaction of chiral aldimines with 2-silyloxybutadienes in the presence of trifluoromethanesulfonic acid has been carried out to give the corresponding products, which are not obtained by general Lewis acid-promoted methods, with 70–92% de in 62–74% yield. No cycloadducts were detected in the crude product by ^{1}H NMR.

Mannich[1,2] or Mannich-type reactions[3] have been widely used for synthesis of many biologically attractive compounds. Recently, we have developed the first zinc triflate and water-promoted Mannich-type reaction of aldimines with 2-silyloxy-1,3-butadienes that affords pharmaceutically attractive Mannich-type products having a terminal olefin.[4] Though reactions of aldimines with silyloxydienes in the presence of Lewis acids give cycloadducts in many cases,[5,6] the Mannich-type products are obtained selectively by using zinc triflate and water (Scheme 1). Some examples have been reported where the reaction of some aldimines gave Mannich-type products; however, the reactions depended on the α-substituent of the aldimines and silyloxydienes.[7–9] We also found that classical Mannich-type reaction using zinc triflate and water also proceeded effectively.[4c] In this paper we wish to report the novel stereoselective Mannich-type reaction of chiral aldimines with 2-silyloxybutadienes using trifloromethanesulfonic acid, in which the major diastereomers are different from those obtained in reaction with zinc triflate and water.[4c]

In our initial studies, the reaction of aldimine **1a** with 2-silyloxybutadiene **2a** (4 equiv. to aldimine) in the presence of TfOH (1 equiv. to aldimine) was carried out in ether at 30°C for 6 h (entry 1 in Table 1).[10] Mannich-type product **3a** was obtained selectively with 70% de in 67% isolated yield. It was interesting to note that no cycloadducts were detected in the crude product by 500 MHz ^{1}H NMR. In addition, the major diastereomer was different from that obtained in reaction with zinc triflate and water.[4c,11] The use of other Brønsted acids



Scheme 1.

Keywords: stereocontrol; imines; dienes; Mannich reactions.

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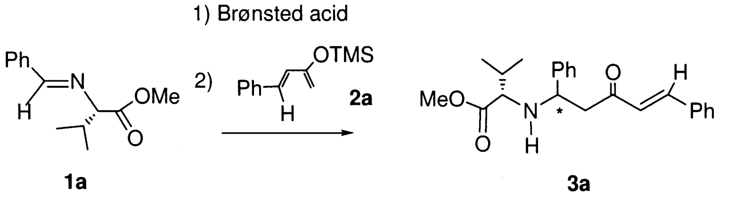
Table 1. Mannich-type reaction of chiral aldimine with 2-silyloxy-1,3-butadiene by using Brønstead acid



Entry	Brønstead acid	Solvent	Conditions	De (%)[a]	Isolated yield (%)[b]
1	TfOH (1 equiv. to aldimine)	Ether	30°C, 6 h	70	67
2	TsOH (1 equiv. to aldimine)	Ether	30°C, 6 h	–	0
3	FSO_3H (1 equiv. to aldimine)	Ether	30°C, 6 h	–	0
4	CF_3COOH (1 equiv. to aldimine)	Ether	30°C, 6 h	–	0
5	TfOH (1 equiv. to aldimine)	Toluene	30°C, 6 h	56	30
6	TfOH (1 equiv. to aldimine)	CH_2Cl_2	30°C, 6 h	54	<20
7	TfOH (1 equiv. to aldimine)	Petroleum ether	30°C, 6 h	–	0
8	TfOH (0.25 equiv. to aldimine)	Ether	30°C, 6 h	26	21
9	TfOH (0.5 equiv. to aldimine)	Ether	30°C, 6 h	52	53
10	TfOH (1.5 equiv. to aldimine)	Ether	30°C, 6 h	50	<20
11	TfOH (1 equiv. to aldimine)+(0.1 equiv. to aldimine)	Ether	30°C, 6 h	28[c]	35

[a] Determined by ^1H NMR of the crude product. Absolute stereochemistry was not determined.

[b] Yields after column chromatography.

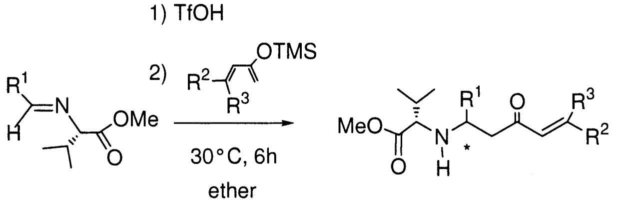
[c] The major isomer was the same as in the case of zinc triflate and water.

such as TsOH, FSO_3H, or CF_3COOH without water did not afford the Mannich-type product but gave decomposed products or the starting material (entries 2–4). Reactions using other solvents such as toluene, dichloromethane, or petroleum ether gave lower diastereoselectivities or no desired product (entries 5–7). We also examined the effect of the amount of TfOH on the diastereoselectivity or the yield (entries 1 and 8–10), and the best result was obtained with 1 equiv. of TfOH. Excess amount of TfOH resulted in decomposition of Mannich-type products, and the reaction with a catalytic amount of TfOH did not proceed to completion. Addition of water (0.1 equiv. to aldimine) to TfOH (1 equiv. to aldimine) gave low yield of the product, but the major diastereomer was the same as in the case of the zinc triflate and water-promoted reaction (entry 11).

Under the best conditions, the reactions of various aldimines (**1a**–**c**) with 2-silyloxy-1,3-butadienes (**2a**–**b**) were carried out (Table 2). In all cases for the reactions in Table 2, no cycloadducts were detected by 500 MHz ^1H NMR. The reactions gave 70–92% de in 62–74% yield of the products. The α-substituent of the aldimine or the substituents at the 4-position of 2-silyloxy-1,3-butadienes did not substantially lower the yields and diastereoselectivities.

Interestingly, the reaction of aldimine **1a** with **2a** in the presence of zinc triflate (4 equiv. to aldimine) and TfOH (1 equiv. to aldimine) at 30°C for 6 h led to 68% de of the product (75% isolated yield) in which the major isomer was the same as in the reaction with zinc triflate and water. The reaction of **1a** with **2a** in the presence of zinc chloride (4 equiv. to aldimine) and

Table 2. Mannich-type reaction of chiral aldimines with 2-silyloxy-1,3-butadienes in the presence of TfOH



Entry	R¹	Aldimine	R²	R³	Diene	Product	De (%)[a]	Isolated yield (%)[b]
1	Ph	**1a**	Ph	H	**2a**	**3a**	70	67
2	*p*-Tolyl	**1b**	Ph	H	**2a**	**3b**	90	70
3	*p*-ClPh	**1c**	Ph	H	**2a**	**3c**	92	62
4	Ph	**1a**	Me	Me	**2b**	**3d**	82	71
5	*p*-Tolyl	**1b**	Me	Me	**2b**	**3e**	80	74

[a] Determined by ^1H NMR of the crude product. Absolute stereochemistry was not determined.

[b] Yields after column chromatography.

TfOH (1 equiv. to aldimine) under similar conditions also gave the same isomer predominantly (86% de) in 10% isolated yield. The reaction mechanism is not clear now, however, the diastereoselectivity might be rationalized assuming that the aldimine with zinc reagent adopts the preferred chelate conformation **4** (Fig. 1),[12] and the nucleophilic attack might occur from the less hindered side of **4**. In contrast, the isomer obtained predominantly in the TfOH-promoted reaction might be a non-chelation product.

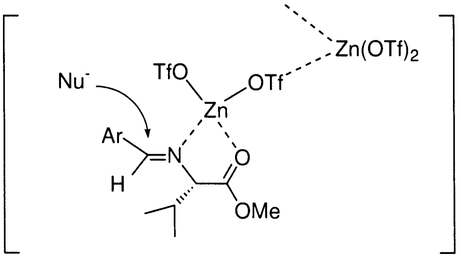


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Figure 1.

In conclusion, we have developed a diastereoselective preparation of Mannich-type products which were not obtained by general Lewis acid-promoted methods in dry solvents. The reaction did not give any cycloadducts, and the major isomers were different from those obtained in the case of reaction with zinc triflate and water. Further studies to investigate the reaction mechanism are now in progress.

Typical experimental procedure for preparation of the Mannich-type products. To a stirred solution of trifluoromethanesulfonic acid (0.044 mL, 0.5 mmol) in dry ether (4 mL) was added 0.5 mmol of aldimine and 2 mmol of 2-silyloxy-1,3-butadiene at rt. The solution was stirred at 30°C for 6 h, and the mixture was quenched with aqueous $NaHCO_3$. After the mixture was extracted with ether, the combined organic layers were dried over $MgSO_4$, and the solvent was evaporated. The crude product was purified by short flash column chromatography (Merck silica gel 60, *n*-hexane/$CH_3COOEt = 3/1$). The chromatographic purification should be performed as quickly as possible because decomposition of the Mannich-type products might occur on silica gel in some cases.

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10. The Mannich-type products were identified by the following data.
3a (major diastereomer): ^1H NMR (500 MHz, $CDCl_3$); δ 0.91 (d, 3H, $J=7.0$ Hz), 0.93 (d, 3H, $J=7.0$ Hz), 1.87–1.91 (m, 1H), 2.92–2.99 (m, 2H), 3.13 (dd, 1H, $J=15.9$, 8.0 Hz), 3.44 (s, 3H), 4.18–4.21 (m, 1H), 6.69 (d, 1H, $J=16.2$ Hz), 7.05–7.77 (m, 11H). HRMS-FAB$(M+H)^+$: Obsd m/z 366.2053. Calcd for $C_{23}H_{28}NO_3$: 366.2069.
3b (major diastereomer): ^1H NMR (500 MHz, $CDCl_3$); δ 0.92 (d, 3H, $J=6.7$ Hz), 0.93(d, 3H, $J=6.7$ Hz), 1.87–2.00 (m, 1H), 2.31 (s, 3H), 2.96 (dd, 1H, $J=16.0$, 5.3 Hz),

3.02 (d, 1H, $J=6.0$ Hz), 3.19 (dd, 1H, $J=16.0$, 8.1 Hz), 3.73 (s, 3H), 4.19 (dd, 1H, $J=7.9$, 5.6 Hz), 6.68 (d, 1H, $J=16.3$ Hz), 7.07–7.63 (m, 10H). HRMS-FAB(M+H)$^+$: Obsd *m*/*z* 380.2235. Calcd for $C_{24}H_{30}NO_3$: 380.2226.

3c (major diastereomer): ^{1}H NMR (500 MHz, $CDCl_3$); δ 0.93 (d, 3H, $J=6.6$ Hz), 0.94 (d, 3H, $J=6.6$ Hz), 1.85–1.95 (m, 1H), 2.94 (dd, 1H, $J=16.2$, 5.9 Hz), 2.98 (d, 1H, $J=5.9$ Hz), 3.15 (dd, 1H, $J=16.2$, 7.7 Hz), 3.49 (s, 3H), 4.20–4.22 (m, 1H), 6.68 (d, 1H, $J=16.2$ Hz), 7.14–7.52 (m, 10H). HRMS-FAB(M+H)$^+$: Obsd *m*/*z* 400.1685. Calcd for $C_{23}H_{27}NO_3Cl$: 400.1679.

3d (major diastereomer): ^{1}H NMR (500 MHz, $CDCl_3$); δ 0.96 (d, 3H, $J=6.8$ Hz), 1.02 (d, 3H, $J=6.8$ Hz), 1.93 (s, 3H), 2.22 (s, 3H), 2.40–2.42 (m, 1H), 2.96–3.21 (m, 2H), 3.29–3.30 (m, 1H), 3.88 (s, 3H), 4.44–4.48 (m, 1H), 6.09 (s, 1H), 7.33–7.53 (m, 5H). HRMS-FAB(M$^+$): Obsd *m*/*z* 317.2007. Calcd for $C_{19}H_{27}NO_3$: 317.1991.

3e (major diastereomer): ^{1}H NMR (500 MHz, $CDCl_3$); δ 0.96 (d, 3H, $J=6.6$ Hz), 1.02 (d, 3H, $J=6.6$ Hz), 1.87 (s, 3H), 2.16 (s, 3H), 2.31 (s, 3H), 2.30–2.40 (m, 1H), 2.87–3.02 (m, 1H), 3.23–3.34 (m, 1H), 3.39–3.40 (m, 1H), 3.69 (s, 3H), 4.34–4.35 (m, 1H), 6.04 (s, 1H), 7.15–7.35 (m, 4H). HRMS-FAB(M+H) $^+$: Obsd *m*/*z* 332.2219. Calcd for $C_{20}H_{30}NO_3$: 332.2226.

11. Reaction in the presence of zinc triflate and water was carried out as follows: To a stirred solution of zinc triflate (0.72 g, 2 mmol) and water (45 μL, 2.5 mmol) in ether (4 mL) was added 0.5 mmol of aldimine and 1 mmol of silyloxydiene at 0°C. The solution was stirred at 0°C, gradually warmed up to room temperature (25°C), and stirred for 1 day (90% de, 82% isolated yield).
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