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Addition of Water to Zinc Triflate Promotes a Novel Reaction: Stereoselective Mannich-Type Reaction of Chiral Aldimines with 2-Silyloxybutadienes

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Abstract: A novel stereoselective Mannich-type reaction of chiral aldimines with 2-silyloxybutadienes in the presence of zinc triflate and water has been achieved. The diastereoselectivities of the products were 74−90% de, and no cycloadducts were detected. Classical Mannich-type products were also obtained by using zinc triflate and water with high diastereoselectivities.

Organic reactions in the presence of water or aqueous reactions of organic compounds have been of particular interest.[1−3]Although many Lewis acids are decomposed or deactivated by water, recent research has shown that addition of water accelerates some reactions,[4] and aldol reactions,[5] allylations,[6] Diels−Alder reactions,[7] and classical Mannich-type reactions[8−10] proceed effectively in the presence of both Lewis acid and water.[11] Despite these many studies, it is known that most reported reactions also proceed in organic solvent without water.[12−16] Recently we reported zinc triflate- and water-promoted reaction that affords Mannich-type products having a terminal olefin by the reaction of aldimines **1** with 2-silyloxy-1,3-butadienes (Scheme 1).[17] Though it is well-known that reactions of aldimines with silyloxydienes in the presence of Lewis acids generally give cycloadducts,[18,19] the Mannich-type products were obtained selectively by using zinc triflate and water. Thus, the reaction extended the scope of classical Mannich-type reactions. The study of the reaction mechanism showed that the reaction proceeded by way of cycloaddition and then C−N bond cleavage of the cycloadduct, indicating that the reaction did not proceed via a typical Mannich-type addition mechanism. In this paper we report the scope of a novel stereoselective Mannich-type reaction of

SCHEME 1. Preparation of Mannich-Type Products by Reaction of Aldimines Having an *N*-Benzyl Group with 2-Silyloxy-1,3-butadienes

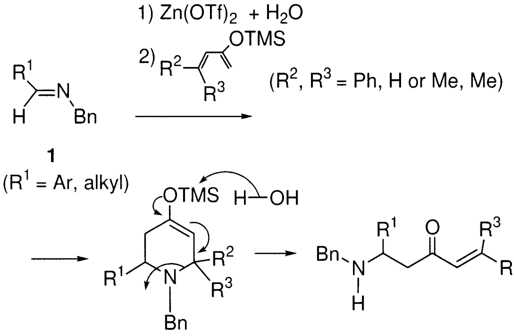

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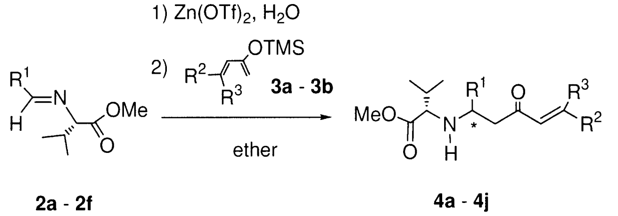
TABLE 1. Reaction of Aldimines Derived from L-Valine Methyl Ester[a]



entry	R^1	aldimine	R^2	R^3	diene	product	de[b] (%)	yield[c] (%)
1	Ph	**2a**	Ph	H	**3a**	**4a**	90	82
2	*o*-tolyl	**2b**	Ph	H	**3a**	**4b**	84	84
3	*m*-tolyl	**2c**	Ph	H	**3a**	**4c**	86	57
4	*p*-tolyl	**2d**	Ph	H	**3a**	**4d**	80	61
5	*o*-MeOPh	**2e**	Ph	H	**3a**	**4e**	88	71
6	*p*-ClPh	**2f**	Ph	H	**3a**	**4f**	92	80
7	Ph	**2a**	Me	Me	**3b**	**4g**	82	71
8	*o*-tolyl	**2b**	Me	Me	**3b**	**4h**	74	83
9	*p*-tolyl	**2d**	Me	Me	**3b**	**4i**	80	74
10	*o*-MeOPh	**2e**	Me	Me	**3b**	**4j**	84	77

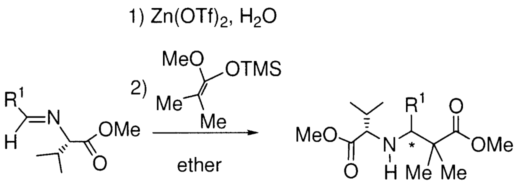
[a] Reaction conditions: aldimine (0.5 mmol), zinc triflate (2.0 mmol), water (2.5 mmol), silyloxydiene (1.0 mmol), ether (4 mL), addition carried out at 0 °C and the reaction mixture gradually warmed to rt, 1 day, under Ar. [b] Determined by 500 MHz ^{1}H NMR. [c] Isolated yields after column chromatography.

chiral aldimines with 2-silyloxybutadienes using zinc triflate and water, and its application to classical stereoselective Mannich-type reactions.

In our initial studies, the reaction of aldimine **2a** with 2-silyloxybutadiene **3a** (4 equiv relative to aldimine) in the presence of zinc triflate (4 equiv relative to aldimine) and water (5 equiv relative to aldimine) was carried out in dry ether (entry 1 in Table 1). Mannich-type product **4a** was obtained with high diastereoselectivity (90% de). No cycloadducts were detected in the crude product by 500 MHz ^{1}H NMR. Although the reaction of aldimine **1** having an *N*-benzyl group (Scheme 1) affords cycloadducts in the presence of Lewis acids without water in dry solvent, the reaction of **2a** with zinc triflate and no water gave only starting material. The use of other strong Lewis acids effective with aldimines, such as $SnCl_4$ or $TiCl_4$ without water, also afforded starting material and a small amount of decomposed silyloxydiene. Attempts to use $BF_3 \cdot Et_2O$, $SnCl_4$, or $TiCl_4$ in the presence of water did not give any products.

Under the best conditions, the reaction of various aldimines (**2a**–**f**) with 2-silyloxy-1,3-butadienes (**3a**,**b**) is quite general with respect to the structures of the aryl moiety of the aldimines or the substituents of the 2-silyloxy-1,3-butadienes. Electron-poor (**2f**) and electron-rich (**2e**) aldimines react with equal facility (entries 5 and 6). In all cases for the reactions in Table 1, no cycloadducts were detected by ^{1}H NMR. The reactions gave 74–90% de of the products, providing excellent levels of diastereocontrol. Other 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.[20–22] The enantioselectivity of the major diastereomer **4a** was examined, and >99% ee was detected by HPLC analysis (*n*-hexane:*i*-PrOH = 95:5), indicating that the valine methyl ester moiety was not racemized by the process.

TABLE 2. Mannich-Type Reaction with Ketene Silyl Acetal[a]



entry	R^1	product	de[b] (%)	yield[c] (%)
1	Ph	**5a**	88	94
2	*o*-tolyl	**5b**	80	84
3	*m*-tolyl	**5c**	86	80
4	*p*-ClPh	**5d**	88	75

[a] Reaction conditions: aldimine (0.5 mmol), zinc triflate (2.0 mmol), water (2.5 mmol), ketene silyl acetal (1.0 mmol), ether (4 mL), 0 °C, 1 h, under Ar. [b] Determined by 500 MHz ^{1}H NMR. [c] Isolated yields after column chromatography.

The study of the use of zinc triflate and water was also extended to classical stereoselective Mannich-type reaction with ketene silyl acetal (Table 2). Under conditions similar to those of the reactions in Table 1, the Mannich-type reaction was carried out with ketene silyl acetal (2 equiv relative to aldimine) at 0 °C for 1 h to give the corresponding Mannich-type products in high yields (75–94% yield) with high diastereoselectivities (80–88% de), showing that zinc triflate and water promoted both classical and the new Mannich-type reactions. The α-substituent of the aldimine did not greatly affect the yields and diastereoselectivities.

We tried to trap cycloadducts in the reaction of aldimine **2a** with **3a** in the presence of zinc triflate (4 equiv relative to aldimine) and water (5 equiv relative to aldimine) at 10 °C for 50 min, but Mannich-type product and starting material were observed in the crude products by ^{1}H NMR. The reaction mechanism in the case of zinc triflate and water is not clear now, but from the results, the reaction might proceed via a Mannich-type reaction mechanism in which the silyl enolate moiety of the silyloxydiene reacts with the aldimine, or cycloadducts might be decomposed rapidly to give Mannich-type products.

Interestingly, the reaction in the presence of TfOH (1 equiv relative to aldimine) without water gave Mannich-type product (70% de, 67% yield). However, a catalytic amount of TfOH (0.1 equiv relative to aldimine) without water gave low yields of product and mostly recovered starting material, and an excess amount of TfOH (2 equiv relative to aldimine) resulted in decomposed products and <30% yield of the product. An amount of TfOH equimolar to that of aldimine was necessary for producing the Mannich-type products effectively; on the other hand, 8 equiv of zinc triflate

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relative to aldimine and 10 equiv of water afforded a yield of product (78%) similar to that of the reaction with 4 equiv of zinc triflate and 5 equiv of water (82%). Thus, the reaction with zinc triflate and water may not follow the same pathway as a Brønsted acid-catalyzed reaction.

In conclusion, we have developed the stereoselective Mannich-type reaction of chiral aldimines with silyloxydienes by using zinc triflate and water. A powerful feature of this reaction with silyloxydienes is the capacity to build Mannich-type products selectively that are not available using conventional Lewis acid-promoted methods.

Experimental Section

General Procedures. All manipulations were carried out under an Ar atmosphere. Reagent-grade ether was distilled under Ar from sodium−benzophenone ketyl just before use. ^{1}H NMR spectra (500 MHz) were recorded at room temperature using TMS as an internal standard.

Mannich-Type Reaction of Aldimines 2 with Silyloxydienes 3. To a stirred solution of zinc triflate (0.72 g, 2 mmol) and water (45 μL, 2.5 mmol) in ether (4 mL) were added 0.5 mmol of aldimine and 1 mmol of silyloxydiene at 0 °C. The solution was stirred at 0 °C, gradually warmed to room temperature (25 °C), and stirred for 1 day. The mixture was quenched with aqueous $NaHCO_3$, and extracted with dichloromethane (20 mL × 3). The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated. The crude product was purified by short flash column chromatography (silica gel 60, *n*-hexane:CH_3CO_2Et = 3:1). The chromatographic purification should be performed as quickly as possible because decomposition of **4** might occur on silica gel in some cases. The Mannich-type products **4** are not stable at room temperature for a long period (>8 h) after aqueous $NaHCO_3$ workup but can be stored below −15 °C with slight decomposition.

Preparation of 4a. Starting from the corresponding aldimine (0.09 mL, 0.5 mmol) with silyloxydiene (0.22 mL, 1.0 mmol) to afford 150 mg (82% yield) of **4a**: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 0.78 (d, 3H, $J = 6.7$ Hz), 0.84 (d, 3H, $J = 6.7$ Hz), 1.76−1.80 (m, 1H), 2.70−2.72 (m, 1H), 2.93−3.00 (m, 2H), 3.66 (s, 3H), 4.03−4.06 (m, 1H), 6.60 (d, 1H, $J = 16.2$ Hz), 7.03−7.56 (m, 11H); HRMS-FAB (M$^+$) m/z calcd for $C_{23}H_{27}NO_3$ 365.1991, found 365.1981.

Preparation of 4b. Starting from the corresponding aldimine (0.09 mL, 0.5 mmol) with silyloxydiene (0.22 mL, 1.0 mmol) to afford 159 mg (84% yield) of **4b**: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 0.83 (d, 3H, $J = 6.7$ Hz), 0.93 (d, 3H, $J = 6.7$ Hz), 1.78−1.90 (m, 1H), 2.30 (s, 3H), 2.71 (d, 1H, $J = 6.8$ Hz), 2.89−2.96 (m, 2H), 3.72 (s, 3H), 4.40−4.43 (m, 1H), 6.66 (d, 1H, $J = 16.2$ Hz), 7.05−7.68 (m, 10H); HRMS-FAB (M + H)$^+$ m/z calcd for $C_{24}H_{30}NO_3$ 380.2226, found 380.2213.

Preparation of 4c. Starting from the corresponding aldimine (0.09 mL, 0.5 mmol) with silyloxydiene (0.22 mL, 1.0 mmol) to afford 108 mg (57% yield) of **4c**: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 0.78 (d, 3H, $J = 6.6$ Hz), 0.84 (d, 3H, $J = 6.6$ Hz), 1.74−1.78 (m, 1H), 2.27 (s, 3H), 2.69−2.70 (m, 1H), 2.90−2.91 (m, 2H), 3.65 (s, 3H), 3.97−3.99 (m, 1H), 6.59 (d, 1H, $J = 16.2$ Hz), 6.99−7.45 (m, 10H); HRMS-FAB (M$^+$) m/z calcd for $C_{24}H_{29}NO_3$ 379.2147, found 379.2151.

Preparation of 4d. Starting from the corresponding aldimine (0.09 mL, 0.5 mmol) with silyloxydiene (0.22 mL, 1.0 mmol) to afford 116 mg (61% yield) of **4d**: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 0.78 (d, 3H, $J = 6.7$ Hz), 0.84 (d, 3H, $J = 6.7$ Hz), 1.74−1.84 (m, 1H), 2.26 (s, 3H), 2.69−2.70 (m, 1H), 2.84−2.96 (m, 2H), 3.65 (s, 3H), 3.98−4.00 (m, 1H), 6.58 (d, 1H, $J = 16.1$ Hz), 6.99−7.51 (m, 10H); HRMS-FAB (M + H)$^+$ m/z calcd for $C_{24}H_{30}NO_3$ 380.2226, found 380.2212.

Preparation of 4e. Starting from the corresponding aldimine (0.10 mL, 0.5 mmol) with silyloxydiene (0.22 mL, 1.0 mmol) to afford 140 mg (71% yield) of **4e**: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 0.87 (d, 3H, $J = 6.8$ Hz), 0.95 (d, 3H, $J = 6.8$ Hz), 1.78−1.90 (m, 1H), 2.75−2.89 (m, 2H), 3.10 (dd, 1H, $J = 15.4$, 4.4 Hz), 3.65 (s, 3H), 3.83 (s, 3H), 4.49 (dd, 1H, $J = 8.8$, 4.0 Hz), 6.73 (d, 1H, $J = 16.2$ Hz), 6.81−7.63 (m, 10H); HRMS-FAB (M$^+$) m/z calcd for $C_{24}H_{29}NO_4$ 395.2096, found 395.2083.

Preparation of 4f. Starting from the corresponding aldimine (0.115 g, 0.5 mmol) with silyloxydiene (0.22 mL, 1.0 mmol) to afford 160 mg (80% yield) of **4f**: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 0.84 (d, 3H, $J = 6.7$ Hz), 0.90 (d, 3H, $J = 6.7$ Hz), 1.72−1.87 (m, 1H), 2.70 (d, 1H, $J = 6.7$ Hz), 2.94−3.01 (m, 2H), 3.73 (s, 3H), 4.07−4.09 (m, 1H), 6.65 (d, 1H, $J = 16.1$ Hz), 7.05−7.62 (m, 10H); HRMS-FAB (M + H)$^+$ m/z calcd for $C_{23}H_{27}NO_3Cl$ 400.1679, found 400.1674.

Preparation of 4g. Starting from the corresponding aldimine (0.09 mL, 0.5 mmol) with silyloxydiene (0.19 mL, 1.0 mmol) to afford 113 mg (71% yield) of **4g**: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 0.76 (dd, 3H, $J = 6.8$, 2.0 Hz), 0.83 (dd, 3H, $J = 6.8$, 2.0 Hz), 1.67−1.75 (m, 1H), 1.78 (s, 3H), 2.07 (s, 3H), 2.61−2.71 (m, 2H), 3.59−3.63 (m, 1H), 3.65 (s, 3H), 3.93−3.95 (m, 1H), 5.91 (s, 1H), 7.15−7.30 (m, 5H); HRMS-FAB (M$^+$) m/z calcd for $C_{19}H_{27}NO_3$ 317.1991, found 317.1995.

Preparation of 4h. Starting from the corresponding aldimine (0.09 mL, 0.5 mmol) with silyloxydiene (0.19 mL, 1.0 mmol) to afford 138 mg (83% yield) of **4h**: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 0.75 (d, 3H, $J = 6.8$ Hz), 0.85 (d, 3H, $J = 6.8$ Hz), 1.59−1.73 (m, 1H), 1.79 (s, 3H), 2.08 (s, 3H), 2.21 (s, 3H), 2.55−2.66 (m, 2H), 3.61−3.62 (m, 1H), 3.64 (s, 3H), 4.24−4.26 (m, 1H), 5.91 (s, 1H), 7.02−7.46 (m, 4H); HRMS-FAB (M + H)$^+$ m/z calcd for $C_{20}H_{30}NO_3$ 332.2226, found 332.2232.

Preparation of 4i. Starting from the corresponding aldimine (0.09 mL, 0.5 mmol) with silyloxydiene (0.19 mL, 1.0 mmol) to afford 123 mg (74% yield) of **4i**: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 0.75 (dd, 3H, $J = 6.5$, 2.1 Hz), 0.82 (dd, 3H, $J = 6.5$, 2.1 Hz), 1.67−1.74 (m, 1H), 1.78 (s, 3H), 2.06 (s, 3H), 2.25 (s, 3H), 2.59−2.69 (m, 2H), 3.61−3.62 (m, 1H), 3.64 (s, 3H), 3.89−3.90 (m, 1H), 5.91 (s, 1H), 7.02−7.19 (m, 4H); HRMS-FAB (M + H)$^+$ m/z calcd for $C_{20}H_{30}NO_3$ 332.2226, found 332.2239.

Preparation of 4j. Starting from the corresponding aldimine (0.10 mL, 0.5 mmol) with silyloxydiene (0.19 mL, 1.0 mmol) to afford 134 mg (77% yield) of **4j**: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 0.77 (d, 3H, $J = 6.7$ Hz), 0.86 (d, 3H, $J = 6.7$ Hz), 1.75−1.79 (m, 1H), 1.79 (s, 3H), 2.07 (s, 3H), 2.67−2.75 (m, 2H), 3.61 (s, 3H), 3.72−3.73 (m, 1H), 3.73 (s, 3H), 4.36−4.37 (m, 1H), 5.97 (s, 1H), 6.74−6.89 (m, 2H), 7.12−7.15 (m, 1H), 7.38−7.45 (m, 1H); HRMS-FAB (M + H)$^+$ m/z calcd for $C_{20}H_{30}NO_4$ 348.2175, found 348.2191.

Mannich-Type Reaction of Aldimines 2 with Ketene Silyl Acetal. To a stirred solution of zinc triflate (0.72 g, 2 mmol) and water (45 μL, 2.5 mmol) in ether (4 mL) were added 0.5 mmol of aldimine and 1 mmol of ketene silyl acetal at 0 °C. The solution was stirred at 0 °C for 1 h, quenched with aqueous $NaHCO_3$, and extracted with dichloromethane. The organic layers were dried over $MgSO_4$, and the solvent was evaporated. The crude product was purified by short flash column chromatography (silica gel 60, *n*-hexane:ether = 1:1).

Preparation of 5a. Starting from the corresponding aldimine (0.09 mL, 0.5 mmol) with ketene silyl acetal (0.20 mL, 1.0 mmol) to afford 151 mg (94% yield) of **5a**: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 0.84 (d, 3H, $J = 6.8$ Hz), 0.92 (d, 3H, $J = 6.8$ Hz), 1.01 (s, 3H), 1.17 (s, 3H), 1.75−1.85 (m, 1H), 2.67 (d, 1H, $J = 6.7$ Hz), 3.68 (s, 3H), 3.69 (s, 1H), 3.72 (s, 3H), 7.22−7.31 (m, 5H); HRMS-FAB (M + H)$^+$ m/z calcd for $C_{18}H_{28}NO_4$ 322.2018, found 322.2015.

Preparation of 5b. Starting from the corresponding aldimine (0.09 mL, 0.5 mmol) with ketene silyl acetal (0.20 mL, 1.0 mmol) to afford 141 mg (84% yield) of **5b**: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 0.78 (d, 3H, $J = 6.7$ Hz), 0.89 (d, 3H, $J = 6.7$ Hz), 1.02 (s, 3H), 1.21 (s, 3H), 1.68−1.78 (m, 1H), 1.90−1.99 (br s, 1H), 2.29 (s, 3H), 2.52 (d, 1H, $J = 7.1$ Hz), 3.70 (s, 3H), 3.75 (s, 3H), 4.12 (s, 1H), 7.10−7.17 (m, 3H), 7.50−7.51 (m, 1H); HRMS-FAB (M + H)$^+$ m/z calcd for $C_{19}H_{30}NO_4$ 336.2175, found 336.2169.

Preparation of 5c. Starting from the corresponding aldimine (0.09 mL, 0.5 mmol) with ketene silyl acetal (0.20 mL, 1.0 mmol) to afford 134 mg (80% yield) of **5c**: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 0.77 (d, 3H, $J = 6.7$ Hz), 0.85 (d, 3H, $J = 6.6$ Hz), 0.93 (s, 3H), 1.09 (s, 3H), 1.69−1.76 (m, 1H), 2.26 (s, 3H), 2.61 (d, 1H, $J = 7.1$ Hz), 3.59 (s, 1H), 3.60 (s, 3H), 3.65 (s, 3H), 7.01 (d, 2H, $J = 7.8$ Hz), 7.11 (d, 2H, $J = 7.8$ Hz); HRMS-FAB $(M + H)^+$ m/z calcd for $C_{19}H_{30}NO_4$ 336.2175, found 336.2179.

Preparation of 5d. Starting from the corresponding aldimine (0.115 g, 0.5 mmol) with ketene silyl acetal (0.20 mL, 1.0 mmol) to afford 126 mg (75% yield) of **5d**: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 0.84 (d, 3H, $J = 6.7$ Hz), 0.91 (d, 3H, $J = 6.7$ Hz), 1.00 (s, 3H), 1.15 (s, 3H), 1.76−1.85 (m, 1H), 2.61 (d, 1H, $J = 6.6$ Hz), 3.67 (s, 1H), 3.68 (s, 3H), 3.72 (s, 3H), 7.24−7.28 (m, 4H); HRMS-FAB $(M + H)^+$ m/z calcd for $C_{18}H_{27}NO_4Cl$ 356.1628, found 356.1626.

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Supporting Information Available: NMR spectra for compounds **4a**−**j** and **5a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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