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Enantioselective Aldol Reaction of Trimethoxysilyl Enol Ether Catalyzed by Lithium Binaphtholate

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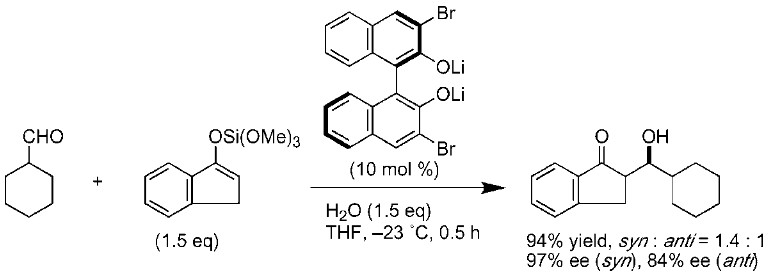
ABSTRACT



An aldol reaction of trimethoxysilyl enol ether catalyzed by lithium binaphtholate, in which water serves as an additive and plays a pivotal role in stereoselectivities, was developed. This is the first example of an aldol reaction of trimethoxysilyl enol ether catalyzed by a chiral base.

The aldol reaction is a powerful method for forming carbon−carbon bonds in organic synthesis.[1] Controlling the absolute configurations of the newly formed stereogenic centers is important in natural product syntheses. Recent significant developments in asymmetric aldol reactions are based on the principles of conventional Mukaiyama-type catalysis using various chiral Lewis acids.[2,3] Lewis base-catalyzed enantioselective aldol reactions of trichlorosilyl enol ethers were developed by employing chiral phosphoramides[4] or *N*-oxides[5] as catalysts and afford the corresponding adducts with high diastereo- and enantioselectivities via hypervalent silicate intermediates.[6] Despite their high syn/anti selectivities, aldol reactions of trichlorosilyl enol ethers are not widely utilized in organic synthesis since the enol ethers are not easily handled. Thus, Lewis base-catalyzed aldol reactions of silyl enol ethers other than trichlorosilyl enol ether are not developed.

Recently, trimethoxysilyl compounds have attracted a lot of attention[7] because they possess unique reactivities that

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(1) (a) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357−389. (b) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem.—Eur. J.* **1998**, *4*, 1137−1141. (c) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095−1120. (d) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352−1374.

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(3) Other recent examples of enantioselective aldol reactions: (a) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418−4420. (b) Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 2648−2649. (c) Yanagisawa, A.; Matsumoto, Y.; Nakashima, H.; Asakawa, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 9319−9320. (d) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871−1873. (e) Kuwano, R.; Miyazaki, H.; Ito, Y. *Chem. Commun.* **1998**, 71−72. (f) List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396. (g) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003−12004. (h) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798−6799. (i) Evans, D. A.; Downey, C. W.; Hubbs, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 8706−8707.

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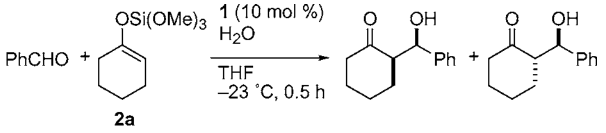
related compounds, trimethylsilyl derivatives, do not. Trimethoxysilyl enol ethers,[8] which are easily prepared from the corresponding lithium enolate with chlorotrimethoxysilane[9] or enone with trimethoxysilane, are so stable that they survive the aqueous workup or silica gel column chromatography. However, examples of base-catalyzed aldol reactions of trimethoxysilyl enol ether have yet to be reported and the reactivity of hypervalent silicate derived from the trimethoxysilyl enol ether remains unknown. In our pursuit of developing base-mediated reactions involving hypervalent silicate,[5,10] we investigated the enantioselective aldol reaction of trimethoxysilyl enol ethers catalyzed by Lewis bases.

Our initial studies examined the addition of trimethoxysilyl enol ether **2a** derived from cyclohexanone (1.5 equiv) to benzaldehyde using a variety of bases (10 mol %) in THF. Among the various chiral bases surveyed, the corresponding aldol adduct was obtained in high yield (98%) by employing 10 mol % lithium binaphtholate[11] as a catalyst, which was prepared in situ from the corresponding binaphthol and BuLi, but diastereo- and enantioselectivity were not observed or were barely observed. Screening binaphthol derivatives revealed that the dilithium salt of 3,3′-dibromobinaphthol (**1**) predominantly gave the anti adduct in high yield (97%, syn:anti = 1:3.7), with moderate enantioselectivity (8% ee (syn), 51% ee (anti)).[12] When optimizing the reaction conditions, we were surprised to find that adding water (1.5 equiv to aldehyde, i.e., 1.0 equiv to silyl enol ether) as an additive predominantly resulted in the syn adduct (syn:anti = 3.2:1) and dramatically increased the ee of the syn adduct (80% ee (syn), 51% ee (anti))[13−15] Stoichiometric studies revealed that equimolar amounts of water to silyl enol ether were sufficient to optimize diastereo- and enantioselectivity (Table 1), which suggests that water (or hydroxy ion) may strongly coordinate to the silicon atom of silyl enol ether. The trimethoxysilyl enol ether, which is stable under anhydrous conditions even in the presence of lithium binaphtholate, quickly decomposed to the corresponding ketone in aqueous solutions in the presence of lithium binaphtholate. This suggests that the coordination of water (or hydroxy ion) to silicon atom may increase the nucleophilicity of the silicate complex to afford the syn adduct predominantly via an acyclic transition state, while under anhydrous conditions the reaction proceeds via a cyclic chairlike transition state[4,5] to predominantly yield the anti adduct, although the details are unclear.

Table 1. Effect of Water as an Additive in Enantioselective Aldol Reaction of Trimethoxysilyl Enol Ether



entry	H_2O (equiv)	yield, %[a]	syn:anti[b]	ee, % (syn, anti)[b]
1	0	97	1:3.7	8, 51
2	0.1	93	1:1.1	15, 46
3	0.5	97	1.7:1	60, 44
4	1.0	93	3.2:1	77, 52
5	1.5	94	3.1:1	80, 50

[a] Combined isolated yield. [b] Determined by HPLC (Daicel chiralcel OD-H).

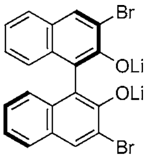


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Table 2 shows select results of the aldol reaction of trimethoxysilyl enol ethers with benzaldehyde under hydrous conditions. (*E*)-Enolates (entries 1, 2) and enolate without substituents on the α-position (entry 3) gave good results, while (*Z*)-enolate afforded low diastereo- and enantioselectivities (entry 4). Triethoxysilyl enol ether[18] gave similar selectivities, though the reaction proceeded slowly (entry 5). The aldol reactions of other aldehydes with **2a** or **2c** were investigated (Table 3). The reaction of aliphatic aldehydes proceeded smoothly with high enantioselectivities of over 90% ee, although the diastereoselectivities decreased (entries 3−5). The best enantioselectivity (97% ee) was obtained for the reaction of cyclohexanecarboxaldehyde (entry 4). It is noteworthy that the aldol reaction of aliphatic aldehydes, which often gives inferior results under Lewis base-catalyzed

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(8) Yamamoto has reported an aldol reaction of trimethoxysilyl enol ether catalyzed by Lewis acid.[7b]

(9) Corriu, R. J. P.; Moreau, J. J. E.; Thepot, P.; Man, M. W. C. *Chem. Mater.* **1992**, *4*, 1217−1224.

(10) (a) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419−6420. (b) Nakajima, M.; Saito, M.; Uemura, M.; Hashimoto, S. *Tetrahedron Lett.* **2002**, *43*, 8827−8829.

(11) Kagan reported an enantioselective reduction of ketones with trimethoxysilane catalyzed by lithium binaphtholate.[7a]

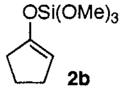
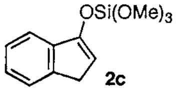
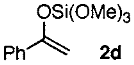
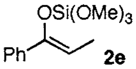
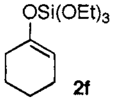
(12) Monolithium salt of 3,3′-dibromobinaphthol gave syn adduct predominantly in moderate yield (42%, syn:anti = 1.8:1) with low enantioselectivity (27% ee (syn), 14% ee (anti)).

(13) **Experimental Procedure.** To a solution of 3,3′-dibromobinaphthol (21 mg, 0.047 mmol) in THF (3 mL) was added H_2O (5% sol in THF, 0.26 mL, 0.70 mmol) and BuLi (0.19 M in hexane, 0.54 mL, 0.094 mmol) at −23 °C under an Ar atmosphere, and the mixture was stirred for 5 min. Benzaldehyde (10% sol in THF, 0.50 mL, 0.47 mmol) and trimethoxysilyl enol ether **2a** (0.15 mL, 0.70 mmol) were successively added to the resulting yellow solution, and the mixture was stirred for 30 min. The reaction was quenched with KF/KH_2PO_4 buffer, and entire mixture was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation followed by SiO_2 column chromatography afforded the corresponding aldol adduct (90 mg, 94%) as a mixture of diastereomers.

(14) Initial product under anhydrous conditions is the silyl ether of the corresponding aldol adduct, whereas silyl ether was not observed under aqueous conditions. The reaction with 0.5 equiv (to silyl enol ether) of water gave a 1:1 mixture of the silyl ether and the alcohol.

(15) Among various binaphthol derivatives screened, the 3,3′-dibromo derivative gave the best result. R on 3,3′-position, % yield, syn:anti, % ee (syn,anti): R = H, 76, 1.2:1, (24, 5); R = Me, 98, 2.3:1, (55, 15); R = CO_2Me, 76, 1:1.1, (17, 46); R = CF_3,[16] 95, 2.6:1, (69, 38); R = Cl, 98, 3.0:1, (78, 48); R = I, 98, 2.9:1, (73, 35).

Table 2. Enantioselective Aldol Reactions of Benzaldehyde with Trimethoxysilyl Enol Ethers

entry	enol ether	yield, %[a]	syn : anti [b]	ee,%(syn, anti)[b]
1	 2b	98	2.9 : 1	72, 6
2	 2c	78	2.9 : 1	83, 48
3	 2d	88	–	75
4	 2e	91	1.9 : 1	19, 38
5	 2f	83	2.9 : 1	77, 45

[a] Combined isolated yield. [b] Determined by HPLC (Daicel chiralcel OD-H or OB−H). Relative configurations of new compounds were assigned on the basis of the splitting pattern of the hydroxyl-bearing methine.[4b]

condition,[4,5,10] affords adducts in high yield and with high enantioselectivity.

In conclusion, an aldol reaction of trimethoxysilyl enol ether catalyzed by lithium binaphtholate, in which water serves as an additive and plays a pivotal role in stereoselectivities, was developed. This is the first example of an aldol reaction of trimethoxysilyl enol ether catalyzed by a chiral base. Mechanistic studies as well as designing a chiral catalyst to enhance the enantioselectivity are currently underway.

Table 3. Enantioselective Aldol Reaction of Aldehydes with Trimethoxysilyl Enol Ethers

entry	enol ether	aldehyde	yield, %[a]	syn:anti[b]	ee, % (syn, anti)[b]
1	**2c**	4-MeOC$_6$H$_4$CHO	89	7.0:1	89, 95
2	**2c**	PhCH=CHCHO	98	3.4:1	73, 10
3	**2c**	PhCH$_2$CH$_2$CHO	90	2.6:1	92, 47
4	**2c**	^{c}HexCHO	94	1.4:1	97, 84
5	**2a**	PhCH$_2$CH$_2$CHO	75	1.2:1	91, 40

[a] Combined isolated yield. [b] Determined by HPLC (Daicel chiralcel OJ-H or chiralpak AS−H). Relative configurations of new compounds were assigned on the basis of the splitting pattern of the hydroxyl-bearing methine.[4b]

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Supporting Information Available: Full experimental procedure and characterization for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Synthesized through trifluoromethylation of MOM-protected 3,3′-diiodo-BINOL with CF$_3$Cu,[17] prepared in situ from CF$_2$Br$_2$, Cd, and CuBr. $[\alpha]^{20}_{D}$ +657° (c 1.0, THF), mp 235−237 °C. See: Kobayashi, S.; Ishitani, H. Jpn. Patent, JP 2001139508, 2001; *Chem. Abstr.* **2001**, *134*, 366697 and Supporting Information.

(17) Wiemers, D. M.; Burton, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 832−834.

(18) Prepared from lithium enolate of cyclohexanone and commercially available chlorotriethoxysilane.