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Enantioselective aldol reactions of trichlorosilyl enol ethers catalyzed by chiral *N*,*N*′-dioxides and monodentate *N*-oxides

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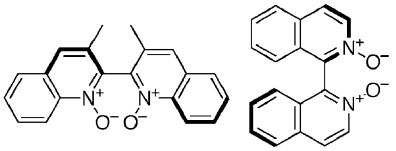
Abstract—Chiral *N*,*N*′-dioxides and monodentate *N*-oxides were employed as catalysts in catalytic, enantioselective aldol reactions of trichlorosilyl enol ethers. The reactions of acyclic enol ethers using *N*,*N*′-dioxides resulted in the *anti*-adducts from (*E*)-enol ethers and the *syn*-adducts from (*Z*)-enol ethers. The reactions of cyclic (*E*)-enol ethers using *N*,*N*′-dioxides gave the *anti*-adducts, whereas monodentate *N*-oxides predominantly gave the *syn*-adducts.

The aldol reaction is a powerful method for forming carbon–carbon bonds. Controlling the absolute configurations of the newly formed stereogenic center is important in natural product syntheses. Although significant developments of the asymmetric aldol reaction[1] are based on the principles of conventional Mukaiyama-type catalysis using various chiral Lewis acids,[2] these processes often preferentially afford the *syn*-aldol adduct from both stereoisomers of trimethylsilyl enol ether via acyclic transition states.

An alternative to the asymmetric aldol reaction is the catalytic activation of the donor rather than the acceptor.[3,4] Recently, Denmark reported enantioselective aldol reactions catalyzed by chiral phosphoramide derivatives involving hypervalent silicate intermediates,[5] which afforded the corresponding adducts with high diastereo- and enantioselectivities.[6]



(*R*)-**1**

(*R*)-**2**

As part of our program directed at developing *N*-oxide-mediated reactions,[7] we previously reported an enantioselective allylation of aldehydes with allyltrichlorosilanes[8] via hexacoordinate silicate complexes as intermediates utilizing chiral bipyridine *N*,*N*′-dioxides **1** and **2** as catalysts, which led to the *anti*-adduct from *E*-allylic trichlorosilane and the *syn*-adduct from *Z*-allylic trichlorosilane with high enantioselectivities. Since trichlorosilyl enol ether is an oxygen analogue of trichloroallylsilane, *N*-oxide-catalyzed aldol reactions of the silyl enol ethers are expected to proceed via a similar mechanism.[9] Herein we describe aldol reactions of trichlorosilyl enol ethers catalyzed by chiral *N*,*N*′-dioxides and monodentate *N*-oxides.

Our initial studies focused on the reaction of trichlorosilyl enol ether **3** derived from acetophenone with benzaldehyde using chiral *N*,*N*′-dioxide (*R*)-**1** or (*R*)-**2** as a catalyst (3 mol%) in the presence of diisopropylethylamine (1.0 equiv) in dichloromethane. Fortunately, the reactions proceeded smoothly at −78 °C to afford the corresponding aldol adducts in high yields, but the observed enantioselectivities were low (Table 1, entries 1 and 2). To confirm the stereochemical relationship of the geometry of enol ether to the product, aldol reactions of (*E*)- and (*Z*)-trichlorosilyl enol ethers **4** derived from heptanal[6d] were investigated. The reaction proceeded smoothly and the stereochemical information present in the trichlorosilyl enol ether was completely transmitted to an *anti* (from (*E*)-**4**) or a *syn* (from (*Z*)-**4**) about the new C–C bond of the product (entries 3–6). This result suggested that the aldol reaction mediated by **1** or **2**

Keywords: aldol reaction; diastereoselectivity; enantioselectivity; catalyst; *N*-oxide; trichlorosilyl enol ether.
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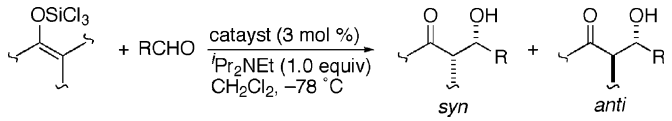
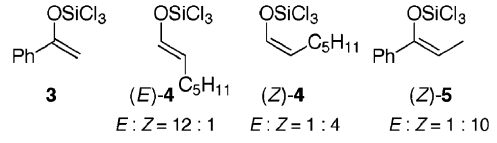
Table 1. Enantioselective aldol reactions of acyclic trichlorosilyl enol ethers with aldehydes catalyzed by chiral *N*,*N*′-dioxides



Entry	Enol ether	Aldehyde, R	Catalyst	Time (h)	Yield[a] (%)	*syn*/*anti*[b]	% Ee (*syn*, *anti*)[c]
1	**3**	Ph	(*R*)-**1**	1	85	—	<5
2	**3**	Ph	(*R*)-**2**	3	87	—	<5
3	(*E*)-**4**	Ph	(*R*)-**1**	0.5	96[d]	1:11	6, 7
4	(*E*)-**4**	Ph	(*R*)-**2**	0.5	86[d]	1:12	81, 23
5	(*Z*)-**4**	Ph	(*R*)-**1**	0.5	88[d]	3:1	9, 12
6	(*Z*)-**4**	Ph	(*R*)-**2**	0.5	90[d]	4:1	79, 23
7	(*Z*)-**5**	Ph	(*R*)-**1**	6	82	7:1	82, 33
8	(*Z*)-**5**	Ph	(*R*)-**2**	0.5	88	9:1	6, <5
9	(*Z*)-**5**	4-$MeOC_6H_4$	(*R*)-**1**	6	86	15:1	67, 13
10	(*Z*)-**5**	PhCH=CH	(*R*)-**1**	6	59	15:1	63, 43
11	(*Z*)-**5**	$PhCH_2CH_2$	(*R*)-**1**	6	Trace	—	—

[a] Isolated combined yield.
[b] Determined by ^1H NMR.
[c] Determined by HPLC (Daicel Chiralcel OB-H, OD-H or OJ-H).
[d] Isolated as dimethyl acetal.

proceeded via six-membered cyclic chair-like transition state involving hypervalent silicate (Fig. 1) similar to the above allylation.[8] The reaction of (*Z*)-**4** with catalyst (*R*)-**2** displayed a high enantioselectivity (79–81% ee) (entries 4 and 6), while a low enantioselectivity was observed with catalyst (*R*)-**1** (entries 3 and 5). Among the various trichlorosilyl enol ether surveyed, (*Z*)-trichlorosilyl enol ether **5** derived from propiophenone predominantly formed the *syn*-aldol adduct in high yield with 82% ee by employing (*R*)-**1** as a catalyst (entry 7),[10] while a low enantioselectivity was observed with catalyst (*R*)-**2** (entry 8). Although the enantioselectivity strongly depended upon the structure of catalyst, the stereochemical relationship of the enol ether to the product was consistent.



Next other aldehydes were examined in the reaction of (*Z*)-**5** with (*R*)-**1** as a catalyst. 4-Methoxybenzaldeyde predominantly gave the *syn*-adduct, though the enantioselectivity slightly decreased (entry 9). A low reactivity was observed with dihydrocinnamaldehyde (entry 11). This trend is similar to those observed in the allylation of aldehyde with allyltrichlorosilane catalyzed by **1** or **2**.[8]

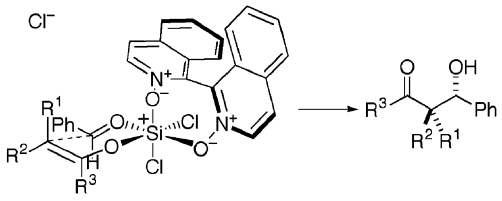
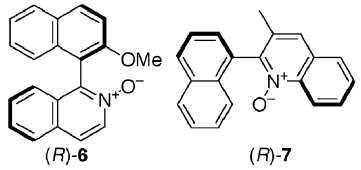


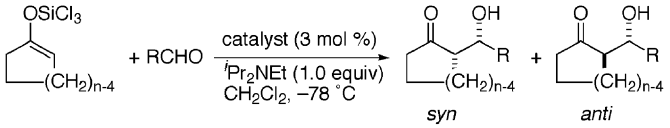
Figure 1. Transition state model for the *N*,*N*′-dioxide-catalyzed aldol reaction.

On the other hand, aldol reactions of the trichlorosilyl enol ethers derived from cyclic ketones were rather intriguing. The reaction of benzaldehyde with (*E*)-enol ether derived from cyclohexanone was investigated using *N*,*N*′-oxide as a catalyst. As expected, (*R*)-**1** predominantly gave the *anti*-adduct, but the enantioselectivity was unsatisfactory (Table 2, entry 1). (*R*)-**2** also resulted in a low enantioselectivity and the diastereoselectivity decreased, but the *anti*-selectivity was maintained (entry 2). Since Denmark reported high enantioselectivities with monodentate chiral phosphoramides, the aldol reaction with chiral monodentate *N*-oxides was investigated. Surprisingly, monodentate *N*-oxide (*R*)-**6**[7e,11] and (*R*)-**7**[12] gave *syn*-adducts with high diastereoselectivity (entries 3 and 4). *syn*-Selectivity was also observed in the reaction of five-membered and seven-membered ring enol ethers (entries 5 and 6) and the best result was obtained in the reaction of 4-trifluoromethylbenzaldehyde with the trichlorosilyl enol ether derived from cyclopentanone using (*R*)-**7** as a catalyst (entry 8). Again a low reactivity was observed with dihydrocinnamaldehyde (entry 10).



This intriguing switch of diastereoselectivity might be explained by the mechanism proposed by Denmark. Denmark observed that a sterically small phosphor-

Table 2. Enantioselective aldol reactions of cyclic trichlorosilyl enol ethers with aldehydes catalyzed by chiral *N*,*N*′-dioxides and monodentate *N*-oxides



Entry	Enol ether, *n*	Aldehyde, R	Catalyst	Time (h)	Yield[a] (%)	*syn*/*anti*[b]	% Ee (*syn*, *anti*)[c]
1	6	Ph	(*R*)-**1**	0.5	80	1:10	39, 30
2	6	Ph	(*R*)-**2**	2	94	1:3	21, 30
3	6	Ph	(*R*)-**6**	3	92	8:1	<5, 30
4	6	Ph	(*R*)-**7**	0.5	92	25:1	47, 60
5	7	Ph	(*R*)-**7**	0.5	93	30:1	50, 11
6	5	Ph	(*R*)-**7**	0.5	94	13:1	62, 66
7	5	4-$MeOC_6H_4$	(*R*)-**7**	0.5	90	14:1	63, 55
8	5	4-$CF_3C_6H_4$	(*R*)-**7**	1	98	14:1	72, 69
9	5	PhCH=CH	(*R*)-**7**	3	93	4:1	28, 42
10	5	$PhCH_2CH_2$	(*R*)-**7**	5	22	1:1	50, 40

[a] Isolated combined yield.
[b] Determined by ^1H NMR.
[c] Determined by HPLC (Daicel Chiralcel OB-H, OD-H or OJ-H).

amide predominantly produced the *anti*-adduct in the reaction of benzaldehyde with the trichlorosilyl enol ether derived from cyclohexanone catalyzed by chiral monodentate phosphoramides, while a bulky phosphoramide predominantly gave the *syn*-adduct.[6b] This phenomenon was explained by the different structures of the six-membered transition state. With a small phosphoramide, two catalyst molecules coordinate to the silicon atom to form an octahedral chair-like transition state **A**, which leads to the *anti*-adduct. With a bulky phosphoramide, a single catalyst coordinates to the silicon atom to form a trigonal bipyramid boat-like transition state **B**, which leads to the *syn*-adduct (Fig. 2).[13] Our result might be explained according to his model. Two oxygen atoms of an *N*,*N*′-dioxide molecule chelate to the silicon atom forming a cationic octahedral intermediate **A**, which affords the *anti*-adduct, while one oxygen atom of a monodentate *N*-oxide molecule coordinates to the silicon atom forming a cationic trigonal bipyramid intermediate **B**, which affords the *syn*-adduct.[14]

In conclusion, we employed chiral *N*-oxides as catalysts for enantioselective aldol reactions of trichlorosilyl enol ethers with aldehydes. In the reaction of acyclic enol ethers, *N*,*N*′-dioxides gave *anti*-adducts from (*E*)-enol ethers and *syn*-adducts from (*Z*)-enol ethers. In the reaction of cyclic (*E*)-enol ethers, *N*,*N*′-dioxides gave *anti*-adducts, whereas monodentate *N*-oxides predominantly gave the *syn*-adducts. Studies on the mechanism and the design of chiral *N*-oxides to improve diastereo- and enantioselectivity are currently in progress.

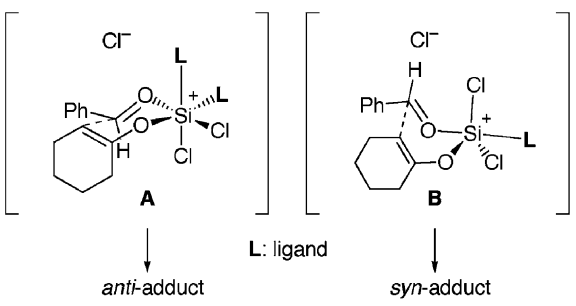


Figure 2. Transition state models for the base-catalyzed aldol reaction.

Acknowledgements

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9. Recently, Denmark has reported the aldol reaction of trichlorosilyl ketene acetal with ketone catalyzed by **1** or **2**, see Ref. 6e.
10. Representative procedure: A solution of (*Z*)-**5** (110 mg, 0.42 mmol, 1.2 equiv) in CH_2Cl_2 (0.5 mL) was added to a solution of benzaldehyde (40 mg, 0.38 mmol), diisopropylethylamine (50 mg, 0.38 mmol), and (*R*)-**1** (3.6 mg, 0.011 mmol, 3 mol %) in CH_2Cl_2 (3.5 mL) at −78 °C under an Ar atmosphere. After the reaction was completed, it was quenched with KF/KH_2PO_4 aq (2 mL). The organic phase was separated and the aqueous phase was extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (SiO_2, hexane/AcOEt = 10/1) to give the corresponding aldol adduct as a diastereomeric mixture.
11. Malkov, A. V.; Dufková, L.; Farrugia, L.; Kocovsky, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3674–3677.
12. Monodentate *N*-oxide **7** was prepared by the condensation of 1-naphthyl ethyl ketone and 2-aminobenzaldehyde followed by oxidation with *m*-CPBA. Optical resolution through hydrogen complex with (*R*)-BINOL afforded optically pure (*R*)-**7** (mp 181.5–182 °C, $[\alpha]_D^{21}$ +466° (*c* 0.9, $CHCl_3$). Absolute configuration of **7** was determined by X-ray crystallography of the hydrogen bond complex of (*R*)-BINOL and (*R*)-**7**. Crystal data for (*R*)-**7**–(*R*)-BINOL: colorless prism, monoclinic, space group $P2_1$, $a = 8.31(5)$ Å, $b = 20.71(6)$ Å, $c = 8.90(5)$ Å, $\beta = 90.8(5)°$, $V = 1530(13)$ Å^3, $D_{calc} = 1.24\,g\,cm^{-3}$, $\mu(MoK\alpha) = 0.78\,cm^{-1}$, $R = 0.077$, $R_w = 0.086$.
13. A calculation study revealed that the cationic trigonal bipyramid structure prefers the boat form Gung, B. W.; Zhu, Z.; Fouch, R. A. *J. Org. Chem.* **1995**, *60*, 2860–2864.
14. The aldol reaction of (*E*)- or (*Z*)-**4** and benzaldehyde did not proceed with the aid of (*R*)-**7**. The reaction of (*Z*)-**5** and benzaldehyde proceeded (−78 °C, 7 h, 85%) in the presence of (*R*)-**7** to predominantly afford the *syn*-adduct (*syn*/*anti* = 24:1) with low enantioselectivity. For steric reasons, a chair-like six-membered structure might be preferred even in a cationic trigonal bipyramid transition state, although the details are unclear at this time.