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Enantioselective construction of quaternary asymmetric carbon centers using an aldol reaction of trimethoxysilyl enol ethers catalyzed by lithium binaphtholate

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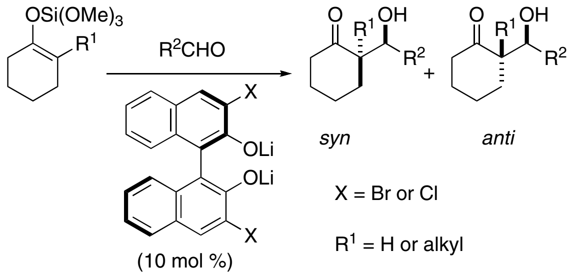
ABSTRACT

An aldol reaction of 2,2-disubstituted trimethoxysilyl enol ethers with aldehydes catalyzed by a dilithium salt of (*R*)-3,3′-dichlorobinaphthol afforded the corresponding aldol adducts with quaternary carbon centers in high *anti*-selectivities (*syn*:*anti* = ~1:50) and enantioselectivities (~90% ee).

The development of catalytic enantioselective methods to construct quaternary asymmetric carbon centers represents a continuing challenge in organic chemistry.[1,2] Although the aldol reaction is one of the most important methods for forming carbon–carbon bonds,[3] there are only few examples of asymmetric aldol reactions creating quaternary stereogenic centers.[4] Although high enantioselectivities have been obtained in some cases, the observed *syn*:*anti* selectivities remain unsatisfactory because sterically congested aldol adducts with a hydroxy group on the β-position of the carbonyl function easily undergoes a retro-aldol reaction to reduce the chemical yields and the stereoselectivities of the product.

The development of asymmetric aldol reactions has been led by Lewis acid-catalyzed reactions of trimethylsilyl enol ethers with carbonyl compounds. Recently Lewis base-catalyzed reactions of trichlorosilyl enol ethers[5,6] have attracted considerable attention because the aldol reaction of the trichlorosilyl enol ether gives the *syn*-adduct from the *Z*-enol ether and the *anti*-adduct from the *E*-enol ether due to their cyclic transition state structures involving hypervalent silicates.[7]

In our pursuit to develop base-catalyzed asymmetric reactions involving hypervalent silicates,[8] we had previously reported an asymmetric aldol reaction of trimethoxysilyl enol ethers (Scheme 1, R^1 = H),[9] which are more stable than trichlorosilyl enol ether. The reaction conditions of the trimethoxysilyl enol ether are sufficiently mild that the retro-aldol reaction, which is the main problem in constructing quaternary stereogenic centers, should be inhibited. Herein we report the construction of quaternary stereogenic centers using the asymmetric aldol reaction of trimethoxysilyl enol ethers (Scheme 1, R^1 = alkyl).[10]



Scheme 1. Aldol reaction of trimethoxysilyl enol ether.

Trimethoxysilyl enol ether[11,12] can be prepared by reacting lithium enolate and trimethoxysilyl chloride, or by reacting enone and trimethoxysilane with a Rh catalyst, but the limitation of the substrate has not been resolved. Thus, to prepare the 2,2-disubstituted trimethoxysilyl enol ethers to construct quaternary carbon centers, we have developed a more practical and convenient method. Instead of trimethoxysilyl chloride, we employed trimethoxysilyl triflate,[13] which was easily prepared in situ by reacting allyltrimethoxysilane and triflic acid. The resulting trimethoxysilyl triflate was reacted with 2-methylcyclohexanone at 0 °C in the presence of triethylamine to smoothly afford the corresponding trimethoxysilyl enol ether in a high yield as a mixture of regioisomers. Fortunately, we have found that refluxing the mixture of regioisomers in chloroform in the presence of tetra-*n*-butylammonium iodide afforded the desired 2,2-disubstituted trimethoxysilyl enol ether (Scheme 2).[14] This method provided facile access to suitable substrates for constructing quaternary asymmetric carbon centers by the aldol reaction.

With the desired substrate in hand, we tested the aldol reaction of the trimethoxysilyl enol ether **2** derived from 2-methylcyclohexanone with benzaldehyde in the presence of dilithium

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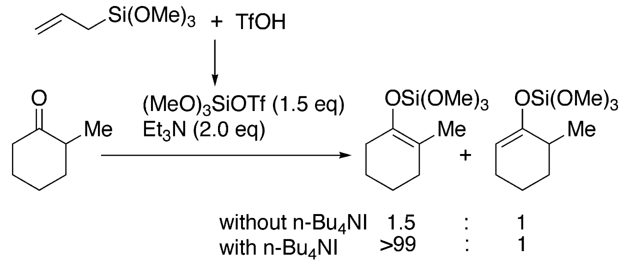


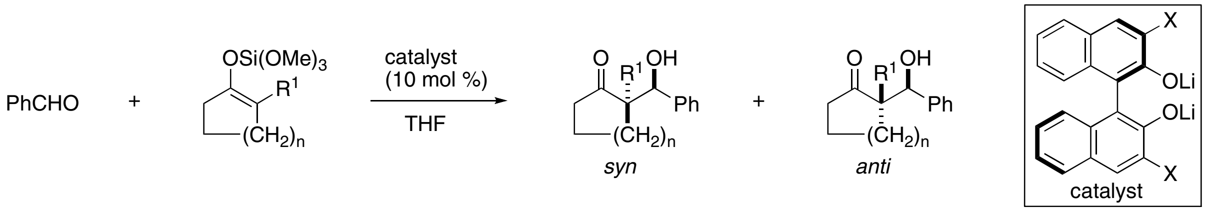
Scheme 2. Preparation of 2,2-disubstituted trimethoxysilyl enol ether.

3,3-bromobinaphtholate (10 mol %), according to the procedure for the aldol reaction of the silyl enol ether **1** derived from cyclohexanone (Table 1, entry 1).[9] The reaction proceeded smoothly, but the chemical yield and stereoselectivities of the product were not reproducible in multiple experiments, because the retro-aldol reaction proceeded under both the quenching condition (HCl aq or KF-buffer) and silica gel column chromatography, wherein a non-catalytic process gave a mixture of isomers. After considerable screening of the quenching conditions, we found that an aqueous solution of potassium fluoride/formic acid minimized the retro-aldol reaction. The crude product before isolation was benzoylated, which suppressed isomerization by the retro-aldol reaction in silica gel column.

Using these work-up conditions and derivatization, we found that the stereoselectivities (*syn*:*anti* = 1:27, 84% ee for *anti* isomer; Table 1, entry 2) of the reaction were dramatically increased (entry 1 vs entry 2).[15] Switching the substituents on the ligand and decreasing the temperature gave better results, but the reaction time was slightly elongated (entry 3). The stereoselectivities were affected by the structure of the enol ether. The high reactivity remained in the reaction of ethyl substituted substrate **3**, although the observed stereoselectivities decreased slightly (entry 4). Surprisingly, reducing the ring number of enol ether from six to five (**4**) gave a lower *anti*-selectivity, but the chemical yield and enantioselectivity were the same as six-membered substrate **2** (entry 5).

Table 2 summarizes the results obtained with other aldehydes and silyl enol ether **2**. Introducing an electron-donating or electron-deficient substituent on the benzene ring diminished the stereoselectivities (entries 2 and 3), but the reaction of 2-naphthaldehyde (entry 4) gave a result similar to that of benzaldehyde. The best result (98% yield, *syn*:*anti* = 1:20, 90% ee (*anti*)) was

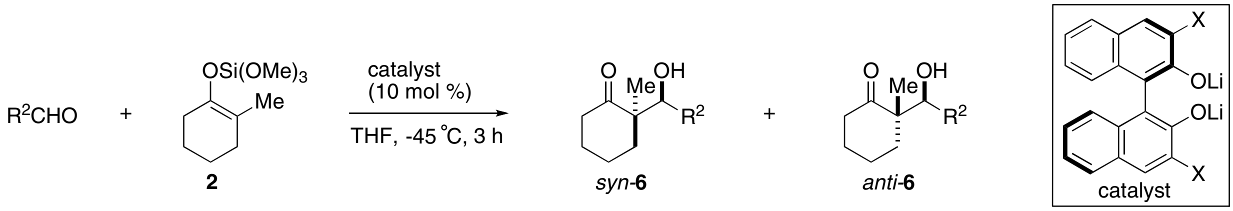
Table 1
Aldol reaction of trimethoxysilyl enol ethers with benzaldehyde



Entry	Enol ether	R^1	*n*	X	Conditions	Adduct	Yield[a] (%)	*syn*:*anti*[b]	ee (%) (*anti*)[c]
1[d]	**1**	H	2	Br	−23 °C, 0.5 h	**5**	97	1:3.7	51
2	**2**	Me	2	Br	−23 °C, 0.5 h	**6a**	97	1:27	84
3	**2**	Me	2	Cl	−45 °C, 3 h	**6a**	94	1:49	87
4	**3**	Et	2	Cl	−45 °C, 3 h	**7**	98	1:10	79
5	**4**	Me	1	Cl	−45 °C, 3 h	**8**	98	1:1.8	83

[a] Isolated as benzoates.
[b] Determined by NMR.
[c] Determined by chiral HPLC.
[d] Previously reported in lit. 9.

Table 2
Aldol reaction of aldehydes



Entry	R^2	X	Adduct	Yield[a] (%)	*syn*:*anti*[b]	ee (%) (*anti*)[c]
1	Ph	Cl	**6a**	94	1:49	87
2	4-$MeOC_6H_4$	Cl	**6b**	98	1:14	81
3	4-$CF_3C_6H_4$	Cl	**6c**	62	1:10	52
4	2-Naphthyl	Cl	**6d**	97	1:50	87
5	(*E*)-PhCH=CH	Cl	**6e**	98	1:20	90
6[d]	$PhCH_2CH_2$	Br	**6f**	75	1:5.3	85

[a] Isolated as benzoates.
[b] Determined by NMR.
[c] Determined by chiral HPLC.
[d] −23 °C, 3 h.

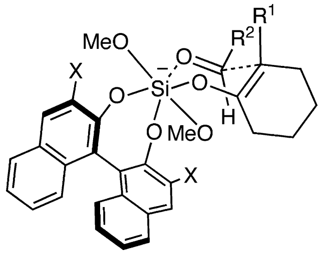


Figure 1. Plausible transition state.

obtained in the reaction of **2** with cinnamaldehyde (entry 5).[16,17] The obtained *syn*:*anti* ratios were far better than the ratios previously reported for the construction of quaternary carbon centers in enantioselective aldol reactions.[18] The reaction of aliphatic aldehyde (entry 6), which often lacks reactivity and selectivity in a Lewis base-catalyzed aldol reaction, maintained a high enantioselectivity using 3,3′-dibromobinaphthol as a catalyst precursor, though the *syn*:*anti* selectivity was unsatisfactory.[19]

In every case, the *anti*-adduct was predominantly formed from *E*-enol ether without exception, which suggests that these reaction proceed via a chair-like six-membered transition state shown in Figure 1, though the details are unclear.

In conclusion, we have developed a novel method to construct quaternary carbon centers employing the aldol reaction of trimethoxysilyl enol ethers, and successfully controlled two successive stereogenic centers. The observed *anti*-selectivity is the highest reported to date for constructing quaternary carbon centers by an enantioselective aldol reaction. These results demonstrate the synthetic utility of trimethoxysilyl enol ethers as aldol donors. Further studies to enhance the enantioselectivity and to explore the mechanism are currently in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.004.

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10. Although *syn* or *anti* may be not truly accurate terms to indicate the stereochemistry of the successive stereogenic centers, including the quaternary carbon centers, herein we use these terms for convenience in order to discuss the relationship of the stereochemistries between enol ethers and aldol adducts.
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14. *A typical experimental procedure to prepare trimethoxysilyl enol ether:* Under an Ar atmosphere, triflic acid (6.75 g, 45 mmol, 1.5 equiv) was added to a solution of allyltrimethoxysilane (7.30 g, 45 mmol, 1.5 equiv) in $CHCl_3$ (15 mL) at 0 °C, and the mixture was stirred for 30 min at the same temperature. The resulting pale yellow solution was transferred by cannula to a mixture of 2-methylcyclohexanone (3.6 mL, 30 mmol), triethylamine (8.35 mL, 60 mmol, 2.0 equiv), and tetra-*n*-butylammonium iodide (11.1 g, 30 mmol, 1.0 equiv) in $CHCl_3$ (50 mL). The resulting mixture was heated to reflux for 3 h. After cooling to rt, the solvent was evaporated in vacuo. The residue was extracted with hexane (100 mL × 2) and dried on Na_2SO_4. Purification with distillation (77–78 °C/4 mmHg) yielded **2** (5.1 g, 73%) as a colorless oil.
15. Relative configurations of new compounds are assigned on the basis of the NMR pattern of the unbenzoylated product in the literature (e.g., Mahrwald, R.; Schetter, B. *Org. Lett.* **2006**, *8*, 281–284.). Absolute configurations of the aldol products are unknown.
16. *A typical experimental procedure for the aldol reaction of trimethoxysilyl enol ether:* Under an Ar atmosphere, *n*-BuLi (0.094 mmol, 20 mol %) in hexane (0.21 M, 0.45 mL) was added to a solution of (*R*)-3,3′-dichlorobinaphthol (16.8 mg, 0.047 mmol, 10 mol %) in THF at −45 °C, and the mixture was stirred for 5 min. Then a solution of cinnamaldehyde (62 mg, 0.47 mmol) in THF (0.47 mL) and silyl enol ether **2** (0.16 mL, 0.71 mmol, 1.5 equiv) were successively added to the above mixture. After 3 h, the reaction was quenched with KF/HCOOH aq (1.5 M KF, 3.0 M HCOOH, 2 mL) and the mixture was stirred for 2 h at rt. The aqueous layer was extracted with AcOEt and the combined organic layers were successively washed with satd $NaHCO_3$ (3 mL) and brine (3 mL). Drying over Na_2SO_4 and evaporating the solvent gave the crude product, which was dissolved in CH_2Cl_2 (2 mL). Benzoyl chloride (0.11 mL, 0.94 mmol, 2.0 equiv) and a solution of DMAP (287 mg, 2.35 mmol, 5.0 equiv) in CH_2Cl_2 (2 mL) were added to the mixture at 0 °C. After stirring for 1 h, 10% HCl aq (5 mL) was added to the mixture and the entire mixture was extracted with AcOEt (20 mL × 3). The organic layer was washed with brine and dried over Na_2SO_4. After evaporating the solvent, the residue was purified by silica gel column chromatography (SiO_4 9.0 g, CH_2Cl_2/hexane = 1/4 then 1/1) to afford the benzoylated product (**6e**, 183 mg, 98% yield, *syn*:*anti* = 1:20, 42% ee (*syn*), 90% ee (*anti*)) as an oil. The ee's were determined via chiral HPLC Daicel chiralpak AD-H, hexane/IPA = 19/1, 1.0 mL/min, tR: 15.4 min (*anti*-major), 17.2 min (*syn*-major), 21.1 min (*anti*-minor), 26.9 min (*syn*-minor).
17. A similar result (97% yield, *syn*:*anti* = 1:18, 89% ee (*anti*)) was obtained using dibromobinaphthol as a catalyst precursor.
18. To the best of our knowledge, the best *syn*:*anti* ratio for constructing quaternary carbon centers by an enantioselective aldol reaction reported to date is 1:6.[4f]
19. A less satisfactory result (64% yield, *syn*:*anti* = 1:2.4, 52% ee (*anti*)) was obtained using dichlorobinaphthol as a catalyst precursor.