Enantioselective Aldol Reaction of Trimethoxysilyl Enol Ethers with Aldehydes Catalyzed by *p*-Tol-BINAP·AgF Complex

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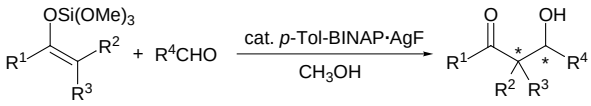
Abstract: New catalytic asymmetric Mukaiyama-type aldol reaction using trimethoxysilyl enol ethers was achieved using *p*-Tol-BINAP·AgF complex as a catalyst. High *syn*- and enantioselectivities were obtained both from the *E*- and *Z*-silyl enol ethers.

Key words: enantioselective aldol reaction, silyl enol ethers, aldehydes, BINAP·silver(I) complex, asymmetric catalysis

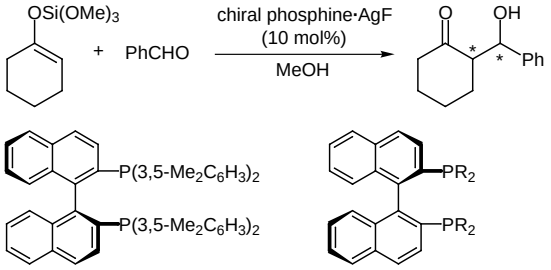
The Mukaiyama aldol reaction is a favorite method for the synthesis of β-hydroxy carbonyl compounds.[1] Although a variety of chiral Lewis acid catalysts have been developed for the asymmetric reaction of trialkylsilyl enol ethers or ketene trialkylsilyl acetals with carbonyl compounds,[1,2] most of those used are main-group metal (B, Zn, Sn, etc.) compounds or first row-transition metal (Ti, Cu, etc.) compounds, and the use of second or third row-transition metal compounds such as silver catalysts has received little attention.[3,4] In a previous paper,[5] we showed a new catalytic asymmetric Sakurai-Hosomi allylation reaction using the *p*-Tol-BINAP·AgF complex. We describe here a new example of catalytic asymmetric aldol condensation using trimethoxysilyl enol ethers and *p*-Tol-BINAP·AgF complex (eq 1).[6]



Equation 1

Using various BINAP derivatives, we studied the enantioselectivity of this process; yields, *syn/anti* ratios, and enantiomeric excesses of the products obtained by the reaction of cyclohexanone-derived trimethoxysilyl enol ether with benzaldehyde under the influence of 10 mol% of various BINAP derivative-AgF complexes in MeOH which are shown in Table 1. Among the BINAP derivatives examined, (*R*)-*p*-Tol-BINAP[7] was found to provide the most satisfactory result (entry 3). Use of (*R*)-*p*-*t*BuC_6H_4-BINAP[7] resulted in a higher yield with slightly better ee, although the *syn/anti* ratio decreased (entry 5).

Table 1 Asymmetric Aldol Reaction of Cyclohexanone-Derived Trimethoxysilyl Enol Ether with Benzaldehyde Catalyzed by Various BINAP·AgF Complexes[a]

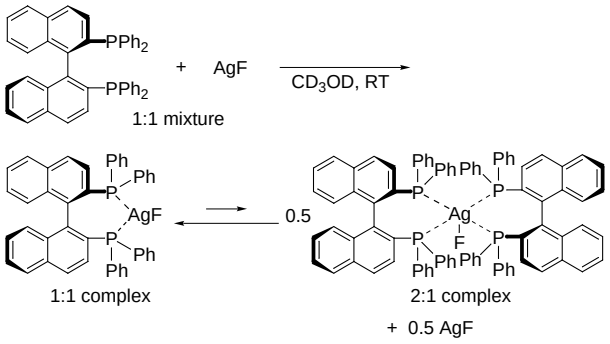


entry	chiral phosphine	conditions	yield,%[b]	*syn/anti*[c]	% ee[d]
1	(*R*)-BINAP	-78 °C, 4 h	64	71/29	71
2	(*S*)-3,5-Xylyl-BINAP	-78~-20 °C, 5 h	30	59/41	15
3	(*R*)-*p*-Tol-BINAP	-78 °C, 4 h	78	84/16	87
4	(*R*)-*p*-Tol-BINAP[e]	-78 °C, 4 h	36	82/18	89
5	(*R*)-*p*-*t*BuC_6H_4-BINAP	-78 °C, 4 h	87	70/30	90

[a] Unless otherwise noted, the reaction was carried out using chiral phosphine·AgF complex (10 mol%), cyclohexanone-derived trimethoxysilyl enol ether (1 equiv), and benzaldehyde (1 equiv) in MeOH. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] The value corresponds to the major diastereomer. Determined by HPLC analysis (Chiralcel OD-H, Daicel Chemical Industries, Ltd.). [e] 5 mol% of the catalyst was used.

The mechanism of the present catalytic reaction has not been fully elucidated; however, the BINAP·AgF complex is thought to behave as a chiral Lewis acid catalyst rather than a silver enolate based on the following NMR results. When trimethoxysilyl enol ether of cyclohexanone was treated with an equimolar mixture of (*R*)-BINAP·AgF complex and DMF in CD_3OD at room temperature, peaks of the silyl enol ether disappeared and a set of new peaks ascribable to the 1-cyclohexenyl group appeared, while peaks of $(MeO)_3SiF$ and cyclohexanone were not observed at all. These observations are a positive proof that none of the silver enolate was generated. Furthermore, we found that when an (*R*)-BINAP was added to an equimolar amount of AgF in CD_3OD at room temperature, a considerable amount of 2:1 complex [FAB- and

ESI-MS: m/z 1353 (M^+ - F)] was formed accompanied by a 1:1 complex (eq 2). The 2:1 complex was found to have no reactivity in the present aldol reaction. The formation of the undesired 2:1 complex, however, can be suppressed to some extent by introducing a bulky substituent at the *para*-position of the phenyl groups of BINAP. Indeed, (*R*)-*p*-Tol-BINAP and (*R*)-*p*-*t*BuC_6H_4-BINAP provided higher chemical yields than did (*R*)-BINAP (compare entries 1, 3, and 5 in Table 1).

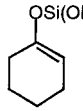
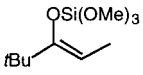


Equation 2

Table 2 summarizes the results obtained for the reaction of (*E*)- and (*Z*)-silyl enol ethers with various aldehydes under the influence of 10 mol% of (*R*)-*p*-Tol-BINAP·AgF in MeOH. All the reaction of cyclohexanone-derived (*E*)-trimethoxysilyl enol ether resulted in remarkable *syn*- and enantioselectivities with aromatic aldehydes (entries 1-6).[8] We found that a 0.6:1 mixture of (*R*)-*p*-Tol-BINAP and AgF gave the desired 1:1 complex without formation of the unreactive 2:1 complex, and thus, when the amount of (*R*)-*p*-Tol-BINAP was reduced to 3 mol%, the aldol product was still formed in high yield without any loss of optical purity even at −40 °C (entries 2 and 3). However, use of less than 2 mol% of the catalyst resulted in a lower yield and ee (entry 4). In contrast, *tert*-butyl ethyl ketone-derived (*Z*)-silyl enol ether gave the *syn* product almost exclusively with high enantioselectivity up to 97% ee in combination not only with aromatic aldehydes but also with α,β-unsaturated aldehyde (entries 7-11). In the reaction with cinnamaldehyde, only a 1,2-adduct was observed (entry 11).

From the aforementioned NMR results and the facts that AgF obviously activated trimethoxysilyl enol ethers[9] and

Table 2 Diastereo- and Enantioselective Aldol Reaction of Trimethoxysilyl Enol Ethers with Aldehydes Catalyzed by (*R*)-*p*-Tol-BINAP·AgF Complex[a]

entry	silyl enol ether	aldehyde	yield,%[b]	*syn/anti*[c]	% ee[d]
1		PhCHO	78	84/16	87
2[e]		PhCHO	73	76/24	87
3[e,f]		PhCHO	83	75/25	88
4[f,g]		PhCHO	53	74/26	85
5		4-MeOC_6H_4CHO	86	75/25	92
6		4-BrC_6H_4CHO	87	76/24	90
7[h]		PhCHO	84	>99/1	97
8[h]		4-MeOC_6H_4CHO	76	>99/1	96
9[h]		4-BrC_6H_4CHO	64	>99/1	87
10[h]		1-naphthyl-CHO	63	94/6	95
11[h]		(*E*)-PhCH=CHCHO	56	>99/1	85[i]

[a] Unless otherwise specified, the reaction was carried out using (*R*)-*p*-Tol-BINAP·AgF (10 mol%), trimethoxylsilyl enol ether (1 equiv), and aldehyde (1 equiv) in MeOH at -78 °C for 4 h. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] The value corresponds to the major diastereomer. Determined by HPLC analysis (Chiralcel OB-H or OD-H, Daicel Chemical Industries, Ltd.). [e] The reaction was performed using 3 mol% of (*R*)-*p*-Tol-BINAP and 5 mol% of AgF. [f] The reaction was performed at -78 °C for 4 h, then at -40 °C for 4 h. [g] The reaction was performed using 1.2 mol% of (*R*)-*p*-Tol-BINAP and 2 mol% of AgF. [h] The reaction was performed at -78 °C for 2 h, then at -40 °C for 2 h, and finally at -20 °C for 2 h. [i] Determined by ^{1}H NMR analysis of the MTPA ester of the product.

that trimethoxysilyl enol ethers reacted with aldehydes, *syn*-selectively irrespective of the *E/Z* stereochemistry in the presence of BINAP·AgF catalyst, the cyclic transition-state structures **A** and **B** shown in Figure can be postulated as models for the aldol reaction. In these models, the BINAP·AgF complex coordinates as a chiral Lewis acid to both an aldehyde and a silyl enol ether to form a six-membered cyclic structure, which is further stabilized by the adjacent four-membered ring formed by AgF and trimethoxysiloxy group.[10] Thus, from the *E*-enol ether, the *syn*-aldol adduct can be selectively obtained via a boat-like transition-state structure **A**, whereas model **B** pos-

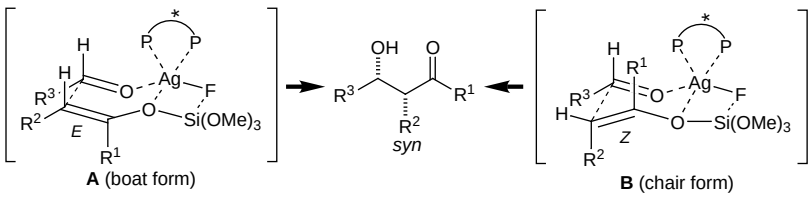


Figure 1 Probable Cyclic Transition-state Structures

sessing a chair conformation connects the *Z*-enol ether to the *syn* product. These models are different from those proposed for asymmetric allylation by allylic trimethoxysilanes[5] which are anticipated to proceed via six-membered cyclic transition-state structures including a BINAP-coordinated allylic silver. The difference in structure is probably due to whether or not the transmetallation to allylic silvers or silver enolates occurs prior to condensation with aldehydes.

In summary, we have demonstrated a novel example of asymmetric Mukaiyama aldol reaction with trimethoxysilyl enol ethers catalyzed by the *p*-Tol-BINAP·AgF complex. We previously showed that BINAP·AgOTf complex is a good catalyst for the asymmetric aldol reaction of trialkyltin enolates,[11] however, the reaction has the disadvantage of requiring the use of toxic trialkyltin compounds, and silyl enol ethers do not react with aldehydes in the presence of this chiral silver(I) catalyst. Main features of our new process are: (1) the procedure can be performed without any difficulty employing readily available chemicals and can provide various optically active β-hydroxy ketones with high enantioselectivity up to 97% ee; (2) remarkable *syn* selectivity is observed for the reaction independent of the *E/Z* stereochemistry of the silyl enol ethers; (3) this process is less damaging to the environment since less toxic trimethoxysilyl enol ether and MeOH are used as a reagent and solvent, respectively. Further work is now in progress on the catalytic aldol reaction and the detailed reaction mechanism.

A representative experimental procedure is given by the reaction of trimethoxysilyl enol ether of cyclohexanone with benzaldehyde catalyzed by (*R*)-*p*-Tol-BINAP·AgF complex (entry 3 in Table 1 and entry 1 in Table 2). A mixture of AgF (13.0 mg, 0.102 mmol) and (*R*)-*p*-Tol-BINAP (67.9 mg, 0.100 mmol) was dissolved in dry MeOH (6 mL) under argon atmosphere and with direct light excluded, and stirred at 20 °C for 10 min. To the resulting solution were added dropwise benzaldehyde (100 μL, 0.98 mmol) and (1-cyclohexenyloxy)trimethoxysilane (220.4 mg, 1.01 mmol)[12] successively at −78 °C. After being stirred for 4 h at this temperature, the mixture was treated with brine (2 mL) and solid KF (ca. 1 g) at ambient temperature for 30 min. The resulting precipitate was filtered off by a glass filter funnel filled with Celite® and silica gel. The filtrate was dried over Na_2SO_4 and concentrated in vacuo after filtration. The residual crude product was purified by column chromatography on silica gel (1:5 ethyl acetate/hexane as the eluant) to afford a mixture of aldol adducts (156.5 mg, 78% yield) as white solids. The *syn/anti* ratio was determined to be 84/16 by ^{1}H NMR analysis. The enantioselectivities of the *syn* and *anti* isomers were determined to be 87% ee and 48% ee, respectively, by HPLC analysis using a chiral column (Chiralcel OD-H, Daicel Chemical Industries, Ltd., hexane/*i*-PrOH = 9/1, flow rate = 0.5 mL/min): $t_{syn\text{-}minor}$ = 13.4 min, $t_{syn\text{-}major}$ = 14.5 min, $t_{anti\text{-}major}$ = 16.1 min (2*S*,1'*R*), $t_{anti\text{-}minor}$ = 22.2 min (2*R*,1'*S*). The absolute configurations of the *syn* isomers are not known. Spectral data of the *syn* isomer (87% ee): $[\alpha]^{25}_D$ = +109.5 (*c* = 1.0, $CHCl_3$); elemental analysis calcd for $C_{13}H_{16}O_2$: C 76.44, H 7.90; found: C 76.10, H 8.23. Other physical and spectral data (TLC, IR, ^{1}H NMR, and ^{13}C NMR) were identical with those in the literature.[11b,14]

Acknowledgement

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References and Notes

(1) Review: Gennari, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 2, p 629.

(2) Reviews for catalytic asymmetric aldol reactions using silyl enol ethers or ketene silyl acetals: (a) Bach, T. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 417. (b) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570. (c) Braun, M. In *Houben-Weyl: Methods of Organic Chemistry*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; Vol. E 21, p 1730. (d) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357. (e) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137. (f) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. (g) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917. (h) Machajewski, T. D.; Wong, C.-H. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 1353.

(3) Chiral rhodium catalysts: (a) Reetz, M. T.; Vougioukas, A. E. *Tetrahedron Lett.* **1987**, *28*, 793. Chiral palladium catalysts: (b) Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 2648. (c) Sodeoka, M.; Tokunoh, R.; Miyazaki, F.; Hagiwara, E.; Shibasaki, M. *Synlett* **1997**, 463. (d) Sodeoka, M.; Shibasaki, M. *Pure Appl. Chem.* **1998**, *70*, 414. (e) Fujii, A.; Sodeoka, M. *Tetrahedron Lett.* **1999**, *40*, 8011. See also: (f) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474. (g) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450. Chiral platinum catalysts: (h) Fujimura, O. *J. Am. Chem. Soc.* **1998**, *120*, 10032.

(4) Recent examples of direct catalytic asymmetric aldol reactions of aldehydes with unmodified ketones are also noteworthy: (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1871. (b) Yamada, Y. M. A.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 5561. (c) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168. (d) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (e) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386.

(5) Yanagisawa, A.; Kageyama, H.; Nakatsuka, Y.; Asakawa, K.; Matsumoto, Y.; Yamamoto, H. *Angew. Chem. Int. Ed.* **1999**, *38*, 3701.

(6) Yamagishi and co-workers independently examined the BINAP·silver(I)-catalyzed asymmetric Mukaiyama aldol reaction using trimethylsilyl enol ethers and found that the reaction was accelerated by BINAP·$AgPF_6$ in DMF containing a small amount of water to give the aldol product with high enantioselectivity: Ohkouchi, M.; Yamaguchi, M.; Yamagishi, T. *Enantiomer* **2000**, *5*, 71.

(7) Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629. (*R*)- and (*S*)-*p*-Tol-BINAP are commercially available (AZmax).

(8) Aliphatic aldehydes were inactive under the standard reaction conditions. For example, the reaction with hydrocinnamaldehyde gave the aldol product in less than 1% yield at -78 °C for 4 h.
(9) The aldol product was obtained only in 3% yield when the reaction of (1-cyclohexenyloxy)trimethoxysilane with benzaldehyde was carried out in the presence of 10 mol% of (*R*)-BINAP·AgOTf in THF at -78 °C ~ r.t. for 12 h.
(10) Bottoni, Tagliavini, and coworkers have suggested similar eight-membered cyclic transition-state models for BF_3-promoted addition of allylsilanes to aldehydes: Bottoni, A.; Costa, A. L.; Tommaso, D. D.; Rossi, I.; Tagliavini, E. *J. Am. Chem. Soc.* **1997**, *119*, 12131.
(11) (a) Yanagisawa, A.; Matsumoto, Y.; Nakashima, H.; Asakawa, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 9319. (b) Yanagisawa, A.; Matsumoto, Y.; Asakawa, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 892.
(12) The trimethoxysilyl enol ether of cyclohexanone was prepared by 1,4-hydrosilylation of 2-cyclohexen-1-one with $(MeO)_3SiH$ catalyzed by $(Ph_3P)_3RhCl$ or $(Ph_3P)_4RhH$.[13] *Tert*-butyl ethyl ketone-derived trimethoxysilyl enol ether was prepared by treating the ketone with LDA in ether followed by silylation with $(MeO)_3SiCl$.
(13) (a) Ojima, I.; Kogure, T. *Organometallics* **1982**, *1*, 1390. (b) Zheng, G. Z.; Chan, T. H. *Organometallics* **1995**, *14*, 70.
(14) (a) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271. (b) Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K.-T. *J. Am. Chem. Soc.* **1996**, *118*, 7404. (c) Denmark, S. E.; Wong, K.-T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333.

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