Aldol Synthesis with an Aqueous Solution of Formalin

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Abstract: With an aqueous solution of formalin, aldol reaction of trimethylsilyl enol ether proceeds moderately using tetrabutyl-ammonium fluoride (TBAF). Furthermore, catalytic asymmetric hydroxymethylation with trimethoxysilyl enol ether using water tolerant (*R*)-BINAP–AgOTf as Lewis acid and KF as Lewis base has been achieved in aqueous media.

Key words: aldol reaction, silyl enol ether, enantioselective, BINAP–AgOTf catalyst, formalin aqueous solution

Although formaldehyde is a useful component for organic synthesis, there are some limitations in developing a general methodology for using formaldehyde for aldol synthesis. In fact, generation of formaldehyde monomer is still quite tedious, and formalin (aq soln), which is readily available and consists of formaldehyde oligomers, cannot be used for aldol synthesis with usual Lewis acid catalysts due to their instability in the presence of water. Therefore, only a few aldol reactions have been reported using formalin (aq soln) with silyl enol ethers catalyzed by Lewis acid or Lewis base.¹ Since our previous observations show that fluoride ion can activate silyl enol ether effectively even in protic solvent,² we attempted to apply this methodology to the aldol synthesis using formaldehyde (aq soln).



Equation 1

Various fluoride sources were tested in the reaction between trimethylsilyl enol ether of cyclohexanone **1** (Equation 1) and formalin (aq soln).³ Among them, tetrabutylammonium fluoride (TBAF) smoothly gave the

SYNLETT 2003, No. 14, pp 2219–2221 Advanced online publication: 15.10.2003 DOI: 10.1055/s-2003-42089; Art ID: U08403ST.pdf © Georg Thieme Verlag Stuttgart · New York hydroxymethyl ketone with high yield. Other fluoride sources such as tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TAS-F) or KF did not give good activating effect because of the low solubility in THF. The usefulness of the new process is apparent from Table 1, which summarizes aldol reaction with various silyl enol ethers in the presence of TBAF. Most of the reactions proceeded smoothly at -20 °C in THF.

Previously, we developed the stereoselective Sakurai– Hosomi allylation and Mukaiyama aldol synthesis of allylsilane and silyl enol ether, respectively, to aldehydes catalyzed by (R)-BINAP, AgOTf, KF and 18-crown-6 in





^a Isolated yield.

^b Diastereomer ratio.

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THF.⁴ In this reaction (*R*)-BINAP·AgOTf complex with fluoride anion showed both Lewis acid and Lewis base activities. Furthermore silver salts are one of the water-stable Lewis acids and have already been used in some reactions in aq or alcoholic media.⁵ Taken together with these properties and the results of the hydroxymethylation process, we tried to extend our bifunctional catalysis for hydroxymethylation reactions in the presence of water (Equation 2).⁶ It should be noted that because of small and symmetrical structure of formaldehyde, there are not many reports about the asymmetric hydroxymethylation of carbonyl compounds.



Equation 2

(R)-BINAP (6 mol%) · AgOTf (10 mol%) with TBAF were added for the reaction between trimethyl silyl enol ether of cyclohexanone **1** and formalin aq solution in THF, but no significant induction was observed (-20 °C, 1 h; 59% yield, 7% ee). This result indicated that the reaction proceeded without (R)-BINAP AgOTf complex. Using KF as a mild fluoride source, instead of TBAF, gave no desired product at -20 °C for 6 h. Trimethoxysilyl enol ether of cyclohexanone 2a can be expected to possess higher reactivity due to its lower HOMO energy level and easier formation of silicate with fluoride anion. Thus 2a gave 2hydromethylketone 3a in the presence of (*R*)-BINAP Ag-OTf and KF (-20 °C, 6 h; 46% yield, racemic). Addition of 18-crown-6 to improved the solubility of KF but had little success (-20 °C, 1 h; 41% yield, 6% ee). Finally, we found that the mixed solvent of water and THF gave the highest enantioselectivity in this reaction. The reaction of trimethoxysilyl enol ether of cyclohexanone 2a (0.5 mmol) and formalin (37% aq solution, 5 equiv) in the presence of KF (5 equiv) at -40 °C in THF (12 mL)-H₂O (2 mL) gave **3a** in 31% yield and 57% ee (Scheme 1).⁷ α -Tetralone also gave high enantioselectivity.^{8,9}

In conclusion, a fluoride source functioned as an activator for the aldol reaction using an aqueous solution of formalin and the bifunctional system (R)-BINAP·AgOTf complex with a fluoride source was useful for asymmetric synthesis. Although there is room for improving the yield and selectivity, this approach will play a crucial role in the development of asymmetric aldol synthesis using formaldehyde.

General Procedure: Formalin (aq soln) (37% aq, 187.4 μ L, 2.50 mmol) was dissolved in anhyd THF (6 mL) under Ar atmosphere with direct light excluded, and stirred at 20 °C for 10 min. To this solution were added trimethylsilyl enol ether (0.50 mmol) and TBAF (2.5 mL, 1.0 M in THF) successively at –20 °C. The mixture was stirred for 1 h at this temperature and then treated with brine (6 mL) and solid KF (ca. 1 g) at ambient temperature for 10 min. The resulting precipitate was filtered off by a glass filter funnel filled with Celite[®] and silica gel and the filterate was extracted with Et₂O. The organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure after filtration. The residual crude product was purified by column chromatography on silica gel (hexane–Et₂O, 3:1 as the eluent) to afford a mixture of the aldol adducts.

References

- (a) Kobayashi, S. Chem. Lett. 1991, 2187. (b) Kobayashi,
 S.; Hachiya, I.; Ishitani, H.; Araki, M. Synthesis 1993, 472.
 (c) Kobayashi, S.; Hachiya, I. J. Org. Chem. 1994, 59, 3590.
 (d) Loh, T.-P.; Pei, J.; Cao, G.-Q. Chem. Commun. 1996, 1819. (e) Kobayashi, S.; Wakabayashi, T.; Nagayama, S.; Oyamada, H. Tetrahedron Lett. 1997, 38, 4559. (f) Loh,
 T.-P.; Chua, G.-L.; Vittal, J. J.; Wong, M.-W. Chem. Commun. 1998, 861. (g) Kobayashi, S.; Manabe, K. Pure Appl. Chem. 2000, 72, 1373. (h) Miura, K.; Nakagawa, T.; Hosomi, A. J. Am. Chem. Soc. 2002, 124, 536.
- (2) (a) Yanagisawa, A.; Nakatsuka, Y.; Asakawa, K.; Kageyama, H.; Yamamoto, H. *Synlett* 2001, 69.
 (b) Yanagisawa, A.; Nakatsuka, Y.; Asakawa, K.; Wadamoto, M.; Kageyama, H.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* 2001, 1477.
- (3) (a) Fluoride mediated aldol synthesis using silyl enol ethers: Kuwajima, I.; Nakamura, E. *J. Am. Chem. Soc.* 1975, *97*, 3257. (b) See also: Noyori, R.; Nishida, I.; Sakata, J. *Tetrahedron Lett.* 1980, *21*, 2085. (c) Asymmetric reactions:Ando, A.; Miura, T.; Tatematsu, T.; Shioiri, T. *Tetrahedron Lett.* 1993, *34*, 1507. (d) See also: Ooi, T.;



Scheme 1 Asymmetric aldol reaction of trimethoxylsilyl enol ethers with formalin aq solution activated by bifunctional system.

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Kameda, M.; Maruoka, K. *Org. Lett.* **2001**, *3*, 1273. (e) See also:Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837.

- (4) Wadamoto, M.; Ozasa, N.; Yanagisawa, A.; Yamamoto, H. J. Org. Chem. 2003, 68, 5593.
- (5) (a) Loh, T.-P.; Zhou, J.-R. *Tetrahedron Lett.* 2000, *41*, 5261. (b) Ohkouchi, M.; Yamaguchi, M.; Yamagishi, T. *Enantiomer* 2000, *5*, 71. (c) Ohkouchi, M.; Masui, D.; Yamaguchi, M.; Yamagishi, T. *J. Mol. Catal. A: Chem.* 2001, *170*, 1.
- (6) To our knowledge, there is now only one report of cat. enantioselective hydroxymethylation using formaline aq solution, and this is the first report in which chiral Lewis acid is utilized for activation: (a) Fujii, M.; Sato, Y.; Aida, S. *Chem. Exp.* **1992**, *7*, 309. (b) Catalytic enantioselective ene reaction using formaldehyde is also reported: Mikami, K.; Yoshida, A. *Synlett* **1995**, 29.
- (7) Baliri, P. L.; Catelani, G.; Giori, R.; Mastrorilli, E. *Enantiomer* **1998**, *3*, 357.
- (8) Schoofs, A.; Guette, J. P.; Horeau, A. Bull. Soc. Chim. Fr. 1976, 7-8, 1215.
- (9) The reaction mixture is barely stirrable without being unfrozen.