Copper (II)-or Iron (III)-Catalyzed Aldol Reactions and Michael Additions Using Silyl Enol Ethers or Silyl Ketene Acetals

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Copper(II)- or Iron(III)-Catalyzed Aldol Reactions and Michael Additions
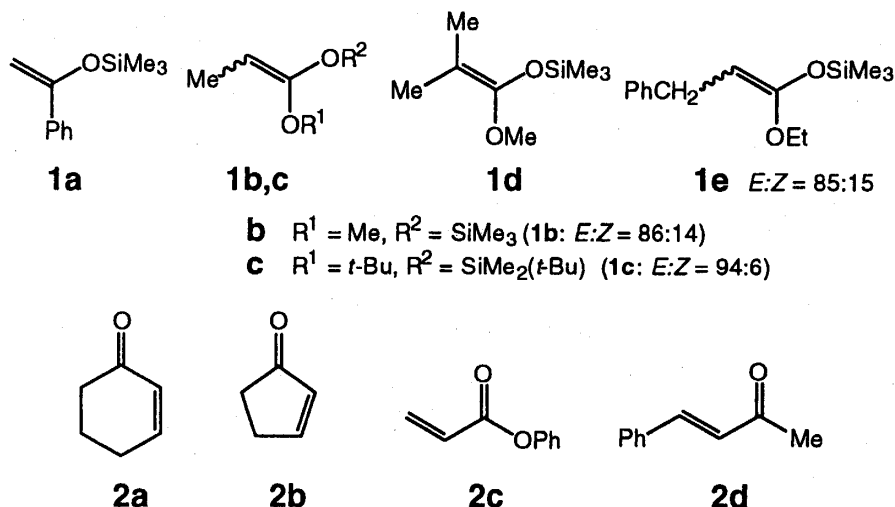# Using Silyl Enol Ethers or Silyl Ketene Acetals

Shuji Kanemasa, Sachiyo Yoshinaga*[1], Yoichiro Shibata*[2],

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Copper(II) trifluoromethanesulfonate and iron(III) chloride, by use of a catalytic
loading, accelerate both the aldol reactions and Michael additions using silyl enol ethers
and silyl ketene acetals. The reactions proceed at –78 °C, but *anti/syn*- and enantio-
selectivities are low.

Lewis acid-catalyzed aldol reactions and Michael additions of silyloxy alkenes provide one of the most useful methodologies for the carbon-carbon bond formation.[1,2] These reactions can be often accelerated by use of catalytic loadings of Lewis acid catalysts; the catalysts ever successfully employed include silyl cations,[3] trityl cations,[4] transition metal complexes,[5] lantanide complexes,[6] and others.[7] However, use of simple transition metal salts is rare for the activation of silyl enol ethers or ketene acetals.[8] In this communication we would like to add two simple transition metal salts, copper(II) trifluoromethane-sulfonate and iron(III) chloride, as effective catalysts for the aldol reactions and Michael additions of silyloxy alkenes.

Among a variety of transition metal salt catalysts examined in the aldol reactions of α-

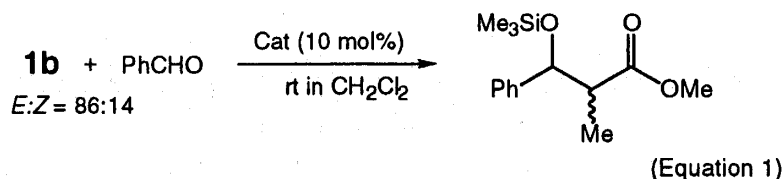$$\mathbf{1b} \quad R^1 = Me, R^2 = SiMe_3 \ (\mathbf{1b}: E:Z = 86:14)$$
$$\mathbf{1c} \quad R^1 = t\text{-Bu}, R^2 = SiMe_2(t\text{-Bu}) \ (\mathbf{1c}: E:Z = 94:6)$$

2a **2b** **2c** **2d**

Scheme 1

1b + PhCHO

$E:Z$ = 86:14

$\xrightarrow[\text{rt in CH}_2\text{Cl}_2]{\text{Cat (10 mol\%)}}$

(Equation 1)

Table 1 Aldol reactions of silyl ketene acetals 1 to PhCHO at –78 °C in CH$_2$Cl$_2$

Donor	Catalyst	Ratio[a]	Mol%[b]	Yield/%[c]	Isomer ratio[d] syn:anti
1b	Cu(OTf)$_2$/A	1/1	10	56	43:57
	Cu(OTf)$_2$/B	1/1	10	89	46:54
	FeCl$_3$/A	1/1	10	92	45:55
	FeCl$_3$/B	1/1	10	90	45:55
	FeCl$_2$/B+I$_2$[e]	1/1	10	91	42:58
	FeCl$_2$/B+I$_2$[e]	1/1	100	65	47:53
	FeCl$_2$/B+I$_2$[e,f]	1/3	10	45	26:74
1c	FeCl$_2$/B+I$_2$[e]	1/1	10	100	40:60

[a]Metal salt/ligand. [b]Molar percentage of the metal salt used. [c]Yields of isolated products. [d]Determined by ^{1}H NMR. [e]Iodine was used in half an equivalent of FeCl$_2$. [f]Solvent: EtCN.

(trimethylsilyloxy)styrene (**1a**) with benzaldehyde, Cu(OTf)$_2$ and FeCl$_3$ were especially effective.[9] In expectation of the improved solubility of the metal salt as well as the chirality control at the newly formed chiral centers in the product, the complexes of Cu(OTf)$_2$ and FeCl$_3$ with enantio-merically pure amine ligands such as (R,R)-N,N'-di(mesitylmethyl)-1,2-diphenylethanediamine (**A**), (S,S)-2,2'-bi(4-isopropyl-2-oxazoline) (**B**), and (R,R)-2,2'-methylenedi(4-phenyl-2-oxazoline) (**C**) were employed. The resulting complexes are highly soluble in dichloromethane so that they show higher catalytic activity than the salt without ligand. Thus, the reaction of 1-methoxy-1-(trimethyl-silyloxy)propene (**1b**, $E:Z$ = 86:14) with benz-aldehyde took place at –78 °C in the presence of 10 mol% amount of Cu(OTf)$_2$/A or Cu(OTf)$_2$/B to give the corresponding aldol product (Equation 1, 56, 89% in each case); FeCl$_3$/A and FeCl$_3$/B were more effective (92, 90% in each case, Table 1). However, the syn:anti- and enantioselectivities were both not satisfactory.[10,11]

Use of excess amounts of ligand **B** (B/FeCl$_3$ = 2 or 5) resulted in rather decreased chemical yields and no improvement of optical yields was recorded. Either when the iron(III) catalyst was in situ prepared by oxidation of FeCl$_2$ with iodine[12] or when t-butyloxy-1-(t-butyldimethylsilyloxy)pro-pene (**1c**) was used as a bulkier donor molecule, comparably low stereo- and enantioselectivities resulted. Use of propionitrile as reaction solvent led to a little higher anti selectivity and enantioselectivity.[13] As a result, these chiral ligands **A-C** have served only to improve the solubility of the metal salt catalysts. These metal salt complexes were also highly effective in the Michael addition reactions of **1b** with 2-cyclohexen-1-one (**2a**, Equation 2). Thus, at –78 °C, the reaction between **1b** and **2a** was promoted in the presence of 5 mol% of Cu(OTf)$_2$/A in dichloromethane to give a mixture of stereoisomers of Michael adduct (100%), while uncatalyzed reaction gave no adducts under various reaction conditions. The complex FeCl$_3$/A is also a reac-

1b + 2a $\xrightarrow[\text{rt in CH}_2\text{Cl}_2]{\text{Cat (10 mol\%)}}$

$E:Z = 86:14$

(Equation 2)
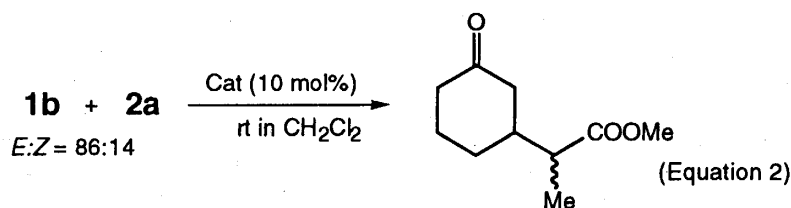
Table 2 Michael additions of silyl ketene acetals or silyl enol ethers 1 to α,β-unsaturated carbonyl compounds

Substrates	Catalyst	Ratio[a]	Mol%[b]	Yield/%[c]	Isomer ratio[d] syn:anti
1b + 2a	Cu(OTf)₂	–	5	21	
	Cu(OTf)₂/A	1/1	5	100	
	FeCl₃/A	1/1	5	100	
1d + 2a	Cu(OTf)₂/A	1/1	5	25	
1d + 2a	FeCl₃/A	1/1	5	56	
1e + 2b	Cu(OTf)₂/A	1/2	5	66	63:37
	Cu(OTf)₂/B	1/1	5	73	66:34
	Cu(OTf)₂/C	1/2	5	58	62:38
1b + 2c	Cu(OTf)₂/A	1/1	10	100	
	FeCl₃/A	1/1	10	0	
1a + 2d	Cu(OTf)₂/A[e]	1/1	10	100	
	Cu(OTf)₂/A	1/1	20	0	

[a]Metal salt/ligand. [b]Molar percentage of the metal salt used. [c]Yields of isolated products. [d]Determined by ^{1}H NMR. [e]In the presence of Me₃SiCl (1 equiv).

tive catalyst (100%, Table 2). 1-Methoxy-1-(tri-methylsilyl)isobutene (1d) having two substi-tuents at the reaction site showed some decreased reactivity in the reactions with 2a in the presence of 10 mol% of Cu(OTf)₂/A: 25%; FeCl₃/A: 56%.

Although silyl enol ether 1a did not react with (E)-4-phenyl-3-buten-2-one (2d) in the presence of Cu(OTf)₂/A (rt, 84 h), the addition of trimethylsilyl chloride (TMSCl, 1 equiv) accelerated the reaction (3 h, 100%).

A reaction mechanism including Lewis acid-mediated electron transfer has been recently reported for the Lewis acid-catalyzed Michael addition reactions of ketene silyl acetals, in which the donor molecules bearing more substituents at the reaction site show much higher reactivity than the less substituted donors.[4] However, the reversed substituent effect was recorded in the present reactions and the electron transfer-caused deactivation of the catalyst[5] was not observed. Addition of radical inhibitors such as 2,6-di-tert-butyl-4-methylphenol and 1,4-benzoquinone did not

inhibit the reaction. The low anti/syn selectivity observed here rules out the liner transition state in which the acceptor molecules are activated by the metal salt. Only in the reactions catalyzed by Cu(OTf)₂ or complexes, there may be a possibility remained that HOTf produced by hydrolysis of Cu(OTf)₂ has worked as a real catalyst. So far we can not propose a likely reaction mechanism. The work along this line is now in progress, and the details of results will be reported elsewhere.

References and Note

1. T. Mukaiyama, Organic Reactions, Ed. by W. G. Dauben, Vol. 28 (1982), John Wiley & Sons, Inc. New York, Chapt. 3, pp. 203-331.
2. P. Perlmutter, Conjugate Addition Reactions in Organic Synthesis, as Vol. 9 of Tetrahedron Organic Chemistry Series, Ed. by J. E. Baldwin and P. D. Magnus, Pergamon Press, Oxford 1992.
3. S. Murata, M. Suzuki, and R. Noyori, J. Am. Chem. Soc., 102 (1980), 3248; N. Iwasawa and T.

Mukaiyama, *Chem. Lett.,* **1987**, 463; E. M. Carreira and R. A. Singer, *Tetrahedron Lett.,* **3** 5(1994), 4323.

4. T. Mukaiyama, S. Kobayashi, and M. Murakami, *Chem. Lett.,* **1984**, 1759; T. Mukaiyama, S. Kobayashi, and M. Murakami, *ibid.,* **1985**, 447; S. Kobayashi, M. Murakami, and T. Mukaiyama, *ibid.,* **1985**, 1535; T. Mukaiyama, S. Kobayashi, M. Tamura, and W. Sagawa, *ibid.,* **1 9 8 7**, 491; S. E. Denmark and C. T. Chen, *Tetrahedron Lett.,* **3** 5(1995), 4327.

5. M. T. Reetz and A. E. Vougioukas, *Tetrahedron Lett.,* **28** (1987), 793; T. K. Hollis, N. P. Robinson, and B. Bosnich, *ibid.,* **33** (1992), 6423; Y. P. Hong, D. J. Norris, and S. Collins, *J. Org. Chem.,* **58** (1993), 3591; K. Mikami and S. Matsukawa, *J. Am. Chem. Soc.,* **115** (1993), 7039; G. E. Keck and D. Krishnamurthy, *J. Am. Chem. Soc.,* **117** (1995), 2363.

6. L. Gong and A. Streitwieser, *J. Org. Chem.,* **55** (1990), 6235; S. Kobayashi, *Chem. Lett.,* **1991**, 2087; K. Uotsu, H. Sasai, and M. Shibasaki, *Tetrahedron-Asymm.,* **6** (1995), 71.

7. E. J. Corey, C. L. Cywin, and T. D. Roper, *Tetrahedron Lett.,* **33** (1992), 6907; M. T. Reetz, B. Raguse, C. F. Marth, H. M. Hugel, T. Bach, and

D. N. A. Fox, *Tetrahedron,* **48** (1992), 5731; C. Leroux, H. Gaspardiloughmane, J. Dubac, J. Jaud, and P. Vignaux, *J. Org. Chem.,* **58** (1993), 1835.

8. T. K. Hollis and B. Bosnich, *J. Am. Chem. Soc.,* **117** (1995), 4570 and references cited therein.

9. The metal salts examined are $CrCl_3$ (10 mol%), $MnBr_2$ (100 mol%), $FeCl_3$ (10 mol%), $CoCl_2$ (10 mol%), $NiBr_2$ (100 mol%), $Cu(OTf)_2$ (5 mol%), $CuCl_2$ (10 mol%), $AgBF_4$ (100 mol%), $CoCl_2/AgBF_4$ (1/1, 10 mol%), and $NiBr_2/AgBF_4$ (1/1, 10 mol%).

10. Desilylation of the silylated aldol product by treatment with $CH_3COOH/THF/H_2O$ (8/8/1 v/v) at room temperature was followed by HPLC analysis using Daicel chiralcel OD with hexane/2-propanol (95:5 v/v).

11. Optical yileds did not exceed 10% ee in each case.

12. E. J. Corey, N. Imai, and H. Y. Zhang, *J. Am. Chem. Soc.,* **113** (1991), 728.

13. The *anti*-adduct: 11% ee. For the use of EtCN, see: E. R. Parmee, O. Tempkin, and S. Masamune, *J. Am. Chem. Soc.,* **113** (1991), 9365.

14. T. Sato, Y. Wakahara, Y. J. Otera, H. Nozaki, and S. Fukuzumi, *J. Am. Chem. Soc.,* **113** (1991), 4028.

15. W. Odenkirk, J. Whelan, and B. Bosnich, *Tetrahedron Lett.,* **33** (1992), 5729.