Remarkable Enhancement of Catalyst Activity of Trialkylsilyl Sulfonates on the Mukaiyama Aldol Reaction: A New Approach Using Bulky Organoaluminum Cocatalysts

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Silylium ion is currently one of the most challenging topics in the chemistry of carbenium ion analogues and has attracted widespread interest in related areas.[1,2] During the continual efforts to isolate the absolutely naked silylium cation from basic species containing a counteranion, solvent and π-electron donor,[3] the representative ionic silicon-based catalysts, Me_3SiOTf (**1**) and Me_3SiClO_4 (**2**) have been well documented in organic synthesis.[4] The activity of these catalysts, however, depends on the reaction employed.[5] Recently, Davis and co-workers reported that the combination of trialkylsilyl triflates or chlorides with $B(OTf)_3$ displays high catalyst activity on the Sakurai allylation and the Mukaiyama aldol reaction.[6] Unfortunately, modification of triflate to a more electron-deficient group often causes the unavoidable formation of byproducts.[7] Recent mechanistic studies imply that some metal triflates, $Zn(OTf)_2$, $Sn(OTf)_2$, $Yb(OTf)_3$, $Cp_2Ti(OTf)_2$, and TrOTf behave as initiators or promotors but that in situ-generated **1** is likely to be the true catalyst in the process.[8] In addition, the aldol methodology remains a major limitation in the catalytic cross-aldol reaction of ketones with currently available Lewis acids.[9] Hence, we focused on developing a new and clean system with high activity toward ketones as well as toward less reactive aldehydes, while suppressing side reactions. Our original strategy involved shifting the equilibrium in the following complexation by preferentially trapping triflate anion rather than Lewis basic substrates and products with Lewis acid-type receptors possessing high molecular recognition ability.

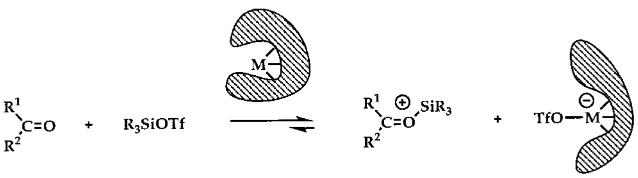
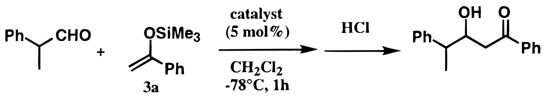


Table 1. Aldol Reaction of 2-Phenylpropanal and Silyl Enol Ether 3A[a]



3a

entry	catalyst[b]	% yield[c]	syn/anti[d]
1	Me_3SiOTf	15	75:25
2	Me_3SiI	0	
3	$Me_3SiOTf/B(OTf)_3$[e]	43	90:10
4	$B(OTf)_3$	41	89:11
5	$Me_3SiOTf/{}^iBu_3Al$	32	65:35
6	Me_3SiOTf/Et_2AlCl	47	61:39
7	Me_3SiOTf/MAD	62	91:9
8	Me_3SiOTf/MABR	76	89:11
9	MABR	7	42:58
10	Me_3SiCl	0	
11	Me_3SiCl/MABR	4	39:61
12	Me_3SiOFs[f]	0	
13	Me_3SiOFs/MABR[f]	78	91:9
14	Me_3SiOMs[g]	0	
15	Me_3SiOMs/MABR[g]	64	88:12

[a] The reaction was carried out at −78 °C for 1 h in the following scale: aldehyde (10 mmol), silyl enol ether (11 mmol), and dichloromethane (20 mL) were used. [b] Of the catalyst or catalyst pair (1:1), 5 mol % was employed. [c] Isolated yield. [d] Determined by 300 MHz ^{1}H NMR analysis. [e] See ref 6b; literature result: 44% yield, syn/anti = 8:1 [f] FsOH:fluorosulfonic acid. [g] MsOH:methanesulfonic acid. [a] The reaction was carried out at −78 °C for 1 h in the following scale: aldehyde (10 mmol), silyl enol ether (11 mmol), and dichloromethane (20 mL) were used. [b] Of the catalyst or catalyst pair (1:1), 5 mol % was employed. [c] Isolated yield. [d] Determined by 300 MHz ^{1}H NMR analysis. [e] See ref 6b; literature result: 44% yield, syn/anti = 8:1 [f] FsOH:fluorosulfonic acid. [g] MsOH:methanesulfonic acid.

Indeed, according to our preliminary ^{13}C NMR results, the equilibrium of a benzaldehyde/**1** complex in $CDCl_3$ at −50 °C seems to be located mostly on the left side since the shifts of the carbonyl carbon and the Me_3Si group of the complex are both negligible. We report here the remarkable rate enhancement on the trialkylsilyl triflate-catalyzed Mukaiyama aldol reaction of silyl enol ethers by using a bulky organoaluminum reagent, i.e.,

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(1) Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1393.

(2) (a) Maerker, C.; Kapp, J.; Schleyer, P. v. R. In *Organosilicon Chemistry: from Molecules to Materials*; Auner, N., Weis, J., Eds.; VCH: Weinheim, 1996; Vol. II. (b) Schleyer, P. v. R. *Science* **1997**, *275*, 39. (c) Olah, G. A.; Heiliger, L.; Li, X.-Y.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1990**, *112*, 5991. (d) Lickiss, P. D. *J. Chem. Soc., Dalton Trans.* **1992**, 1333. (e) Pauling, L. *Science* **1994**, *263*, 983. (f) Olah, G. A.; Rasul, G.; Li, X.-Y.; Buchholz, H. A.; Sandford, G.; Prakash, G. K. S. *Science* **1994**, *263*, 983.

(3) (a) Lambert, J. B.; Zhang, S.; Stern, C. L.; Huffman, J. C. *Science* **1993**, *260*, 1917. (b) Reed, C. A.; Xie, Z.; Bau, R.; Benesi, A. *Science* **1993**, *262*, 402. (c) Lambert, J. B.; Zhang, S. *Science* **1994**, *263*, 984. (d) Reed, C. A.; Xie, Z. *Science* **1994**, *263*, 985. (e) Lambert. J. B.; Zhang, S. *J. Chem. Soc., Chem. Commun.* **1993**, 383. (f) Xie, Z.; Manning, J.; Reed, R. W.; Mathur, R.; Boyd. P. D. W.; Reed, C. A. *J. Am. Chem. Soc.* **1996**, *118*, 2922. (g) Lambert, J. B.; Zhao, Y. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 400.

(4) For reviews of **1** and **2** in organic synthesis see: (a) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899. (b) Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Götz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krägeloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1. (c) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4259. (d) Simchen, G. In *Advances in Silicon Chemistry*; Larson, G. L., Ed.; JAI: London, 1991; Vol. 1, pp 189−301.

(5) For the scope and limitation of **1** as a Lewis acid catalyst, see: (a) Mukaiyama aldol reaction of silyl enol ethers, Mukai, C.; Hashizume, S.; Nagami, K.; Hanaoka, M. *Chem. Pharm. Bull.* **1990**, *38*, 1509. (b) Sakurai reaction, see ref 4a. (c) Cyanosilylation of aldehydes and ketones, Kaur, H.; Kaur, G.; Trehan, S. *Synth. Commun.* **1996**, *26*, 1925.

(6) (a) Davis, A. P.; Jaspars, M. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 470. (b) Davis, A. P.; Plunkett, S. J. *J. Chem. Soc., Chem. Commun.* **1995**, 2173. (c) Davis, A. P.; Muir, J. E.; Plunkett, S. J. *Tetrahedron Lett.* **1996**, *37*, 9401.

(7) Significant amounts of nonpolar byproducts are produced, particularly in Sakurai allylation. (a) See ref 6a. (b) Ishii, A.; Kotera, O.; Saeki, T.; Mikami, K. *Synlett* **1997**, 1145.

(8) (a) Carreira, E. M.; Singer, R. A. *Tetrahedron Lett.* **1994**, *35*, 4323. (b) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570.

(9) For cross-aldol reactions of ketones via Reformatsky-type reactions, see: (a) Maruoka, M.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 7705. (b) Wessjohann, L.; Wild, H. *Synthesis* **1997**, 512.

(10) (a) Maruoka, K.; Araki, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 2650. (b) Maruoka, K.; Nagahara, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 6115. (c) Maruoka, K.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 1089.

(11) Maruoka, K.; Sato, J.; Yamamoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 4422.

(12) Trimethylsilyl sulfonates can be prepared from allyltrimethylsilane and the corresponding sulfonic acid in dichloromethane without triflic acid. (a) Morita, T.; Okamoto, Y.; Sakurai, H. *Synthesis* **1981**, 745. (b) Lipshutz, B. H.; Burgess-Henry, J.; Roth, G. P. *Tetrahedron Lett.* **1993**, *34*, 995.

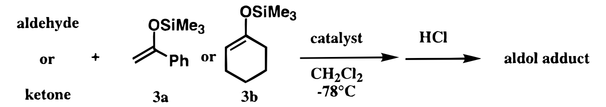
(13) *Stability Constants of Metal-ion Complexes*; Special Publication No. 7; The Chemical Society: London, 1964; Section 1.

(14) (a) Stoichiometric reaction: Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. (b) Zr(IV)- and Ti(IV)-catalyzed reactions at room temperature: Hollis, T. K.; Robinson, N. P.; Bosnich, B. *Tetrahedron Lett.* **1992**, *33*, 6423. (c) $BiCl_3$-catalyzed or -mediated reaction at room temperature: Wada, M.; Takeichi, E.; Matsumoto, T. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 990.

(15) See Supporting Information.

S0002-7863(98)01464-4 CCC: $15.00

Table 2. Catalytic Aldol Reaction of Silyl Enol Ether 3A or 3b with Aldehyde or Ketone[a]



entry	substrates	catalyst (mol %)	time (h)	yield[b] (%)
1	Ph(CH$_2$)$_2$CHO/**3a**	Me$_3$SiOTf(1)	0.5	20
2		Me$_3$SiOTf-MAD(1)		61
3		Me$_3$SiOTf-MABR(1)		83
4		^{t}BuMe$_2$SiOTf(1)		14
5		^{t}BuMe$_2$SiOTf -MABR(1)		72
6	(CH$_3$)$_3$CCHO/**3a**	Me$_3$SiOTf(5)	1	2
7		Me$_3$SiOTf-MABR(5)		74
8	(CH$_3$)$_3$CCHO/**3b**	Me$_3$SiOTf(5)	1	0
9		Me$_3$SiOTf-MABR(5)		87[c]
10	cyclohexanone/**3a**	Me$_3$SiOTf(5)	0.5	30
11		Me$_3$SiOTf-MAD(5)		86
12		Me$_3$SiOTf-MABR(5)		90
13	PhCOCH$_3$/**3a**	Me$_3$SiOTf(5)	2	3
14		Me$_3$SiOTf-MAD(5)		60
15		Me$_3$SiOTf-MABR(5)		72
16	(CH$_3$)$_2$CHCOCH$_3$/**3a**	Me$_3$SiOTf(5)	1.5	1
17		Me$_3$SiOTf-MAD(5)		77
18		Me$_3$SiOTf-MABR(5)		91
19	PhCOCH$_3$/**3b**	Me$_3$SiOTf(5)	2	14[d]
20		Me$_3$SiOTf-MABR(5)		90[d]

[a] The reaction was performed at −78 °C in the following scale: aldehyde or ketone (10 mmol), **3a** or **3b** (11 mmol), dichloromethane (20 mL) were used. [b] Isolated yield. [c] The syn/anti ratio was determined by 300 MHz ^{1}H NMR to be 15:85. [d] The syn/anti ratios were determined by 300 MHz ^{1}H NMR to be 35:65 (entry 19) and 28:72 (entry 20), respectively. The stereochemical assignment was made by comparison with the ^{1}H NMR spectrum of the authentic sample (Ghera, E.; Shoua, S. *J. Org. Chem.* **1972**, *37*, 1292).

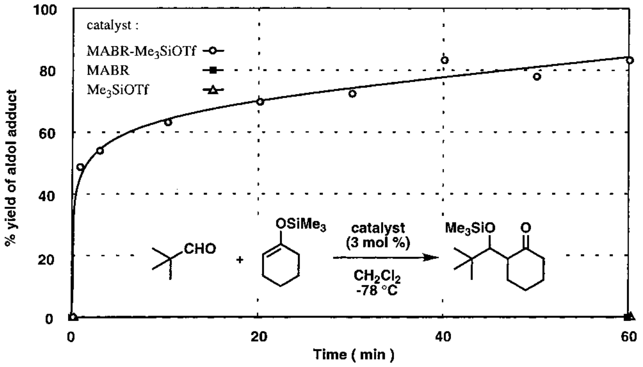


Figure 1. Reaction profile of the catalytic aldol addition of **3b** (20 mmol) to pivalaldehyde (20 mmol) in dichloromethane (40 mL) at −78 °C.

methylaluminum bis(4-substituted-2,6-di-*tert*-butylphenoxide), MAD or MABR, as a cocatalyst.[10,11]

Initially, we examined the relative activities of various combined catalysts on the aldol reaction of less reactive 2-phenylpropanal and **3a** under the reaction conditions shown in Table 1. The catalyst pair of **1** and B(OTf)$_3$ resulted in a moderate yield similar to that of B(OTf)$_3$ (entries 3 and 4). In marked contrast to the disappointing results with both **1** and MABR (entries 1 and 9), the combination of **1** with MAD or MABR appeared to be an optimal choice to attain higher chemical yield (entries 7 and 8). Other organoaluminum reagents gave less satisfactory results with a lower syn/anti ratio (entries 5 and 6). It should be noted that Me$_3$SiOFs and Me$_3$SiOMs are also employable as active catalysts in the presence of an equimolar amount of MABR reagent (entries 13 and 15), indicating that interaction between aluminum and fluorine is not necessarily important.[12,13]

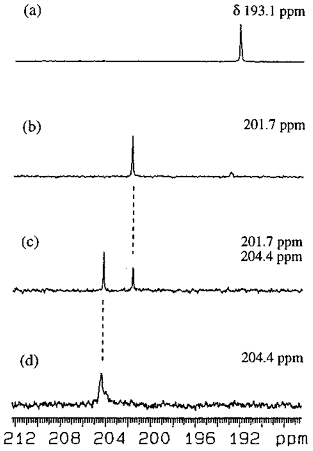
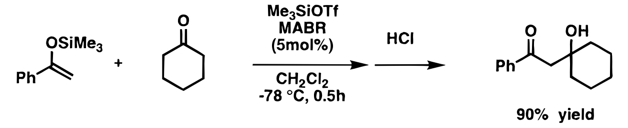


Figure 2. ^{13}C NMR spectra at −50 °C in CDCl$_3$ of (a) free PhCHO, (b) MAD/PhCHO (1:1) complex, (c) MAD/PhCHO/**1** (1:1:1) complex, and (d) MAD/PhCHO/**1** (1:1:2) complex.

This remarkably active catalyst system was then applied to a range of less reactive carbonyl substrates (Table 2). As can be seen in Table 2, aliphatic and sterically hindered aldehydes undergo smooth aldol addition with silyl enol ether **3a** or **3b** into the corresponding aldol adducts (entries 1−9). Surprisingly, the present system supersedes any previously reported Lewis acid catalysis, and makes the catalytic cross-aldol reaction between simple ketones feasible under mild reaction conditions (entries 10−18).[14] For example, exposure of isopropyl methyl ketone and **3a** to 5 mol % of **1** and MABR (1:1) in dichloromethane at −78 °C for 1.5 h followed by acidic workup gave the corresponding β-hydroxy ketone in 91% yield without the formation of a dehydrated byproduct, while a trace amount of the adduct was produced in the absence of MABR. Furthermore, catalytic cross-aldol coupling between acetophenone and cyclohexanone leads to a desired aldol product in high yield, as illustrated below. The reaction profile of the aldol reaction of pivalaldehyde with **3b** clearly shows a multiplier effect of **1** and MABR (Figure 1).[15]



This new finding prompted us to explore the active species in the catalyst system. Accordingly, a ^{13}C NMR spectral study of benzaldehyde/**1**/MAD complexes was carried out at −50 °C in CDCl$_3$, where the downfield shift of carbonyl carbon in the complex from the aldehyde coordinated with MAD was observed (204.4 ppm) as revealed in Figure 2.[15] The peak (201.7 ppm) of the carbonyl carbon based on the benzaldehyde−MAD complex disappeared completely when 2 equiv of **1** were added (Figure 2d). Similar results were obtained for the addition of benzaldehyde and **1** in the reverse order. These observations indicate that *a more strongly Lewis acidic species forms from two different Lewis acids of the bulky organoaluminum reagent and* ***1*** *in the presence of an aldehyde.*

In conclusion, we have demonstrated that the new combined system of trialkylsilyl sulfonate-MAD or -MABR exhibits exceedingly high activity on the catalytic Mukaiyama aldol reaction of silyl enol ethers with aldehydes and ketones, where MAD and MABR are currently thought to be cocatalysts stabilizing a silyl counteranion. Studies on the development of chiral super Lewis acid catalysts are now underway.

Supporting Information Available: Experimental procedures and ^{13}C NMR data (3 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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