A High Yield Procedure for the Me_3SiNTf_2-Induced Carbon-Carbon Bond-Forming Reactions of Silyl Nucleophiles with Carbonyl Compounds: The Importance of Addition Order and Solvent Effects

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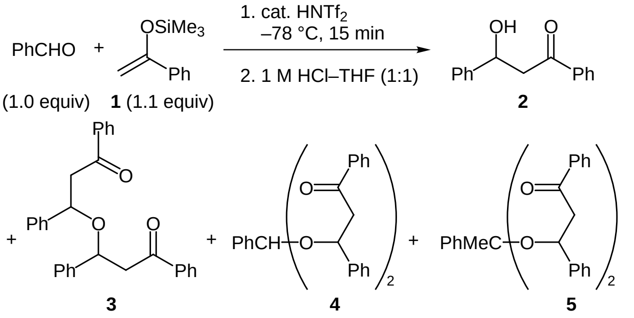
Abstract: We demonstrate the efficiency of Me_3SiNTf_2 (0.3–1.0 mol%) as a strong Lewis acid catalyst for the Mukaiyama aldol and Sakurai–Hosomi allylation reactions, and that the slow addition of carbonyl compounds to a solution of acid catalyst and Me_3Si-Nu is very important for suppressing side products; this may be widely accepted as a common and reasonable general procedure for the Lewis acid-induced reaction of Me_3Si-Nu with carbonyl compounds.

Key words: Lewis acid, catalyst, Mukaiyama aldol reaction, Sakurai–Hosomi allylation reaction, green chemistry

Lewis acid-induced carbon-carbon bond-forming reactions of silyl nucleophiles (R_3Si-Nu) with carbonyl compounds are some of the most powerful and versatile synthetic methods.[1] Ghosez[2i] and Mikami[2j] have independently introduced an extremely powerful carbonyl-activating reagent, *N*-(trimethylsilyl)triflylimide (Me_3SiNTf_2).[2] In many cases, however, it is difficult to control the catalytic activity of Me_3SiNTf_2 to induce only the desired reaction. For example, its catalytic use for the reaction of allyltrimethylsilane with benzaldehyde in dichloromethane at room temperature gives the bis-allylation adduct (49%) in place of the desired homoallyl alcohol (<1%).[2j] Nevertheless, its strong Lewis acidity is very attractive as an ideal common catalyst for the versatile reactions of Me_3Si-Nu with carbonyl compounds, if its catalytic activity can be controlled by the reaction conditions. We describe here a general solution to solve this problem by using the proper solvent choice as well as addition order. A high turnover frequency of Me_3SiNTf_2 (0.3–1.0 mol%) without any significant side products was now achieved for the Mukaiyama aldol and Sakurai–Hosomi allylation reactions.

Table 1 Me_3SiNTf-Catalyzed Mukaiyama Aldol Reaction of **1** with Benzaldehyde



Entry	$HNTf_2$ (mol %)	Procedure (solvent)[a]	Isolated yield (%) **2**	**3**	**4**	**5**
1	0.5	**A** (CH_2Cl_2)	46	54	0	0
2	0.5	**A** (Et_2O)	66	34	0	0
3	0.3	**B** (CH_2Cl_2)	81	0	17	2
4	0.3	**B** (Et_2O)	>96	0	<2	<2
5	0.5	**C** (Et_2O)	92	0	0	0

[a] Procedure **A**: Slow addition of **1** to a solution of $HNTf_2$ and benzaldehyde over 2 h at –78 °C; Procedure **B**: Usual addition of $HNTf_2$ to a solution of **1** and benzaldehyde; Procedure **C**: Slow addition of benzaldehyde to a solution of $HNTf_2$ and **1** over 2 h at –78 °C.

The efficiency of Me_3SiNTf_2 as a catalyst for the Mukaiyama aldol reaction was examined in the reaction of 1-phenyl-1-(trimethylsiloxy)ethylene (**1**) with benzaldehyde (Table 1). Me_3SiNTf_2 was generated in situ by protodesilylation of **1** with commercially available triflylimide ($HNTf_2$).[2i,3] First, silyl enol ether **1** (1.1 equiv) was added to a solution of benzaldehyde (1 equiv) and $HNTf_2$ (0.5 mol%) in dichloromethane at –78 °C over a period of 2 h (Entry 1, Procedure **A**). After acidic workup, the desired aldol **2** was obtained in 46% yield along with **3** (54% yield). The chemical yield of **2** increased to 66% yield by using diethyl ether, but the undesired dimeric ether **3** was still produced in 34% yield (Entry 2). It was ascertained that no dimerization of trimethylsilyl ether of **2** occurred in the presence of Me_3SiNTf_2 at –78 °C by a control experiment. Therefore, the dimeric ether **3** would be formed by aldol reaction of **1** with acetal **6** (Figure 1), which is generated from trimethylsilyl ether of **2** and benzaldehyde. Next, $HNTf_2$ (0.3 mol%) was added to a solution of silyl enol ether **1** (1.1 equiv) and benzaldehyde (1 equiv) in dichloromethane at –78 °C to suppress the generation of **3** (Entry 3, Procedure **B**). As expected, **3** was not formed at all: the desired aldol **2**, its benzaldehyde ac-

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etal **4**, and its acetophenone acetal **5** were obtained in a molar ratio of 81:17:2. Unexpectedly, the use of diethyl ether almost completely suppressed byproducts **4** and **5** (Entry 4, yield of **2**: >96%). To suppress the formation of dimeric ether **3** and acetals **4** and **5** more reasonably, benzaldehyde was added dropwise over a period of 2 h at –78 °C to a solution of silyl enol ether **1** and HNTf$_2$ in diethyl ether (Entry 5, Procedure **C**). The reaction proceeded very cleanly to give **2** almost exclusively in 92% yield.

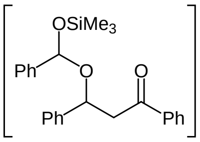

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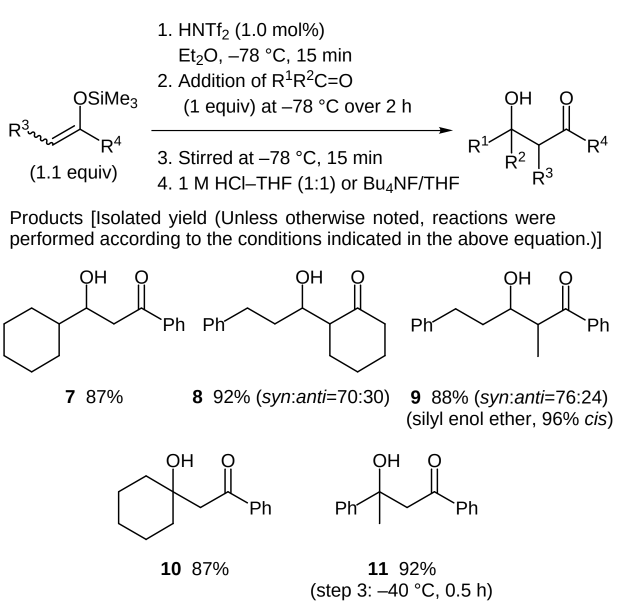
Figure 1

Other examples using this new procedure (**C**) in diethyl ether are shown in Scheme 1. The reaction of **1** with an aliphatic aldehyde such as cyclohexanecarboxaldehyde also proceeded smoothly to give the desired aldol **7** in 87% yield. *Syn* aldols were obtained as major diastereomers independent of the stereochemistry of silyl enol ethers (products **8** and **9**). It is noteworthy that the aldol reaction of **1** with ketones also gave the desired aldols in high yields (products **10** and **11**).

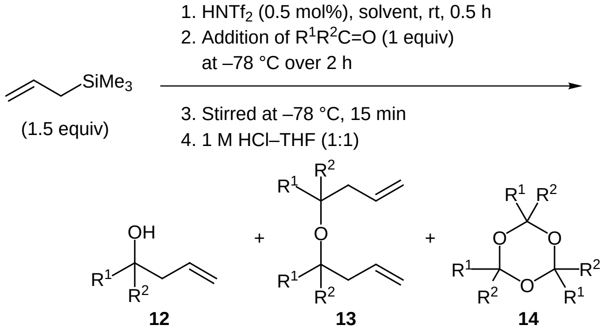


Products [Isolated yield (Unless otherwise noted, reactions were performed according to the conditions indicated in the above equation.)]

Scheme 1 Examples of the Mukaiyama aldol reaction of **1** with aldehydes and ketones (procedure **C**)

The efficiency of Me$_3$SiNTf$_2$ as a catalyst for Sakurai-Hosomi allylation was also examined in the reaction of allyltrimethylsilane (1.5 equiv) with aldehydes or ketones (1.0 equiv) using the best procedure **C** for the Mukaiyama reaction (Table 2). Me$_3$SiNTf$_2$ was prepared in situ, according to the Ghosez's procedure, from allyltrimethylsilane and HNTf$_2$ at room temperature.[2i,3] The reaction of benzaldehyde proceeded smoothly at –78 °C in dichloromethane, and after acidic work-up, the desired homoallyl alcohol **12** was obtained in 89% yield along with dimeric ether **13** (8% yield), which would be formed via intermediate **15** (Figure 2) which is analogous to **6** (Entry 1). The reaction proceeded cleanly in diethyl ether at room temperature and gave **12** in 98% yield after acidic work-up (Entry 2).[4] The reaction of an aliphatic aldehyde such as cyclohexanecarboxaldehyde proceeded cleanly in dichloromethane (Entry 3), while the reaction in diethyl ether surprisingly gave only the cyclic trimer of an aldehyde such as **14** (Entry 5).[5] Allylation of hydrocinnamaldehyde, 2-octanone, and cyclohexanone in dichloromethane also gave the desired homoallyl alcohols **12** in high yields. It is noteworthy that chlorobenzene could be used as a less toxic solvent, but the reactivity was a little lower than with dichloromethane.

Table 2 Solvent Effect on the Sakurai–Hosomi Allylation of Carbonyl Compounds (Procedure **C**)



Entry	$R^1R^2C=O$	solvent	Isolated yield (%) 12	13	14
1	PhCHO	CH_2Cl_2	89 (**12a**)	8 (**13a**)	0 (**14a**)
2	PhCHO	Et_2O[a]	98 (**12a**)	<2 (**13a**)	0 (**14a**)
3	*c*-C_6H_{11}CHO	CH_2Cl_2	92 (**12b**)	0 (**13b**)	<1 (**14b**)
4	*c*-C_6H_{11}CHO	PhCl	82 (**12b**)	0 (**13b**)	<7 (**14b**)
5	*c*-C_6H_{11}CHO	Et_2O	0 (**12b**)	0 (**13b**)	<95 (**14b**)
6	$PhCH_2CH_2CHO$	CH_2Cl_2	90 (**12c**)	0 (**13c**)	trace (**14c**)
7	$PhCH_2CH_2CHO$	PhCl[b]	84 (**12c**)	0 (**13c**)	trace (**14c**)
8	*n*-C_6H_{13}COMe	CH_2Cl_2[c]	89 (**12d**)	0 (**13d**)	0 (**14d**)
9	*n*-C_6H_{13}COMe	PhCl[d]	85 (**12d**)	0 (**13d**)	0 (**14d**)
10	*c*-C_6H_{10}O	CH_2Cl_2	91 (**12e**)	0 (**13e**)	0 (**14e**)
11	*c*-C_6H_{10}O	PhCl[b]	89 (**12e**)	0 (**13e**)	0 (**14e**)

[a] The reaction was carried out at room temperature for 15 min (step 3).
[b] The reaction was carried out at –40 °C (steps 2 and 3).
[c] The reaction was carried out at –20 °C (step 3).
[d] The reaction was carried out at –40 °C (step 2) and 0 °C (step 3).

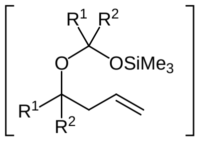


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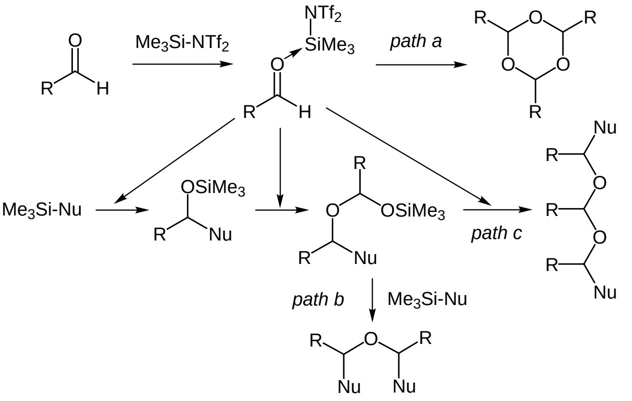
Figure 2

In light of the above experiments, a reasonable mechanistic hypothesis for the Me_3SiNTf_2-induced reaction of Me_3Si-Nu with carbonyl compounds is shown in Scheme 2. The presence of excess molar amounts of carbonyl compounds per desired adduct produced in the reaction concurrently promotes at least three reactions: (1) cyclic trimerization of the aldehyde (*path a*), (2) dimerization of the desired adducts (*path b*), and (3) acetalization of the desired adducts (*path c*). The slow addition of carbonyl compounds to a mixed solution of Me_3Si-Nu and Me_3SiNTf_2 (procedure **C**) was the best solution to give the desired products selectively.



Scheme 2 General outline for the Me_3SiNTf_2-induced addition reaction of carbonyl compounds with Me_3Si-Nu

The catalytic activities in the Mukaiyama aldol and Sakurai–Hosomi allylation reactions induced by representative acids are compared in Table 3. The replacement of current chemical processes with more environmentally benign alternatives is an important topic. Considering environmental benefits, the efficiency of Me_3SiNTf_2 as a catalyst is striking. In particular, Me_3SiNTf_2 has the great advantage of allowing the use of diethyl ether and chlorobenzene as less-toxic solvents. In contrast, the other acids in Table 3 work in dichloromethane, which is not environmentally friendly, and it would be difficult to effectively use their catalytic loading in diethyl ether because of the strong affinity between the Lewis acidic metal atom and ethereal oxygen atoms. Fluorosulfonylimide is also a remarkably strong acid like $HNTf_2$,[1b,2b] but is relatively unstable.[6] Furthermore, this Brønsted acid, which is not commercially available, must be prepared from urea and fluorosulfonic acid, wich is highly toxic.[7]

Table 3 Comparison of Catalytic Activities in the Mukaiyama Aldol and Sakurai–Hosomi Allylation Reactions Induced by Representative Acids

	Yield, % (Catalyst, mol %)			
	Aldol products		Allylation products	
Catalyst, Solvent, Procedure[a]	**2**	**7**	**12a**	**12b**
Me_3SiNTf_2, Et_2O, **C**	92(0.5)	87(1)	98(0.5)	92(0.5)[b]
Me_2AlNTf_2, CH_2Cl_2,[c] **C’**	90(2)	92(2)	93(5)	–
$HN(SO_2F)_2$, CH_2Cl_2,[d,e]	–	–	94(5)	86(5)
Me_3SiOTf-MABR, CH_2Cl_2,[f] **C’**	94(1)	90(5)	–	–
$Me_3SiB(Otf)_4$, CH_2Cl_2,[g] **B’**	–	–	80(1)	84(1)
$B(C_6F_5)_3$, CH_2Cl_2,[h] **A’**	96(1)	–	n.r.[i]	n.r.[i]

[a] Procedure **C**: Slow addition of carbonyl compounds to a solution of catalyst and Me_3Si-Nu; Procedure **A’**: Usual addition of Me_3Si-Nu to a solution of catalyst and carbonyl compounds; Procedure **B’**: Usual addition of catalyst to a solution of carbonyl compounds and Me_3Si-Nu; Procedure **C’**: Usual addition of carbonyl compounds to a solution of catalyst and Me_3Si-Nu.

[b] CH_2Cl_2 was used instead of Et_2O.

[c] Reference 2p.

[d] Reference 1b.

[e] No report.

[f] Reference 1c.

[g] Reference 1d.

[h] References 1e and 1f.

[i] No reaction.

In conclusion, we demonstrated the efficiency of Me_3SiNTf_2 as an ideal common catalyst (0.3–1.0 mol%) for addition reactions of Me_3Si-Nu to carbonyl compounds. The slow addition of carbonyl compounds to a solution of acid catalyst and Me_3Si-Nu and the choice of solvents are very important to suppress side products. This may be widely accepted as a general procedure for the Lewis acid-induced reaction of Me_3Si-Nu with carbonyl compounds.

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(3) The use of Me$_3$SiNTf$_2$,[2c,i,l] prepared from chlorotrimethylsilane and silver triflylimide,[2c] for the Mukaiyama and Sakurai–Hosomi reactions gave the same experimental results as when HNTf$_2$ was used.

(4) A typical procedure (**C**) for the reaction of allyltrimethylsilane with benzaldehyde: Commercially available triflylimide (556 μL of 0.072 M solution in diethyl ether, 0.04 mmol) was added at room temperature under argon to a solution of allyltrimethylsilane (1.90 mL, 12 mmol)in diethyl ether (2 mL). After stirring the mixture for 0.5 h, benzaldehyde (8.0 mL of 1.0 M solution in diethyl ether, 8.0 mmol)was added dropwise over a period of 2 h at –78 °C, and the reaction mixture was allowed to warm up to room temperature. After stirring for 0.5 h, 1 M HCl (10 mL) and THF (10 mL) were added. The reaction mixture was stirred for 0.5 h, poured into NaHCO$_3$ solution, and extracted with diethyl ether. The combined organic extracts were dried over MgSO$_4$ and concentrated, and the residue was purified by column chromatography on silica gel (ethyl acetatehexane, 1/10)to give **12** (1.16 g, 98% yield) as a colorless liquid.

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