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Bismuth Trichloride as a New Efficient Catalyst in the Aldol Reaction and the Michael Reaction

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In the presence of a catalytic amount of bismuth(III) trichloride (5 mol%), silyl enol ethers react with aldehydes at room temperature in dichloromethane to give the corresponding aldols in good yields. Silyl enol ethers also have been found to react with α,β-unsaturated ketones at room temperature in dichloromethane to afford the corresponding 1,5-dicarbonyl compounds, the Michael adducts in good yields. The intermediate adducts of the aldol reaction (the silyl ethers) and the Michael reaction (the silyl enol ethers) were also obtained in good yields.

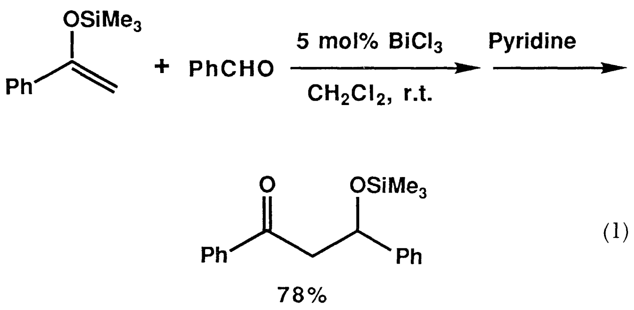
In view of elemental resources for the future, it is important to use various elements for organic synthesis. Among group 15 elements, bismuth metal is cheaper and less toxic than arsenic or antimony and can be expected to play some role in organic synthesis according to its enhanced metallic character. To our knowledge, however, organic synthesis, especially carbon–carbon bond forming reaction by using bismuth and bismuth compounds has been scarcely studied.[1] Recently, the first example of chemoselective metallic bismuch[2] and bismuth (III) chloride ($BiCl_3$)–metallic zinc-,[3] iron-,[3] or aluminium[4]-mediated allylation of aldehydes with allylic halides to homoallylic alcohols was reported by us.[5] We also found that $BiCl_3$ (5 mol%) promotes aldol reaction between silyl enol ethers and aldehydes in CH_2Cl_2 at room temperature.[6] In the course of our continuous investigations, we have found that $BiCl_3$ activates α,β-unsaturated ketones. Herewith, we wish to disclose in full the $BiCl_3$ catalyzed aldol reaction and Michael reaction.

Results and Discussion

Bismuth Trichloride ($BiCl_3$) Promoted Aldol Reaction between Silyl Enol Ethers and Aldehydes. The aldol reactions is one of the standard tools for creating new carbon–carbon bonds, and numerous methods have been developed[7] including the catalytic aldol reaction by the aid of TBAF (tetrabutylammonium fluoride),[8] TASF [Tris(diethylamino)sulfonium (TAS) difluorotrimethylsiliconate],[9] trityl perchlorate,[10] and rhodium complex.[11] Concerning the cross-aldol reaction using silyl enol ethers,[12] the $TiCl_4$-promoted reaction (Mukaiyama method) is the first example, and the reaction has been carried out at −78 °C using an equimolar amount of $TiCl_4$ in most cases to obtain the aldols in good yields.[13] However, it is still desirable to find a new efficient catalyst of cross-aldol reaction between silyl enol ethers and aldehydes under extremely mild conditions (room temperature and weak acid).

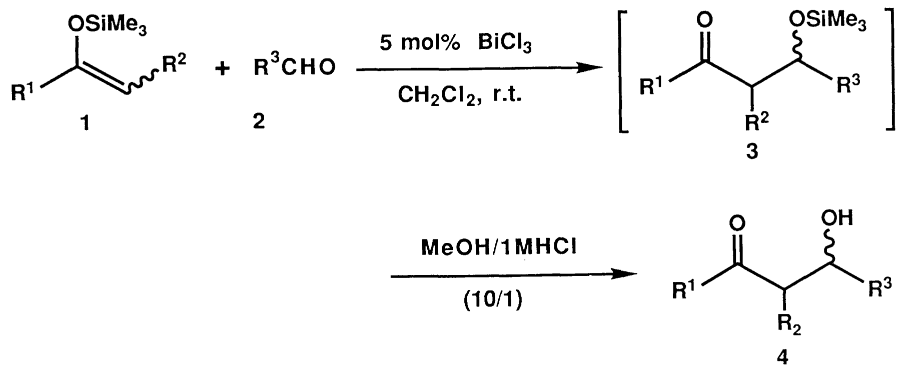
In relation to aldol reaction by using bismuth and bismuth compounds, the reaction between 1-trimethylsiloxy-1-cyclohexene and benzaldehyde in the presence of $BiCl_3$ (5 mol%) in $CDCl_3$ at room temperature was monitored by ^{1}H NMR spectroscopy. The NMR signals at 0.17 ppm (s, O–Si$\underline{\text{Me}}_3$), 4.87 ppm (t, vinyl-$\underline{\text{H}}$), and 10.00 ppm (s, aldehyde-$\underline{\text{H}}$) disappeared within 1 h, and new signals appeared at −0.02 ppm (s, O–Si$\underline{\text{Me}}_3$ of the threo product), 0.03 ppm (s, O–Si$\underline{\text{Me}}_3$ of the erythro product), 5.10 ppm (d, O–C$\underline{\text{H}}$ of the threo product, J=7.91 Hz), and 5.37 ppm (d, O–C$\underline{\text{H}}$ of the erythro product, J=3.95 Hz). The above results illustrate that the silyl enol ether reacts with benzaldehyde smoothly under the influence of a catalytic amount (5 mol%) of $BiCl_3$, giving the aldol silyl ether.

Practically, the reaction of 1-phenyl-1-trimethylsiloxyethylene and benzaldehyde followed by the quenching of the reaction mixture using pyridine gave 78% isolated yield of the corresponding silyl ether (Eq. 1). The corresponding aldol was obtained in 94% yield when the reaction mixture was treated with CH_3OH/1M HCl (10/1, 1 M=1 mol dm^{-3}), then H_2O was added.



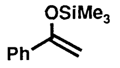
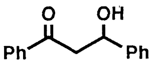
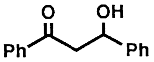
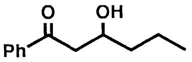
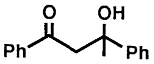
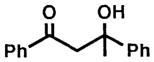
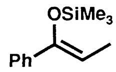
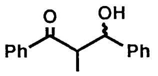
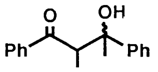
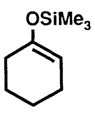
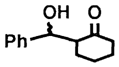
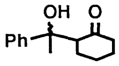
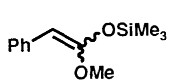
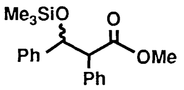
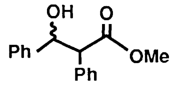
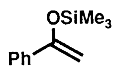
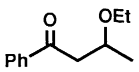
(1)

The overall reaction is shown in Scheme 1 and typical results are summarized in Table 1. Silyl enol ethers of acetophenone, propiophenone, cyclohexanone, and methyl phenylacetate could be used. Both benzaldehyde and butanal are usable to obtain aldols



Scheme 1.

Table 1. BiCl$_3$ Mediated Synthesis of Aldols (**4**)

Entry	Silyl enol ether	Receptor	Reaction time	Product (**4**)	Yield[a]/%
1		PhCHO	25 min		94
2		PhCHO	25 min		0[b]
3		CH$_3$(CH$_2$)$_2$CHO	40 min		85
4		PhCOCH$_3$	6 h		65
5		PhCOCH$_3$	11 h		73[c]
6		PhCHO	50 min		95 (56: 44)[d]
7		PhCOCH$_3$	40 h		22[e]
8		PhCHO	1 h		84 (25: 75)[d]
9		PhCOCH$_3$	11 h		Low yield[f]
10		PhCHO	1 h	 	40[e,g] 32[e,g]
11		CH$_3$CH(OEt)$_2$	6 h		41

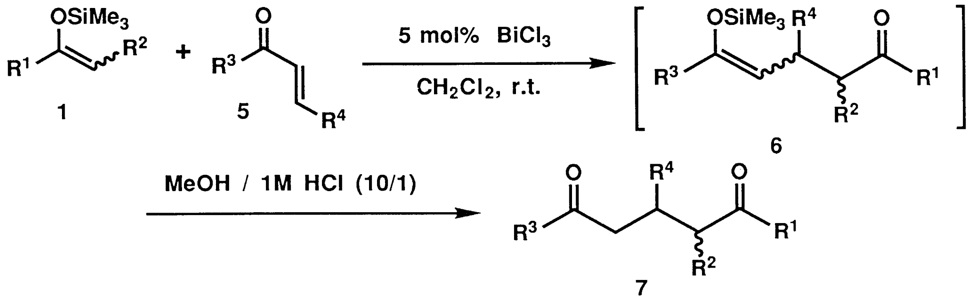
a) Isolated yields are given. b) The reaction was carried out at −78 °C and quenched at that temperature. c) 20 mol% BiCl$_3$ was used. d) The ratio of erythro: threo determined by ^{1}H NMR. e) The ratio of diastereomers was not determined. f) One equivalent of BiCl$_3$ was used. g) The reaction mixture was treated with H$_2$O instead of MeOH/1 M HCl for the workup.

in good yields, and an aldehyde serves naturally as a better receptor than acetophenone (Entries 4, 5, 7, and 9). The reaction proceeded very sluggishly at −78 °C and an ambient reaction temperature was required (Entry 2). 1-Phenyl-1-trimethylsiloxyethylene/acetaldehyde dimethyl acetal reaction gave the aldol-type product in 41% unoptimized yield (Entry 11).

In the connection of studies concerning the interaction of silyl enol ethers with Lewis acids, Kuwajima and Nakamura found that the transmetallation reaction occurs via either and O– or a C–metalation pathway, in which $SnCl_4$, $TeCl_4$, and $SbCl_5$ took the former pathway and $TiCl_4$ took the latter.[14] Based on the above results, the reaction between 1-trimethylsiloxy-1-cyclohexene and one equivalent of $BiCl_3$ in $CDCl_3$ at room temperature was monitored by ^1H NMR spectroscopy. We found that the transmetalation reaction does not occur, and consequently, it is of note that the active intermediate of the present reaction is not the bismuth enolate. Although the reaction mechanism of the catalytic $BiCl_3$ mediated aldol reaction is not clear, a catalytic cycle can be presumed in which the carbonyl compounds activated by $BiCl_3$, react with silyl enol ethers to give the aldol silyl ethers by Prins or Friedel–Crafts type reaction, regenerating $BiCl_3$.

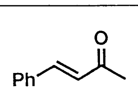
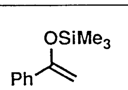
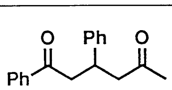
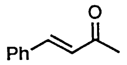
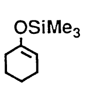
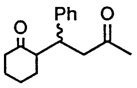
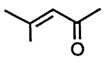
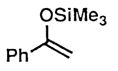
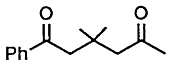
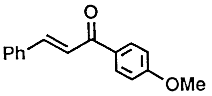
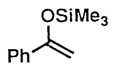
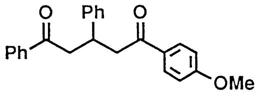
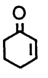
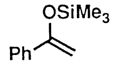
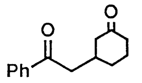
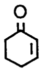
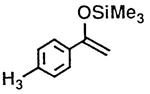
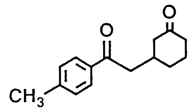
Bismuth Trichloride ($BiCl_3$) Promoted Michael Reaction. In the course of our continuous investigations to explore useful synthetic reactions using $BiCl_3$, we have found that it also activates α,β-unsaturated aldehydes and ketones.[15] Herewith, we wish to describe the $BiCl_3$ catalyzed Michael reaction, and also the isolation of the intermediate adduct, the synthetically valuable silyl enol ether.

When 1-phenyl-1-trimethylsiloxyethylene was reacted with crotonaldehyde in the presence of $BiCl_3$ (5 mol%) in CH_2Cl_2 at room temperature, 1,2-addition product and 1,4-addition product were obtained in 68% and 31% yields, respectively. Noteworthy is the fact that 1,5-dicarbonyl compound, the Michael adduct, was obtained in good yield, and 1,2-addition product was not detected by the reaction of a silyl enol



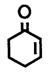
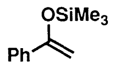
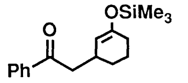
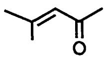
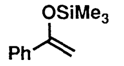
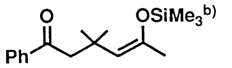
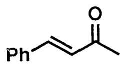
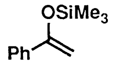
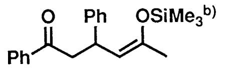
Scheme 2.

Table 2. $BiCl_3$ Mediated Synthesis of 1,5-Dicarbonyl Compounds (**7**)

Entry	Enone	Silyl enol ether	Product (**7**)	Yield[a]/%
a				80
b				79[b]
c				75
d				70
e				65
f				71

a) Isolated yields are given. b) The ratio of diastereomers was not determined.

Table 3. Isolation of the Silyl Enol Ethers (**6**)

Entry	Enone	Silyl enol ether	Product (**6**)	Yield[a)]/%
a				70
b				75
c				77

a) Isolated yields are given. b) The geometry of the double bond was presumed to be cis by comparing the ^{1}H NMR data with those reported.[15,16)]

ether with an α,β-unsaturated ketone. The overall reaction is shown in Scheme 2 and typical results are summarized in Table 2.

Quenching of the reaction mixture using pyridine gave the satisfactory yield of the intermediate silyl enol ether. Some of the results are summarized in Table 3.

The present reaction is the first example of the cross-aldol reaction and the Michael reaction using $BiCl_3$. It should be stressed that cheap and commercially available $BiCl_3$ is a new efficient catalyst of the present reaction under extremely mild conditions [room temperature and weak acid ($BiCl_3$ is a weak Lewis acid)].

Experimental

General Methods. Infrared spectra were recorded on a Hitachi 215 spectrophotometer. ^{1}H NMR spectra were recorded with JEOL PMX 60Si spectrometer and chemical shifts (δ) were reported in ppm using internal tetramethylsilane. Bismuth (III) chloride was commercial material and used without further purification. Aldehydes and α,β-unsaturated ketones were distilled before use. Trimethylsilyl enol ethers were prepared following the procedure of House.[17)]

Isolation of the Aldol Silyl Ether. Bismuth (III) chloride (0.1 mmol) was placed in a 50 ml two-necked flask and dried in vacuo by heating. Anhydrous CH_2Cl_2 (10 ml) was introduced under nitrogen, and then, using a syringe 1-phenyl-1-trimethylsiloxyethylene (2.0 mmol) and benzaldehyde (2.0 mmol) were added at room temperature. The reaction mixture was stirred for 1 h at that temperature and quenched with pyridine (1 ml) followed by the treatment of water (10 ml). The organic materials were extracted with Et_2O (20 ml×3). After drying ether layer over anhydrous $MgSO_4$, the solvent was evaporated to give the oily product in 78% yield. This product was pure by ^{1}H NMR without purification, and it was identified by comparison with an authentic sample prepared from the known procedure.[10)]

General Procedure of the Aldol Reaction. In a 50 ml two-necked flask under nitrogen atmosphere, were placed bismuth (III) chloride (0.05 mmol) and dry CH_2Cl_2 (3 ml). Then, an aldehyde (1.1 mmol) and a silyl enol ether (1.0 mmol) were added sequentially at room temperature, and the reaction mixture was stirred at that temperature. The resulting reaction mixture was treated with CH_3OH/1M HCl (10/1, 0.1 ml), then H_2O (10 ml) was added, and the product was extracted with CH_2Cl_2 (10 ml×3). After drying the CH_2Cl_2 layer over anhydrous $MgSO_4$, the solvent was evaporated in vacuo. The crude product was purified on thin-layer chromatography to afford the corresponding aldol in good yield.

3-Hydroxy-1,3-diphenyl-1-propanone: Purified by thin-layer chromatography (SiO_2, hexane:AcOEt=8:1), 94% yield. This product was identified by comparison with an authentic sample prepared from the known procedure.[13b)]

3-Hydroxy-1-phenyl-1-hexanone: Purified by thin-layer chromatography (SiO_2, hexane:AcOEt=9:1), 85% yield. This product was identified by comparison with an authentic sample prepared from the known procedure.[13b)]

3-Hydroxy-1,3-diphenyl-1-butanone: Purified by thin-layer chromatography (SiO_2, hexane:AcOEt=9:1), 73% yield. This product was identified by comparison with an authentic sample prepared from the known procedure.[18)]

3-Hydroxy-2-methyl-1,3-diphenyl-1-propanone: Purified by thin-layer chromatography (SiO_2, hexane:AcOEt=7:1), 95% yield. This product was identified by comparison with an authentic sample prepared from the known procedure.[13b)]

3-Hydroxy-2-methyl-1,3-diphenyl-1-butanone: Purified by thin-layer chromatography (SiO_2, hexane:AcOEt=9:1), 22% yield. This product was identified by comparison with an authentic sample.[18)]

2-(α-Hydroxybenzyl)-1-cyclohexanone: Purified by thin-layer chromatography (SiO_2, hexane:Et_2O=5:1), 84% yield. This product was identified by camparison with an authentic sample.[10a)]

Methyl 3-Hydroxy-2,3-diphenylpropionate: Purified by thin-layer chromatography (SiO_2, CH_2Cl_2), 32% yield. This product was identified by comparison with an authentic sample prepared from the known procedure.[19)]

3-Ethoxy-1-phenyl-1-butanone: Purified by thin-layer chromatography (SiO_2, hexane:AcOEt=15:1), 41% yield. This product was identified by comparison with an authentic sample prepared from the known procedure.[20)]

Isolation of an Intermediate of the Michael Reaction, an Silyl Enol Ether. Bismuth(III) chloride (0.05 mmol) was placed in a 50 ml two-necked flask and dried in vacuo by heating. Anhydrous CH_2Cl_2 (5 ml) was introduced under nitrogen, and then, using a syring a silyl enol ether (1.0 mmol) and an α,β-unsaturated ketone (1.1 mmol) were added at room temperature. The reaction mixture was stirred for 1 h at that temperature and quenched with pyridine (1 ml) followed by the treatment of water (10 ml).

The organic materials were extracted with Et_2O (20 ml×3). After drying the ether layer over anhydrous $MgSO_4$, the solvent was evaporated to give the oily product in good yield. This product was pure by ^1H NMR without purification. This product was identified by comparison with an authentic sample.

The Silyl Enol Ether (6a): Purified by thin-layer chromatography (SiO_2, hexane:AcOEt=9:1), 70% yield. This product was identified by comparison with an authentic sample prepared from the known procedure.[15]

The Silyl Enol Ether (6b): Purified by thin-layer chromatography (SiO_2, hexane:AcOEt=9:1), 75% yield. This product was identified by comparison with an authentic sample.[15]

The Silyl Enol Ether (6c): Purified by thin-layer chromatography (SiO_2, hexane:AcOEt=9:1), 77%. This product was identified by comparison with an authentic sample. [15]

General Procedure of the Michael Reaction. In a 50 ml two-necked flask under nitrogen atmosphere, were placed bismuth(III) chloride (0.05 mmol) and dry CH_2Cl_2 (3 ml). Then, an α,β-unsaturated ketone (1.1 mmol) and a silyl enol ether (1.0 mmol) were added sequentially at room temperature, and the reaction mixture was stirred for 6 h at that temperature. The resulting mixture was treated with CH_3OH/1M HCl (10/1, 0.1 ml), then H_2O (10 ml) was added and the product was extracted with CH_2Cl_2 (10 ml×3). After drying the CH_2Cl_2 layer over anhydrous $MgSO_4$, the solvent was evaporated in vacuo. The crude product was purified on thin-layer chromatography to afford the corresponding 1,5-dicarbonyl compound in good yield.

The 1,5-Dicarbonyl Compound (7a): Purified by thin-layer chromatography (SiO_2, hexane:AcOEt=7:1), 80% yield. This product was identified by comparison with an authentic sample.[15]

The 1,5-Dicarbonyl Compound (7b): Purified by thin-layer chromatography (SiO_2, hexane:AcOEt=9:1), 79% yield. This product was identified by comparison with an authentic sample prepared from the known procedure.[15]

The 1,5-Dicarbonyl Compound (7c): Purified by thin-layer chromatography (SiO_2, hexane:AcOEt=9:1), 75% yield. This product was identified by comparison with an authentic sample.[15]

The 1,5-Dicarbonyl Compound (7d): Purified by thin-layer chromatography (SiO_2, hexane:AcOEt=9:1), 70% yield. This product was identified by comparison with an authentic sample prepared from the known procedure.[15]

The 1,5-Dicarbonyl Compound (7e): Purified by thin-layer chromatography (SiO_2, hexane:AcOEt=8:1), 65% yield. This product was identified by comparison with an authentic sample.[15]

The 1,5-Dicarbonyl Compound (7f): Purified by thin-layer chromatography (SiO_2, hexane:AcOEt=9:1), 71% yield. This product was identified by comparison with an authentic sample prepared from the known procedure.[15]

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