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Bismuth Triflate Catalyzed Mukaiyama Aldol Reaction in an Ionic Liquid

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We have developed an efficient, bismuth triflate catalyzed Mukaiyama aldol reaction. The reaction proceeds rapidly and affords the corresponding β-hydroxy carbonyl compound in moderate to very good yields (up to 92 %).

The development of new methods for the synthesis of β-hydroxy carbonyl compounds is an important area of synthetic efforts. β-Hydroxy ketones and esters are extremely important compounds as biologically active molecules.[1] The Lewis acid mediated reactions of aldehydes with silyl enolates are among the most efficient for the synthesis of β-hydroxy carbonyl compounds.[2a] Therefore, the development of new catalytic methods for their preparation is of first importance in organic synthesis. Catalytic Mukaiyama aldol reactions have been reported by several groups as an efficient method to prepare aldols.[2b] Synthetic methods involving lanthanide triflates as catalysts for Mukaiyama aldol reactions have been reported.[3] High catalytic activity, moisture and air tolerance make lanthanide triflates attractive catalysts. However, the high cost of these catalysts restricts their use.

Bismuth compounds, too, have attracted recent attention due to their low toxicity, low cost, and good stability.[4] Bismuth salts have been reported as catalysts for Mannich-type reactions,[5] opening of epoxides,[6] allylation of imines,[7] aldol reactions,[8] formation and deprotection of acetals,[9] Friedel–Crafts reactions,[10] Diels–Alder reactions,[11] Fries rearrangements,[12] Claisen rearrangements,[13] and intramolecular Sakurai cyclizations.[14] $Bi(OTf)_3$ is particularly attractive because it is commercially available or can be easily prepared from commercially available starting materials.[15]

Bismuth triflate has been reported by Dubac as efficient catalyst for the Mukaiyama aldol reaction in dichloromethane.[8a] However, organic solvents, and in particular chlorinated solvents, have some drawbacks associated with volatility and toxicity. In this context, ionic liquids are becoming increasingly popular as solvents in organic synthesis for various reasons.[16] They are practically nonvolatile, nonflammable and can be recycled easily without any significant loss in activity. In addition, one can take advantage of the unique solubility properties of ionic liquids to facilitate product isolation. Interestingly, bismuth triflate has already been reported as catalyst in ionic liquids for Friedel–Crafts acylation,[17] epoxide opening,[18] and heterocycle formation.[19]

As a part of our ongoing interest in bismuth(III)-catalyzed condensation reactions, we report herein a bismuth(III)-catalyzed Mukaiyama aldol reaction in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ($[Bmim]BF_4$), as an alternative to dichloromethane. β-Hydroxy ketones and esters are obtained efficiently in the presence of 10 mol% of $Bi(OTf)_3{\cdot}nH_2O$ (with $1 < n < 4$).

Initially, we screened various conditions for the Mukaiyama aldol reaction of benzaldehyde (**1a**) and (1-phenylvinyloxy)trimethylsilane (**2a**) in the presence of $Bi(OTf)_3{\cdot}nH_2O$ (Table 1). The effect of the catalyst loading was examined in the test reaction, using $[Bmim]BF_4$ at 25 °C. When the reaction was carried out with 10 mol% of $Bi(OTf)_3{\cdot}nH_2O$, the product was obtained with the best yield (3-hydroxy-1,3-diphenylpropan-1-one, 86%; silylated 3-hydroxy-1,3-diphenylpropan-1-one: 6%) (Table 1, Entry 1).

Several examples of $Bi(OTf)_3$-catalyzed Mukaiyama aldol reactions with various silyl enolates are summarized in Table 1. Several silyl enol ethers derived from aromatic ketones were treated with benzaldehyde (**1a**) in the presence of 10 mol% of $Bi(OTf)_3{\cdot}nH_2O$. The corresponding β-hydroxy ketones **3a–d** were obtained in moderate to very good yields (Table 1, Entries 1–4). Trimethyl(prop-1-en-2-yloxy)silane (**2e**) afforded β-hydroxy ketone **3e** in moderate yield (Table 1, Entry 5). The silyl enol ether **2f** derived from cyclopentanone afforded the corresponding β-hydroxy ketone **3f** with a good yield (Table 1, Entry 6). Silyl ketene acetals were also treated with benzaldehyde (**1a**) under the same conditions. The trimethylsilylketene acetal **2g** of phenyl acetate afforded the β-hydroxy ester **3g** with a moderate yield (Table 1, Entry 7). Thioester **3h** was obtained using the same conditions, albeit with poor *syn*/*anti* selectivity (Table 1, Entry 8).

Next, various aldehydes were tested and the results are summarized in Table 2. (1-Phenylvinyloxy)trimethylsilane

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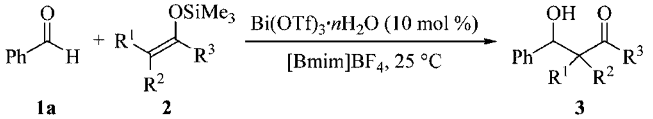
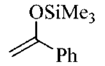
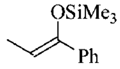
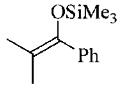
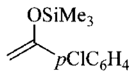
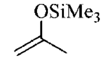
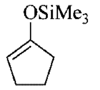
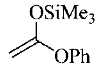
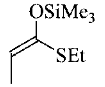
Table 1. $Bi(OTf)_3$-catalyzed Mukaiyama aldol reaction involving benzaldehyde (**1a**) and silyl enolates.[a]



1a **2** **3**

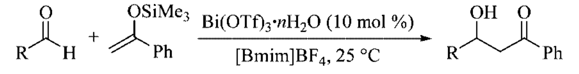
Entry	Silyl enolate **2**	t [h]	Product **3**	Yield of product **3** [%][b]
1		5	**3a**	92[c]
2		8	**3b**	83[d]
3		23	**3c**	77
4		6	**3d**	56[c]
5		22	**3e**	63[c,e]
6		23	**3f**	81[c,f]
7		21	**3g**	56
8		19	**3h**	64[g]

[a] Conditions: benzaldehyde (**1a**) (1.0 equiv.), silyl enolate (2 equiv.), $Bi(OTf)_3 \cdot nH_2O$ (0.10 equiv.), concentration = 2 M. [b] Isolated yield. [c] Including TMS-protected aldol product. [d] A 50:50 mixture of *syn*/*anti* stereoisomers was obtained. [e] 4 equiv. of silyl enol ether were used. [f] A 55:45 mixture of *syn*/*anti* stereoisomers was obtained. [g] A 61:39 mixture of *syn*/*anti* stereoisomers was obtained.

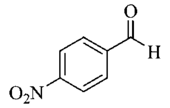
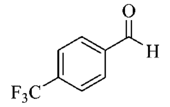
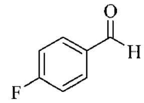
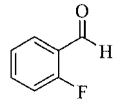
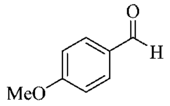
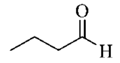
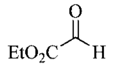
was chosen as the silyl enol ether partner. Generally, moderate to very good yields of β-hydroxy ketone **3** were obtained with 2 equiv. of (1-phenylvinyloxy)trimethylsilane (**2a**) and 0.10 equiv. of $Bi(OTf)_3 \cdot nH_2O$ at 25 °C in $[Bmim]BF_4$. Aromatic aldehydes reacted smoothly to give the corresponding β-hydroxy ketone derivatives **3** (Table 2, Entries 1–5). The reaction worked well with a variety of aldehydes including those bearing an electron-withdrawing group, and the corresponding β-hydroxy ketone **3** was obtained with moderate to very good yields (Table 2, Entries 1–4). Electron-rich *p*-methoxybenzaldehyde led to the desired product in moderate yield (Table 2, Entry 5). Aliphatic aldehydes reacted with (1-phenylvinyloxy)trimethylsilane (**2a**) under the same conditions and afforded the corresponding β-hydroxy ketones **3** in moderate yield (Table 2, Entries 6 and 7). Replacing the aldehyde by a ketone has not been successful as no conversion was observed in the reaction of acetophenone with (1-phenylvinyloxy)trimethylsilane (**2a**).

In view of "green chemistry", reuse of solvent is preferable. In the reaction of benzaldehyde (**1a**) with (1-phenylvinyloxy)trimethylsilane (**2a**), the ionic liquid and the Lewis acid were recovered after extracting the product with diethyl ether. Successive reuse of the recovered ionic liquid in the same reaction afforded the products in good yield. The study of the recycling is still in progress and the detailed results will be disclosed soon in a full paper.

Table 2. $Bi(OTf)_3$-catalyzed Mukaiyama aldol reaction involving various aldehydes and (1-phenylvinyloxy)trimethylsilane (**2a**).[a]



1 **2a** **3**

Entry	Aldehyde **1**	t [h]	Product **3**	Yield of product **3** (%)[b]
1		6	**3i**	79
2		40	**3j**	58
3		27	**3k**	87
4		23	**3l**	89
5		26	**3m**	47
6		7	**3n**	51
7		40	**3o**	48

[a] Conditions: aldehyde (1.0 equiv.), (1-phenylvinyloxy)trimethylsilane (**2a**) (2 equiv.), $Bi(OTf)_3 \cdot nH_2O$ (0.10 equiv.), concentration = 2 M. [b] Isolated yield.

In summary, we have found that the Mukaiyama aldol reaction in an ionic liquid proceeds smoothly with silyl enolates and a catalytic amount of $Bi(OTf)_3 \cdot nH_2O$. This method offers several advantages including mild reaction conditions, green solvent chemistry, and no formation of by-products. The β-hydroxy carbonyl compound is easily purified. Because of its numerous benefits, the $Bi(OTf)_3 \cdot nH_2O$ protocol should find utility in the synthesis of biologically active compounds. Development of other $Bi(OTf)_3 \cdot nH_2O$-catalyzed condensation reactions and related mechanistic studies will be reported in due course.

Experimental Section

General Procedures: Infrared spectra were recorded with an FT IR spectrometer and are reported in cm^{-1}. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded with a 400 MHz NMR spectrometer in $CDCl_3$. For ^1H NMR, tetramethylsilane (TMS) served as internal standard (δ = 0 ppm). For ^{13}C NMR, $CDCl_3$ was used as internal standard (δ = 77.0 ppm) and spectra were obtained with complete proton decoupling. For ^{19}F NMR, $CFCl_3$ was used as internal standard (δ = 0 ppm). The ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate ($[Bmim]BF_4$) was stirred under vacuum (0.1 Torr, 1 h) prior to use.

General Procedure for the Mukaiyama Aldol Reaction: Under argon, the aldehyde (0.50 mmol) and silyl enolate (1.0 mmol) were added dropwise successively to a solution of $Bi(OTf)_3\cdot nH_2O$ (0.10 mmol) in 0.25 mL of dry [Bmim]BF_4. The mixture was stirred at room temperature until the reaction was completed as indicated by TLC. The reaction mixture was extracted with diethyl ether. The ethereal phase was concentrated under vacuum (rotary evaporator). The crude product was purified by silica gel chromatography (hexane/ethyl acetate, 85:15–95:5). β-Hydroxy carbonyl compounds **3a**–**o** accord exactly with those that have been previously reported in the literature.

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