

# Recent Advances in Bismuth Mediated Aldol and Mannich Reactions

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**Dedicated to Professor Alain Krief on the occasion of his 65<sup>th</sup> birthday**

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## Abstract

Bismuth metal and bismuth salts have been used for various aldol and Mannich type reactions. Bismuth(III) salts, and bismuth(III) triflate in particular, are cheap and environmentally benign Lewis acids. This account highlights the scope and applications of bismuth(0) and bismuth(III) salts in fundamental reactions like the aldol and Mannich reactions. Various bismuth mediated Mukaiyama aldol and Mannich type reactions are presented. Bismuth(0) mediated Reformatsky and imino Reformatsky reactions are also disclosed in this account.

**Keywords:** Bismuth, Bismuth triflate, Aldol, Mukaiyama aldol, Mannich, Multicomponent reactions, Green chemistry

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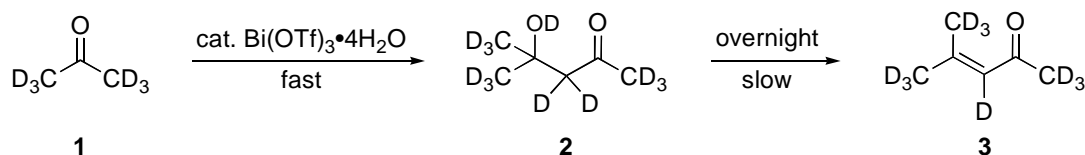
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## 1. Introduction

Bismuth compounds have recently attracted much attention due to low toxicity, low cost, and good stability.<sup>1</sup> Bismuth has an electron configuration of  $[\text{Xe}]4f^{14}5d^{10}6s^26p^3$ , and due to weak shielding of the 4f electrons, bismuth compounds exhibit Lewis acidity. Among all, bismuth(III) salts have been widely used and were reported as effective catalysts for an array of synthetic transformations: opening of epoxides,<sup>2</sup> formation and deprotection of acetals,<sup>3</sup> Friedel-Crafts reactions,<sup>4</sup> Fries and Claisen rearrangements,<sup>5</sup> and Sakurai reactions.<sup>6</sup> Bismuth triflate  $[\text{Bi}(\text{OTf})_3]$  is particularly attractive due to its commercial availability or ease of preparation from commercially available starting materials.<sup>7</sup>

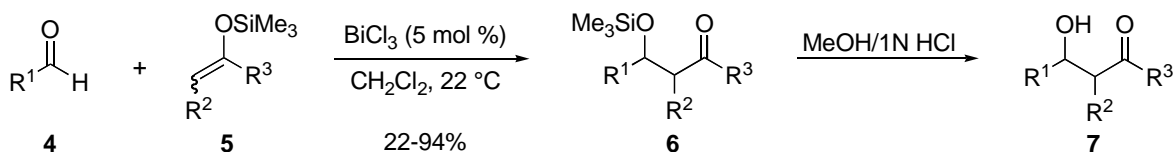
## 2. Bismuth mediated aldol reactions

There has been a few preparations of interest reported for the synthesis of  $\text{Bi}(\text{OTf})_3$ .<sup>7</sup> Noteworthy is the work of Torisawa for an expedient preparative protocol and characterization of  $\text{Bi}(\text{OTf})_3$ .<sup>8</sup> NMR analysis of  $\text{Bi}(\text{OTf})_3$  in acetone-*d*<sub>6</sub> **1** revealed that  $\text{Bi}(\text{OTf})_3$  was able to promote the aldol reaction of acetone to yield the corresponding aldol **2**, itself undergoing slow dehydration to mesityl-*d* oxide **3**. The catalytic activities of a series of prepared metal triflates, including  $\text{Bi}(\text{OTf})_3$ , were tested in this aldol reaction on an analytical scale (Scheme 1). This catalytic activity of  $\text{Bi}(\text{OTf})_3$  was also shown to be higher than that of other bismuth salts and metal triflates.<sup>8</sup> To our knowledge, this is the only example of direct aldol reaction catalyzed by Bi(III) salts.



Scheme 1

**2.1 Bismuth(III) catalyzed Mukaiyama aldol reactions.** Numerous examples of aldol and aldol type reactions have been studied using bismuth(III) salts in catalytic amounts. Wada was first to report the Mukaiyama aldol reaction between various aldehydes **4** and silyl enol ethers **5** at room temperature in the presence of 5 mol %  $\text{BiCl}_3$  (Scheme 2).<sup>9</sup>

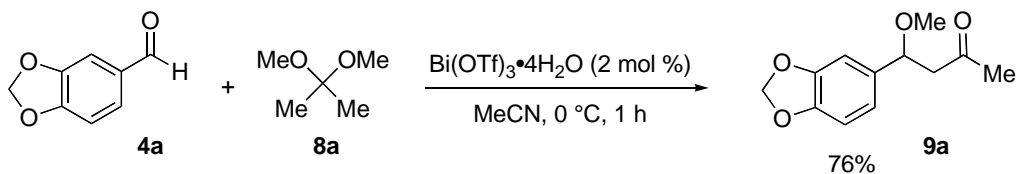


Scheme 2



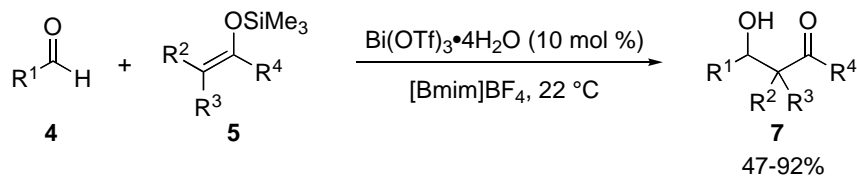
Given the efficiency of the catalyst, Choudary investigated in a logical extension a new recoverable and reusable encapsulated  $\text{Bi}(\text{OTf})_3$  catalyst.<sup>14</sup> It was reported to be effective for allylation reactions, Michael type additions, acylation of alcohols, Baeyer-Villiger oxidations and aldol condensations. The microencapsulated  $\text{Bi}(\text{OTf})_3$  [ $\text{MCBi}(\text{OTf})_3$ ] was prepared using a standard microencapsulated procedure: powdered  $\text{Bi}(\text{OTf})_3$  was added as a solid core to a solution of polystyrene and cyclohexane at 40 °C. After stirring for 1 h, the solution was cooled to 0 °C.  $\text{Bi}(\text{OTf})_3$  encapsulated in polystyrene was used for the reaction of various aromatic aldehydes with acetone for three cycles without significant loss in activity. There was almost no leaching of  $\text{Bi}(\text{OTf})_3$  observed from the  $\text{MCBi}(\text{OTf})_3$ .

More recently, from Mohan's group,  $\text{Bi}(\text{OTf})_3$  was shown to catalyze efficiently the aldol condensation between piperonal **4a** and 2,2-dimethoxypropane **8a** (Scheme 6).<sup>15</sup> In these conditions, 2-methoxypropene was assumed to be generated from 2,2-dimethoxypropane.



### Scheme 6

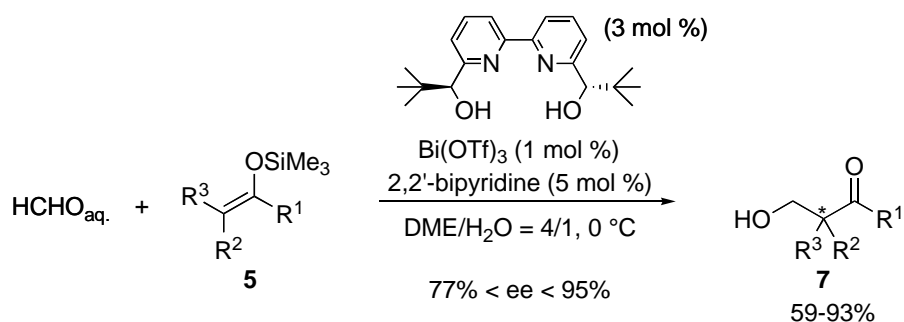
As part of our ongoing interest in replacing classical organic solvents, the Mukaiyama aldol reaction procedure was improved using the ionic liquid  $[\text{Bmim}]\text{BF}_4$  as a substitute to dichloromethane.<sup>16</sup> Various silyl enol ethers **5** and silyl ketene acetals **10** were reacted with substituted benzaldehydes **4** in the presence of 10 mol %  $\text{Bi}(\text{OTf})_3 \cdot 4\text{H}_2\text{O}$  to give the corresponding aldol in yields up to 92% (Scheme 7). The reaction was also studied between various aldehydes and (1-phenylvinyloxy)trimethylsilane. Aromatic aldehydes including those bearing an electron-withdrawing group furnished the corresponding adduct in a better yield than aliphatic aldehydes and electron-rich *p*-methoxybenzaldehyde.



### Scheme 7

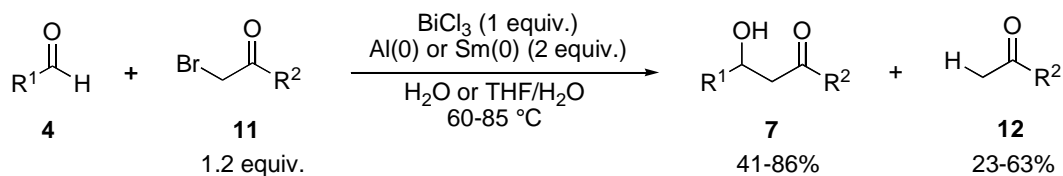
Significant progress was made with the development of an asymmetric version by Kobayashi in the hydroxymethylation of silyl enolates with an aqueous formaldehyde solution, using  $\text{Bi}(\text{OTf})_3$  stabilized by chiral pyridine complexes (Scheme 8).<sup>17</sup> Moderate to excellent yields and

enantioselectivities up to 95% ee were achieved. This was the first example of a highly enantioselective Mukaiyama aldol reaction using a chiral bismuth catalyst in aqueous media.



### Scheme 8

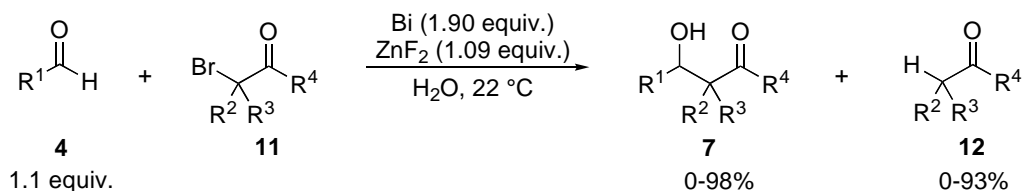
**2.2 Bismuth(0) mediated Reformatsky reactions.** Zhang reported a one pot Reformatsky type reaction using bismuth(III) salts.<sup>18</sup>  $\alpha$ -Halo carbonyl compounds **11** reacted with aldehydes in water to give  $\beta$ -hydroxy carbonyl compounds **7** in the presence of bismuth(III) chloride and metallic aluminum (Scheme 9). The reaction gave yields up to 86%. Reduction of the  $\alpha$ -bromocarbonyl compound was found to be a major side reaction affording carbonyl compounds **12**. It is not clear whether the reactive species is a C or a O metallated intermediate. More recently, another group disclosed the aldol type reaction in a tetrahydrofuran-water mixed solvent using a samarium/BiCl<sub>3</sub> catalyst, and reported moderate to good yields (52-81%).<sup>19</sup>



### Scheme 9

Metallic bismuth was found to catalyze efficiently the aldol type reaction of  $\alpha$ -bromoketones **11** with various aldehydes (Scheme 10). Atomized metals, in this case bismuth(0) powder, are much less reactive than those prepared from the reduction of the corresponding salts with alkali metals. This can be explained by the presence of a metal oxide layer that prevents high reactivity by minimizing the reactive metallic surface of metal particles. Hence, further activation is required. Chan used zinc fluoride efficiently to promote the crossed aldol reaction in a both regioselective and *syn* diastereoselective manner.<sup>20</sup>  $\alpha$ -Bromoisobutyrophenone would react smoothly in water with a variety of aliphatic and aromatic aldehydes and ketones to yield the corresponding aldol products. Reduction of the bromocarbonyl compound was found to be the major product for branched electrophiles ( $\text{R}^4 = \text{CH}(\text{C}_3\text{H}_7)\text{CH}_3$ ) and ketones (acetophenone), as

very little of the expected aldol product was obtained. The generality of the reaction was further examined with the reaction of various  $\alpha$ -bromocarbonyl compounds with benzaldehyde.  $\alpha$ -Bromoketones derived from aromatic ketones were clearly found to give the best yields.

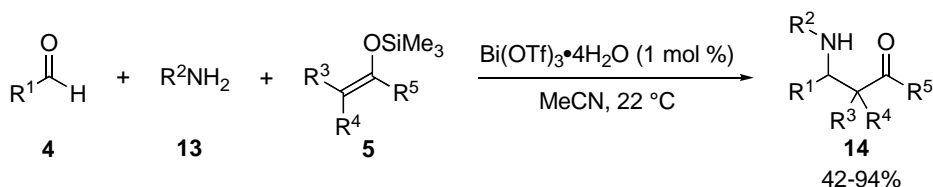


Scheme 10

### 3. Bismuth mediated Mannich type reactions

#### 3.1 Bismuth(III) catalyzed Mannich type reactions

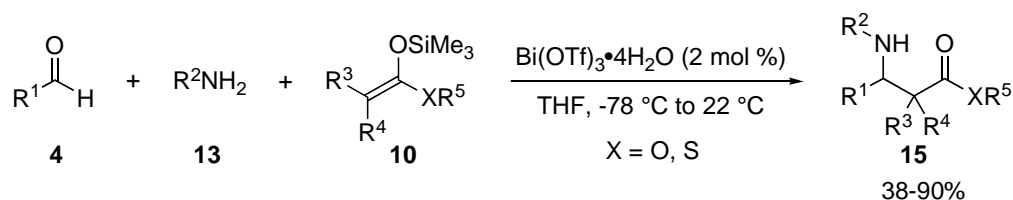
**3.1.1 One pot bismuth(III) catalyzed Mannich type reactions.** Silyl enolates **5** derived from aromatic and aliphatic ketones were reacted with *in situ* formed imines in the presence of catalytic amount of Bi(OTf)<sub>3</sub>•4H<sub>2</sub>O (Scheme 11).<sup>21</sup>  $\beta$ -amino ketones **14** were obtained in very good yields (up to 94%) with imines derived from aromatic, heteroaromatic,  $\alpha$ ,  $\beta$ -unsaturated, and aliphatic aldehydes. The reaction proceeded smoothly with substituted and unsubstituted aromatic amines or with carbamates. Our method offers several advantages including mild reaction conditions, very low catalyst loading (1 mol %) and no need for prior isolation of the imine. The reaction afforded a clean product without side reactions such as deamination. In addition, complete chemoselectivity was observed between Mukaiyama aldol and Mannich type reaction. A similar trend was reported by Kobayashi in a competition reaction in which BiCl<sub>3</sub> proved to be aldimine selective.<sup>22</sup>



Scheme 11

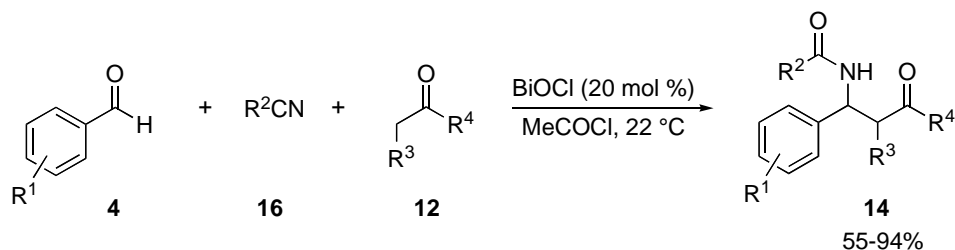
In a similar one pot strategy, our method was extended to using silyl ketene acetals **10**.  $\beta$ -amino esters and  $\beta$ -amino thioesters **15** were smoothly obtained with 0.02 equivalent of Bi(OTf)<sub>3</sub>•4H<sub>2</sub>O (Scheme 12).<sup>23</sup> Good to excellent yields were achieved with aromatic aldehydes, aniline, and di-, tri-, or tetra-substituted silyl ketene acetals, but  $\alpha$ ,  $\beta$ -unsaturated or aliphatic

aldehydes did not show to be as reactive. This method provides easy access to compounds bearing a  $\beta$ -amino ester core structure, in a mild and highly catalytic process.



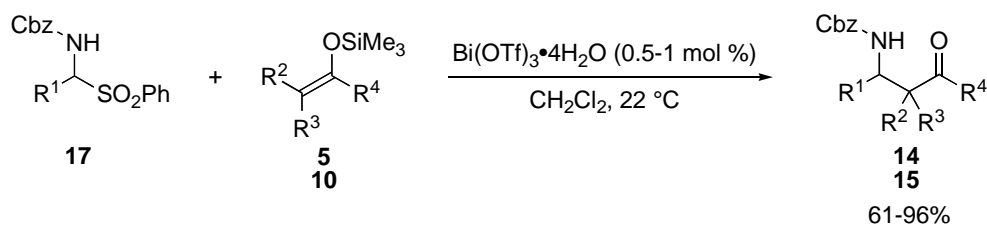
## Scheme 12

**3.1.2 Bismuth(III) catalyzed Mannich type reactions with nitriles.**  $\beta$ -Amido ketones **14** were efficiently synthesized in a multicomponent process from aromatic aldehydes **4**, enolizable ketones **12**, and acetyl chloride in the presence of nitrile **16** used as the solvent (Scheme 13). BiOCl was selected as a procatalyst to generate BiCl<sub>3</sub> *in situ*.<sup>24</sup> More examples were also disclosed with BiCl<sub>3</sub> and Bi(OTf)<sub>3</sub>.<sup>25</sup>



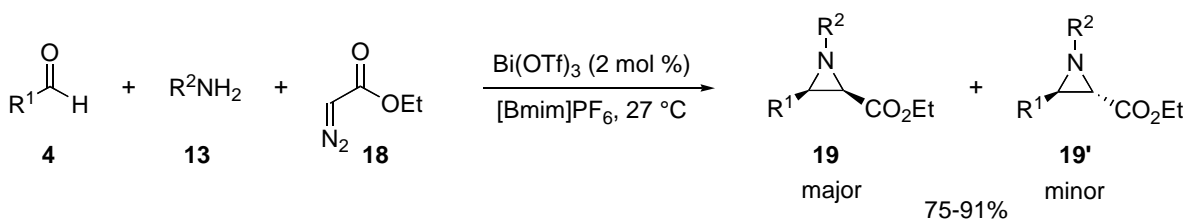
## Scheme 13

**3.2 Bismuth(III) catalyzed Mannich type reactions of *N*-alkoxycarbonylamino sulfones.** *N*-alkoxycarbonylamino sulfones **17** are stable as imine precursors and are known to be in equilibrium with their corresponding imine or iminium under Lewis acidic conditions, to provide an *in situ* source of electrophile. When *N*-alkoxycarbonylamino sulfones **17** were reacted with silyl enolates **5** or **10** in the presence of catalytic amount of Bi(OTf)<sub>3</sub>·4H<sub>2</sub>O, protected  $\beta$ -amino carbonyl compounds **14** were readily isolated (up to 96% yield) (Scheme 14).<sup>26</sup> Silyl enolates derived from ketones (**5**), as well as esters and thioesters (**10**), could also be employed. The reaction proceeded with *N*-alkoxycarbonylamino sulfones prepared from both aromatic aldehydes and aliphatic aldehydes (R<sup>1</sup> = aryl or alkyl). The main advantage of this method is obviously the very low catalyst loading required (typically 0.5–1 mol %). This is a major improvement in regard of the stoichiometric amount of activator usually required for this transformation.<sup>27</sup>



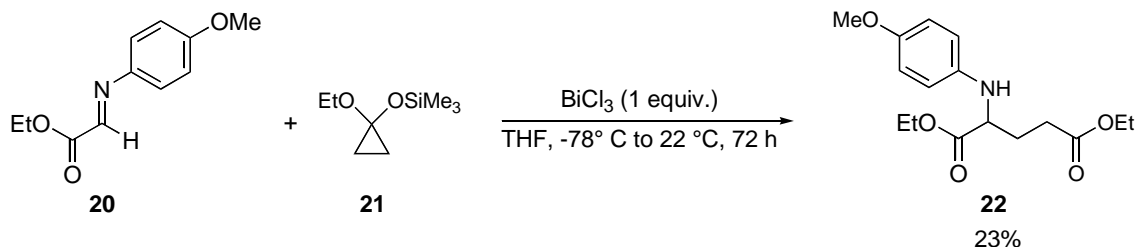
Scheme 14

**3.3 Bismuth(III) catalyzed aziridination reactions.** Aziridination reactions were reported with imines generated *in situ* and ethyl diazoacetate **18** in ionic liquids (Scheme 15).<sup>28</sup> Catalytic amount of Bi(OTf)<sub>3</sub> was required for this transformation which was proposed to proceed *via* an imino aldol type mechanism. The corresponding aziridine carboxylates **19** were obtained in both very good yield and excellent *cis* diastereoselectivity. Bi(OTf)<sub>3</sub> was successfully recycled for three to four subsequent runs with slow and gradual decrease in yield.



Scheme 15

**3.4 Bismuth(III) mediated homo Mannich type reactions.** Nakamura demonstrated that cyclopropanone acetal **21** could act as an homoenolate precursor when treated with Lewis acid such as TiCl<sub>4</sub>, ZnCl<sub>2</sub>, and BiCl<sub>3</sub>.<sup>29</sup> Recently, Wastermann reported the first homo Mannich type reaction. Although Cu(OTf)<sub>2</sub> proved to be the best catalyst for this reaction, BiCl<sub>3</sub> also catalyzed the reaction but led to lower yields of **22** (Scheme 16).<sup>30</sup>

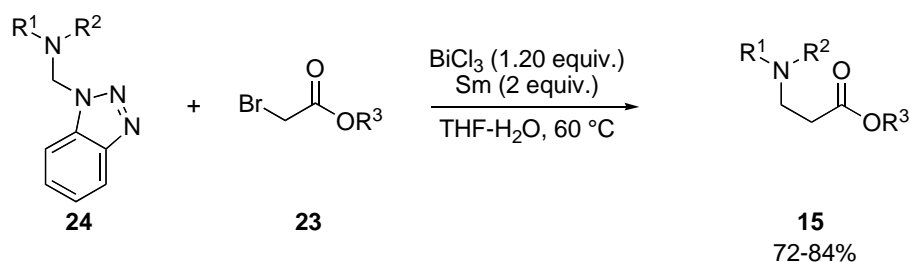


Scheme 16

**3.5 Bismuth(0) mediated imino Reformatsky reactions.**  $\alpha$ -Bromoesters **23** were efficiently activated by metal bismuth generated *in situ* *via* a BiCl<sub>3</sub>/Sm system in aqueous medium (Scheme



17). The reaction with 1-( $\alpha$ -aminoalkyl)-benzotriazoles **24** led to  $\beta$ -amino esters **15** in moderate to good yields.<sup>31</sup>



**Scheme 17**

## 4. Conclusions

Easy preparation of  $\text{Bi}(\text{OTf})_3$  in a large quantity (from triphenylbismuth or bismuth(III) oxide) as well as a stable and recyclable nature demonstrate its superiority to other triflates for contemporary synthesis. Exceptionally low toxicity is another benefit of bismuth salts, which will certainly spread out their catalytic and stoichiometric use in medicinal chemistry.

## Acknowledgements

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