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## Article

# A general and efficient Lewis acid catalysed Mukaiyama-aldol reaction of difluoroenoxy silanes and ketones

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## ABSTRACT

We report a general and highly efficient Mukaiyama-aldol reaction of ketones and difluoroenoxy silanes. While the reaction of aryl ketones worked efficiently in the presence of  $\text{Bi}(\text{OTf})_3$ , that of aliphatic ketones required the use of  $\text{Sc}(\text{OTf})_3$ . In addition,  $\text{Sc}(\text{OTf})_3$  was capable of achieving excellent 1,2-selectivity in the corresponding reaction of  $\alpha,\beta$ -unsaturated ketones. This method provides a facile access to differently substituted  $\beta$ -hydroxy  $\alpha,\alpha$ -difluoro ketones, versatile synthons for difluoromethylated tertiary alcohols.

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## 1. Introduction

The selective incorporation of a fluoroalkyl group is a powerful and routine strategy in drug design to modulate pharmacological properties of bioactive molecules [1–10]. Accordingly, it is of current interests to develop efficient synthesis of fluoroalkyl-containing synthons for various transformations. However, while selective trifluoromethylation has been intensively studied [11], the selective introduction of *gem*-difluoroalkyl groups are much less studied [12–23]. The presence of a *gem*-difluoromethylene group ( $\text{CF}_2$ ) may also affect the electronic properties of its neighboring groups and lead to beneficial effects such as the enhancement in lipophilicity [24–29]. For example, several drugs such as eflornithine [25] and gemcitabine [26] are rationally designed by introducing a  $\text{CF}_2$  group. The difluoro analogues of rhodopeptin [27], docetaxel [28] and Vitamin D [29] all exhibited improved properties. Therefore, facile synthesis of versatile  $\text{CF}_2$ -containing building blocks to allow the selective difluoroalkylation is highly desirable.

Recently, catalytic functionalization of difluoroenoxy silanes, readily accessed from  $\alpha\text{-CF}_3$  ketones [30–31], has emerged as a fruitful method for the selective introduction of an  $\alpha$ -difluorinated ketone moiety as a synthetic handle for various

reactions [32]. To date, they have been found utility in aldol [33–39], Mannich [40–48], Michael [49] and olefination reaction [50]. Particularly, the aldol reaction of difluoroenoxy silanes and carbonyl compounds is very attractive for the synthesis of  $\beta$ -hydroxy  $\alpha,\alpha$ -difluoro ketones [51–53] as valuable synthons to access difluorinated products such as 1,3-diols, 1,3-aminoalcohols and  $\beta$ -hydroxy acid derivatives [35,38]. However, while the corresponding aldol reaction of aldehydes was well developed, ketones were still presented as problematic substrates in terms of the scopes and catalyst systems. To our knowledge, only one report was known that Uneyama and co-workers [54] tried using 50 mol%  $\text{TiCl}_4$  to mediate the aldol reaction of **1a** with acetophenone and two cyclic ketones, to give adducts in moderate to good yields (Eq. (1), Scheme 1).

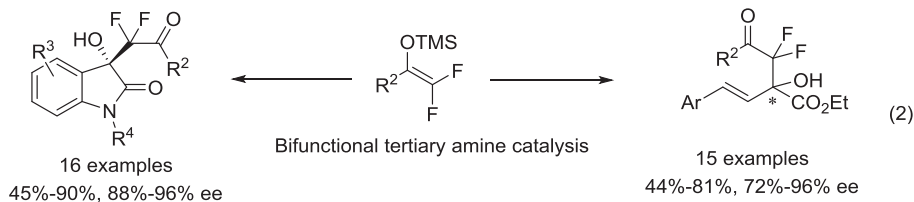
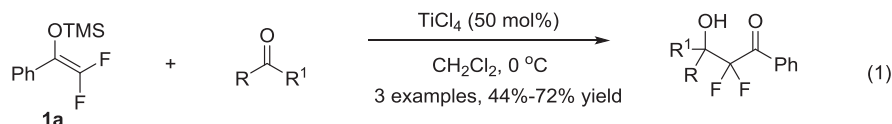
With our interest in exploring the potential of fluorinated enol silyl ethers in selective fluoroalkylation [35–39,46,47,49,50], we found that tertiary amines could activate difluoroenoxy silanes **1** to react with highly active ketones such as isatins [35] and  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters [36] (Eq. (2), Scheme 2).

We also developed a highly efficient on-water catalyst-free aldol reaction of difluoroenoxy silanes with aldehydes or activated ketones [38]. However, common unactivated ketones are not workable in both protocols. To date, the use of acyclic aliphatic ketones, functionalized ketones and  $\alpha,\beta$ -unsaturated enones for the diverse synthesis of tertiary alcohols featuring an

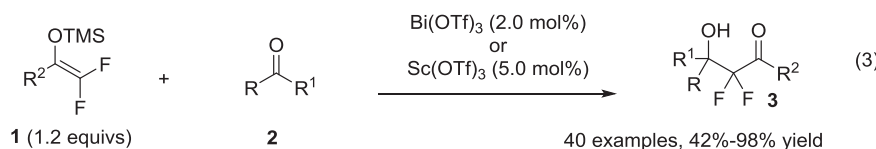
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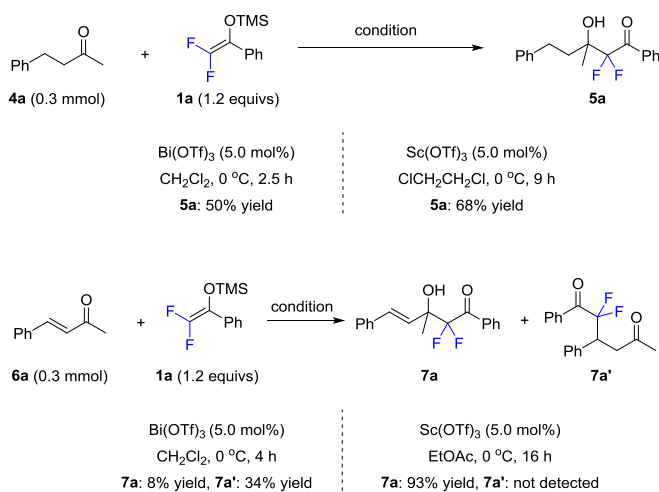
## Previous reports



## This work



Scheme 1. Advances in the Mukaiyama-aldol reaction of difluoroenoxysilanes and ketones.

Scheme 2. The optimal conditions for the reaction of alkyl ketones or  $\alpha,\beta$ -unsaturated enones.

$\alpha$ -difluorinated ketone moiety is still undeveloped [55]. Therefore, it is necessary to identify efficient catalysts to develop a general Mukaiyama-aldol reaction of **1** and ketones. Here, we wish to report our finding that Bi(OTf)<sub>3</sub> [56] and Sc(OTf)<sub>3</sub> [57] were powerful catalysts for this reaction.

## 2. Materials and methods

Typical procedure for the reaction (**3a** as an example): under an atmosphere of N<sub>2</sub>, to a 25 mL oven-dried Schlenk tube were added Bi(OTf)<sub>3</sub> (5.3 mg, 0.008 mmol, 2.0 mol%), followed by anhydrous CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) and acetophenone **2a** (0.40 mmol). The mixture was stirred at 0 °C for 10 min and then difluoroenol silyl ethers **1a** (0.48 mmol) was added. The reaction was continually stirred at 0 °C till the full consumption of **1a** by TLC analysis (about 7.5 h), and then the reaction mixture was directly subjected to the column chromatography by using petroleum ether/acetone (20/1,

v:v) as the elution to afford product **3a** in 90% yield as white solid [51]. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.92 (d, *J* = 8.0 Hz, 2H), 7.59–7.55 (m, 3H), 7.42–7.38 (m, 2H), 7.36–7.27 (m, 3H), 3.52 (s, 1H), 1.82 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  191.60 (t, *J* = 30 Hz, 1C), 140.22, 134.20, 133.15 (d, *J* = 2 Hz, 1C), 130.21 (t, *J* = 3 Hz, 1C), 128.34, 128.05, 127.98, 126.31 (d, *J* = 2 Hz, 1C), 116.55 (t, *J* = 262 Hz, 1C), 76.39 (t, *J* = 24 Hz, 1C), 23.93 (t, *J* = 3 Hz, 1C); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):  $\delta$  -107.55.

## 3. Results and discussion

We began conditions optimization by evaluating different metal triflates in the reaction of difluoroenoxysilane **1a** and acetophenone **2a**. It turned out that metal Lewis acids played an important role in reaction development, as shown in Table 1.

When the reaction was carried out in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C, Yb(OTf)<sub>3</sub>, Cu(OTf)<sub>2</sub>, Ni(OTf)<sub>2</sub> and Zn(OTf)<sub>2</sub> failed to catalyse the reaction; however, we were pleased to find that a number of metal triflates could mediate this reaction at a catalyst loading of 2.0 mol%. The reaction time was referred to that required for the full consumption of difluoroenoxysilane **1a**. The use of Mg(OTf)<sub>2</sub> and Ga(OTf)<sub>3</sub> gave the desired product **3a** in only moderate yields (entries 1, 2); however, Hg(OTf)<sub>2</sub> and Fe(OTf)<sub>3</sub> as the catalysts substantially improved the yields of **3a** to 62% (entries 3, 4). Gratifyingly, Sc(OTf)<sub>3</sub> and Bi(OTf)<sub>3</sub> proved to be more efficient (entries 5, 6). In particular, Bi(OTf)<sub>3</sub> could catalyse the reaction to finish within 7 h to give **3a** in 90% yield (entry 6). Further examination of solvent effects revealed that when using Bi(OTf)<sub>3</sub> as the catalyst, CH<sub>2</sub>Cl<sub>2</sub> was the solvent of choice (entry 6 vs. entries 7–12). Considering the possibility of the hydrolysis of Bi(OTf)<sub>3</sub> to produce HOTf as the real catalytic species, we also tried using HOTf as the catalyst. When using 2 mol% HOTf, the reaction gave **3a** in only 52% yield (entry 13). If the loading of HOTf was increased to 10 mol%, the reaction could complete within 1.5 h and afforded **3a** in a slightly higher 66% yield (entry 14). This suggested that metal triflates were the real catalytic species.

Under the best conditions, we examined the substrate scopes of differently substituted ketones and difluoroenoxysilanes, as shown in Table 2.

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