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# "All-water" synthesis of $\beta$ -amino $\alpha$ , $\alpha$ -difluoro ketones from fluorinated enol silyl ethers and imines

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**Abstract:** A one-pot synthesis of  $\beta$ -amino  $\alpha, \alpha$ -difluoro ketones is developed without any additives. Through a series of control experiments we found that water plays a crucial and indispensable role. The hydrogen bond between water and fluorinated enol silyl ether has a significant impact on the addition reaction.

#### Introduction

Fluorine, emerged as a magic element in pharmaceuticals, agrochemicals and functional materials, has become more and more significant for a large range of applications.<sup>[1]</sup> Unique physical and chemical advantages conferred by the C-F bond usually result in enhanced membrane permeability, elevated electronegativity and oxidation resistance.<sup>[2]</sup> Compounds containing-CF<sub>2</sub>R groups have been widely applied in the preparation of pharmaceuticals, agrochemicals, and enzyme inhibitors. Difluoroalkylation can not only introduce fluorine atoms into a molecule, but also install a nonfluorinated moiety simultaneously which can be further modified into various CF<sub>2</sub> containing functional groups.<sup>[3]</sup>

Alkyl amines are common structural features in natural products, pharmaceutical agents, and other small-molecule probes of biological function.<sup>[4]</sup> Among them,  $\beta$ -amino  $\alpha, \alpha$ -difluoro ketones as valuable intermediates for drug design have received considerable attention.<sup>[5]</sup> For example, rhodopeptin derivative which contained a  $\beta$ -amino- $\alpha, \alpha$ -difluoro carbonyl unit exhibited improved physical and biological properties while retaining its antifungal activity.<sup>[6]</sup> And it has been proved that the introduction of  $\beta$ -amino  $\alpha, \alpha$ -difluoro ketone units into peptides is successful in designing enzyme inhibitors such as protease inhibitors.<sup>[7]</sup>

The traditional synthetic methods for preparing  $\beta$ -amino  $\alpha, \alpha$ difluoro ketones rely on deoxydifluorination of  $\beta$ -keto carbonyl compounds with diethylaminosulfur trifluoride,<sup>[8]</sup> the Reformatsky reaction of  $\alpha$ -bromo  $\alpha, \alpha$ -difluoroacetate with aldimines <sup>[9]</sup> and the Mannich-type reaction of difluorinated silyl enol ether with aldimines.<sup>[10]</sup> <sup>[11]</sup> Although remarkable progress has been made, most current methods still suffer from harsh reaction conditions. Therefore, further developments are needed to enable the use of cheap and abundantly available starting materials as well as mild reaction conditions. In 2014, Zhou et.al reported an on water reaction of the difluoroenoxysilanes with aldehydes, ketones, and isatylidene malononitriles without catalyst.<sup>[12]</sup> That process implied that the C-F···H-O interactions between the difluoroenoxysilane and water at the phase boundary cooperate

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with the hydrogen-bonding activation of the electrophile to facilitate on water reactions. Inspired by that result, we wonder if aldimines, generated in situ from carbonyl compounds and amino compounds, could react with difluoroenoxysilanes in water offering a direct entry towards the  $\beta$ -amino  $\alpha$ , $\alpha$ -difluoro ketones without any additives. To this end, we report herein a novel "all-water" synthesis of  $\beta$ -amino  $\alpha$ , $\alpha$ -difluoro ketones from fluorinated enol silyl ethers and imines.

#### **Results and Discussion**

Initially, we commenced our investigation by treating benzaldehyde (1a), aniline (2a) and difluoroenoxysilane (3a) in water without any additives. To our delight, the reaction provided a 65% yield of the desired product 4a. The impact of various solvents was also evaluated, and the water gave the highest yield of 4a. When twice equivalent 3a was added, the yield was greatly improved to 89%. To our delight, the yield had no significant effect when the time was reduced to 6 hours. In the screening of the solvents, we found MeCN also afforded a good result just a bit worse than water, but it was hard to confirm if MeCN had some special effects to promote the reaction. Therefore, control experiments were made to reveal this phenomenon.

Table 1. optimization of reaction conditions <sup>a</sup>.

CHO + 1a	NH <sub>2</sub> + F	OTMS Ph solvent 3a	O HN F F 4a
Entry	Solvent	Time [h]	Yield <sup>b</sup> [%]
1	H <sub>2</sub> O	24	65
2	EtOAc	24	15
3	MeCN	24	60
4	DMF	24	19
5	THF	24	11
6 <sup>c</sup>	H <sub>2</sub> O	24	89
7 °	H <sub>2</sub> O	12	87
8 °	H <sub>2</sub> O	6	90 (88) <sup>d</sup>
9 °	MeCN	6	85

<sup>a</sup> Reaction conditions: **1a** (0. 25 mmol), **2a** (1 equiv.), **3a** (1 equiv.), solvent (1 mL), vigorous stirring under at room temperature. <sup>b</sup> Yield based on <sup>19</sup>F NMR spectroscopy using trifluoroacetophenone as an internal standard. <sup>c</sup> **3a** (2 equiv.). <sup>d</sup> Value in parentheses refers to the isolated yield.

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#### Scheme 1. control experiments a.

(1)	+ 1a'	OTMS F Ph Solver F 3a	nt (dry) , rt O HN F F F 4a
	Entry	Solvent (dry)	Yield <sup>b</sup> [%]
	1	MeCN	19
	2	DMF	11
	3	EtOAc	5
	4	THF	6





R=NO<sub>2</sub>, **4e**, 65% (H<sub>2</sub>O), 42% (D<sub>2</sub>O)

<sup>a</sup> Reaction conditions: **1a**' (0. 25 mmol), **3a** (1 equiv.), solvent (1 mL), vigorous stirring under at room temperature, 6h. <sup>b</sup> Yield based on <sup>19</sup>F NMR spectroscopy using trifluoroacetophenone as an internal standard. <sup>c</sup> Reaction conditions: **1a** (0. 25 mmol), **2a** (1 equiv.), **3e** (1 equiv.), H<sub>2</sub>O (1 mL), vigorous stirring under at room temperterature. <sup>d</sup> Reaction conditions: **1a** (0. 25 mmol), **2a** (1 equiv.), **3a** (1 equiv.), **3a** (1 equiv.), D<sub>2</sub>O (1 mL), vigorous stirring under at room temperature.

In this reaction, imine was generated in situ from corresponding aldehyde and amine, and a molecule H<sub>2</sub>O was also produced. In order to rule out the effect of water, we carried out a series of reactions under Ar atmosphere and used imine 1a' as started substrate (Scheme 1). It was found that the yield of 4a was drastically reduced when the water in the reaction was strictly controlled. Therefore we speculate the small amount of water in the reaction plays a key role to promote the nucleophilic addition reaction. On the other hand, we should also figure out why only in MeCN could get a good yield. Then the hydrolysis of 3a in different solvents was tested. Just as expected, 3a was more stable in MeCN than other water-soluble solvents (Scheme S1, ESI†). It took 6 h for the complete hydrolysis of 3a in EtOAc. However the reaction of 1a' and 3a gave the adduct 4a in only 5% in EtOAc. At last, the hydrogen bond effect between C-F...H-O was also investigated. When 3a was replaced by 3e, trace corresponding product 5 was got. And monofluorinated analogue 3f reacted sluggishly to give 6 in 35% yield (NMR) under the same reaction conditions. However, the reactivity of 3a, 3e and 3f is different, so it is not enough to estimate whether the HB effect took a significant impact.<sup>[13]</sup> Then, using D<sub>2</sub>O as solvent was tested under standard conditions.<sup>[14]</sup> To our surprise, the almost similar yield of **4a** was obtained in D<sub>2</sub>O compared in water. Then another substrate which contains a nitro group was tested too. In this case, the yield of **4e** was significantly reduced. Based on this studies, we speculate that the HB effect plays an important role in promoting the reaction. According to this mechanistic insight, a proposed mechanism is illustrated in Figure 1.

Figure 1. a proposed mechanism.



Scheme 2. scope of the Nucleophilic Addition Reaction <sup>a, b</sup>.



 $^a$  Reaction conditions: 1 (0. 25 mmol), 2 (1 equiv.), 3a (2 equiv.), H\_2O (1 mL), vigorous stirring under at room temperature., 6 h.  $^{\rm b}$  isolated yield.

With the optimized reaction conditions established, the substrate scope of the protocol was surveyed (Scheme 2). Owing

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to the mild reaction conditions, the reaction condition has shown excellent tolerance to electron-donating substituents while got somewhat lower yields for electron-withdrawing substituents, tolerating many common functional groups such as cyano, nitro, trifluoromethyl, methoxy, and halogen. Also, 2-substituted and 3-substituted aldehydes or amines reacted efficiently to generate  $\beta$ -amino  $\alpha$ ,  $\alpha$  -difluoro ketones (**4h-4k**, **4n-4q**). Fortunately, heteroaromatic aldehydes or amines including furfural and furylamine also underwent the nucleophilic addition successfully (**4s**, **4t**). Inspired by these results, we tried to expand this kind of reaction to other silyl enol ethers. To our delight, the  $\beta$ -amino  $\alpha$ ,  $\alpha$ -difluoro ketones were generated in good yield (**4u-4z**). But when we tried to expand this kind of reaction to other fluorinated TMS-sources, such as TMSCF<sub>2</sub>Br and TMSCF<sub>2</sub>COOEt. However, trace desired product could be observed via GC-MS analysis.

#### Conclusions

In conclusion, we have developed a simple and efficent "all water" synthesis of  $\beta$ -amino  $\alpha$ , $\alpha$ -difluoro ketones. By experimental studies, we found that the water environment is important to prevent fluorinated enol silyl ethers from hydrolysis while trace of water is enough to promote the reaction, and the hydrogen bond between water and fluorinated enol silyl ether significantly impact the nucleophilic addition process. Based on these findings, more "all water" reactions are now in progress.

#### **Experimental Section**

To a 5 mL vial was added amines 1 (0.25 mmol) and aldehydes 2 (0.25 mmol), followed by 1 mL H<sub>2</sub>O and difluoroenoxysilane 3 (0.5 mmol). The reaction mixture was stirred at room temperature for 6 h, and then the mixture was extracted with EtOAc (3 \* 5.0 mL). The combined organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by flash chromatography using petrol ether/ethyl acetate as the eluent. The conditions for chromatography and data for characterization of the products are given in Supporting Information.

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Mannish reaction\*

"All-water" synthesis of  $\beta$ -amino  $\alpha$ , $\alpha$ -difluoro ketones from fluorinated enol silyl ethers and imines