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Reaction of aldimines and difluoroenoxysilane, an unexpected protocol for the synthesis of 2,2-difluoro-3-hydroxy-1-ones

Zhi-Liang Yuan[a], Yin Wei[b], Min Shi[a,b,*]

[a] Laboratory for Advanced Materials & Institute of Fine Chemicals, School of Chemistry & Molecular Engineering, East China University of Science and Technology, 130 Mei Long Lu, Shanghai 200237, China

[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032 China

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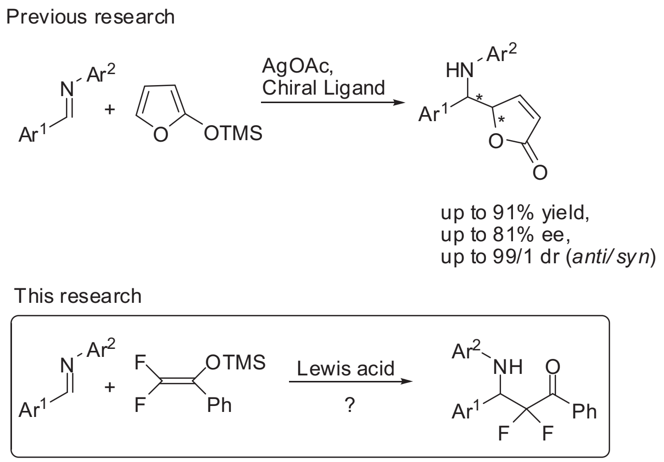
ABSTRACT

An unexpected reaction of aldimines and difluoroenoxysilane promoted with $Zn(OTf)_2$ was disclosed. The reaction gave the unexpected Mukaiyama-aldol adducts **3** in excellent yields (up to 87%) with the addition of H_2O and the corresponding Mannich-type adduct **4** was not observed in this catalytic system.

1. Introduction

Since the introduction of fluorine atoms into organic molecules causes changes in physical, chemical and pharmacological properties,[1] organofluorine chemistry provides stimulation in synthetic, biomedical, and material science.[2] Among some reported fluorine-containing units, a difluoromethylene unit, which plays a significant role in current organofluorine chemistry,[3] was revealed containing in some biologically interesting compounds, such as in phosphotyrosine (pTyr) mimetics,[4] anticancer agent gemcitabine,[5] and HIV-1 protease inhibitors.[6] Furthermore, due to the importance in chemical biology, α,α-difluoro-β-amino acids have attracted much interest in the past decades.[7] Recently, scientists have developed a variety of methods for the preparation of difluoromethylene units containing compounds. Among them, difluoroenolsilylanes, which could be readily prepared by Mg(0) promoted selective defluorination of trifluoromethyl ketones in the presence of TMSCl,[8] are considered as excellent building blocks for the synthesis of *gem*-difluorinated compounds.

Our previous research has disclosed a catalytic asymmetric vinylogous Mannich (AVM) reaction of readily available aldimines with trimethylsiloxyfuran promoted by silver salts.[9] The catalytic system gave the AVM products in high yields along with good enantioselectivities (Scheme 1). We envisioned that the use of difluoroenoxysilanes in the AVM reaction instead of trimethylsiloxyfuran might be a novel method to achieve chiral *gem*-difluorinated compounds. To the best of our knowledge, the direct catalytic asymmetric difluoromethylation of imines has not been reported. However, it was found that the reaction of aldimines **1** and difluoroenoxysilane **2** formed an unexpected Mukaiyama-aldol adducts **3** rather than the corresponding Mannich adduct **4**, which we expected to obtain. Therefore, we wish to investigate this novel route for the synthesis of 2,2-difluoro-3-hydroxy-1-ones via the reaction of aldimines and difluoroenoxysilane promoted by Lewis acids.



Scheme 1. Previously studied Lewis acid catalyzed AVM reaction and the proposal in this research.

2. Results and discussion

We initially investigated the reaction of aldimine **1a** with difluoroenoxysilane **2** in the presence of a catalytic amount of AgOAc. Unfortunately, the reaction could not be promoted by AgOAc that has shown good catalytic activity in our previously studied AVM

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* Corresponding author. E-mail address: mshi@mail.sioc.ac.cn (M. Shi).

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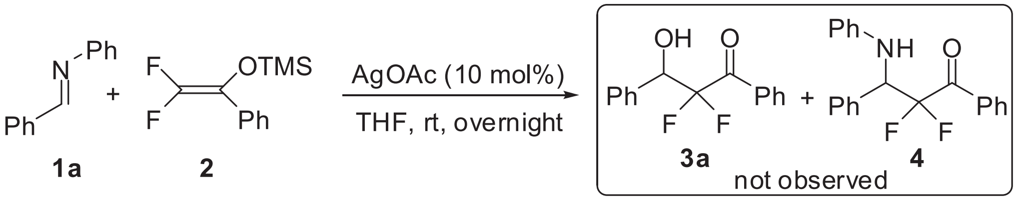
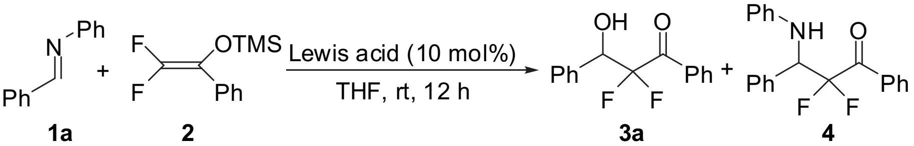


Scheme 2. Initial survey in the reaction of aldimine **1a** with difluoroenoxysilane **2**.

reaction (Scheme 2). Then another Lewis acid $Zn(OTf)_2$ was tested as a promoter. To our surprise, the reaction of aldimine **1a** and difluoroenoxysilane **2** proceeded efficiently when 10 mol % $Zn(OTf)_2$ was used as the promoter, giving an unexpected Mukaiyama-aldol adduct **3a** in 67% yield instead of Mannich adduct **4** (Table 1, entry 1).

Table 1

Reaction of aldimine **1a** (1.0 equiv) with difluoroenoxysilane **2** (1.5 equiv) in the presence of Lewis acids (10 mol %) at ambient temperature[a]



Entry	Lewis acid	Yield/(%)[b]	
		3a	**4**
1	$Zn(OTf)_2$	67	0
2	$Cu(OTf)_2$	52	13
3[c]	$(CuOTf)_2 \cdot C_6H_6$	60	0
4	AgOTf	66	0
5	$Sc(OTf)_3$	30	29
6	$Yb(OTf)_3$	45	25

[a] The reaction was carried out with 0.20 mmol of **1a**, 0.30 mmol of **2**, and 10 mol % of Lewis acids in THF (2.0 mL) at room temperature.

[b] Isolated yield.

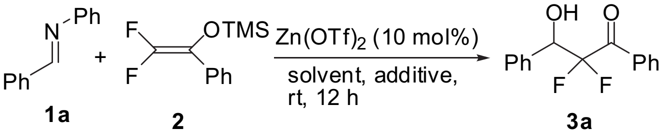
[c] $(CuOTf)_2 \cdot C_6H_6$ (5 mol %) was used.

An extensive survey of several commonly used Lewis acids (10 mol %) was carried out in the reaction of aldimine **1a** (0.20 mmol) with difluoroenoxysilane **2** (0.30 mmol) in 2 mL tetrahydrofuran (THF) at ambient temperature. The results are summarized in Table 1. It was found that the reaction proceeded smoothly when using $(CuOTf)_2 \cdot C_6H_6$ and AgOTf as the promoters (Table 1, entries 3 and 4), affording aldol-type adduct **3a** in up to 66% yield without forming adduct **4**. When several other Lewis acids were applied into this reaction, such as $Cu(OTf)_2$, $Sc(OTf)_3$, and $Yb(OTf)_3$, however, the reactions proceeded inefficiently (Table 1, entries 2, 5, and 6). For example, it was found that Mannich adduct **4** was formed in up to 29% yield along with aldol-type adduct **3a** in 30% yield when $Sc(OTf)_3$ was used as a Lewis acid (Table 1, entry 5), and the main product **3a** was achieved in 52% yield along with 13% of adduct **4** when $Cu(OTf)_2$ was employed as a Lewis acid (Table 1, entry 2).

Subsequently, we carried out the reaction of aldimine **1a** with **2** in different solvents and additives with 10 mol % of $Zn(OTf)_2$, which has been identified as the best Lewis acid in this reaction. Mannich adduct **4** was not observed yet when other solvents were used. The results are outlined in Table 2. When the reaction was carried out in dichloromethane (DCM), aldol-type adduct **3a** was obtained in 57% yield, lower than in THF (Table 2, entry 1). Solvents, such as CH_3CN and toluene are not suitable for this reaction, providing **3a** in very low yields (Table 2, entries 3 and 4). It was also observed that the reactions proceeded efficiently to give the adduct **3a** in Et_2O and 1,4-dioxane in up to 62% and 66% yields, respectively (Table 2, entries 2 and 5). Hypothetically, the water in the catalytic system may play an important role in this reaction, leading to the formation of the unexpected adduct **3**. Thus, the further studies were performed to identify the effect of H_2O in this reaction. We found that the addition of MS 4 Å (molecular sieves 4 Å, 100 mg) affected the result of the reaction of aldimine **1a** with difluoroenoxysilane **2**. When MS 4 Å was added into the reaction, only trace amount of adduct **3a** was formed (Table 2, entry 6). On the other hand, the addition of 1.0 equiv of H_2O could improve the yield of adduct **3a** up to 87% (Table 2, entry 7).

Table 2

Solvent and additive effects on the $Zn(OTf)_2$-catalyzed reaction of aldimine **1a** (1.0 equiv) with difluoroenoxysilane **2** (1.5 equiv)[a]



Entry	Solvent	Additive	Yield/(%)[b]
			3a
1	DCM	None	57
2	Et_2O	None	66
3	MeCN	None	Trace
4	Toluene	None	37
5	1,4-Dioxane	None	62
6[c]	THF	MS 4 Å	Trace
7[d]	THF	H_2O	87

[a] The reaction was carried out with 0.20 mmol of **1a**, 0.30 mmol of **2**, and 10 mol % of $Zn(OTf)_2$ in solvents (2.0 mL) at room temperature.

[b] Isolated yield.

[c] MS 4 Å (100 mg) was used as additive.

[d] H_2O (0.20 mmol, 1.0 equiv) was used as an additive.

With these optimized reaction conditions in hand, we next turned our attention to the reactions of a variety of aldimines **1** with difluoroenoxysilane **2**. The results are summarized in Table 3. For aldimines **1d–f** bearing electron-donating groups on the benzene rings, the reaction proceeded smoothly to afford corresponding aldol-type adducts **3a** and **3d** in good yields (Table 3,