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Letter

Synthesis of β-CF₃ Ketones through Copper/Silver Cocatalyzed Oxidative Coupling of Enol Acetates with ICH₂CF₃

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Abstract A simple method for the synthesis of β -CF₃ ketones through copper/silver cocatalyzed oxidative coupling of enol acetates with ICH₂CF₃ has been developed. Enol acetates were chosen as the source of carbonyl group, giving the β -CF₃ ketones in moderate yields. Control experiments imply that a radical process maybe involved in this reaction.

Key words $\beta\text{-}CF_3$ ketone, oxidative coupling, radical reaction, enol acetate

Incorporation of fluorine atoms into organic molecules significantly enhances many of their properties, such as solubility, metabolic stability, and bioavailability,¹ as fluorinated functional groups can beneficially modify the electronic properties of compounds. Among organofluorine molecules, CF₃-containing compounds play a unique and important role in agricultural and medicinal chemistry.²

Recently, significant progress has been made in the synthesis of CF₃-containing molecules,³ including the α -CF₃ ketones⁴ and β -CF₃ ketones.^{5,6} For the synthesis of β -CF₃ ketones, the trifluoromethyl group can be derived from Togni reagents,^{5c-e,Si-j} ICF₃,^{5b} ICH₂CF₃,⁶ and other fluorination reagents. Among them, Togni reagents are most expensive, and ICF₃ is a gas at normal temperature, which is inconvenient to use. Compared to the Togni reagents and ICF₃, ICH₂CF₃ is more suitable to be used as the source of trifluoromethyl group because of economic benefits and convenient operation.

Enol acetate is an inexpensive and stable reagent, and substituted enol acetates can be easily made from ketones.⁷ More importantly, enol acetate is a good object as the source Ar + ICH₂CF₃

Ar CH₂CH

19 examples 21–70% yield Simple substrates High regio-selectivity

Cu(OAc)₂·H₂O

Ag₂SO₄

TBHP. Et₃N

CH2CN, 100 °C

of carbonyl group.⁸ For example, in 2009, Shi's group reported the direct cross-coupling to construct $C(sp^3)-C(sp^3)$ bonds via Fe-catalyzed benzylic C–H activation with aryl enol acetate, giving α -alkylated carbonyl compounds in moderate yields (Scheme 1, reaction 1).^{8a} Then, alcohols and enol acetates were chosen as the starting materials, and the same product α -alkylated carbonyl compounds were obtained in good yields under the conditions of InI₃, GaBr₃, or FeBr₃, reported by Baba's group (Scheme 1, reaction 2).^{8b} In 2014, Li's group realized the synthesis of α -CF₃ ketones through Cu-catalyzed CF₃ radical addition reaction of aryl enol acetates (Scheme 1, reaction 3).^{8c} Moreover, iodoesters or iodonitriles were also used as the raw materials to react



with enol acetates to give the ketoesters or ketonitriles (Scheme 1, reaction 4).^{8d} Based on the above reports and on our research on synthesizing α -functionalized carbonyl compounds,⁹ herein, we describe a straightforward synthesis of β -CF₃ ketones through copper/silver cocatalyzed oxidative coupling of enol acetates with ICH₂CF₃.

We commenced our study with the reaction of enol acetate **1a** with ICH₂CF₃ (Table 1). The desired β -CF₃ ketone **3a** was obtained in 22% yield under the conditions of CuBr₂ (10 mol%), Et₃N (1 equiv), TBHP (3 equiv), and CH₃CN (1 mL) in a sealed tube at 100 °C for 24 h (entry 1). Other copper catalysts, such as CuI, CuSO₄, Cu(OAc)₂·H₂O, Cu(OTf)₂, and Cu(acac)₂, were examined, and Cu(OAc)₂·H₂O performed the best (up to 40% yield; entries 2-6). Then, we tried the non-copper catalysts, Co(OAc)₂, Fe(OAc)₂, and AgOAc, but the results were not satisfactory (entries 7-9). A variety of oxidants were examined, such as di-tert-butyl peroxide (DTBP), K₂S₂O₉, tert-butyl peroxybenzoate (TBPB), and benzoyl peroxide (BPO), and the results showed that TBHP was the best choice (entries 10-13). Moreover, although base played an important role in this reaction, to our disappointment, no better result was achieved when 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), Et₂NH, and K₂CO₃ were chosen as the base, respectively (entries 14-16). Different solvents were then examined, and none of the other solvents was superior to CH₃CN (entries 17–19). Interestingly, when AgOAc was used as a cocatalyst, the yield of 3a increased significantly from 40 to 62%, but other additives had little impact on the reaction (entries 20-22). It was exciting that a better result could be obtained when AgOAc was replaced with Ag₂SO₄ (up to 70% isolated yield; entry 23).

With the optimal conditions in hand, a series of enol acetates 1 were chosen to react with ICH₂CF₃, and the desired β -CF₃ ketones were obtained in moderate yields (Scheme 2). Enol acetates having electron-withdrawing groups such as halogen (F-, Cl-, Br-, and I-) at the para-position, could give the corresponding products in moderate yields (3b-e). Moreover, strong electron-withdrawing groups, such as -CO₂Me, -CF₃, and -CN, could also be applied to the reaction and afford the desired products in 55, 45, and 54% yields, respectively (3f-h). Unexpectedly, when 1-(4-nitrophenyl) vinyl acetate (1i) was used as the substrate, the reaction did not occur. In addition, the halogen substituents at *m*- and *o*-position were examined, and gave the desired products in moderate yields, but the conversion rate of 11 was slow, likely due to the steric hindrance. Enol acetates having electron-donating groups such as -Me, -OMe, and -OAc, also smoothly generated the corresponding products (**3m–o,3q**). For the large conjugate system, 1-([1,1'-biphenyl]-4-yl) vinyl acetate (1p) and 1-(naphthalen-2-yl) vinyl acetate (1r) were chosen as the substrates, and the desired products 3p and 3r were obtained in moderate yields. However, to our disappointment, heterocyclic sub-

Table 1 Optimization of the Reaction Conditions^a

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	Ph + ICH_2CF_3 1a 2	Cocatalyst cocatalyst [O], Et ₃ N CH ₃ CN, 100 °C	Ph 3a	℃F₃
Entry	Catalyst	Cocatalyst	Oxidant	Yield (%) [♭]
1	CuBr ₂	_	TBHP	22
2	Cul	-	TBHP	18
3	CuSO ₄	-	TBHP	27
4	Cu(OAc) ₂ ·H ₂ O	-	TBHP	40
5	Cu(OTf) ₂	-	TBHP	31
6	Cu(acac) ₂	-	TBHP	34
7	Co(OAc) ₂	-	TBHP	11
8	Fe(OAc) ₂	-	TBHP	13
9	AgOAc	-	TBHP	26
10	Cu(OAc) ₂ ·H ₂ O	-	DTBP	18
11	Cu(OAc) ₂ ·H ₂ O	-	$K_2S_2O_8$	9
12	Cu(OAc) ₂ ·H ₂ O	-	TBPB	24
13	Cu(OAc) ₂ ·H ₂ O	-	BPO	28
14 ^c	Cu(OAc) ₂ ·H ₂ O	-	TBHP	18
15 ^d	Cu(OAc) ₂ ·H ₂ O	-	TBHP	23
16 ^e	$Cu(OAc)_2 \cdot H_2O$	-	TBHP	26
17 ^f	$Cu(OAc)_2 \cdot H_2O$	-	TBHP	20
18 ^g	$Cu(OAc)_2 \cdot H_2O$	-	TBHP	23
19 ^h	$Cu(OAc)_2 \cdot H_2O$	-	TBHP	15
20	Cu(OAc) ₂ ·H ₂ O	Co(OAc) ₂	TBHP	42
21	$Cu(OAc)_2 \cdot H_2O$	$Fe(OAc)_2$	TBHP	45
22	$Cu(OAc)_2 \cdot H_2O$	AgOAc	TBHP	62
23	$Cu(OAc)_2 \cdot H_2O$	Ag_2SO_4	ТВНР	73 (70)

^a Reaction conditions: **1a** (0.75 mmol), **2** (0.5 mmol), catalyst (10 mol%), cocatalyst (20 mol%), Et₃N (0.5 mmol), oxidant (1.5 mmol), and CH₃CN (1 mL) in sealed tube at 100 $^{\circ}$ C for 24 h.

^b The yield was determined by ¹⁹F NMR analysis with trifluoromethyl-

benzene as an internal standard; isolated yield is given in parentheses.

^c Et₃N was replaced by DBU. ^d Et₃N was replaced by Et₂NH.

^e Et₃N was replaced by K₂CO₃.

 $^{\circ}$ Et₃N was replaced by K₂CO₃. $^{\circ}$ CH₃CN was replaced by 1,4-dioxane.

⁹ CH₃CN was replaced by 1,2-dichloroethane (DCE).

^h CH₃CN was replaced by DMSO.

strates, 1-(thiophen-3-yl) vinyl acetate (**1s**) and 1-(furan-3-yl) vinyl acetate (**1t**), were not suitable for the reaction. Moreover, the method could also be used to synthesize β -CHF₂ ketone. When ICH₂CF₃ was replaced with ICH₂CHF₂ to react with **1a**or**1m**, the desired products **4a** and **4m** were obtained in 41 and 38% yield, respectively.

To explore the reaction mechanism, several control experiments were carried out (Scheme 3). 2,2,6,6-Tetramethyl-1-piperidinyloxy (TEMPO), as a free radical inhibitor, was used to react with ICH₂CF₃ under the standard conditions,

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Scheme 2 Substrate scope for the reaction of enol acetates with ICH_2CF_3 . *Reagents and conditions*: **1** (0.75 mmol), **2** (0.5 mmol), $Cu(OAc)_2$ · H_2O (10 mol%), Ag_2SO_4 (20 mol%), Et_3N (0.5 mmol), TBHP (1.5 mmol, 70% in water), and CH_3CN (1 mL) in sealed tube at 100 °C for 24 h. Isolated yields are given. ^a ICH_2CHF_2 (0.5 mmol) was used as the substrate.

and the product TEMPO–CH₂CF₃ (**5**) was detected by GC-MS, with 75% ¹⁹F NMR yield (Scheme 3A). When TEMPO was added to the reaction of **1a** and ICH₂CF₃ under the standard conditions, the β -CF₃ ketone **3a** was not detected, but product **5** was formed in 62% ¹⁹F NMR yield (Scheme 3B). The two experiments show that the reaction may proceed through a radical process.

Based on the experimental results and on previous reports, ^{6a,8d} we propose a possible radical mechanism for the reaction (Scheme 4). Initially, ICH₂CF₃ generates radical I in the presence of copper/silver catalysts and a base. Radical I is then captured by enol acetate **1**, generating radical **II**,



Scheme 3 Control experiments

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which can be oxidized by TBHP to form cation **III**. Intermediates **III** or **IV** are finally hydrolyzed in the reaction media to afford the product β -CF₃ ketone **3**.



In conclusion, we have developed a new method to synthesize β -CF₃ ketones through copper/silver cocatalyzed oxidative coupling of enol acetates with ICH₂CF₃.¹⁰ Enol acetates, as the starting materials, are more extensive, which can be easily made from ketones. Therefore, we have every reason to believe that this will be a good way synthesize β -CF₃ ketones.

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Supporting Information

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- (10) **Typical Procedure**: To a sealed tube were added enol acetate (0.75 mmol), ICH₂CF₃ (0.5 mmol, 105 mg), Cu(OAc)₂·H₂O (0.05 mmol, 10 mg), Ag₂SO₄ (0.1 mmol, 31 mg), Et₃N (0.5 mmol, 50 mg), TBHP (1.5 mmol, 193 mg, 70% in water), and CH₃CN (1 mL), then the tube was stirred at 100 °C for 24 h. After completion of the reaction, the resulting mixture was diluted with dichloromethane and washed with water. The separated aqueous phase was washed with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under vacuo. The crude mixture was purified by column chromatography on silica gel (petroleum ether/ethyl acetate) to afford the desired product **3**.

4,4,4-Trifluoro-1-phenylbutan-1-one (3a)

Yield: 71 mg (70%); white solid; mp 56–58 °C; ¹H NMR (400 MHz, CDCl₃): δ = 7.98 (d, *J*= 7.6 Hz, 2 H), 7.61 (t, *J*= 7.2 Hz, 1 H), 7.49 (t, *J*= 7.6 Hz, 2 H), 3.27 (t, *J*= 7.6 Hz, 2 H), 2.66–2.54 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃): δ = 196.3, 136.1, 133.6, 128.8, 128.0, 127.1 (q, *J*= 274.2 Hz), 31.2 (d, *J*= 2.9 Hz), 28.3 (q, *J* = 29.9 Hz); ¹⁹F NMR (376 MHz, CDCl₃): δ = –66.45.