

Copper/Silver Cocatalyzed Oxidative Coupling of Vinylarenes with ICH₂CF₃ or ICH₂CHF₂ Leading to β-CF₃/CHF₂-Substituted Ketones

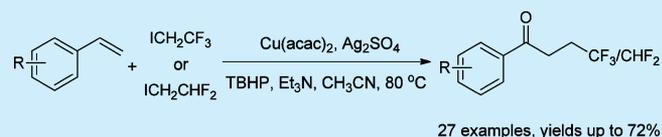
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S Supporting Information

ABSTRACT: A novel copper/silver cocatalyzed oxidative coupling of vinylarenes with ICH₂CF₃ or ICH₂CHF₂ through a radical process has been developed. The transformation provides an attractive approach to β-CF₃/CHF₂-substituted ketones, with the advantages of easily available starting materials and operational simplicity.



As one of the most important parts of fluorine chemistry, looking for new methods to access fluorine-containing molecules has been a challenging project. Recently, significant progress has been made in the synthesis of CF₃-containing molecules.¹ A number of methods have been reported for the synthesis of α-CF₃ ketones.² However, although unique and useful chemical properties can be expected for β-CF₃ ketones, reports on them are rare, probably due to the lack of efficient synthetic methods.³

To access β-CF₃ ketones, Xiao's group reported ring-opening reactions of *gem*-difluorocyclopropyl ketones promoted by boron trifluoride [Scheme 1, reaction 1].^{3a} The reaction has been simply accomplished in relatively good yield, despite the challenging approach to *gem*-difluorocyclopropyl ketones. Then, the propargylic alcohols and ICF₃ were used as the

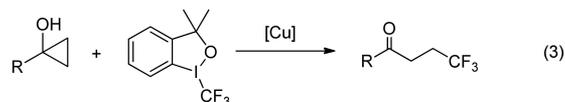
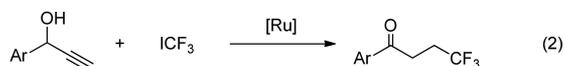
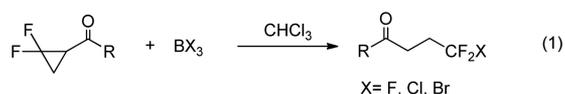
starting materials for the synthesis of β-CF₃ ketones, reported by Cho's group [Scheme 1, reaction 2].^{3b} The complicated and expensive ruthenium catalyst should be involved in such a developed method. Kananovich^{3c} and Dai's group^{3d} reported Cu-catalyzed trifluoromethylation of cyclopropanols to give β-CF₃ ketones, respectively [Scheme 1, reaction 3]. However, the Togni reagent, an expensive trifluoromethylation reagent, is necessary in those two reactions. Therefore, a simple and inexpensive way to access β-CF₃ ketones still remains elusive.

Based on our continuous research of synthesizing α-functionalized carbonyl compounds,⁴ herein we describe a straightforward synthesis of β-CF₃ ketones via copper/silver cocatalyzed oxidative coupling of vinylarenes with ICH₂CF₃. Compared to previous work, this work avoids the use of the Togni reagent, and β-CF₃ ketones are generated from inexpensive ICH₂CF₃ and vinylarenes in a one-step reaction. More importantly, the reaction is also applicable to the synthesis of β-CHF₂ ketones^{2u,5} when the vinylarenes and ICH₂CHF₂ are used as the starting materials.

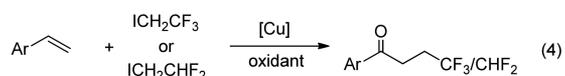
We began our investigation with the use of 4-*tert*-butylstyrene and ICH₂CF₃ as the model reaction (Table 1). The desired β-CF₃ ketone (3a) was obtained in 12% yield under the conditions of NiSO₄ (10 mol %), TBHP (3 equiv), Et₃N (1 equiv), and CH₃CN (1 mL) in a sealed tube at 80 °C for 24 h (entry 1). A variety of transition-metal salts were examined, and the results were shown in entries 2–11. Among the salts tested, Cu(acac)₂ performed better than other catalysts, with an up to 42% yield. The reactions with other oxidants, such as DTBP, K₂S₂O₈, and H₂O₂, gave products in low yields (entries 12–14). Then, different solvents were examined, and the results indicated that none of the other solvents was superior to CH₃CN (entries 15–18). Moreover, a base played an important role in the reaction. Organic bases

Scheme 1. Synthesis of β-CF₃ Ketones

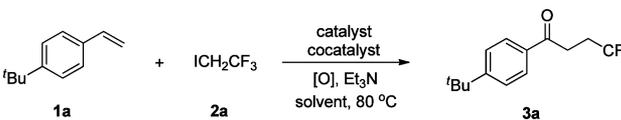
Previous Works



This Work



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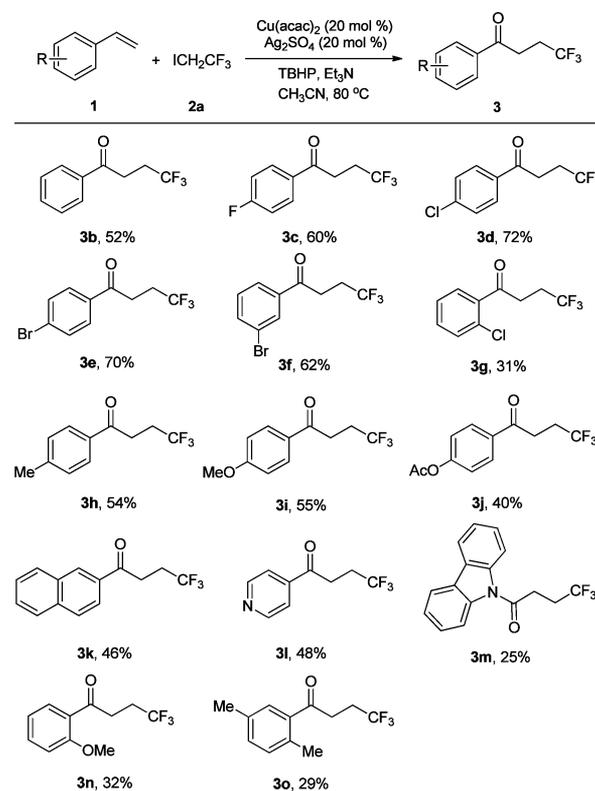
Table 1. Screening the Optimal Reaction Conditions^a


entry	catalyst	cocatalyst	oxidant	solvent	yield (%) ^b
1	NiSO ₄		TBHP	CH ₃ CN	12
2	CoSO ₄		TBHP	CH ₃ CN	20
3	Ag ₂ SO ₄		TBHP	CH ₃ CN	23
4	Fe ₂ (SO ₄) ₃		TBHP	CH ₃ CN	17
5	CuSO ₄		TBHP	CH ₃ CN	30
6	CuBr		TBHP	CH ₃ CN	22
7	CuBr ₂		TBHP	CH ₃ CN	25
8	Cu(OAc) ₂		TBHP	CH ₃ CN	27
9	Cu(NO ₃) ₂		TBHP	CH ₃ CN	34
10	Cu(OTf) ₂		TBHP	CH ₃ CN	32
11	Cu(acac) ₂		TBHP	CH ₃ CN	42
12	Cu(acac) ₂		DTBP	CH ₃ CN	5
13	Cu(acac) ₂		K ₂ S ₂ O ₈	CH ₃ CN	17
14	Cu(acac) ₂		H ₂ O ₂	CH ₃ CN	23
15	Cu(acac) ₂		TBHP	DCE	11
16	Cu(acac) ₂		TBHP	DMF	24
17	Cu(acac) ₂		TBHP	DMSO	21
18	Cu(acac) ₂		TBHP	THF	28
19 ^c	Cu(acac) ₂		TBHP	CH ₃ CN	19
20 ^d	Cu(acac) ₂		TBHP	CH ₃ CN	11
21 ^e	Cu(acac) ₂		TBHP	CH ₃ CN	7
22	Cu(acac) ₂	NiSO ₄	TBHP	CH ₃ CN	45
23	Cu(acac) ₂	CoSO ₄	TBHP	CH ₃ CN	48
24	Cu(acac) ₂	Ag ₂ SO ₄	TBHP	CH ₃ CN	57
25	Cu(acac) ₂	Fe ₂ (SO ₄) ₃	TBHP	CH ₃ CN	40
26 ^f	Cu(acac) ₂	Ag ₂ SO ₄	TBHP	CH ₃ CN	68 (62)
27 ^g	Cu(acac) ₂		TBHP	CH ₃ CN	49

^aReaction conditions: **1a** (0.75 mmol), **2a** (0.5 mmol), catalyst (10 mol %), cocatalyst (10 mol %), Et₃N (0.5 mmol), oxidant (1.5 mmol), solvent (1 mL) in sealed tube at 80 °C for 24 h. ^bThe yield was determined by ¹⁹F NMR with trifluoromethylbenzene as an internal standard. ^cEt₃N was replaced by DBU (0.5 mmol). ^dEt₃N was replaced by pyridine (0.5 mmol). ^eEt₃N was replaced by K₂CO₃ (0.5 mmol). ^fCu(acac)₂ (20 mol %) and Ag₂SO₄ (20 mol %) were used, and the number in parentheses was isolated yield. ^gCu(acac)₂ (20 mol %) was used.

were relatively better than the inorganic, and Et₃N was the best choice (entries 19–21). Interestingly, further exploration showed that the yield increased significantly from 42% to 57% when Ag₂SO₄ was used as a cocatalyst (entry 24), but other additives had little impact on the reaction (entries 22, 23, and 25). Increasing the loading of Cu(acac)₂ and Ag₂SO₄ to 20 mol % led to a considerable increase in the yield up to 68% (entry 26). When 20 mol % Cu(acac)₂ was used separately, the product **3a** was obtained in 49% yield (entry 27).

With the optimized conditions in hand, the substrate scope of the transformation was then investigated. A variety of terminal vinylarenes could efficiently undergo the desired β -CF₃ ketones in moderate to good yields (Scheme 2). Terminal vinylarenes bearing electron-withdrawing substituents such as fluoro- (**3c**), chloro- (**3d**), and bromo- (**3e**) at the *para*-position afforded the corresponding products in good yields. However, when 1-nitro-4-vinylbenzene was used as a substrate, the reaction could hardly occur. Other halostyrenes at the *m*- and *o*-position, 3-bromostyrene and 2-chlorostyrene, were

Scheme 2. Substrate Scope for the Reaction of Vinylarenes with ICH₂CF₃^{a,b}

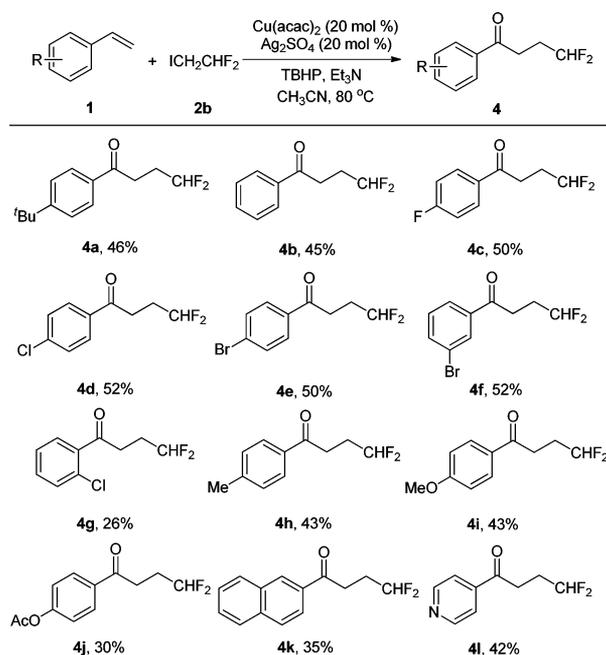
^aReaction conditions: **1** (0.75 mmol), **2a** (0.5 mmol), Cu(acac)₂ (20 mol %), Ag₂SO₄ (20 mol %), Et₃N (0.5 mmol), TBHP (1.5 mmol, 70% in water), and CH₃CN (1 mL) in sealed tube at 80 °C for 24 h. ^bIsolated yield.

examined and gave the desired products (**3f** and **3g**). Terminal vinylarenes bearing electron-donating substituents such as methyl (**3h** and **3o**), methoxy (**3i** and **3n**), and acetoxy (**3j**) were also tolerated under the reaction conditions. However, the yields of **3g**, **3n**, and **3o** were about 30%, likely due to the steric effect of substituents on aromatic rings. 2-Vinylnaphthalene was also a suitable substrate for the reaction (**3k**). Interestingly, when heterocyclic alkenes were used as the substrates, the corresponding products were successfully achieved (**3l** and **3m**). Unfortunately, the desired β -CF₃ ketones would not be obtained when aliphatic alkenes were applied.

Moreover, we explored the reactivity of various terminal vinylarenes with ICH₂CHF₂ under the optimized conditions, and the corresponding β -CHF₂ ketones were smoothly achieved in moderate yields (Scheme 3). Similarly, the bulky aromatic rings impacted the yields of the reaction due to the steric effect of substituents. However, the reaction could hardly occur when CH₃CH₂I was used as the starting material.

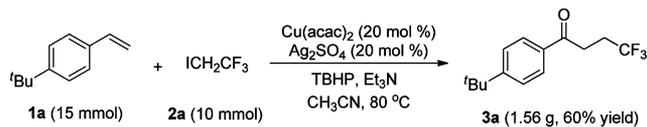
We also explored the reactivity of the Cu(acac)₂/Ag₂SO₄ cocatalyzed oxidative coupling reaction for large-scale synthesis of **3a** (Scheme 4). The reaction of 4-*tert*-butylstyrene (**1a**, 15 mmol) with ICH₂CF₃ (**2a**, 10 mmol) gave the desired β -CF₃ ketone (**3a**) in 60% yield under the standard conditions.

Control experiments were carried out in order to explore the reaction mechanism (Scheme 5). The reaction using ICH₂CF₃ and TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was tested under the standard conditions, and the desired product TEMPO-CH₂CF₃ was detected by GC-MS, and the yield

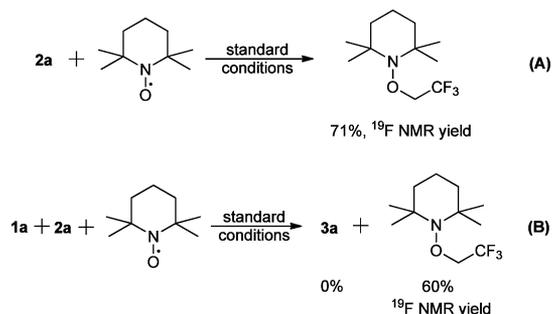
Scheme 3. Substrate Scope for the Reaction of Vinylarenes with ICH₂CHF₂^{a,b}

^aReaction conditions: **1** (0.75 mmol), **2b** (0.5 mmol), Cu(acac)₂ (20 mol %), Ag₂SO₄ (20 mol %), Et₃N (0.5 mmol), TBHP (1.5 mmol, 70% in water), and CH₃CN (1 mL) in sealed tube at 80 °C for 24 h. ^bIsolated yield.

Scheme 4. Large-Scale Synthesis of 3a



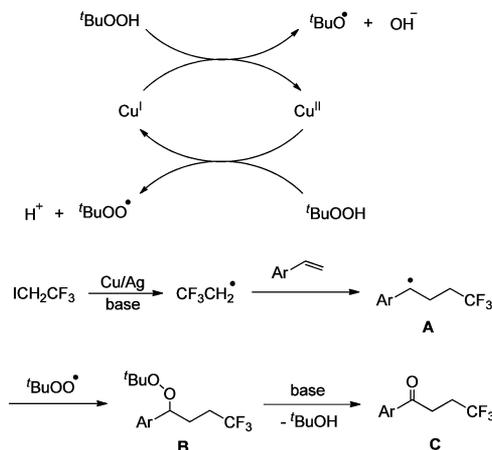
Scheme 5. Control Experiments



was estimated as 71% by ¹⁹F NMR (Scheme 5A). Notably, when TEMPO was added to the reaction of 4-*tert*-butylstyrene and ICH₂CF₃ under the standard conditions, the desired β-CF₃ ketone (**3a**) was not detected and TEMPO-CH₂CF₃ was formed in 60% yield by ¹⁹F NMR (Scheme 5B). The control experiments showed that the reaction proceeded through a radical process.

Based on our experimental results and previous reports,^{1n,6} a possible radical mechanism for oxidative coupling of vinylarenes is proposed in Scheme 6. Initially, ^tBuOOH is excited to form the ^tBuO[•] radical and the ^tBuOO[•] radical by a copper catalyst, and ICH₂CF₃ generates the CF₃CH₂[•] radical in the presence of copper/silver catalysts and a base. Then, the

Scheme 6. Possible Mechanism



CF₃CH₂[•] radical is captured by styrene to produce an intermediate **A**, which can be combined with the ^tBuOO[•] radical to afford an intermediate **B**. Finally, the intermediate **B** is converted into the β-CF₃ ketone (**C**) by removing one ^tBuOH under the reaction conditions.

The theory of Hard-Soft-Acid-Base (HSAB) likely explains the reason why Ag₂SO₄ plays an important role in this reaction.⁷ According to the HSAB theory, Ag⁺ belongs to the soft acid and I⁻ belongs to the soft base. The soft acid is combined with the soft base to form a stable compound. In other words, ICH₂CF₃ is easier to split into the CF₃CH₂[•] radical when Ag₂SO₄ presents in the reaction system.

In summary, a simple and effective approach to the synthesis of β-CF₃/CHF₂ ketones via the direct copper/silver cocatalyzed oxidative coupling of vinylarenes with ICH₂CF₃ or ICH₂CHF₂ has been developed. Meanwhile we also demonstrate that the reaction is accomplished through a radical process, though the catalyst silver salt is intriguing and not clear yet. Further study for insights into reaction mechanism and for synthetic applications to other bioactive molecules by using the oxidative coupling reaction is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00498.

Experimental procedure, mechanistic study, characterization data, and copies of ¹H, ¹³C, and ¹⁹F NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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