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Copper/Silver Cocatalyzed Oxidative Coupling of Vinylarenes with ICH_2CF_3 or ICH_2CHF_2 Leading to β-CF_3/CHF_2-Substituted Ketones

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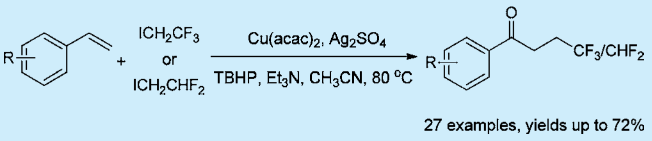
Ⓢ *Supporting Information*

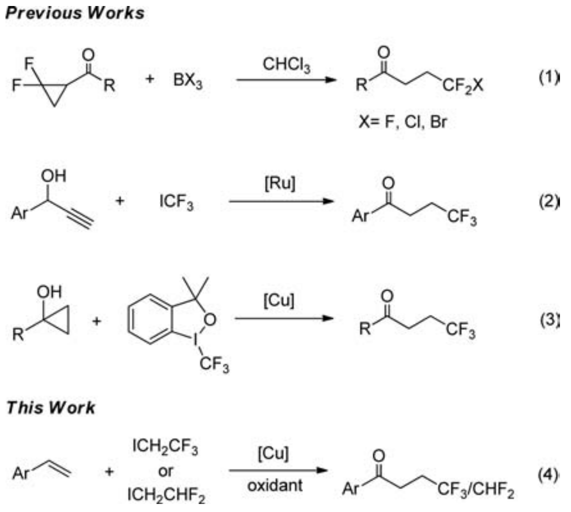
ABSTRACT: A novel copper/silver cocatalyzed oxidative coupling of vinylarenes with ICH_2CF_3 or ICH_2CHF_2 through a radical process has been developed. The transformation provides an attractive approach to β-CF_3/CHF_2-substituted ketones, with the advantages of easily available starting materials and 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 CF_3-containing molecules.[1] A number of methods have been reported for the synthesis of α-CF_3 ketones.[2] However, although unique and useful chemical properties can be expected for β-CF_3 ketones, reports on them are rare, probably due to the lack of efficient synthetic methods.[3]

To access β-CF_3 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 ICF_3 were used as the starting materials for the synthesis of β-CF_3 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-CF_3 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-CF_3 ketones still remains elusive.

Scheme 1. Synthesis of β-CF_3 Ketones



Based on our continuous research of synthesizing α-functionalized carbonyl compounds,[4] herein we describe a straightforward synthesis of β-CF_3 ketones via copper/silver cocatalyzed oxidative coupling of vinylarenes with ICH_2CF_3. Compared to previous work, this work avoids the use of the Togni reagent, and β-CF_3 ketones are generated from inexpensive ICH_2CF_3 and vinylarenes in a one-step reaction. More importantly, the reaction is also applicable to the synthesis of β-CHF_2 ketones[2u,5] when the vinylarenes and ICH_2CHF_2 are used as the starting materials.

We began our investigation with the use of 4-*tert*-butylstyrene and ICH_2CF_3 as the model reaction (Table 1). The desired β-CF_3 ketone (**3a**) was obtained in 12% yield under the conditions of $NiSO_4$ (10 mol %), TBHP (3 equiv), Et_3N (1 equiv), and CH_3CN (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, $K_2S_2O_8$, and H_2O_2, 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 CH_3CN (entries 15−18). Moreover, a base played an important role in the reaction. Organic bases

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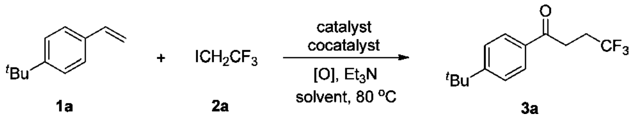
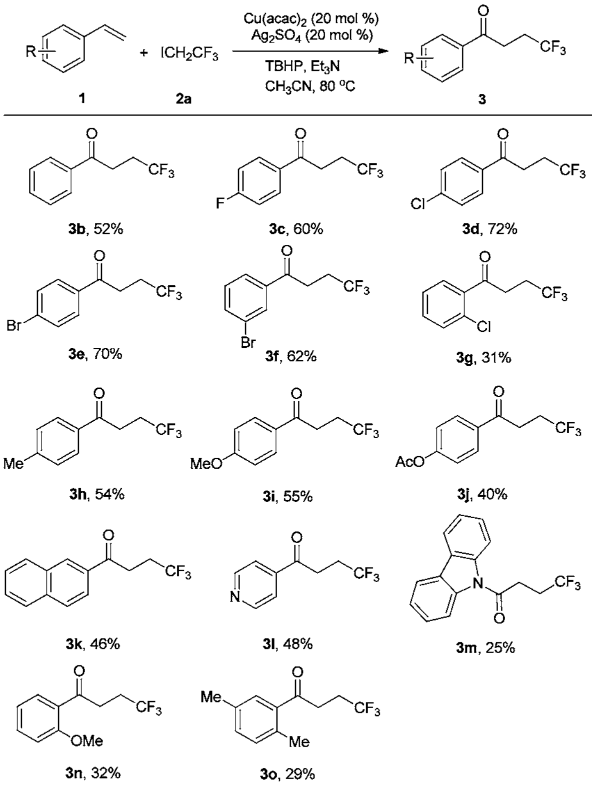
Table 1. Screening the Optimal Reaction Conditions[a]



entry	catalyst	cocatalyst	oxidant	solvent	yield (%)[b]
1	$NiSO_4$		TBHP	CH_3CN	12
2	$CoSO_4$		TBHP	CH_3CN	20
3	Ag_2SO_4		TBHP	CH_3CN	23
4	$Fe_2(SO_4)_3$		TBHP	CH_3CN	17
5	$CuSO_4$		TBHP	CH_3CN	30
6	CuBr		TBHP	CH_3CN	22
7	$CuBr_2$		TBHP	CH_3CN	25
8	$Cu(OAc)_2$		TBHP	CH_3CN	27
9	$Cu(NO_3)_2$		TBHP	CH_3CN	34
10	$Cu(OTf)_2$		TBHP	CH_3CN	32
11	$Cu(acac)_2$		TBHP	CH_3CN	42
12	$Cu(acac)_2$		DTBP	CH_3CN	5
13	$Cu(acac)_2$		$K_2S_2O_8$	CH_3CN	17
14	$Cu(acac)_2$		H_2O_2	CH_3CN	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_3CN	19
20[d]	$Cu(acac)_2$		TBHP	CH_3CN	11
21[e]	$Cu(acac)_2$		TBHP	CH_3CN	7
22	$Cu(acac)_2$	$NiSO_4$	TBHP	CH_3CN	45
23	$Cu(acac)_2$	$CoSO_4$	TBHP	CH_3CN	48
24	$Cu(acac)_2$	Ag_2SO_4	TBHP	CH_3CN	57
25	$Cu(acac)_2$	$Fe_2(SO_4)_3$	TBHP	CH_3CN	40
26[f]	$Cu(acac)_2$	Ag_2SO_4	TBHP	CH_3CN	68 (62)
27[g]	$Cu(acac)_2$		TBHP	CH_3CN	49

[a] Reaction conditions: **1a** (0.75 mmol), **2a** (0.5 mmol), catalyst (10 mol %), cocatalyst (10 mol %), Et_3N (0.5 mmol), oxidant (1.5 mmol), solvent (1 mL) in sealed tube at 80 °C for 24 h. [b] The yield was determined by ^{19}F NMR with trifluoromethylbenzene as an internal standard. [c] Et_3N was replaced by DBU (0.5 mmol). [d] Et_3N was replaced by pyridine (0.5 mmol). [e] Et_3N was replaced by K_2CO_3 (0.5 mmol). [f] $Cu(acac)_2$ (20 mol %) and Ag_2SO_4 (20 mol %) were used, and the number in parentheses was isolated yield. [g] $Cu(acac)_2$ (20 mol %) was used.

Scheme 2. Substrate Scope for the Reaction of Vinylarenes with ICH_2CF_3[a,b]



[a] Reaction conditions: **1** (0.75 mmol), **2a** (0.5 mmol), $Cu(acac)_2$ (20 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 80 °C for 24 h. [b] Isolated yield.

were relatively better than the inorganic, and Et_3N was the best choice (entries 19−21). Interestingly, further exploration showed that the yield increased significantly from 42% to 57% when Ag_2SO_4 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 Ag_2SO_4 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).

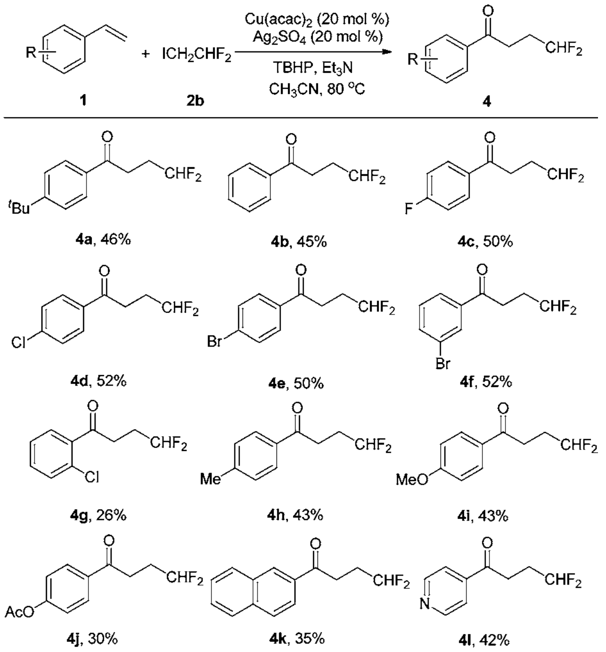
With the optimized conditions in hand, the substrate scope of the transformation was then investigated. A variety of terminal vinylarenes could efficiently undergo the desired β-CF_3 ketones in moderate to good yields (Scheme 2). Terminal vinylarenes bearing electron-withdrawing substituents such as 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 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-CF_3 ketones would not be obtained when aliphatic alkenes were applied.

Moreover, we explored the reactivity of various terminal vinylarenes with ICH_2CHF_2 under the optimized conditions, and the corresponding β-CHF_2 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 CH_3CH_2I was used as the starting material.

We also explored the reactivity of the $Cu(acac)_2/Ag_2SO_4$ cocatalyzed oxidative coupling reaction for large-scale synthesis of **3a** (Scheme 4). The reaction of 4-*tert*-butylstyrene (**1a**, 15 mmol) with ICH_2CF_3 (**2a**, 10 mmol) gave the desired β-CF_3 ketone (**3a**) in 60% yield under the standard conditions.

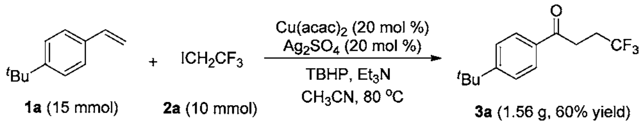
Control experiments were carried out in order to explore the reaction mechanism (Scheme 5). The reaction using ICH_2CF_3 and TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was tested under the standard conditions, and the desired product TEMPO−CH_2CF_3 was detected by GC-MS, and the yield

Scheme 3. Substrate Scope for the Reaction of Vinylarenes with ICH_2CHF_2[a,b]

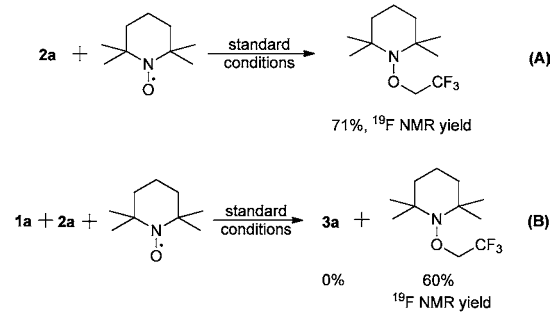


[a] Reaction conditions: **1** (0.75 mmol), **2b** (0.5 mmol), $Cu(acac)_2$ (20 mol %), Ag_2SO_4 (20 mol %), Et_3N (0.5 mmol), TBHP (1.5 mmol, 70% in water), and CH_3CN (1 mL) in sealed tube at 80 °C for 24 h. [b] Isolated yield.

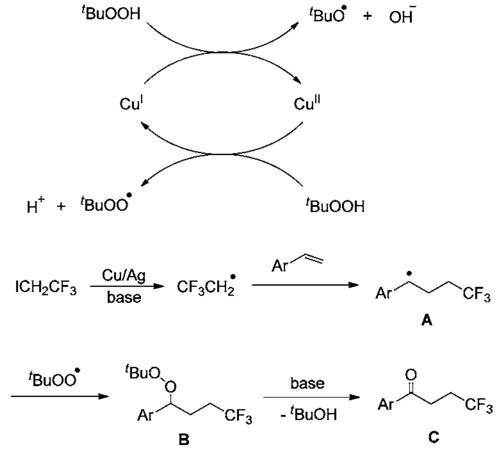
Scheme 4. Large-Scale Synthesis of 3a



Scheme 5. Control Experiments



Scheme 6. Possible Mechanism



was estimated as 71% by ^{19}F NMR (Scheme 5A). Notably, when TEMPO was added to the reaction of 4-*tert*-butylstyrene and ICH_2CF_3 under the standard conditions, the desired β-CF_3 ketone (**3a**) was not detected and TEMPO−CH_2CF_3 was formed in 60% yield by ^{19}F 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 $^tBuO^\bullet$ radical and the $^tBuOO^\bullet$ radical by a copper catalyst, and ICH_2CF_3 generates the $CF_3CH_2^\bullet$ radical in the presence of copper/silver catalysts and a base. Then, the $CF_3CH_2^\bullet$ radical is captured by styrene to produce an intermediate **A**, which can be combined with the $^tBuOO^\bullet$ radical to afford an intermediate **B**. Finally, the intermediate **B** is converted into the β-CF_3 ketone (**C**) by removing one ^tBuOH under the reaction conditions.

The theory of Hard-Soft-Acid-Base (HSAB) likely explains the reason why Ag_2SO_4 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, ICH_2CF_3 is easier to split into the $CF_3CH_2^\bullet$ radical when Ag_2SO_4 presents in the reaction system.

In summary, a simple and effective approach to the synthesis of β-CF_3/CHF_2 ketones via the direct copper/silver cocatalyzed oxidative coupling of vinylarenes with ICH_2CF_3 or ICH_2CHF_2 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, ^{13}C, and ^{19}F NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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