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# Radical hydrotrifluoromethylation of ynamides: a route toward $\beta$ -CF<sub>3</sub> enamides†

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We report here a radical hydrotrifluoromethylation of ynamides to provide an alternative route toward  $\beta$ -CF $_3$  enamides. By using PhICF $_3$ Cl as the CF $_3$  reagent and DMF as the H-donor, the reaction occurred smoothly in the presence of NaH at room temperature. Further reduction of the resulting  $\beta$ -CF $_3$  enamides efficiently delivered  $\beta$ -CF $_3$  amines. Gram-scale synthesis was conducted to demonstrate the practicability of the method.

#### Introduction

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Molecules containing two powerful functionals, trifluoromethyl and amino, in adjacent positions are valuable targets in drug design and synthetic chemistry. 1 Consequently, great efforts have been focused on the assembly of amino and trifluoromethyl at the ortho position.2 In this field, the aminotrifluoromethylation of alkenes provides the main and step-economical route toward  $\beta$ -CF<sub>3</sub> amines (Scheme 1A). <sup>2i,j</sup> On the other hand, enamines have found wide synthetic applications,<sup>3</sup> which also encouraged investigations on the vicinal trifluoromethylated enamines. However, to date, there have been limited approaches established for preparing β-CF<sub>3</sub> enamines. Apart from several works on utilizing the amination of pre-synthesized CF3-containing substrates,4 as well as a recent report involving a three-component reaction between trifluorodiazoethane, aldehydes, and imines,5 trifluoromethylation-based methods have been documented to deliver β-CF<sub>3</sub> enamines, including via the aminotrifluoromethylation of alkynes (Scheme 1A)6 and direct Csp2-H trifluoromethylation of enamines (Scheme 1B).<sup>7</sup>

During our ongoing explorations in the field of trifluoromethylation, an externally coordinated  $CF_3$ -containing  $\lambda^3$ -iodane (PhICF $_3$ Cl) $^8$  was synthesized to be used in a set of trifluoromethylation reactions. $^9$  Efficient trifluoromethylative bifunctionalization reactions of alkenes have been developed by our group recently. $^{9a-d}$  In order to extend the synthetic applications of PhICF $_3$ Cl, the trifluoromethylation of alkynes

enamides. β-CF<sub>3</sub> amines were obtained by further reduction. Herein, we report a new hydrotrifluoromethylation of ynamides (Scheme 1C).

was investigated in the follow-up work. As a result, when yna-

mides<sup>10</sup> were chosen as alkyne substrates for the reaction with

PhICF<sub>3</sub>Cl in DMF, unprecedented β-CF<sub>3</sub> enamides were pro-

duced. It provides an alternative and mild route toward β-CF<sub>3</sub>

#### Results and discussion

It was reported that CF<sub>3</sub> radical addition onto *N*-benzoyl ynamides afforded aryltrifluoromethylative cyclization products.<sup>11</sup> In order to avoid such possible side reactions, *tert*-butyl ethynyl(phenyl)carbamate **1a** was chosen in our initial attempt to carry out the trifluoromethylation of ynamides using

A. Aminotrifluoromethylation of Alkenes/Alkynes

B. Trifluoromethylation of Enamines

C. Hydrotrifluoromethylation of Ynamides This Work

Scheme 1 Trifluoromethylation-based route toward  $\beta\text{-CF}_3$  amines/enamines.

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 $\dagger$  Electronic supplementary information (ESI) available:  $^{1}\text{H},~^{13}\text{C},~^{19}\text{F}$  and NOE NMR spectra and crystallographic data. CCDC 2141492. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d2q000045h  $\ddagger$  These authors contributed equally to this work.

PhICF<sub>3</sub>Cl as the trifluoromethylating reagent. Notably, the hydrotrifluoromethylation product 2a was obtained in 57% NMR yield, accompanied by 3a in 36% NMR yield only by stirring a mixture of 1a and PhICF3Cl in DMF at room temperature (Table 1, entry 1). DMF was likely the H-donor in such a simple reaction mixture and a radical process was proposed for the formation of 2a. According to our previous work in which radical trifluoromethylation of alkenes with PhICF<sub>3</sub>Cl could not occur at room temperature without the assistance of a reductant, 9d ynamide substrate 1a likely acted as a tertiary amine type electron donor<sup>12</sup> for the generation of the CF<sub>3</sub> radical from PhICF<sub>3</sub>Cl. Thus, an additional reductant was used for the above hydrotrifluoromethylation of 1a. As we hypothesized, the addition of tertiary amines, including triethylamine (TEA), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and N,N-diisopropylethylamine (DIPEA), could indeed help increase the yield of 2a a little bit (entries 2-4). Tetrabutylammonium iodide (TBAI) and zinc iodide showed poor performance (entries 5 and 6), and triethylsilane had no obvious influence on this reaction (entry 7). In comparison, NaH was proven to be an optimal reductant, leading to 2a in 81% NMR yield (entry 8). No 3a was detected in these cases (entries 2-6 and 8). Solvent screening showed that 2a could also be obtained in good to moderate yields in N,N-dimethylacetamide (DMAc, entry 9), tetrahydrofuran (THF, entry 10) and N-methylpyrrolidone (NMP, entry 11). However, dichloromethane (DCM, entry 12) was not suitable for the reaction. The reaction time was then controlled precisely (entries

Table 1 Optimization of reaction conditions<sup>a</sup>

Entry	Reductant	Solv.	t/h	2a <sup>b</sup> /%	3a <sup>c,d</sup> /%
1	_	DMF	12	50	36
2	TEA	DMF	12	61	N.D.
3	DBU	DMF	12	65	N.D.
4	DIPEA	DMF	12	67	N.D.
$5^e$	TBAI	DMF	12	14	Trace
6	$ZnI_2$	DMF	12	23	Trace
7	Et <sub>3</sub> SiH	DMF	12	52	17
8	NaH	DMF	12	$81(75)^f$	N.D.
9	NaH	DMAc	12	69	N.D.
10	NaH	NMP	12	52	9
11	NaH	THF	12	54	21
12	NaH	DCM	12	9	Trace
13	NaH	DMF	1	66	N.D.
14	NaH	DMF	2	$75(72)^f$	N.D.
15	NaH	DMF	6	72	N.D.
16 <sup>g</sup>	NaH	DMF	2	$75(70)^f$	N.D.

 $<sup>^</sup>a$  Reaction conditions: 1a (0.2 mmol), PhICF $_3$ Cl (1.5 eq.), reductant (1.5 eq.), solvent (2.0 mL), 25 °C, N $_2$ .  $^b$   $^{19}{\rm F}$  NMR yield using benzotrifluoride as the internal standard. <sup>c</sup> <sup>1</sup>H NMR yield using dibromomethane as the internal standard. d N.D. = not detected. e 80% of 1a was recovered. f Isolated yields of E-2a are shown in brackets. g Gram-scale reaction was performed at the 5.5 mmol scale.

13-15). It was found that the NMR yield of 2a was 75% within 2 h (entry 14). Finally, a gram-scale experiment was conducted and 2a was obtained in 70% isolated yield, which demonstrated the robustness of the protocol (entry 16).

After establishing the optimal conditions for this reaction (Table 1, entry 14), the generality of this protocol was examined by using various kinds of ynamide substrates (Table 2).

First, a series of N-phenyl-substituted ynamides were selected and tested in this reaction. We were pleased to see that electronically and sterically distinct substituents at different positions were tolerated, affording the β-CF<sub>3</sub> enamides (2b-x) in good yields. Ynamides bearing electron-withdrawing groups, such as halide (1b-e, 1q, 1t, and 1w), fluoroalkyl (1p) or carbonyl groups (1k and 1l), could all provide the desired products in good yields. Electron-rich substituents like alkyl (1f-h, 1j, 1r, 1u and 1v), aryl (1i), and alkoxyl/aryloxy (1m-o, 1s, and 1x) did not have obvious influences on the reactions. Remarkably, enamide 2w could be generated in 90% vield from the reaction of sterically hindered vnamide 1w. Secondly, the protecting groups of the ynamides were tested. Both N-Ac and N-Cbz ynamides were suitable for this reaction although the reactions afforded 2a and 2aa in reduced yields under identical conditions. However, p-toluenesulfonylynamide 1ab was not suitable for this reaction. The reaction was complex and the desired product 2ab was not detected. Next, hydrotrifluoromethylations of N-benzyl ynamides were carried out under identical conditions. A series of N-benzyl ynamides substituted at different positions were selected and tested in this reaction. It was found that all the tested N-benzyl ynamides 1ac-ag were efficiently transformed into the corresponding products 2ac-ag. In addition, the enamide product 2ah could also be generated from N-phenylethyl ynamide 1ah in 70% yield.

Finally, non-terminal ynamides were synthesized to test the substrate scope. As shown in Table 2, the desired products 2 could be obtained in moderate to good yields when the reaction time was prolonged. Long-chain alkyl- (1ai-an), cycloalkyl-(1ao) and ester-ynamides (2ap) all proved to be suitable for this reaction. In comparison, phenyl substituted ynamide 1aq delivered 2aq in 28% yield, along with the generation of regiomeric isomers. 13 Note that the hydrotrifluoromethylation of ynamides 1 stereoselectively afforded enamines Thermodynamically stable E-isomeric enamines were obtained as the main products in most cases, which was proved by the X-ray crystal structure of 2e.14 In comparison, lower stereoselectivities were observed in some cases, such as 2am, 2an and 2ap, likely caused by the little difference in the thermodynamic stability of the products.

As described above, we have established a novel hydrotrifluoromethylation reaction of ynamides, which provides a trifluoromethylative bifunctionalization pathway to synthesize β-CF<sub>3</sub> enamides. Further transformation of β-trifluoromethyl enamides 2 was investigated to highlight the synthetic potential of the approach. As shown in Table 3, by using silyl hydride as the reductant, reduction/deprotection products 4,  $\beta$ -CF<sub>3</sub> amines,  $^{1a,b,15}$  could be obtained in good to

Table 2 Substrate scope of hydrotrifluoromethylation of ynamides<sup>a,b</sup>

**Table 3** Deprotected reduction of  $\beta$ -CF<sub>3</sub> enamines<sup>a,b</sup>

Boc R' R CF <sub>3</sub>	Et <sub>3</sub> SiH (1.5 eq.)  TFA (0.1 M)  0 °C, 24 h  R  R  CF <sub>3</sub>
R	CI CF3
R = H, <b>4a</b> , 91% R = 4- <sup>1</sup> Bu, <b>4b</b> , 89% R = 4-Ph, <b>4c</b> , 85%	<b>4h</b> , 81%
R = 3-Br, <b>4d</b> , 92% R = 3,5-Me <sub>2</sub> , <b>4e</b> , 83% R = 2-I-5-F, <b>4f</b> , 90%	Ph CF <sub>3</sub>
	R' = n-Hex, 4i, 93% R' = n-Decyl, 4j, 84% R' = (CH <sub>2</sub> ) <sub>3</sub> Cl, 4k, 89%
<b>4g</b> , 91%	R' = Cyclopropyl, 4I, 95%

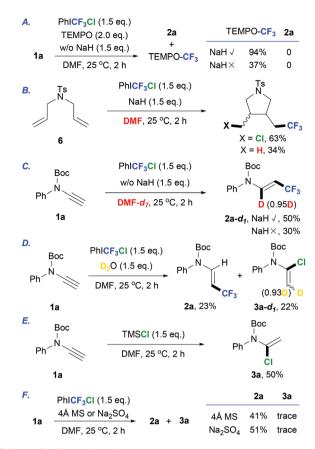
 $^a$  Reaction conditions: 2 (0.1 mmol), Et<sub>3</sub>SiH (0.15 mmol, 1.5 eq.), TFA (1.0 mL), 0 °C, N<sub>2</sub>, 24 h.  $^b$  Isolated yields of 4.

excellent yields in the presence of trifluoroacetic acid. <sup>16</sup> β-CF<sub>3</sub> enamides generated from substituted N-phenyl ynamides (1a, 1h, 1j, 1t, 1v, 1w, and 1x), N-benzyl ynamide (1ae) and nonterminal ynamides (1ai, 1ak, 1an and 1ao), were all suitable

for this reductive deprotection reaction to generate the corresponding β-CF<sub>3</sub> amines 4a-l.

A set of control experiments were conducted to verify the possible reaction mechanism. Radical trapping experiments were carried out under the standard conditions by the addition of 2,2,6,6-tetramethylpiperidine-1-oxide (TEMPO, Scheme 2A). The desired product 2a could not be obtained in the presence or absence of NaH, which suggested the involvement of a radical process. A radical clock experiment was also conducted by using N,N-diallyl-4-methylbenzenesulfonamide under the standard reaction conditions (Scheme 2B). As a result, both chloro-9d and hydro-cyclization products17 were obtained to demonstrate a radical mechanism. To identify the hydrogen source, deuterated DMF was used in the reaction of 1a. As shown in Scheme 2C, the reactions were carried out in DMF- $d_7$ with or without NaH, and the deuterated product 2a-d1 was obtained, demonstrating an H-abstraction process from the solvent involved in the reaction. No deuterated β-CF<sub>3</sub> enamide was detected when D2O was added in this reaction (Scheme 2D), which excluded the formation of 2a via protonation from water; meanwhile, the deuterated chloro-enamide  $3a-d_1$  was detected as the background product. To further verify the formation of 3a from an electrophilic addition of alkynes, we performed an additional reaction of 1a in DMF using TMSCl as the Cl-source instead of PhICF3Cl. 3a was obtained in 50% yield, suggesting that a background reaction

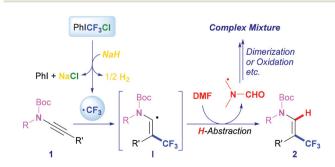
<sup>&</sup>lt;sup>a</sup> Reaction conditions: 1 (0.2 mmol), PhICF<sub>3</sub>Cl (0.3 mmol, 1.5 eq.), NaH (0.3 mmol, 1.5 eq.), DMF (2.0 mL), 25 °C, N<sub>2</sub>, 2 h. <sup>b</sup> Isolated yields of E-2 unless the E/Z ratio is otherwise noted in the brackets. Expression conditions: 30 °C, 12 h.



Scheme 2 Control experiments.

existed in our hydrotrifluoromethylation of ynamides 1. This experimental result indicated that NaH may also help in the removal of water from the reaction mixture, which is beneficial for inhibiting the formation of byproducts 3. Further investigations on the role of NaH were carried out by the reaction of 1a and PhICF<sub>3</sub>Cl in the presence of desiccants without NaH (Scheme 2F). As a result, the formation of 3a was inhibited, but the yield of 2a was still moderate. These experimental results showed that NaH not only acted as a water removal reagent but also assisted in the radical hydrotrifluoromethylation of ynamides.

According to the literature 12c,18 and experiment results, a plausible mechanism is proposed as described in Scheme 3.



Scheme 3 A plausible radical mechanism.

PhICF<sub>3</sub>Cl is reduced by NaH to release the trifluoromethyl radical, which is added to substrate 1 immediately to generate alkenyl radical intermediate I. Meanwhile, iodobenzene and hydrogen<sup>19</sup> are generated, respectively, suggesting that NaH acts as a reductant of PhICF<sub>3</sub>Cl through an electron transfer pathway. An H-atom-abstraction of I from the solvent DMF subsequently occurred and gave the hydrotrifluoromethylation product 2. In this case, it is proposed that the N-methyl-H of DMF is abstracted<sup>20</sup> by the electrophilic trifluoromethylated radical I, which is supported by the fact that good transformations could also be obtained in either DMAc or NMP (Table 1, entries 9 and 10). The generated DMF-based carbon radical would further undergo dimerization, oxidation, hydrolysis, or other processes, resulting in the formation of mixed products.21 Note that although this proposed mechanism is preferred, other plausible H-abstraction processes or reaction mechanisms cannot be ruled out at this stage.

#### Conclusions

In conclusion, by using PhICF<sub>3</sub>Cl as the trifluoromethyl source, the hydrotrifluoromethylation of ynamides was achieved successfully, in which a series of β-CF<sub>3</sub> enamides were synthesized efficiently. The mild and transition-metal free reaction conditions, the good functional group tolerance and the capability to be performed at the gram scale make this method valuable and practical. Control experiments proved that the reaction occurred via a radical process, which is a new achievement in the field of underexplored free radical reactions of ynamides.

#### Author contributions

W. Huang and R. Z. Zhang performed the experiments and cowrote the ESI.† W. Huang wrote the initial draft of this manuscript. R. X. Zhang and J. Yu helped in preparing several substrates. Prof. M. Wang conceived the project and concept reviewed the manuscript. All authors read and contributed to the revisions and approved the final version to be published.

#### Conflicts of interest

There are no conflicts to declare.

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