Site-specific Deaminative Trifluoromethylation of Aliphatic Primary Amines

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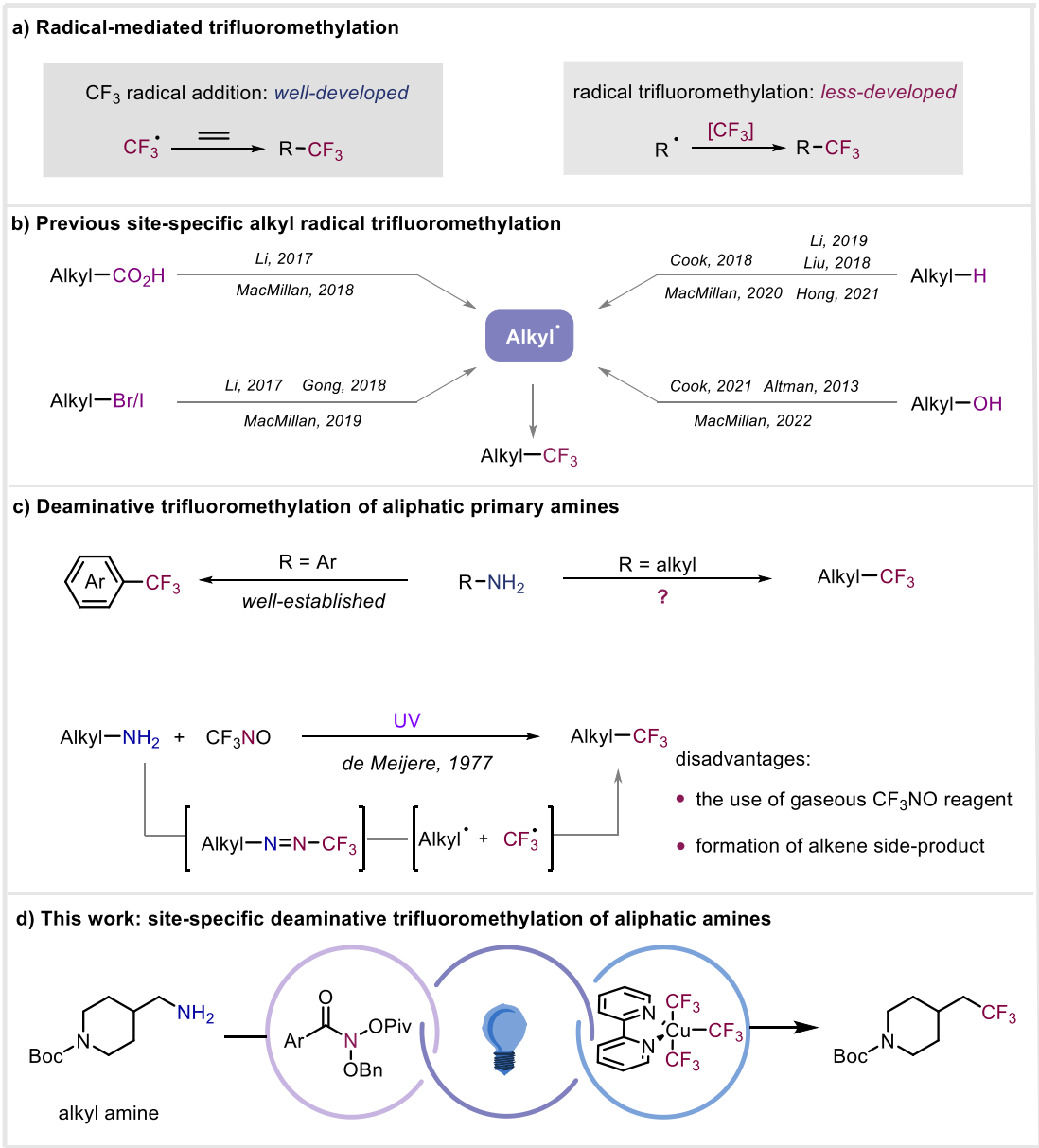
ABSTRACT: The introduction of trifluoromethyl groups into organic molecules is of paramount importance in modern synthetic chemistry and medicinal chemistry. While methods for constructing C(sp^2)-CF_3 bonds have been well established, the advancement of practical and comprehensive approaches for forming C(sp^3)-CF_3 bonds remains considerably restricted. In this work, we describe an efficient and site-specific deaminative trifluoromethylation reaction of aliphatic primary amines to afford the corresponding alkyl trifluoromethyl compounds. The reaction proceeds at room temperature with readily accessible *N*-anomeric amide and bench-stable bpyCu(CF_3)$_3$ (Grushin's reagent) under blue light. The protocol features mild reaction conditions, good functional group tolerance, and moderate to good yields. Remarkably, the method can be applied to the direct, late-stage trifluoromethylation of natural products and bioactive molecules. Experimental mechanistic studies were conducted, and a radical mechanism is proposed, wherein the dual roles of Grushin's reagent have been elucidated.

INTRODUCTION

Trifluoromethyl is a prevalent structural motif in pharmaceuticals owing to its unique properties, which play a crucial role in modulating drug lipophilicity, permeability, and metabolic stability.[1-2] However, CF_3-containing compounds are not naturally occurring, making the incorporation of trifluoromethyl into molecules a subject of great interest for chemists. While the construction of C(sp^2)-CF_3 bonds has been extensively investigated, the introduction of alkyl trifluoromethyl groups has lagged by comparison.[3-6] In the past few decades, with the advancement of fundamental radical chemistry and the development of diverse trifluoromethylation reagents, radical trifluoromethylation has injected new vitality into the efficient construction of alkyl-CF_3 bonds.[7-8] In general, two types of radical-mediated trifluoromethylation have been reported, including the well-developed addition of CF_3 radicals

to alkenes[9-10] and the trifluoromethylation of alkyl radicals[7] (Scheme 1a). In this context, the advantages of the latter approach have been demonstrated by elegant examples on the site-specific trifluoromethylation of alkyl radicals that are generated from readily available and abundant aliphatic carboxylic acids,[11-12] halides,[13-15] alcohols,[16] or their derivatives,[17-18] and in some cases, simple alkanes[19-23] (Scheme 1b). However, at present, the use of amines as radical precursors for the construction of alkyl-CF_3 bonds remains largely underexplored.



Scheme 1. Radical-mediated trifluoromethylation for alkyl-CF_3 formation.

Amines are ideal building blocks for organic synthesis due to their highly accessible, stable, and low-cost nature.[24] While fruitful deaminative functionalizations of amines have been achieved,[25-28] such as deaminative halogenation,[29] hydroxylation,[30] borylation,[31-32] cyanation,[33] and sulfuration,[34] methods for deaminative trifluoromethylation are limiting. Research groups of Fu,[35] Wang,[36] Goossen,[37] Grushin,[38] and others[39-40] have developed

useful Sandmeyer-like deaminative trifluoromethylations, but the only aromatic amines are applicable. In 1977, de Meijere reported a deaminative trifluoromethylation of aliphatic amines (Scheme 1c).[41] The reaction proceeded through a two-step sequence involving the condensation of primary amines with trifluoronitrosomethane, followed by the photolysis of the formed trifluoromethylazo compounds under ultraviolet irradiation in hexadecane or *tert*-butyl alcohol. However, the need for very low temperatures, the difficulty of handling gaseous CF_3NO limit its widespread synthetic applications. Consequently, there is a high demand to develop a practical and general method for deaminative trifluoromethylation of alkyl amines.

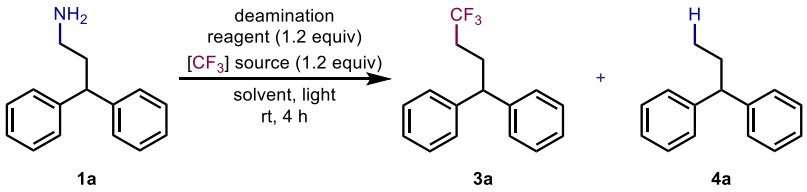
Though compounds containing amino groups are widespread, it is challenging to convert the amino group to other functional groups due to the high bond dissociation energy of the C-N bond and the nonnegligible basicity of the amino group.[42-44] The main methods used to transform the amino group to other functional groups rely on amino preactivation strategies, involving intermediates such as Sandmeyer-type diazonium ion,[45-46] Katrizky-type pyridinium salts,[47-52] or electron-rich imines.[53-54] We are fascinated by the recent renaissance of 1,1-diazene chemistry, which has proven successful in various challenging transformations, such as deaminative ring contraction,[55-57] reduction,[58] and functionalization reactions.[59-60] Mechanistically, the formation of the 1,1-diazene intermediate is achieved through the reaction of an amine with either an *N*-anomeric amide[56, 58] or an in-situ-generated iodonitrene,[57] or via a Curtius-type rearrangement of sulfamoyl azide.[55, 61] Subsequently, this intermediate can undergoe thermal homolytic N_2 extrusion to form a geminate radical pair, which can undergo either in-cage radical recombination or out-cage radical trapping to form the final products. Inspired by these elegant works and our continuous interest in organofluorine chemistry,[62-65] we hypothesized that Grushin's reagent [bpyCu$(CF_3)_3$] could potentially be reactive for the deaminative trifluoromethylation of aliphatic primary amines (Scheme 1d). The photolysis of bpyCu$(CF_3)_3$ could generate a highly active bpyCu$(CF_3)_2$ and CF_3 radical species.[66] The CF_3 radical could then undergo a hydrogen atom transfer (HAT) from the in-situ generated isodiazene intermediate, leading to the formation of the corresponding alkyl radical. The recombination of the newly formed alkyl radical with bpyCu$(CF_3)_2$, followed by reductive elimination, would furnish the desired deaminative trifluoromethylation product. Herein, we disclose our detailed studies on the site-specific deaminative trifluoromethylation of aliphatic primary amines with Grushin's reagent under blue light irritation. The reaction proceeds under mild conditions with good functional group tolerance.

RESULTS AND DISCUSSION

Initially, the site-specific deaminative trifluoromethylation of aliphatic primary amine **1a** was investigated by exploring different deamination promoters in the presence of Togni-II as the trifluoromethyl source at room temperature (Table 1). While the use of iodonitrene or $N_3SO_2N_3$, previously used by Antonchick[57] and Lu[55], respectively, led to no reaction (entries 1

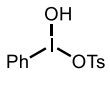
and 2), the use of *N*-anomeric amide **2** as the promoter successfully produced the corresponding deaminative trifluoromethylation product **3a** in 45% yield (entry 3). The trifluoromethyl source also played a very important role in this reaction (entries 3-7). The utilization of Togni-I reagent, CF_3SO_2Na, or trifluoroacetic anhydride did not lead to the desired **3a**. Instead, the exclusive formation of the deaminative protonation product **4a** was observed (entries 4-6). This compound was formed via competitive hydrogen abstraction of the generated alkyl radical from the isodiazene intermediate, as previously reported by Levin.[58] Thus, we speculated that a trifluoromethyl reagent with dual functionalities, serving as the CF_3 source and engaging in a competitive HAT process from the isodiazene intermediate, would be beneficial for the reaction. As expected, the bench-stable Grushin's reagent **5** [$bpyCu(CF_3)_3$] showed outstanding reactivity and gave **3a** in acceptable yield (62%) and trace amount of **4a** (entry 7). While heating hindered the reaction (entry 8), irritation with 365 nm light improved the yield of **3a** to 74% (entry 9). This enhancement can be attributed to the increased generation of CF_3 radical under light irradiation, thereby facilitating HAT from the isodiazene intermediate. Further solvent and temperature screening did not result in improved results (entries 10-13). Gratifyingly, when 425 nm blue light was used instead of the 365 nm ultraviolet light, a comparable yield of **3a** (77%) was achieved (entry 14).

Table 1. Optimization of Reaction Conditions[a]

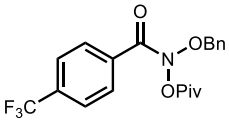


entry	deamination reagent	solvent	light	[CF_3] source	yield of **3a** (%)	yield of **4a** (%)
1	HTIB, $NH_2CO_2NH_4$	TFE	none	Togni-II	N. D.	N. D.
2	$N_3SO_2N_3$	MeCN	none	Togni-II	N. D.	N. D.
3	**2**	MeCN	none	Togni-II	45	26
4	**2**	MeCN	none	Togni-I	N. D.	50
5	**2**	MeCN	none	CF_3SO_2Na	N. D.	58
6	**2**	MeCN	none	$(CF_3CO)_2O$	N. D.	33
7	**2**	MeCN	none	**5**	62	trace
8[b]	**2**	MeCN	none	**5**	43	Trace
9	**2**	MeCN	365 nm	**5**	74	N. D.
10	**2**	DMSO	365 nm	**5**	60	trace
11	**2**	DMF	365 nm	**5**	27	14
12	**2**	THF	365 nm	**5**	48	trace

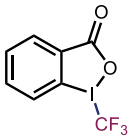
13[b]	**2**	MeCN	365 nm	**5**	58	trace
14	**2**	MeCN	425 nm	**5**	77% (72%)	N. D.



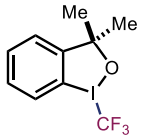
HTIB



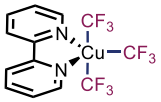
*N-anomeric amide (**2**)*



Togni-II



Togni-I

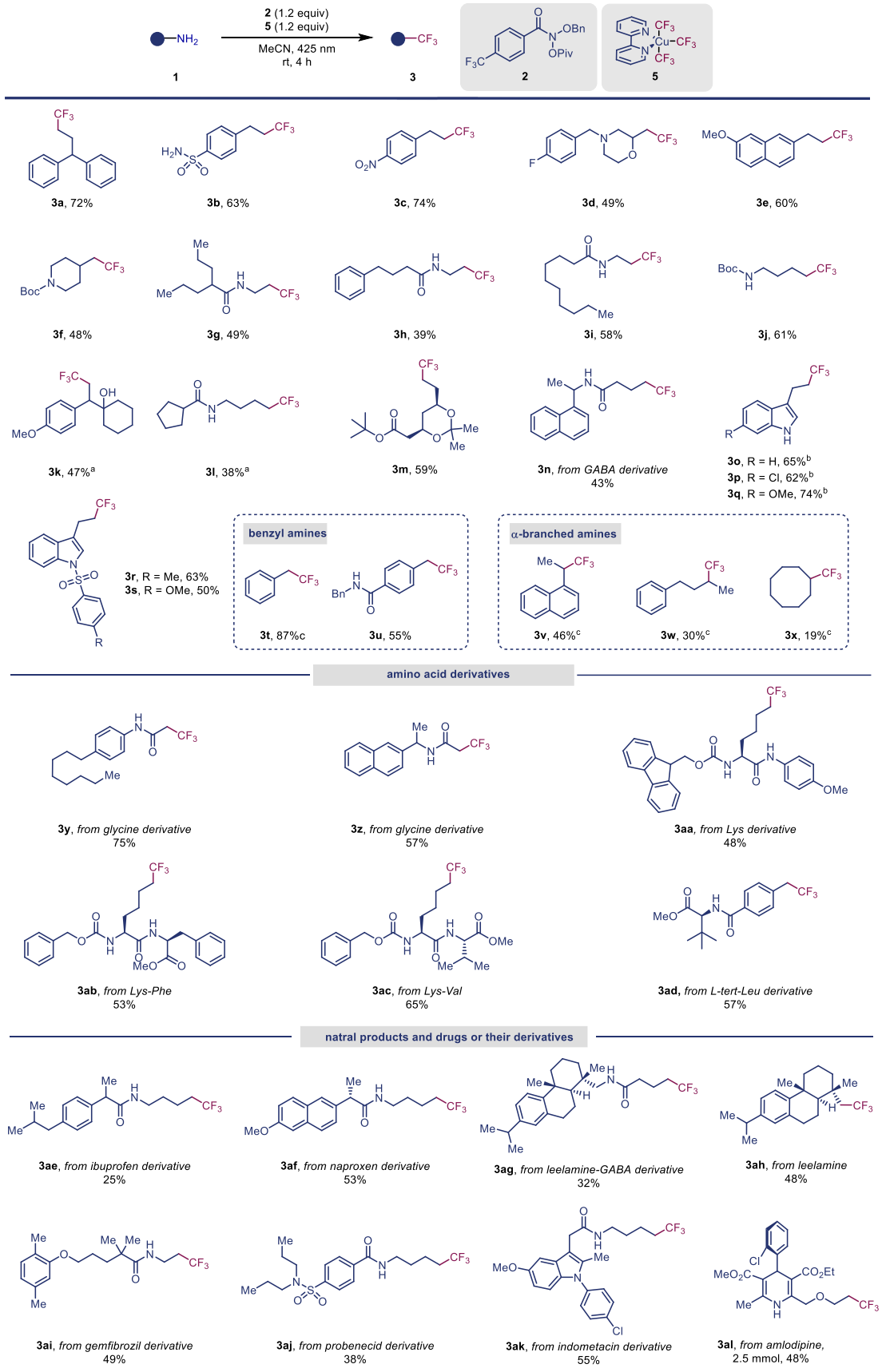


*Grushin's reagent (**5**)*

[a]General reaction conditions: **1a** (0.20 mmol, 1.0 equiv), **2** (0.24 mmol, 1.2 equiv), [CF_3] source (0.24 mmol, 1.2 equiv), solvent (2.5 mL), with or without light, rt, 4 h. Yields determined by ^{1}H NMR using 4-iodoanisole as the internal standard; isolated yield in parentheses. [b]60 °C. N. D. = not detected.

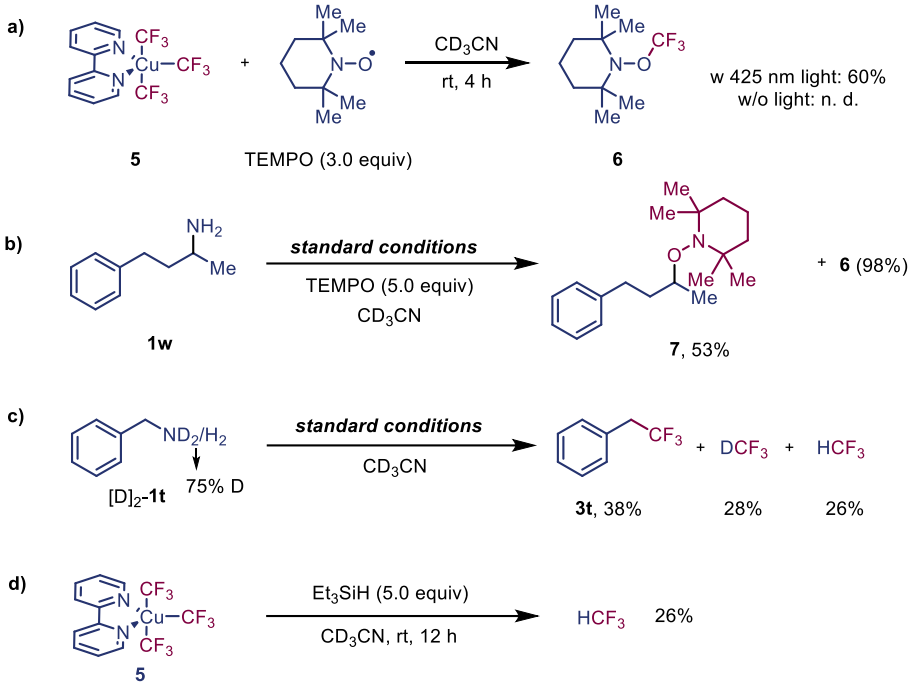
With the optimized conditions in hand (Table 1, entry 12), we next turned our attention to investigate the generality of this protocol. As shown in Scheme 2, a diverse set of aliphatic primary amines were readily converted to the corresponding trifluoromethylation products (**3a**-**3x)** in moderate to good yields. A wide range of commonly encountered functional groups were well tolerated in this reaction. For example, sulfonamide (**3b**), nitro (**3c**), halide (**3d** and **3p**), methoxy (**3e**, **3k**, **3q**), *N*-Boc (**3f** and **3j**), amide (**3g-3i**, **3l**, **3n**, **3u**), hydroxyl (**3k**), ester (**3m**), acetal (**3m**), *N*-Ts (**3r**) were all amenable to this protocol. In addition, substrates bearing morpholine (**3d**), naphthalene (**3e**, **3n**, **3v**) and indole (**3o**-**3s**) motifs underwent the reaction smoothly, affording the trifluoromethylation products in reasonable yields. Notably, even α-branched primary amines (**3v-3x**), which are sterically demanding, were also compatible with the reaction conditions, albeit in lower yields.

A variety of biologically relevant substrates were also employed. We found that the CF_3 group could be easily installed in GABA derivatives (**3n**, **3ag**), unnatural amino acids (**3y**, **3z**, **3aa**), dipeptides (**3ab** and **3ac**), natural product scaffolds (**3ag** and **3ah**), drugs and their derivatives (**3ae**, **3af**, **3ai-3al**). These results further confirmed the mildness of the conditions and highlighted the potential of this protocol in chemical biology. Moreover, the successful scale-up synthesis of trifluoromethylated medicine amlodipine (**3al**) demonstrated the synthetic practicality of this methodology.



Scheme 2. Scope of the deaminative trifluoromethylation. Unless otherwise noted, the reactions were performed with **1** (0.20 mmol) under the optimized conditions. Isolated yields.

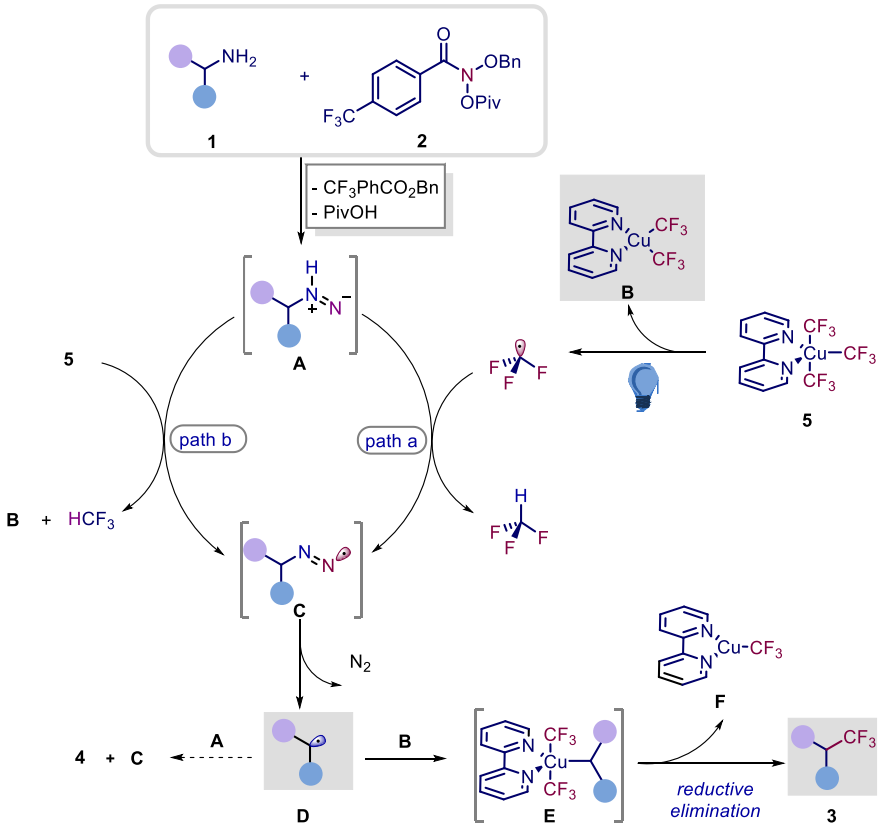
[a]Without light irritation. [b]**2** was added to the reaction mixture at the last sequence. [c]NMR yield due to the volatility of this product.



Scheme 3. Mechanistic studies.

To gain more insight into the present deaminative trifluoromethylation reaction, preliminary mechanistic studies were carried out (Scheme 3). First, the influence of blue light irradiation on the reaction was explored. As depicted in Scheme 3a, the photolysis of complex **5** with blue light in the presence of 2,2,6,6-tetramethylpiperidineoxy (TEMPO) afforded the TEMPO-CF_3 adduct **6** in 60% yield (as determined by ^{19}F NMR), whereas no detectable formation of **6** was observed without light. This outcome suggests the generation of trifluoromethyl radical from bpyCu$(CF_3)_3$ upon photostimulation. Second, in an additional investigation, the introduction of TEMPO to the standard reaction of **1w** led to the formation of both TEMPO inclusion products **7** and **6** in yields of 53% and 98%, respectively (Scheme 3b). This experiment provided unequivocal evidence for the involvement of alkyl and CF_3 radicals as intermediates. To further elucidate the applicability of the in-situ generated CF_3 radical as a HAT reagent from the isodiazene intermediate, a deuterium labelling experiment using [D]$_2$-**1t** was also conducted (Scheme 3c). This experiment revealed the formation of both deuterated fluoroform (28% yield) and fluoroform (26% yield), as determined by ^{19}F NMR spectroscopy, suggesting that the CF_3 radical's hydrogen abstraction likely originates from the isodiazene intermediate. Interestingly, during the optimization of reaction conditions, a satisfactory yield of 62% was achieved without light irradiation (Table 1, entry 7), implying an alternative HAT process might be involved in the mechanism. Furthermore, upon treatment of Grushin's reagent with triethylsilane at room temperature for 12 hours, fluoroform was generated as well (Scheme 3d). This observation

implies that complex **5** could directly undergo the HAT process from the isodiazene intermediate.



Scheme 4. Plausible mechanism.

Based on the aforementioned results and preceding reports,[56,58-60] a mechanistic scenario has been proposed to rationalize the observed reaction outcomes, as illustrated in Scheme 4. Initially, the interaction between amines **1** and *N*-anomeric amide **2** generates the isodiazene intermediate **A**. Meanwhile, the photolysis of complex **5** under blue light produces the active Cu(II) species **B** along with a relatively long-lived CF_3 radical. The CF_3 radical subsequently abstracts a hydrogen atom from **A** to give fluoroform and diazenyl radical **C**. The latter undergoes thermal N_2 extrusion, leading to the formation of a new carbon-based radical **D**. Ultimately, the recombination of radical **D** with the active Cu(II) species **B** generates alkyl copper(III) species **E**, which undergoes rapid reductive elimination to provide the desired products **3** and unreactive Cu(I)CF_3 (**F**). Previous investigations have excluded the possibility of forming **3** through the direct coupling of radical **D** with the CF_3 radical.[21] The competitive hydrogen abstraction of alkyl radical **D** from the isodiazene intermediate **A** could result in the undesired deaminative protonation product **4**. Notably, given the moderate yield of the desired product even in the absence of light, it is plausible that the diazenyl radical **C** may be formed from the reaction Grushin's reagent and isodiazene intermediate **A** (path b).

In conclusion, we have developed a mild and convenient method for the site-specific deaminative trifluoromethylation of aliphatic primary amines, offering a valuable complement to established methods for aryl amines. This reaction is promoted by the readily accessible *N*-anomeric amide in conjunction with the bench-stable Grushin's reagent as the CF_3 source under blue light irradiation. The protocol features mild reaction conditions, good functional group tolerance, and moderate to good yields. Moreover, this method can also be applied to the late-stage trifluoromethylation of complex molecules and bioactive compounds. Experimental mechanistic investigations have unveiled a radical mechanism and shed light on the dual roles of Grushin's reagent. Given the potential applications of the products and the synthetic practicality of the protocol, we anticipate that this method will find valuable utility in the realms of organic synthesis and medicinal chemistry.

Acknowledgements

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