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Direct synthesis of N-trifluoromethyl amides via photocatalytic trifluoromethylamidation

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N-CF_3 amides are promising targets for pharmaceutical and agrochemistry. Unfortunately, there is a defluorination problem of *N*-CF_3 amine starting materials when using common amide bond formation method. Recently, elegant alternative approaches emerged. However, none have used the well known amidyl radical chemistry to directly prepare *N*-CF_3 amides. We describe here a convenient preparation of *N*-(*N*-CF_3 imidoyloxy) pyridinium salts and their applications as efficient trifluoromethylamidyl radical precursors in photocatalytic trifluoromethylamidations of (hetero)arenes, alkenes, alkynes, silylenol ethers, and isocyanides. The rapid construction of diverse *N*-CF_3 amides, particularly the synthesis of cyclic *N*-CF_3 amides, demonstrates the uniqueness and flexibility of the method. This method is expected to provide a platform for directly synthesizing *N*-CF_3 amides and to inspire the discovery of more redox molecular systems that can handle challenging trifluoromethylamidations.

Trifluoromethyl (CF_3) modification has become an important strategy for discovering functional molecules, as the introduction of the CF_3 group can adjust the biophysical properties of the parent molecules, such as solubility, basicity, lipophilicity, permeability, and metabolic stability[1–3]. Amides play a prominent role in the fields ranging from drug design, agrochemical industry to organic synthesis[4,5]. To modify amide molecules by introducing the CF_3 group onto the amide N atom is of interest[6]. However, the limitations of synthetic method greatly hinder the application of *N*-CF_3 amides.

The preparation of *N*-CF_3 amides using traditional amide bond formation method remains challenging due to the ease of defluorination when dealing with primary/secondary *N*-CF_3 amine starting materials[7,8]. Solving such problem and seeking alternative approaches are currently the research focuses in this field. With the development of basic strategies for constructing the NCF_3 unit[9–11], including fluorine exchange strategy[12–17] and *N*-trifluoromethylation strategy[18–23], significant progress has recently been made in the preparation of *N*-CF_3 amides. In 2020, Fang and Li synthesized *N*-CF_3 tertiary amides via Ag-mediated oxidative *N*-trifluoromethylation of secondary amides (Fig. 1A, *a*)[24]. Such *N*-trifluoromethylation route is straightforward and simple, but only this method has been applied in synthesis, as there is still a lack of effective methods for bonding the CF_3 onto the N atom. By comparison, the step-by-step synthesis of *N*-CF_3 tertiary amides developed by Schoenebeck in 2019 presents a wide range of applications. Starting from isothiocyanates, AgF and bis(trichloromethyl) carbonate (BTC), *N*-CF_3 carbamoyl fluorides were synthesized at first via a fluorination and acylation sequence, in which they utilized Ag^+ to stabilize the in situ formed NCF_3 anion for avoiding defluorination. Then the cross-coupling reaction of *N*-CF_3 carbamoyl fluorides with Grignard reagents was carried out to afford diverse *N*-CF_3 tertiary amides (Fig. 1A, b1)[6]. Moreover, the synthesis of *N*-CF_3 alkynamides and *N*-CF_3 formamides could also be achieved from *N*-CF_3 carbamoyl fluorides, respectively[25,26]. Soon after, a one-pot synthesis of *N*-CF_3 amides was reported by Toste and Wilson, which was realized by direct acylation of similar Ag^+-stabilized NCF_3 anion with carboxylic acid halides (Fig. 1A, b2)[27].

As described above, Ag^+-stabilized NCF_3 anion can act as an in situ generated NCF_3 transfer species for constructing *N*-CF_3 compounds. Recently, stable NCF_3 transfer precursors have emerged for practical applications, such as N_3CF_3 reported by Beier as the precursor for trifluoromethyl nitrene[28], and *N*-protected *N*-CF_3 hydroxylamine esters reported by Huang and Xu as the precursor for NCF_3 radical[29]. The latter reagents were prepared through oxidative *N*-trifluoromethylation[24] of pre-synthesized *N*-Boc/Cbz hydroxylamine esters. Taking these *N*-CF_3

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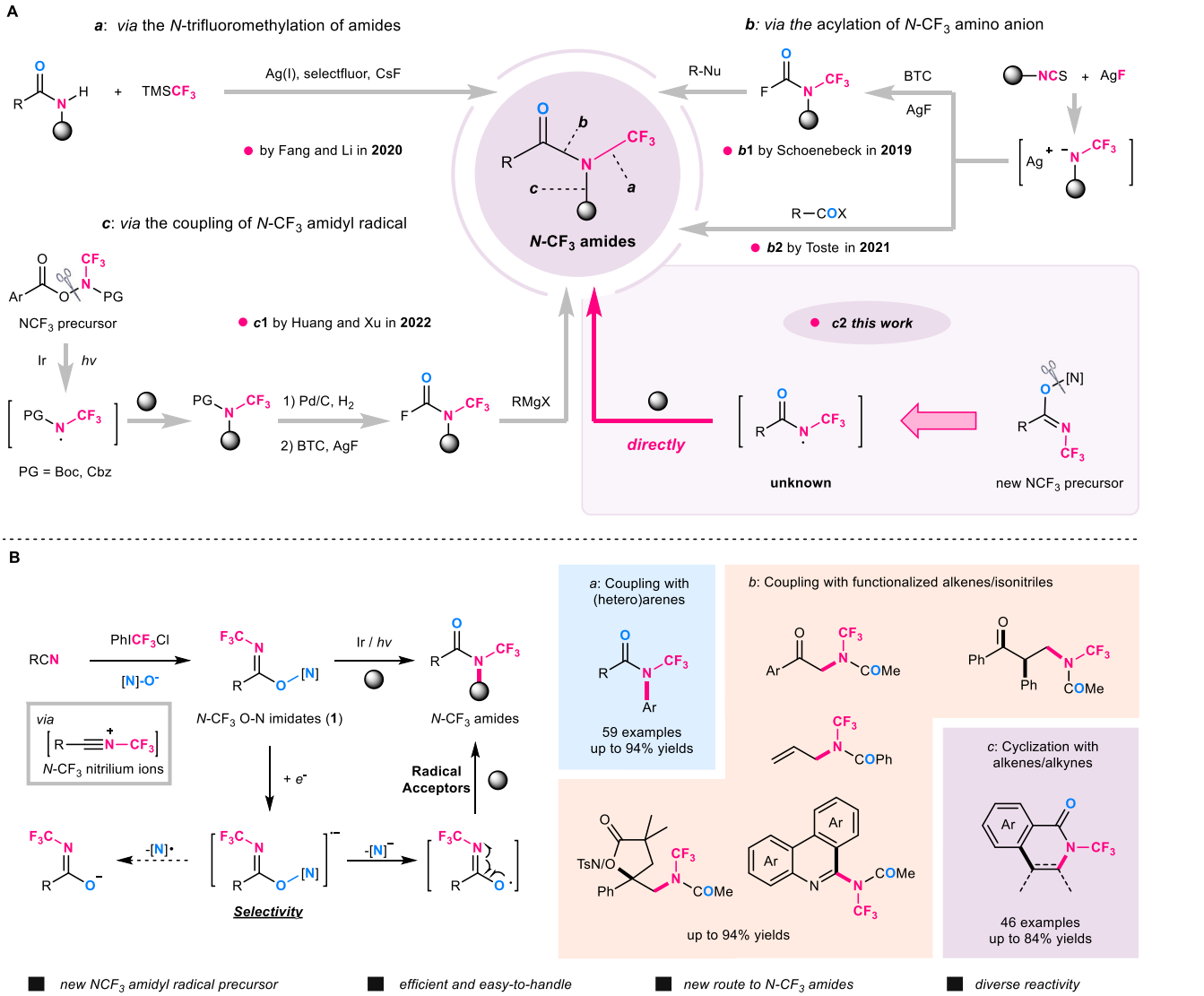

Fig. 1 | Known methods for the synthesis of *N*-CF_3 amides & our work design. A Known route to *N*-CF_3 amides. **B** Our design on the generation of *N*-CF_3 amidyl radical & challenges. BTC bis(trichlormethyl)carbonate, PG Protecting group.

N-O reagents as the *N*-CF_3 amidyl radical source, a set of radical cross-coupling reactions have been established. Among them, the C-H trifluoromethylamination of arenes delivered *N*-Boc/Cbz *N*-CF_3 aromatic amines. After deprotection, the in situ generating *N*-CF_3 amines could be further converted into *N*-CF_3 tertiary amides by using the synthetic procedures developed by Schoenebeck mentioned above[6], including fluoroformylation with BTC/AgF and cross-coupling with Grignard reagents (Fig. 1A, c1). It is worth noting that, unlike NCF_3 anion[6,30], such NCF_3 radical-involved process has less risk of defluorination. Meanwhile, the amidyl radical has diverse reactivity, indicating that a wide range of radical acceptors can be utilized, such as arenes, alkenes, alkynes and so on[31,32]. In fact, it provides a much more promising approach to *N*-CF_3 amides. However, to the best of our knowledge, real trifluoromethylamidyl radical (Fig. 1A, c2) directly used for constructing *N*-CF_3 amides has not been reported yet.

In our ongoing interest in developing synthetic methods of *N*-CF_3 compounds[33–36], we have recently established a synthetic method for *N*-CF_3 imidate esters via the reaction of *N*-CF_3 nitrilium ions (Fig. 1B) and alcohols. In continuing investigations, we tried to prepare *N*-CF_3 O-N imidates (**1**) by expanding alcohol-based reaction partners to *N*-oxide-type O-nucleophiles (Fig. 1B). Given great advances in the use of redox-active O-N reagents as O-centered radical source[37–42], we further envisioned a generation of imidoyloxy radical (O-radical) from **1** via the fragmentation of the O-N bond under photoredox catalysis, and its cross-coupling reactions in the form of trifluoromethylamidyl radical resonance hybrid (N-radical)[43,44], which would be for developing alternative route to *N*-CF_3 amides. However, the first step in utilizing such synthetic strategy is to address the selectivity issue of the O-N bond cleavage, that is, to control the formation of imidoyloxy radical instead of imidoyloxy anion under photocatalysis (Fig. 1B). Suitable redox active *N*-CF_3 N-O imidates are indeed necessary for efficient formation of amidyl radical and the development of trifluoromethylamidation reaction. Herein, we would like to report a kind of *N*-CF_3 amidyl radical precursors for directly preparing diverse *N*-CF_3 tertiary amides through coupling of them with (hetero)arenes, functionalized alkenes and isonitriles (Fig. 1B, *a* and *b*). It is worth noting that, taking advantage of the structural diversity of nitrile starting materials, we can also synthesize interesting *N*-CF_3 cyclic amides (Fig. 1B, *c*), demonstrating the uniqueness and flexibility of the method.

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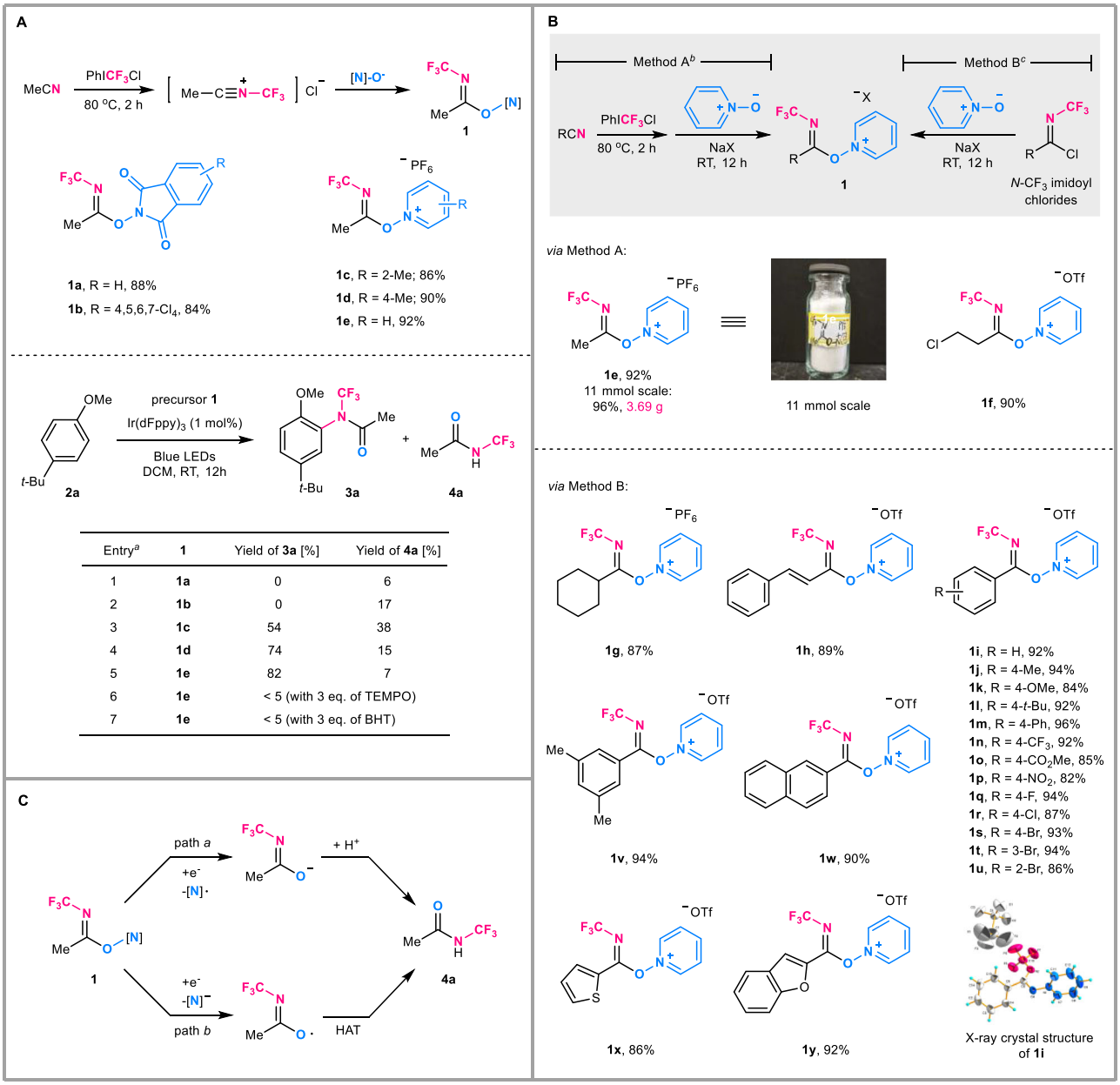

Entry[a]	1	Yield of 3a [%]	Yield of 4a [%]
1	1a	0	6
2	1b	0	17
3	1c	54	38
4	1d	74	15
5	1e	82	7
6	1e	< 5 (with 3 eq. of TEMPO)	
7	1e	< 5 (with 3 eq. of BHT)	

Fig. 2 | Screening and synthesis of *N*-CF_3 amidyl radical precursors. A Synthesis of *N*-CF_3 O-N imidates **1** from acetonitrile for radical trifluoromethylamidation of arene **2a**. **B** Possible pathways for the formation of by-product **4a**. **C** Preparation of *N*-CF_3 imidoxyl pyridinium salts from diverse nitriles. [a]Reaction conditions: **1** (0.1 mmol), **2a** (0.3 mmol), Ir(dFppy)$_3$ (0.001 mmol), DCM (3 mL), Blue LEDs, under N_2, rt, 12 h, ^{19}F NMR yields using $PhCF_3$ as an internal standard. [b]Reaction conditions: step1: $PhICF_3Cl$ (1.5 mmol), RCN (3.5 mL), 80 °C, 2 h; step 2: pyridine-*N*-oxide (1.0 mmol), NaX (2.0 mmol), isolated yields. [c]Reaction conditions: *N*-CF_3 imidoyl chlorides (1.1 mmol), pyridine-*N*-oxide (1.0 mmol), NaX (2.0 mmol), MeCN (4 mL), RT, 12 h. BHT Butylated hydroxytoluene, TEMPO 2,2,6,6-Tetramethylpiperidinyloxy.

Results

Screening and synthesis of *N*-CF_3 amidyl radical precursors

Initially, the preparation of *N*-CF_3 imidate ester-based O-N reagents (**1**) (Fig. 2A) was tested through nucleophilic addition reaction of in situ formed *N*-CF_3 nitrilium ions by employing both hydroxylamine derivatives and heterocyclic *N*-oxides as O-nucleophiles. Considering that the reductive fragmentation of O-N reagents containing electron-deficient N-leaving group is more conducive to the release of O-radical under photoredox catalysis[41], we focused on the synthesis of **1** with phthalimidyl group and pyridyl group. Although the nucleophilic addition is methodological inefficient in these cases, several *N*-hydroxyphthalimides (NHPI) and pyridine-*N*-oxides were delightfully found to react with *N*-CF_3 nitrilium ion derived from acetonitrile, affording desired imidates (**1a**-**e**) in good yields (Fig. 2A). As a result, we decided to evaluate the reactivity of N-O reagents (**1a**-**e**) as potential trifluoromethylamidyl radical source in the trifluoromethylamidation of arenes and selected 4-*tert*-butylanisole (**2a**) as the model substrate (Fig. 2A). By screening of reaction conditions including the photocatalyst, the light, the solvent, and the ratio of the substrates (see Supplementary Table S1), the reactions of NHPI imidates (**1a** and **1b**) with **2a** were proven to be ineffective (Fig. 2A, Entries 1 and 2). No desired trifluoromethylamidated product (**3a**) was obtained except that a species, assigned as *N*-CF_3 secondary amide (**4a**), was detected by both ^{19}F NMR (−57.3 ppm) and MS ($[M+H]^+$ = 128.0313)[45]. The formation of **4a** may originate from two undesired competing processes: the protonation of unwanted imidoyloxy anion (Fig. 2B, path a); or

undesired H-abstraction of imidoyloxy radical (Fig. 2B, path b). By comparison, pyridinium imidates (**1c**-**e**) could furnish desired **3a** with satisfactory yield in DCM at room temperature in the presence of 1 mol% $Ir(dFppy)_3$ under blue LEDs irradiation, while also producing **4a** (Fig. 2A, Entries 3-5). Among these N-O reagents, **1e** is a more proper candidate for the trifluoromethylamidation. **1c** and **1 d** produced more **4a**, showing that pyridinium imidates containing electron-donating substituent on the pyridine ring are more inclined to release undesired imidoyloxy anion by reductive fragmentation. It is worth noting that no O-coupling product of imidoyloxy radical was detected. The cyclic voltammetry (CV) studies of both reagents (**1a**-**e**) and photocatalyst $Ir(dFppy)_3$ were then conducted to understand such redox process (see Supplementary Fig. 1-6). Obviously, **1e** with a reduction potential of −0.67 V can be reduced by the Ir-catalyst (−0.8 V) under current conditions. Furthermore, mechanistic studies by performing the reaction with radical scavenger revealed that this trifluoromethylamidation reaction likely proceeded through a radical pathway (Fig. 2A, Entries 6 and 7).

After determining *N*-CF_3 imidoxyl pyridinium scaffold can serve as a suitable trifluoromethylamidyl radical source, we tried to prepare a series of *N*-(*N*-CF_3imidoxyl)pyridinium salts (**1**) through nucleophilic addition reaction of the in situ formed *N*-CF_3 nitrilium salts[34] with pyridine-*N*-oxide. By screening reaction conditions, **1e** and **1 f** could be obtained directly from nitriles in one-pot two-step procedures (Fig. 2C, method A). 11 mmol scaled-up reaction was proved to have similar efficiency, which afforded pyridinium salts (**1e**) in 96% isolated yield (3.69 g). As for those *N*-CF_3 imidoxyl pyridinium salts (**1**) derived from nitriles with high viscosity or solid nitriles, *N*-CF_3 imidoyl chlorides[35] were required to be pre-synthesized as the precursor of *N*-CF_3 nitrilium salts (Fig. 2C, method B). In these cases, a broad range of alkyl, vinyl and aryl *N*-CF_3 imidoyl chlorides worked well and afford structurally diverse N-O reagents (**1g**-**y**) in excellent yields. Generally, these reagents are white solids, which exhibit complete air tolerance under ambient conditions. X-ray diffraction analysis of compound (**1i**) unambiguously confirmed its structure.

Scope of the trifluoromethylamidation of (hetero)arenes

Next, the scope of (hetero)arenes in the trifluoromethylamidation were investigated by using reagent (**1e**) as trifluoromethylamidyl radical precursor under the optimized conditions (Fig. 2A, Entry 5, also see Supplementary Table S1). Amidyl radicals have electrophilic nature, which often lead to low reaction efficiency with electron deficient radical acceptors. That's indeed the case. In our experiments, electron-rich (hetero)arenes generally showed more reactive than electron-deficient ones. In the cases of those reaction partners with electron-deficient groups or without stronger electron-donating groups, sluggish reactions usually resulted in more **4a** likely because the generated imidoyloxy radical has more opportunity for the H-abstraction from the reaction mixture (see Supplementary Fig. 9). As described in Fig. 3, among the tested arenes (**2a**-**j**) with one or more electron-donating groups, most provided amide products (**3a, 3c**-**f** and **3h**-**j**) with a yield of over 70%, while benzene (**2b**), 4-bromoanisole (**2 g**) and p-xylene (**2 h**) gave **3b, 3 g** and **3 h** in 43%, 44% and 50% yields, respectively, along with the formation of by-product **4a** with a yield of about 40%. The reaction of **2a** with **1e** could be performed on a gram scale (10 mmol) to afford **3a** in 65% yield (1.89 g). The C-H trifluoromethylamidations of naphthalene (**2k**) and 2-methoxynaphthalene (**2 l**) also proceeded smoothly, affording *N*-CF_3 amides (**3k** and **3 l**) in excellent yields. As for heterocyclic substrates, including pyrroles (**2m**-**o**), furan (**2p**), thiophenes (**2q**-**s**), indoles (**2t** and **2 u**), benzofuran (**2 v**), benzothiophene (**2w**), coumarin (**2x**) and 2,6-dimethoxy pyridine (**2 y**), they all regioselectively provided trifluoromethylamidated products (**3m**-**y**) with moderate to excellent yields ranging from 46% to 94%. It should be pointed out that the tested heterocycles with carbonyl and ester groups are compatible with the reaction though benzene derivatives with strong electron-deficient groups were not suitable radical acceptors as mentioned above. By comparison, those arenes containing free NH or OH groups, as well as 3,5-dimethoxy pyridine were sensitive to the N-O reagent (**1**) and usually resulted in complex mixture (see Supplementary Fig. 9)[39]. In addition, indole (**2t**) without 3-substituent produced **3t** with lower yield. To further illustrate the practice ability of the method, we investigated the late-stage functionalization of several bioactive molecules and drug derivatives. It was found that naproxen (**2z**), L-menthol (**2aa**), cholesterol (**2ab**) derivatives, and nature products including caffeine (**2ac**), pentoxifylline (**2ad**), 1,3-dimethyluracil (**2ae**), they all tolerated the reaction, giving **3z**-**ae** in 34-87% yields, respectively. In addition, alkyl imidoxyl pyridinium salts (**1 f, 1 g**) and vinyl imidoxyl pyridinium salt (**1 h**) were used as NCF_3 amidyl radical source to react with **2 m**. As a result, corresponding products (**3af**-**ah**) were obtained in 73-84% yields.

Then, aromatic imidoxyl pyridinium salts were chosen to explore their reactivity in the C-H trifluoromethylamidation of (hetero)arenes. As described in Fig. 3, when treating **1i** derived from benzonitrile with 1,4-disubstituted arene (**2a**), 1,3,5-trisubstituted arene (**2i**), or heteroarenes (**2p** and **2q**) under identical reaction conditions, to our delight, *N*-benzoyl trifluoromethylamidyl radical was efficiently generated and smoothly reacted as the N-centered radical with the tested arene substrates, affording *N*-CF_3 benzamide products (**3ai**-**al**) in good yields. The structure of **3al** was confirmed by its X-ray analysis. The reactivity of different aromatic *N*-CF_3 imidoxyl pyridinium salts were then evaluated in the reaction with **2 m**. It was found that phenyl substituted N-O reagents (**1j**-**v**) with a diverse array of functional groups delivering desired **3am**-**az** in 70-92% yields. 2-Naphthylimidoxyl pyridinium salt (**1w**), as well as 2-thienyl and 2-benzofuryl ones (**1x** and **1 y**) were also proven to be tolerated to this reaction, giving products (**3ba**-**bc**) in good yields.

Extended applications of radical trifluoromethylamidations

After establishing aromatic C-H trifluoromethylamidation, we decided to further expand the applications of this synthetic method by exploring the reactions of **1** with other radical acceptors. As presented in Fig. 4, trifluoromethylamidation and intramolecular arylation of 2-isocyanobiphenyls (**5a** and **5b**) with **1e** gave *N*-trifluoromethylamido phenanthridine derivatives (**6a** and **6b**) in 58% and 64% yields, respectively (Fig. 4A). When employing silylenol ethers (**7a** and **7b**) as alkene substrates in the reaction with **1e**, α-trifluoromethylamido ketones (**8a** and **8b**) were obtained as the final product (Fig. 4B). In addition, the reaction of allylsilane (**9**) with **1i** furnished *N*-trifluoromethylallylamide (**10**) in 85% yield (Fig. 4C). The NCF_3 radical-initiated lactonization/lactamidation of 2,2-dimethyl-4-phenylpent-4-enoic acid (**11**)/2,2-dimethyl-4-phenyl-*N*-tosylpent-4-enamide (**13**) were also tested, providing corresponding cyclic products (**12** and **14**) in excellent yields, respectively (Fig. 4D, E). Finally, sequential trifluoromethylamidation and 1,2-migration reaction of 1,1-diphenylprop-2-en-1-ol (**15**) and **1e** was carried out and afforded *β*-trifluoromethylamido ketone (**16**) in 60% yield (Fig. 4F).

Scope of the aryltrifluoromethylamidation of alkenes/alkynes

Bifunctionalization of alkenes presents important applications in preparing densely functionalized organics[46]. Encouraged by the successful development of intramolecular trifluoromethylamidative bifunctionalization of alkenes (Fig. 4D-F), we turned to investigate their intermolecular versions. Thus, the oxytrifluoromethylamidation and the thiocyanotrifluoromethylamidation were initially attempted with both aliphatic and aromatic trifluoromethylamidyl radical precursors (**1e** and **1i**), respectively. However, when 1-decene (**17a**) was treated with **1e** or **1i** in MeOH under basic and photoredox catalytic conditions, no desired bifunctionalized product was obtained. Similarly, the attempt on the thiocyanotrifluoromethylamidation of **17a** with KSCN also failed. Both **1e** and **1i** were found to be sensitive to basic

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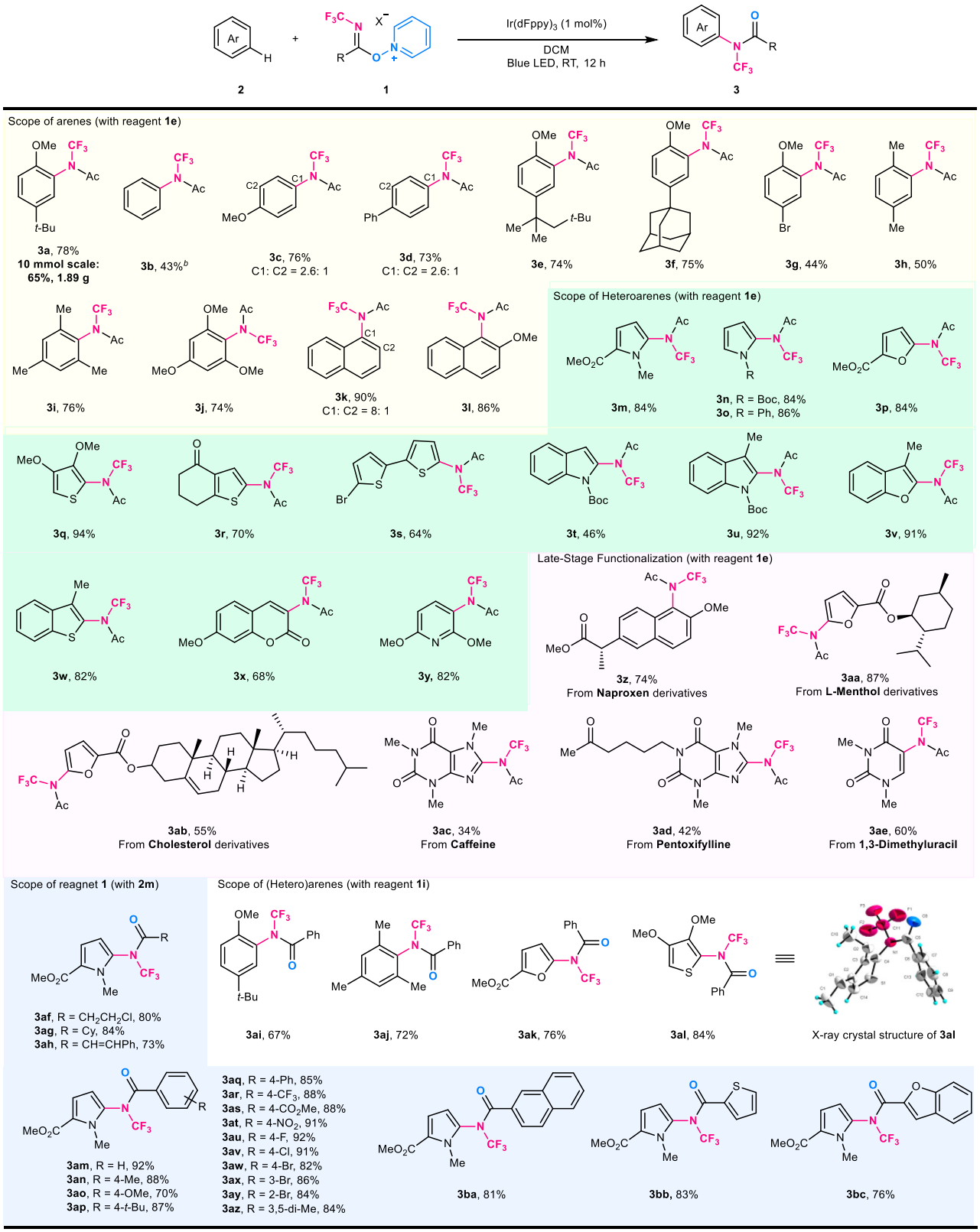

Fig. 3 | Trifluoromethylamidation of (hetero)arenes[a]. [a]Reaction conditions: **1** (0.3 mmol), **2** (0.9 mmol), $Ir(dFppy)_3$ (0.003 mmol), DCM (9 mL), Blue LEDs, under N_2, RT, 12 h, isolated yields. [b]**2b** (1.5 mmol).

reaction condition. Interestingly, in the reaction mixture of **17a** and **1i**, an intramolecular aryltrifluoromethylamidation product, namely *N*-CF_3 3,4-dihydroisoquinolin-1(*2H*)-one (**18a**) (Fig. 5) was isolated and identified. In the case of 1-octyne (**19a**) as the substrate toward above identical reaction conditions, *N*-CF_3-isoquinolin-1(*2H*)-one (**20a**) was also yielded as cyclic product. As a class of lactams, isoquinolin-1(*2H*)-one derivatives are frequently found in natural products and pharmaceuticals[47,48]. Given that CF_3 modification can enhance the

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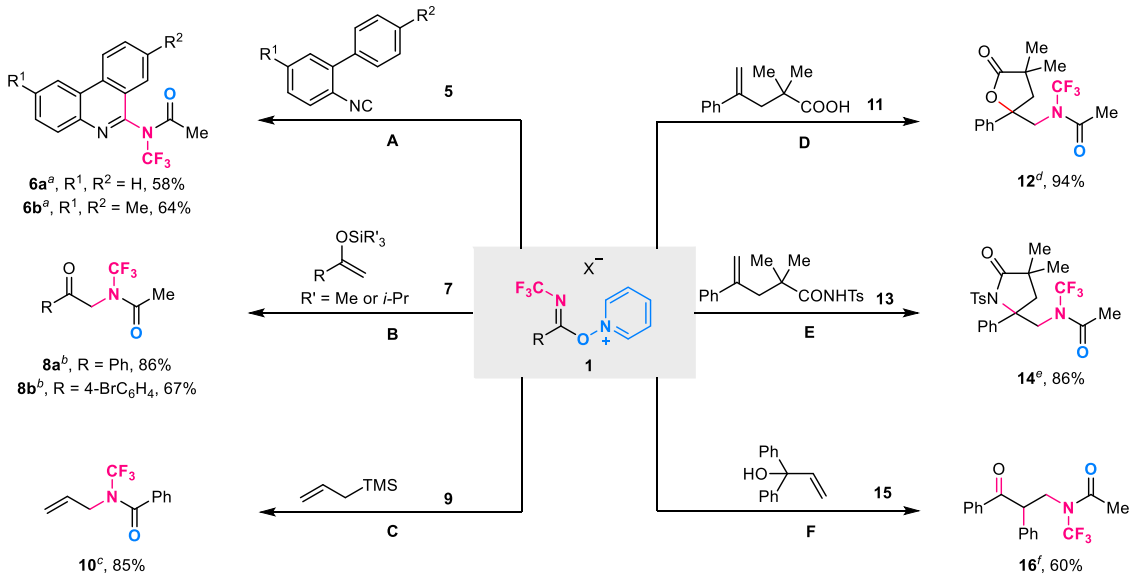

Fig. 4 | Extended applications of radical trifluoromethylamidations. A Radical trifluoromethylamidations of compounds **5**. **B** Radical trifluoromethylamidations of compounds **7**. **C** Radical trifluoromethylamidation of compound **9**. **D** Radical trifluoromethylamidation of compound **11**. **E** Radical trifluoromethylamidation of compound **13**. **F** Radical trifluoromethylamidation of compound **15**. General reaction conditions: $Ir(dFppy)_3$ (0.003 mmol), DCM (9 mL), Blue LEDs, under N_2, RT, 12 h, isolated yields. [a]**1e** (0.3 mmol), **5** (0.9 mmol). [b]**1e** (0.3 mmol), **7** (0.9 mmol). [c]**1i** (0.3 mmol), **9** (0.9 mmol). [d]**1e** (0.45 mmol), **11** (0.3 mmol). [e]**1e** (0.45 mmol), **13** (0.3 mmol). [f]**1e** (0.3 mmol), **15** (0.9 mmol).

bioactivity of molecules, *N*-CF_3 lactams are of highly desired in both synthetic and medicinal chemistry. Unfortunately, their synthetic method is limited. In 2021, Schoenebeck reported an access to *N*-CF_3 quinolones and *N*-CF_3 oxindoles through the cyclization of pre-synthesized *N*-CF_3 alkynamides[25]. By comparison, the radical trifluoromethylamidative cyclization method described here utilizes **1** as a four-component synthon containing NCF_3 in the [4 + 2] cyclization with alkenes/alkynes and takes advantage of the structural characters of *N*-CF_3 amidyl radical precursors (**1**). As starting materials, both nitriles and alkenes/alkynes are readily available, which allows the synthesis of *N*-CF_3 cyclic amides with diverse structures. Thus, we carefully screened the conditions for such cyclization (see Supplementary Table S2). As a result, [4 + 2] cyclization of **17a** and **1i** was found to deliver **18a** in 66% yield when three equivalents of **17a** were employed in the presence of 1 mol% $Ir(dFppy)_3$ in DCM under Blue LEDs irradiation at room temperature. It should be pointed out that, despite many efforts to screen the reaction conditions, such trifluoromethylamidative cyclization was inevitably accompanied by the formation of *N*-CF_3 secondary amide (**4b**)[49,50] generated from **1i**, which makes it difficult to improve the yield of expected **18a**. Next, we investigated the alkene scope under relatively better reaction conditions mentioned above. As shown in Fig. 5, all tested unactivated mono-substituted alkenes could furnish cyclic products (**18a-l**) in 52-78% yields. The substrates based on tosylate, phthalimide and carboxylic ester (**17e-l**) were compatible with the conditions. Poly-substituted alkenes, including 1,1-disubstituted alkenes (**17m-o**), 1,2-disubstituted alkenes (**17p-r**) and trisubstituted alkene (**17 s**) could also smoothly afford corresponding cyclic amide products (**17m-s**) in moderate to good yields. Among them, asymmetric internal alkenes (**17p**) afforded a mixture of regioisomeric products (**18p** and **18p'**) with a ratio of 1.5 to 1. However, tetrasubstituted alkenes (**17t**) could not give desired *N*-CF_3 3,4-dihydroisoquinolin-1(*2H*)-one (**18t**). Furthermore, several drug molecules, including L-menthol (**17 u**), febuxostat (**17 v**), ibuprofen (**17w**), fenofibric acid (**17x**) and isoxepac (**17 y**) were tested and provided *N*-CF_3 3,4-dihydroisoquinolin-1(*2H*)-ones (**18u-y**) in 54-79% yields. It should be noted that styrene derivatives were not suitable substrates likely because the involved radical adducts, benzyl radicals, often engage in unproductive side reactions, such as oligomerization and isomerization. As for electron-deficient alkenes, they were also not compatible with this intramolecular aryltrifluoromethylamidation and gave complex mixture, among which by-proudct **4b** could be detected. (see Supplementary Fig. 10)

Next, we turned our attention to the trifluoromethylamidative cyclization of alkynes. As shown in Fig. 5, a wide variety of alkynes, including terminal alkyl alkynes (**19a-e**) and aryl alkynes (**19f-l**), afforded *N*-CF_3 isoquinolin-1(*2H*)-ones (**20a-l**) in moderate to good yields under identical reaction conditions. Among them, aryl alkynes substrates bearing electron-donating groups, such as –Me, –OMe, exhibiting superior reactivity compared to those bearing electron-withdrawing groups. The molecular structure of **20 g** was established unequivocally by X-ray crystal structure determination. Furthermore, internal alkynes (**19 m** and **19n**) could also undergo such radical cyclization with good yields. This cyclization method has also been successfully applied to the modification of bioactive molecules. In particular, *N*-CF_3 trotabresib[51] (**20o**) was obtained to demonstrate the practical application of the developed approach in drug discovery. Finally, we explored the scope of *N*-CF_3 aryl imidoxyl pyridinium salts using alkyne (**19 g**) as the reaction partner. It was found that the cyclizations of all tested **1j-1l, 1q, 1 s** and **1 v** delivered *N*-CF_3 isoquinolin-1(*2H*)-ones (**20p-u**) in 54-70% isolated yields.

Plausible reaction mechanism

Based on previous literatures[39,44] and our experimental results, a plausible mechanism was proposed using **1e** as the trifluoromethylamidyl radical source and the trifluoromethylamidation of **2b** as an example (Fig. 6A). Initially, $Ir^{III}(dFppy)_3$ is excited to a triplet state $Ir^{III}(dFppy)_3$* under blue LEDs illumination. A SET process between $Ir^{III}(dFppy)_3$* and **1e** occurs, providing $Ir^{IV}(dFppy)_3(PF_6)$ and radical (**Int-I**). *N*-CF_3 imidoyloxy radical (**Int-II'**) is then generated from the fragmentation of **Int-I** along with the release of pyridine. In the following step, the trifluoromethylamidyl radical (**Int-II**), a resonance hybrid of O-centered radical (**Int-II'**)[44], serves as a real reactive N-centered radical to attack benzene, leading to adduct **Int-III**. Finally, a SET process between **Int-III** and Ir^{IV}, followed by deprotonation, delivers trifluoromethylamidated product (**3b**) with the recovery of $Ir^{III}(dFppy)_3$ for the next catalytic process. It is worth noting that in our

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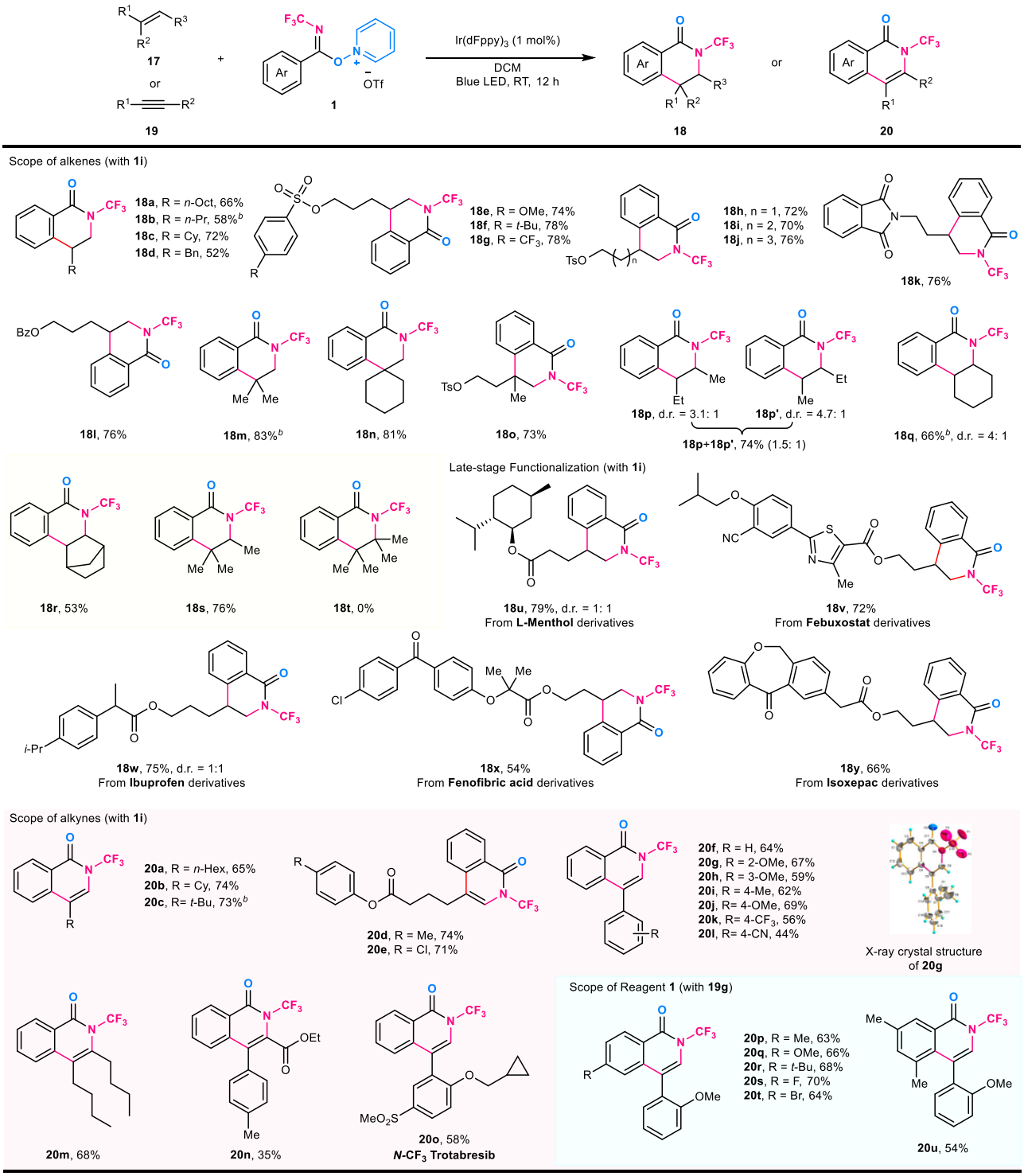

Fig. 5 | Radical aryltrifluoromethylamidations of alkenes/alkynes[a]. [a]Reaction conditions: **1** (0.3 mmol), **17** or **19** (0.9 mmol), $Ir(dFppy)_3$ (0.003 mmol), DCM (9 mL), Blue LEDs, under N_2, RT, 12 h, isolated yields. [b]With **17** or **19** in the amount of 1.5 mmol.

reaction, the trifluoromethylamidyl radical (**Int-II**) takes priority over the imidoyloxy radical (**Int-II'**) in coupling with benzene. This selectivity encouraged us to conduct the density functional theory (DFT) calculations to compare the reactivity of two resonant radicals (**Int-II** and **Int-II'**) in the reaction with benzene. As shown in Fig. 6B, **Int-III** is formed via **TS** with a barrier of 7.5 kcal mol^{-1}, whereas the generation of **Int-III'** via **TS'** has to overcome a barrier of 15.4 kcal mol^{-1}. Obviously, the barrier of the C-N coupling is lower than that of the C-O coupling, demonstrating that the C-N coupling process is more favorable. In addition, the site selectivity of C-H trifluoromethylamidation of **2c** using **1e** was studied by DFT calculations. As shown in Fig. 6C, the formation of **Int-III**-*para* by the addition of trifluoromethylamidyl radical (**Int-II**) to **2c** via **TS**-*pata* requires the lowest energy, which suggested that *para*-**3c** is main product.

Discussion

In conclusion, we have developed a trifluoromethylamidation strategy for direct synthesis of *N*-CF_3 amides. Starting from efficient

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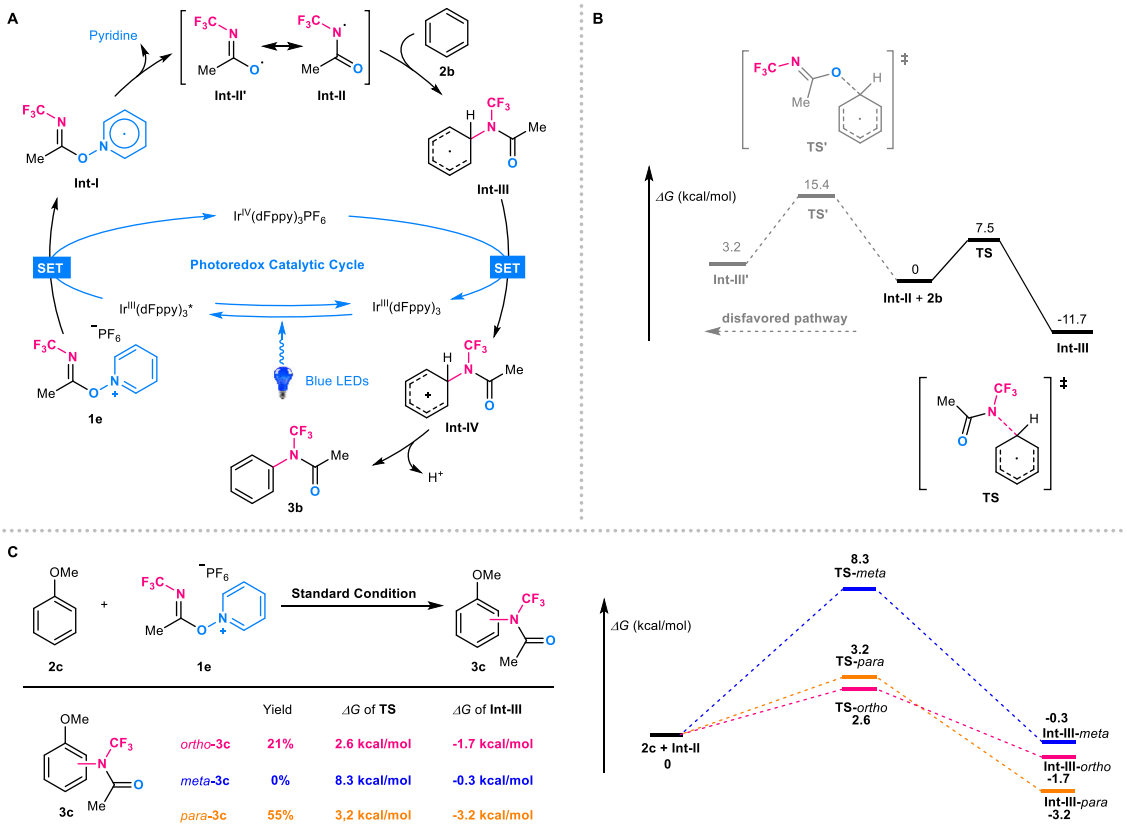

Fig. 6 | Plausible reaction mechanism & DFT studies. A Plausible reaction mechanism. **B, C** DFT calculations. TS Transition state.

N-trifluoromethylation reaction of nitriles using $PhICF_3Cl$, O-N reagents based on *N*-CF_3 imidoyl easters have been synthesized and developed as the precursor of trifluoromethylamidyl radical. With these trifluoromethylamidating reagents, a variety of trifluoromethylation reactions have been developed. These reactions are robust, can occur under mild photoredox-catalytic conditions, and exhibit wide application scopes of substrates. *N*-CF_3 amides with various functional groups are formed in a modular fashion. The use of the method for late-stage modification of drugs has also been investigated. More importantly, the uniqueness of the method has been presented by the synthesis of *N*-CF_3 lactams. We expect that this method will not only provide a versatile and flexible preparation platform for *N*-CF_3 amides but also inspire the discovery of more redox molecular systems that can handle challenging trifluoromethylamidations.

Methods

General procedure for the synthesis of *N*-(*N*-CF_3imidoxyl) pyridinium salts

Method A: A 10 mL Schlenk tube was charged with $PhICF_3Cl$ (1.5 mmol, 1.5 equiv.), RCN (3.5 mL) and a stir bar under N_2. The reaction mixture was stirred at 80 °C for 2 h and cooled to room temperature. pyridine-*N*-oxide (1.0 mmol) and NaX (2.0 mmol, 2 equiv.) were added for reacting additional 12 h at room temperature. Then, resulting mixture was added to H_2O (15 mL) and extracted with DCM (20 mL × 3). The organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated in vacuo, followed by adding diethyl ether (20 mL). The resulting precipitate was washed by diethyl ether to give the desired products.

Method B: A 10 mL Schlenk tube was charged with *N*-CF_3 imidoyl chloride (1.1 mmol, 1.1 equiv.), pyridine-*N*-oxide (1.0 mmol), NaX ((2.0 mmol, 2 equiv.) and a stir bar in MeCN (3 mL). The reaction mixture was stirred at room temperature for 12 h. Then, resulting mixture was added to H_2O (15 mL) and extracted with DCM (20 mL × 3). The organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated in vacuo, followed by adding diethyl ether (20 mL). The resulting precipitate was washed by diethyl ether to give the desired products.

General procedure for the trifluoromethylamidations of arenes

A 35 mL flask was charged with **1** (0.3 mmol), $Ir(dFppy)_3$ (0.003 mmol, 0.01 equiv.) and a stir bar under N_2, then a solution of **2** (0.9 mmol, 3 equiv.) in DCM (9 mL) was added. The reaction mixture was stirred for 12 h under the irradiation of blue LED light (18 W) at room temperature. After the completion of the reaction as indicated by TLC, resulting mixture was added to H_2O (15 mL) and extracted with DCM (20 mL × 3). The organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by silica column chromatography to give the desired products.

General procedure for the aryltrifluoromethylamidations of alkenes/alkynes

A 35 mL flask was charged with **1** (0.3 mmol), $Ir(dFppy)_3$ (0.003 mmol, 0.01 equiv.) and a stir bar under N_2, then a solution of **17** or **19** (0.9 mmol, 3 equiv.) in DCM (9 mL) was added. The reaction mixture was stirred for 12 h under the irradiation of blue LED light (18 W) at room temperature. After the completion of the reaction as indicated by TLC, resulting mixture was added to H_2O (15 mL) and extracted with DCM (20 mL × 3). The organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by silica column chromatography to give the desired products.

Data availability

The data supporting the findings of this study are available within the article and its Supplementary Information. Source Data are provided with this paper. Data supporting the findings of this manuscript are also available from the corresponding author upon request.

Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2323804 for **1i**, 2323803 for **3al**, 1984011 for **4b**, 2323802 for **20 g**. Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/. Source data are provided with this paper.

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Author contributions

M.W. directed the projects and wrote the manuscript. C.X. was responsible for mechanism discussions and calculations. R.Z.Z performed the experiments, obtained all data, and analyzed the results. Y.L. checked the manuscript and Supporting Information.

Competing interests

The authors declare no competing interests.

Additional information

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