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COMMUNICATION

An efficient and facile strategy for trifluoromethylation and perfluoroalkylation of isoquinolines and heteroarenes

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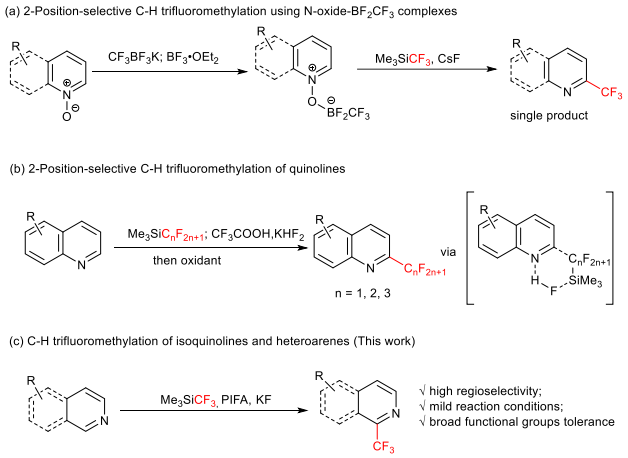
An effective and regioselective trifluoromethylation and perfluoroalkylation of isoquinolines and heteroarenes was developed. By combination of TMSC_nF_{2n+1} (n=1,2,3) with PIFA, the method achieved the corresponding perfluoroalkylated products with broad functional groups tolerance.

Owing to unique size and electronic properties of fluorine atom, the perfluoroalkylation of organic substrates can remarkably improve the molecular lipophilicity, metabolic stability and bioavailability. These advantages therefore make the perfluoroalkylation, especially, trifluoromethylation of aromatic compounds as hot research topics in the pharmaceuticals, agrochemicals and materials science.[1] Most of the current strategies for introduction CF_3 in these aromatic motifs require pre-functionalized substrates, such as aryl halides,[2] aromatic diazonium salts (from corresponding aromatic amines)[3] and aromatic boronic derivatives[4] catalyzed by a suitable transition metal catalyst. Though some elegant strategies have been developed, the cross-coupling reaction requires multiple steps for the preparation of functional substrates that would reduce the practicability and efficiency of such methodologies. Consequently, development of the methods for regioselective direct C-H trifluoromethylation of aromatic systems has become increasingly important in the last few years.

Even though in some cases, poor yield and selectivity were observed, direct trifluoromethylation of electron-rich aromatic and heteroaromatic systems now are increasing prospering via a radical process under photochemical or oxidation conditions,[5] whereas the related direct trifluoromethylation of electron-deficient systems have not reached the same level of development. Within this context, in 2014, Kanai et al. revealed a regioselective direct approach for α-trifluoromethylation of *N*-heteroaromatic *N*-oxides (Scheme 1a).[6] Despite its high regioselectivity, the pre-preparation of *N*-oxide–BF_2CF_3 complex is still required. Larionov and co-workers, in the same year, also presented a 2-position-selective C-H trifluoromethylation of six-membered *N*-heteroaromatic *N*-oxides.[7] Nevertheless, the cumbersome pre-activation processes made them less attractive. Until 2018, Yoichiro and co-workers disclosed a 2-position direct selective C-H trifluoromethylation and perfluoroalkylation of quinoline derivatives (Scheme 1b).[8] In the protocol, the in situ formed hydrogen fluoride (HF) from reaction of KHF_2 and CF_3COOH (TFA) can activate quinoline and trifluoromethyl trimethylsilane ($TMSCF_3$) simultaneously, which prompted trifluoromethyl group nucleophilic attack to activated quinoline via a six-membered transition state. Apart from this, there were also some radicals based direct trifluoromethylation of six-membered *N*-heteroaromatic systems, including pyridines, quinoxalines, pyrimidines, pyridazines and others.[9] These methods avoid substrates pre-functionalization and pre-activation, as well as obtain various trifluoromethylated nitrogen heterocycles. However, without ring pre-activation, the regioselectivity of these reactions are generally difficult to control.

Over the past few years, there were some works revealed direct single-electron oxidation of $TMSCF_3$ using hypervalent iodine can generate CF_3 radical,[10] which was applied to the



Scheme 1 Regioselective direct C-H trifluoromethylation of six-membered *N*-heteroaromatic systems.

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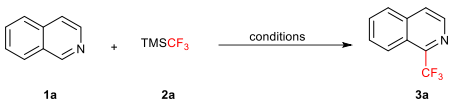
Table 1 Optimization of the reaction conditions[a]



1a 2a 3a

Entry	Oxidant	F⁻	Temp. (°C)	Solvent	Yield[b] (%)
1	PIFA	KF	r.t.	CH_3CN	trace
2	PIFA	KF	r.t.	dioxane	n.r.
3	PIFA	KF	r.t.	MeOH	n.r.
4	PIFA	KF	r.t.	toluene	n.r.
5	PIFA	KF	r.t.	THF	trace
6	PIFA	KF	r.t.	DMF	10
7	PIFA	KF	r.t.	NMP	57
8	PIDA	KF	r.t.	NMP	6
9	Koser's reagent	KF	r.t.	NMP	4
10	PhIO	KF	r.t.	NMP	7
11	TBHP	KF	r.t.	NMP	n.r.
12	$K_2S_2O_8$	KF	r.t.	NMP	n.r.
13	PIFA	CsF	r.t.	NMP	52
14	PIFA	TBAF	r.t.	NMP	trace
15	PIFA	AgF	r.t.	NMP	n.r.
16	PIFA	KF	0	NMP	73
17	PIFA	KF	-10	NMP	66

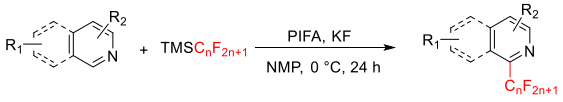
[a] Reaction conditions: **1a** (0.2 mmol), $TMSCF_3$ (3.0 equiv.), oxidant (3.0 equiv.), and fluoride source (4.0 equiv.) in 2.0 mL anhydrous solvent for 24 h under Ar. [b] Isolated yield, n.r. = no reaction.

direct C-H trifluoromethylation of vinyl azides,[10b] alkenes,[10c-10e] and electron-rich arenes.[10f, 10g] Due to our continuing interests in the study of heterocyclic compounds,[11] the further research was inspired by a recent hypervalent iodine induced acylation of *N*-heterocycles with aldehydes via an acyl radical.[12] We hence envisioned that a regioselective trifluoromethylation of the electron-deficient *N*-heterocycles could be achieved by a similar radical process. Herein, the direct C-H trifluoromethylation and perfluoroalkylation of isoquinolines and other *N*-heteroaromatic compounds is disclosed.

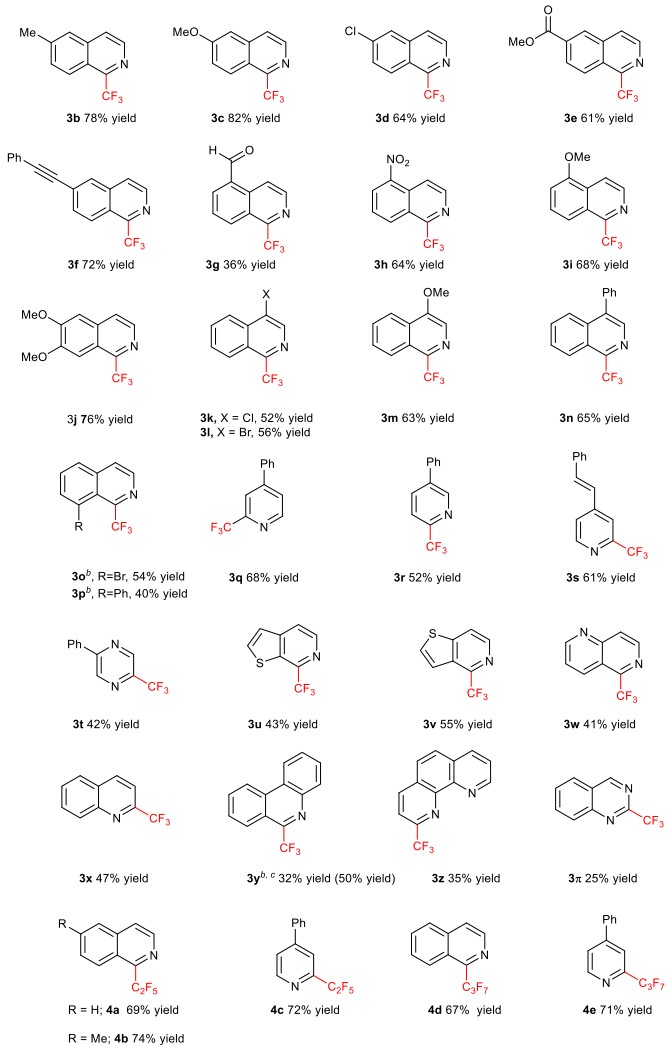
We initiated our investigation by using isoquinoline as model substrate. The [Bis(trifluoroacetoxy)iodo]benzene (PIFA) and $TMSCF_3$ were employed as the source of CF_3 radical. CH_3CN was chosen for solvent priority as it is generally a reliable solvent in this kind of reaction.[10b, 10d] However, under the condition, only trace amount of product was detected (Table 1, entry 1). We then screened a series of solvents, and delightedly found that the desired product **3a** was isolated in 10% yield in DMF (Table 1, entry 6). By switching the solvent to NMP, the yield of trifluoromethylated product was increased dramatically to 57% (Table 1, entry 7).

Due to the hypervalent iodine reagents (HIRs) were effective for organic transformations as selective oxidants,[13] a series of HIRs were examined (Table S2, ESI†). However, **3a** was only produced in low yields (Table 1, entries 8-10). Besides, no desired transformation took place when other oxidants *t*-butylhydroperoxide (TBHP) and $K_2S_2O_8$ were employed (Table 1, entries 11 and 12). Same results were obtained when the fluoride source was changed from KF to CsF (Table 1, entry 13). While under the same conditions, TBAF and AgF given no target product (Table 1, entries 14 and 15). Performing the reaction at 0 °C, the hightest yield was obtained, but with temperature of reaction decreased to -10 °C, the yield reduced to 66% (Table 1, entries 16 and 17). Thus,

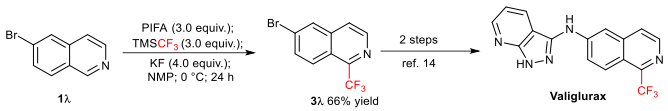
Table 2 Substrate scope of isoquinolines and *N*-heteroarenes [a]



1 2 3, n=1 4, n=2, 3



[a] Reaction conditions: unless otherwise stated, substrate **1** (0.2 mmol), PIFA (3.0 equiv.), KF (4.0 equiv.), $TMSC_nF_{2n+1}$ (3.0 equiv.) in NMP (2.0 mL) at 0 °C for 24 h. [b] PIFA (4.0 equiv.) was used at room temperature. [c] The number in parentheses is the yield based on recovered starting material.



Scheme 2 Synthetic application.

PIFA (3.0 equiv.), $TMSCF_3$ (3.0 equiv.), and KF (4.0 equiv.) in NMP at 0 °C was chosen as the optimal reaction condition for the trifluoromethylation.

Having the optimal conditions in hand, the substrates scope of isoquinoline and heteroarenes were explored (Table 2). A variety of isoquinoline derivatives bearing electron-donating and electron-withdrawing groups at the 6-position were firstly tested. We found that the substrates with electron-donating groups, such as methyl and methoxy groups offered corresponding compounds (**3b** and **3c**) in higher yields (78% and 82% respectively), while electron-withdrawing groups resulted in lower yields (**3d** and **3e**). Additionally, the reaction tolerated a broad range of functional groups on benzene ring part. For example, substrates with alkyne and aldehyde substituents, which were easily oxidized by hypervalent iodine,[13f] were smoothly converted into the corresponding trifluoromethylated derivatives in 72% and 36% yield respectively (**3f** and **3g**). The nitro group at 5-position of isoquinoline was tolerated as well (**3h**). Placement of a methoxy or di-methoxy groups on other positions of benzene unit was also achieved in good yields (**3i** and **3j**). When 4-position of isoquinoline was substituted with halogen, methoxy and phenyl groups, the transformation gave desired products in 52%-65% yields (**3k-3n**). Different substituted groups at the 8-position were also acceptable, which achieved the trifluoromethylated isoquinolines (**3o** and **3p**).

To explore the scope of the method, we then turned our attention to other *N*-heterocyclic compounds**.** The pyridines, quinoline, pyrazine, thienopyridines, 1,6-naphthyridine, phenanthridine and phenanthroline were explored under the standard reaction conditions, which delivered the products in 32% to 68% yields (**3q-3z**). Interestingly, the trifluoromethyl group reaches the 2-position of quinazoline **1π**, which was different from the regioselectivity of isoquinoline.

Moreover, our direct C-H trifluoromethylation methodology can also be extended to perfluoroethylation of isoquinolines and pyridines. As shown in Table 2, exposure of $TMSC_2F_5$ and $TMSC_3F_7$ to the same conditions as trifluoromethylation process, the desired perfluoroethylation products (**4a-4e**) were obtained in 67% to 74% yields.

At this stage, we have successfully prepared a wide range of trifluoromethylated products under mild, direct, and metal free conditions with high regioselectivity and multifunctional groups toleration. The synthetic utility of the trifluoromethyltion reaction was further demonstrated by preparing 6-bromo-1-(trifluoromethyl)isoquinoline **3λ**, which is a pre-requisite intermediate for the synthesis of Valiglurax, a potential candidate for the treatment of Parkinson's disease. Generally, **3λ** was synthesized from 6-bromoisoquinoline **1λ** via 2 steps reaction in 37% to 43% total yield.[14] In our case, **3λ** was conveniently obtained in 66% yield in one step (Scheme 2).

In order to study the reaction mechanism, several control experiments were performed (Scheme S3, ESI†). The radical quenchers such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and butylated hydroxytoluene (BHT) were added to the model reaction, which was inhibited dramatically. Meanwhile, the TEMPO-CF_3 adduct was detected by LC-MS.

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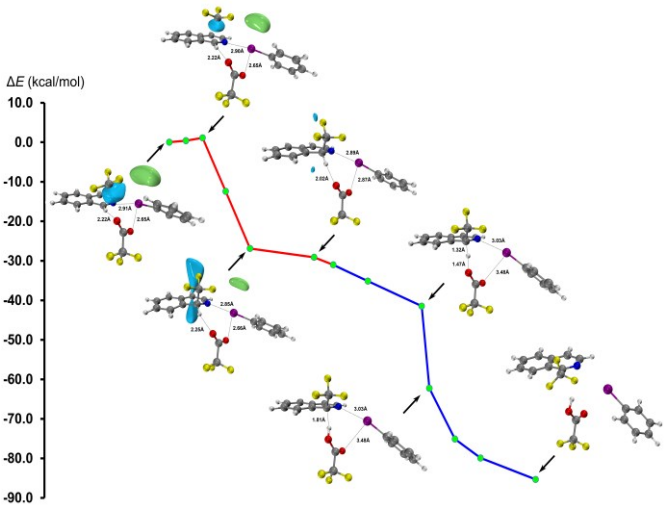
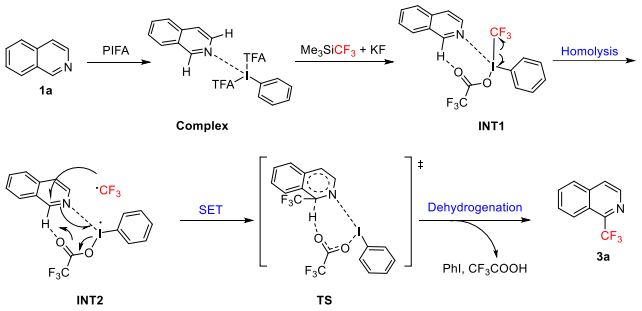


Fig. 1 IRC plot of the key transition state TS with representative structures. The red curve is the process of the electron transfer, and the blue curve is dehydrogenation process. green: α electron, blue: β electron.



Scheme 3 Plausible mechanistic pathways.

These results suggest a free-radical pathway is probably involved in this process and the CF_3 radical take part in our system. The generally accepted mechanism for the hypervalent iodine induced functionalization of electron-rich arenes was the generation of radicals can occur through a single electron transfer (SET) oxidation of arenes via a charge-transfer (CT) complex.[15] However, for the electron-deficient system, because of the high reactivity of intermediates formed from hypervalent iodine reagents, it is difficult to understand how the hypervalent iodine reagents interact with electron-deficient heteroarenes in radical reaction through the conventional experimental protocols. To further understand the mechanism of the direct C–H trifluoromethylation, DFT calculations were performed on the reaction of isoquinoline **1a** and PIFA.[16, 17]

Based on the above experimental results, a plausible mechanism for direct C-H trifluoromethylation of isoquinoline and its analogues was proposed, which was shown in Scheme 3. At the initial stage of the reaction, isoquinoline **1a** forms a weak complex with PIFA. After the activation of fluoride, CF_3^- was released from $TMSCF_3$ and then through ligand exchange with PIFA to form intermediate **INT1**. Subsequently, homolysis of **INT1** could give rise to CF_3 radical. The released CF_3 radical would attack the 1-position of **1a**, which is the most reactive site of isoquinoline.[18] The transition state **TS** went through a

single electron transfer (SET) and a dehydrogenation process to give the product **3a**, and the intrinsic reaction coordinate (IRC) shows the detailed process from the transition state to the generation of trifluoromethylated product **3a** (Fig. 1).[19]

In conclusion, we have developed a direct, mild easily operated and highly regioselective method for the C–H trifluoromethylation and perfluoroalkylation of isoquinolines and heteroarenes with readily available $TMSC_nF_{2n+1}$ and hypervalent iodine under metal-free conditions. The advantage of the transformation is the synthetic simplicity and diversity. The application of this reaction was illustrated by preparation of useful medicinal molecules.

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Conflicts of interest

There are no conflicts to declare.

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18 In order to explain the selectivity and provide the prediction profile, the electron localization function (ELF), average Local ionization energy (ALIE), total electrostatic potential (ESP) and atomic charge (NPA charge) were evaluated for **1a-1π** and **3a-3π**. See ESI† for the details.

19 The intrinsic reaction coordinate (IRC) clearly shows the process of single electron transfer and dehydrogenation. See ESI† for the details.

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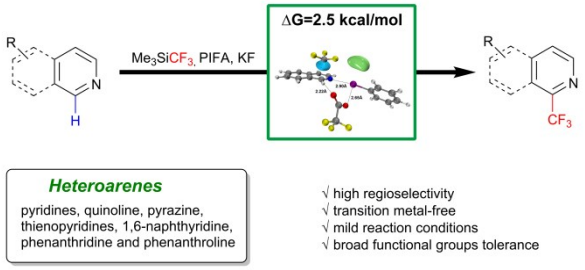

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