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Regioselective Direct C−H Trifluoromethylation of Pyridine

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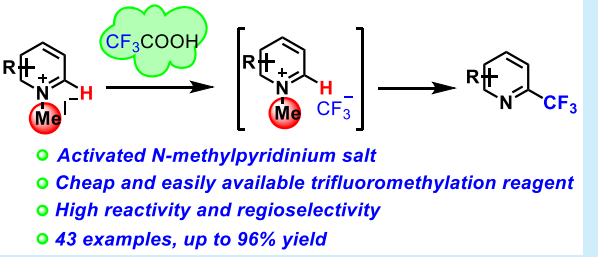
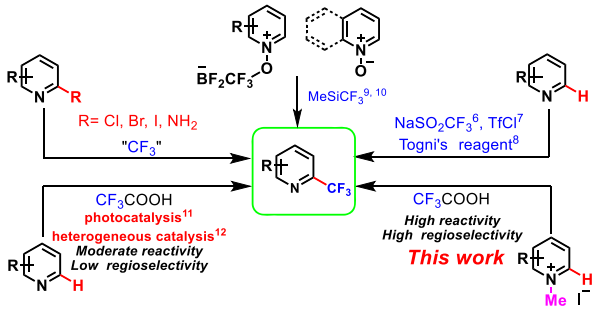
ABSTRACT: A highly efficient and regioselective direct C−H trifluoromethylation of pyridine based on an *N*-methylpyridine quaternary ammonium activation strategy has been developed. A variety of trifluoromethylpyridines can be obtained in good yield and excellent regioselectivity by treating the pyridinium iodide salts with trifluoroacetic acid in the presence of silver carbonate in *N*,*N*-dimethylformamide. The protocol features good functional group compatibility, easily available starting materials, and operational simplicity. Controlled experiments showed that the reaction may involve a nucleophilic trifluoromethylation mechanism.



Trifluoromethyl has been proven to be an essential group in pharmaceutical chemistry and material science.[1] When it is introduced into the molecule, it can significantly improve the lipophilicity, metabolic stability, and bioavailability of compounds.[2] Pyridines are valuable pharmacophores, and the development of methodology for introducing the trifluoromethyl and its related groups onto the pyridine has received great interest.[3]

Traditionally, CF_3 is installed by transitional metal mediated or catalyzed cross-coupling reaction with prefunctionalized pyridines (Scheme 1).[4] From the viewpoint of step and atom economy, direct C−H trifluoromethylation of pyridine would be a more straightforward and efficient method for installing the CF_3 group to the pyridine ring.[5] However, the direct C−H trifluoromethylation of pyridine is a quite challenging task, and only a handful of successful examples have been reported in the literature to date. Among them, this transformation has been achieved by using a radical, electrophilic, or nucleophilic trifluoromethylating reagents. In 2011, Baran[6] and co-workers used a benchtop stable trifluoromethyl radical source, Langlois reagent $NaSO_2CF_3$, to achieve direct pyridine trifluoromethylation, which suffered from low regioselectivity and resulted in mixed C_2 and C_3 trifluomethylation products. In the same year, MacMillan[7] reported the first example of a photoredox-based method for direct C−H trifluoromethylation of pyridine using triflyl chloride, TfCl, as the CF_3 source. Togni[8] later developed a rhenium catalyzed electrophilic trifluoromethylation protocol with the expensive hypervalent iodine reagent 1-(trifluoromethyl)-1,2-benziodoxol-3(1*H*)-one.

Scheme 1. Preparation of 2-Trifluoromethylpyridine from Pyridine Derivatives



The system features a broad substrate scope, but the yields and regioselectivities are generally low. In 2014, Kanai[9] et al. disclosed a direct pyridine C−H nucleophilic trifluoromethylation with the Ruppert−Prakash reagent ($MeSiCF_3$) by employing pyridine *N*-oxides activated by trifluoromethyldifluoroborane (BF_2CF_3). Although the reaction exhibits excellent regioselectivity, the activated substrate *N*-oxide−BF_2CF_3 complex brought about inconvenient multiple synthetic procedures. In the same year, the Larionov[10] group also used the $MeSiCF_3$ reagent to carry out the trifluoromethylation reaction of quinoline on a quinoline nitrogen oxide substrate, but in this nitrogen oxide compound system, the reaction activity of pyridine is very low.

Despite these advancements in pyridine C−H direct trifluoromethylation, a number of limitations still remain, such as narrow substrate cope, low activity and regioselectivity, or using expensive trifluoromethylating reagents. Thus, a

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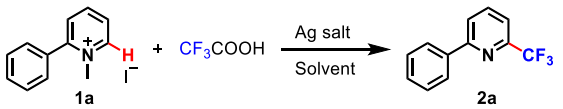
simple protocol for the direct C−H trifluoromethylation of pyridine with high site selectivity and activity is still desirable.

The cheap and easily available trifluoroacetic acid would be an appealing trifluoromethylating reagent, which releases the carbon dioxide as only a side product after the reaction. However, to our surprise, only rare examples of pyridine trifluoromethylation using trifluoroacetic acid has been reported. Very recently, Li[11] and Budnikova[12] groups independently achieved (hetero)arene trifluoromethylation using trifluoroacetic acid, by means of photocatalysis and Ag/SiO_2-based heterogeneous catalysis, respectively. Nonetheless these systems suffered from the low reactivity and regioselectivity, particularly for pyridine compounds. In recent years, our group has developed a new activation strategy for pyridine C−H functionalization by using pyridinium salts as the pyridine surrogate.[13,14] The formation of pyridinium salts greatly increases the acidity of C−H bond *ortho* to the pyridine nitrogen and, hence, improves the reaction reactivity and site selectivity.[15] We envision that an efficient and regioselective pyridine trifluoromethylation would be achievable by using the same strategy. Herein, we report a regioselective trifluoromethylation of pyridines by using *N*-methylpyridinium iodide salts in combination with trifluoroacetic acid.

We initiated our investigation by coupling *N*-methyl-2-phenylpyridinium iodide (**1a**) with trifluoroacetic acid (**2a**) in the presence of $AgNO_3$ as an oxidant in *N*,*N*-dimethylacetamide (0.25 M) at 150 °C under air for 24 h (Table 1). Gratifyingly, the desired product 2-phenyl-6-trifluoromethylpyridine was successfully obtained in 32% yield (entry 1), with the majority of the substrate pyridinium salt recovered, and a small amount of byproduct 2-phenylpyridine (resulted from the *N*-demethylation of the substrate) being detected. The structure of the product was fully characterized by NMR spectra. Then, different silver sources such as CF_3COOAg, AgOAc, Ag_2O, and Ag_2CO_3 were investigated, and Ag_2CO_3 afforded the desired product in the best yield (entries 2−5). The most appropriate amount of Ag_2CO_3 was proven to be 2 equiv (entries 6−9). Either increasing or decreasing the amount of Ag_2CO_3 decreased the yields gradually. The attempt to make the reaction catalytic by using $K_2S_2O_8$ also failed (entries 10−11). Investigation of the solvent effect revealed that the polar solvent DMA is the best one. The reaction also occurs in *N*,*N*-dimethylformamide (DMF), but gave a significantly lower yield of 57%. Whereas the use of nonpolar or less polar solvent such as toluene, acetonitrile, dioxane, and 1,2-dichloroethane only led to a trace amount of products (entries 12−16). In consideration of the good solubilities of pyridinium salts in water, an aqueous system was also employed, but still no reaction took place (entry 17). Using the traditional Minisci reaction conditions, the reaction did not occur (entry 18). In the case of CF_3COOAg instead of Ag_2CO_3/CF_3COOH as the CF_3 precursor, the desired products were only obtained in moderate yields, which highlights the high efficiency of the *in situ* generated silver trifluoroacetate on this transformation (entry 19). Finally, the optimal conditions were selected as follows: treatment of 0.25 mmol of *N*-methyl-2-phenylpyridinium iodide with 0.75 mmol of trifluoroacetic acid in the presence of 2.0 equiv of Ag_2CO_3 in DMA (0.25 M) at 150 °C under air for 24 h.

Table 1. Optimization of the Reaction Conditions[a]



entry	Ag salt (equiv)	solvent (1 mL)	yield (%)[b]
1	$AgNO_3$ (2)	DMA	32
2	CF_3COOAg (2)	DMA	57
3	Ag_2O (2)	DMA	68
4	AgOAc (2)	DMA	59
5	Ag_2CO_3 (2)	DMA	74
6	Ag_2CO_3 (1)	DMA	57
7	Ag_2CO_3 (1.5)	DMA	70
8	Ag_2CO_3 (2.5)	DMA	56
9	Ag_2CO_3 (3)	DMA	48
10[c]	Ag_2CO_3 (0.1)	DMA	trace
11[c]	Ag_2CO_3 (0.2)	DMA	trace
12	Ag_2CO_3 (2)	DMF	56
13	Ag_2CO_3 (2)	toluene	trace
14	Ag_2CO_3 (2)	CH_3CN	trace
15	Ag_2CO_3 (2)	dioxane	trace
16	Ag_2CO_3 (2)	DCE	trace
17	Ag_2CO_3 (2)	H_2O	trace
18[d]	$AgNO_3$ (0.1)	DMA	N.R.
19[e]	CF_3COOAg (3)	DMA	55%

[a]Reaction conditions: **1a** (0.25 mmol), CF_3COOH (0.75 mmol), 24 h, 150 °C under air. [b]Isolated yield. [c]4.0 equiv of $K_2S_2O_8$ were used. [d]Conditions of Minisci reaction: $AgNO_3$ (0.025 mmol), $(NH_4)_2S_2O_8$ (0.75 mmol), CF_3COOH (0.75 mmol), H_2SO_4 (20 mol %). [e]Without CF_3COOH. DMA = *N*,*N*-dimethylacetamide. DMF = *N*,*N*-dimethylformamide. DCE = 1,2-dichloroethane.

With the optimized reaction conditions in hand, we set out to explore the scope of *N*-methylpyridinium iodide salts (Scheme 2). For the 2-arylpyridinium salts with substituents at the 3, 4, or 5 position of the pyridine ring, the corresponding trifluoromethylated pyridine can be obtained in good yield (**2a**−**h**). When the substituents are electron-donating groups (EDGs), the corresponding products can be obtained in good to excellent yields (**2b**, **2d**−**e**), with the exception of the 3-MeO substituent which only resulted in a low yield of 38% (**2c**). However, the presence of electron-withdrawing groups (EWGs) on the pyridine ring totally inhibited the reaction and resulted in an unidentified complex mixture. For 2-arylpyridinium salts, good yields of trifluoromethylation products were obtained (**2i**−**r**) regardless of whether there are electron-rich or electron-poor substituents on the 2-aryl ring. In general, the substrates bearing the EDGs at its 2-aryl groups afforded a slightly higher yield than those with EWGs. Importantly, the heteroaryl substituted substrates were also compatible with this protocol, delivering the products (**2s**−**u**) with moderate yields of 44−67%. The pyridinium salts containing the branched alkyl groups at the 2-position of the pyridine ring gave moderate to good yields (**2v**−**z**), whereas those with straight alkyl groups, such as 1-methyl-2-pentylpyridin-1-ium iodide, only gave a trace amount of product.[14] The present reaction protocol was extremely effective for the 3-arylpyridinium salts which have two *ortho*-C−H bonds available. For instance, yields higher than 90% were obtained for products **2aa**−**ae**. Importantly, exclusive monoselectivity was observed in all cases without ditrifluoromethylation products being detected, but the two different monotrifluoromethylation products were produced with nearly equal amounts. For example, the pyridinium salt of an antiprostate cancer drug, abiraterone acetate,[16] reacted under the standard conditions to afford two trifluoromethylated products (**2af**) in a total yield of 91% with a ratio of

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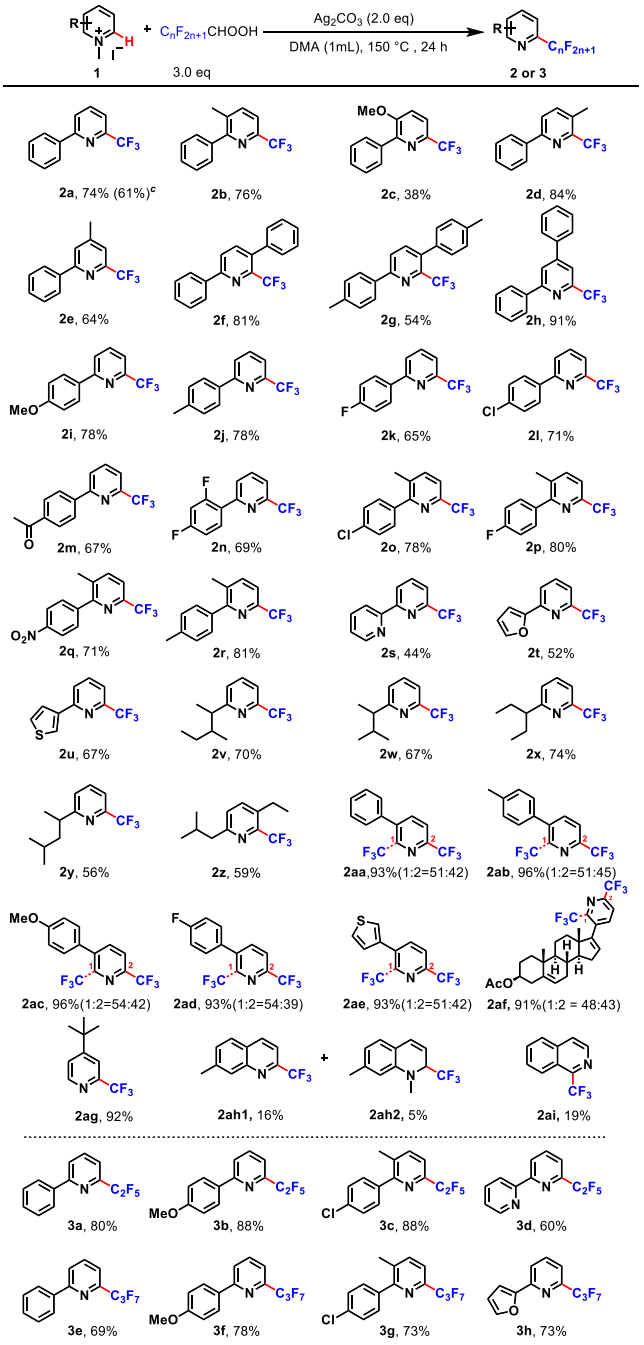
Scheme 2. Substrate Scope of *N*-Methylpyridinium Salts and Perfluoroalkyl Carboxylic Acid[a,b]



[a]Reaction conditions: **1a–z**, **1aa-ai** (0.25 mmol), $C_nF_{2n+1}COOH$ (0.75 mmol), Ag_2CO_3 (0.5 mmol), 24 h, 150 °C under air in a sealed tube. [b]Isolated yield. [c]1.0 mmol of *N*-methyl-2-phenylpyridinium iodide was used.

48:43. Whereas the symmetrical 4-*tert*-butylpyridinium salt gave rise to a very clean reaction, affording monotrifluoromethylated product **2ag** in 92% yield. It should be noted that quinolium and isoquinolinium iodide salts are less reactive under the standard conditions. For instance, the 7-methyl *N*-methylquinolinium iodide salt only delivered the desired product **2ah1** in less than 16% yield, accompanied by a small amount of quinolinium dearomatizating addition byproduct 1,7-dimethyl-2-(trifluoromethyl)-1,2-dihydroquinoline (**2ah2**).

The newly developed reaction conditions were also applicable for polyfluoroalkylation of pyridine (Scheme 2). For example, both the pentafluoropropionic acid and heptafluorobutyric acid could successfully react with *N*-methyl-2-(hetero)arylpyridinium iodide to give the corresponding polyfluoroalkylation products **3a–h** in good to excellent yields.

Subsequently, the two independent parallel reactions and a one-pot intermolecular competitive reaction between **1a** and **1a**-d_1 or **1a**-d_4 were performed to determine the kinetic isotopic effects (KIE) of this reaction (see Supporting Information (SI) for details). The KIE values of 1.9 and 1.6 were obtained, respectively, suggesting that the cleavage of the C–H bond might be the rate-determining step of the reaction.

In order to verify whether the reaction is a radical or an ionic mechanism, we added the free radical inhibitors 2,2,6,6-tetramethylpiperidinooxy (TEMPO) into the reaction system under the standard conditions, and found that the reaction proceeded equally efficiently without a significant decrease in yield. In addition, the free radical trapping experiments by reacting TEMPO, butylated hydroxytoluene (BHT), or 1,1-diphenylethylene with trifluoroacetic acid under standard conditions resulted in no formation of CF_3 radical combined products, which indicated that the reaction is not likely to involve the radical mechanism (see the SI for details).

Of note, either 2-phenylpyridine itself or its *N*-oxide and *N*-ylide failed to undergo the trifluoromethylation reaction under the standard conditions (see the SI for details). In order to further understand the advantages of the *N*-methylpyridinium salt activation strategy, the energy of the LUMO of 2-phenylpyridine, 2-phenylpyridine *N*-oxide, 2-phenylpyridinium ylide, and *N*-methylpyridine quaternary ammonium salt were calculated with the Gaussian algorithm. The calculated LUMO energies are −1.14, −1.30, −1.89, and −6.19 eV, respectively (Figure 1). Kuninobu and Kanai[9] have reported that the *N*-

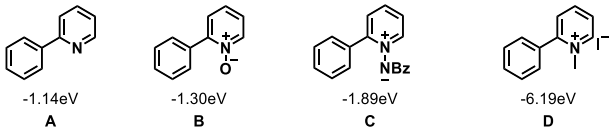


Figure 1. Comparison of LUMO levels of several pyridine derivatives. rb3lyp/6-31g* for (A-C); rb3lyp/6-31$^+$g* for (D). Bz = benzoxyl.

heteroaromatics with a lower LUMO level is more prone to occur in the dearomatizing nucleophilic addition by the CF_3 group. Accordingly, the trifluoromethylation of the *N*-methylpyridinium salt, which has the lowest LUMO level, most likely proceeds via dearomatizing nucleophilic addition of the CF_3 group to the pyridinium salt, followed by a rearomatization mechanism. In addition, the comparison of chemical shifts of protons at the 6-position of the aforementioned four pyridine derivatives (see the SI for details) revealed that *N*-methyl-2-phenylpyridinium iodide has the lowest electron density at the C_6–H bond. This experimental evidence further supported that the prior formation of the pyridinium salt is the most efficient activation strategy for pyridine C–H bond functionalization.

Lindhardt's group[17] has developed a decarboxylative trifluoromethylation of (iso)quinoline derivatives by using methyltrifluoroacetate (MTFA) as the CF_3 anion precursor, wherein 2-methyl-(1-trifluoromethyl)-1,2-dihydro(iso)-quinolines were produced as the product. The author

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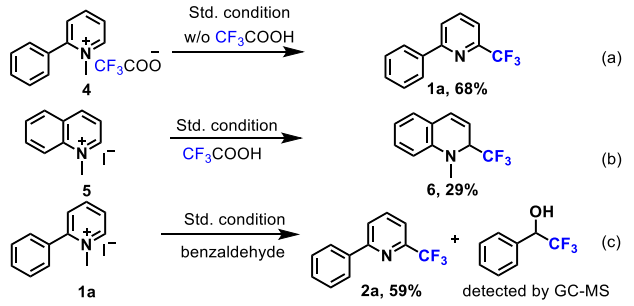
attributed the reaction efficiency to the in situ formation of the (iso)quinolinium trifluoroacetate, and the DMF solvent cage stabilized (iso)quinolinium−CF_3 anion ion pairs. In our system, the in situ formed CF_3COOAg by the reaction of Ag_2CO_3 and CF_3COOH in DMA could serve as a CF_3 anion precursor. The anion exchange between CF_3COOAg and pyridinium iodide salts would occur to produce pyridinium trifluoroacetate. Indeed, the reaction of the preformed *N*-methylpyridinium trifluoroacetate (**4**) under the standard conditions in the absence of CF_3COOH afforded the 2-phenyl-6-trifluoromethylpyridine in a comparable yield of 68% (Scheme 3a). By analogy, the reaction might also proceed via a

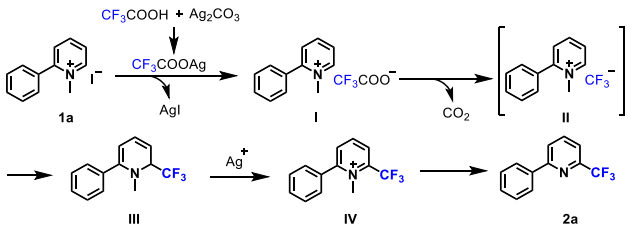
Scheme 3. CF_3 Anion Verification Experiment



nucleophilic addition of the CF_3 anion to the pyridinium salts pathway.[17,18] Although the corresponding CF_3 anion adduct product could not be detected, possibly due to its rapid transformation to the trifluoromethylated pyridine, subjecting the 1-methylquinolinium iodide (**5**) under the standard conditions led to formation of 1-methyl-2-(trifluoromethyl)-1,2-dihydroquinoline (**6**) in 29% isolated yield (Scheme 3b). In addition, a CF_3 anion captured product, 2,2,2-trifluoro-1-phenylethanol, was detected by GC-MS in the CF_3 anion trapping experiment using benzaldehyde as the electrophile (Scheme 3c). This result further indicated that the reaction followed a nucleophilic trifluoromethylation pathway.

On the basis of the literature and our experimental results, a plausible mechanism shown in Scheme 4 was proposed. First,

Scheme 4. Proposed Reaction Mechanism



the reaction of trifluoroacetic acid with silver carbonate produces silver trifluoroacetate, which undergoes the anion exchange with substrate *N*-methyl-2-phenylpyridinium iodide to give *N*-methylpyridinium trifluoroacetate (**I**). Then the decarboxylation occurs on **I** under high temperature (150 °C)[19] to form a solvent cage stabilized intermediate (**II**).[17] Subsequently the CF_3 anion nucleophilically attacks the pyridinium salt in a regioselective manner to produce the dearomatizated intermediate (**III**), which is then oxidized[18b,20] by silver salt to afford the trifluoromethylated *N*-methylpyridinium salts (**IV**), and then the methyl group might be removed by the nucleophilic attack with the anion in the system[13,15] to give the final product (Scheme 4)

In summary, a highly selective direct C_2−H trifluoromethylation of pyridine using cheap and commercially available trifluoroacetic acid has been developed by employing the *N*-methylpyridinium salt activation strategy. Compared with the reported pyridine trifluoromethylation system, the present system features high reactivity, excellent regioselectivity, and good functional group tolerance. The preliminary mechanism studies showed that a nucleophilic trifluoromethylation process might be involved.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02413.

Experimental details and full spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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