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Coordinating Activation Strategy-Induced Selective C-H Trifluoromethylation of Anilines

Jun Xu,[a,c] Ke Cheng,[b] Chao Shen,[c] Renren Bai,[b] Yuanyuan Xie,*[a,b] and Pengfei Zhang*[b,c]

Abstract: A novel and simple protocol for the synthesis of 2-(trifluoromethyl)aniline derivatives through coordinating activation strategy has been developed. This reaction shows good reactivity, gives target products in moderate to good yields. Pleasingly, the directing group can be recovered in excellent yield. Furthermore, this strategy provides an efficient access to the synthesis of floctafenine. A single electron transfer (**SET**) mechanism is proposed responsible for this trifluoromethylation.

Introduction

Over the past decades, the ubiquity of trifluoromethylated arene among pharmaceuticals, agrochemicals, dyes and organic functional materials continues to inspire the development of approaches that introduce trifluoromethyl group into organic molecules (**Figure 1)**.[1] However, the traditional trifluoromethylation of arene in the industry is cumbersome and perilous. Firstly, the benzotrichloride intermediate is obtained from toluene in the presence of excessive chlorine followed by the substitution reaction with dangerous fluorinating reagents.[2] Subsequently, a good deal of investigations have been made for trifluoromethylation by utilizing aryl boronic acids, aryl acids, arylamines and aryl halides as starting materials through the transition metal catalyzed cross-couplings.[3]

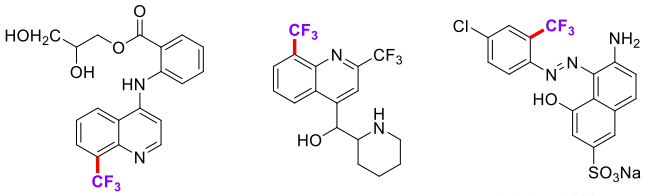
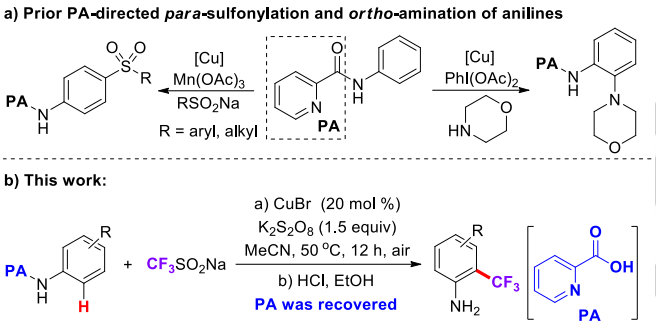


Figure 1 The application of trifluoromethylated anilines.

In recent years, direct C-H trifluoromethylation has got a fast development which benefited from the tireless efforts and arduous exploration of researchers.[4] Among them, transition-metal-catalyzed C-H trifluoromethylation of anilines has obtained considerable attention.[5] In 2013, Shi *et al.* demonstrated palladium-catalyzed trifluoromethylation of acetanilide assisted by *O* atom of the amide.[5a] Soon after, Xi and co-workers developed CuCl-catalyzed *ortho*-trifluoromethylation of pivalamido arenes facilitated by *O* atom of amide too. Unfortunately, this reaction reveals poor regioselectivity.[5b] Furthermore, harsh reaction conditions including expensive metal catalyst or trifluoromethylating reagent, an inert atmosphere and high temperature are indispensable in these two reactions. Recently, Cao and co-workers reported copper-free direct C-H trifluoromethylation of acetanilides with Langlois' reagent *via* a radical pathway.[6] However, the substrates are limited to electron-deficient 4-substituted acetanilides. Besides, the reaction was extended in five days during this transformation. Although above methods indeed represent significant advances, further improvements are still highly required in light of the feasibility.



Scheme 1 PA-directed C-H functionalization of anilines

For the past few years, the utilization of *N*-containing bidentate directing groups has been confirmed to be successful tactics to improve the reactivity and selectivity of C-H functionalization reactions.[7] Since Daugulis utilized the picolinamide (PA) moiety as *N*-containing bidentate directing group,[8] a series of works about PA-directed functionalization of naphthylamine have been established.[9] In stark contrast, only a few examples of PA-directed functionalization of anilines were reported (**Scheme 1, a**).[10] Under such a background**,** we report a copper-catalyzed PA-directed selective C-H trifluoromethylation of anilines

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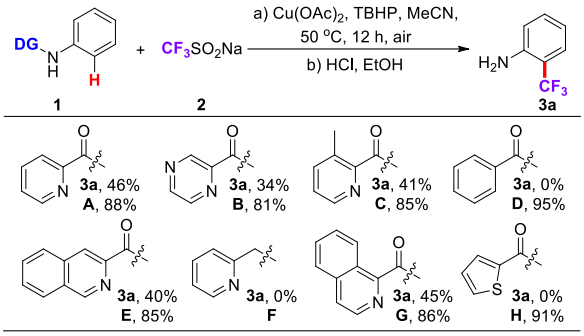
Table 1 Influence of the directing group[a,b]



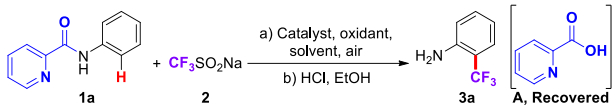
[a] Reaction conditions: **1** (1.0 mmol), **2** (234 mg, 1.5 mmol), $Cu(OAc)_2$ (36 mg, 0.2 mmol), TBHP (192 mg, 1.5 mmol), MeCN (5 mL), stirred at 50 °C, under air, for 12 h. [b] HCl (2 mL), EtOH (5 mL), isolated yields of **3a** and directing groups.

with Langlois' reagent (CF_3SO_2Na).

Results and Discussion

Initially, the influence of directing groups was studied (**Table 1**). Eight aniline derivatives with different directing groups were selected as substrates, Langlois' reagent as the trifluoromethylating reagent, $Cu(OAc)_2$ as a catalyst, *tert*-butyl hydroperoxide (TBHP) as an oxidant and MeCN as solvent, and the reactions were performed at 50 °C under air atmosphere for 12 h. After that, successive extraction, drying and hydrolysis to afford the desired product **3a**. According to the experimental results (**Table 1**), picolinic acid **A** gave target product **3a** in 46% yield. Other bearing *N*-containing

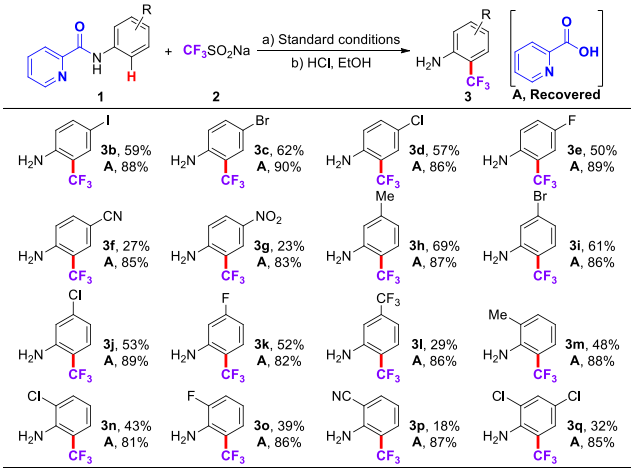
Table 2 Optimization of the reaction conditions[a,b]



Entry	Catalyst	Oxidant	Solvent	Yield [%][c] 3a / A
1	$Cu(OAc)_2$	TBHP	MeCN	46 / 88
2	$NiCl_2$	TBHP	MeCN	Trace / 92
3	$CoCl_2$	TBHP	MeCN	18 / 88
4	CuCl	TBHP	MeCN	38 / 90
5	CuI	TBHP	MeCN	47 / 89
6	CuBr	TBHP	MeCN	55 / 87
7	-	TBHP	MeCN	0 / 93
8	CuBr	DTBP	MeCN	Trace / 90
9	CuBr	H_2O_2	MeCN	Trace / 91
10	CuBr	$Na_2S_2O_8$	MeCN	68 / 85
11	CuBr	$(NH_4)_2S_2O_8$	MeCN	63 / 83
12	**CuBr**	**$K_2S_2O_8$**	**MeCN**	**80 / 89**
13	CuBr	-	MeCN	0 / 91
14	CuBr	$K_2S_2O_8$	DMF	29 / 88
15	CuBr	$K_2S_2O_8$	DCE	23 / 90
16	CuBr	$K_2S_2O_8$	toluene	Trace / 81
17[d]	CuBr	$K_2S_2O_8$	MeCN	37 / 91
18[e]	CuBr	$K_2S_2O_8$	MeCN	78 / 83
19[f]	CuBr	$K_2S_2O_8$	MeCN	75 / 87
20[g]	CuBr	$K_2S_2O_8$	MeCN	77 / 88

[a] Reaction conditions: **1a** (198 mg, 1.0 mmol), **2** (234 mg, 1.5 mmol), catalyst (0.2 mmol), oxidant (1.5 mmol), solvent (5 mL), stirred at 50 °C, under air, for 12 h. [b] HCl (2 mL), EtOH (5 mL). [c] Isolated yields. [d] Stirred at RT. [e] Stirred at 80 °C. [f] Under N_2. [g] Under O_2.

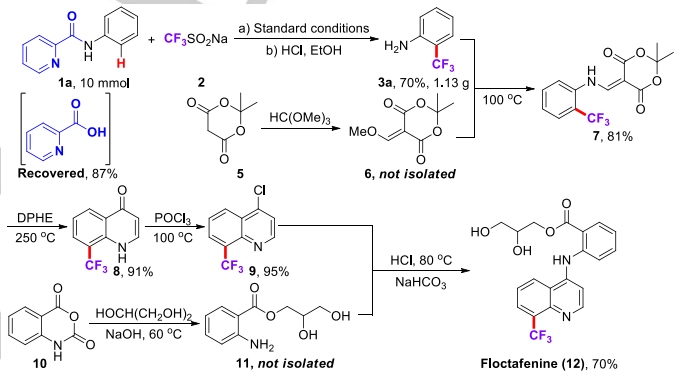
Table 3 Substrate scope of anilines[a,b]



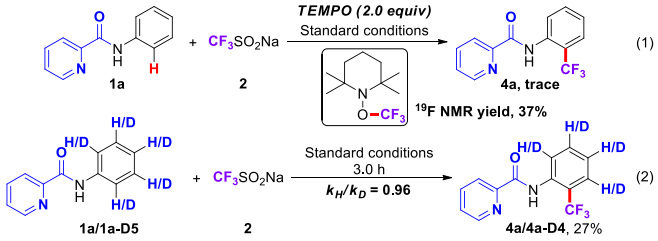
[a] Standard conditions: **1** (1.0 mmol), **2** (234 mg, 1.5 mmol), CuBr (29 mg, 0.2 mmol), $K_2S_2O_8$ (405 mg, 1.5 mmol), MeCN (5 mL), stirred at 50 °C, under air, for 12 h. [b] HCl (2 mL), EtOH (5 mL), isolated yields of **3** and 2-picolinic acid.

bidentate directing groups (**B**, **C**, **E**, **G**) except **F** reacted with a low yield, and directing groups **D**, **F** and **H** did not have directing effect. These phenomena also implied that both nitrogen heterocycle and amide bond played crucial roles in this transformation. Finally, picolinic acid **A** (PA) was employed as the directing group for trifluoromethylation of anilines. It is noteworthy that the directing groups except **F** were recovered in excellent yield through hydrolysis reaction, and we would continue to recover picolinic acid **A** in the next reactions. In addition, several CF_3 sources such as $TMSCF_3$, CF_3COOH and Togni's reagent were tested under the standard conditions, but only trace of desired product was obtained when Togni's reagent was employed as CF_3 sources.

We have gained **3a** in 46% yield in the previous experiment (**Table 1**; **Table 2, entry 1**). Encouraged by this result, the reaction conditions were screened. Firstly, various metal catalysts including $NiCl_2$, $CoCl_2$, CuCl, CuI as well as CuBr were tested (**Table 2, entries 2-7**), and the yield of product **3a** was improved to 55%. Subsequently, the effect of oxidant was investigated (**Table 2, entries 8-12**). We found that the persulphates have positive impact on this reaction, especially the yield was raised to 80% by using potassium persulfate as the oxidant. No product was generated in the



Scheme 2 Gram-scale trifluoromethylation and synthetic application

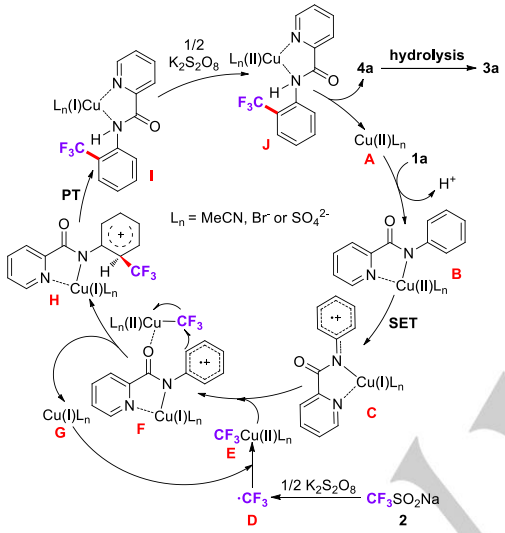


Scheme 3 Mechanism investigations

absence of metal catalyst or oxidant (**Table 1, entried 7 and 13**). Finally, the influences of solvent, temperature and atmosphere on the trifluoromethylation were also explored, but no better results were acquired **(Table 1, entries 14–20**).

After obtaining the optimal reaction conditions, the substrate scope of anilines was studied (**Table 3**). Some anilines with different substituent groups facilitated by picolinic acid **A** were investigated. Pleasingly, all substrates could be converted into relevant products smoothly. Comparatively speaking, anilines with substituent groups at *para*-position (**3b−g**) and *meta*-position (**3h−l**) showed better reactivity than anilines with *ortho*-substituent groups (**3m−p**). For the *meta*-substituted substrates, the trifluoromethylation tends to take place on the less hindered site because of the steric bias. The trifluoromethylation of *ortho*-substituted anilines did furnish the *ortho*-trifluoromethylated products in 18-48% yields (**3m−p**). Interestingly, anilines bearing electron-withdrawing groups, did react, albeit with low yields (18-29%). Besides, disubstituted aniline could be transformed into related product **3q** in moderate yield as well. It was well to be reminded that electron-withdrawing substituent bearing arylamines (**3f**, **3g**, **3l**, **3p**) are strong electron-deficient substrates, which were detrimental to the process of single electron transfer, so the yields of these substrates were lower.

Next, the application value of this method was evaluated for the synthesis of floctafenine which is a nonsteroidal anti-inflammatory drug (**Scheme 2**). Firstly, gram-scale synthesis was conducted under standard conditions followed by a hydrolysis reaction to obtain the desired product **3a** in 70% yield, and picolinic acid **A** was recovered in 87% yield.



Scheme 4 Proposed mechanism

Secondly, Meldrum's acid **5** was transformed into compound **6** in the presence of trimethyl orthoformate. Subsequently, successive nucleophilic substitution, cyclization and chlorination gave the intermediate **9**. In the meantime, under the catalysis of sodium hydroxide, intermediate **11** was obtained by mixing isatoic anhydride **10** with glycerine. Finally, the nucleophilic substitution was performed, and the final product floctafenine **12** was gained in 70% yield.

Additional control experiments were performed to explore the mechanism. First of all, the reaction was absolutely suppressed when 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was used as a free radical inhibitor (**Scheme 3**, **eq 1**). Furthermore, 37% yield of TEMPO-CF_3 adduct was detected by ^{19}F NMR, revealing that a radical pathway was involved. In the end, the test about kinetic isotope effect (KIE) gave a low ratio (k = 0.96) (**Scheme 3**, **eq 2**), declaring that the C-H cleavage process was not the rate determining step.[11] We suspected that maybe the free-radical addition process was the rate determining step. Finally, the free aniline was also tested under the standard conditions, but only trace of desired product was detected. Furthermore, the selectivity of this transformation was very poor. This result revealed that both N atom of pyridine and amide bond (including O atom and free NH) were indispensable. So the PA moiety played an important role in this transformation.

In the light of the experiment conclusions (**Table 1** and **Scheme 3**) and previous reports,[10b] a plausible mechanism was suggested (**Scheme 4**). Firstly, $L_nCu(II)$ could be obtained from $L_nCu(I)$ in the presence of $K_2S_2O_8$, which would combine with substrate **1a** to generate the metal complex **B**. Subsequently, the generation of metal complex **C** was proposed *via* a single electron transfer (**SET**) process. Meanwhile, Langlois' reagent was converted into trifluoromethyl radical **D** by oxidation of $K_2S_2O_8$. Then, $CF_3Cu(II)L_n$ species (**E**) was formed through the combination of trifluoromethyl radical **D** and $L_nCu(I)$. Next, metal complex **F** was formed by the weak coordination of $CF_3Cu(II)L_n$ species with the oxygen atom of an amide bond. After that, metal complex **F** undergone intramolecular trifluoromethylation to afford cationic metal complex **H**. Afterwards, metal complex **I** could be obtained *via* proton transfer (**PT**) process. Through the oxidation of $K_2S_2O_8$, metal complex **J** was gained. After a metal dissociation process of copper complex **J**, target product **3a** was finally acquired via the hydrolysis of product **4a**.

Conclusions

We have developed a novel and facile method for the selective installation of trifluoromethyl group onto the *ortho*-position of anilines through Cu-catalyzed picolinamide-directed C-H trifluoromethylation. This transformation revealed a broad substrate scope, versatile products were obtained in moderate to good yields, and the directing group could be recovered in excellent yield. Subsequently, the application of this trifluoromethylation was further demonstrated by the efficient synthesis of floctafenine.

Finally, control experiments indicated that a single electron transfer (**SET**) mechanism was probable for this valuble trifluoromethylation.

Experimental Section

General Information

All the chemicals were obtained commercially and used without any prior purification. All products were isolated by short chromatography on a silica gel (200-300 mesh) column using petroleum ether (60-90°C) and ethyl acetate. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on Bruker Advance 500 and 600 spectrometers at ambient temperature with $CDCl_3$ as solvent and tetramethylsilane (TMS) as the internal standard. Analytical thin layer chromatography (TLC) was performed on Merk precoated TLC (silica gel 60 F254) plates.

General procedure for the synthesis of compounds 3

A mixture of **1** (1.0 mmol), Langlois reagent **2** (234 mg, 1.5 mmol), CuBr (29 mg, 0.2 mmol) and $K_2S_2O_8$ (405 mg, 1.5 mmol) in MeCN (5 mL) in a 25 mL tube was stirred at 50 °C for 12 h. After cooling to room temperature, the mixture was poured into water and extracted with EtOAc. The crude product **4** was obtained under reduced pressure. Then, concentrated hydrochloric acid (2 mL) and EtOH (5 mL) was added respectively. Upon completion of the reaction at 100 °C for 12 h, the mixture was cooled to room temperature and neutralized with $NaHCO_3$ aqoeous solution, extracted with EtOAc (2 × 15 mL). The collected organic layer was washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The gathered residue was then purified by silica gel column chromatography to afford the product **3** (200–300 mesh silica gel, PE/EA = 20:1). Then 1 M HCl was added in aqueous layer until pH 4. The aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine (15 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to afford 2-picolinic acid (200–300 mesh silica gel, PE/EA = 5:1).

General procedure for gram-scale synthesis of compound 3a

A mixture of **1a** (2.5 g, 10.0 mmol), Langlois reagent **2** (2.4 g, 15.0 mmol), CuBr (286 mg, 2.0 mmol) and $K_2S_2O_8$ (4.0 g, 15 mmol) in MeCN (50 mL) in a 250 mL tube was stirred at 50 °C for 12 h. After cooling to room temperature, the mixture was poured into water and extracted with EtOAc. The crude product **4a** was obtained under reduced pressure. Then, concentrated hydrochloric acid (20 mL) and EtOH (50 mL) was added respectively. Upon completion of the reaction at 100 °C for 12 h, the mixture was cooled to room temperature and neutralized with $NaHCO_3$ aqoeous solution, extracted with EtOAc (2 × 100 mL). The collected organic layer was washed with brine (100 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The gathered residue was then purified by silica gel column chromatography to afford the product **3a** in 70% yield. Then 1 M HCl was added in aqueous layer until pH 4. The aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried with $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel to afford the 2-picolinic acid.

General procedure for the synthesis of compound 7

A stirred mixture of Meldrum's acid (1.8 g, 12.0 mmol) and trimethyl orthoformate (5.1 g, 48.0 mmol) was refluxed for 30 min. Then aniline (1.6 g, 10.0 mmol) was added dropwise at the same temperature, and the solution was stirred for 40 min. After the solution was cooled to room temperature, the resulting precipitate was filtered, washed with *n*-hexane, and dried in *vacuo* to provide 2,2-dimethyl-5-(2-(2-(trifluoromethyl)phenyl)ethylidene)-1,3-dioxane-4,6-dione (2.5 g, 81%), which was used directly in the next step.

General procedure for the synthesis of compound 8

Diphenyl ether (15 mL) was heated to 250 °C and stirred vigorously under N_2. 2,2-Dimethyl-5-(2-(2-(trifluoromethyl)phenyl)ethylidene)-1,3-dioxane-4,6-dione (2.5 g, 8.0 mmol) was added and the reaction mixture was stirred for 30 min at this temperature. The resulting solution was cooled to 70 °C and diluted with *n*-hexane (20 mL). The precipitate was filtered, washed with *n*-hexane, and dried in *vacuo* to give product **8** as a brown solid (1.6 g, 91%).

General procedure for the synthesis of compound 9

8-(Trifluoromethyl)quinoline-4(1H)-one **8** (1.5 g, 7.0 mmol) was furnished in a 25 mL tube with reflux condenser. Phosphoryl chloride (1.9 g, 12.0 mmol) was added under an argon atmosphere, and the mixture was heated at 100 °C. The solution was cooled after 15 min. Excess phosphoryl chloride was hydrolyzed at 0 °C with H_2O (5 mL) and concentrated aqueous ammonia (15 mL). The mixture was extracted with dichloromethane (2 × 15 mL), and the organic phase was dried with $MgSO_4$. After removal of the solvent in *vacuo*, the product **9** (1.5 g, 95%) was purified by flash chromatography (200–300 mesh silica gel, PE/EA = 20:1).

General procedure for gram-scale synthesis of floctafenine (12)

Glycerol (6.0 g, 65 mmol) and sodium hydroxide pellets (32 mg, 0.8 mmol) were charged into a 25 mL tube. Isatoic anhydride (1.0 g, 6.0 mmol) was then added and the reaction mixture was slowly warmed to 60 °C. The evolved carbon dioxide was trapped by extractor and the mixture was heated at 80 °C for 1 h. Then, a glycerol solution of **11** obtained as described above, was added 1 N HCl (6 mL) and 4-chloro-8-trifluoromethylquinoline **9** (1.2 g, 5.0 mmol). The mixture was heated at 80 °C for 1 h, allowed to cool to room temperature, and neutralized by addition of 1 N $NaHCO_3$ solution (10 mL). The coarse Floctafenine (1.4 g, 70%) crystallised out and was purified by recrystallization from 1:1 chloroform /ethanol.

Radical inhibition experiment

A mixture of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) (312 mg, 2.0 mmol), **1a** (198 mg, 1.0 mmol), Langlois reagent **2** (234 mg, 1.5 mmol), CuBr (29 mg, 0.2 mmol) and $K_2S_2O_8$ (405 mg, 1.5 mmol) in MeCN (5 mL) in a 25 mL tube was stirred at 50 °C for 12 h. After the reaction was completed, α,α,α-trifluorotoluene (internal standard, 292 mg, 2.0 mmol) was added. ^{19}F NMR analysis of this reaction mixture showed that no product was obtained and TEMPO-CF_3 was formed in 37% yield.

Kinetic isotope effect

A mixture of **1a** (99 mg, 0.5 mmol), **1a-D5** (102 mg, 0.5 mmol), Langlois reagent **2** (234 mg, 1.5 mmol), CuBr (29 mg, 0.2 mmol) and $K_2S_2O_8$ (405 mg, 1.5 mmol) in MeCN (5.0 mL) in a 25 mL tube was stirred at 50 ^oC for 3 h. In the end, product **4a/4a-D4** was acquired in 27% yield. ^1H NMR analysis of the isolated product demonstrated the KIE of 0.96 was resolved for the trifluoromethylation reaction.

Acknowledgements

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Keywords: Picolinic Acid • Trifluoromethylation • Anilines • Coordinating Activation Strategy • Single Electron Transfer

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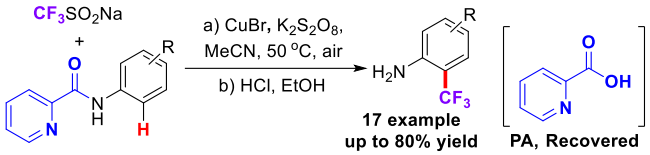

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Coordinating Activation Strategy-Induced Selective C-H Trifluoromethylation of Arylamine