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Transition Metal-Free Regioselective Remote C-H Bond 2,2,2-Trifluoroethoxylation of 8-Aminoquinoline Derivatives at the C5 Position

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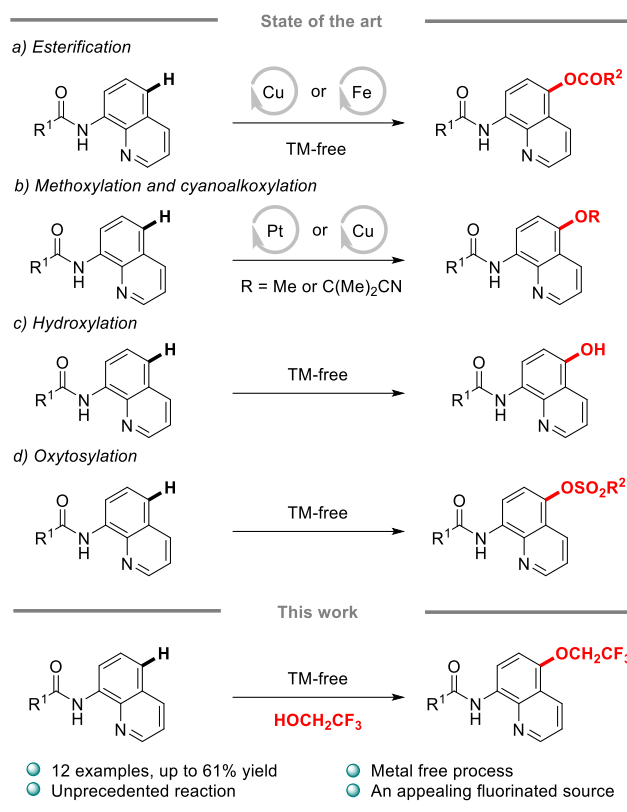
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Abstract: The regioselective 2,2,2-trifluoroethoxylation at the C5 position of amides derived from the 8-aminoquinoline has been developed. In the presence of PIDA, an unprecedented and undirected transition metal-free transformation was achieved using the readily available and appealing 2,2,2-trifluoroethanol as the fluorinated source. The selective distal 2,2,2-trifluoroethoxylation of an array of amides was achieved in moderate to good yields (12 examples, up to 61% yield). This approach provided efficient access to high-value added fluorinated quinoline derivatives, key building blocks for bulk and fine chemical industry.

With more than 20% of pharmaceuticals and 35% of agrochemicals containing at least one fluorine atom,^[1] the organofluorine chemistry is a blossoming research field, which displays a pivotal role in organic synthesis.^[2] Indeed, fluorinated compounds have interesting features taking benefit from the unique properties of the fluorine atom, which upon its introduction onto organic molecules can readily modify their biological and physico-chemical properties.^[3] Therefore, the demand for fluorinated molecules from the pharmaceutical and agrochemical industries is steadily increasing to discover new biorelevant molecules. To this end, the development of efficient and innovative tools to access fluorinated molecules is of prime importance.

Besides, quinolines are prevalent, as these key scaffolds are found in material science, agrochemicals, pharmaceuticals and natural products.^[4] Hence, the challenging task to selectively functionalize such electron deficient heterocycles has aroused the interest of the scientific community. In particular, with the impressive advances made in C-H bond functionalization,^[5] several methodologies were developed over the years to selectively functionalize the amides derived from 8-aminoquinoline at the C5 position of the quinoline residue with various functional groups (halogen, thiol, thiocyanate, nitro, amine, allyl and alkyl groups, chalcogen, fluorinated moieties, among others).^[6] In sharp contrast, only a handful of approaches has been reported for the direct formation of a C-O bond using different catalysts or under transition metal free conditions (Scheme 1). Most of them are restricted to esterification,^[7] methoxylation,^[8] cyanoalkoxylation,^[9] hydroxylation^[10] and oxytosylation.^[11]



Scheme 1. State of the art and this work. TM = Transition Metal.

Interestingly, the direct 2,2,2-trifluoroethoxylation of such derivatives remains elusive, despite the indisputable interest of the corresponding products. Indeed, the synthesis of fluorinated ethers is of high interest^[12] and especially, molecules containing the 2,2,2-trifluoroethoxy moiety (OCH₂CF₃), an important fluorinated group present in several bioactive compounds such as Flecanide^[13] and Lansoprazole,^[14] for instance (Figure 1).

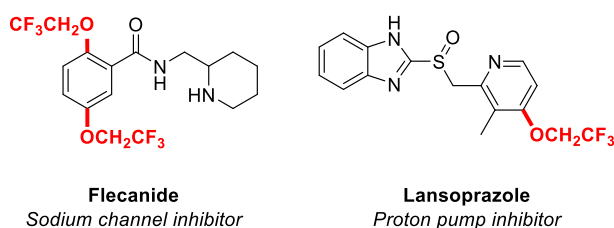


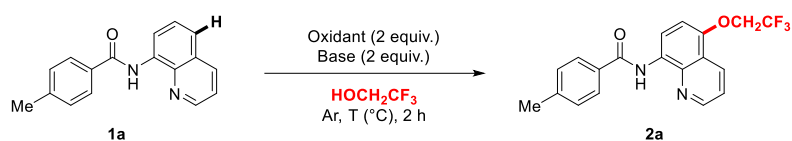
Figure 1. 2,2,2-Trifluoroethoxylated Drugs.

In our research program dedicated to the synthesis of fluorine-containing molecules by C–H bond functionalization, we focused on the remote introduction of the 2,2,2-trifluoroethoxyl group onto quinoline derivatives using the 2,2,2-trifluoroethanol, a readily available, inexpensive and green solvent.^[15] Indeed, the development of an efficient protocol to access

2,2,2-trifluoroethoxylated quinolines would be of high interest for pharmaceutical and agrochemical industries. Herein, the unprecedented transition metal-free remote C–H bond 2,2,2-trifluoroethoxylation of amide derived from 8-aminoquinoline at the C5 position using the 2,2,2-trifluoroethanol as the fluorinated source is reported.

We embarked on this project using the derivative **1a** as the model substrate. Initially, the copper-catalyzed 2,2,2-trifluoroethoxylation of the amide **1a** was first investigated in the presence of Na₂CO₃ and PIDA in trifluoroethanol at 25 °C.

Table 1. Optimization of the 2,2,2-trifluoroethoxylation reaction.^[a]



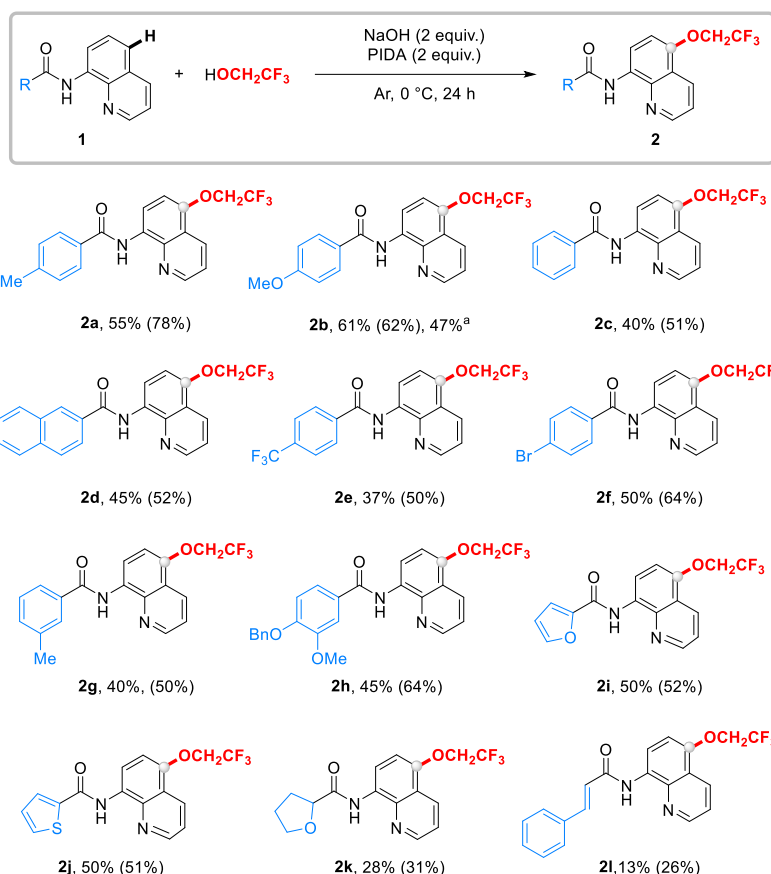
Entry ^[a]	Oxidant	Base	T (°C)	Yield (%)
1 ^[a]	PIDA	Na ₂ CO ₃	25	14
2	PIDA	Na ₂ CO ₃	25	18 (29)
3	PIFA	Na ₂ CO ₃	25	(16)
4	K ₂ S ₂ O ₈	Na ₂ CO ₃	25	NR
5	/	Na ₂ CO ₃	25	NR
6	PIDA	CsOPiv	25	20
7	PIDA	KOH	25	25
8	PIDA	NaOH	25	40
9 ^[b]	PIDA	NaOH	10	36
10^[b]	PIDA	NaOH	0	55 (78)
11 ^[b]	PIDA	NaOH	-10	31
12 ^[c]	PIDA	NaOH	0	53
13 ^[b]	PIDA	/	0	19

Reaction conditions: amide **1a** (0.2 mmol, 1 equiv.), base (2 equiv.), oxidant (2 equiv.), TFE (0.1 M), Argon, T (°C), 2 h. ¹⁹F NMR yields were determined using the α,α,α-trifluoroacetophenone as the

internal standard and were given in parenthesis. [a] Cu(OAc)₂ (5 mol%) was used. [b] 24 h. [c] 48 h. PIDA = (Diacetoxyiodo)benzene. PIFA = [Bis(trifluoroacetoxy)iodo]benzene. NR: no reaction.

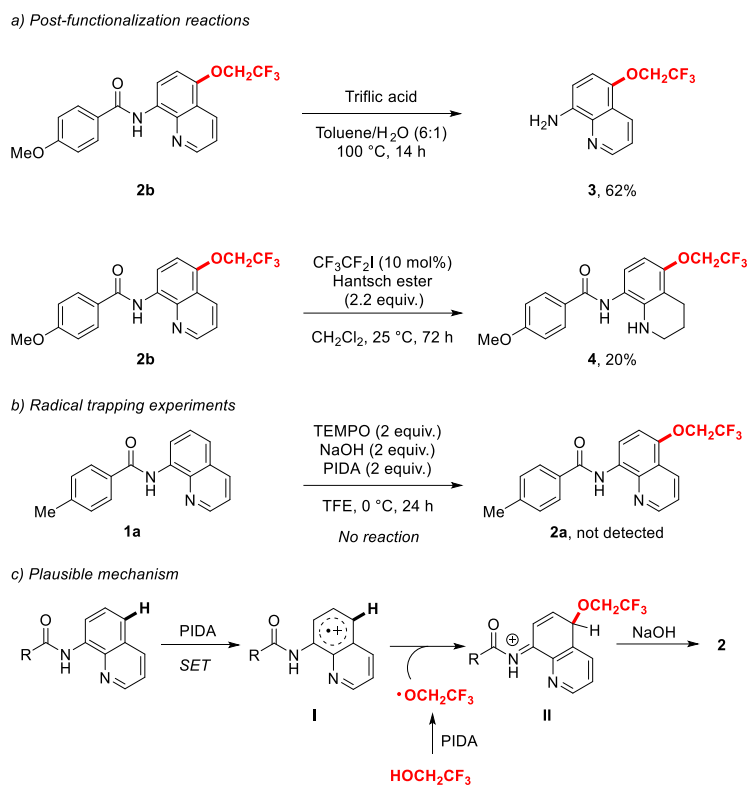
Pleasingly, **2a** was isolated in a modest 14% yield (Table 1, entry 1) and the reaction was completely selective towards the functionalization at the C5 position of the 8-aminoquinoline part, as no functionalization at the *ortho* position of the amide part was observed.^[16] Interestingly, a control experiment in the absence of the copper catalyst showed that **2a** was obtained in 18% yield (Table 1, entry 2). We then pursued our investigations to further optimize this transition metal-free process. Several oxidants were tested (table 1, entries 2–4) and PIDA turned out to be the most efficient one. Note that no reaction occurred in the absence of oxidant, highlighting hence its key role in the depicted process (Table 1, entry 5). Then, the influence of the nature of the base was studied (Table 1, entries 6–8) and when NaOH was used, **2a** was isolated in 40% yield. The efficiency of the reaction was fine-tuned by decreasing the reaction temperature (Table 1, entries 8-11), and the best yield was obtained when the reaction was carried out at 0 °C for 24 h (Table 1, entry 10). Extension of the reaction time to 48 h gave a similar result (Table 1, entry 12). Note that in absence of base, **2a** was obtained in only 19% yield (Table 1, entry 13).

With the best reaction conditions in hand, the scope of the transition metal-free 2,2,2-trifluoroethoxylation reaction was studied (Scheme 2). A panel of benzamide derivatives from the 8-aminoquinoline was functionalized. Note that decent yields were obtained taking into consideration tedious purifications. Not only *para*-substituted amides with a methyl or a methoxy group (**1a** and **1b**) were functionalized but also amides bearing a phenyl or a naphthyl group (**1c** and **1d**) were suitable substrates. The 2,2,2-trifluoroethoxylation of different *para*-substituted benzamides with an electron withdrawing group (CF₃, **1e**) or a halogen (Br, **1f**) went smoothly. The reaction was scaled up 10-fold and **2b** was isolated



Scheme 2. Scope of the 2,2,2-trifluoroethoxylation reaction. Reaction conditions: amide **1** (0.2 mmol, 1 equiv.), NaOH (2 equiv.), PIDA (2 equiv.), TFE (0.1 M), 0 °C, 24 h. Isolated yields were given. ¹⁹F NMR yields were given in parenthesis and were determined using the α,α,α -trifluoroacetophenone as the internal standard. [a] the reaction was carried out on a 2 mmol scale.

in 47% yield. The transformation turned out to be sensitive to the substitution pattern and compounds **2g** and **2h** were isolated in low to moderate yields, probably due to a less conjugated system in case of *meta* substituted ones. Pleasingly, the amide derived from the vanillin **1h** was functionalized, leading to the expected product **2h** in 45% yield. The reaction was not restricted to benzamide derivatives as amides derived from furan and thiophene provided the corresponding 2,2,2-trifluoroethoxylated products **2i** and **2j** in both 50% yield. Finally, even the aliphatic amide **1k** derived from tetrahydrofuran and the cinnamamide **1l** were also suitable substrates in this transformation, albeit the products were obtained in low yields.



Scheme 3. Post-functionalization reactions and mechanistic investigations.

To further demonstrate the synthetic utility of this approach, the amine **3** was smoothly obtained in 62% yield, upon acidic treatment with TfOH (Scheme 3, eq. a). Note that attempts to reduce the quinoline part of **2b** led to the expected product **4** in a moderate 20% yield. To get a better understanding of the reaction mechanism, radical trapping experiments using TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl, 2 or 5 equiv.) were performed, and no product was obtained, suggesting a radical process (Scheme 3, eq. b). Based on this observation and the literature data,^[7a, 7c, 8, 10] the following mechanism was suggested (Scheme 3, eq. c). First, in the presence of PIDA, a radical cation was generated (intermediate I) upon a Single Electron Transfer (SET), which would then react with the OCH₂CF₃ radical generated *in situ* from the 2,2,2-trifluoroethanol and PIDA. Finally, the resulting iminium species II would lead to the expected product **2** after deprotonation in the presence of the base. Note that a mechanism involving a nitrenium intermediate generated in the presence of PIDA cannot be precluded.^[7c, 12]

In summary, an original methodology for the synthesis of 2,2,2-trifluoroethoxylated quinoline derivatives at the C5 position was developed under mild reaction conditions (0 °C). Using the readily available and appealing 2,2,2-trifluoroethanol as the fluorinated source, a panel of protected aminoquinoline derivatives was functionalized (12 examples, up to 61% yield) at a

remote position under oxidative conditions. Key salient features of this unprecedented transformation are the distal 2,2,2-trifluoroethoxylation reaction, the total control of the selectivity (mono-functionalization, regioselectivity) as well as the mildness of this transition metal-free process.

Acknowledgements

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Keywords: 8-aminoquinoline • transition metal-free • 2,2,2-trifluoroethoxylation • fluorine chemistry • remote C-H functionalization

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