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Access to a new class of synthetic building blocks via trifluoromethoxylation of pyridines and pyrimidines†

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Since the first synthesis of trifluoromethyl ethers in 1935, the trifluoromethoxy (OCF₃) group has made a remarkable impact in medicinal, agrochemical, and materials science research. However, our inability to facily incorporate the OCF₃ group into molecules, especially heteroaromatics, has limited its potential across a broad spectrum of technological applications. Herein, we report a scalable and operationally simple protocol for regioselective trifluoromethoxylation of a wide range of functionalized pyridines and pyrimidines under mild reaction conditions. The trifluoromethoxylated products are useful scaffolds that can be further elaborated by amidation and palladium-catalysed cross coupling reactions. Mechanistic studies suggest that a radical *O*-trifluoromethylation followed by the OCF₃-migration reaction pathway is operable. Given the unique properties of the OCF₃ group and the ubiquity of pyridine and pyrimidine in biologically active molecules and functional materials, trifluoromethoxylated pyridines and pyrimidines could serve as valuable building blocks for the discovery and development of new drugs, agrochemicals, and materials.

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Introduction

The trifluoromethoxy (OCF₃) group has made a significant impact in medicinal, agrochemical, life- and materials science research^{1–5} since Booth and Burchfield reported the first synthesis of trifluoromethyl ethers in 1935.⁶ The increasing importance of the OCF₃ group can be attributed to its unique structural and electronic properties. First of all, in aryl trifluoromethyl ethers the OCF₃ moiety lies in the plane orthogonal to arene ring (Fig. 1a)⁷ and studies have shown that this unusual orientation may be beneficial for providing additional binding affinity in drug–target complexes.⁸ In addition, the OCF₃ group is among the most electronegative groups ($\chi(F) = 4.0$, $\chi(OCF_3) = 3.7$).⁹ Molecules bearing an electron-withdrawing group have better metabolic stability. Moreover, the OCF₃ group has an excellent lipophilicity ($\pi_x(SCF_3) = +1.44$, $\pi_x(SF_5) = +1.23$, $\pi_x(OCF_3) = +1.04$, $\pi_x(CF_3) = +0.88$, $\pi_x(OCH_3) = -0.02$);¹⁰ compounds with higher lipophilicity show enhancement in their *in vivo* uptake and transport in biological systems. Therefore, the OCF₃ group is introduced into biologically active

molecules to improve their efficacy and minimize their side effects (Fig. 1b).^{1,2,5} Furthermore, incorporation of the OCF₃ group into organic molecules can increase their melting point and boiling point difference under ambient pressure, and lower their surface tension, dielectric constant, and pour point.^{1,11,12} These properties are particularly useful in designing electronic devices and materials; as a result, the OCF₃-containing molecules can be found in electro-optical materials used for the development of liquid crystal displays,¹³ soluble organic semiconductor,¹⁴ and melt-processable fluoropolymers such as perfluoroalkoxy alkanes.¹²

Given the unique properties of the OCF₃ group and the ubiquity of pyridines and pyrimidines in biologically active molecules and functional materials, trifluoromethoxylated pyridines and pyrimidines could serve as valuable synthetic building blocks for the discovery and development of new drugs, agrochemicals, and functional materials. However, synthesis of OCF₃ containing heteroarenes through either O–CF₃ or C–OCF₃ bond formation remains a formidable challenge in organic synthesis (Fig. 1c).^{1–5,15} Unlike its analogous methoxy (OCH₃) group, the OCF₃ group cannot be formed *via* trifluoromethylation of hard nucleophiles such as phenoxides with CF₃I through S_N2 type mechanism.^{11,16,17} This is due to (i) strong electron repulsion between three fluorine atoms and an incoming nucleophile; (ii) formation of energetically disfavoured CF₃ carbocation transition state structure (TS); and (iii) competing iodination of nucleophiles due to the reversed electron density. In addition, the thermal instability of transition

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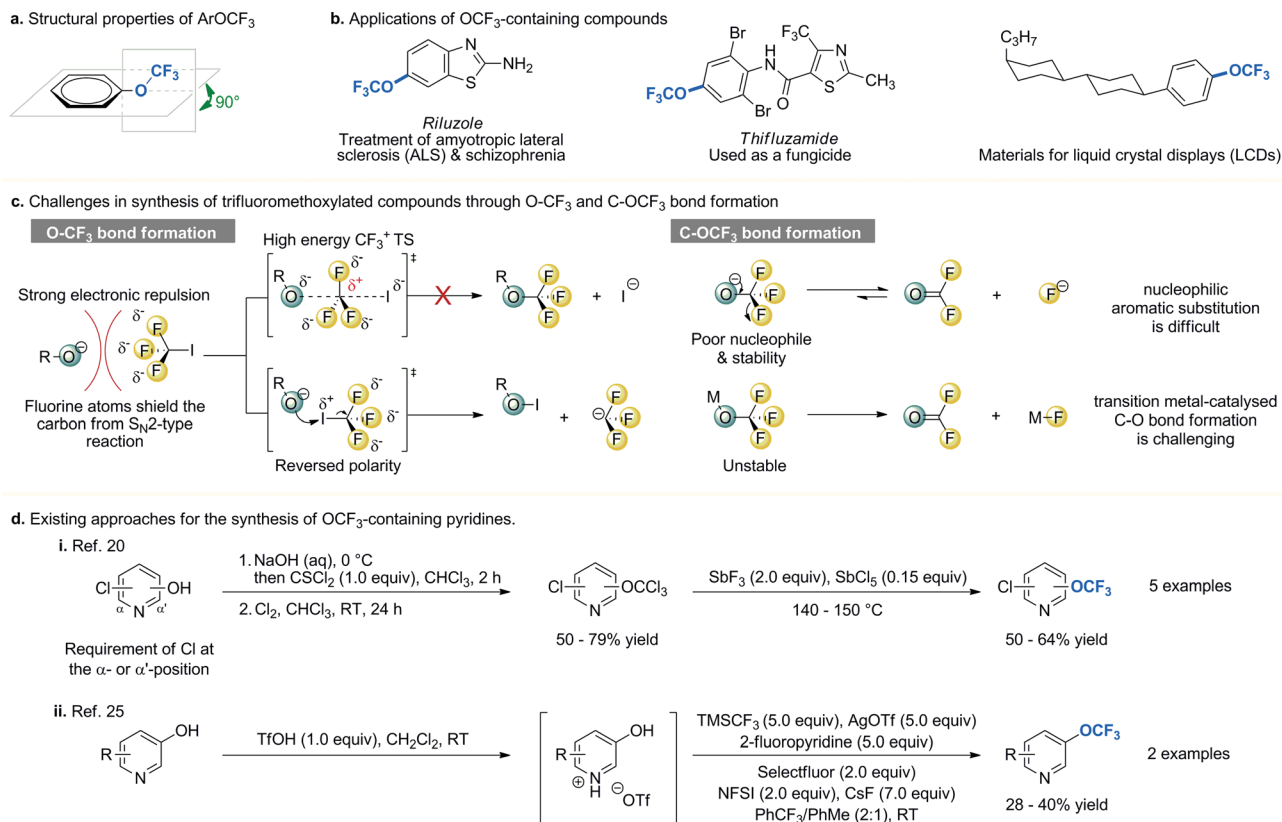


Fig. 1 Properties, applications, synthetic challenges and methods of synthesis of OCF₃-containing compounds. NFSI = *N*-fluorobenzenesulfonimide, TMSCF₃ = trifluoromethyltrimethylsilane.

metal-OCF₃ complexes (they readily decompose to form fluorophosgene and metal fluoride)¹⁸ and the poor nucleophilicity of the OCF₃ anion (a reactive electrophile is needed for the C-OCF₃ bond formation)¹⁹ have hampered the development of the C-OCF₃ bond formation through either transition metal-catalysed C-O bond formation or nucleophilic substitution. Strategies for the synthesis of trifluoromethoxylated heteroaromatic compounds are very rare.^{20–25} Leroux and co-workers reported a detailed examination of several different approaches and concluded that the presence of a chlorine atom at the α -, and/or α' - position of hydroxy-pyridines is critical (Fig. 1d).²⁰ Without it, little or no desired product was isolated. This requirement greatly limited its application. Recently, Qing and co-workers reported a novel, direct synthesis of pyridyl trifluoromethyl ethers from unprotected hydroxypyridines.²⁵ However, excess amounts of reagents and oxidants were required. In addition, only two examples with moderate yield were reported. Due to the lack of a general synthetic method for the synthesis of trifluoromethoxylated pyridines and pyrimidines, their full potential has not been fully exploited in pharmaceutical, agrochemical, and materials applications.

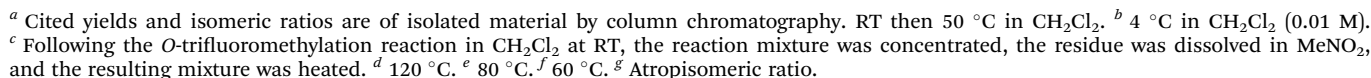
Herein, we report a scalable and operationally simple protocol for regioselective synthesis of trifluoromethoxylated functionalized pyridines and pyrimidines. Several unique features distinguish our strategy from the existing approaches: (i) many substrates with complex skeletons are trifluoromethoxylated at or below room temperature (17 out of the

30 examples); (ii) a wide range of functional groups and substitution patterns are tolerated; (iii) this transformation is amenable to gram-scale synthesis; (iv) halogen or amino group is used as synthetic handles for further elaborations, and (v) the operational simplicity of our protocol would render trifluoromethoxylation available to broader synthetic community. More importantly, this strategy allows access to a new class of synthetic building blocks to aid the discovery and development of new functional molecules.

Results and discussion

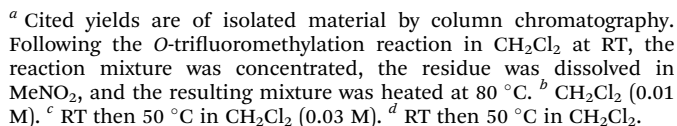
It is known that the N–O bond is relatively weak (bond dissociation energy = ~ 57 kcal mol⁻¹) due to the lone-pair electron repulsion between the nitrogen and the oxygen atoms. In addition, electron withdrawing *O*-substituent and/or electron donating *N*-substituent could promote heterolytic cleavage of the N–O bond to form nitrenium ion and oxy-anion.²⁶ Recently, we took advantage of these properties and successfully synthesized trifluoromethoxylated aromatic compounds through *O*-trifluoromethylation of *N*-aryl-*N*-hydroxylamine derivatives to form N-OCF₃ compounds followed by thermally induced OCF₃-migration.²⁷ However, to apply this strategy to the synthesis of trifluoromethoxylated heteroaromatic compounds such as pyridine and pyrimidine, two challenges had to be addressed.

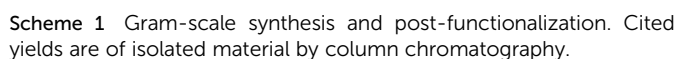
First of all, reaction conditions for the synthesis of *N*-acetyl/methoxycarbonyl-*N*-pyridinylhydroxylamine precursors are very



To ensure that our products can serve as useful building blocks for molecular screening, our protocol must be scalable and further functionalization of the trifluoromethoxylated products must be possible. To evaluate the reaction efficacy on preparative scale, a gram-scale reaction of **1a** (1.39 g, 5.00 mmol) was performed (Scheme 1a) and the efficiency of the small-scale reaction was retained upon scale-up. Our trifluoromethoxylated products also proved to be versatile (Scheme 1b). For instance, **2a** could be further elaborated through palladium-catalysed Suzuki and Sonogashira couplings to afford the desired products (**6a**, **8a**) in good yields. In addition, deprotected amino-pyridine (**2a'**) could be efficiently

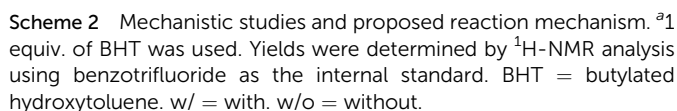
Table 3 Selected examples of trifluoromethoxylation of pyrimidines





Although our strategy is operationally simple and scalable, has broad substrate scope, and tolerates a wide range of functional groups, this procedure, much like other methods, is not without limitations. First of all, substrates with the protected *N*-hydroxylamino-group at α -, γ -, or α' -position do not give the product of trifluoromethoxylation. Presumably, the formation of nitrenium ion is energetically disfavoured in these cases, because it involves placing the positive charge on the endocyclic nitrogen atom.⁴⁶ In addition, preparation of *N*-heteroaryl-*N*-hydroxylamine precursors is required for this transformation. Furthermore, Togni reagent I is relatively expensive, and thus large-scale synthesis would be costly. Therefore, more improvements are needed for the development of a truly general and industrially practical trifluoromethoxylation reaction. Nevertheless, with the method accessing unprecedented and versatile synthetic building blocks in hand, the discovery and development of new pharmaceuticals, agrochemicals, and functional materials can be expected.

To gain some insight into the reaction mechanism, we performed reactions in the presence of radical trap butylated hydroxytoluene (BHT) (Scheme 2a). We chose to use substrate **1d** because we could isolate the *O*-trifluoromethylated intermediate **1d'** and study each step (*i.e.* *O*-trifluoromethylation and OCF₃-migration) separately. Addition of BHT (1 equiv.) to a reaction mixture of **1d** and Togni reagent I had detrimental effect to the formation of *O*-trifluoromethylated *N*-hydroxylamine intermediate **1d'**. This result strongly suggests the involvement of radical species in the reaction pathway, which is in agreement with literature precedents.^{47,48} On the other hand, BHT did not affect the reaction yield for the OCF₃-migration process (step 2, Scheme 2a). These experiments argue against the presence of long-lived radical species in the OCF₃-migration process and are consistent with our previous finding.²⁷ Moreover, introduction of electron rich substituent para to the N-OCF₃ group facilitates the OCF₃-migration process. These observations support the formation of



nitrenium ion and trifluoromethoxide.^{26,27} On the basis of these results, a plausible mechanism for the trifluoromethoxylation reaction is illustrated in Scheme 2b. Deprotonation of **1d** forms *N*-hydroxyl anion **9**, which undergoes single-electron transfer (SET) with Togni reagent I to generate *N*-hydroxyl radical **10**, trifluoromethyl radical, and alkoxide **11**.⁴⁸ Reaction of *N*-hydroxyl radical and trifluoromethyl radical affords the *O*-trifluoromethylated hydroxylamine **1d'**, which could be isolated and characterized. This intermediate will then undergo thermally induced heterolytic cleavage of the N–O bond to form a tight ion pair of nitrenium ion **12** and trifluoromethoxide. Rapid recombination of this ion pair gives **13**, which upon tautomerization (*i.e.* migration of proton) yields the desired product **2d**.

In summary, we reported an operationally simple protocol for the regioselective trifluoromethoxylation of functionalized pyridines and pyrimidines. The strategy uses commercially available and bench stable Togni reagent I, features a broad substrate scope, tolerates a wide range of functional groups, and is amenable to gram scale synthesis. With this procedure, a variety of highly functionalized pyridines and pyrimidines could be trifluoromethoxylated under mild reaction conditions. Since heteroarenes are ubiquitous in biologically active natural products, pharmaceuticals, and agrochemicals, we expect that our work will provide valuable OCF₃-containing heteroaromatic building blocks for the discovery and development of new drugs, agrochemicals, and functional materials.

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