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Transition-Metal-Free Decarboxylation of 3,3,3-Trifluoro-2,2-dimethylpropanoic Acid for the Preparation of $C(CF_3)Me_2$-Containing Heteroarenes

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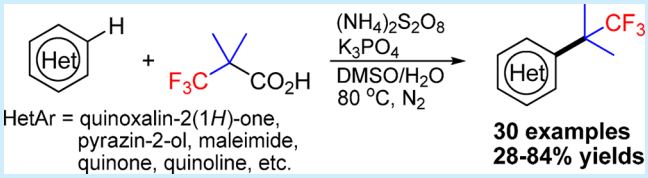
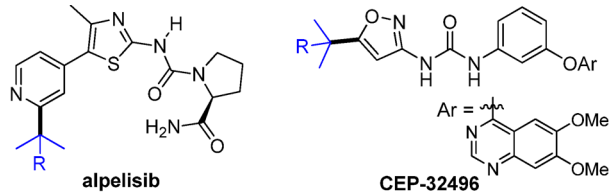
Supporting Information

ABSTRACT: The direct synthesis of $C(CF_3)Me_2$-substituted heteroarenes by decarboxylative 1,1-dimethyltrifluoroethylation of heteroarenes with 3,3,3-trifluoro-2,2-dimethylpropanoic acid is reported. This method does not need the transition-metal catalyst, and the base is crucial for this reaction. A series of previously unknown $C(CF_3)Me_2$-containing heteroarenes were obtained in high yields and have potential applications in the drug discovery process.



In structure−activity relationship (SAR) studies, the *tert*-butyl group is frequently critical for biological activity by means of binding to a hydrophobic pocket in the receptor.[1] Besides its excellent lipophilicity (π = 1.98),[2] the steric hindrance of *tert*-butyl is also useful in the design of valuable compounds. Thus, compounds bearing *tert*-butyl often demonstrate high anticancer, antimicrobial, and antibacterial activities.[3] However, these compounds sometimes are susceptible to rapid metabolic degradation, probably due to the easy abstraction of H from all fully sp^3 C−Hs of the *tert*-butyl group.[4] In order to prevent this oxidative metabolism, much effort is expended to replace *tert*-butyl with metabolically stable derivatives or bioisosteres.

Trifluoromethyl (CF_3) is a strongly electron-withdrawing and highly hydrophobic group widespread in bioactive compounds and functional materials.[5] The replacement of a single CH_3 of *tert*-butyl with CF_3 would lead to more stable derivatives with similar or even higher potency profiles. For example, the $C(CF_3)Me_2$-containing PI3Kα inhibitor alpelisib is more active than *tert*-butyl-substituted analogue **A** in inhibiting of PI3Kα with improved metabolic stability (Figure 1).[6] Similarly, the $C(CF_3)Me_2$-substituted $BRAF^{V600E}$ inhibitor CPE-32496 exhibited higher cellular potency and metabolic stability than the nonfluorinated compound **B**.[7] These results, together with other SAR studies,[8] clearly demonstrate that $C(CF_3)Me_2$ moiety may serve as an advantageous replacement for *tert*-butyl in the design and development of bioactive compounds. However, synthetic methods of $C(CF_3)Me_2$-substituted (hetero)arenes are limited. Normally, these compounds are synthesized by two approaches. The first is transformation of (hetero)aryl methyl ketones via trifluoromethylation, mesylation, and methylation (Scheme 1a).[4a,8c,d,f,9] The second is construction of aromatic systems from $C(CF_3)Me_2$-containing building blocks (Scheme 1b).[6,7,8a,b,e,g,10] Nevertheless, both approaches require prefunctionalized substrates and several synthetic steps, which seriously hamper the synthesis and application of $C(CF_3)Me_2$-substituted (hetero)arenes.



	IC_{50} for inhibition of P110α (μM)	microsomal clearance rat (μL/min/mg)
alpelisib (R = CF_3)	0.005	29
A (R = CH_3)	0.014	77
	IC_{50} for inhibition of A375 proliferation (nM)	microsomal clearance rat (mL/min/kg)
CEP-32496 (R = CF_3)	78	5.0
B (R = CH_3)	328	17.6

Figure 1. Effect of bioactivities and metabolic stability by replacing CH_3 with CF_3 in the *tert*-butyl substituents.

Recently, radical fluoroalkylation has attracted much attention because of its mild reaction conditions and broad functional-group tolerance.[11] We envisioned that if the $C(CF_3)Me_2$ group could be directly introduced to (hetero)arenes by radical processes it would not only significantly improve the synthetic efficiency but also dramatically expand the substrate scope. However, because $C(CF_3)Me_2$ group has

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Scheme 1. Synthesis of $C(CF_3)Me_2$-Substituted Heteroarenes

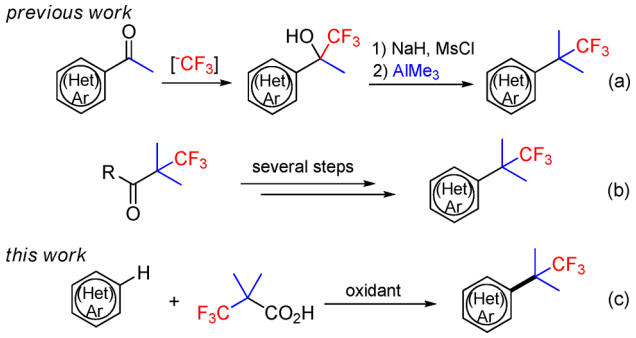
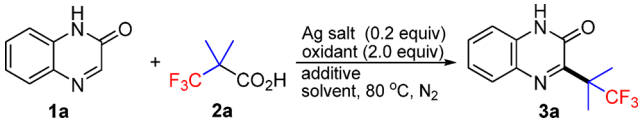


Table 1. Optimization of Reaction Conditions[a]

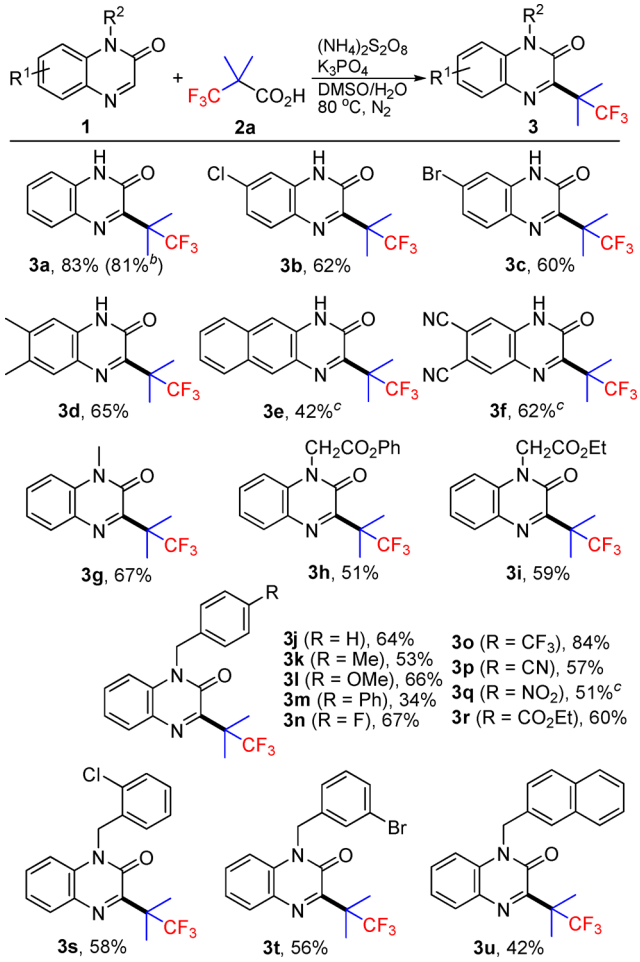


entry	Ag salt	oxidant	additive	solvent	yield[b] (%)
1	$AgNO_3$	$Na_2S_2O_8$	H_2SO_4	DMSO/H_2O	0
2	$AgNO_3$	$Na_2S_2O_8$	TFA	DMSO/H_2O	0
3	$AgNO_3$	$Na_2S_2O_8$	$NaHCO_3$	DMSO/H_2O	6
4	$AgNO_3$	$Na_2S_2O_8$	K_3PO_4	DMSO/H_2O	18
5	Ag_2CO_3	$Na_2S_2O_8$	K_3PO_4	DMSO/H_2O	21
6	AgOAc	$Na_2S_2O_8$	K_3PO_4	DMSO/H_2O	16
7		$Na_2S_2O_8$	K_3PO_4	DMSO/H_2O	54
8		$PhI(OAc)_2$	K_3PO_4	DMSO/H_2O	23
9		$K_2S_2O_8$	K_3PO_4	DMSO/H_2O	12
10		$(NH_4)_2S_2O_8$	K_3PO_4	DMSO/H_2O	76
11		$(NH_4)_2S_2O_8$	K_3PO_4	DMSO	32
12		$(NH_4)_2S_2O_8$	K_3PO_4	H_2O	trace
13		$(NH_4)_2S_2O_8$	K_3PO_4	MeCN/H_2O	45
14[c]		$(NH_4)_2S_2O_8$	K_3PO_4	DMSO/H_2O	91
15[c]		$(NH_4)_2S_2O_8$		DMSO/H_2O	trace
16[c,d]		$(NH_4)_2S_2O_8$	K_3PO_4	DMSO/H_2O	trace

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), Ag salt (0.04 mmol), oxidant (0.4 mmol), additive (0.4 mmol), DMSO/H_2O (2.0/1.0 mL), N_2, 80 °C, 12 h. [b]Yields determined by ^{19}F NMR spectroscopy using trifluoromethoxybenzene as an internal standard. [c]**2a** (0.5 mmol), $(NH_4)_2S_2O_8$ (0.5 mmol), K_3PO_4 (0.5 mmol). [d]2,2,6,6-Tetramethyl-1-piperidinyloxy (TEMPO, 0.6 mmol) was added.

not received enough attention from synthetic chemists, few reagents are available for transferring this group, except 3,3,3-trifluoro-2,2-dimethylpropanoic acid (TFDMPA). In continuation of our recent research interest in radical fluoroalkylation reactions,[12] we disclose the convenient synthesis of $C(CF_3)$-Me_2-substituted heteroarenes by radical 1,1-dimethyltrifluoroethylation of heteroarenes with TFDMPA (Scheme 1c).

Scheme 2. Substrate Scope of C−H 1,1-Dimethyltrifluoroethylation of Quinoxalin-2(1*H*)-ones[a]



[a]Reaction conditions: **1** (0.6 mmol), **2a** (1.5 mmol), $(NH_4)_2S_2O_8$ (1.5 mmol), K_3PO_4 (1.5 mmol), DMSO/H_2O (6.0/3.0 mL), N_2, 80 °C, 12 h, isolated yields. [b]The reaction was performed on 8.0 mmol. [c]**2a** (1.8 mmol), $(NH_4)_2S_2O_8$ (1.8 mmol), K_3PO_4 (1.8 mmol), DMSO/H_2O (2.3/0.7 mL).

Initially, we examined the decarboxylative 1,1-dimethyltrifluoroethylation of the privileged structural motif quinoxalin-2(1*H*)-one (**1a**)[13,14] with TFDMPA under the classical Minisci reaction conditions[15] (Table 1, entry 1). None of the desired product **3a** was detected in the presence of $AgNO_3$, $Na_2S_2O_8$, and H_2SO_4, which is consistent with the previous results, *"Minisci conditions generally fail when using fluorinated acids"*.[16] Then different additives were investigated (entries 2−4), and **3a** was formed in 18% yield in the presence of K_3PO_4 (entry 4). Switching $AgNO_3$ to other silver salts led to comparable yields (entries 5 and 6). Surprisingly, the yield was sharply improved to 54% in the absence of silver salt (entry 7), although the exact reason remains unclear at the moment. Further evaluation revealed that the use of $(NH_4)_2S_2O_8$ as the oxidant could improve the reaction efficiency (entry 10). Subsequently, a series of solvents were tested, which revealed that DMSO/H_2O was still the most efficient (entries 11−13). Finally, the yield of **3a** was improved to 91% by increasing the amounts of TFDMPA, $(NH_4)_2S_2O_8$, and K_3PO_4 (entry 14). The control experiment showed that K_3PO_4 was crucial for this reaction (entry 15). Furthermore, only a trace amount of **3a**

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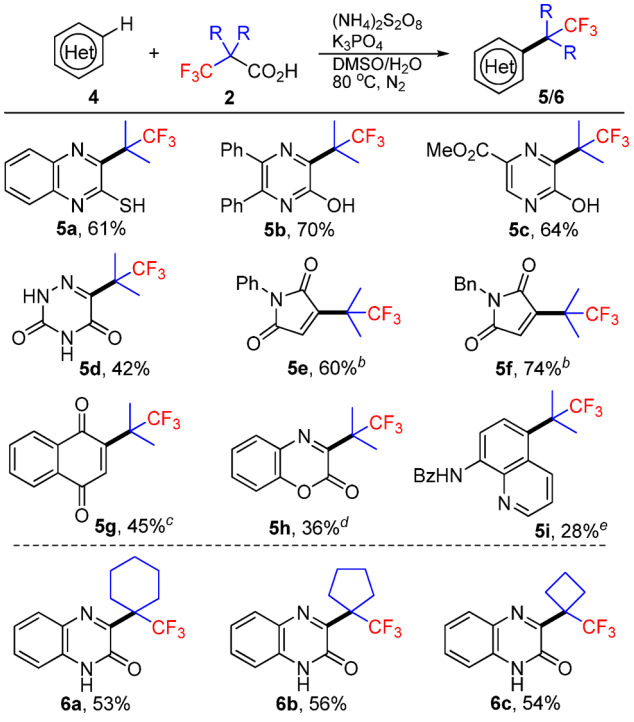
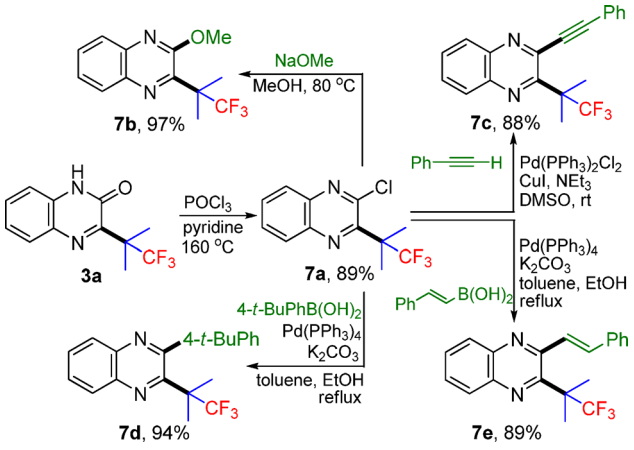
Scheme 3. Decarboxylative C−H Fluoroalkylation of Heterocycles[a]



[a]Reaction conditions: **4** (0.6 mmol), **2** (1.5 mmol), $(NH_4)_2S_2O_8$ (1.5 mmol), K_3PO_4 (1.5 mmol), DMSO/H_2O (6.0/3.0 mL), N_2, 80 °C, 12 h, isolated yields. [b]**2a** (3.0 mmol), $(NH_4)_2S_2O_8$ (0.9 mmol), K_3PO_4 (0.9 mmol), 70 °C, 6 h. [c]3 h. [d]$FeSO_4{\cdot}7H_2O$ (0.3 mmol) was added, 3 h. [e]A second portion of **2a** (1.5 mmol), $(NH_4)_2S_2O_8$ (1.5 mmol) and K_3PO_4 (1.5 mmol) was added after 12 h, and then the mixture was stirred for a further 12 h.

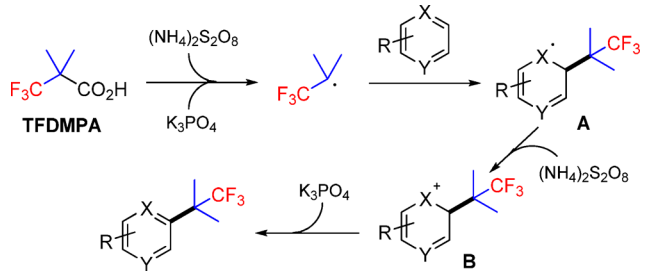
Scheme 4. Transformation of 3a



was detected when TEMPO was added, which indicated that a radical pathway was probably involved in this reaction (entry 16).

With the optimized reaction conditions in hand (Table 1, entry 14), the substrate scope of various quinoxalin-2(1*H*)-ones was then investigated (Scheme 2). Quinoxalin-2(1*H*)-ones **1b−f** bearing electron-donating or electron-withdrawing substituents reacted smoothly to give the corresponding products in good yields. A series of *N*-substituted quinoxalin-2(1*H*)-ones (**1g−u**) were also compatible with the reaction.

Scheme 5. Proposed Reaction Mechanism



Notably, a variety of functionalities, including ether, ester, fluoro, chloro, bromo, trifluoromethyl, cyano, and nitro were well tolerated. Furthermore, this reaction could be performed on gram scale, delivering **3a** with a slightly decreased isolated yield. Finally, the structure of **3e** was unambiguously established by X-ray diffraction studies (see the Supporting Information).

The successful C−H 1,1-dimethyltrifluoroethylation of quinoxalin-2(1*H*)-ones encouraged us to explore the 1,1-dimethyltrifluoroethylation of other heterocycles. As shown in Scheme 3, 1,1-dimethyltrifluoroethylation of quinoxaline-2-thiol (**4a**), pyrazin-2-ols (**4b,c**), and 1,2,4-triazine-3,5(2*H*,4*H*)-dione (**4d**) proceeded efficiently to afford the desired products in good yields. When maleimides (**4e,f**)[17] were subjected to the slightly modified reaction conditions, the $C(CF_3)Me_2$-substituted products were isolated in high yields. The other notable variations in the substrate included 1,4-naphthoquinone (**4g**),[18] benzoxazin-2-one (**4h**),[19] and 8-aminoquinoline (**4i**),[20] although low conversions and yields were obtained in these cases. However, 1,1-dimethyltrifluoroethylation of typical electron-poor and electron-rich heteroarenes, such as pyridine and pyrrole, failed. We also extended this methodology to the introduction of other CF_3-containing groups using the corresponding carboxylic acids. To our delight, CF_3-containing tertiary carboxylic acids **2b−d** underwent decarboxylative fluoroalkylation smoothly, leading to products **6a−c** in moderate yields. Unfortunately, 1-(trifluoromethyl)-cyclopropanecarboxylic acid did not react under the optimized conditions.

The 1,1-dimethyltrifluoroethylated quinoxalin-2(1*H*)-ones could be transformed to quinoxaline derivatives (Scheme 4). For instance, treatment of **3a** with $POCl_3$ afforded the chlorinated quinoxaline **7a** in high yield. Further transformation of **7a** with different reaction conditions gave alkoxylated (**7b**), alkynylated (**7c**), arylated (**7d**), and alkenylated (**7e**) quinoxaline derivatives. These results clearly demonstrate the synthetic utility of this protocol.

On the basis of previous reports,[21] a plausible reaction mechanism is depicted in Scheme 5. TFDMPA is oxidized by $(NH_4)_2S_2O_8$ to furnish the $C(CF_3)Me_2$ radical. The addition of $C(CF_3)Me_2$ radical to heteroarenes generates intermediate **A**, which is converted to the final products via an oxidation/deprotonation sequence. According to this mechanism, K_3PO_4 promotes decarboxylation of TFDMPA and assists deprotonation for the formation of the final products.

In conclusion, we have demonstrated the convenient synthesis of various $C(CF_3)Me_2$-substituted heterocycles through direct C−H functionalization of heteroarenes. Because of their synthetic simplicity, environmentally benign nature, broad substrate scope, high efficiency, and excellent regioselectivity, these protocols offer convenient access to

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$C(CF_3)Me_2$-containing heteroarenes, which are potentially valuable in drug discovery and materials science. Further explorations of the reaction mechanism and direct introduction of $C(CF_3)Me_2$ to other challenging substrates are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02451.

Experimental procedures, characterization data, copies of ^1H, ^{19}F, and ^{13}C NMR spectra, and X-ray crystal structure of **3e** (PDF)

Accession Codes

CCDC 1849134 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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