3-Position-Selective C–H Trifluoromethylation of Pyridine Rings Based on Nucleophilic Activation

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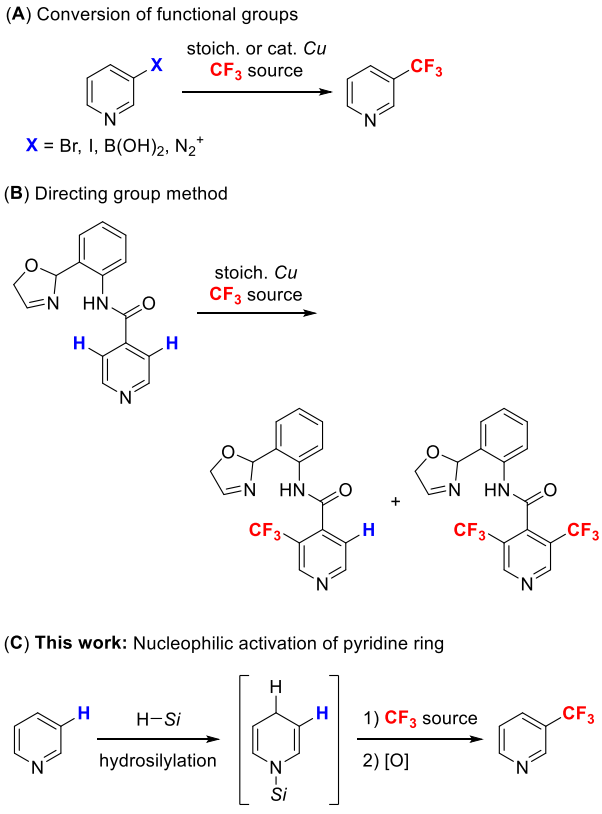
ABSTRACT: The first example of the 3-position-selective C(sp^2)–H trifluoromethylation of pyridine rings was established. 3-Position-selective trifluoromethylation was achieved by the nucleophilic activation of pyridine and quinoline derivatives through hydrosilylation and successive electrophilic trifluoromethylation of the enamine intermediate. This reaction was applicable to perfluoroalkylation at the 3-position of the pyridine rings and late-stage trifluoromethylation of a bioactive molecule. Mechanistic studies indicated that the reaction proceeds via the formation of *N*-silyl enamine and trifluoromethylated enamine intermediates.

Fluorine-containing functional groups, such as trifluoromethyl groups, play important roles in the production of drugs, agrochemicals, and organic functional materials because the introduction of fluorine atoms into organic compounds can improve the hydrophobicity and metabolic stability of organic molecules. Because organofluorine compounds rarely exist in nature, the development of effective methods to introduce fluorine-containing functional groups into organic compounds is an important research topic in organic chemistry. Regioselective C(sp^2)–H trifluoromethylation is an efficient method for the synthesis of organofluorine compounds.[1] Although trifluoromethyl radical is generally employed in conventional C(sp^2)–H trifluoromethylation,[2] it is difficult to control the regioselectivity because of its high reactivity. For instance, the reaction of pyridine with the trifluoromethyl radical gave a mixture of 2-, 3-, and 4-trifluoromethylated products.[3]

The regioselective transformations of pyridine rings have been intensively investigated.[4] Pyridines are electron-deficient aromatics that react with nucleophiles at the C2[5,6] and C4[7] positions of pyridine rings. Based on their reactivity, we developed 2- and 4-position-selective trifluoromethylation of pyridines and their related compounds using a nucleophilic trifluoromethylation reagent (CF_3 anion source) with mild reactivity.[8,9] The 2-position-selective trifluoromethylation was achieved by the introduction of a strong electron-withdrawing group on the nitrogen atom of the pyridine rings.[8] We succeeded in developing steric repulsion-controlled 4-position-selective trifluoromethylation based on the electrophilic activation of pyridines using a bulky Lewis acid.[9] However, these methods do not apply to trifluoromethylation at the C3 position of pyridine derivatives. Although this position is a potential reaction site with the CF_3 cation, such a reaction does not proceed under mild conditions because of the electron deficiency of the pyridine rings. Instead, conventional transformations at this position based on electrophilic aromatic substitutions require harsh conditions.[4]

Scheme 1. Synthetic Methods of 3-(Trifluoromethyl)pyridines

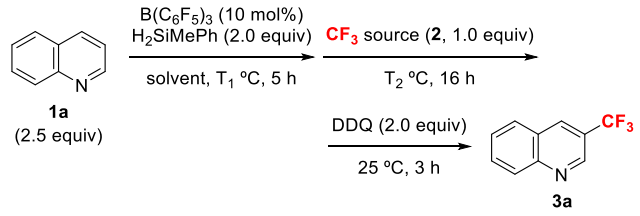


Several synthetic methods for the preparation of 3-trifluoromethyl pyridine derivatives have been reported (Scheme 1). The

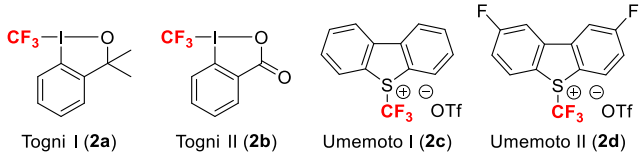
trifluoromethylation of aryl halide or boronic acid with stoichiometric[10] or catalytic[11] amounts of copper salts has been developed, and these methods were used to synthesize 3-trifluoromethyl pyridines (Scheme 1A). Grushin et al. reported a Sandmeyer-type reaction of aniline derivatives via diazonium salts (Scheme 1A).[12] Because these reactions require functionalized substrates, the direct transformation of C(sp^2)–H bonds is highly desirable. To the best of our knowledge, the sole example of such a reaction was reported by Yu et al. (Scheme 1B).[13] They introduced a directing group at the 4-position of the pyridine, and C–H trifluoromethylation occurred at the *ortho*-position (formal 3-position) instead. The reaction afforded a mixture of mono- and di-trifluoromethylated products and the directing group limited the structure of the substrates. Herein, we report the first 3-position-selective trifluoromethylation of pyridine rings based on nucleophilic activation.[14] To do so, we focused on hydrosilylation for the nucleophilic activation of the pyridine rings (Scheme 1C).

Quinoline (**1a**, 2.5 equiv) was reacted with methylphenylsilane (2.0 equiv) in the presence of tris(pentafluorophenyl)borane (10 mol%) in $CHCl_3$ at 25 °C for 5 h (Table 1, entry 1). Togni reagent I (**2a**) was added to the reaction mixture at 0 °C, and the resulting mixture was stirred at 25 °C for 16 h. The reaction mixture was then treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 2.0 equiv) to develop

Table 1. Screening of Solvents and Temperatures



entry	solvent	CF_3 source	T_1 (°C)	T_2 (°C)	yield of **3a** (%)[a]
1	$CHCl_3$	**2a**	65	0 to 25	57
2	toluene	**2a**	110	0 to 25	40
3	1,2-DCE	**2a**	65	0 to 25	76
4	1,2-DCE	**2b**	65	0 to 25	46
5	1,2-DCE	**2c**	65	0 to 25	6
6	1,2-DCE	**2d**	65	0 to 25	<5
7[b]	1,2-DCE/ DMSO	**2d**	65	0 to 25	24
8	1,2-DCE	**2a**	65	25	67
9	1,2-DCE	**2a**	65	-20	73

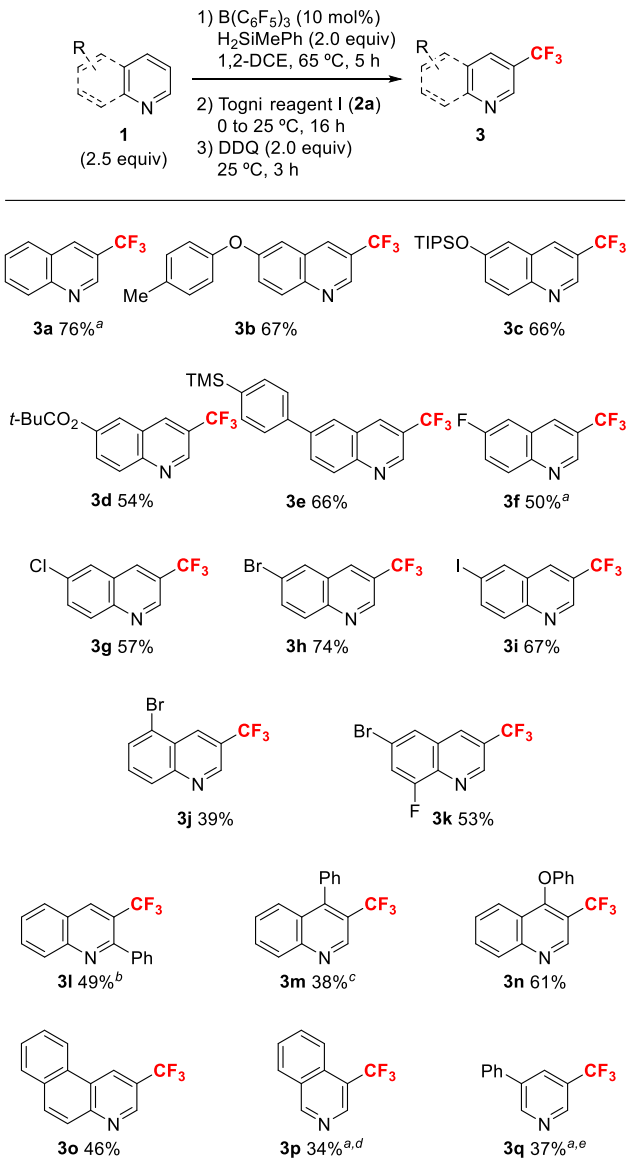


[a]^{19}F NMR yield. [b]Trifluoromethylation and oxidation steps were carried out in a mixed solvent (1,2-DCE : DMSO = 2:1).

3-trifluoromethylquinoline (**3a**) in 59% yield (Table 1, entry 1). Although the full conversion of hydrosilylation of **1a** in toluene required 110 °C, the yield of **3a** decreased (entry 2). 1,2-Dichloroethane (1,2-DCE) was selected as the solvent, and **3a** was obtained in 76% yield (entry 3). The use of Togni reagent II (**2b**) instead of **2a** resulted in the formation of **3a** in 46% yield (entry 4). However, Umemoto reagents I (**2c**) and II (**2d**) were unsuitable (entries 5 and 6). We considered that the low solubility of Umemoto reagents **2c** and **2d** in 1,2-DCE resulted in the use of dimethyl sulfoxide as a co-solvent (entry 7). Although the efficiency of the reaction was improved, the yield was lower than those of Togni reagents **2a** and **2b**. The addition of **2a** without cooling resulted in a slight decrease in the yield, while a lower temperature did not improve the yield of **3a** (entries 8 and 9).

Under the optimized conditions, various substrates were subjected to trifluoromethylation (Scheme 2). 3-Trifluoromethyl quinoline (**3a**) was obtained in 76% yield. The reactions of substrates **1b**-**1d** bearing aryl ether, silyl ether, or pivalate produced the corresponding products **3b**–**3d** in good yields. Arylsilane **1e** was tolerated, giving the 3-trifluoromethylated product **3e** in 66% yield. This reaction was applicable to a variety of substrates with functional groups. Carbon–halogen bonds were tolerated under the reaction conditions, yielding a moderate to good amount of the desired products **3f**–**3k** without loss of halogen atoms. Despite steric hindrance, 2-phenyl quinoline (**1l**) was also successfully converted to the desired product **3l** in 49% yield. 4-Position-substituted substrates were converted to the corresponding 3-trifluoromethylated products to avoid steric hindrance. 4-Phenylquinoline (**1m**) was reacted with hydrosilane at 50 °C for 7 h, and the resulting mixture was treated with **2a** to obtain the desired product **3m** in 38% yield. The reaction of 4-phenoxyquinoline (**1n**) proceeded under standard reaction conditions, and the 3-trifluoromethylated product **3n** was obtained in 61% yield. 3-Trifluoromethyl benzo[*f*]quinoline **3o** was obtained in moderate yield. In the case of isoquinoline (**1p**), hydrosilylation was carried out at 110 °C for 16 h in chloroform, and the resulting mixture was reacted with **2a** to obtain the corresponding product **3p** in 34% yield. In these cases, the formation of 1,2-dihydroquinoline was confirmed by ^{1}H NMR measurements of the reaction mixture (for details, see Supporting Information). The reaction of 3-phenylpyridine (**1q**) afforded the corresponding product **3q** in moderate yields. 8-Methylquinoline did not produce the desired 3-trifluoromethylated product because hydrosilylation did not proceed, probably because of steric hindrance.

Scheme 2. 3-Position-Selective C(sp^2)–H Trifluoromethylation of Quinoline and Pyridine Derivatives

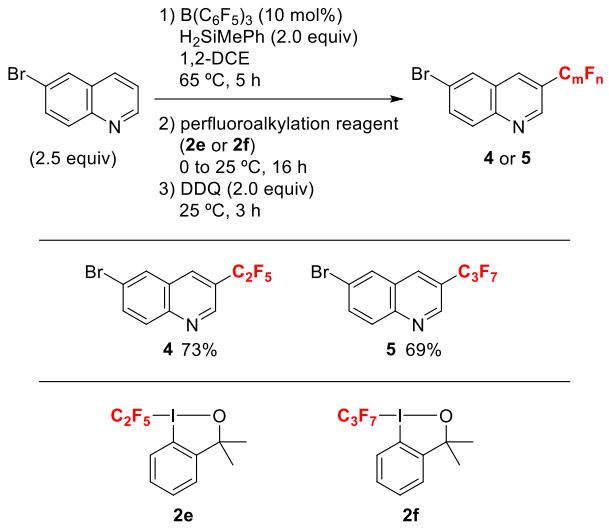


[a]^{19}F NMR yield. [b]Hydrosilylation: 25 °C, 24 h. [c]Hydrosilylation: 50 °C, 7 h. [d]$CHCl_3$ instead of 1,2-DCE, hydrosilylation: 110 °C, 24 h. [e]$H_2SiMePh$ (2.5 equiv), **1q** (2.0 equiv), 85 °C, 40 h; **2a** (1.0 equiv), -20 °C, 16 h.

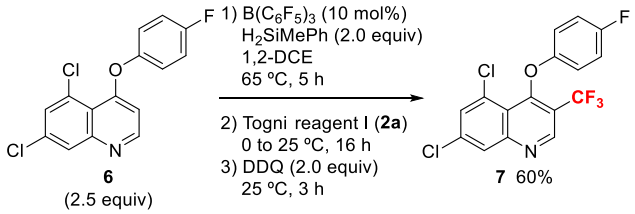
This method can be applied for the introduction of perfluoroalkyl groups at the 3-position of the pyridine ring (Scheme 3). 6-Bromo-3-pentafluoroethylquinoline (**4**) and 6-bromo-3-heptafluoropropylquinoline (**5**) were obtained in 72% and 69% yields, respectively.

Late-stage trifluoromethylation of the bioactive molecule was successful (Scheme 4). In this study, we focused on the trifluoromethylation of quinoxyfen (**6**), an agrochemical. The reaction of **6** afforded 3-trifluoromethyl quinoxyfen **7** in 60% yield (Scheme 4).

Scheme 3. Perfluoroalkylation of 6-Bromoquinoline 1h

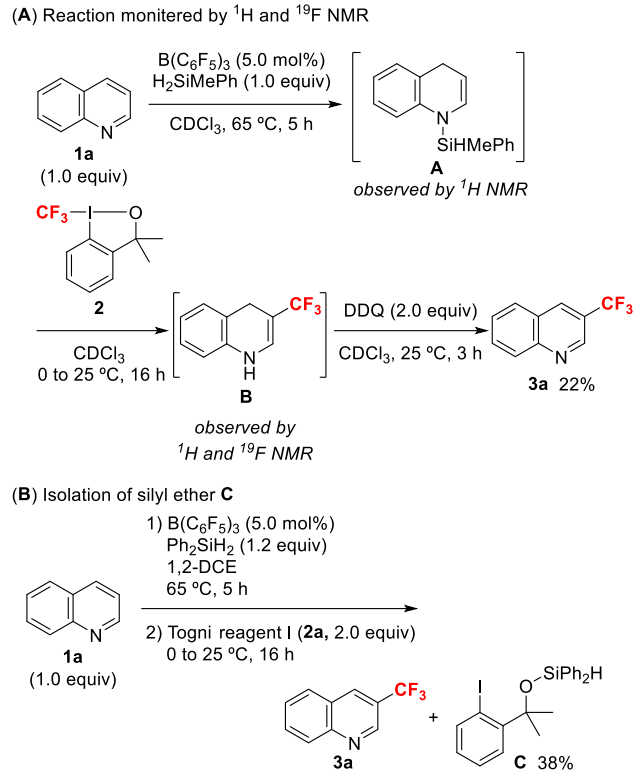


Scheme 4. Trifluoromethylation of Quinoxyfen (6)



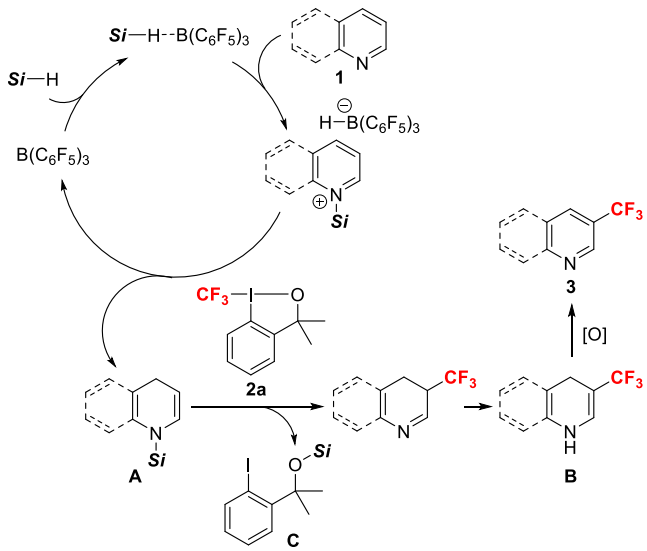
To reveal the reaction mechanism, the reaction system was monitored using ^{1}H NMR spectroscopy (Scheme 5A). The reaction of **1a** with methylphenylsilane in the presence of tris(pentafluorophenyl)borane (5.0 mol%) at 65 °C for 5 h in $CDCl_3$ resulted in the formation of *N*-silyl enamine intermediate **A**, which was observed by ^{1}H NMR analysis (for more detail, see Supporting Information). **2a** was added to the resulting mixture at 0 °C, and the mixture was stirred at 25 °C for 16 h. ^{1}H and ^{19}F NMR measurements indicated the formation of 3-trifluoromethylated 1,4-dihydroquinoline **B**, which might be formed via isomerization of 3-trifluoromethylated 3,4-dihydroquinoline (for details, see Supporting Information). The oxidation of intermediate **B** with DDQ produced **3a** in 22% yield as the sole regioisomer. We then investigated the isolation of the byproduct silyl ether (Scheme 5B). The mixture of **1a** with diphenylsilane in the presence of tris(pentafluorophenyl)borane (5.0 mol%) was heated at 65 °C for 5 h in 1,2-DCE.[15] **2a** was added to the resulting mixture at 0 °C and stirred at 25 °C for 16 h. The reaction mixture was purified by column chromatography on silica gel to obtain the corresponding silyl ether **C** in 38% yield.

Scheme 5. Mechanistic Studies



The plausible reaction mechanism is illustrated in Scheme 6. Hydrosilane was activated by tris(pentafluorophenyl)borane and behaved as the equivalent of the silyl cation and hydride.[16] Pyridine derivatives **1** reacted with the activated hydrosilane to form *N*-silylenamine **A** accompanied by the regeneration of the borane catalyst. Intermediate **A** reacted with **2a**, and the silyl group on the nitrogen atom transferred to the oxygen atom of the alkoxide derived from **2a**. The trifluoromethylated intermediate isomerized to intermediate **B**. Oxidation of intermediate **B** resulted in the 3-trifluoromethylated product **3**.

Scheme 6. Plausible Mechanism



In summary, we developed a 3-position-selective trifluoromethylation of pyridine rings based on nucleophilic activation via hydrosilylation. A variety of 6-membered heteroaromatic compounds, such as quinolines, benzoquinoline, isoquinoline, and pyridine, were converted to their corresponding trifluoromethylated products. The reaction proceeded with high regioselectivity, and 3-position trifluoromethylated products were obtained as the sole regioisomer. Carbon–halogen bonds, esters, aryl ethers, and silyl ethers were tolerated under the reaction conditions. The reaction was applicable to perfluoroalkylation at the 3-position of the pyridine rings and late-stage trifluoromethylation of the bioactive molecule quinoxyfen. Mechanistic studies revealed that the reaction proceeds via the formation of *N*-silyl enamine and 1,4-dihydroquinoline intermediates. We hope that this study will provide significant insights into the 3-position-selective transformation of pyridine rings.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and characterization data of the compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(14) During the preparation of this manuscript, C3-selective functionalization of pyridines through hydroboration has been reported. Liu, Z.; He, J.-H.; Zhang, M.; Shi, Z.-J.; Tang, H.; Zhou, X.-Y.; Tian, J.-J.; Wang, X.-C. Borane-Catalyzed C3-Alkylation of Pyridines with Imines, Aldehydes, or Ketones as Electrophiles. *J. Am. Chem. Soc.* **2022**, *144*, 4810-4818.

(15) Diphenylsilane instead of methylphenylsilane gave **3a** in 35% yield.

(16) Catalytic cycle of hydrosilylation. Gandhamsetty, D.; Park, S.; Chang, S. Selective Silylative Reduction of Pyridines Leading to Structurally Diverse Azacyclic Compounds with the Formation of sp^3 C−Si Bonds. *J. Am. Chem. Soc.* **2015**, *137*, 15176−15184.

The first example of 3-position-selective C(sp^2)–H trifluoromethylation of pyridine rings was established. The C3 trifluoromethylation was achieved by nucleophilic activation of pyridine and quinoline derivatives through hydrosilylation and successive electrophilic trifluoromethylation of the enamine intermediate. This reaction was applicable to perfluoroalkylation at the C3-position of pyridine rings and the late-stage trifluoromethylation of a bioactive molecule. Mechanistic study indicated that the reaction proceeded via the formation of *N*-silyl enamine and trifluoromethylated enamine intermediates.