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4-Position-Selective C−H Perfluoroalkylation and Perfluoroarylation of Six-Membered Heteroaromatic Compounds

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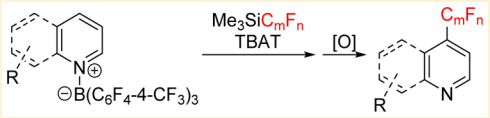
Supporting Information



ABSTRACT: The first 4-position-selective C−H perfluoroalkylation and perfluoroarylation of six-membered heteroaromatic compounds were achieved using nucleophilic perfluoroalkylation and perfluoroarylation reagents. The regioselectivity was controlled by electrophilically activating the heteroaromatic rings, while sterically hindering the 2-position, with a sterically bulky borane Lewis acid. The reaction proceeded in good yield, even in gram scale, and by a sequential reaction without isolating the intermediates. This reaction could be applied to late-stage trifluoromethylation of a bioactive compound.

Perfluoroalkyl and perfluoroaryl groups that include a trifluoromethyl group play an important role in many drugs,[1] agrochemicals,[2] and organic functional materials.[3] Therefore, the development of regioselective and efficient reactions to introduce such functional groups is very important.[4] One of the most direct and efficient methods is direct C−H perfluoroalkylation and perfluoroarylation, but until recently, it was quite difficult to promote regioselective C−H perfluoroalkylation and perfluoroarylation of six-membered heteroaromatic compounds. In many cases, a mixture of regioisomers is formed because highly reactive perfluoroalkyl radicals are used as perfluoroalkylation reagents.[5] Recently, our group succeeded in 2-position-selective C−H trifluoromethylation of six-membered heteroaromatic compounds.[6,7] The key to our success was the use of a less reactive trifluoromethyl anion as the trifluoromethylation source. There are no reports, however, of 4-position-selective C−H perfluoroalkylation and perfluoroarylation of six-membered heteroaromatic compounds. Syntheses of 4-(trifluoromethyl)pyridines from 4-halopyridines (or 4-pyridylboronic acids or 4-diazoquinolines) and CF_3-copper reagents have been reported (Figure 1a).[8] In some cases, the CF_3-copper reagents are prepared *in situ*. Catalytic versions of such reactions (cross-coupling reactions) are also reported (Figure 1b).[9,10] In 2012, Hartwig and Shen independently reported the synthesis of 4-trifluoromethylated pyridine derivatives by 4-position-selective iridium-catalyzed C−H borylation of a 2,6-disubstituted pyridine derivative and successive trifluoromethylation by converting the boryl groups (Figure 1c).[11] The substrate scope of six-membered heteroaromatic compounds, however, is quite limited. We report herein the first 4-position-selective C−H perfluoroalkylation of six-membered heteroaromatic compounds. Regioselectivity was controlled using a bulky borane Lewis acid (Figure 1d).

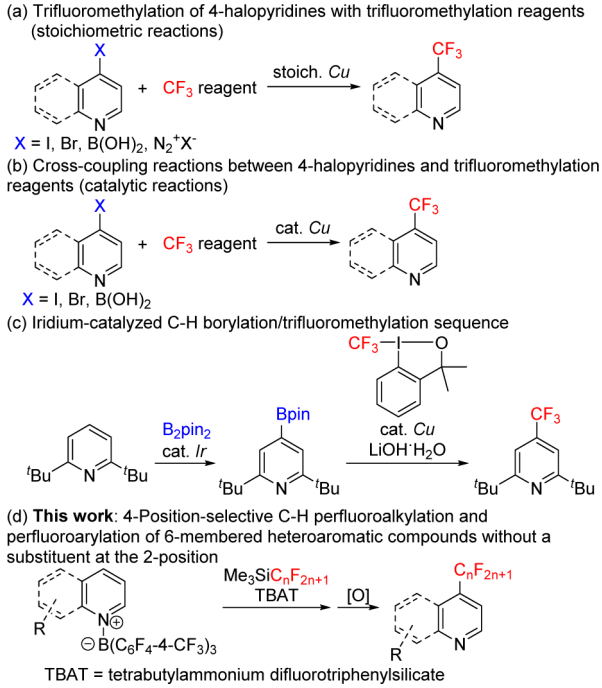


Figure 1. Synthesis of 4-trifluoromethylpyridines and quinolines by C−H transformations.

To achieve 4-position-selective C−H trifluoromethylation, we designed a new reaction system, in which a bulky Lewis acid electronically activates six-membered heteroaromatic compounds and sterically protects the 2-position of the heteroaromatic rings. As described above, we recently achieved 2-position-selective C−H trifluoromethylation of six-membered heteroaromatic compounds using six-membered heteroaromatic-*N*-oxide-BF_2CF_3 complexes as substrates. We used a more bulky Lewis acid $B(C_6F_5)_3$ instead of BF_2CF_3 to protect the 2-position of the heteroaromatic rings (Scheme 1a).

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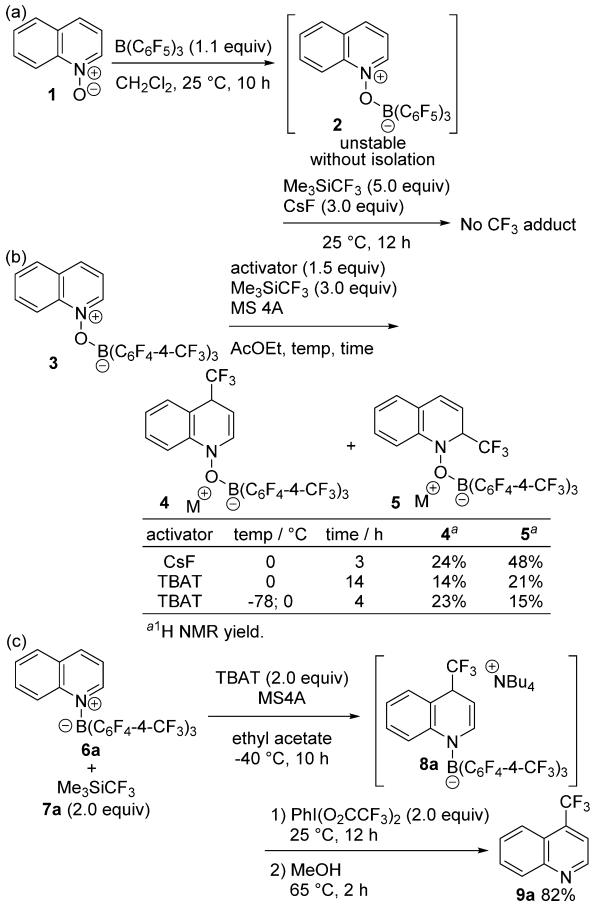
Scheme 1. 4-Position-Selective C−H Trifluoromethylation of Six-Membered Heteroaromatic Compound



Unfortunately, quinoline *N*-oxide-B(C_6F_5)$_3$ complex **2** was unstable during silica gel purification; thus, the trifluoromethylation reaction was conducted without isolating the complex. The desired trifluoromethylation, however, did not proceed at all. Next, we used a stronger Lewis acid B(C_6F_4-4-CF_3)$_3$ to stabilize the corresponding quinoline *N*-oxide-borane complex **3** (Scheme 1b). In this case, quinoline *N*-oxide-B(C_6F_4-4-CF_3)$_3$ complex **3** remained stable during silica gel purification, and the trifluoromethylation was investigated using the isolated complex **3**. A mixture of trifluoromethylated dihydroquinoline *N*-oxide-B(C_6F_4-4-CF_3)$_3$ complexes **4** and **5** was formed with low C4/C2 selectivity. In addition, it was difficult to rearomatize the formed heterocyclic rings. The reason for the low regioselectivity was assumed to be the lower steric hindrance from the borane moiety due to the presence of an oxygen atom. Therefore, we investigated the direct activation of quinoline with B(C_6F_4-4-CF_3)$_3$ using quinoline-tris(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)borane complex **6a**, which was also stable during silica gel purification. By the reaction of complex **6a** with trifluoromethyltrimethylsilane (**7a**) and tetrabutylammonium difluorotriphenylsilicate (TBAT) with successive oxidation of the formed intermediate **8a** by phenyl-λ3-iodanediyl bis(2,2,2-trifluoroacetate), the desired 4-(trifluoromethyl)quinoline **9a** was obtained in 82% yield (Scheme 1). Other oxidants, such as pyridinium dichromate (PDC), 2,3-dichrolo-4,5-dicyano-*p*-benzoquinone (DDQ), and tritylium tetrafluoroborate (TrBF_4), were effective for rearomatization (see the Supporting Information, Scheme S2). It also turned out that the two-step sequence, trifluoromethylation and rearomatization, was necessary because the desired reaction did not proceed and complex **6a** was recovered when trifluoromethylation was conducted in the presence of the oxidant.

We then investigated the substrate scope of six-membered heteroaromatic compounds (Scheme 2).[12] In the case of quinoline derivatives, the 4-position-selective C−H trifluoromethylation generally proceeded in good to excellent yields. We obtained the trifluoromethylated products **9b−9e** in moderate to good yields from 3-, 5-, 6-, or 7-methylated quinolines **6b−6e**. On the other hand, in the case of 2- or 8-methylquinolines, the corresponding quinoline−borane complexes were not formed, which was probably due to steric hindrance. The trifluoromethylation reaction proceeded with high functional group tolerance, such as alkenyl, alkynyl, amide, ester, amino, and methoxy groups and halogen atoms, and gave the desired trifluoromethylated quinoline derivatives **9f−9r** in moderate to excellent yields. The reaction was also applicable for pyridine derivatives, and products **9s−9z** and **9A−9C** were obtained, despite slightly lower yields than those of trifluoromethylquinolines **9a−9r**. The trifluoromethylation reaction proceeded regioselectively using other six-membered heteroaromatic compounds **6D−6G** with two heteroatoms and gave the corresponding trifluoromethylated products **9D−9G**.

We then investigated the substrate scope of the introduced perfluoroalkyl and perfluoroaryl groups (Scheme 3). Perfluoroalkylation reactions, such as pentafluoroethylation and heptafluoropropylation, proceeded well, and we obtained the corresponding 4-(pentafluoroethyl)quinoline (**10**) and 4-(heptafluoropropyl)quinoline (**11**) in 90% and 89% yields, respectively. The reactivity of Me_3SiCF_2H was lower than that of Me_3SiCF_3, probably due to the stronger bond energy of the C−Si bond of Me_3SiCF_2H.[13] The reaction of Me_3SiCF_2H was conducted using CsF as the base and DMF as the solvent to produce 4-(difluoromethyl)quinoline (**12**) in 56% yield. The perfluoroarylation reaction also proceeded, affording the corresponding 4-(pentafluorophenyl)quinoline (**13**) in 74% yield.

We propose the following reaction mechanism (Scheme 4): (1) formation of nucleophilically activated C_mF_n species from $Me_3SiC_mF_n$, **7**, and TBAT; (2) nucleophilic attack of the C_mF_n species at the 4-position of pyridine, quinoline, or their related compound−B(C_6F_4-4-CF_3)$_3$ complex **6**, to avoid the steric repulsion between the borane and C_mF_n anion; and (3) aromatization of intermediate **8** by oxidation to give the desired 4-perfluoroalkyl-pyridine, -quinoline, or their related compound **9−13**.

The 4-position-selective C−H trifluoromethylation proceeded in excellent yield, even in gram scale (Scheme 5). Treatment of 6-iodoquinoline-tris(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-borane complex **6r** (5.00 mmol) with trifluoromethyltrimethylsilane (**7a**) and TBAT, and successive oxidation by phenyl-λ3-iodanediyl bis(2,2,2-trifluoroacetate) produced 1.31 g (4.07 mmol) of 6-iodo-4-(trifluoromethyl)quinoline **9r** in 81% yield. The gram scale yield of **9r** was comparable to that on a smaller scale (78% yield, 127 mg) in Scheme 1c.

The 4-position-selective trifluoromethylated product **9r** was obtained from quinoline **14** without isolating the intermediates **6r** and **8r** (Scheme 6). 6-Iodoquinoline-tris(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)borane complex **6r** was prepared by the reaction between **14** and *in situ* prepared tris(2,3,5,6-

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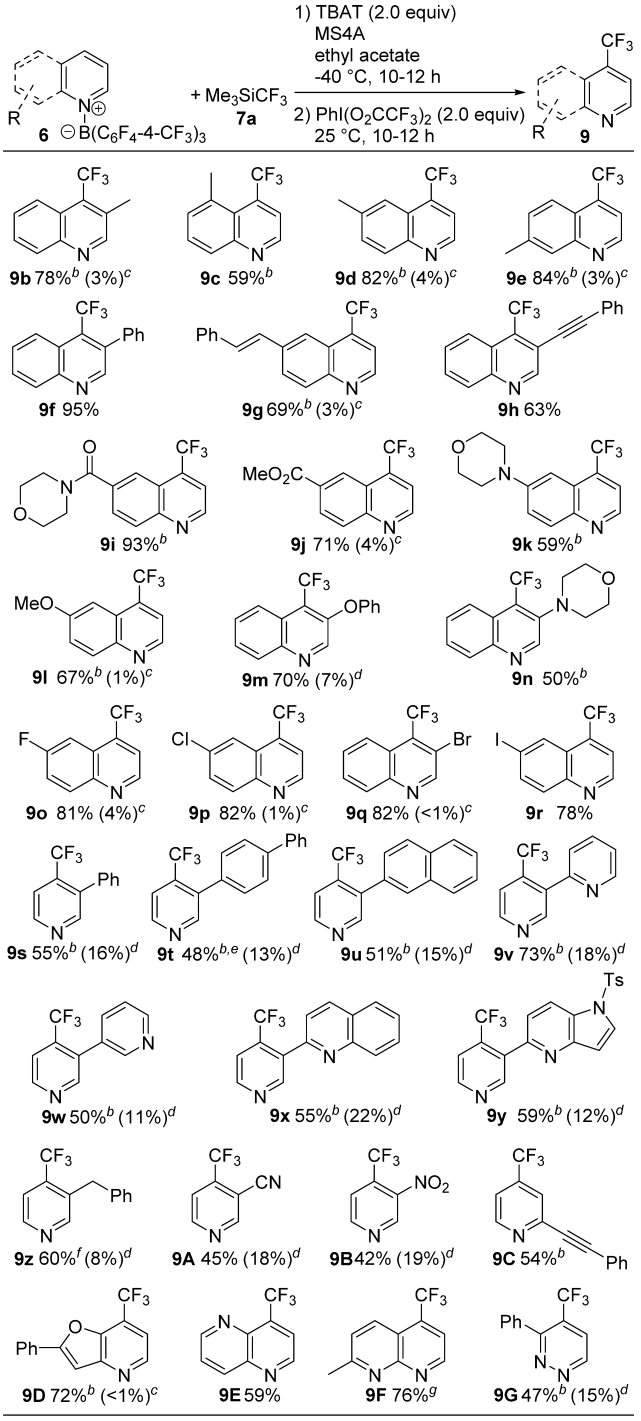
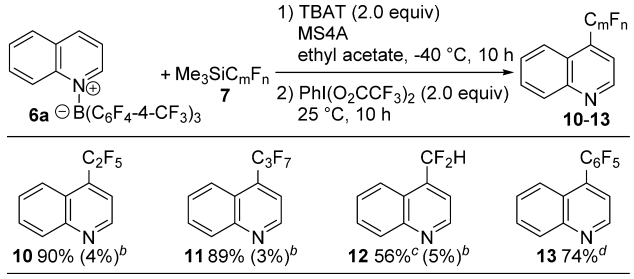
Scheme 2. Investigation of Six-Membered Heteroaromatic Compounds 6[a]



[a]**7a** (2.0 equiv). [b]After the reaction, MeOH was added and the mixture was heated at 65 °C for 2 h to cleave the boron complex. [c]^{19}F NMR yield of C-2 (or C-6) regioisomer is shown in parentheses. [d]Isolated yield of C-2 (or C-6) regioisomer is shown in parentheses. [e]Trifluoromethylation reaction was carried out at 0 °C. [f]After the reaction, MeOH was added and the mixture was heated at 65 °C for 4 h. [g]After the reaction, MeOH was added and the mixture was heated at 65 °C for 10 h.

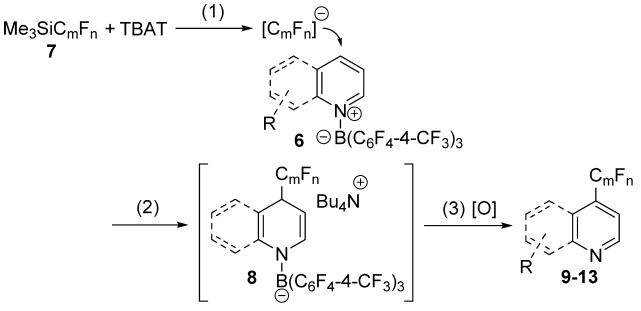
tetrafluoro-4-(trifluoromethyl)phenyl)borane in diethyl ether at 25 °C for 10 h. The solvent was then replaced with ethyl acetate, and the mixture was treated with trifluoromethyltrimethylsilane (**7a**) and TBAT. Successive oxidation by phenyl-λ3-iodanediyl bis(2,2,2-trifluoroacetate) gave 4-(trifluoromethyl)quinoline **9r** in 63% overall yield.

Scheme 3. Investigation of Fluoroalkylation and Perfluoroarylation Reagents 7[a]

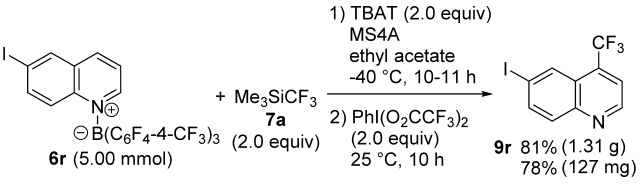


[a]**7** (2.0 equiv). [b]^{19}F NMR yield of C-2 regioisomer is shown in parentheses. [c]Me_3SiCF_2H (3.0 equiv), CsF (3.0 equiv), and DMF were used instead of TBAT and ethyl acetate, respectively. See the Supporting Information for the details. [d]After the reaction, MeOH was added and the mixture was heated at 60 °C for 2 h.

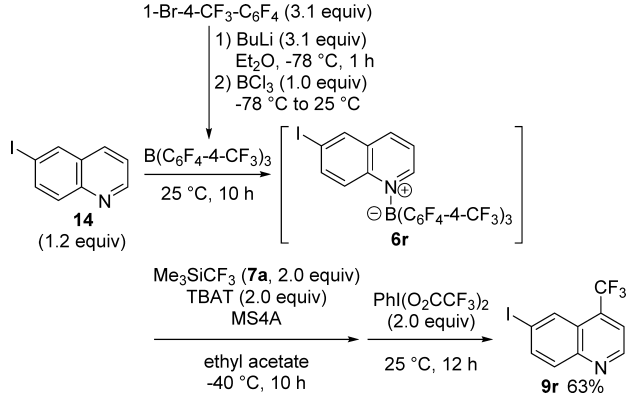
Scheme 4. Proposed Mechanism for 4-Position-Selective C–H Perfluoroalkylation and Perfluoroarylation



Scheme 5. Gram-Scale Reaction



Scheme 6. Sequential Reaction without Isolation of Intermediates



The 4-position-selective trifluoromethylation could be applied to a late-stage reaction (Scheme 7). Abiraterone acetate

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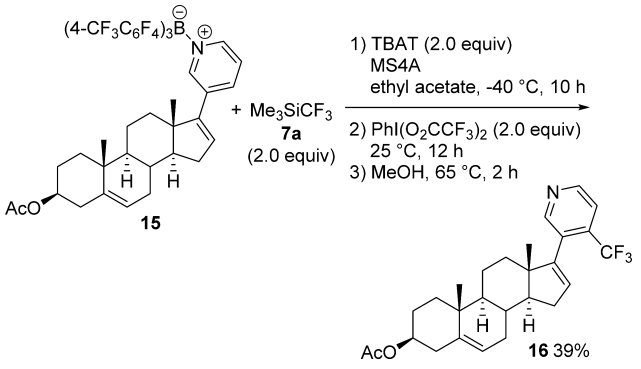
Scheme 7. 4-Position-Selective C−H Trifluoromethylation of Drug Molecule



is an antiprostate cancer drug with a pyridyl group on the steroid skeleton.[14] Treatment of abiraterone acetate−B-(C_6F_4(4-CF_3)$_3$) complex **15** with a mixture of **7a** and TBAT, successive oxidation with a hypervalent iodine compound, and elimination of the borane from the product with MeOH gave trifluoromethylated abiraterone acetate **16** in 39% yield.

In summary, we successfully achieved a 4-position-selective C−H trifluoromethylation, pentafluoroethylation, heptafluoropropylation, difluoromethylation, and pentafluorophenylation of six-membered aromatic compounds. This is the first example of a 4-position-selective C−H fluoroalkylation and perfluoroarylation of six-membered heteroaromatic compounds. The 4-position-selective C−H fluoroalkylation and perfluoroarylation were realized by electronically activating six-membered heteroaromatic rings and sterically protecting the 2-position of the substrates by a bulky borane, B(C_6F_4-4-CF_3)$_3$. The reaction proceeded in good yield, even in gram scale, and by sequential reactions without isolating the intermediates. This reaction could be applied to late-stage trifluoromethylation of a drug, abiraterone acetate. We expect that this will become a useful reaction for synthesizing 4-position-fluoroalkylated and perfluoroarylated six-membered heteroaromatic compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b01753.

General experimental procedure and characterization data for six-membered heteroaromatic compound−borane complexes, and perfluoroalkylated and perfluoroarylated products (PDF)

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Notes

The authors declare no competing financial interest.

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