Cp*-CoIII-Catalyzed Directed C-H Trifluoromethylthiolation of 2-Phenylpyridines and 6-Arylpurines

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Cp*-CoIII-catalyzed directed C-H trifluoromethylthiolation using N-trifluoromethylthiodibenzenesulfonimide as an electrophilic SCF₃ source is described. 6-Arylpurines, an important structural motif in medicinal chemistry, and 2-phenylpyridines selectively afforded mono-trifluoromethylthiolated products in moderate to good yields using an inexpensive first-row transition metal catalyst.

Introduction of a trifluoromethylthio (SCF₃) group into biologically active molecules improves their bioavailability and transmembrane permeability by increasing their lipophilicity (Hansch parameter π = 1.43). Therefore, a synthetic method for SCF₃-containing compounds can contribute to drug discovery and other biological studies, and has attracted much attention in the organic synthetic community. Most of the classical methods for synthesizing aryl-SCF₃ compounds rely on the conversion of other sulfur-containing functional groups to an SCF₃ group, which often requires elaborate starting materials or harsh reaction conditions, thus limiting the accessible structures. Recent studies enabled a general and direct introduction of an SCF₃ group to aryl halides using trifluoromethylthiolate anion equivalents, such as AgSCF₃, CuSCF₃, and NR₄SCF₃, under transition metal-catalyzed cross-coupling conditions.

On the other hand, recent advances in transition metal-catalyzed directed C-H bond activation-functionalization provide an attractive strategy to site-selectively introduce various functional groups without the preparation of aryl halides or organometallic reagents. In this context, several C-H trifluoromethylthiolation reactions were reported using electrophilic trifluoromethylthiolating reagents or oxidative conditions. Daugulis and co-workers reported a C-H trifluoromethylthiolation using toxic and volatile (CF₃S)₂ and a substoichiometric amount of Cu(OAc)₂, but only di-trifluoromethylthiolated products were obtained (Scheme 1a). Shen and Besset reported PdII-[SCF₃]⁺ catalyzed trifluoromethylthiolation of indoles and 2-phenylpyridine (Scheme 1d). Although these reactions using more convenient SCF₃ sources selectively afforded the mono-trifluoromethylthiolated products, the requirement of precious second-row transition metal catalysts was a major drawback. This background prompted us to investigate directed C-H trifluoromethylthiolation using an inexpensive metal catalyst.

Scheme 1. Transition metal-catalyzed directed C-H trifluoromethylthiolation

[Diagram of Scheme 1]
The reactions were run using 1a (0.10 mmol), 2 (0.05 mmol), catalyst (10 mol %), and additive (5–20 mol %) in the indicated solvent at 80 °C for 12 h. Determined by GC-MS analysis using dodecane as an internal standard. *MS 3 Å (200 mg/mmol) was added. **Isolated yield in 0.40 mmol scale.

We previously reported that Cp*Co(II) catalysts act as alternatives to expensive Cp*Rh(III) catalysts for C–H functionalization, and we and others developed a number of synthetic reactions. The unique properties of cobalt contribute to the distinct reactivity and selectivity of Cp*Co(II) catalysis compared with Cp*Rh(III). We envisaged that Cp*Co(III) would facilitate S$_2$N$_2$-type C–H trifluoromethylthiolation using electrophilic SCF$_3$ reagents due to the high nucleophilicity of the organocobalt intermediate. We initiated our investigation with trifluoromethylthiolation of 2-phenylpyridine 1a using [Cp*Co(CH$_3$CN)$_3$][SbF$_6$]$_2$ and an electrophilic SCF$_3$ source, N-trifluoromethylthiocarbazin 2a, which was used in the Cp*Rh(III)-catalyzed reaction. Initial solvent screening revealed that the use of fluorinated solvent led to relatively good reactivity (entries 1–4), and 1,1,1,3,3-hexafluoro-2-propanol (HFIP) afforded the desired trifluoromethylthiolated product 3a in 46% yield (entry 4). Neither changing the catalyst precursors to Cp*Co(CO)$_2$I$_2$ and AgSbF$_6$ (entry 5) nor the addition of acetate bases (entries 6, 7) improved the yield. The diluted conditions (0.05 M) resulted in the similar yield (entry 8). The recent report by Xue, Lu, and Shen demonstrated that N-trifluoromethylthiodibenzesulfon fluoride 2b is a more electrophilic SCF$_3$ source. Although 2b was ineffective under the concentrated conditions (entry 9, 0.2 M), the diluted conditions afforded good yield (entry 10). The addition of MS 3 Å improved the yield probably due to the instability of the highly reactive reagent 2 towards water (entry 11). Finally, we found a catalytic amount of AgSbF$_6$ as a Lewis acidic additive accelerated the reaction, and product 3a was isolated in 94% yield under the optimized conditions shown in entry 12. TLC and GC-MS analysis revealed no formation of the di-trifluoromethylthiolated product in all cases probably because the second C–H metallation is hampered by the steric repulsion between the trifluoromethylthiogroup and the hydrogen of the pyridyl group of the product. The reaction did not proceed without the cobalt catalyst (entry 13).

The substrate scope of 2-phenylpyridine derivatives is summarized in Scheme 2. The optimized conditions exhibited good functional group compatibility. The corresponding products were obtained in good to moderate isolated yields in the presence of both electron-donating (3b) and electron-withdrawing (3c, 3d) groups. A substrate bearing a m-MeO-substituent 1f afforded the corresponding products in moderate regioselectivity (78:22 by GC-MS analysis), and the major isomer 3f was isolated in 72% yield. A substrate with a m-carbomethoxy group 1g exclusively afforded 3g in 43% yield. In contrast, when a m-fluoro substituted substrate 1h was used, selective trifluoromethylthiolation proceeded at the opposite to the fluoride (84:16 by GC-MS analysis) to afford 3h as a major product. 6-Arylpurines are important molecules in medicinal chemistry due to their anti-mycobacterial, anti-HCV, and cytostatic activity. Although several transition metal-catalyzed directed C–H functionalization reactions have been developed, trifluoromethylthiolation has not yet been reported. We assumed that introducing an SCF$_3$ group into these molecules would provide biologically useful compounds. After re-optimization of the reaction conditions, trifluoromethylthiolation of 6-arylpurines 4 using [Cp*Co(CH$_3$CN)$_3$][SbF$_6$]$_2$ and reagent 2b successfully afforded...
desired products 5 in the presence of catalytic amounts of AgOAc and Gd(OTf)₃ (Scheme 3). AgOAc would work as a base to facilitate the C-H activation step, and Gd(OTf)₃ was the catalyst with the release of product 4b.

In summary, we developed Cp*Co III-catalyzed directed C-H trifluoromethylthiolation using electrophilic trifluoromethylthiolating reagent 2b. In addition to 2-phenylpyridines 1, 6-arylpurines 4 afforded the trifluoromethylthiolated products in moderate to good yields. This method can be used to provide useful molecules for medicinal chemistry.²⁴

This work was supported in part by JSPS KAKENHI Grant Number JP15H05802 in Precisely Designed Catalysts with Customized Scaffolding, and JSPS KAKENHI Grant Number JP15H05993.

Notes and references


[CpCo(CH3CN)3](SbF6)2 (10 mol %)
AgOAc (10 mol %)
Gd(OTf)3 (30 mol %)
reagent 2b (1.5 eq.)
MS 3Å, HFIP (0.1 M)
90 °C, 24 h
<10%