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Cp*Co^{III}-Catalyzed Directed C-H Trifluoromethylthiolation of 2-Phenylpyridines and 6-Arylpurines

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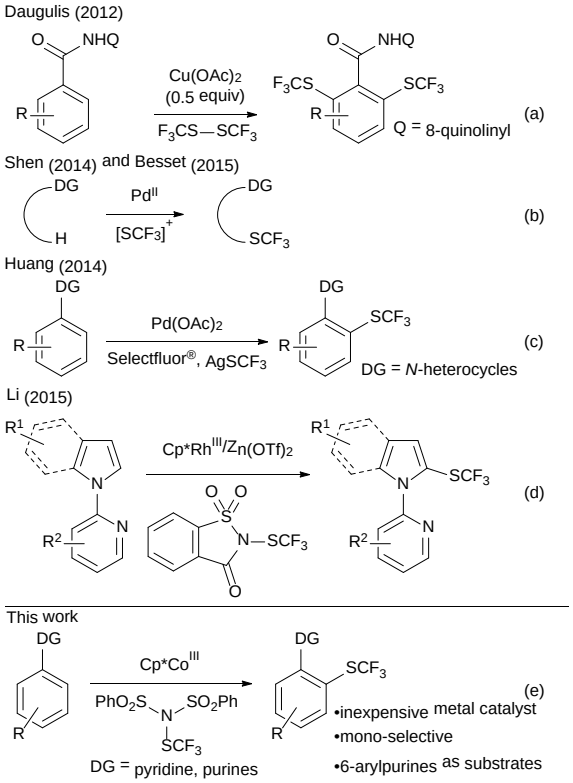
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Misaki Yoshida,[a] Kentaro Kawai,[a] Ryo Tanaka,[a] Tatsuhiko Yoshino*[a,b] and Shigeki Matsunaga*[a,b]

Cp*Co^{III}-catalyzed directed C-H trifluoromethylthiolation using *N*-trifluoromethylthiodibenzenesulfonimide as an electrophilic SCF_3 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 (SCF_3) group into biologically active molecules improves their bioavailability and transmembrane permeability by increasing their lipophilicity (Hansch parameter π = 1.43).[1] Therefore, a synthetic method for SCF_3-containing compounds can contribute to drug discovery and other biological studies, and has attracted much attention in the organic synthetic community.[2] Most of the classical methods for synthesizing aryl-SCF_3 compounds rely on the conversion of other sulfur-containing functional groups to an SCF_3 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 SCF_3 group to aryl halides using trifluoromethylthiolate anion equivalents, such as $AgSCF_3$, $CuSCF_3$, and NR_4SCF_3, under transition metal-catalyzed cross-coupling conditions.[3-5]

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.[6] In this context, several C-H trifluoromethylthiolation reactions were reported using electrophilic trifluoromethylthiolating reagents[7,8] or oxidative conditions.[9,10] Daugulis and co-workers reported a C-H trifluoromethylthiolation using toxic and volatile $(CF_3S)_2$ and a substoichiometric amount of $Cu(OAc)_2$, but only di-trifluoromethylthiolated products were obtained (Scheme 1a).[7a] Shen,[7b] Besset,[7c] and Huang[9] developed palladium-catalyzed trifluoromethylthiolation (Scheme 1b and 1c), and Li developed a Cp*Rh^{III}-catalyzed trifluoromethylthiolation of indoles and 2-phenylpyridine (Scheme 1d).[7d] Although these reactions using more convenient SCF_3 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



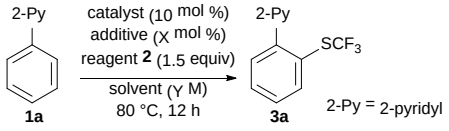
Scheme 1. Transition metal-catalyzed directed C-H trifluoromethylthiolation

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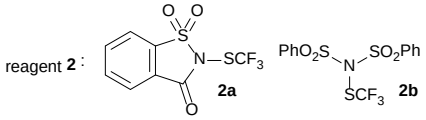
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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Table 1. Optimization of reaction conditions[a]



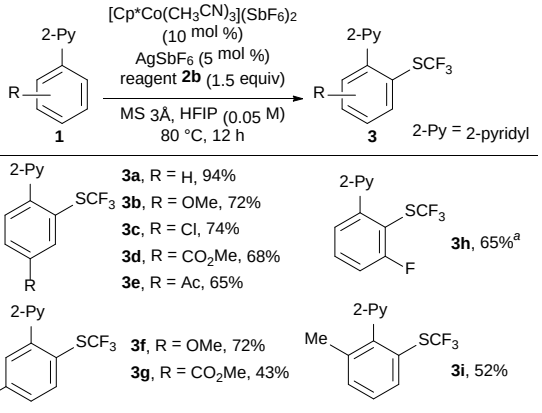
Entry	Catalyst	2	Additive (X)	Solvent (Y)	% Yield[b]
1	$Cp^*Co(CH_3CN)_3(SbF_6)_2$	**2a**	none	DCE (0.2)	11
2	$Cp^*Co(CH_3CN)_3(SbF_6)_2$	**2a**	none	toluene (0.2)	7
3	$Cp^*Co(CH_3CN)_3(SbF_6)_2$	**2a**	none	TFE (0.2)	26
4	$Cp^*Co(CH_3CN)_3(SbF_6)_2$	**2a**	none	HFIP (0.2)	46
5	$Cp^*Co(CO)I_2$/2$AgSbF_6$	**2a**	none	HFIP (0.2)	20
6	$Cp^*Co(CH_3CN)_3(SbF_6)_2$	**2a**	KOAc (20)	HFIP (0.2)	40
7	$Cp^*Co(CH_3CN)_3(SbF_6)_2$	**2a**	AgOAc (20)	HFIP (0.2)	36
8	$Cp^*Co(CH_3CN)_3(SbF_6)_2$	**2a**	none	HFIP (0.05)	43
9	$Cp^*Co(CH_3CN)_3(SbF_6)_2$	**2b**	none	HFIP (0.2)	17
10	$Cp^*Co(CH_3CN)_3(SbF_6)_2$	**2b**	none	HFIP (0.05)	51
11[c]	$Cp^*Co(CH_3CN)_3(SbF_6)_2$	**2b**	none	HFIP (0.05)	72
12[c]	$Cp^*Co(CH_3CN)_3(SbF_6)_2$	**2b**	$AgSbF_6$ (5)	HFIP (0.05)	94[d]
13[c]	none	**2b**	$AgSbF_6$ (5)	HFIP (0.05)	0



[a]The reactions were run using **1a** (0.10 mmol), **2** (0.15 mmol), catalyst (10 mol %), and additive (5–20 mol %) in the indicated solvent at 80 °C for 12 h. [b]Determined by GC-MS analysis using dodecane as an internal standard. [c]MS 3 Å (200 mg/mmol) was added. [d]Isolated yield in 0.40 mmol scale.

earth-abundant inexpensive first-row transition metal catalyst,[11] and here we report a Cp^*Co^{III}-catalyzed C-H trifluoromethylthiolation of 2-phenylpyridines and 6-arylpurines (Scheme 1e).[12]

We previously reported that Cp^*Co^{III} catalysts act as alternatives to expensive Cp^*Rh^{III} catalysts[13] for C-H functionalization,[14] and we[15] and others[16,17] developed a number of synthetic reactions. The unique properties of cobalt contribute to the distinct reactivity and selectivity of Cp^*Co^{III} catalysis compared with Cp^*Rh^{III}.[18] We envisaged that Cp^*Co^{III} would facilitate S_N-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 $[Cp^*Co(CH_3CN)_3](SbF_6)_2$ and an electrophilic SCF_3 source, *N*-trifluoromethylthiosaccharin **2a**,[8b] which was used in the Cp^*Rh^{III}-catalyzed reaction.[7d] Initial solvent screening revealed that the use of fluorinated solvent led to relatively good reactivity (entries 1–4), and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) afforded the desired trifluoromethylthiolated product **3a** in 46% yield (entry 4). Neither changing the catalyst precursors to $Cp^*Co(CO)I_2$ 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*-trifluoromethylthiodibenzenesulfonimide **2b** is a more electrophilic SCF_3 source.[8g] 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 3Å



Reaction conditions: **1** (0.40 mmol), **2b** (0.60 mmol), $[Cp^*Co(CH_3CN)_3](SbF_6)_2$ (10 mol %), $AgSbF_6$ (5 mol %), and MS 3Å (80 mg) in HFIP (8 mL) at 80 °C for 12 h. The indicated values are isolated yields. [a]Without $AgSbF_6$.

Scheme 2. Substrate scope of 2-phenylpyridines

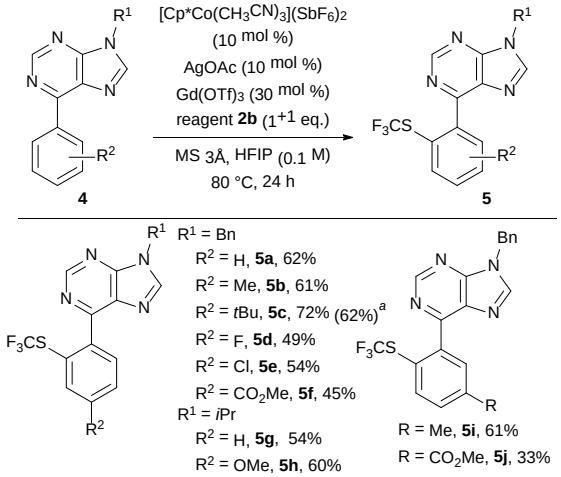
improved the yield probably due to the instability of the highly reactive reagent **2b** towards water (entry 11). Finally, we found a catalytic amount of $AgSbF_6$ as a Lewis acidic additive accelerated the reaction, and product **3a** was isolated in 94% yield under the optimized conditions shown in entry 12. TLC and GC-MS analysis revealed no formation of the di-trifluoromethylthiolated product in all cases probably because the second C-H metalation is hampered by the steric repulsion between the trifluoromethylthio group 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 *o*-position to the fluorine (84:16 by GC-MS analysis) to afford **3h** as a major product.[19]

6-Arylpurines are important molecules in medicinal chemistry due to their anti-mycobacterial, anti-HCV, and cytostatic activity.[20] Although several transition metal-catalyzed directed C-H functionalization reactions have been developed,[16d,h,j,k,18g,21] 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 $[Cp^*Co(CH_3CN)_3](SbF_6)_2$ and reagent **2b** successfully afforded

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desired products **5** in the presence of catalytic amounts of AgOAc and $Gd(OTf)_3$ (Scheme 3). AgOAc would work as a base



Reaction conditions: **4** (0.40 mmol), **2b** (0.40 mmol), $[Cp^*Co(CH_3CN)_3](SbF_6)_2$ (10 mol %), AgOAc (10 mol %), $Gd(OTf)_3$ (30 mol %) and MS 3Å (80 mg) in HFIP (4 mL) at 80 °C for 12 h; then additional **2b** (0.40 mmol) at 80 °C for 12 h. The indicated values are isolated yields. [a]3.0 mmol scale, 85 °C.

Scheme 3. Trifluoromethylthiolation of 6-arylpurines.

to facilitate the C-H activation step,[22] and $Gd(OTf)_3$ was the best Lewis acid among screened. Both benzyl- (**5a–f,i,j**) and 2-propyl- group (**5g**,**h**) on the nitrogen are compatible, and the products were obtained in 33–72% yield. The reaction selectively proceeded at the less hindered position with substrates bearing a *m*-Me and a *m*-CO_2Me group (**5i,j**). We also carried out a gram-scale reaction using **4c**, and the product **5c** was obtained in 62% yield by slightly increasing the reaction temperature, demonstrating the scalability of this transformation.

A proposed catalytic cycle for the trifluoromethylthiolation is shown in Figure 1.[23] The ligand dissociation from $[Cp^*Co(CH_3CN)_3](SbF_6)_2$ would form coordinatively unsaturated intermediate **I**. After the coordination of a substrate, C-H activation is assumed to proceed via aromatic electrophilic substitution or acetate-assisted concerted metalation-deprotonation[22] to afford **II**. The C-H metalation step of **1a** is almost irreversible in the presence of **2b** as indicated by an H/D exchange experiment using **1a**-d_5 (see Supplementary Information). Coordination of reagent **2b** (**III**) and subsequent nucleophilic attack of the Co-C bond to the S-N bond would afford intermediate **IV**. Either $AgSbF_6$ or $Gd(OTf)_3$ might activate **2b** as a Lewis acid to facilitate this C-S bond forming step. Proto-demetalation regenerates the catalyst with the release of product **3** or **5**. We consider that the C-S bond-forming step proceeds via the S_N-type mechanism proposed by Glorius in the Cp^*Co^{III}-catalyzed C-H halogenation reaction.[16a] The addition of TEMPO as a radical scavenger did not completely inhibit the reaction of **1a** (see Supplementary Information), and thus a radical pathway would not be dominant.

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

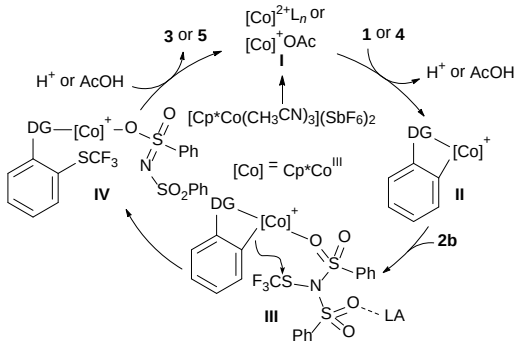


Figure 1. Proposed catalytic cycle for trifluoromethylthiolation of **1** or **4**.

medicinal chemistry.[24]

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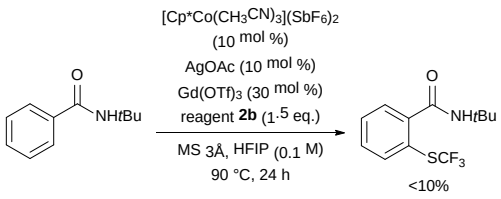
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23 For more details for each substrate, see Supplementary Information.

24 *N*-(tert-butyl)benzamide gave the desired product in less than 10%, and further optimization is required.


[Cp*Co(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
O
NHtBu
O
NHtBu
SCF3

<10%