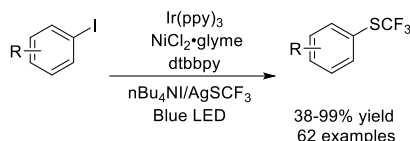


Photoredox-Mediated, Nickel-Catalyzed Trifluoromethylthiolation of Aryl and Heteroaryl Iodides

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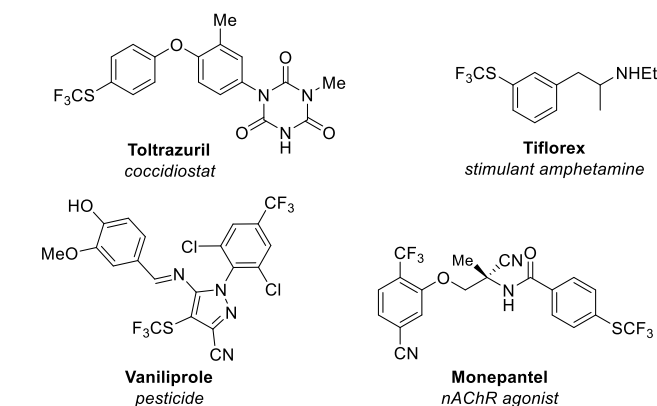
Supporting Information



Abstract: While the area of trifluoromethylthiolation of aryl halides has been extensively explored, the current methods require complex and/or air-sensitive catalysts. Reported here is a method employing a bench-stable nickel(II) salt and an iridium photocatalyst that can mediate the trifluoromethylthiolation of a wide range of electronically diverse aryl and heteroaryl iodides, likely via a Ni(I)/Ni(III) catalytic cycle. The reaction has broad functional group tolerance and potential for application in medicinal chemistry, as demonstrated by a late-stage functionalization approach to access (racemic)-Monepantel.

Aryl SCF₃-containing compounds are important building blocks for the pharmaceutical and agrochemical industry due to the unique properties associated with the trifluoromethylthio (SCF₃) functional group. The SCF₃ functional group has a very large Hansch lipophilicity parameter ($\pi = 1.44$) for its size, making it a useful moiety in the design of bioactive compounds capable of crossing the lipid membrane.¹ Aryl SCF₃ containing compounds are well represented in both pharmaceutical and agrochemical molecules¹ (Scheme 1), highlighting the need for a robust, straightforward methodology to access this functionality.

Scheme 1. Industrially and Pharmaceutically Relevant Aryl SCF₃ Compounds

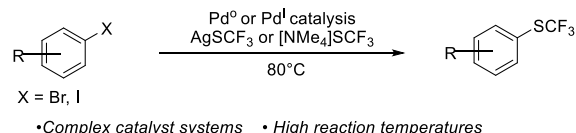


The synthesis of aryl SCF₃ compounds has been extensively explored utilizing a range of M-SCF₃ sources (M = Ag, Cu, Hg, Me₄N);¹ however, many methods require pre-functionalized arenes that are not readily commercially available.² The more desirable cross coupling of readily available aryl halides with anionic SCF₃ under mild conditions has received considerable attention. The first broad strategy, disclosed by Buchwald and co-workers, utilizes a palladium(0) catalyst and AgSCF₃, and enables the trifluoromethylthiolation of a broad scope of aryl bromides.³ Successful transmetalation of -SCF₃ to the palladium center was shown to be dependent on activation of the poorly nucleophilic AgSCF₃ via formation of a tetraalkyl ammonium iodide -ate complex,

a strategy initially introduced by Adams and Clark.⁴ While a useful approach, the complex, air-sensitive catalyst system and high reaction temperatures required are not particularly practical. Schoenebeck and co-workers disclosed a more robust palladium(I) dimer catalyst strategy using [NMe₄]SCF₃ as a source of -SCF₃ applicable to both aryl iodides and bromides (Scheme 2a).^{5,6}

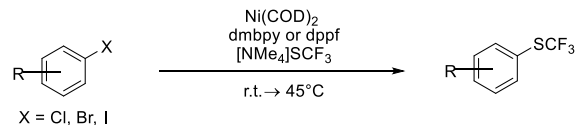
Scheme 2: Previous Methods for Trifluoromethylthiolation of Aryl Halides

a) Previous Work: Palladium (0,I) Catalysis (Buchwald, Schoenebeck)



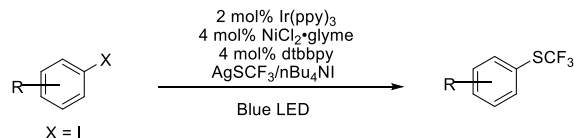
• Complex catalyst systems • High reaction temperatures

b) Previous Work: Nickel (0) Catalysis (Vicic, Schoenebeck)



• Milder reaction conditions • High catalyst loadings
• Air-sensitive catalyst • Electron-poor substrates recalcitrant

c) This Work: Nickel(II)/Iridium Metallaphotoredox



• Low catalyst loadings • Reaction not air-sensitive
• Bench-stable inexpensive reaction components
• Electronically diverse substrates tolerated

More recently, attention has shifted toward using more abundant nickel catalysis to affect the synthesis of aryl SCF₃ compounds. Vicic and co-workers disclosed a room temperature coupling of aryl iodides and bromides using bipyridyl ligated Ni(0); however, the scope was limited to only electron-rich substrates.⁷ Schoenebeck and co-workers demonstrated that using the bulky 1,1'-bis(diphenylphosphino)ferrocene (dppf) ligand to favor a more

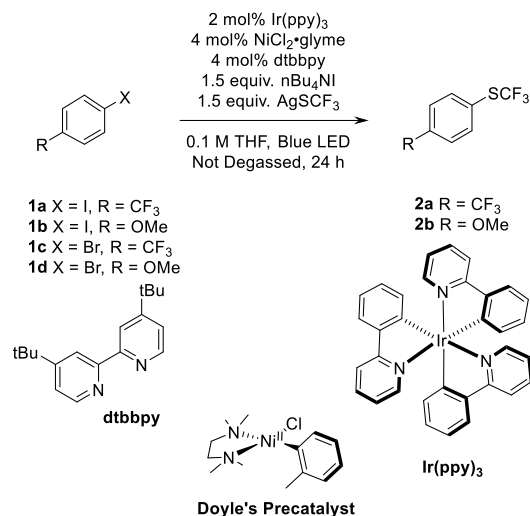
reactive monoligated (dppf)Ni(0)(MeCN) complex allowed access to aryl chlorides as substrates, but aryl bromides and iodides were found to be unreactive (Scheme 2b).⁸ While these studies are substantial advances in the area of trifluoromethylthiolation of aryl halides using earth-abundant nickel catalysts, the current requirement of high catalyst loadings of the air-sensitive Ni(COD)₂ precatalyst limits these transformations to rigorously air-free conditions. Furthermore, they lack the broad substrate scope demonstrated by the previously reported palladium-catalyzed processes.

Our group has recently disclosed a broad, unified method for carbon-heteroatom cross-coupling utilizing a highly reducing Ir(ppy)₃ photocatalyst in the presence of a bipyridyl nickel (II) complex, allowing for the cross coupling of aryl halides with oxygen, nitrogen, and sulfur nucleophiles.⁹ The use of Ir(ppy)₃ displayed wide functional group tolerance, presumably due to the very low oxidation potential of the photocatalyst excited state (0.31 V vs. SCE), which prevents undesirable oxidation of sensitive functional groups. We hypothesized that this would be a viable platform for -SCF₃ couplings under mild, air-tolerant conditions employing bench-stable reagents (Scheme 2c).

Employing electron-poor aryl iodide **1a**, we found that Ir(ppy)₃ in the presence of (dtbbpy)NiCl₂ (dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridyl) gave high yields of the trifluoromethylthiolation product when employing an *in situ* generated 1:1 AgSCF₃/nBu₄Ni ate complex as the nucleophile (Table 1, entry 1). Electron-rich arene **1b** also furnished the desired product in only slightly diminished yield, demonstrating that both electron-rich and electron-poor substrates are viable (entry 2). This reactivity is unique compared to the previous reports with Ni(0) that are far less reactive towards electron-poor aryl iodides.⁶ Conducting the reaction in the absence of the nickel precatalyst, ligand, photocatalyst, and light all resulted in no product formation (entries 3-6). Only trace product was observed in the absence of nBu₄Ni activator, demonstrating the requirement of *in situ* generation of the more nucleophilic silver iodo-ate complex (entry 7). Using previously employed [Me₄N]SCF₃ in place of AgSCF₃ gave no desired product, likely due to the complete decomposition of [Me₄N]SCF₃, as observed by ¹⁹F NMR (entry 8). Utilizing aryl bromides in place of aryl iodides resulted in a lower yield (62%) for electron-poor aryl bromide **1c** and only trace product formation for electron-rich aryl bromide **1d**, suggesting that high barriers to oxidative addition for **1d** are prohibitive (entries 9-10). These findings are consistent with a Ni(I)/Ni(III) cycle in which rate-limiting oxidative addition to Ni(I) is in direct competition with other oxidative deactivation processes, such as comproportionation with Ni(III) or reoxidation by the photocatalyst.¹⁰ Replacing NiCl₂•glyme with NiBr₂•glyme resulted in lower yields of the desired product, possibly due to a greater driving force for transmetalation of AgSCF₃ with dtbbpyNi(I)Cl vs. dtbbpyNi(I)Br (entry 11). A wide range of bipyridyl type ligands work well in this reaction; however, electron-rich ligands tend to give higher yields (entries 12-16). While 4,4'-dimethoxybipyridine gave comparable yields to the standard conditions, higher yields across a broader range of substrates were observed using the optimal conditions with dtbbpy. Since well-established chemistry involving Ni(0) effects trifluoromethylthiolation,⁷ we wondered if we were generating Ni(0) via two sequential single electron transfer (SET) events. However, conducting the same reaction using Ni(COD)₂ and shielding the reaction from light resulted in no desired product formation, suggesting that a Ni(0)/Ni(II) cycle is not active without reductive elimination from Ni(II) requiring photocatalyst excitation (entry 17). However, in the presence of light, employing Doyle's Ni(0) precatalyst [(TMEDA)Ni(o-tolyl)Cl] or Ni(COD)₂ in place of

NiCl₂•glyme resulted in only slightly diminished yields of the desired product (entries 18-19). These experiments suggest that disproportionation of (dtbbpy)Ni(II)ArX via photocatalyst excitation could generate the active Ni(I) species.¹¹

Table 1: Iridium Photoredox/Ni Dual-Catalyzed Trifluoromethylthiolation of Aryl Iodides: Effect of Reaction Parameters



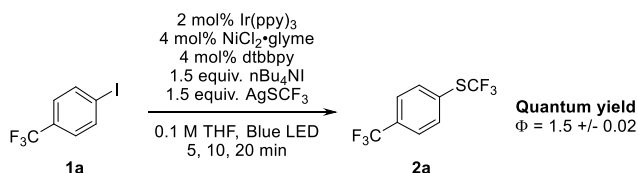
Entry ^a	Variation from Standard Conditions	Yield ^b
1	1a , None	93%
2	1b , None	85%
3	1a , No NiCl ₂ • Glyme	0%
4	1a , No dtbbpy	0%
5	1a , No Photocatalyst	0%
6	1a , No Light	0%
7	1a , No nBu ₄ Ni Activator	9%
8	1a , [Me ₄ N]SCF ₃ instead of AgSCF ₃ Complex	0%
9	1c , None	62%
10	1d , None	2%
11	1a , NiBr ₂ • Glyme	78%
12	1a , 4,4'-dMeObpy	95%
13	1a , 4,4'-dMebpy	81%
14	1a , bpy	78%
15	1a , 4,4'-dPhbpy	74%
16	1a , 4,4'-dCF ₃ bpy	19%
17	1a , Ni(COD) ₂ , No Light	0%
18	1a , [(TMEDA)Ni(o-tolyl)Cl]	79%
19	1a , Ni(COD) ₂	74%

a) Reactions conducted in a HepatoChem PhotoRedOx box with 440 nm Kessil LED at 0.3 mmol scale, without cooling (internal reaction temperature = 55°C). b) Yields determined by ¹⁹F NMR analysis using 1,4-difluorobenzene as an internal standard.

Having established that light input is required for productive reactivity, we wondered whether the reaction proceeds via a closed cycle with the iridium photocatalyst or if the photocatalyst instead

initiates a self-sustaining Ni(I)/Ni(III) cycle. A quantum yield of 1.5 was measured at short time points (5, 10, and 20 min), revealing that a thermal Ni(I)/Ni(III) cycle is a substantial component of the observed reactivity (Scheme 3, see Supporting Information for details).^{10,12} As greater than one turnover per photon was observed, it is unlikely that reductive elimination arises from an excited state Ni(II) complex; the quantum yield for such a reaction theoretically cannot exceed one, requiring photonic input for each catalytic turnover.¹¹

Scheme 3: Quantum Yield



Previous studies on photoredox Ni(I)/Ni(III) catalytic cycles demonstrated that higher catalytic efficiency is achieved at lower nickel concentrations. This is a consequence of deleterious bimetallic comproportionation reactions that lead to off-cycle Ni(II) complexes at higher catalyst concentrations.¹² The relationship between nickel catalyst loading and yield at short reaction times was probed (Table 2); we found that varying the nickel/dtbbpy complex loading from 0.5–4 mol% gave very similar yields. Higher turnover numbers were observed at lower catalyst loadings (entries 1–3). As the concentration of nickel was increased, lower turnover numbers were observed, until diminished yield at 10 mol% indicated the need to keep the nickel concentration low to prevent facile deactivation by Ni(I)/Ni(III) comproportionation (entry 4).^{10,11}

Table 2: Effect of Nickel Catalyst Loading on Catalyst Turnover

Entry ^a	Nickel/Ligand Loading	Yield ^b	TON
1	0.5 mol%	62%	207
2	2 mol%	68%	57
3	4 mol%	66%	28
4	10 mol%	43%	7

a) Reactions conducted in a HepatoChem PhotoRedOx box with 440 nm Kessil LED at 0.3 mmol scale, without cooling (internal reaction temp = 55°C). b) Yields determined by ¹⁹F NMR analysis using 1,4-difluorobenzene as an internal standard.

Although all mechanistic data suggested the formation of an active Ni(I) species, we wondered if this species arose via photocatalytic single-electron reduction of Ni(II) or disproportionation of an excited state Ni(II) species via triplet sensitization. A screen of homoleptic iridium photocatalysts with similar triplet energies (Table 3, See Supporting Information for photocatalyst structures) demonstrated that photocatalysts with high Ir(III)*/Ir(IV) reduction potentials and lower Ir(IV)/Ir(III) oxidation potentials gave the highest yields, regardless of their triplet energies (entries 1–3). Utilizing a phenazine-based

photocatalyst with a much lower oxidation potential resulted in low yield of the desired product (entry 4). A phenoxazine-based photocatalyst designed to mimic Ir(ppy)₃ in both redox properties and triplet energy resulted in nearly identical yields as those obtained from the optimal conditions (entry 5).

Our current hypothesis is that the reduction of (dtbbpy)Ni(I)Cl from (dtbbpy)Ni(II)Cl₂ (−1.34 V vs. SCE)¹³ by the Ir(III)* excited state is thermodynamically favorable for all catalysts tested. However, photocatalysts with higher Ir(IV) oxidation potentials are more effective at reoxidation of Ni(I), thus depleting the active Ni(I) species in solution, resulting in lower yields. While reoxidation of Ni(I) depletes the active catalyst, it is likely required for photocatalyst turnover and regeneration of the active catalyst, demonstrated by the low yield observed with phenazine photocatalyst, which is likely not oxidizing enough to reoxidize Ni(I) (Table 3, entry 4). Based on the above mechanistic studies, we believe that the photocatalyst reduces Ni(II) to a Ni(I) complex via single-electron transfer (SET) rather than a triplet sensitization manifold. However, without being able to isolate Ni(II) or Ni(SCF₃)bipyridine complexes for stoichiometric studies¹⁴ it is unclear which nickel species is reduced by the photocatalyst and at what stage of the catalytic cycle transmetalation occurs.

Table 3: Photocatalyst Screen: Reduction vs. Triplet Sensitization

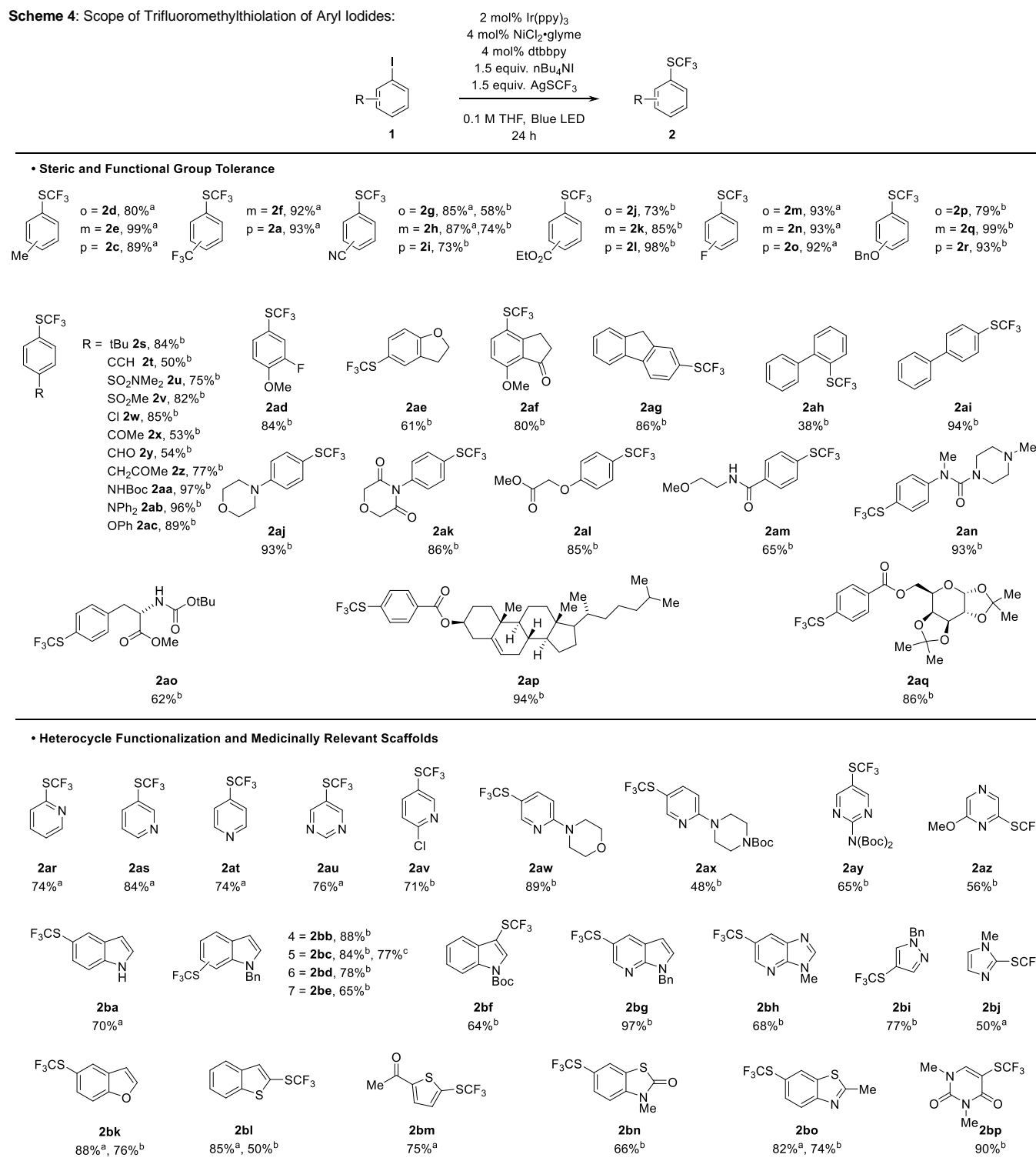
Entry ^a	Photocatalyst	E^0 (² PC* / PC')	$E_{1/2}$ (² PC* / PC)	E_{Triplet} kcal/mol	Yield ^b
1	Ir(ppy) ₃ ¹⁵	−1.77 V	+0.73 V	55.2	56%
2	Ir(p-Fppy) ₃ ¹⁵	−1.60 V	+0.97 V	58.6	45%
3	Ir(dFppy) ₃ ¹⁵	−1.44 V	+1.13 V	60.1	10%
4	Phenazine PC ¹⁶	−1.67 V	+0.21 V	43.8	7%
5	Phenoxazine PC ¹⁶	−1.80 V	+0.65 V	56.5	58%

a) Reactions conducted in a HepatoChem PhotoRedOx box with 440 nm Kessil LED at 0.3 mmol scale, without cooling (internal reaction temp = 55°C). b) Yields determined by ¹⁹F NMR analysis using 1,4-difluorobenzene as an internal standard.

The light dependence of the reaction was examined using on/off experiments to assess the lifetime of the Ni(I) active catalyst. In the absence of light, the reaction rapidly stalled, demonstrating the short lifetime of the active Ni(I) species (See Supporting Information). This finding, combined with the quantum yield not greatly exceeding one, indicates that the active nickel catalyst rapidly undergoes deactivation, likely to a Ni(II) species via Ni(I)/Ni(III) comproportionation or Ir(IV) reoxidation. This establishes the importance of perpetual re-formation of the active catalyst via the photocatalyst cycle.

With optimized reaction conditions for trifluoromethylthiolation, we set out to explore the substrate scope (Scheme 4). A range of both electronically neutral (−Me), electron-withdrawing (−CF₃, −CN, −CO₂Et, −F) and electron-donating (−OBn) substituents are well tolerated at all positions on the aryl ring, res-

Scheme 4: Scope of Trifluoromethylthiolation of Aryl Iodides:



a) Reactions conducted in HepatoChem PhotoRedOx box with 440 nm kessil LED without the cooling fan (internal reaction temp. = 55°C). Reactions conducted on 0.3 mmol scale for NMR yields and 0.5 mmol scale for isolations a) Yield determined by ¹⁹F NMR analysis with trifluorotoluene as an internal standard for volatile compounds. b) Isolated yield

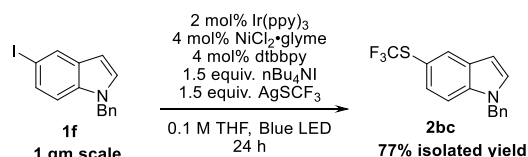
-ulting in only slightly diminished yield for more sterically hindered *ortho*-substituted substrates **2a–2r**. A wide range of functionality is tolerated in the 4-position including terminal alkynes **2t**, sulfonamides **2u**, sulfones **2v**, chlorides **2w**, aldehydes **2y**, ketones **2x**, **2z**, protected amines **2aa–2ab**, and phenyl ethers **2ac**. Substrates bearing multiple ring substitutions and orthogon-

-al electronic affects are also readily functionalized (**2ad–2af**). Biaryl systems are well tolerated (**2ag–2ai**); however, sterically hindered **2ah** resulted in diminished yield. A range of medicinally relevant moieties including morpholines, diketomorpholines, acetate-protected phenols, amides, ureas and protected amino acids are all viable functionality in this transformation (**2aj–2ao**).

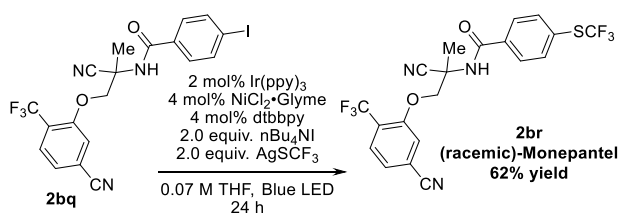
Complex natural products such as cholesterol- and sugar-containing scaffolds are also readily functionalized using this method (**2ap–2aq**).

Upon exploration of the heterocycle scope, we observed that all positions of pyridine are readily functionalized (**2ar–2at**). Substituted pyridines, pyrimidines, and pyrazines **2au–2az** are suitable coupling partners. Unprotected 5-iodoindole **2ba** was readily functionalized; however, protecting the indole nitrogen with commonly used benzyl (Bn) or Boc protecting groups allowed for functionalization of all positions of indole in high yields (64–97% yield) including an aza-indole **2bb–2bg**. Protected imidazoles and pyrazoles, which are important scaffolds in medicinal chemistry, are also viable substrates **2bh–2bj**. Other important medicinal scaffolds including benzofuran, benzothiophene, thiophene, benzothiazalone, benzothiazole, and Uracil all resulted in the formation of desired -SCF₃ products in 50–90% yields (**2bk–2bp**). The reaction is also readily scalable, demonstrated by a gram scale (3 mmol) reaction furnishing **2bc** in 77% isolated yield (Scheme 5). This methodology is amenable to late-stage functionalization, as exemplified by the trifluoromethylthiolation of aryl iodide **2bq** to access (racemic)-Monepantel (**2br**), an aryl SCF₃ containing organic althelmintic (Scheme 6).¹⁷ The broad functional group tolerance, scalability, and demonstration of late-stage functionalization of complex drug scaffolds highlights the possibility for wide utility of this reaction in the drug discovery process.

Scheme 5: Reaction Scalability



Scheme 6: Synthesis of (Racemic)-Monepantel via Late-Stage Functionalization of **2bq**



In summary, we have developed a Ir(III)/Ni(II) metalphotoredox strategy for the trifluoromethylthiolation of (hetero)aryl iodides that employs bench-stable, commercially available components and does not require rigorous exclusion of air or moisture. The reaction has a broad substrate scope, tolerating a wide range of medically relevant scaffolds and allowing for its use in late-stage functionalization to access Monepantel as a racemate. Preliminary mechanistic studies suggest that the facile reduction of a Ni(II) precatalyst by Ir(ppy)₃ likely generates a reactive Ni(I) species that can undergo a Ni(I)/Ni(III) photochemically sustained cycle. We envision application of this strategy to other nucleophiles upon further study.

ASSOCIATED CONTENT

Supporting information

The Supporting Information is available free of charge.

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Notes

The authors declare no competing financial interest.

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