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Chemoselective nickel-catalyzed difluoromethylation of aryl halides with (SIPr)AgCF₂H as transmetalation reagent
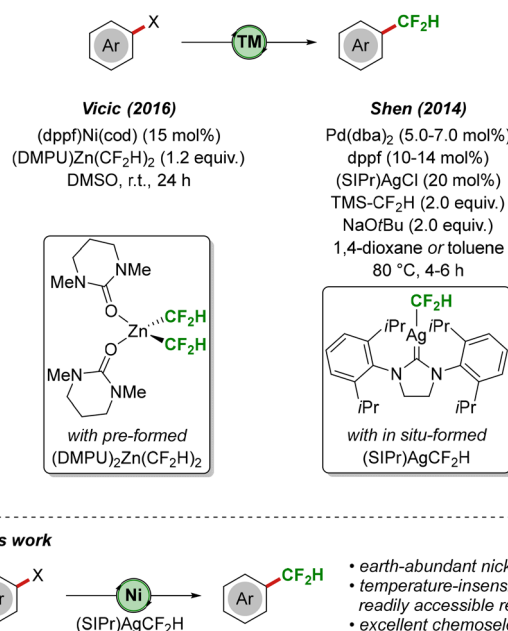
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A user-friendly method for the difluoromethylation of aryl iodides under nickel catalysis has been developed, employing readily accessible, light- and temperature-insensitive (SIPr)AgCF$_2$H as CF$_2$H source. A variety of electronically diverse arenes was smoothly transformed and the reaction displayed excellent levels of chemoselectivity, tolerating *inter alia* synthetically valuable triflates.

Difluoromethylated molecules have attracted considerable attention due to their unique properties, such as an increased lipophilicity, strong hydrogen bonding and high metabolic stability. Furthermore, difluoromethyl substituents are considered bioisosteres of hydroxy, thio and amino groups and have consequently found widespread application in agrochemicals[1] and medicinal chemistry.[2] Over the past decade, a number of difluoromethylation strategies has been developed under thermal as well as photochemical conditions.[3] In particular, transition metal-mediated or -catalyzed approaches have proven highly efficient, utilizing *inter alia*[4] copper[5] and palladium.[6] In a seminal report, Vicic reported the direct difluoromethylation of aryl (pseudo-)halides under nickel catalysis (Scheme 1, top).[7] Key to success was the use of a novel difluoromethyl source, (DMPU)$_2$Zn(CF$_2$H)$_2$, which was accessed from ZnEt$_2$ and HCF$_2$I.[8] In addition, Shen demonstrated a palladium/silver co-catalyzed difluoromethylation of aryl iodides and bromides, proceeding *via in situ*-generation of the (NHC)silver(ı)difluoromethyl complex (SIPr)AgCF$_2$H.[9] The same group later extended their strategy towards the transformation of (hetero)aryl (pseudo-)halides, albeit requiring the use of stoichiometric amounts of pre-formed (SIPr)AgCF$_2$H.[10]

In light of the continuing demand for new, user-friendly strategies for the selective installation of difluoromethyl groups in organic molecules, we set out to explore whether (SIPr)AgCF$_2$H can serve as a light- and temperature-insensitive, easily accessible reagent[11] in earth-abundant nickel-catalyzed difluoromethylations

of aryl halides, on which we report herein (Scheme 1, bottom). Notable results of this study comprise (i) an efficient transformation of aryl iodides bearing electron-donating as well as electron-withdrawing functional groups, (ii) excellent levels of chemoselectivity (I > Br ≫ OTf, Cl), (iii) very good scalability of the reaction, and (iv) the use of apolar reaction media and mild reaction conditions.

We initiated our investigation by exploring different reaction conditions for the envisioned difluoromethylation with (SIPr)AgCF$_2$H, employing methyl 4-iodobenzoate (**1a**) as substrate (Table 1 and Table S-1 in the SI). While the use of 4,4′-bis(*tert*-butyl)-2,2′-bipyridine (dtbbpy) or dppe as ligand resulted in an unsatisfactory reaction outcome, significant amounts of product **2a** were formed with dppf and Xantphos,

Scheme 1 Transition metal-catalyzed difluoromethylation of aryl (pseudo-)halides.

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Table 1 Optimization studies for difluoromethylation of aryl halides under nickel catalysis[a]

Entry	Ligand (x mol%)	T/°C	Yield/%
1	dtbbpy (10)	90	8
2	dppe (10)	90	9
3	dppf (10)	90	27
4	Xantphos (10)	90	46
5	Xantphos (15)	90	67
6[b]	Xantphos (15)	90	80
7[b]	**Xantphos (15)**	**60**	**89 (70)**
8[b]	Xantphos (15)	40	84
9[b]	Xantphos (15)	r.t.	68
10[bc]	Xantphos (15)	60	63
11[bd]	Xantphos (15)	60	Traces
12[b]	—	60	n.d.
13[be]	Xantphos (15)	60	n.d.

[a] Reaction conditions: **1a** (0.10 mmol), Ni(cod)$_2$ (10 mol%), **L** (10–15 mol%), (SIPr)AgCF$_2$H (0.11 mmol), 1,4-dioxane (1.0 mL), 16 h. Yields were determined by GC analysis with n-decane as internal standard. Isolated yield (0.20 mmol scale) is shown in parenthesis. [b] In toluene (1.0 mL). [c] Aryl bromide (**1a′**) used instead of **1a**. [d] Aryl triflate (**1a″**) or aryl nonaflate (**1a‴**) used instead of **1a**. [e] Without Ni(cod)$_2$.

with Xantphos proving optimal (entries 1–4). Increasing the amount of Xantphos to 15 mol% and employing toluene as reaction medium led to a further improved outcome (entries 5 and 6). Surprisingly, lowering the temperature to 60 °C proved beneficial, which can likely be attributed to a higher stability of the employed (SIPr)AgCF$_2$H reagent at milder reaction temperatures (entry 7). The reaction also proceeded smoothly at even lower temperatures of 40 °C and room temperature, albeit with a decreased yield (entries 8-9). Replacing aryl iodide **1a** with less reactive methyl 4-bromobenzoate (**1a′**) led to formation of the desired product **2a** in 63% (entry 10). In contrast, **2a** was detected in only trace amounts, when the corresponding triflate (**1a″**) or nonaflate (**1a‴**) was employed as the substrate (entry 11). Furthermore, no desired product was formed in the absence of either Xantphos or Ni(cod)$_2$ (entries 12-13).

With the optimized reaction conditions identified, the scope of the nickel-catalyzed difluoromethylation was explored with diversely substituted aryl iodides and as well as some aryl bromides (Scheme 2). A broad range of electron-withdrawing substituents, such as ester (**2a** and **2b**), acetyl (**2m**) and trifluoromethyl (**2p**), was well-tolerated in the para- and meta-position, even on 1.0 mmol scale. Substrates bearing sterically demanding substituents in ortho-position delivered the desired products **2c** and **2i** only in low yield and significant amounts of unreacted starting material were observed. Furthermore, substrates bearing electron-donating functional groups, e.g. ortho-, meta- and para-methylether (**2d–2f**), phenylether (**2g**) and thioether (**2l**), reacted smoothly. In contrast, alkyl substitution (**2k** and **2s**) resulted in a significantly diminished conversion – an effect that was also previously noted by Vicic.[7] In addition to
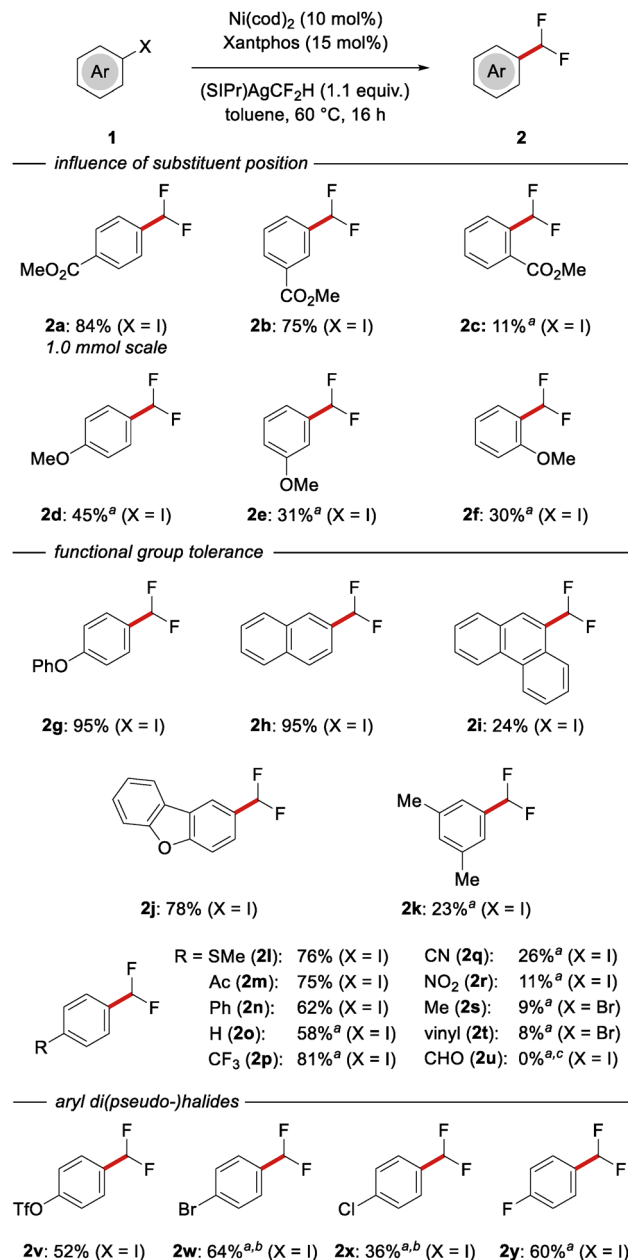
Scheme 2 Scope of the nickel-catalyzed difluoromethylation. [a] Determined by ^{19}F NMR spectroscopy with 4-fluorotoluene as internal standard. [b] Traces (< 2%) of disubstituted product were detected. [c] Decomposition of starting material was observed.

phenyl substrates, the transformation was likewise applicable to naphthyl, phenanthryl and dibenzofuranyl halides, delivering the desired products **2h**, **2i** and **2j** in excellent to low yield. Other heterocyclic substrates, such as benzofuran and benzothiophene, have thus far proven unsuccessful. Gratifyingly, and in contrast to previous reports,[7] excellent levels of chemoselectivity were observed, when aryl di(pseudo-)halides were employed as substrates. When 4-iodophenyl triflate (**1v**) or 4-iodophenyl bromide (**1w**) were subjected to the reaction conditions, the reaction took place at the iodide, delivering products **2v** and **2w** in 52% and 64% yield, respectively, and preserving
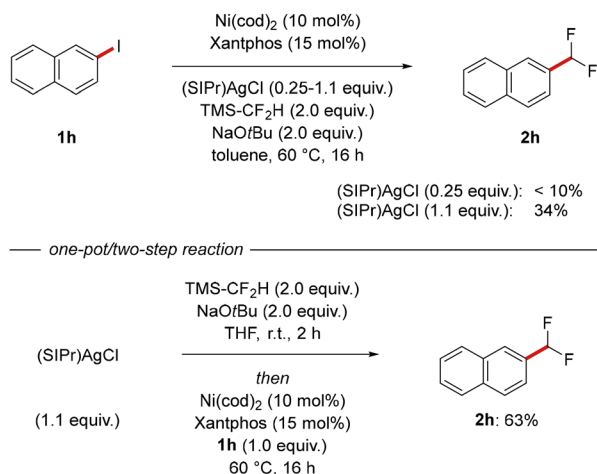
Scheme 3 Difluoromethylation with *in situ*-generated (SIPr)AgCF$_2$H.
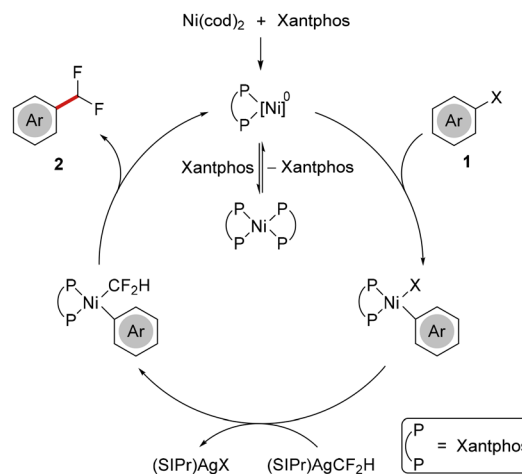
Scheme 4 Plausible catalytic cycle (X = I, Br).

the (pseudo-)halide motif as a convenient synthetic handle for further diversifications. Surprisingly, when 4-iodobenzonitrile (**1q**), 4-iodo-nitrobenzene (**1r**) or 4-bromostyrene (**1t**) were employed as substrates, the desired products were only obtained in low yields, which can likely be attributed to an unfavorable coordination of the cyano, nitro and vinyl substituent to either the nickel catalyst or the silver reagent. Indeed, when the transformation of **1a** was performed in the presence of 0.5 equiv. of styrene or benzonitrile, the yield dropped from 89% (Table 1, entry 7) to 77% and 54%, respectively (for details, see the SI). A carbaldehyde substituent was not tolerated under the reaction conditions and decomposition of the substrate was observed.

In a next step, we investigated whether our approach is amendable to the *in situ*-formation of (SIPr)AgCF$_2$H from bench-stable (SIPr)AgCl, (difluoromethyl)trimethylsilane and sodium *tert*-butoxide. When catalytic amounts of (SIPr)AgCl were employed, negligible amounts of desired product were detected (Scheme 3, top). However, in the presence of stoichiometric amounts of (SIPr)AgCl, (difluoromethyl)naphthalene (**2h**) was obtained in 34% isolated yield. A one-pot/two-step approach led to an improved efficacy of the transformation, delivering **2h** in 63% yield and thus confirming that the use of isolated (SIPr)AgCF$_2$H is not strictly required although being highly beneficial for an optimal reaction outcome (Scheme 3, bottom).

A plausible reaction mechanism proceeds with formation of a [(Xantphos)Ni]^0 species, which can likely be stabilized through reversible coordination of a second Xantphos ligand. Thereafter, facile oxidative addition of aryl halide **1** takes place, followed by transmetalation with (SIPr)AgCF$_2$H. Finally, reductive elimination results in the formation of difluoromethylated arene **2** and regenerates the catalytically active [(Xantphos)Ni]^0 complex (Scheme 4).

In conclusion, a new strategy for difluoromethylations of aryl iodides and bromides *via* earth-abundant nickel catalysis with readily accessible and easy-to-handle (SIPr)AgCF$_2$H as difluoromethyl source was developed. The transformation is applicable to a broad range of diversely substituted aryl iodides, tolerating *inter alia* synthetically useful triflates and bromides,

and delivering the desired products in up to 95% isolated yield. Furthermore, *in situ*-formed (SIPr)AgCF$_2$H could also be employed in our strategy, thus allowing for the installation of difluoromethyl motifs in a convenient manner.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: https://doi.org/10.1039/d5cc06479a.

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