Photoredox/Nickel Dual-Catalyzed Reductive Cross Coupling of Aryl Halides Using an Organic Reducing Agent

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ABSTRACT: A successful protocol for the reductive aryl-aryl cross-coupling of polyfluorinated arenes with a broad range of aryl halides has been developed. Sequential carbon-fluorine bond cleavage and carbon-carbon bond formation are two of the important features of the reaction. Addition of an aryl radical anion to a nickel intermediate was achieved for the first time using polyfluoroarenes as radical precursors. This, in combination with the excellent *para*-selectivity, paves the way for the synthesis of various new multifluorinated biaryl compounds.

The combination of visible light with transition metal-catalysis has recently paved the way to more elaborated transformations.¹ The photoredox cycle serves as a milder alternative for an oxidant or reductant,^{2,1g} as an energy-transfer-agent,³ or it directly intercepts the transition metal catalytic cycle.⁴ In the latter case, a free radical species, generated by the photoredox cycle, reacts with an in situ formed organometallic intermediate to furnish a new organometallic species (Scheme 1). This single-electron step provides either improved reactivity or an alternative to the traditional two-electron steps of transition metal-catalysis.

Nickel salts are among the most versatile metal catalysts applied in the field of metallaphotoredox chemistry, being employed in various C-C^{3c,d,4,6} and C-X (X=heteroatom)^{2d,3b,3e,5} bond formation reactions. Regarding the C-C bond formation reactions, these have been mainly limited to C(sp³)-C(sp³/sp²/sp) variants with a few exceptions involving acyl radicals.⁶ This is because the photochemically generated free radical has almost always been a C(sp³)-centered radical. From a mechanistic point of view, generating and handling C(sp²)-centered aryl and vinyl radicals is more difficult, as these radicals are less stable and often cause undesired side reactions leading to an inefficient catalytic cycle.⁷ This problem does not arise in the case of alkyl and acyl radicals, as they are more stabilized compared to the aryl and vinyl radicals.

Scheme 1.

Previous work:

When **R·** is a C(sp³) centered radical: MacMillan, Molander, Doyle, Rueping
When **R·** is a heteroatom centered radical: Johannes, Molander, Xiao, Rueping

This work: aryl radical cross coupling

When **R·** is an **aryl** radical: C(sp²)-C(sp²) bond formation.

Therefore, we took the endeavor to photochemically generate an aryl radical and use it in a nickel/photoredox catalytic cycle to perform aryl-aryl reductive cross-couplings (Scheme 1). Reductive cross-coupling reactions of C(sp²) electrophiles have been extensively studied since the discovery of the Ullmann reaction.^{8,9} However, they involve either superstoichiometric amounts of metallic reducing agents (Zn, Mn, Mg etc.)⁸ or sacrificial metallic electrodes (Zn, Mg, Fe)⁹ which produce substantial amount of metal-waste. In this regard, our method could offer a valuable alternative as we aimed to use an organic reductant¹⁰ (e.g. an amine) for the reductive quenching of the photocatalyst.

Under photoredox conditions, aryl halides ranging from aryl iodides¹¹ to polyfluoroarenes¹² have been successfully reduced to the corresponding aryl radicals *via* electron transfer. As such, we started our investigation with electron-deficient pentafluoropyridine (**1a**) as radical precursor since it gives a longer-lived radical anion upon single-electron-reduction.¹² In the initial trials, **1a** was subjected to reaction with 2-naphthyl triflate in the presence of Ir(ppy)₃ as photocatalyst under irradiation with blue LED strips with DIPEA (ⁱPr₂NEt) as reducing agent and acetonitrile as solvent. Unfortunately, none of the three different nickel salts used along with a phosphine ligand gave rise to our desired product (see Supporting Information, Table S1). However, we observed trace amount of the hydrodefluorinated side-product in GC-MS.^{11d} This observation is in line with the findings of Weaver^{12a,f} and Hashmi^{12e} in their C-F functionalization approach. Assuming that the DIPEA radical cation [ⁱPr₂NEt]^{•+} is the source of H-atoms (see also Scheme 5a), we hoped that a tertiary amine with no α -hydrogen atoms could furnish the desired product. However, using triphenylamine under otherwise identical conditions failed as well. Notably, the hydrodefluorinated side-product was not observed any more. Switching to other nickel salts, solvents and ligands did not improve the reaction outcome either.

Table 1. Optimization of the reaction conditions^a

Photocatalyst (PC)

Ligand L1

Reductant

entry	deviation from standard conditions	result
1	none	65% ^b
2	1 equiv of 1a was used	43% ^c
3	1 equiv 1a and 2 equiv 2a was used	55% ^c
4	1.5 equiv of ⁱ Pr ₂ NEt used	61% ^b
5	Without photocatalyst	No reaction
6	Without NiCl ₂ ·6H ₂ O	No desired product ^d
7	Without ⁱ Pr ₂ NEt	No reaction
8	In the dark	No reaction

^aReaction conditions: **1a** (0.2 mmol, 2 equiv), **2a** (0.1 mmol, 1 equiv), photocatalyst (0.002 mmol, 2 mol%), nickel salt (0.01 mmol, 10 mol%), **L1** (0.025 mmol, 25 mol%), amine (0.2 mmol, 2 equiv) and base (0.2 mmol, 2 equiv) in 1 mL of solvent under argon for 22 hrs; ^bYield after isolation; ^cNMR yield calculated from ¹⁹F NMR with PhCF₃ (0.2 mmol) as internal standard; ^d**1a** remaining: 39%; HDF side-product: 12%.

We hypothesized that the H-atom donation from [ⁱPr₂NEt]^{•+} could be suppressed by deprotonating the α -position with a stronger base as shown by Hashmi and Weaver.^{13, 12b,e,h} Also, a

photocatalyst which is cationic in its ground-state [unlike Ir(ppy)₃], might stabilize the [C₅F₅N]^{•+} radical anion.^{12e} Therefore, we decided to conduct the reaction replacing Ir(ppy)₃ with [Ir(ppy)₂dtbbpy]PF₆ in the presence of an inorganic base i.e. cesium carbonate. However, formation of side-products arising from the hydrolysis of the triflate substrate was observed. To avoid that, we changed the electrophile to 2-bromo naphthalene (**2a**) and interestingly, the desired cross-coupling product was observed while conducting the reaction in THF. Pleasingly, with addition of Cs₂CO₃, the desired cross-coupling product **3a** was isolated in 65% yield and excellent *para*-selectivity (Table1, entry 1). Varying the stoichiometry of the substrates led to lower yields (entries 2-3). The reaction also worked with similar efficiency with 1.5 equivalents of DIPEA (entry 4). Finally, control experiments showed that each component (photocatalyst, nickel salt, reductant and irradiation) is essential for the reaction to occur (entries 5-8).

Scheme 2. Scope of bromoarenes^a

^aReaction conditions: **1a** (0.2 mmol, 2 equiv), **2** (0.1 mmol, 1 equiv), photocatalyst (0.002 mmol, 2 mol%), nickel salt (0.01 mmol, 10 mol%), **L1** (0.025 mmol, 25 mol%), ⁱPr₂NEt (0.2 mmol, 2 equiv) and Cs₂CO₃ (0.2 mmol, 2 equiv) in THF (1 mL) under argon for 22 hrs.

With the optimized reaction conditions in hand, we explored the scope of the reaction with respect to bromoarenes bearing various substituents and the results are summarized in Scheme 2. Highly electron deficient 4-bromo benzotrifluoride gave the desired cross-coupling product **3b** in 57% yield. The cyano group was tolerated both in the *para* (82%) and *meta* (59%) positions with good to excellent yields (**3c** and **3d**). Esters of bromo substituted benzoic acids worked efficiently as well. The methyl and the benzyl derivatives gave the corresponding desired products **3e** and **3f** in 56% and 53% yields, respectively. The coupling product **3g** was isolated in 67% yield when methyl-(4-bromo phenyl)-sulfone was treated with **1a**. In addition, a heteroaromatic system, bromoquinoline **2h** was also tested and performed well in the desired cross-coupling

reaction, affording **3h** in good yield (73%). To our delight, beside electron-poor arenes, electron-rich naphthalene **2i** also showed excellent reactivity to form **3i** (75%). Next, we tested the reactivity of aryl iodides (Scheme 3). Our first attempt with *para*-iodo toluene afforded **3j** in 75% yield. *Meta*-iodo toluene and *para*-ethyl iodobenzene also reacted well to produce the corresponding coupling products **3k** and **3l** in good yields (81% and 65%). Derivative **3m** was produced in 62% yield when the corresponding substrate containing a *tert*-butyl group was treated with **1a**. Notably, electron rich *para*-iodo anisole also furnished biaryl **3n** efficiently (65%). Acetal functional group was also tolerated on the iodoarene giving the desired product **3o** in 70% yield. Electron-poor 4-fluoroiodobenzene gave the biaryl **3p** in 51% yield. Iodobiphenyl reacted with moderate efficiency and we could isolate **3q** in 47% yield.

Scheme 3. Scope of iodoarenes^a

^aReaction conditions: **1a** (0.2 mmol, 2 equiv), **4** (0.1 mmol, 1 equiv), photocatalyst (0.002 mmol, 2 mol%), nickel salt (0.01 mmol, 10 mol%), **L1** (0.025 mmol, 25 mol%), ^tPr₂NEt (0.2 mmol, 2 equiv) and Cs₂CO₃ (0.2 mmol, 2 equiv) in THF (1 mL) under argon for 22 hrs.

It is worth mentioning that unlike the bromoarenes, the iodoarenes worked with fairly electron rich substrates. This indicates that the ease of oxidative addition by nickel is important for a successful reaction.

We next tested the reactivity of other polyfluorinated arenes under our optimized conditions (Scheme 4). We chose iodoarenes as coupling partners as they showed better reactivity compared to bromoarenes. Reaction of octafluorotoluene (**1b**) with four different iodoarenes resulted in the desired products **5a-d** with moderate yields.¹⁴ Next, we applied pentafluorobenzonitrile (**1c**) in reaction with 4-iodo toluene, and, to our delight, it gave the coupling product **6a** in an excellent yield of 90%. Replacing the methyl group with ethyl and *tert*-butyl did not affect the reactivity and **6b** and **6c** were isolated in 89% and 78% yield, respectively. Use of other perfluoroarenes

resulted in either trace amount of product or no reaction. We performed the reaction to obtain **6a** in 1.0 mmol scale and isolated the desired product in 66% yield (for detailed procedure, see SI).

Scheme 4. Scope of polyfluoroarenes^a

^aReaction conditions: **1b/c** (0.2 mmol, 2 equiv), **4** (0.1 mmol, 1 equiv), photocatalyst (0.002 mmol, 2 mol%), nickel salt (0.01 mmol, 10 mol%), **L1** (0.025 mmol, 25 mol%), ^tPr₂NEt (0.2 mmol, 2 equiv) and Cs₂CO₃ (0.2 mmol, 2 equiv) in THF (1 mL) under argon for 22 hrs. ^bReaction performed on 1 mmol scale.

As mentioned before, 2,3,5,6-tetrafluoropyridine (**7**) was observed as a side-product during the optimization studies. It indicates to an electron transfer process to **1a** with the generation of the radical anion [C₅F₅N]^{•-}. Subsequent H-atom abstraction from ^tPr₂NEt^{•+} (in absence of Cs₂CO₃) and F⁻ elimination, gives rise to the hydrodefluorinated product **7** (Scheme 5a).

However, it may also be envisaged that iodoarenes can be reduced via SET under these conditions. This competition could be avoided by choosing electron-rich and difficult to reduce aryl iodides. To confirm our hypothesis, we performed control experiments (see SI, Table S2). C₅F₅N was irradiated under the optimized conditions in the absence of the nickel salt and ligand and in the presence of 4-iodotoluene, 4-iodo ethylbenzene and 4-iodo *tert*-butyl benzene, in three separate experiments. The nickel catalytic components were left out in order to test the difference in reactivity between **1a** and iodoarenes towards SET.

In all three cases, the perfluoroarene showed higher conversion than the iodoarene after 8 hours. Under our optimized conditions, where the nickel catalyst is present, the SET to Ar-I will be even more suppressed due to an efficient oxidative addition. The major products were perfluoroarylated analogues of DIPEA and THF along with the hydrodeiodinated product (see SI). Notably, ¹⁹F NMR analysis (prior to work up) showed that the hydrodefluorinated product formation was suppressed owing to the presence of Cs₂CO₃. Thus, we decided to investigate whether the unpaired-electron species inter-

cepted by the Ni complex is the stabilized radical anion $[C_5F_5N]^{\bullet-}$ or the $\bullet C_5F_4N$ radical. In principle, the $\bullet C_5F_4N$ radical formed via fluoride fragmentation at the 4-position, should be too unstable to selectively couple with Ni. Instead, it will immediately undergo fast side-reactions with other more abundant reaction components (e.g. HAT from solvent). Therefore, we decided to test the 4-chloro and 4-bromo analogue of **1a** as the perfluoroarene source (Scheme 5b). As per our expectations, Cl- C_5F_4N gave a diminished yield of 56% (determined by NMR) and Br- C_5F_4N gave only 5% of the desired product **3j**. This observation is in line with the relative rate of fragmentation of halides, i.e., $F^- < Cl^- < Br^-$ and indicates that the radical anion $[C_5F_5N]^{\bullet-}$ is more prone to be trapped by Ni, instead of $\bullet C_5F_4N$ radical. Besides, this observation also rules out a mechanism where Ni^0 oxidatively adds to the C-F bond and the subsequent Ni^{II} species traps an aryl radical from aryl iodide- because, in such a case, the reaction with Br- C_5F_4N should have provided a substantial amount of desired coupling product.

Scheme 5. Side reaction and mechanistic experiments.

^aReaction conditions: **8/9/1a** (0.2 mmol, 2 equiv), 4-iodotoluene/**2e** (0.1 mmol, 1 equiv), photocatalyst (0.002 mmol, 2 mol%), nickel salt (0.01 mmol, 10 mol%), **L1** (0.025 mmol, 25 mol%), iPr_2NEt (0.2 mmol, 2 equiv) and Cs_2CO_3 (0.2 mmol, 2 equiv) in THF (1 mL) under argon for 22 hrs; ^bNMR yield calculated from ^{19}F NMR with $PhCF_3$ (0.2 mmol) as internal standard; ^cReaction conditions: **1a** (0.2 mmol, 2 equiv), **10** (0.1 mmol, 1 equiv), photocatalyst (0.002 mmol, 2 mol%), iPr_2NEt (0.2 mmol, 2 equiv) and Cs_2CO_3 (0.2 mmol, 2 equiv) in THF (1 mL) under argon for 22 hrs.

Next, we shifted our focus to identify the Ni species that traps the $[C_5F_5N]^{\bullet-}$. The two most probable candidates are Ni^0 and $Ar-Ni^{II}-X$ (formed via oxidative addition of Ni^0 to ArX) complexes. Therefore, we prepared such a Ni^{II} complex **10** and subjected 0.1 mmol of that under identical photochemical

reaction conditions (Scheme 5c). Interestingly, 18% (NMR yield) of desired cross-coupled product was formed (average of two experiments). This shows us that, $Ar-Ni^{II}-X$ can intercept **A**. In a separate experiment, when we used the complex **10** as the nickel catalyst in our otherwise unchanged reaction conditions, the NMR yield of **3e** increased to 39% (Scheme 5d). In this case, the nickel catalytic cycle is initiated by **10** intercepting **A**, thereby prompting us to propose a similar mechanism for our reactions as well, where $NiCl_2 \cdot 6H_2O$ is used as catalyst (Scheme 6).

Based on our observations and previous reports on both Ni/photoredox¹⁵ and polyfluoroarene systems,^{12a,e,f} a plausible mechanism is outlined in Scheme 6. In the first step, iPr_2NEt [$E_{1/2}^{ox} = +0.68$ V vs. SCE]^{16a} is oxidized by the photoexcited Ir^{III} [$E(*Ir^{III}/Ir^{II}) = +0.66$ V vs. SCE]^{16b} to give a highly reducing Ir^{II} [$E(Ir^{III/II}) = -1.51$ V vs. SCE]^{16b} species. The Ir^{II} then makes an endergonic electron transfer to C_5F_5N [$E_{1/2}^{red} = -2.12$ V vs. SCE] driven by the electrostatic stabilization of $[C_5F_5N]^{\bullet-}$ by the ground-state cationic Ir^{III} photocatalyst.^{12c} Subsequently, the stabilized and longer-lived radical anion **A** reacts with a Ni^{II} species **B** to form Ni^{III} intermediate **C** after F^- elimination. Upon subsequent reductive elimination, the cross-coupling product and Ni^I complex **D** are formed. Finally, **D** is reduced via electron transfer to give Ni^0 which does oxidative addition to the aryl halide to regenerate **B** and that completes the catalytic cycle. The other plausible underlying mechanism where Ni^0 traps the $[C_5F_5N]^{\bullet-}$ first and the resulting Ni^I complex **E** oxidatively adds to the aryl halide is also depicted in Scheme 6.¹⁷

Scheme 6. Plausible mechanism.

In conclusion, we described the first reductive aryl-aryl cross-coupling utilizing a combination of photoredox and nickel catalysis. The stability of the resulting radical anion arising from the reduction of polyfluoroarenes was exploited in reaction with a catalytic nickel intermediate. The transformation could be applied to the synthesis of multifluorinated compounds in moderate to excellent yields, starting from different aryl fluorides and a broad scope of electron-rich as well as

electron-deficient aryl bromides and iodides. The use of an organic reducing agent instead of a metal reductant, mild reaction conditions, and an excellent *para*-selectivity make this approach a valuable alternative to reported reductive cross-coupling methods.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Supplementary table for optimization, detailed experimental procedure, spectral data and ^1H , ^{13}C and ^{19}F spectra for all compounds.

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Notes

Any additional relevant notes should be placed here.

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ABBREVIATIONS

LED, Light-Emitting Diode; DIPEA, Diisopropylethylamine; THF, Tetrahydrofuran; SI, Supporting Information; PC, Photocatalyst; GC-MS, Gas Chromatography-Mass Spectrometry; HPLC, High-performance Liquid Chromatography; HAT, Hydrogen Atom Transfer.

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