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Harnessing the Intrinsic Reactivity of 2-Cyano-Substituted Heteroarenes to Achieve Programmable Double Alkylation

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Abstract. Herein, we report our study of tertiary radicals, generated through visible light decarboxylation, alkylating 2-cyanoarenes through radical cross-coupling at the *ipso*- or the *para*- positions of the cyano groups. Synthesis of a variety of α-tertiary amines containing quaternary centers is described. The approach enables regioselective sequential double alkylation on either 2-cyanopyridine or 2-cyanopyrimidine with high efficiency. Our report illustrates the synthetic utility of α-heteroatom-substituted tertiary radicals in the synthesis of substituted heteroarenes.

Keywords: photocatalysis; heterocycles; radical reactions; C-C coupling

Heterocycles are important pharmacophores in small molecule drug discovery and hence synthetic methods to readily modify them are strategically important in expanding structure-activity relationship (SAR) studies in modern pharmaceutical research.[1] Recent innovative photoredox methods have made tremendous progress in radical-based alkylation on heteroarenes.[2] These established methods include photoredox/nickel dual catalysis developed by MacMillan, Molander and Doyle,[3] photo-Minisci reactions advanced by Glorius, Overman, Chen and Wang,[4] and light-mediated alkylation on cyanoarenes via radical-radical coupling described by MacMillan, Smith, Opatz and Wang.[5] Based on the latter methodology, it has been shown that 4-substituted pyridines can be synthesized from 4-cyanopyridine via SET reduction to the corresponding radical anion, followed by radical addition and decyanation (Scheme 1A).[6] By extension, we postulated that that other cyanoarenes such as 2-cyano-3-(trifluoromethyl)pyridine **1a** and 2-cyanopyrimidine **1b** could potentially be reduced via SET in an analogous manner (Scheme 1B). However, the subsequent cross-coupling on their radical anions might prefer the *para*- position of the cyano group over the *ipso*-addition and decyanation pathway, due to their different spin-density properties. Spin-density controlled regio-selectivity has been previously illustrated by Shteingarts, where an alkaline-metal-mediated 1,2-dicyanobenzene radical anion could be coupled with a variety of alkyl radicals (Scheme 1A).[7] In the Shteingarts study it was shown that the alkyl radical added *para* to the cyclohexadienyl anion species, which was subsequently oxidized and deprotonated to afford the re-aromatized product.

In our proposed studies, we rationalized that as electron-deficient heteroarenes, both **1a** and **1b** could not only serve as effective *para*-coupling partners, but also act as potential oxidants in a catalytic system.[8] This alkylation mode leaves the 2-cyano group in **1c** and **1d** intact, and as a result different alkyl radical can subsequently couple via *ipso*-addition and decyanation (Scheme 1B). To the best of our knowledge, this would represent a novel programmable alkylation strategy towards functionalized heteroarenes. In addition, tertiary radicals with α-heteroatom substitution have not been previously explored in literature. These could be ideal partners for coupling reactions due to their enhanced stability.[9] The difficulty to access α-heteroaryl cyclic amine products otherwise was also an appealing impetus.[10] Herein we report our initial studies using α-NHBoc and other tertiary radicals to alkylate various 2-cyanoarenes under mild non-acidic conditions without addition of external oxidants. Programmable double alkylation was investigated as well.

For our exploratory model study, we utilized a commercially available amino acid **2a** (Scheme 2). When $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ was applied as the catalyst, **2a** underwent successful decarboxylation to generate the corresponding tertiary radical, which subsequently reacted with Michael acceptor **3** to form Giese product **4** in high yields.[11] Under the same conditions, the sp^3-sp^2 radical cross-coupling between **2a** and 5-(trifluoromethyl)-2-cyanopyridine **1e** was observed, with a modest 35% yield of **5a** (Table 1, entry 3). Encouraged by this initial result, we reasoned the bulky *t*-butyl groups on this photocatalyst could potentially impede the substrate-photocatalyst interaction. Subsequent screening of four other common catalysts (Table 1, entry 1, 2, 4, 5) showed

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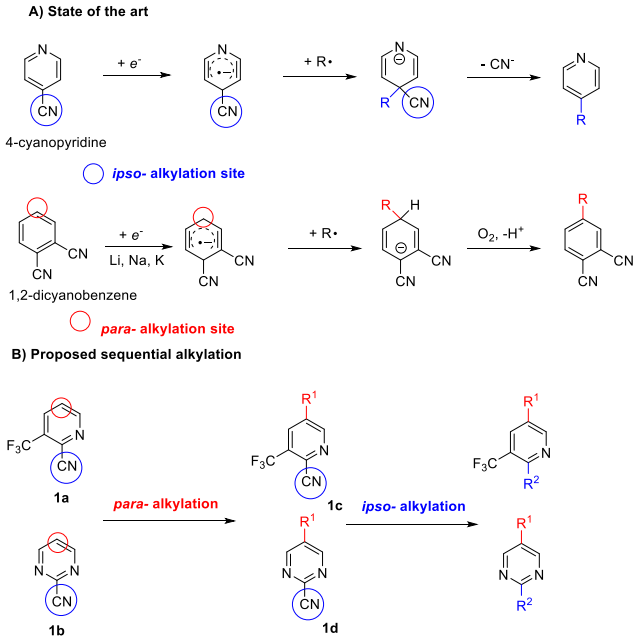
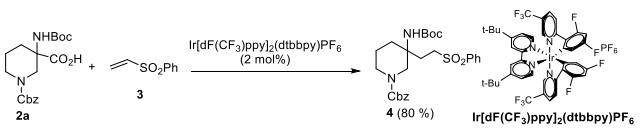
that in fact *fac*-Ir(dfppy)$_3$ was the superior catalyst, yielding 94% of **5a** (Table 1, entry 5). In the following control experiments, we found no reaction occurred under the 26W CFL exposure or without base (Table 1, entry 6, 7). Switching the base to Cs_2CO_3, without N_2 bubbling the yields decreased (Table 1, entry 8, 9). DMF was inferior to DMSO as solvent (Table 1, entry 10). Lower catalyst loading required prolonged reaction time and resulted in a decreased yield (Table 1, entry 11). Using a 40W blue LED lamp under fan-cooling, **1e** (0.37 mmol), **2a** (1.1 mmol), K_2HPO_4 (0.41 mmol) and *fac*-Ir(dfppy)$_3$ (7.4 μmol) in DMSO (12 mL) gave the desired product **5a** in 87% isolated yield.

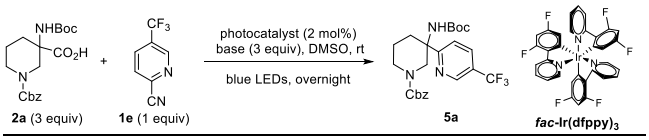


Scheme 1. Proposed 2-cyanoarenes as cross-coupling partners at *para* and *ipso* positions of the cyano groups as a programmable double alkylation strategy.



Scheme 2. Giese addition of acid **2a** and phenyl vinyl sulfone **3**. Reaction conditions: 40W Kessil blue LED lamp under fan-cooling, **2a** 1.1 mmol, **3** 0.37 mmol, K_2HPO_4 0.41 mmol, photocatalyst 7.4 μmol, DMSO 12 mL, 30 min N_2 bubbling, overnight rt.

Table 1. Photoredox radical coupling of acid **2a** and 2-cyanopyridine **1e** to synthesize **5a**.



Entry	Photocatalyst	Base	Yield (%)[a]
1[b]	Ir[*p*-F(t-Bu)-ppy]$_3$	K_2HPO_4	14
2	Ir(ppy)$_2$(dtbbpy)PF$_6$	K_2HPO_4	22
3	Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$	K_2HPO_4	35
4	Ir[dF(Me)ppy]$_2$(dtbbpy)PF$_6$	K_2HPO_4	34
5	*fac*-Ir(dfppy)$_3$	K_2HPO_4	94
6[c]	*fac*-Ir(dfppy)$_3$	K_2HPO_4	0
7	*fac*-Ir(dfppy)$_3$	No base	0
8	*fac*-Ir(dfppy)$_3$	Cs_2CO_3	47
9[d]	*fac*-Ir(dfppy)$_3$	Cs_2CO_3	12
10[e]	*fac*-Ir(dfppy)$_3$	K_2HPO_4	43
11[f]	*fac*-Ir(dfppy)$_3$	K_2HPO_4	59
12[g]	*fac*-Ir(dfppy)$_3$	K_2HPO_4	87

[a] General conditions: Chemtech (2W) blue LED reactor under fan-cooling, **2a** 0.28 mmol, **1e** 0.1 mmol, base 0.1 mmol, photocatalyst 1.9 μmol, DMSO 3 mL, 30 min N_2 bubbling, overnight rt. Yields were determined by LCMS trace integration compared to the standard solution of **5a**.
[b] Structure of the individual photocatalyst is shown in SI.
[c] Compact fluorescent lightbulb as the light source.
[d] No N_2 bubbling.
[e] DMF as the solvent.
[f] 1 mol%, *fac*-Ir(dfppy)$_3$ loading, 48h.
[g] 40 W Kesil blue LED setup as the light source, isolated yield.

With these optimal conditions in hand, we then explored the cyanoarene scope with several different tertiary radicals derived from the corresponding acids (Scheme 3). 1,4-Dicyanobenzene **1d**, a well-known persistent radical source,[5, 6] formed product with cyclic acids (**5b-c)** and α-ether acid (**5d)**. Similarly, 2-cyano-5-(trifluoromethyl)pyridine **1e** reacted with different acids (**5e-f)**. Its regio-isomer 2-cyano-4-(trifluoromethyl)pyridine could also couple to a variety of tertiary radicals (**5g-k).** In **5j**'s case, all carbon 2-methyl-2-phenylpropanoic acid proceeded with a very high yield. 2-Cyano-4-carbomethoxypyridine and 4-cyano-3-fluoropyridine were also suitable substrates (**5l-m**). These examples demonstrated a facile approach to synthesize heteroarenes with steric hindered and challenging substitutions. When natural product Enoxolone was used to react with 2-cyano-4-(trifluoromethyl)pyridine, both cyano *ipso*-substitution product **5n** and 6-proton replaced product **5o** were identified. This observation suggested the multiple roles of 2-cyano-4-(trifluoromethyl)pyridine. It could function as both the coupling partner and an oxidant to drive the photocatalyst mediated oxidation (via anionic radical formation in the system) to furnish the C(sp^2)-H activated product **5o**.

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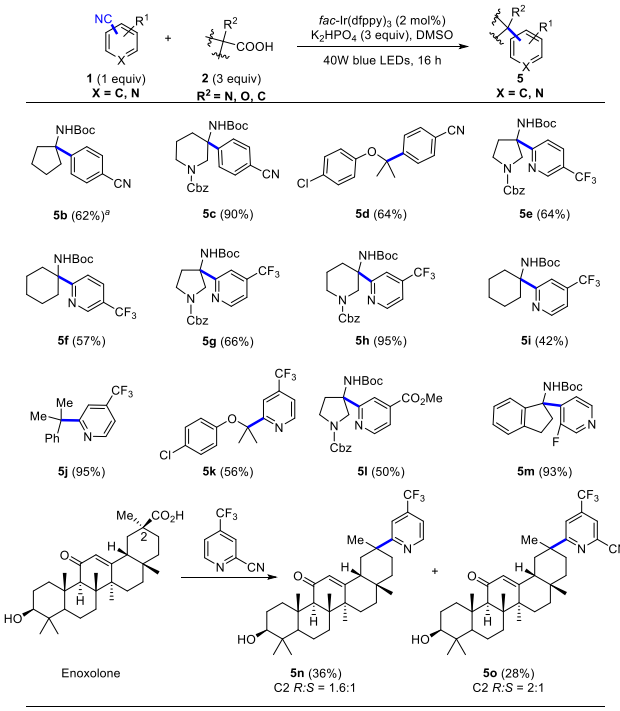
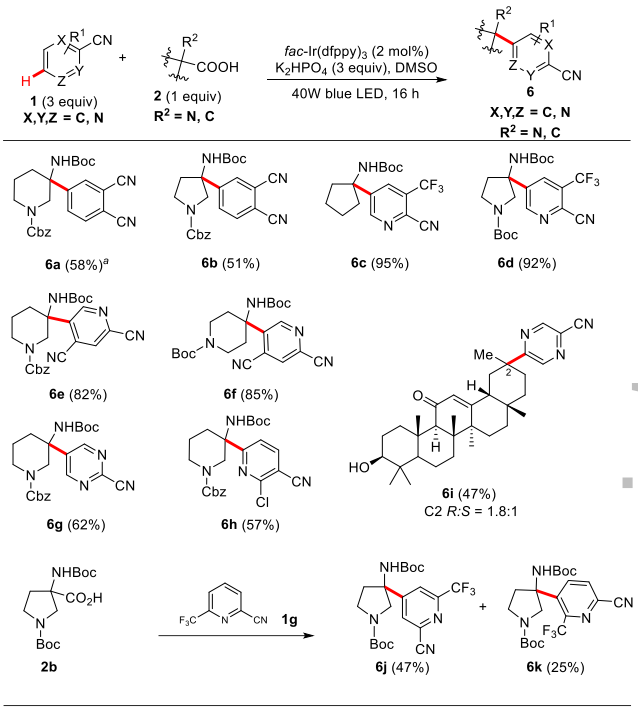


Scheme 3. Cyanoarene *ipso*- cross-coupling with tertiary radicals. [a] Reaction conditions: carboxylic acid **2** (1.0 mmol, 3 equiv), arene/heteroarene **1** (0.33 mmol, 1 equiv), potassium phosphate, dibasic (1.0 mmol, 3 equiv), *fac*-Ir(dfppy)$_3$ (6.5 µmol, 0.02 equiv), DMSO (12 mL), blue LED, RT, 16h. All isolated yields calculated based on arene equiv.

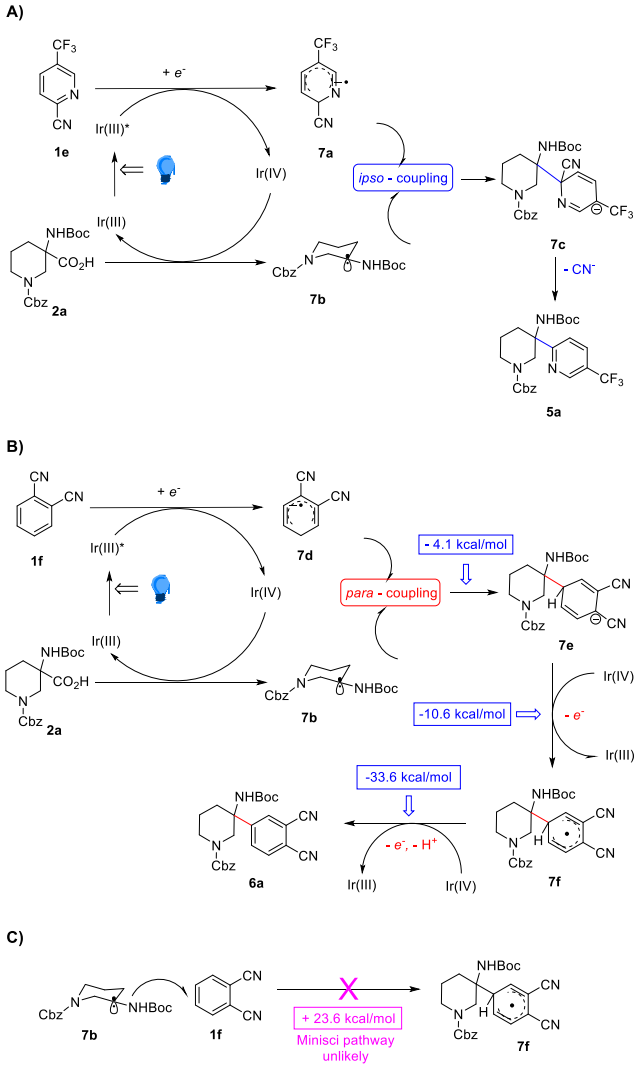


Scheme 4. Cyanoarene para- cross-coupling with tertiary radicals. [a] Reaction conditions: carboxylic acid 2 (0.33 mmol, 1 equiv), arene/heteroarene 1 (1.0 mmol, 3 equiv), potassium phosphate, dibasic (1.0 mmol, 3 equiv), fac-Ir(dfppy)3 (6.5 µmol, 0.02 equiv), DMSO (12 mL), blue LED, RT, 16h. All isolated yields calculated based on acid equiv.

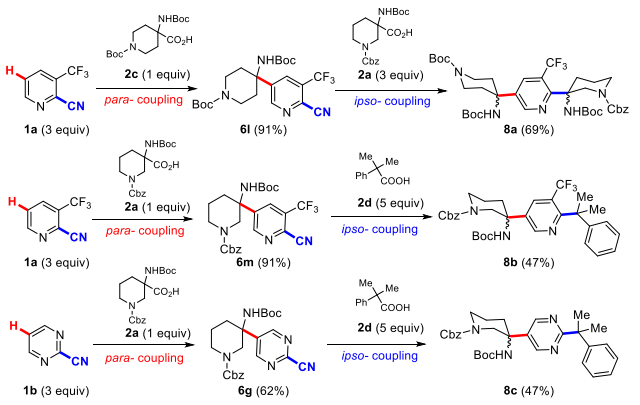
Further study revealed several cyanoarenes only underwent *para*-alkylation and afforded the Ar-H replaced products. Without losing the CN group, only **6a** was isolated when 1,2-dicyanobenzene **1f** reacted with **2a** (Scheme 4). To optimize the reaction yield, we increased arene to acid ratio from 1:3 to 3:1 to ensure enough arenes in the system to act as reactants and oxidants at the same time. This improved the yield of **6a** from 31% to 58% based on limiting reagent **2a**. Similar result was obtained with pyrrolidine acid (**6b**). 2-Cyano-3-(trifluoromethyl)pyridine **1a** and 2,4-dicyanopyridine gave excellent yields reacting with cyclic acids (**6c**-**6f**). 2-Cyanopyrimidine and 2-chloro-3-cyanopyridine were also capable in this "arene-as-oxidant" coupling (**6g-h**). The spin-density of the anionic radical formed likely accounted for the excellent regio-selectivity in most cases. When Enoxolone reacted with pyrazinecarbonitrile, the new C-C bond formed exclusively at the sp^2 carbon *para* to the nitrile group (**6i**). However, steric factors might play a role as well. In the reaction between pyrrolidine acid **2b** and 2-cyano-6-(trifluoromethyl)pyridine **1g**, two isomers were formed. Only 25% of *para*-alkylation product **6k** was isolated while *meta*-alkylation product **6j** (47%) accounted for the majority of the isolated product possibly due to the *meta* position was more accessible.

Mechanism for radical *ipso*-addition to 2-cyano-5-(trifluoromethyl)pyridine **1e** and decyanation was well established in literature (Scheme 5A). [5] The photocatalyst *fac*-Ir(dfppy)$_3$ is transformed to its excited-state Ir(III)* under irradiation. As an excellent reductant ($E_{1/2}^{red}[Ir^{IV}/*Ir^{III}]$ = -1.44 V vs SCE),[5c] it converts **1e** into a persistent radical anion **7a**. The oxidized iridium species Ir(IV) is reduced by the carboxylic acid **2a**, and returns to its baseline state. The resulting tertiary radical **7b** is captured by the persistent radical **7a**. In this event, the spin-density of **7a** predicts an *ipso*-addition to form **7c**, which is then de-cyanated to give **5a**. We propose para- alkylation of 1,2-dicyanobenzene **1f** starts with a similar photocatalytic cycle (Scheme 5B). However, the spin-density of radical anion **7d** makes it couple with the tertiary radical **7b** at the *para*-position toward one of its cyano groups.[12] Our *in silico* calculation (DFT/B3LYP)[13] indicates formation of **7e** has a 4.1 kcal/mol $\Delta G^{\#}$ loss. The subsequent 1e^- oxidation from **7e** to **7f** lowers another 10.6 kcal/mol in $\Delta G^{\#}$. The de-protonation and the second oxidation from **7f** to **6a** brings in a big $\Delta G^{\#}$ loss (-33.6 kcal/mol). Thus, these three thermodynamically downhill events make para-addition hugely favored. In this pathway, two excess equivalent of 1,2-dicyanobenzene **1f** is needed as an oxidant to recycle the Ir catalysts. This fully matches our stoichiometry used (**2a** 1 equiv, **1f** 3 equiv). The

alternative SOMO-LUMO guided Minisci type addition pathway is less likely due to the initial 23.6 kcal/mol $\Delta G^{\#}$ penalty (Scheme 5C).[13]



Scheme 5. A) *ipso*- Alkylation of **2a** (3 equiv) and **1e** (1 equiv). B) *para*- Alkylation of **2a** (1equiv) and **1f** (3 equiv). All Ir(IV) species are formed by arene-driven Ir(III)* oxidation. C) Radical **7b** attacking neutral arene **1f** results in $\Delta G^{\#}$ penalty.



Scheme 6. Programmable alkylation on **1a** or **1b**. All isolated yields calculated based on the limiting substrates.

Combining these two different coupling modes, programmable sequential alkylation was achieved on cyano-heteroarenes **1a** and **1b** respectively (Scheme 6). The first step was a *para*-alkylation, in which the arenes play a 'dual role'. It was followed by *ipso*-alkylation with either α-amino cyclic acid **2a** or all-carbon quaternary acid **2d**. These reactions introduced two highly steric hindered substitutions onto pyridine and pyrimidine regioselectively. The results demonstrated the prowess of this photoredox sequence as an enabling technology in pharmaceutical research to access previously under-explored structures.

In conclusion, we have described a visible-light mediated decarboxylative method to generate various tertiary radicals and coupled them onto cyanoarenes. We explored substrate scopes of the photoredox *ipso*- and *para*-alkylation reactions, and proposed the mechanisms for these two modes in this account. Spin-density calculation could be used to predict this novel photoredox *para*-alkylation on cyanoarenes, expanding its synthetic utility. Our study provided a mild and practical enhancement to the synthetic toolbox of substituted heteroarenes, as illustrated by examples of programmable alkylation on the same cyano-substituted heteroarenes. These scaffolds enriched with sp^3-carbon and stereocenters could serve as better starting points for drug candidates.[14]

Experimental Section

General Procedures 1: For *ipso*-alkylation, to a 40 mL vial containing a stirring bar were the carboxylic acid (1.0 mmol, 3 equiv), potassium phosphate, dibasic (1.0 mmol, 3 equiv), *fac*-Ir(dfppy)$_3$ (6.5 µmol, 0.02 equiv) and arene/heteroarene (0.33 mmol, 1 equiv) mixed in DMSO (Volume:12 mL, ReagentPlus®, Aldrich). The mixture was bubbled by industry grade N_2 using long-neck syringes for 30 min. The cap was wrapped by parafilm. The vial was put on an IKA basic stir plate and was subjected to the 40W Kesil blue LED exposure. The distance of the bulb and the vial was roughly 2~4 cm. Unless noted specifically, the reaction was allowed overnight i.e., 12~16 h. The reaction mixture was poured onto brine and water, the crude product was extracted by ethyl acetate (3 X 40 mL). The organic layer was combined and was dried with $MgSO_4$, then was filtered and concentrated *in vacuo*. The crude product was purified by column chromatography using a Combiflash workstation. Some products were further purified by preparational HPLC.

General procedures 2: For *para*-alkylation, carboxylic acid (1 equiv), arene/heteroarene (3 equiv) and base (1 equiv) were used. Other conditions were the same as in the **general procedures 1**.

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