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Arene Cyanation via Cation-Radical Accelerated-Nucleophilic Aromatic Substitution

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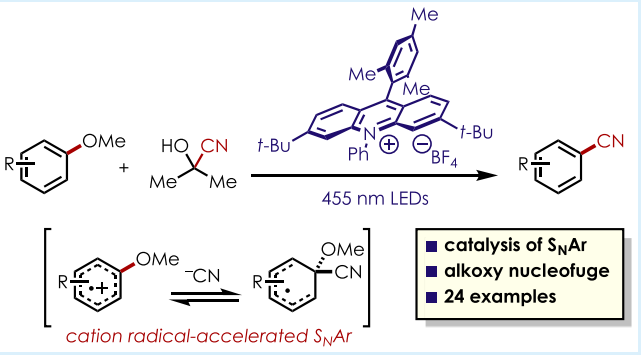
Supporting Information

ABSTRACT: Herein we describe a cation radical-accelerated-nucleophilic aromatic substitution (CRA-S_NAr) of alkoxy arenes utilizing a highly oxidizing acridinium photoredox catalyst and acetone cyanohydrin, an inexpensive and commercially available cyanide source. This cyanation is selective for carbon−oxygen (C−O) bond functionalization and is applicable to a range of methoxyarenes and dimethoxyarenes. Furthermore, computational studies provide a model for predicting regioselectivity and chemoselectivity in competitive C−H and C−O cyanation of methoxyarene cation radicals.

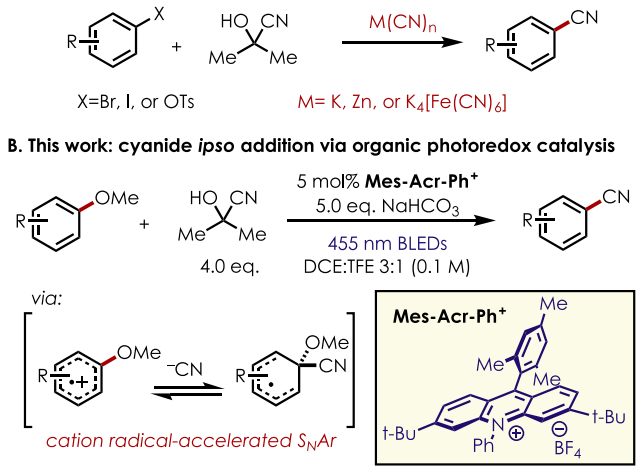


Aryl nitriles are important functional groups within the structures of pharmaceutical and agrochemical compounds. Nitriles can serve as bioisosteres for hydroxy or carbonyl moieties and have been implicated in key binding interactions of aldosterone, aromatase, and phosphodiesterase inhibitors.[1] Moreover, benzonitriles serve as an effective functional handle for the late stage installation of amides,[2] amines,[3] and esters.[4]

Classically, benzonitriles are synthesized via the Sandmeyer reaction that converts anilines to highly reactive diazonium intermediates. When using metal cyanides as nucleophiles, the diazonium undergoes nucleophilic substitution to yield the desired cyanoarene.[5] While this transformation is utilized extensively in preparative organic synthesis, diazonium salts are prone to explosive decomposition making such transformations difficult to scale. Modern approaches have since focused on transition metal catalyzed cross-coupling methods utilizing an aryl halide or pseudohalide (Scheme 1A).[6] Despite significant advances, these cross-coupling methods can suffer from catalyst deactivation due to ligand displacement by cyanide at the metal centers.[7] Furthermore, these transformations are limited to the availability of halogenated arene starting materials, thus requiring prefunctionalization for more complex aromatic substrates. Additionally, these preassembled leaving groups, such as halides, triflates or other pseudohalides are synthetically labile across many synthetic conditions, which may make late-stage functionalization challenging.[8]

A complementary and economically attractive alternative functional handle is the alkoxy moiety. Aryl ethers are ubiquitous in commercially available and naturally occurring molecules and can also be easily prepared from phenols. Furthermore, methoxy groups are tolerant of many harsh synthetic conditions, making them ideal substrates for late stage functionalization.[8]

Scheme 1. Catalytic Approaches to Benzonitrile Synthesis



Current methods for the functionalization of aryl ethers include substitution using alcohols, amines, sulfur and organometallic nucleophiles.[8−11] The synthesis of benzonitriles via aryl ether substitution has only been reported using UV light to promote the direct excitation of ortho- and para-substituted dimethoxybenzenes in the presence of 1,4-dicyanobenzene.[12] A donor−acceptor π-complex between the two species is formed, enabling nucleophilic cyanation and severely limits the scope of this transformation. Reports of other C−C bond forming

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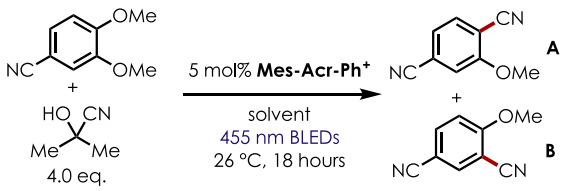
reactions via C−OMe cleavage are limited, likely due to the high activation energy barrier for breaking the C−OMe bond.[13]

Recently, our group published a cation radical-accelerated-nucleophilic aromatic substitution (CRA-S_NAr) of methoxy or benzyloxy-substituted arenes using azoles, ammonia, and trifluoroethano as nucleophiles.[14] Cyanide has shown to be a competent nucleophile for arene C−H functionalization,[15] thus we believed we could extend the CRA-S_NAr methodology for the synthesis of benzonitriles. Herein, we report the use of cyanide as a nucleophile in C−C bond formation for benzonitrile synthesis utilizing a highly oxidizing acridinium photoredox catalyst (Scheme 1B).[16]

We began by adapting our conditions previously developed for arene C−H cyanation using TMSCN as the cyanide source.[15] Using 3,4-dimethoxybenzonitrile as a model substrate, treatment with a catalytic quantity of acridinium salt **Mes-Acr-Ph$^+$** under irradiation with 455 nm LEDs yielded the desired C−O cyanation product in 18% yield as a mixture of two regioisomers (Table 1, entry 1). In comparison to TMSCN, acetone cyanohydrin was found to be higher yielding and a more economic cyanide source (entries 2−7). Other organic cyanide sources or cyanide salts failed to improve the reaction yields (Supporting Information, pages S7 and S8). A screen of common organic and inorganic bases identified solid or aqueous sodium bicarbonate as the optimal base for the generation of free cyanide *in situ* (Supporting Information, pages S7 and S8).

Table 1. Optimization for Catalytic S_NAr Cyanation[a]



entry	solvent	base	yield (A:B)
1[b]	MeCN	10% v/v pH 8 buffer	18% (2.6:1)
2	MeCN	10% v/v pH 8 buffer	24% (2.4:1)
3	DCE	10% v/v pH 8 buffer	24% (2.4:1)
4	DCE	33% $NaHCO_3$(aq)	35% (2.2:1)
5	DCE/TFE (3:1)	33% $NaHCO_3$(aq)	80% (2.4:1)
6	**DCE/TFE**(3:1)	**$NaHCO_3$ (5.0 equiv)**	**90%** (2.4:1)
7	DCE/HFIP (3:1)	$NaHCO_3$ (5.0 equiv)	53% (2.5:1)
8[c]	DCE/TFE (3:1)	$NaHCO_3$ (5.0 equiv)	n/a
9[d]	DCE/TFE (3:1)	$NaHCO_3$ (5.0 equiv)	n/a

[a]Reactions run at 0.1 M with respect to substrate. [b]TMSCN (4.0 equiv) used as a cyanide source. [c]The reaction was run without LEDS. [d]No photocatalyst.

Under these reaction conditions, the weak basicity of sodium bicarbonate may improve reactivity by keeping the concentration of the cyanide anion low, which helps to prevent undesired degradation pathways via oxidation of the cyanide anion by the photoredox catalyst.[17] When examining solvents, we found that the inclusion of 2,2,2-trifluoroethanol (TFE) resulted in a significantly enhanced yield of the desired product (Table 1, entries 5 and 6). In contrast, 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) only marginally increased the yields relative to those observed in DCE (entry 7). No reaction was observed in the absence of irradiation or the acridinium photoredox catalyst (entries 8 and 9, respectively).

The scope of this transformation was then examined using the optimized conditions (Figure 1). Simple mono- and disubstituted arenes were investigated first. Arenes bearing 1,2-dimethoxy substituents (**1**−**5**) were found to be the highest yielding of this group. 2-Chloro substituted anisole derivatives (**6**−**8**) also gave moderate to good yields of the desired product. A variety of 1,2-dimethoxybenzophenone derivatives (**12**−**17**) performed well with yields ranging from 48 to 83%. To our surprise, selective cyanation was observed for 3-bromoveratrole (**9**) and 1,2,3-trimethoxybenzene (**10**) yielding the products as single regioisomers.

Aryl ethers bearing *para*-pyridine and pyrimidine substituents (**19**−**22**) also produced the expected adducts, albeit in lower yields. More complex substrates such as the noradrenaline (**23**) and letrozole derivatives (**24**) also gave the desired benzonitrile products in low to moderate yields.

The mass balance of this C−O cyanation reaction is excellent with crude reaction mixtures typically consisting of only product and unreacted starting material as the main chemical components. Neither the inclusion of additional equivalents of cyanohydrin nor extended reaction times were effective in converting the remaining starting material to product, suggesting that catalyst decomposition may be responsible. The mass of a cyanide−acridinium adduct was detected by HRMS supporting catalyst decomposition by adventitious cyanide (Supporting Information, page 33).

Having evaluated the scope of this transformation, we sought to investigate the mechanism and origins of regioselectivity of this *ipso*-functionalization using a combination of experimental and computational data. Examining the initial rates of a variety of varying benzophenone derivatives, no linear free energy relationship was observed. However, these experiments did reveal an induction period (Supporting Information, pages 35−40). This is likely caused by a thermal barrier for the release of cyanide from acetone cyanohydrin.

We previously reported that in the presence of a terminal oxidant, nucleophilic attack of the anisole cation radical will occur at the para- or ortho-position, which requires a second irreversible oxidation to afford the C−H amination product.[18] Without a terminal oxidant, however, the reaction pathway is steered toward the ipso-product. Intriguingly, substrates which underwent *ipso*-C−O cyanation efficiently were not competent substrates under C−H cyanation conditions and *vice versa*. We then sought to demonstrate that the absence of oxygen would not simply allow a substrate to undergo ipso-substitution and that the chemoselectivity is determined by the electronics of the arene in the cation radical and ground state. To exemplify this, we turned to computational modeling.

Our group has previously demonstrated that natural population analysis (NPA) can be employed to computationally predict the regioselectivity of cation radical mediated arene C−H functionalization reactions.[19] Upon oxidation, the ortho-, para- and ipso-carbons of anisole are activated by an increase in positive charge density, allowing for nucleophilic addition at these positions.[19] The difference between the predicted NPA values of each carbon of the cation radical and ground state arene were largely accurate in modeling the regioselectivity observed for photoredox catalyzed C−H aminations. We elected to apply this method to understand the chemoselectivity of arene C−O cyanation. Utilizing the B3LYP/6-31-G+(d) level of theory, the NPA for the arene neutral state and cation radical state were determined for a variety of substrates. Comparing these values with experimental results, we found that the largest

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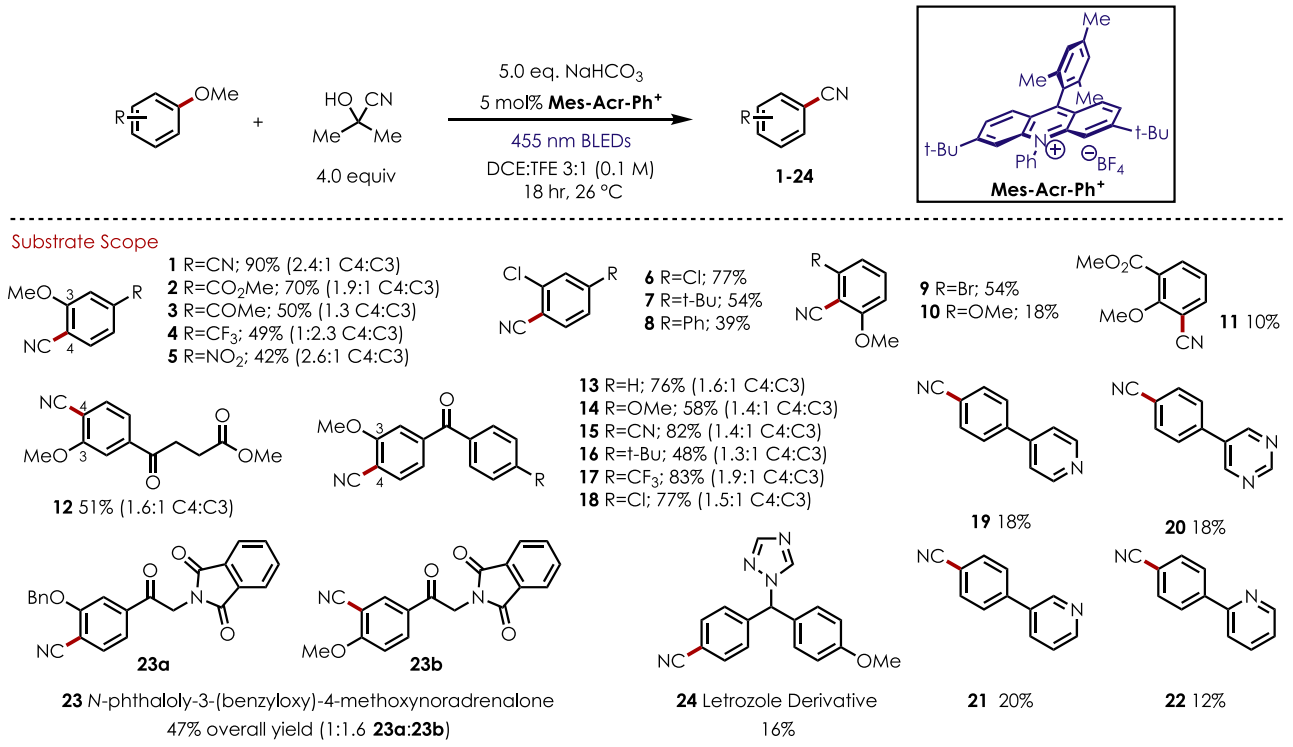


Figure 1. Scope of catalytic S_NAr arene cyanation.

difference of NPA values between the cation radical and ground state correlated experimentally to the favored major substitution position (Figure 2). If the difference is greatest at the aryl C−O

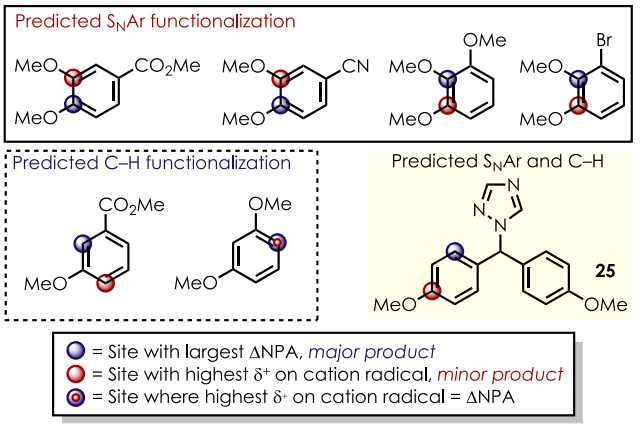
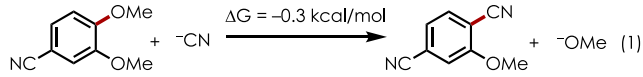


Figure 2. Prediction of chemoselectivity for benzonitrile synthesis via photoredox catalysis.

position, ipso-substitution is preferred. Additionally, the largest calculated NPA value in the cation radical arene correlated with the minor isomer. This model successfully predicts the regioselectivity for the cyanation of 3-bromoveratrole and 1,2,3-trimethoxybenzene.

We sought to demonstrate the predictive power of this method by targeting a pharmaceutical molecule for functionalization and chose a letrozole precursor as a test case (**25**). This model predicted the primary site of reactivity, the largest difference in NPA, at the carbon meta to the methoxy group. In the cation radical state, the most positive cation radical charge is at the ipso-position. Under the optimized conditions for ipso-substitution, both the ipso- product and *ortho*-C−H substituted product were isolated (~<5%). Although this model predicted meta-selectivity, the second largest difference was ortho-, exemplifying that while there will be exceptions, nonetheless this model provided insight into the chemo- and regioselectivity of the cyanation.

To further understand the mechanism and thermodynamics of this transformation, the overall change in Gibb's free energy for an example C−O cyanation was calculated (eq 1). Overall,



this reaction lacks a significant driving force as ΔG for 3,4-dimethoxybenzonitrile is nearly thermoneutral (−0.3 kcal/mol). It was observed that methoxyarenes bearing electron donating and withdrawing groups in a 1,3 relationship were particularly effective in this cyanation reaction. This increased reactivity relative to other substrate classes may be due to enhanced stability of the corresponding aryl radical intermediate via a captodative-type effect (eq 2). After cyanide addition, the aryl

radical can be stabilized by both the electron donating and withdrawing group, thus favoring C−O substitution; this is supported by the NPA analyses in Figure 2.

This stabilization is further supported when comparing the relative transition state energy for cyanide addition into veratrole or 3,4-dimethoxymethylbenzoate cation radicals. The presence of the para-electron withdrawing ester lowers the transition state energy by 5.1 kcal/mol (Figure 3). Following the addition step to afford this Meisenheimer-like intermediate, we postulate a

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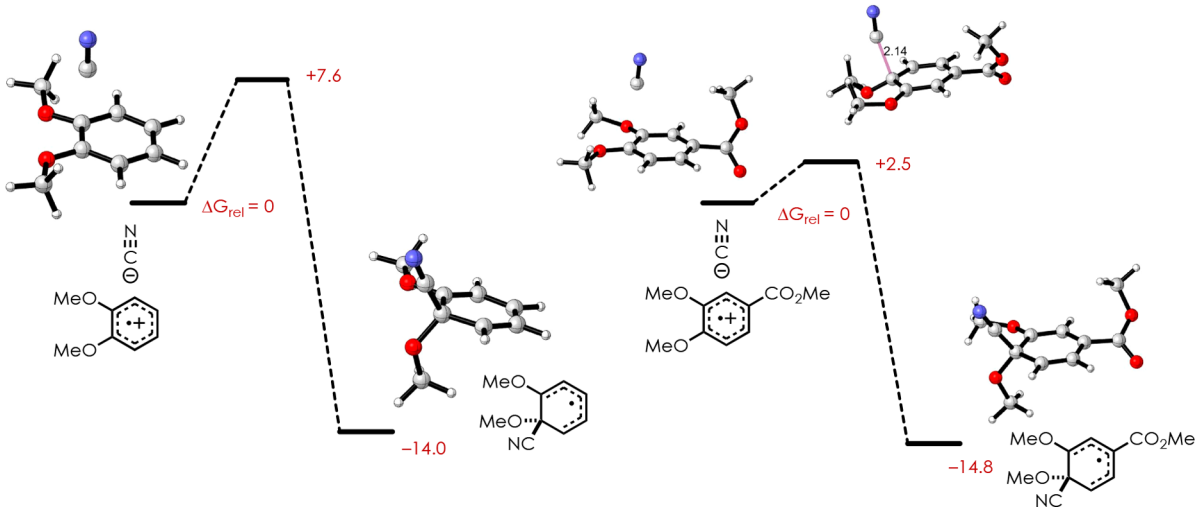

Figure 3. Relative transition state energies for cyanide addition into veratrole (left) or 3,4-dimethoxymethylbenzoate (right) cation radicals calculated using DFT (B3LYP, 6-31+g(d) basis set).

similar mechanistic pathway as before: loss of methoxide and single electron reduction to furnish the final product.[14]

In conclusion, we have developed a photoredox-catalyzed ipso-cyanation of aryl ethers. These mild conditions utilize a highly oxidizing, transition metal-free photoredox catalyst and have been successfully demonstrated for the cyanation of methoxyarenes and dimethoxyarenes in moderate to excellent yields. This method uses mild reactions conditions for the synthesis of benzonitriles via selective S_NAr C−OMe bond cleavage. In addition, we have provided a method for predicting the chemoselectivity of benzonitrile synthesis via photoredox catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02678.

Experimental procedures and supporting ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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