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Jordan D. Galloway and Ryan D. Baxter
5200 N. Lake Road, Merced, CA 95343

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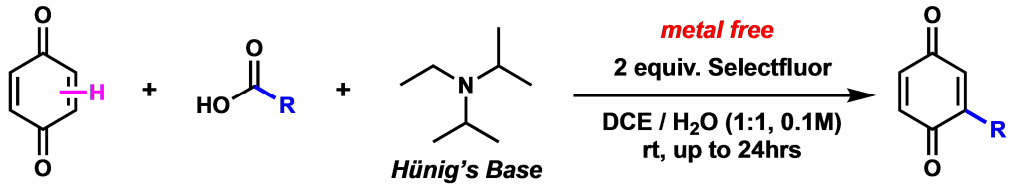

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Progress towards metal-free radical alkylations of quinones under mild conditions.

Jordan D. Galloway, Ryan D. Baxter *

Department of Chemistry & Chemical Biology, University of California, Merced, 5200 N. Lake Road, Merced, CA, 95343, USA

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ABSTRACT

A new method for the radical alkylation of quinones is reported. Lewis basic nitrogen additives increase the efficacy of quinone alkylations from carboxylic acids using catalytic $AgNO_3$ and Selectfluor as a mild oxidant. Electrochemical data suggests that certain Lewis basic additives are capable of directly reducing Selectfluor through a single-electron transfer, presumably via a charge-transfer complex. This process yields intermediates capable of promoting oxidative decarboxylation of alkyl carboxylic acids without an added metal initiator. Using this strategy, we have demonstrated progress towards a metal-free C–H quinone alkylation reaction that proceeds at room temperature under mild conditions.

* Corresponding author. Tel.: +0-000-000-0000; fax: +0-000-000-0000; e-mail: author@university.edu

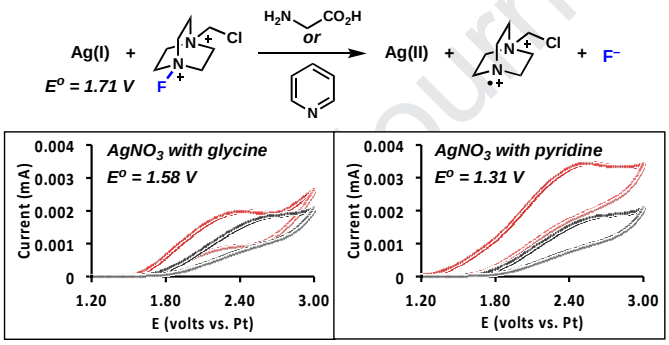
1. Introduction

In the past decade, significant progress has been made in the development of synthetic methods that combine nucleophilic radicals with unsaturated π-electrophiles. Renewed interest in established chemically-initiated methods, such as the Minisci reaction, have led to improvements in scope, efficiency, and operational simplicity (Scheme 1A).[1] One significant advancement in this area has been the use of boronic acids and esters as radical precursors, enabling the generation of aryl radicals from widely available materials. The 'Borono-Minisci' reaction was shown to be effective for nucleophilic arylation of both electron-deficient heterocycles and several 1,4 quinones, although alkylation from alkylboronic acids was generally less effective (Scheme 1B).[2] Our own recent work in this area has focused on identifying alternative oxidants to promote oxidative decarboxylation or deborylation for heterocycle and quinone functionalization.[3] We found that Selectfluor (E^o = -0.04 V) served as a suitable replacement for the traditionally used inorganic persulfate oxidants ($S_2O_8^{2-}$, E^o = 2.01 V), although diminished reactivity generally accompanied the milder reaction conditions.[4] In spite of these improvements, little progress has been made in reducing or eliminating the requirement of metal initiators while maintaining mild reaction conditions.[5] In the interest of modernizing all aspects of Minisci-type reactions, we sought to develop a metal-free variant that utilizes a mild oxidant under ambient conditions. Progress towards this goal has been achieved by promoting single-electron reduction of Selectfluor using Hunig's base, presumably via a charge-transfer complex (Scheme 1C).

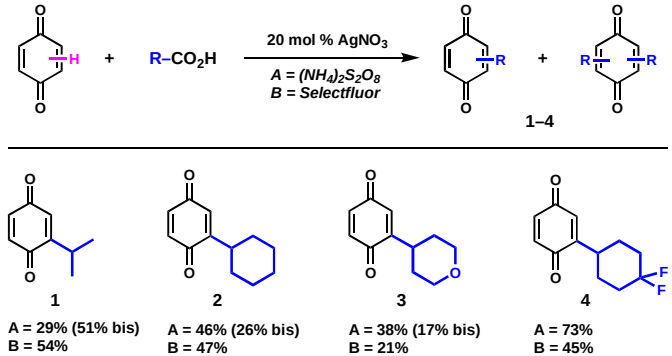
Scheme 1. Historical development of Minisci-type reactions.

2. Results and Discussion

Our interest in metal-free Minisci-type processes resulted from mechanistic findings that bridged several distinct projects in our research group. Through our work on radical fluorination we had shown that Selectfluor was capable of promoting Ag(I) to Ag(II) oxidation (E^o = 1.71 V) when unprotected amino acids, such as glycine, served as electron-donating ligands for Ag(I).[6] This effect could be reproduced with various pyridines, which altered the oxidation potential of Ag(I) to an even greater extent (Scheme 2).



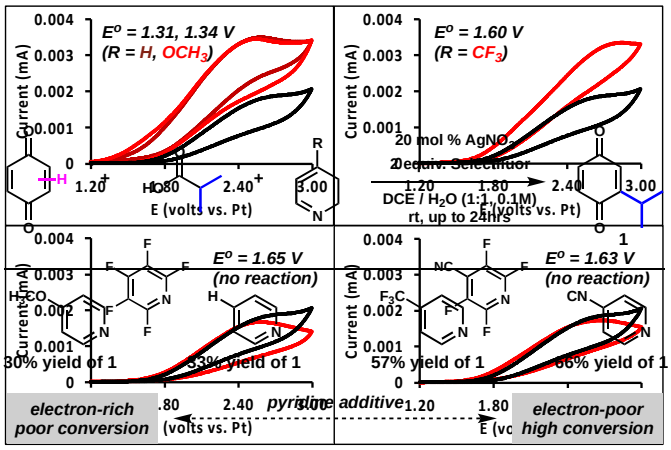
Scheme 2. Ligand-dependent oxidation potentials for Ag(I). Electrochemical experimental conditions: $AgNO_3$ (0.4 mmol) in 5 mL CH_3CN, tetrabutylammonium tetrafluoroborate supporting electrolyte (0.1 M), additive, where applicable, (0.4 mmol). Left: $AgNO_3$ alone (black curve), $AgNO_3$ with glycine added (red curve). Right: $AgNO_3$ alone (black curve), $AgNO_3$ with pyridine added (red curve). E^o values are determined as the minimum voltage producing 100 μA of current in the oxidizing direction (left-to-right).



Because the Ag(I)/Ag(II) couple is implicated in radical decarboxylation and deborylation, we used the electrochemical information above to guide our development of a Minisci reaction that uses Selectfluor as a mild oxidant.[3] We believed the presence of a heterocyclic substrate would be sufficient to promote Ag(I) oxidation, as even electron-deficient heteroarenes yielded Ag(I) species with lower oxidation potentials than $AgNO_3$ alone (*vide infra*). During the development of that previous work, we were surprised to discover that quinone alkylation and arylation was also possible with Selectfluor in the absence of any suitable heterocyclic ligands for Ag(I). Reasonable yields were observed for quinone alkylation using Selectfluor as an oxidant, although subsequent work from our group showed that Minisci conditions using persulfate oxidants were generally superior for alkylations from carboxylic acids, except for select cases where undesired bis-alkylation was observed (Scheme 3).[4b]

Scheme 3. Comparison of $(NH_4)_2S_2O_8$ and Selectfluor as oxidants. Select examples from *Synthesis*, 2018;50:2915–2923. General reaction conditions: quinone (0.2 mmol), carboxylic acid (0.4 mmol), oxidant (0.4 mmol), $AgNO_3$ (0.04 mmol) in 2 ml of DCE/H_2O (1:1) at room temperature for up to 24 hours. Isolated yields of chromatographically pure materials are shown. Method 'A' oxidant is $(NH_4)_2S_2O_8$. Method 'B' oxidant is Selectfluor.

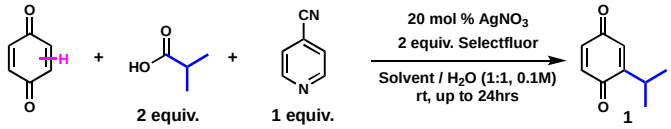
Several methods for quinone functionalization are available; including palladium-catalyzed couplings[7], alkylation/oxidation of hydroquinones and phenols[8], and direct radical functionalizations from allylic alcohols[9], organotellurium reagents[10], and diaryliodonium salts.[11] To further complement these established quinone functionalization methods, we sought to improve the efficacy of our Selectfluor-mediated protocol while maintaining mild reaction conditions. Because we observed enhanced reactivity using pyridine additives in the context of Ag(I)-initiated radical fluorination, we wondered whether a similar strategy would improve the moderate yields observed for quinone



alkylation. We began by exploring a small series of electronically diverse pyridines for the reaction of 1,4-benzoquinone with isobutyric acid, catalytic $AgNO_3$, and 2.0 equivalents of Selectfluor as the oxidant. As shown in Scheme 4, an unexpected trend in reaction efficiency was observed. Although cyclic voltammetry suggests that electron-rich pyridines form Ag(I) species that are most easily oxidized, electron-poor pyridines are the most effective additives for enhancing reaction conversion. There is a clear limit to this effect that can be visually demonstrated by cyclic voltammetry. Very electron-poor pyridines, such as pentafluoropyridine or tetrafluoro-4-pyridinecarbonitrile, are not Lewis basic enough to sufficiently bind Ag(I), producing a Ag(I)/Ag(II) waveform that is nearly identical to $AgNO_3$ alone.

Scheme 4. Pyridine additives in quinone alkylation. General reaction conditions: quinone (0.2 mmol), carboxylic acid (0.4 mmol), Selectfluor (0.4 mmol), pyridine additive (0.2 mmol), $AgNO_3$ (0.04 mmol), in 2 ml of DCE/H_2O (1:1) at room temperature for up to 24 hours. Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as a standard. Electrochemical experimental conditions: $AgNO_3$ (0.4 mmol) in 5 mL CH_3CN, tetrabutylammonium tetrafluoroborate supporting electrolyte (0.1 M), additive, where applicable, (0.4 mmol). Top Left: $AgNO_3$ alone (black curve), $AgNO_3$ with pyridine added (maroon curve), $AgNO_3$ with 4-methoxypyridine added (red curve). Top Right: $AgNO_3$ alone (black curve), $AgNO_3$ with 4-trifluoromethylpyridine added (red curve). Bottom Left: $AgNO_3$ alone (black curve), $AgNO_3$ with pentafluoropyridine added (red curve). Bottom Right: $AgNO_3$ alone (black curve), $AgNO_3$ with 4-cyanoperfluoropyridine added (red curve). E^o values are determined as the minimum voltage producing 100 μA of current in the oxidizing direction (left-to-right).

With pyridines having a clear effect on the efficiency of 1,4-benzoquinone alkylation, we sought to optimize solvent conditions to maximize the additive effect and further improve reaction conversion. Scheme 5 shows that the additive effect was not universal across solvents examined (yield without 4-cyanopyridine is shown in parenthesis). We were intrigued to find that alkylation was not effective in polar solvents that were miscible with water, although these conditions were suitable for radical fluorination (entries 2-3, 10, 12). Heterogeneous solvent conditions gave the highest conversion, although a clear trend



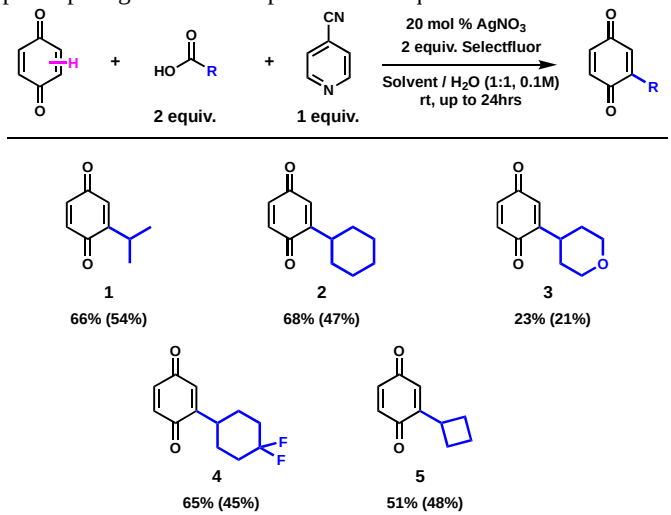
entry	deviation from standard conditions	yield of 1
1	dichloroethane	66% (54%)
2	acetone	17% (25%)
3	acetonitrile	3% (3%)
4	benzene	52% (41%)
5	perfluorobenzene	14% (43%)
6	trifluorotoluene	12% (43%)
7	1,2-dichlorobenzene	22% (57%)
8	*n*-hexane	4% (40%)
9	perfluorohexane	4% (37%)
10	isopropanol	0% (12%)
11	hexafluoroisopropanol	15% (23%)
12	ethanol	0% (4%)
13	trifluoroethanol	15% (2%)
14	1,4-dioxane	10% (8%)

regarding solvent properties was not obvious.

Scheme 5. Solvent screen for quinone alkylation. General reaction conditions: quinone (0.2 mmol), carboxylic acid (0.4 mmol), Selectfluor (0.4 mmol), 4-cyanopyridine (0.2 mmol), $AgNO_3$ (0.04 mmol), in 2 ml of organic solvent/H_2O (1:1) at room temperature for up to 24 hours. Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as a standard. Yields in parenthesis are for reactions run without 4-cyanopyridine as an additive.

With optimized conditions in hand, we explored a brief scope of carboxylic acids that would alkylate 1,4-benzoquinone using one equivalent of 4-cyanopyridine as an additive. In all cases examined, significant improvement was observed compared to running the reaction without 4-cyanopyridine. We were pleased to note that the efficiency of these reactions is similar to alkylation via standard Minisci conditions, suggesting we had improved the reactivity of the Selectfluor-mediated oxidation while maintaining mild reaction conditions. These results are especially intriguing considering that 4-cyanopyridine itself is a suitable electrophile for the isopropyl radical (albeit typically as the protonated pyridinium)[12], demonstrating that 1,4-benzoquinone is far more electrophilic under the given reaction conditions.

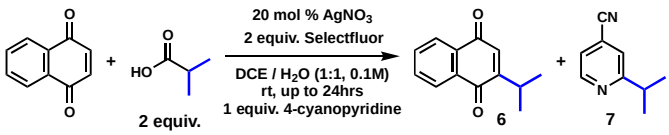
The use of 4-cyanopyridine was advantageous for several alkylations of 1,4-benzoquinone, but becomes problematic when moving to less reactive quinone substrates. As stated above, electron-poor pyridines are good substrates for radical alkylation via Minisic-type reactions, resulting in an unintended competition between pyridine and quinone alkylation. This unwanted side-reaction was observed when examining 4-cyanopyridine as an additive for the alkylation of 1,4-naphthoquinone using isobutyric acid (Scheme 7). Significant conversion to alkylated pyridine **7** was observed, eliminating the additive effect for the desired quinone alkylation. It was clear we needed to explore Lewis basic additives that were capable of enhancing the reactivity of the Ag(I)/Selectfluor system without participating as an electrophilic radical quencher. A small screen



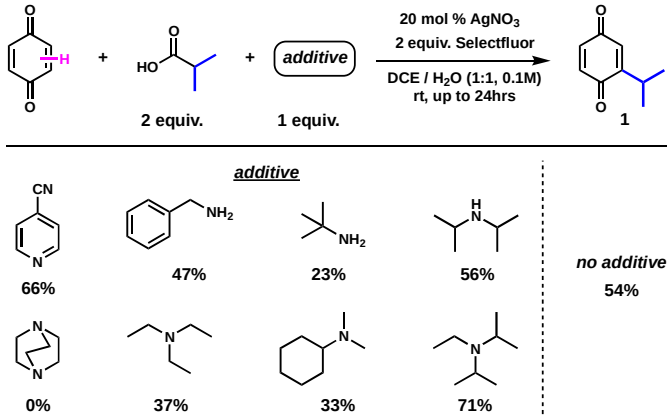
of such additives is shown in Scheme 8.

Scheme 6. Scope of radicals highlighting additive effect. General reaction conditions: quinone (0.2 mmol), carboxylic acid (0.4 mmol), Selectfluor (0.4 mmol), 4-cyanopyridine (0.2 mmol), $AgNO_3$ (0.04 mmol), in 2 ml of DCE/H_2O (1:1) at room temperature for up to 24 hours. Isolated yields of chromatographically pure material are shown. Yields in parenthesis are for reactions run without 4-cyanopyridine as an additive.

Scheme 7. Additive effect with 1,4-naphthoquinone. General reaction conditions: 1,4-napthoquinone (0.2 mmol), carboxylic acid (0.4 mmol), Selectfluor (0.4 mmol), 4-cyanopyridine (0.2 mmol), $AgNO_3$ (0.04 mmol), in 2 ml of DCE/H_2O (1:1) at room temperature for up to 24 hours. Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as a standard.



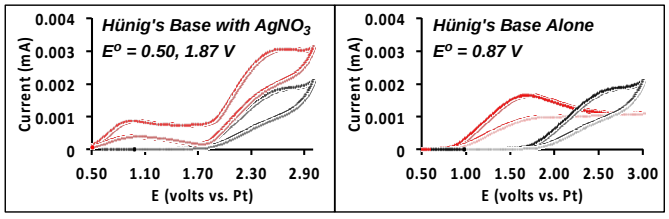
Many of the Lewis basic additives screened had either no effect or were deleterious to reaction conversion compared to the



standard reaction with no additive. From our screen, Hünig's base (*N*,*N*-diisopropylethylamine) was the only additive with activity surpassing that of 4-cyanopyridine. This was an especially promising lead due to its low cost and status as a common reagent in many organic laboratories. In addition, Hünig's base is not expected to electrophilically sequester radicals intended for quinone alkylation, theoretically enhancing reaction efficiency for substrates less electrophilic than 1,4-benzoquinone. At this point we became interested in exploring the scope of carboxylic acids and quinones that would efficiently react in the presence of Hünig's base but were troubled by an oddity observed when monitoring the time course of a standard experiment. Our typical experimental procedure for kinetic analysis involved removing an aliquot of the reaction medium prior to adding the Ag(I) initiator to get an accurate analytical measurement of initial concentrations. This 'time-zero' data point consistently displayed a notable amount of product in the reaction mixture prior to the addition of any metal initiator. To us, this suggested that a radical process is initiated via electron-transfer between two organic species present within the reaction medium.

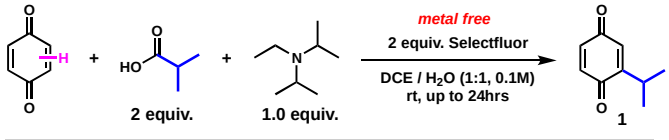
Scheme 8. Amine additive screen. General reaction conditions: quinone (0.2 mmol), carboxylic acid (0.4 mmol), Selectfluor (0.4 mmol), nitrogen-additive (0.2 mmol), $AgNO_3$ (0.04 mmol), in 2 ml of DCE/H_2O (1:1) at room temperature for up to 24 hours. Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as a standard.

We have recently reported spectroscopic evidence for interactions between pyridines and Selectfluor via an $[N–F–N]^+$ halogen bonding motif.[13] In addition, a report by Van Humbeck proposed a single-electron transfer event between electron-rich pyridines and Selectfluor via a charge-transfer intermediate.[14] An analogous electron-transfer between Hünig's base and Selectfluor seemed reasonable based on the precedence of using trialkylamines as reductive quenchers in photocatalysis due to their favorable redox potentials compared to $Ru(bpy)_3^{2+}$ ($E1/2^{II*/I}$ = 0.77 V vs SCE).[15] Electrochemical analysis confirmed that Hünig's base possessed an onset oxidation potential lower than



that of $AgNO_3$ (Figure 1).

Figure 1. Cyclic voltammetry of Hünig's base. Electrochemical experimental conditions: $AgNO_3$, where applicable, (0.4 mmol) in 5



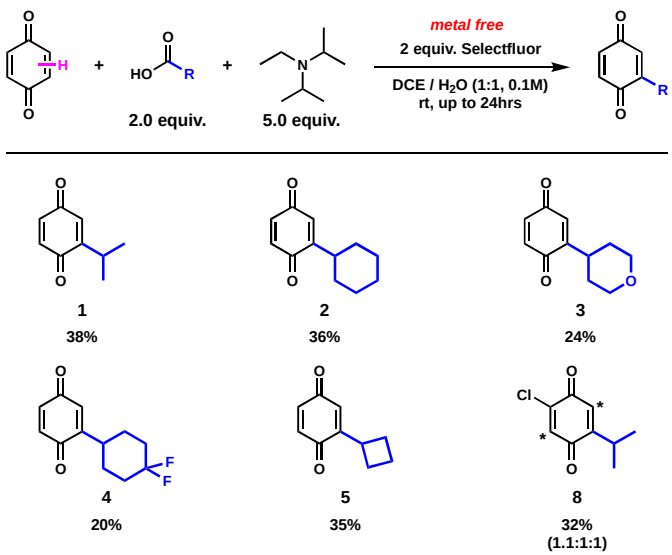
entry	deviation from standard conditions	yield of 1
1	none	18%
2	*n*-hexane	11%
3	dichloroethane, 5.0 equiv Hünig's base	38%
4	acetone, no water	13%
5	acetonitrile, no water	5%

mL CH_3CN, tetrabutylammonium tetrafluoroborate supporting electrolyte (0.1 M), Hünig's base, where applicable, (0.4 mmol). Left: $AgNO_3$ alone (black curve), $AgNO_3$ with Hünig's base added (red curve). Right: $AgNO_3$ alone (black curve), Hünig's base alone (red curve). E^o values are determined as the minimum voltage producing 100 μA of current in the oxidizing direction (left-to-right).

Based on these results we sought to optimize metal-free alkylations of quinones using Hünig's base as a single-electron reductant for Selectfluor. As shown in Scheme 9, dichloroethane is the optimum co-solvent when using Hünig's base, although only moderate yields can be achieved with just one equivalent of the additive (entry 1). Increasing the equivalents of Hünig's base led to higher conversion, suggesting that the protocol may be amenable to further optimizations. New stir bars and disposable glassware were used to minimize the possibility of trace metal contaminants initiating the radical reaction. No desired product is observed in the absence of Hünig's base, and trace metal analysis of this reagent suggests the reaction is occurring without metal-initiators (see *Supporting Information* for details). Although this work is in its early stages, these preliminary results show promise for developing a general strategy for Minisci-type reactions that do not rely on metal initiators. A brief screen of quinones and carboxylic acids showed that modest conversion to the alkylated quinone could be achieved for a variety of structures (Scheme 10).

Scheme 9. Metal-free radical addition to 1,4-benzoquinone. General reaction conditions: quinone (0.2 mmol), carboxylic acid (0.4 mmol), Selectfluor (0.4 mmol), Hünig's base (0.2 – 1.0 mmol), in 2 ml of organic solvent/H_2O (1:1) at room temperature for up to 24 hours. Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as a standard.

Scheme 10. Metal-free radical addition to 1,4-benzoquinone. General reaction conditions: quinone (0.2 mmol), carboxylic acid (0.4 mmol), Selectfluor (0.4 mmol), Hünig's base (1.0 mmol), in 2 ml of DCE/H_2O (1:1) at room temperature for up to 24 hours. Isolated yields of chromatographically pure material are shown.



3. Conclusions

In summary, we have described progress towards the development of metal-free radical additions to quinones under mild conditions. We have demonstrated that Lewis basic additives affect the Ag(I)/Ag(II) redox couple that is common to many reactions relying on radical decarboxylation, allowing for mild oxidants to promote this transformation. Through the course of this work we have identified Hünig's base as an optimum additive to facilitate Ag(I)/Ag(II) mediated decarboxylation with Selectfluor due to its low cost, commonplace presence in most laboratories, and resistance to unwanted side reactions. In addition, we found that an unexpected single-electron transfer event between Hünig's base and Selectfluor promotes oxidative decarboxylation without a metal initiator. Future work will involve further optimization of the metal-free protocol, including examination of the scope of radical precursors and quinone substrates that will participate in the reaction.

4. Experimental section

Reagents and solvents were purchased at the highest commercial quality and used without purification. NMR Yields were calculated by selecting proton peaks from products that were previously isolated. 1,3,5–trimethoxybenzene was used as the NMR standard. The yields describe the result of a single experiment. Reactions were monitored by NMR spectra which were recorded on a Varian-INOVA 400 MHz or 500 MHz spectrometer and calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$ – ^{1}H NMR 7.26 ppm, ^{13}C NMR 77.16 ppm). The following abbreviations were used to explain multiplicities (s – singlet, d – doublet, t – triplet, q – quartet, m – multiplet). GCMS data was obtained using an Agilent Technologies 5975 Series MSD GCMS with *tert*-butylbenzene as the standard.

4.1 General electrochemical conditions

$AgNO_3$ (0.4 mmol) in 5 mL CH_3CN, tetrabutylammonium hexafluorophosphate supporting electrolyte (0.1 M), glycine (0.4 mmol) or pyridine (0.4 mmol) where appropriate. $AgNO_3$ alone is given as the black curve in Scheme 2 for reference (E^o = 1.71 V) E^o values are determined as the minimum voltage producing 100 uA of current in the oxidizing direction.

4.2 General procedure for the functionalization of 1,4-benzoquinone with Selectfluor as the oxidant with pyridine additives shown in Scheme 4

To a vial containing a stir bar was added 1,4-benzoquinone (22 mg, 0.2 mmol), isobutyric acid (37 µL, 0.4 mmol, 2 equiv), pyridine additive (0.2 mmol), and Selectfluor (142 mg, 0.4 mmol, 2 equiv). Dichloroethane (1 mL) and H_2O (0.9 mL) were then added and stirred for approximately 1 minute at room temperature. A solution of $AgNO_3$ (0.1 mL of a 0.4M solution in H_2O, 0.04 mmol) was added in one portion. The reaction was capped with a screw cap and stirred at room temperature for 24 hours. Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as a standard. (see Supporting Information for spectra).

4.3 General procedure for the functionalization of quinones with selectfluor as the oxidant with 4-cyanopyridine

To a vial containing a stir bar was added quinone (0.2 mmol, 1 equiv), carboxylic acid (0.4 mmol, 2 equiv), 4-cyanopyridine (21 mg, 0.2 mmol, 1 equiv) and Selectfluor (142 mg, 0.4 mmol, 2 equiv). Dichloroethane (1 mL) and H_2O (0.9 mL) were then added and stirred for approximately 1 minute at room temperature. A solution of $AgNO_3$ (0.1 mL of a 0.4M solution in H_2O, 0.04 mmol) was added in one portion.The reaction was capped with a screw cap and stirred at room temperature for 24 hours. Upon completion, the reaction was transferred to a test tube containing saturated sodium bicarbonate (2 mL). The aqueous phase was extracted with ethyl acetate (3 x 3 mL) and the combined organic layers were dried over $MgSO_4$, filtered and carefully concentrated *in vacuo*.

2-isopropylcyclohexa-2,5-diene-1,4-dione (1): The general procedure was followed using 1,4-benzoquinone (22 mg, 0.2 mmol) and isobutyric acid (37 µL, 0.4 mmol, 2 equiv). The reaction afforded **1** (19.8 mg, 66% yield) as a yellow oil. The data for **1** matches those previously reported.[3] ^{1}H NMR (400 MHz, $CDCl_3$) 6.75 (d, *J* = 10.1 Hz, 1H), 6.69 (dd, *J* = 10.1, 2.3 Hz, 1H), 6.53 (s, 1H), 3.03 (dt, *J* = 13.7, 6.8 Hz, 1H), 1.13 (d, *J* = 6.9 Hz, 6H).

[1,1'-bi(cyclohexane)]-3,6-diene-2,5-dione (2): The general procedure was followed using 1,4-benzoquinone (22 mg, 0.2 mmol) and cyclohexanoic acid (51 mg, 0.4 mmol, 2 equiv). The reaction afforded **2** (25.8 mg, 68% yield) as a pale yellow oil. The data for **2** matches those previously reported.[3] ^{1}H NMR (400 MHz, $CDCl_3$): 6.74 (d, *J* = 10.1 Hz, 1H), 6.69 (dd, *J* = 10.1, 2.4 Hz, 1H), 6.50 (dd, *J* = 2.4, 1.1 Hz, 1H), 2.74 – 2.62 (m, 1H), 1.88 – 1.69 (m, 5H), 1.47 – 1.31 (m, 2H), 1.27 – 1.09 (m, 3H).

2-(tetrahydro-2H-pyran-4-yl)cyclohexa-2,5-diene-1,4-dione (3): The general procedure was followed using 1,4-benzoquinone (22 mg, 0.2 mmol) and tetrahydropyran4-yl-carboxylic acid (52 mg, 0.4 mmol, 2 equiv). The reaction afforded **3** (8.8 mg, 23% yield) as a yellow solid (m.p. 95 – 98 °C). The data for **3** matches those previously reported.[4b] ^{1}H NMR (400 MHz, $CDCl_3$): 6.77 (d, *J* = 10.1 Hz, 1H), 6.73 (dd, *J* = 10.1, 2.3 Hz, 1H), 6.52 (dd, *J* = 2.3, 1.2 Hz, 1H), 4.05 (dd, *J* = 11.6, 4.4 Hz, 2H), 3.53 (td, *J* = 11.8, 2.1 Hz, 2H), 3.01–2.90 (m, 1H), 1.72–1.64 (m, 2H), 1.56 (ddd, *J* = 25.1, 12.5, 4.4 Hz, 2H).

4',4'-difluoro-[1,1'-bi(cyclohexane)]-3,6-diene-2,5-dione (4): The general procedure was followed using 1,4-benzoquinone (22 mg, 0.2 mmol) and 4,4-difluorocyclohexanecarboxylic acid (66 mg, 0.4 mmol, 2 equiv). The reaction afforded **4** (29.4 mg, 65% yield) as a yellow solid. The data for **4** matches those previously reported.[3] ^{1}H NMR (400 MHz, $CDCl_3$): 6.78 (d, *J* = 10.1 Hz, 1H), 6.73 (dd, *J* = 10.1, 2.4 Hz, 1H), 6.55 (dd, *J* = 2.2, 1.0 Hz, 1H), 2.79 (t, *J* = 12.5 Hz, 1H), 2.20 (ddd, *J* = 14.9, 5.6, 2.9 Hz, 2H), 1.97 – 1.76 (m, 4H), 1.63 – 1.48 (m, 2H).

2-cyclobutylcyclohexa-2,5-diene-1,4-dione (5): The general procedure was followed using 1,4-benzoquinone (22 mg, 0.2 mmol) and cyclobutane carboxylic acid (39 µL, 0.4 mmol, 2 equiv). The reaction afforded **5** (16.5 mg, 51% yield) as a yellow oil. The data for **5** matches those previously reported.[3] ^{1}H NMR (400 MHz, $CDCl_3$): 6.70 (s, 2H), 6.54 (s, 1H), 3.51 (t, *J* = 8.3 Hz, 1H), 2.33 – 2.23 (m, 2H), 2.12 – 1.93 (m, 3H), 1.84 (ddd, *J* = 16.4, 7.4, 4.4 Hz, 1H).

4.4 General procedure for the functionalization of 1,4-naphthoquinone with Selectfluor as the oxidant with 4-cyanopyridine shown in Scheme 7

To a vial containing a stir bar was added 1,4-naphthoquinone (32 mg, 0.2 mmol), isobutyric acid (37 µL, 0.4 mmol, 2 equiv), 4-cyanopyridine (21 mg, 0.2 mmol, 1 equiv), and Selectfluor (142 mg, 0.4 mmol, 2 equiv). Dichloroethane (1 mL) and H_2O (0.9 mL) were then added and stirred for approximately 1 minute at room temperature. A solution of $AgNO_3$ (0.1 mL of a 0.4 M solution in H_2O, 0.04 mmol) was added in one portion. The reaction was capped with a screw cap and stirred at room temperature for 24 hours. Yields determined by ^{1}H NMR using

1,3,5-trimethoxybenzene as a standard (see Supporting Information for spectra).

2-isopropylnaphthalene-1,4-dione (6): Previously reported methods were used to synthesize compound **6.**[3] The data for **6** matches those previously reported.[4b] ^{1}H NMR (400 MHz, $CDCl_3$): 8.14 – 8.09 (m, 1H), 8.08 – 8.03 (m, *J* = 6.9, 2.7 Hz, 1H), 7.76 – 7.68 (m, 2H), 6.77 (s, 1H), 3.31 – 3.20 (m, 1H), 1.20 (d, *J* = 6.9 Hz, 6H).

2-isopropylisonicotinotrile (7): Previously reported methods were used to synthesize compound **7**.[3] The data for **7** matches those previously reported.[3] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (d, *J* = 4.9 Hz, 1H), 7.40 (s, 1H), 7.33 (d, *J* = 4.5 Hz, 1H), 3.12 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.32 (d, *J* = 6.9 Hz, 6H).

4.5 General procedure for the functionalization of quinones with selectfluor as the oxidant metal-free

To a vial containing a stir bar was added quinone (0.2 mmol, 1 equiv), carboxylic acid (0.4 mmol, 2 equiv), hünig's base (174 µL, 1.0 mmol, 5 equiv) and Selectfluor (142 mg, 0.4 mmol, 2 equiv) followed by 1 mL of H_2O and 1 mL of 1,2-dichloroethane. The reaction was capped with a screw cap and stirred at room temperature for 24 hours. Upon completion, the reaction was transferred to a test tube containing saturated sodium bicarbonate (2 mL). The aqueous phase was extracted with ethyl acetate (3 x 3 mL) and the combined organic layers were dried over $MgSO_4$, filtered and carefully concentrated *in vacuo*.

2-isopropylcyclohexa-2,5-diene-1,4-dione (1): The general procedure was followed using 1,4-benzoquinone (22 mg, 0.2 mmol) and isobutyric acid (37 µL, 0.4 mmol, 2 equiv). The reaction afforded **1** (11.5 mg, 38% yield) as a yellow oil.

[1,1'-bi(cyclohexane)]-3,6-diene-2,5-dione (2): The general procedure was followed using 1,4-benzoquinone (22 mg, 0.2 mmol) and cyclohexanoic acid (51 mg, 0.4 mmol, 2 equiv). The reaction afforded **2** (13.5 mg, 36% yield) as a pale yellow oil.

2-(tetrahydro-2H-pyran-4-yl)cyclohexa-2,5-diene-1,4-dione (3): The general procedure was followed using 1,4-benzoquinone (22 mg, 0.2 mmol) and tetrahydropyran4-yl-carboxylic acid (52 mg, 0.4 mmol, 2 equiv). The reaction afforded **3** (9.1 mg, 24% yield) as a yellow solid (m.p. 95 – 98 °C).

4',4'-difluoro-[1,1'-bi(cyclohexane)]-3,6-diene-2,5-dione (4): The general procedure was followed using 1,4-benzoquinone (22 mg, 0.2 mmol) and 4,4-difluorocyclohexanecarboxylic acid (66 mg, 0.4 mmol, 2 equiv). The reaction afforded **4** (9.0 mg, 20% yield) as a yellow solid.

2-cyclobutylcyclohexa-2,5-diene-1,4-dione (5): The general procedure was followed using 1,4-benzoquinone (22 mg, 0.2 mmol) and cyclobutane carboxylic acid (39 µL, 0.4 mmol, 2 equiv). The reaction afforded **5** (11.4 mg, 35% yield) as a yellow oil. The data for **5** matches those previously reported.

2-chloro-3-isopropylcyclohexa-2,5-diene-1,4-dione (8-C3), 2-chloro-5-isopropylcyclohexa-2,5-diene-1,4-dione (8-C5), 2-chloro-6-isopropylcyclohexa-2,5-diene-1,4-dione (8-C6): The general procedure was followed using 2-Chloro-1,4-benzoquinone (29 mg, 0.2 mmol) and isobutyric acid (37 µL, 0.4 mmol, 2 equiv). The reaction afforded **8-C3** (4.0 mg, 11% yield) as a yellow oil, **8-C5** (4.1 mg, 11% yield) as a yellow solid (m.p. 48 – 51 °C) , and **8-C6** (3.8 mg, 10% yield) as a yellow oil. The regioisomeric ratio of C3:C5:C6 was determined to be 1.1:1.0:1.1 by crude ^{1}H NMR. **Data for 8-C3:** ^{1}H NMR (400 MHz, $CDCl_3$): 6.84 (d, *J* = 10.0 Hz, 1H), 6.74 (d, *J* = 10.0 Hz, 1H), 3.53 – 3.37 (m, 1H), 1.31 (d, *J* = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, CDC_3): 185.0, 179.7, 149.8, 140.3, 137.6, 135.2, 30.0, 19.7. HRMS (ESI-TOF): calcd for $C_9H_9ClO_2$ $[M+H]^+$ 185.0364 found 185.0349. **Data for 8-C5:** ^{1}H NMR (500 MHz, $CDCl_3$): 6.97 (s, 1H), 6.66 (d, *J* = 1.2 Hz, 1H), 3.08 – 2.98 (m, 1H), 1.14 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, CDC_3): 185.1, 180.3, 155.9, 143.7, 134.2, 130.2, 27.1, 21.5. HRMS (ESI-TOF): calcd for $C_9H_9ClO_2$ [M+H]+ 185.0364 found 185.0347. **Data for 8-C6:** ^{1}H NMR (500 MHz, $CDCl_3$): 6.95 (d, *J* = 2.5 Hz, 1H), 6.56 (dd, *J* = 2.4, 1.2 Hz, 1H), 3.15 – 3.06 (m, 1H), 1.16 (d, *J* = 6.9 Hz, 7H). ^{13}C NMR (125 MHz, CDC_3): 185.7, 179.6, 155.3, 144.6, 133.3, 130.8, 27.8, 21.6. HRMS (ESI-TOF): calcd for $C_9H_9ClO_2$ [M+H]+ 185.0364 found 185.0347.

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16. Complete spectral data for compound **1**-**4** and **6** are provided in the Supporting Information of reference 4b. Complete spectral data for compounds **5** and **7** are provided in the Supporting Information for reference 3.