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Aerobic Organocatalytic Photoinitiated Arene Oxidations: Application to Electron Transfer Initiated Cyclization Reactions

V. Satish Kumar, Danielle L. Aubele, and Paul E. Floreancig*

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

florean@pitt.edu

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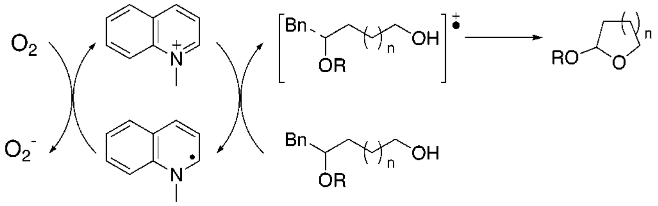
ABSTRACT



Electron transfer initiated oxidative cyclization reactions can be effected by catalytic amounts of *N*-methylquinolinium hexafluorophosphate through photoirradiation in the presence of dioxygen. Solid sodium thiosulfate serves as an effective reducing agent to remove the reactive oxygen species formed from catalyst regeneration and radical coupling reactions with O_2, allowing these cyclizations to proceed efficiently on preparatively useful scales.

Dioxygen, by virtue of its abundant availability and nontoxic reduction products, represents an ideal reagent for the design of economical and environmentally benign organic transformations.[1] Numerous examples of oxidation reactions have been reported in which O_2 or air serves as a terminal oxidant in conjunction with transition metal based catalysts.[2] Organic molecules such as benzoquinone or TEMPO have been employed in these reactions as cocatalysts to facilitate the relay of electrons from the reduced catalyst to O_2.[3] The use of organic compounds as catalysts for aerobic oxidation reactions in the absence of a transition metal complex, though precedented,[4−6] is considerably less common. In this communication we report that *N*-methylquinolinium hexafluorophosphate ($NMQPF_6$) is an effective catalyst and that air functions as a proficient terminal oxidant in photoinitiated single-electron arene oxidation reactions. Applying these unique organocatalytic conditions to a class of oxidative cyclizations results in significant increases in both the potential scale and efficiency for these reactions and in a substantial reduction of waste production that facilitates product purification.

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(1) (a) Barton, D. H. R.; Martell, A. E.; Sawyer, D. T. *The Activation of Dioxygen and Homogeneous Catalytic Oxidation*; Plenum Press: New York, 1993. (b) Simandi, L. L. *Dioxygen Activation and Homogeneous Catalytic Oxidation*; Elsevier: Amsterdam, 1991.

(2) Representative examples: (a) Barton, D. H. R. *Tetrahedron* **1998**, *54*, 5805. (b) Sheldon, R. A.; Arends, I. W. C. E.; Dijksman, A. *Catal. Today* **2000**, *57*, 157. (c) Tsuji, J. *Synthesis* **1984**, 369. (d) Döbler, C.; Mehltretter, G. M.; Sundermeier, U.; Beller, M. *J. Am. Chem. Soc.* **2000**, *122*, 10289. (e) Jonasson, C.; Horváth, A.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2000**, *122*, 9600.

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(4) Electron-transfer reactions: (a) Ohkubo, K.; Fukuzami, S. *Org. Lett.* **2000**, *2*, 3647. (b) Fujita, M.; Ishida, A.; Tamamuku, S.; Fukuzumi, S. *J. Am. Chem. Soc.* **1996**, *118*, 8566. (c) Ye, H.; Tong, W.; D'Souza, V. T. *J. Am. Chem. Soc.* **1992**, *114*, 5470. (d) Kumar, V.; Woode, K. A.; Bryan, R. F.; Averill, B. A. *J. Am. Chem. Soc.* **1986**, *108*, 492.

(5) Singlet oxygen generation: (a) Gollnick, K.; Kuhn, H. J. In *Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Eds.; Academic Press: New York, 1979; p 287. (b) Hecht, S.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2001**, *123*, 6961.

(6) Hydrogen atom abstraction: Einhorn, C.; Einhorn, J.; Marcadal,-Abbadi, C.; Pierre, J.-L. *J. Org. Chem.* **1999**, *64*, 4542.

10.1021/ol016996f CCC: $20.00

We recently reported[7] an electron transfer initiated cyclization (ETIC) reaction in which homobenzylic ethers containing pendent nucleophiles are converted to cyclic acetals (Figure 1). This transformation employs $NMQPF_6$ as a single-electron oxidant in a photoinitiated carbon−carbon σ-bond activation process. Although this procedure has been used in efficient syntheses of several cyclic acetals, we noted that these transformations occasionally do not progress to completion, especially when the reactions were conducted on >0.5 mmol scale and when cyclizations proceed slowly. We concluded that this problem arises from the formation of covalent adducts between the *N*-methylquinoline radical ($NMQ^\bullet$) produced from the initial electron transfer and the benzyl radical produced in the displacement reaction.[8] These adducts are expected to be oxidized in preference to the substrate,[9] producing a range of aromatic products while consuming the oxidant. As a consequence of the need for at least 2 equiv of $NMQPF_6$, large quantities of aromatic byproducts are generated in these reactions, necessitating product isolation by laborious chromatographic separations.

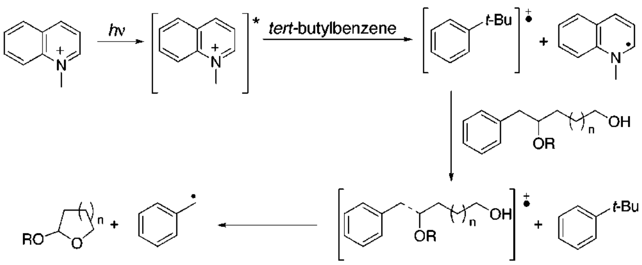


Figure 1. Electron transfer initiated cyclization.

In transient absorption spectroscopy studies of $NMQPF_6$-mediated arene oxidations, Dinnocenzo and co-workers observed[10] that signals arising from $NMQ^\bullet$ could be suppressed by conducting the reactions in the presence of O_2. This result was attributed to an essentially diffusion-controlled oxidation of $NMQ^\bullet$ to NMQ^+ through a single-electron-transfer reaction. We postulated that aerobic $NMQ^\bullet$ oxidation could be used in the design of a catalytic variant of the ETIC reaction as illustrated in Figure 2. Dioxygen was also expected to trap the benzyl radicals to form benzyl peroxy radicals.

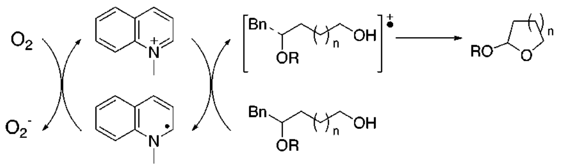
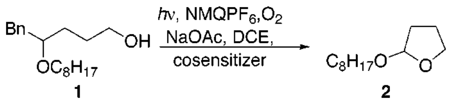


Figure 2. Aerobic quinolinium catalyst regeneration.

To test this proposal homobenzylic ether **1**, a substrate that cyclized only to partial conversion under the original reaction conditions,[7] was photoirradiated with concurrent aeration in the presence of substoichiometric amounts of $NMQPF_6$ (Table 1). These experiments showed that *the efficiency of these cyclizations actually increased as the catalyst loading was lowered*. Reactions using as little as 2.5 mol % of the catalyst were shown to proceed to completion in good yield and in a reasonable amount of time. The characteristic pink color of the stoichiometric reactions, resulting from the oxidative decomposition of quinoline-derived products, was not observed in these cyclizations. These studies also showed that *tert*-butylbenzene, used as the cosensitizer in the initial studies, can be replaced by toluene, a more volatile and much less expensive solvent. The ease of solvent removal and the minimization of aromatic waste production significantly facilitate product isolation. Since O_2 is known to quench triplet excited states,[11] these results also provide evidence that the singlet excited state of $NMQPF_6$ is the relevant oxidant for this process.

Table 1. Examination of Catalyst Loading and Cosensitizer[a]



entry	$NMQPF_6$ (mol %)	cosensitizer	time (h)	yield (%)[b]
1	200[c]	TBB[d]	4	55[e]
2	50	TBB	1.5	79
3	10	TBB	1.5	82
4	2.5	TBB	2	86
5	2.5	toluene	3	82

[a] Reaction conditions: **1** (50 mg), $NMQPF_6$, NaOAc (100 mg), 1,2-dichloroethane (6 mL), cosensitizer (1 mL), gentle air bubbling, irradiation with a medium-pressure mercury lamp. [b] Reported yields are of isolated, purified products unless noted otherwise. [c] Air was not used in this example. [d] TBB = *tert*-butylbenzene. [e] 74% yield based on 76% conversion.

Attempts to apply these conditions to larger scale (≥1 g) reactions, however, resulted in very low isolated product yields despite the complete consumption of starting material. For example, the cyclization of 1 g of **3a** only provided a 15% isolated yield of **4**. We ascribed these low yields to

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[7] Kumar, V. S.; Floreancig, P. E. *J. Am. Chem. Soc.* **2001**, *123*, 3842.

[8] Fukuzumi, S.; Ohkubo, K.; Suenobu, T.; Kato, K.; Fujitsuka, M.; Ito, O. *J. Am. Chem. Soc.* **2001**, *123*, 8459 and references therein. Adducts can also be formed between $NMQPF_6$ and benzyl radicals; see: Minisci, F.; Vismara, E.; Fontane, F.; Morini, G.; Serravalle, M.; Giordano, C. *J. Org. Chem.* **1987**, *52*, 730.

[9] (a) Aromatic amines are oxidized much more readily than alkylarenes. For a list of ionization potentials of organic molecules, see: Rosenstock, H. M.; Draxl, K.; Steiner, B. W.; Herron, J. T. *J. Chem. Phys. Ref. Data* **1997**, *6*, Suppl. 1. Ionization potentials can be correlated to oxidation potentials according to relationships established in ref 9b. (b) Howell, J. O.; Goncalves, J. M.; Amatore, C.; Klasinc, L.; Wightman, R. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 3968.

[10] Dockery, K. P.; Dinnocenzo, J. P.; Farid, S.; Goodman, J. L.; Gould, I. R. *J. Am. Chem. Soc.* **1997**, *119*, 1876.

[11] Kopecky', J. *Organic Photochemistry: A Visual Approach*; VCH: New York, 1991.

oxidative decomposition reactions caused by prolonged exposure to reactive oxygen species that arise from the formation of superoxide and benzylperoxy radicals.

To suppress the destructive pathways without hindering cyclization, we surveyed several mild reducing agents as additives in these reactions. While adding soluble reducing agents, such as DMSO, completely inhibited the reaction, adding solid, anhydrous $Na_2S_2O_3$ resulted in a marked enhancement of reaction efficiency with no retardation of reaction rates. In the presence of $Na_2S_2O_3$, gram-scale cyclizations of **3a** and **3b** provided **4** in 75% and 83% yields after 2.5 and 4.5 h, respectively, using 2.5 mol % of $NMQPF_6$ (Figure 3).[12] Benzaldehyde, formed by benzyl radical oxidation, is the only other substrate-derived product isolated from these reactions, allowing product purification to be effected by a simple wash with aqueous sodium bisulfite.

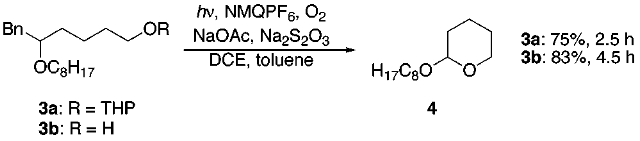
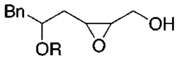
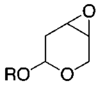
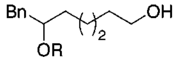
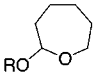
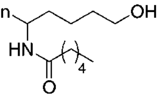
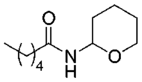
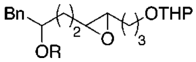
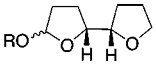


Figure 3. Gram-scale cyclization reactions.

To probe the generality of these conditions, we conducted catalytic cyclization reactions of structurally varied substrates that either progressed slowly or did not proceed to completion when subjected to stoichiometric oxidation conditions (Table 2). The yields of these reactions were, in general, either comparable or superior relative to those previously observed. The reduction of aromatic byproduct formation was particularly beneficial in the purification of the polar acylaminal product (entry 3).[13] The inclusion of $Na_2S_2O_3$ in cascade cyclizations that proceed through sensitive epioxonium ions (entry 4) is essential even for small scale reactions to ensure an efficient transformation.

Table 2. Aerobic ETIC Reactions of Several Substrates[a]

Entry	Substrate[b]	Product	Yield (cat.)[c]	Yield (stoic.)[d]
1[e]			90	78
2			85	82
3			75	78
4			73	82

[a] Reaction conditions: 50−150 mg substrate, 2.5 mol % $NMQPF_6$, 2 wt equiv of NaOAc, 2 wt equiv of $Na_2S_2O_3$, DCE/toluene (6:1), gentle air bubbling, irradiation with a medium-pressure mercury lamp. [b] R = n-C_8H_{17}. [c] Reported yields are of isolated, purified products. [d] Procedures for the stoichiometric reactions in entries 1 and 2 can be found in ref 5. [e] A 1.3:1 ratio of diastereomers was isolated. The relative stereochemistry of the isomers was not determined.

In summary, we have developed a method for conducting aerobic, organocatalytic single-electron photooxidation reactions. This method, when applied to electron transfer initiated cyclization reactions, results in enhanced efficiency and easier product isolation. Solid $Na_2S_2O_3$ proved to be an effective additive for reducing the reactive oxygen species formed in these reactions without affecting the rate of the cyclizations, allowing reactions to be conducted on >1 g scale. The applicability of these conditions to other electron transfer initiated reactions is currently under investigation.

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Supporting Information Available: Synthetic schemes and procedures for cyclization substrates and procedures and product characterizations for cyclization reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) **Representative Procedure.** To **3b** (1.0 g, 3.3 mmol) in anhydrous 1,2-dichloroethane (120 mL) and toluene (20 mL) were added $NMQPF_6$ (24 mg, 0.08 mmol), NaOAc (2.0 g, 24 mmol), and $Na_2S_2O_3$ (2.0 g, 16 mmol). The mixture was irradiated at room temperature (medium-pressure mercury lamp, Pyrex filter) while air was added through a dispersion tube. After 4.5 h the mixture was filtered, washed with aqueous sodium bisulfite, and concentrated to provide **4** (584 mg, 83%).

(13) All new compounds have been characterized by ^1H NMR, ^{13}C NMR, IR, and HRMS. See Supporting Information for details.