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Photoinduced Electron-Transfer-Promoted Redox Fragmentation of *N*-Alkoxyphthalimides

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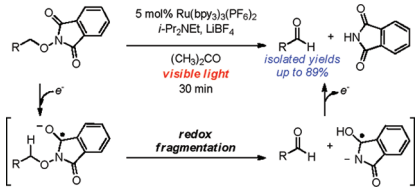
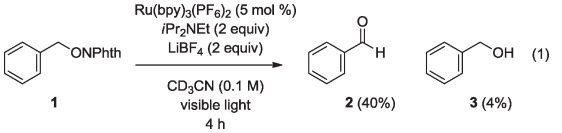
ABSTRACT



A new photoinduced electron-transfer-promoted redox fragmentation of *N*-alkoxyphthalimides has been developed. Mechanistic experiments have established that this reaction proceeds through a unique concerted intramolecular fragmentation process. This distinctive mechanism imparts many synthetic advantages, which are highlighted in the redox fragmentation of various heterocyclic substrates.

Despite the prominence of photochemistry in biological processes, organic photochemistry has traditionally been limited by the necessity of high-energy UV radiation.[1] Recently, there has been a renaissance in visible-light-mediated photoinduced electron transfer (PET) processes with new applications of $Ru(bpy)_3^{2+}$ photocatalysts.[2] Following seminal reports by MacMillan[3] and Yoon,[2a−c] there has been a rapid expansion in the scope of viable PET substrates.[4,5] Of all the structural motifs that have been examined, it is noteworthy that there is only one example of a PET acceptor adjacent to a weak heteroatom−heteroatom bond.[6] This underrepresented substrate class has great synthetic potential in visible-light-promoted processes as the latent reactivity of the weak bond may be released under mild conditions to undergo numerous fragmentation possibilities or provide ready access to heteroatom-centered radicals.



Our studies on the visible light photocatalysis of substrates containing weak heteroatom−heteroatom bonds focused on *N*-alkoxyphthalimide derivatives. While phthalimides are well-known to undergo a variety of photoreactions with UV light,[7] surprisingly only one phthalimide derivative, an *N*-acyloxyphthalimide, has been studied

(1) For reviews on photoredox catalysis, see: (a) Yoon, T. P.; Ischay, M. A.; Du, J. *Nat. Chem.* **2010**, *2*, 527–532. (b) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102–113.

(2) (a) Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 12886–12887. (b) Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2009**, *131*, 14604–14605. (c) Ishay, M. A.; Lu, Z; Yoon, T. P. *J. Am. Chem. Soc.* **2010**, *132*, 8572–8574. (d) Nicewicz, D.; MacMillan, D. W. C. *Science* **2008**, *322*, 77–80.

(3) (a) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875–10877.

(4) For selected examples of ruthenium photocatalysts, see: (a) Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756–8757. (b) Tucker, J. W.; Narayanam, J. M. R.; Krabbe, S. W.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 368–371. (c) Furst, L.; Matsuura, B. S.; Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 3104–3107. (d) Dai, C.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nat. Chem.* **2011**, *3*, 140–145. (e) Andrews, S. R.; Becker, J. J.; Gagne, M. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 7274–7276. (f) Rueping, M.; Vila, C.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C. *Chem. Commun.* **2011**, *47*, 2360–2362. (g) Lu, Z.; Shen, M.; Yoon, T. P. *J. Am. Chem. Soc.* **2011**, *133*, 1162–1164.

(5) For selected examples of iridium photocatalysts, see: (a) Condie, A. G.; Gonzlez-Gómez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464–1465. (b) Shih, H.-W.; Vander Wal, M. N.; Grange, R. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 13600–13603. (c) Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2011**, *133*, 4160–4163. (d) Reference 3.

(6) (a) Okada, K.; Okamoto, K.; Morita, N.; Okubo, K.; Oda, M. *J. Am. Chem. Soc.* **1991**, *113*, 9401–9402. (b) Okada, K.; Okubo, K.; Morita, N.; Oda, M. *Tetrahedron Lett.* **1992**, *33*, 7377–7380. (c) Okada, K.; Okubo, K.; Morita, N.; Oda, M. *Chem. Lett.* **1993**, 2021–2024.

(7) For a review on the photochemistry using *N*-alkylphthalimides, see: Yoon, U. C.; Mariano, P. S. *Acc. Chem. Res.* **2001**, *34*, 523–533.

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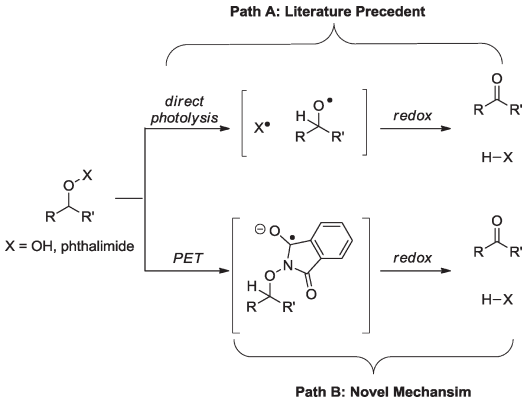
using visible light PET.[6] Based on this precedent, we hypothesized that we may be able to induce N–O bond homolysis of *N*-alkoxyphthalimide **1** under standard visible light photochemical conditions[8] to provide an alternative to standard metal-hydride alkoxy radical formation methodologies.[9] Unexpectedly, the major product observed was not alcohol **3**, formed from reduction of an alkoxy radical, but rather benzaldehyde (**2**).[10,11] While the benzylic carbon is oxidized, there is no net change in the oxidation state of the *N*-alkoxyphthalimide. This process, otherwise known as a redox fragmentation,[12] results in the formation of an aldehyde (**2**) and phthalimide, the oxidized and reduced components respectively.

A survey of the literature revealed that there are no examples of photocatalyst-mediated PET redox fragmentations. Given the paucity of this type of photochemical transformation, we speculated that the mechanism of the redox fragmentation may not be promoted by light.[13] In fact, during reaction optimization[14] a good yield of benzaldehyde was obtained when only the $Ru(bpy)_3^{2+}$ catalyst was excluded, suggesting a possible base-mediated elimination.[15] However, excluding light from the reaction conditions resulted in no change in the starting material, indicating that this redox fragmentation is indeed photochemical.[16]

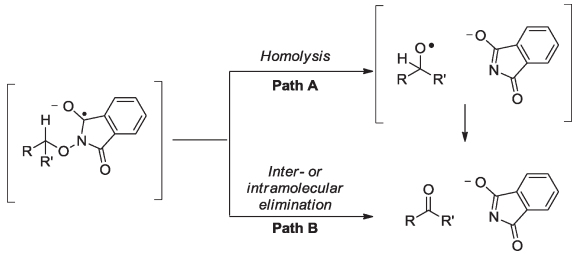
Mechanistically, there are two general classes of photoreactions that may be occurring in this new redox fragmentation: direct homolysis of the oxygen–heteroatom bond and subsequent redox behavior, similar to what is observed in peroxy species (Scheme 1, path A)[17] or a PET process followed by a novel redox fragmentation (path B). Omission of the base led to no reaction, indicating that the reaction does not proceed through direct photolysis of the *N*-alkoxyphthalimide. Utilization of pyridine as the amine additive, a poor PET donor, led to no change in the starting material. In combination, these mechanistic experiments suggest that this redox process goes through a single electron transfer mechanism rather than direct homolysis analogous to peroxide decomposition. Further supporting

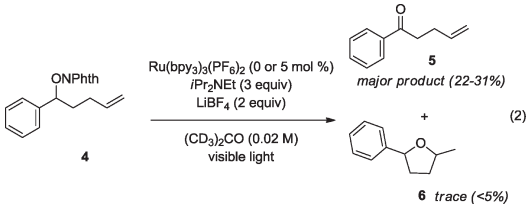
Scheme 1. Two Possible Photochemical Redox Mechanisms



a PET mechanism, the conjugation in the *N*-alkoxyphthalimide moiety is necessary as demonstrated by the lack of reactivity of *N*-benzyloxysuccinimide.

Scheme 2. Stepwise or Concerted Redox Fragmentations





With evidence for a PET-initiated fragmentation, we investigated if the redox fragmentation is stepwise, akin to peroxide decomposition (Scheme 2, path A), or concerted (Scheme 2, path B). Phthalimide substrate **4** (eq 2) was utilized as a probe to differentiate these two mechanistic possibilities. If PET is followed exclusively by N–O homolysis to first provide an alkoxy radical (path A, Scheme 2), then we should expect the major product to be tetrahydrofuran **6**; the rate of cyclization of an alkoxy radical onto a terminal alkene is fast ($\sim 6 \times 10^8$ s^{-1})[18] and will outcompete any intermolecular redox reaction leading to ketone **5**, especially under the dilute reaction conditions. Treatment of **4**, both with and without inclusion of the $Ru(bpy)_3^{2+}$ catalyst, provided **5** as the major product, with only trace

(8) We utilized the photoreaction conditions developed by Yoon and co-workers (ref 2a).

(9) Kim, S.; Lee, T. A.; Song, Y. *Synlett* **1998**, 471–472.

(10) All of the reactions were run under N_2, and oxygen was rigorously excluded.

(11) For the PET oxidation of simple aryl alcohols, see: Cano-Yelo, H.; Deronzier, A. *Tetrahedron Lett.* **1984**, *25*, 5517–5520.

(12) Salomon, R. G.; Reuter, J. M. *J. Am. Chem. Soc.* **1977**, *99*, 4372–4379.

(13) For an example of the pyrolitic conversion of *N*-alkoxyphthalimides to carbonyls, see: Al-Etaibi, A. M.; Al-Awadi, N. A.; Ibrahim, M. R.; Ibrahim, Y. A. *ARKIVOC* **2010**, 149–162.

(14) See Supporting Information for details on the optimization.

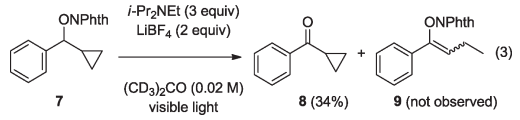
(15) Consonni, P.; Favara, D.; Omodei-Salé, A. *J. Chem. Soc., Perkin Trans. 2* **1983**, 967–973.

(16) It is noteworthy that the LUMO of the *N*-alkoxyphthalimide is sufficiently low in energy that visible light is sufficient to promote the transfer on an electron directly from the tertiary base. For representative examples of PET reactivity without the inclusion of a photocatalyst, see: (a) Cossy, J.; Belotti, D. *Tetrahedron* **2006**, *62*, 6459–6470. (b) Pham, P. V.; Nagib, D. A.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 6119–6122.

(17) Saito, I; Takayama, M; Matsuura, T. *J. Am. Chem. Soc.* **1990**, *112*, 883–884.

(18) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1988**, *110*, 4415–4416.

amounts of **6**, suggesting that path B (Scheme 2) is the dominant mechanism.

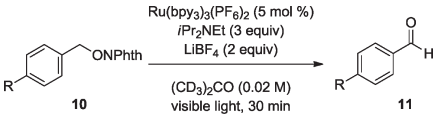


Another possible stepwise fragmentaion reaction involves the formation of a benzylic radical prior to fragmentation. This mechanistic possibility was tested using a radical clock experiment (eq 3). If the reaction proceeds through a discrete carbon radical alpha to the phenyl group, then cyclopropyl-opened product **9** should be observed.[19] Consistent with a concerted mechanism, no ring-opening product is formed when cyclopropane **7** is subjected to the reaction conditions. Furthermore, the reaction efficiency improved at greater dilution,[20] which supports an intramolecular, rather than intermolecular, elimination.

We next examined the electronic effects of various substitution patterns both with and without the addition of the $Ru(bpy)_3^{2+}$ catalyst (Table 1). Overall, there is no clear trend between the reaction rate and the electronics of the aryl ring. Fluoro-substituted aryl derivative **10a** provided comparably high yields to the unsubstituted substrate (**1**), while less electron-withdrawing substituents than fluorine, such as chlorine (**10b**) and bromine (**10c**), provided similar yields to the electron-donating methoxy-substituted aryl substrate (**10d**). This general lack of dependence on the electronics of the aryl ring suggests that there is no significant anionic or radical character in the rate-determining step.

The reaction mechanism shown in Figure 1 is consistent with these mechanistic experiments. Single electron transfer, either from the $Ru(bpy)_3^{2+}$ catalyst or directly from the amine base, to the carbonyl of the phthalimide results in intermediate **12**. Either a radical or anionic elimination then follows to provide the formally oxidized aldehydic product **2** and formally reduced phthalimide (**14**).[21] Consistent with a redox process, there is no net electron change in this transformation. An electron is donated to the phthalimide in the first PET step, and following the fragmentation, an electron is transferred back from the phthalimide radical anion **13** to either the radical cation of *i*-Pr_2NEt or the photoexcited $Ru(bpy)_3^{2+}$* catalyst. Further supporting this mechanism, the PET-promoted redox reaction of substrate **1** could be carried out to completion with substoichiometric amounts (0.5 equiv) of the amine.

Table 1. Oxidation of *N*-Benzyloxyphthalimides[a]



entry	R	substrate **10**	product **11**	yield (%)[b,c]
1	F	**10a**	**11a**	82 (81)
2	Cl	**10b**	**11b**	62 (54)
3	Br	**10c**	**11c**	62 (64)
4	H	**1**	**2**	86 (78)
5	OMe	**10d**	**11d**	55 (50)[d]
6	NO_2	**10e**	**11e**	<5 (<5)

[a] Conditions: $Ru(bpy)_3(PF_6)_2$ (5 mol %), *i*Pr_2NEt (3 equiv), $LiBF_4$ (2 equiv), $(CD_3)_2CO$, 23 °C. Reactions were irradiated with a 275 W GE floodlight (see Supporting Information). [b] Determined by ^{1}H NMR. Numbers in brackets indicate the reaction yield without $Ru(bpy)_3^{2+}$ catalyst. [c] In all of the reactions there is <5% benzyl alcohol formed. [d] The yield of this reaction can be improved if the reaction time is increased to 40 min. See Supporting Information for details.

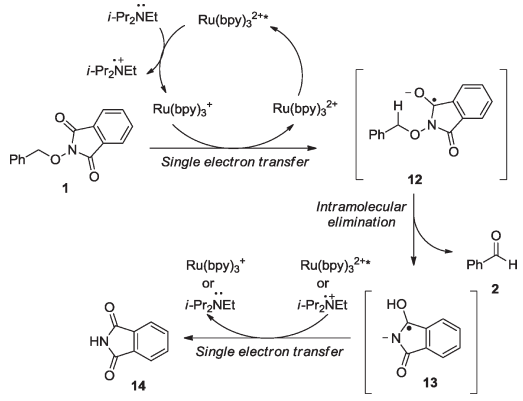


Figure 1. Proposed redox fragmentation mechanism.[22]

In addition to being mechanistically novel, this transformation imparts many synthetic advantages over existing oxidation methodologies. Primarily, the conditions needed to promote the redox fragmentation are extremely mild, as all that is required is an amine base, a commercially available lithium salt, a catalytic amount of $Ru(bpy)_3^{2+}$, and light. The redox process also is run in acetone and does not require halogenated solvents. The mild reaction conditions of this new PET-promoted redox fragmentation are particularly well-suited to challenging aromatic nitrogen-containing substrates (Table 2, entries 1−3). Oxidations of these aromatic heterocycles typically employ superstoichiometric amounts of manganese dioxide (typically over 5 equivalents).[23,24] Furthermore, these heterocycles can be challenging to oxidize using conventional oxidation methodologies due to problems

(19) The rate of a cyclopropylcarbinyl radical opening is 9.4×10^7 s^{-1}: (a) Newcomb, M.; Glenn, A. G. *J. Am. Chem. Soc.* **1989**, *111*, 275–277. (b) Beckwith, A. L. J.; Bowry, V. W. *J. Org. Chem.* **1989**, *54*, 2681–2688.

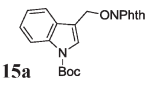
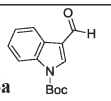
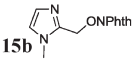
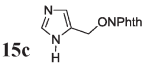
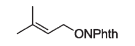
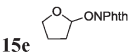
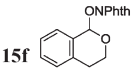
(20) To rule out the possibility of self-quenching of the $[Ru(bpy)_3)]^{2+*}$ by $[Ru(bpy)_3]^{2+}$, the PET photoredox reaction of **1** was run at a higher concentration (0.1 M) both with and without the addition of a catalyst. Both reactions provided comparable yields.

(21) The difference in reactivity between the radical anion generated upon PET and a tin-bound phthalimide radical formed during alkoxy-radical generation (ref 9) is likely simply a result of coordination of the tin to the carbonyl oxygen preventing the cyclic redox process.

(22) In the absence of $Ru(bpy)_3^{2+}$, the first electron transfer occurs directly from *i*-Pr_2NEt.

(23) For representative examples of the oxidation of imidazole alcohols, see: (a) Basso, D.; Broggini, G.; Passarella, D.; Pilati, T.; Terraneo, A.; Zecchi, G. *Tetrahedron* **2002**, *58*, 4445–4450. (b) Batten, M. P.; Canty, A. J.; Cavell, K. J.; Ruether, T.; Skelton, B. W.; White, A. H. *Inorg. Chim. Acta* **2006**, *359*, 1710–1724. (c) McNab, H. J. *Chem. Soc. Perkin Trans. 1* **1987**, *1*, 653–656.

Table 2. Expanded Substrate Scope[a]

entry	substrate	product	yield (%)[b]
1	 **15a**	 **16a**	76 (41)
2	 **15b**	 **16b**	81 (72)
3	 **15c**	 **16c**	71 (59)
4	 **15d**	 **16d**	72 (59)
5	 **15e**	 **16e**	63 (71)
6	 **15f**	 **16f**	>95 (86)

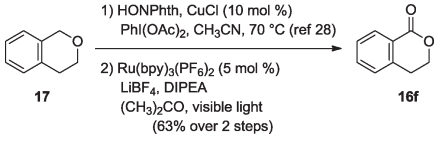
[a] Conditions: $Ru(bpy)_3(PF_6)_2$ (5 mol %), *i*Pr_2NEt (3 equiv), $LiBF_4$ (2 equiv), $(CD_3)_2CO$, 23 °C. Reactions were irradiated with a 275 W GE floodlight for 15–90 min (see Supporting Information). [b] Determined by ^1H NMR. Numbers in brackets indicate the reaction yield without $Ru(bpy)_3^{2+}$ catalyst.

with overoxidation.[25] A PET redox fragmentation provides a mild and selective alternative. Under the standard $Ru(bpy)_3^{2+}$ photocatalytic conditions, indole containing *N*-alkoxyphthalimide **15a** was oxidized in high yield (Table 2, entry 1). In contrast to simple benzyl derivatives (Table 1), the reaction was significantly lower yielding under the metal catalyst-free conditions. Notably, since the reaction proceeds under mild, basic conditions, the acid-sensitive Boc group remains intact. The reaction efficiency was comparably high even upon scale-up, with the $Ru(bpy)_3^{2+}$ conditions affording indole **16a** in 83% isolated yield.

The redox fragmentation was also successfully applied to the oxidation of imidazole derivatives (entries 2–3). Imidazole derivative **15b** displayed a comparable reactivity profile as indole derivative **15a**, with the $Ru(bpy)_3^{2+}$ photocatalytic conditions providing notably higher yields than under ruthenium-free conditions. Unprotected imidazole substrate **15c** efficiently underwent the redox fragmentation process to afford **16c** in high yields both with and without $Ru(bpy)_3^{2+}$. The scope of the reaction extends beyond the oxidation of aryl alcohol derivatives. *N*-Allyloxyphthalimide **15d** was readily oxidized to the α,β-unsaturated aldehyde **16d** (Table 3, entry 4). Higher oxidation states can also be accessed from *N*-alkoxyphthalimides (entries 5 and 6). With benzylic activation (entry 6), the oxidation proceeds in quantitative yield in the presence of the $Ru(bpy)_3^{2+}$ catalyst. Both lactol oxidations also proceeded comparably well on a larger scale, with the metal-free conditions providing lactone **16e** in 61% isolated yield and the $Ru(bpy)_3^{2+}$ conditions providing lactone **16f** in 89% isolated yield.

The *N*-alkoxyphthalimide required for the PET redox fragmentation is a versatile synthetic motif. Not only can *N*-alkoxyphthalimides be readily installed through a simple S_N2 reaction, but they can also be incorporated by copper-mediated C–H functionalization.[26] This redox fragmentation process, therefore, allows a rapid method for the conversion of hydrocarbons to carbonyl derivatives (Scheme 3).[27] Additionally, *N*-alkoxyphthalimides can be used effectively as protected carbonyls. Once installed, *N*-alkoxyphthalimides are stable to a wide range of reaction conditions.[28] These latent carbonyls can then be selectively unmasked under very mild redox fragmentation conditions.

Scheme 3. Two-Step Oxidation of Benzylic C–H Bonds



In summary, we have developed a mild method for the redox fragmentation of activated *N*-alkoxyphthalimides. The reactions proceed through a PET from *i*-Pr_2NEt to the *N*-alkoxyphthalimide followed by a concerted elimination to afford an oxidized carbon and a reduced phthalimide, *via* a process that is mechanistically distinct from previous photoinduced redox fragmentations. Through a series of mechanistic experiments, we established that this process constitutes the first example of a visible-light-promoted PET redox fragmentation. The redox fragmentation of *N*-alkoxyphthalimides was applied to the mild and selective redox fragmention of sensitive nitrogen-containing heterocycles. Furthermore, the *N*-hydroxyphthalimides can be readily installed using simple substitution or C–H activation reactions. The resulting *N*-alkoxyphthalimides can then either serve as a protecting group or be unmasked under mild reaction conditions.

Acknowledgment. This work was supported by the University of British Columbia and the Natural Sciences and Engineering Research Council of Canada.

Supporting Information Available. Experimental details and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(24) For representative examples of the oxidation of indole alcohols, see: (a) Zheng, C.; Lu, Y.; Zhang, J.; Chen, X.; Chai, Z.; Ma, W.; Zhao, G. *Chem–Eur. J.* **2010**, *16*, 5853–5857. (b) Tidwell, J. H.; Peat, A. J.; Buchwald, S. L. *J. Org. Chem.* **1994**, *59*, 7164–7168.

(25) For representative examples of the manganese dioxide overoxidation, see: (a) Kumar, C. N. S. S. P.; Devi, C. L.; Rao, V. J.; Palaniappa, S. *Synlett* **2008**, 2023–2027. (b) Mohanakrishnan, A. K.; Srinivasan, P. C. *Synth. Commun.* **1995**, *25*, 2407–2414.

(26) Lee, J. M.; Park, E. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 7824–7825.

(27) For a direct $Ru(bpy)_3^{2+}$ catalyzed C–H oxidation that requires doubly benzylic C–H bonds, see: Su, Y.; Zhang, L.; Jiao, N. *Org. Lett.* **2011**, *13*, 2168–2171.

(28) For a representative example of the use of *N*-alkoxyphthalimides in small molecule synthesis, see: Zhu, H.; Wickenden, J. G.; Campbell, N. E.; Leung, J. C. T.; Johnson, K. M.; Sammis, G. M. *Org. Lett.* **2009**, *11*, 2019–2022.