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Revisiting the Reactivity of the Dismissed Hydrogen Atom Transfer Catalyst Succinimide-*N*-oxyl

Cheng Yang, Luke A. Farmer, Derek A. Pratt,* Stephen Maldonado,* and Corey R. J. Stephenson*

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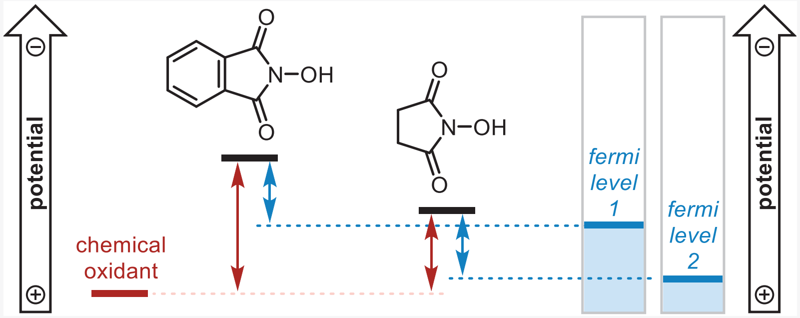

ABSTRACT: Phthalimide-*N*-oxyl (PINO) and related radicals are promising catalysts for C−H functionalization reactions. To date, only a small number of *N*-oxyl derivatives have demonstrated improved activities over PINO. We postulate that the lack of success in identifying superior catalysts is associated not only with challenges in the design and synthesis of new structures, but also the way catalysts are evaluated and utilized. Catalyst evaluation typically relies on the use of chemical oxidants to generate *N*-oxyl radicals from their parent *N*-hydroxy compounds. Herein we provide an example where a potential-controlled electrochemical analysis reveals that succinimide-*N*-oxyl (SINO) compares favorably to PINO as a hydrogen atom transfer (HAT) catalyst−in contrast to previous claims based on other approaches. Our efforts to understand the basis for the greater reactivity of SINO relative to PINO have underscored that the HAT kinetics are significantly influenced by factors beyond changes in thermodynamics. This is perhaps best illustrated by the similar reactivity of tetrachloro-PINO and SINO despite the latter engaging in substantially more exergonic reactions. The key role of HAT transition state (TS) polarization prompted the design and initial characterization of a chlorinated SINO derivative, which we found to be the most reactive *N*-oxyl HAT catalyst reported to date.

■ INTRODUCTION

Phthalimide-*N*-oxyl (PINO) is an appealing hydrogen atom transfer (HAT) catalyst, enabling the direct generation of radical intermediates from fairly activated starting materials.[1] Recent developments in selective lignin oxidation,[2] benzylic iodination,[3] and allylic C−H oxidation,[4] for example, have made use of PINO or similar derivatives. Since the first use of PINO as a HAT reagent for organic synthesis in 1978,[5] there have been numerous efforts to identify and/or design improved structures. Although many candidates have been evaluated over the years, improvements in reactivity have been modest.[6−8]

Typically, PINO and other similar catalysts are generated by a chemical oxidant from parent *N*-hydroxyphthalimides (NHPIs).[1,8] While often effective, it can be difficult to assess the intrinsic reactivity of the catalyst since their catalytic efficiency is then a function of the rates of PINO generation, the subsequent HAT, and all chemical steps which follow (Figure 1A). We suggest that a more systematic approach to evaluating catalytic efficiency could accelerate the identification and/or design of new and promising HAT catalysts.

Electrocatalytic reactions performed with solid electrodes are attractive for several practical reasons,[9] but also present a fundamental advantage over chemical oxidants. While the latter have discrete chemical potentials (Figure 1B), electrons at an electrode surface have an electrochemical potential (i.e., Fermi level)[10] that can be varied continuously over the continuum of values accessible in a given solution (Figure 1C). This difference arises because the electrostatics of a molecule are set by the surrounding medium, while the electrostatic charge of an electrode can be instantaneously and deterministically changed with a power supply or a potentiostat. Heterogeneous oxidations at an electrode can therefore be controlled by tuning the thermodynamic driving force (or overpotential η)[10] at which the catalyst is generated, affording

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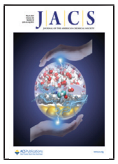

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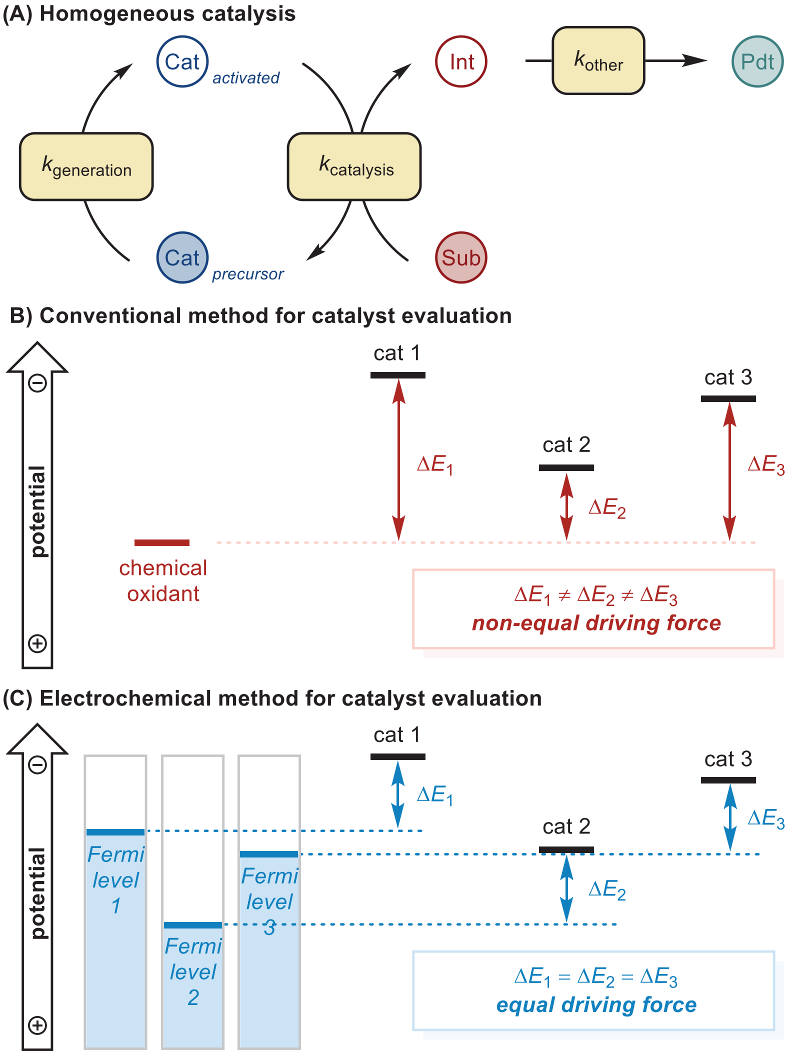

Figure 1. Approaches for assessing efficiency of redox-promoted homogeneous catalysis. Cat = catalyst; Sub = substrate; Int = intermediate; Pdt = product.

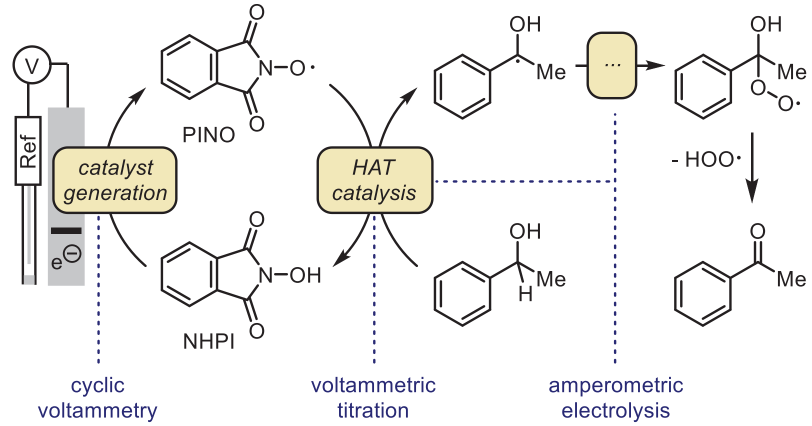

Figure 2. Potential-controlled electrochemical approach for assessment of *N*-oxyl HAT catalysts.

more direct insight on the catalytic reaction and subsequent chemical steps.

In the present work we provide a robust exhibition of this approach by comparing a previously dismissed[3,4,11] HAT catalyst, succinimide-*N*-oxyl (SINO), to PINO. The current understanding is that SINO is an inferior HAT mediator compared to PINO,[3,4,11] ascribed mostly to a "likely" lower stability.[3,4] Consequently, the use of the NHS/SINO redox couple in reaction development has been seldom reported.[12−15] We demonstrate that SINO has higher activity than PINO when assessed appropriately, and as such, could be an attractive alternative in the context of HAT catalysis. On

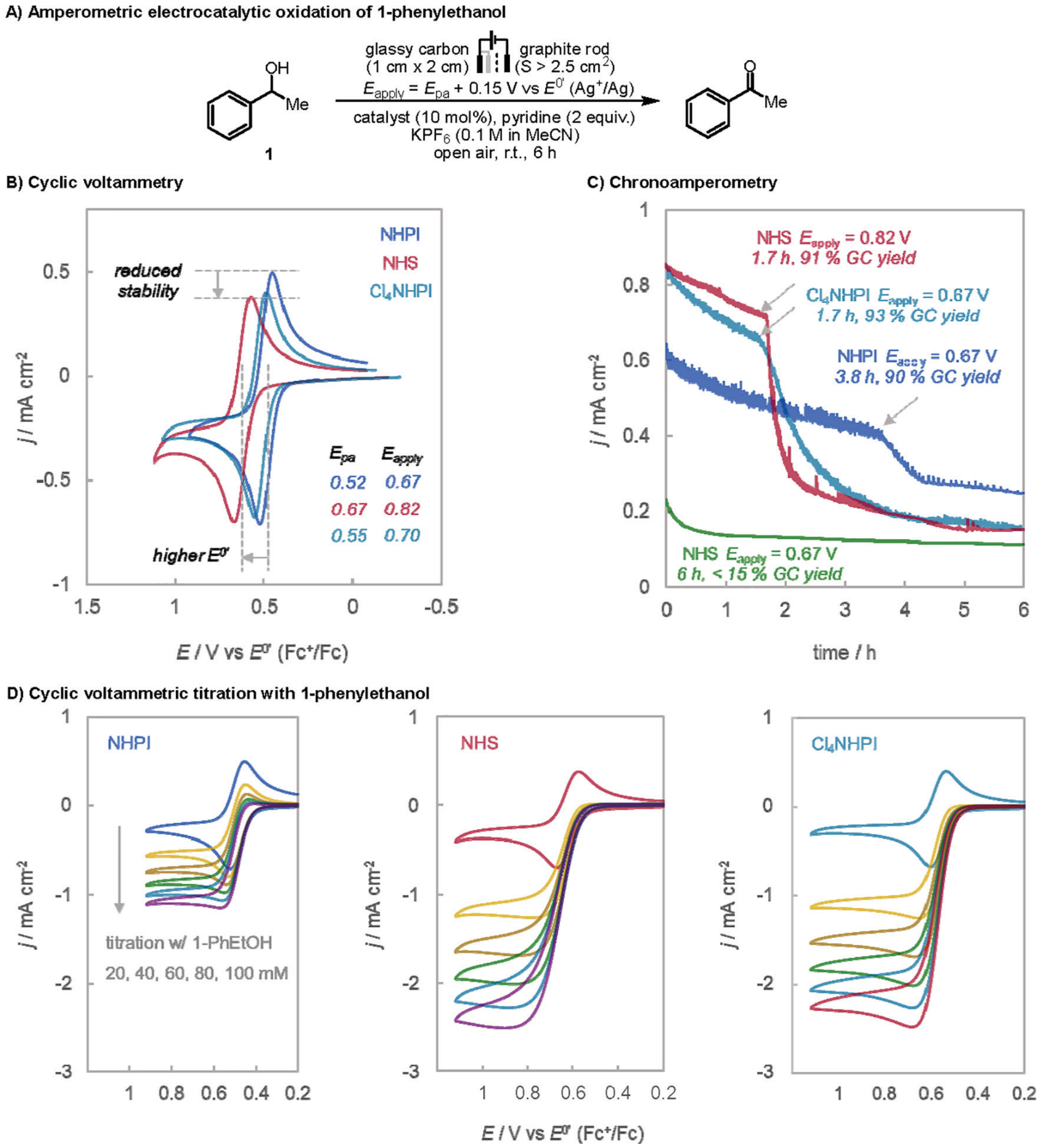

Figure 3. Comparison of NHPI/PINO, Cl_4NHPI/Cl_4PINO, and NHS/SINO activity using electrochemical methods. (A) Amperometric oxidation of 1-phenylethanol (20 mM) catalyzed by electrochemically generated *N*-oxyl radicals. Divided cell. (B) Cyclic voltammagrams of 2 mM *N*-hydroxy compounds in the presence of 0.1 M NBu_4PF_6,[21] 0.2 M pyridine, 0.2 pyridinium tetrafluoroborate[22] at a scan rate of 0.1 V s^{-1}. (C) Bulk electrolysis *i*−*t* curve for catalytic oxidation of 1-phenylethanol for 6 h. (D) Cyclic voltammetric titration of NHPI, NHS, Cl_4NHPI (2 mM) with 1-phenylethanol (20, 40, 60, 80, and 100 mM).

one hand, the succinimide species can be easily prepared via Diels−Alder reactions between maleic anhydride and a variety of dienes, providing an open-ended opportunity for catalyst design. On the other hand, SINO and its derivatives are expected to activate a broader range of substrates compared to PINO due to greater thermodynamic driving forces.[16,17] This work provides new insights on the merits of SINO and showcases possible applications in benzylic alcohol oxidations.

■ RESULTS

Evaluation of *N*-oxyl HAT Catalysts by a Potential-controlled Approach. Our strategy to compare the catalytic efficiency between PINO and SINO involves interrogation of each of the key steps in the mechanism of *N*-oxyl mediated C−H abstraction (Figure 2).[18] The anodic oxidation of the *N*-hydroxy precursors and the key HAT step were investigated by cyclic voltammetry and voltammetric titration, respectively. The overall catalytic performance of HAT and the subsequent chemical steps were studied under potential-controlled conditions.

The key experiments which demonstrate SINO as a more efficient HAT catalyst than PINO are amperometric (i.e., potential-controlled) electrocatalytic oxidations of 1-phenylethanol (Figure 3A). These reactions were performed in divided cells for the purpose of preventing crossover from the counter electrode to facilitate comparison. The reaction components shown in Figure 3A were added to the anodic chamber, while only electrolyte was added to the cathodic chamber. A flat, chemically inert glassy carbon plate was used as the anode material to maintain the same reactive surface area. In order to evaluate the activity of the NHPI/PINO and NHS/SINO couples under the same reaction driving force, the applied potential for each reaction was set to +0.15 V relative to the anodic peak potential recorded in the absence of 1-phenylethanol at a scan rate of 0.1 V s^{-1} (Figure 2B).[19] The larger initial current density in reactions with NHS than with NHPI (0.8 vs 0.6 mA/cm^2) indicated a faster HAT rate with SINO compared to PINO (Figure 3C).[20] Indeed, SINO-catalyzed benzylic alcohol oxidation was complete in 1.7 h (0.67 V vs $E(Fc^{+/0})$) with a 91% yield (by gas chromatography−mass spectroscopy), while the PINO-promoted reaction required 3.8 h (0.82 V vs $E(Fc^{+/0})$) to provide the oxidized product in a similar yield (90%). Importantly, SINO exhibited lower efficiency than PINO when the optimized potential of NHPI oxidation (0.67 V vs $E(Fc^{+/0})$) was applied (15% vs <90% yield after 6 h), i.e., experimental conditions akin to the use of a chemical oxidant (Figure 3C). Considering there is a 0.15 V difference in formal standard potentials ($E^{0\prime}$) between these two catalysts (Figure 3B), the previously reported low efficiency of SINO-catalyzed HAT reactions could simply be due to an artificially slow oxidation of NHS, which becomes rate-limiting for the entire reaction.

To complement the foregoing observations, a series of electroanalytical experiments were conducted to understand the kinetic and thermodynamic aspects of the catalytic reaction. Cyclic voltammetric titration within the kinetic regime[23] demonstrated a first-order dependence on 1-phenylethanol (Figure 3D). The rate constants of the second-order HAT reactions (k_{HAT}) between 1-phenylethanol and electrochemically generated PINO or SINO were determined to be 24.3 and 97.2 M^{-1} s^{-1}, respectively (Figure 3D). Furthermore, the persistence of each *N*-oxyl radical was evaluated by determination of the cathodic/anodic peak current ratio ($i_{\mathrm{pc}}/i_{\mathrm{pa}}$) at the scan rate of 0.1 V s^{-1}. Consistent with previous reports,[3,4] SINO was less persistent than PINO on this basis ($i_{\mathrm{pc}}/i_{\mathrm{pa}}$ = 0.93 vs 0.86) (Figure 3B). Similar to the PINO−PINO charge transfer decomposition mechanism proposed by our laboratories,[18] our calculations suggest that SINO also reacts with another of itself to open the ring.[24] Moreover, the calculated barriers for the SINO−SINO reaction are lower (Supporting Information), and the product is much more thermodynamically stable, which provides a theoretical basis for the lower persistence/stability of SINO compared to PINO. However, the bulk electrolyses under potential-controlled conditions suggest that catalyst stability was not the determining factor in the prior assessment of SINO's utility (or lack thereof) as a HAT catalyst. These data suggest that when evaluated with equivalent reaction driving forces, SINO is a more efficient HAT catalyst than PINO, despite its shorter lifetime.

Given that tetrachlorophthalimide-*N*-oxyl (Cl_4PINO) is often promoted as a more potent alternative to PINO,[4,6] we measured corresponding k_{HAT} values to compare with SINO and PINO. Our voltammetric data suggests that the kinetics of the Cl_4PINO-promoted HAT reaction with 1-phenylethanol are nearly identical to SINO (98.1 vs 97.2 M^{-1} s^{-1}). Additionally, SINO and Cl_4PINO seem to have similar stability according to their almost identical $i_{\mathrm{pa}}/i_{\mathrm{pc}}$ (SI). Moreover, use of Cl_4NHPI in potential-controlled oxidations of 1-phenylethanol gave very similar performance to NHS (1.7 h, 91% vs 1.7 h, 93%) (SI).

Computational Insights on the Reactivity of *N*-oxyl Promoted HAT. To provide insight on the greater HAT reactivity of SINO relative to PINO we turned to computation. Earlier density functional theory (DFT) studies comparing NHS/SINO and NHPI/PINO suggested that the barrier for HAT from ethylbenzene was lower for SINO and was due to a much higher bond dissociation enthalpy of NHS relative to NHPI (ΔBDE_{O-H} = +4.8 kcal/mol).[17] These computational results were corroborated by Hermans et al., but were interpreted more cautiously.[12] Our own high-accuracy CBS-QB3 calculations predict that the BDE_{O-H} of NHS (88.1 kcal/mol) is indeed significantly greater than that of NHPI (83.6 kcal/mol). However, the modest increase in k_{HAT} for SINO compared to PINO across the range of tested substrates (ca. 2 to 4-fold) suggests that the $\Delta\Delta G^{\ddagger}$ for their respective HAT reactions should be considerably smaller. Indeed, when we mapped out the energy surface for HAT from 1-phenylethanol to each of SINO and PINO using M06-2X/cc-pVTZ while applying solvent (IEF-PCM/MeCN) and dispersion (GD3) corrections,[25,26] we found a much smaller difference in the barriers ($\Delta\Delta G^{\ddagger}$ = −2.1 kcal/mol), as shown in Figure 4A.[27−29] Since these reactions are exergonic, the difference in BDEs is not expected to be fully manifested in the relative barrier heights since O−H bond formation at the transition state (TS) is largely incomplete, but the much smaller differences in barrier and observed reactivity suggest other factors play a role.

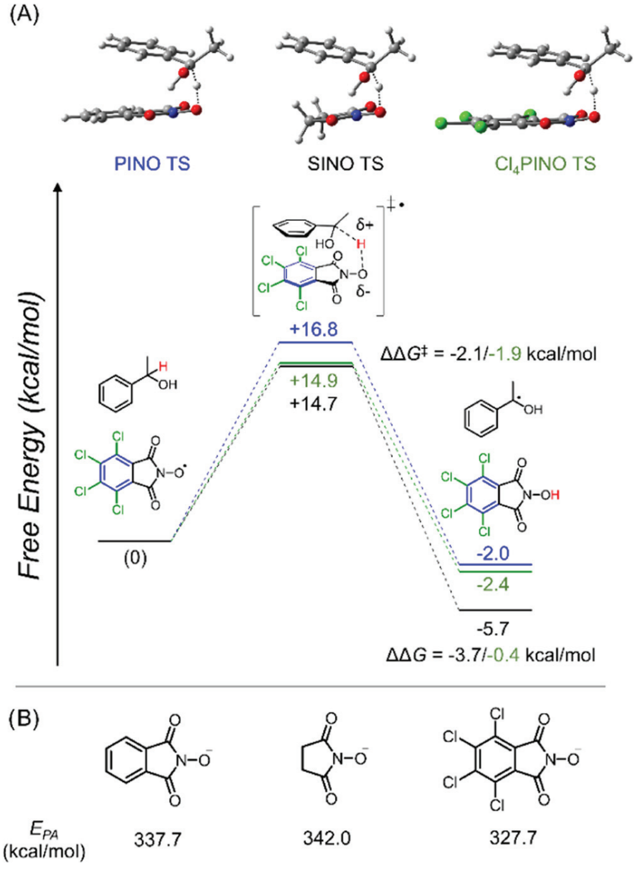

Figure 4. (A) Energetics of HAT between PINO, SINO, and Cl_4PINO and 2-phenylethanol determined by M06-2X/cc-pVTZ with IEF-PCM solvation (acetonitrile) and GD3 dispersion corrections. (B) Gas phase proton affinities (E_{PA}) of $PINO^-$, $SINO^-$ and Cl_4PINO^- determined by CBS-QB3.

Earlier mechanistic work by Minisci and co-workers demonstrated that benzaldehydes are formed selectively over benzoic acids when benzyl alcohols are oxidized using a NHPI/Co(II) system because of favorable polarization of the HAT TS between PINO and benzyl alcohol. The benzylic carbon of benzyl alcohol can better accommodate the partial positive charge developing at this position at the TS as compared to the benzoyl carbon of benzaldehyde, such that the reaction stops there.[12,30−35] To provide insight on the ability of different *N*-oxyl catalysts to stabilize corresponding partial negative charge developing on oxygen in the polarized TS, consideration of the pK_as of the corresponding *N*-hydroxy precursors could be useful. However, since these values (6.3 and 6.0 for NHPI and NHS, respectively)[36] have been recorded in water where extensive H-bonding interactions are likely to obscure the intrinsic stabilities of the anions, we determined the gas phase proton affinities (E_{PA}) of PINO$^-$ and SINO$^-$ using CBS-QB3 (Figure 4B). The calculated difference (ΔE_{PA} = +4.3 kcal/mol) is consistent with the notion that PINO can better stabilize negative charge density than SINO and would therefore enhanced polarization of the TS.

Consistent with the increased reactivity of Cl_4PINO relative to PINO, the calculated $\Delta G^\ddagger$ for HAT from 1-phenylethanol was determined to be 1.9 kcal/mol lower for the former than the latter (Figure 4A).[37] This difference is essentially identical to that determined for SINO relative to PINO, although the reaction with Cl_4PINO is not nearly as exergonic ($\Delta\Delta G$ = −0.4 vs −3.7 kcal/mol, respectively). At first glance, it is difficult to reconcile the increased k_{HAT} values for Cl_4PINO over PINO on the basis of the modest increase in reaction enthalpy (ΔBDE_{O-H} = +0.6 kcal/mol, as determined by CBS-QB3) for HAT reactions of Cl_4PINO. However, the sharp decrease in proton affinity of Cl_4PINO relative to PINO (ΔE_{PA} = −10.0 kcal/mol) suggests a far more polarized TS. This suggestion is in line with the results of Hammett correlations of k_{HAT} for substituted benzyl alcohols, which are characterized by a notable decrease in ρ for more electron-deficient derivatives of NHPI, consistent with an increasingly polarized TS.[28] Thus, while Cl_4PINO and SINO both possess similarly enhanced activity over PINO, the underlying factors appear to be quite different, and clearly not based solely on the thermodynamics of HAT − a fact that is easily overlooked.

Building on the SINO Scaffold. Given the improvement of HAT reactivity of Cl_4PINO vs PINO, we sought to investigate the reactivity of a highly chlorinated SINO derivative. Catalyst precursor Cl_6NHS was synthesized from a condensation reaction between chlorendic anhydride and a hydroxylamine derivative (Figure 5A). From a theoretical perspective, the higher BDE_{O-H} (88.8 kcal/mol) and lower E_{PA} (328.2 kcal/mol) of Cl_6NHS (both determined by CBS-QB3) would suggest more thermodynamically and kinetically favorable HAT reactions of Cl_6SINO relative to SINO. Indeed, voltammetric titration suggested that the Cl_6SINO promoted HAT reaction with 1-phenylethanol was ~5 times faster than that promoted by SINO and therefore ~20 times faster than PINO (Figure 5B). Accordingly, much shorter reaction times were required to obtain similar yields when using Cl_6NHS in place of NHPI in electrocatalytic oxidations of 1-phenylethanol (0.7 h, 88% vs 3.8 h, 91%) (Figure 5B).

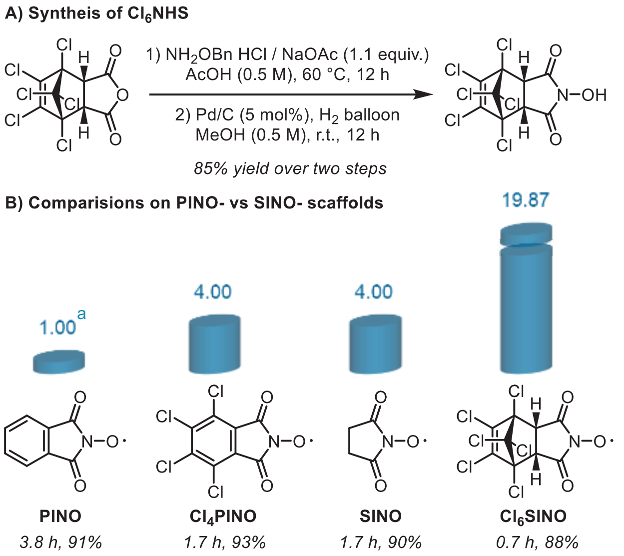

Figure 5. Reactivity of Cl_6SINO. [a]Relative rates of HAT are shown for reactions with 1-phenylethanol.

Table 1. Measured k_{HAT} Values between *N*-oxyls and Various Substrates by Cyclic Voltammetric Titration

	k_{HAT} (M^{-1} s^{-1})			
substrate	PINO	SINO	Cl_4PINO	Cl_6SINO
1-phenylethanol	24.3	97.2	95.3	482.8
cyclohexene	20.2	56.6	40.4	110.6
diphenylmethane	11.6	32.6	24.7	-[a]
toluene	≤11	13.5	13.5	65.4
ethanol	≤11	15.6	15.7	112.5
tetrahydrofuran	≤11	47.3	23.5	239.8
tetrahydropyran	≤11	<11	<11	89.6

[a]Unable to determine due to potential overlap.

The ability of SINO and Cl_6SINO to activate a wider range of substrates than PINO derivatives was demonstrated using a series of substrates for which the k_{HAT} values are given in Table 1. The premise that SINO should activate more challenging C−H bonds than PINO was also evaluated. In addition to 1-phenylethanol, PINO reacted with cyclohexene with a rate constant of 20.2 M^{-1} s^{-1} and diphenylmethane at 11.6 M^{-1} s^{-1}. However, reactions between PINO and a variety of more challenging substrates including toluene, ethanol and tetrahydrofuran were too slow to promote high enough current increases at the scan rate of 0.1 V s^{-1} for the determination of k_{HAT} (≤11 M^{-1} s^{-1}). In contrast, SINO reacted with these substrates at measurable rates. When using diphenylmethane, toluene, ethanol and tetrahydrofuran as substrates, the HAT rate constants were determined to be 32.6, 13.5, 15.6, and 47.3 M^{-1} s^{-1}, respectively. Cl_4PINO showed similar HAT reactivity to SINO among some of the substrates, though tended to be slower in others. Cl_6SINO exhibited 5 to 20 times faster HAT reactivity than PINO. These results suggest that SINO is a promising scaffold for *N*-oxyl HAT catalyst development. Notably, during these voltammetric studies, we noted that the shape of the catalytic current vs potential profile for each substrate was subtly different (SI), suggesting possible differences in the mechanisms (rate-determining step) of each HAT reaction,[37] an observation which will be explored in future work.

The catalytic performance of PINO, SINO, Cl_4PINO, and Cl_6SINO were further compared during oxidations of several electron-deficient benzylic alcohols (Figure 6).[38] Their k_{HAT} values were measured by cyclic voltammetric titration and

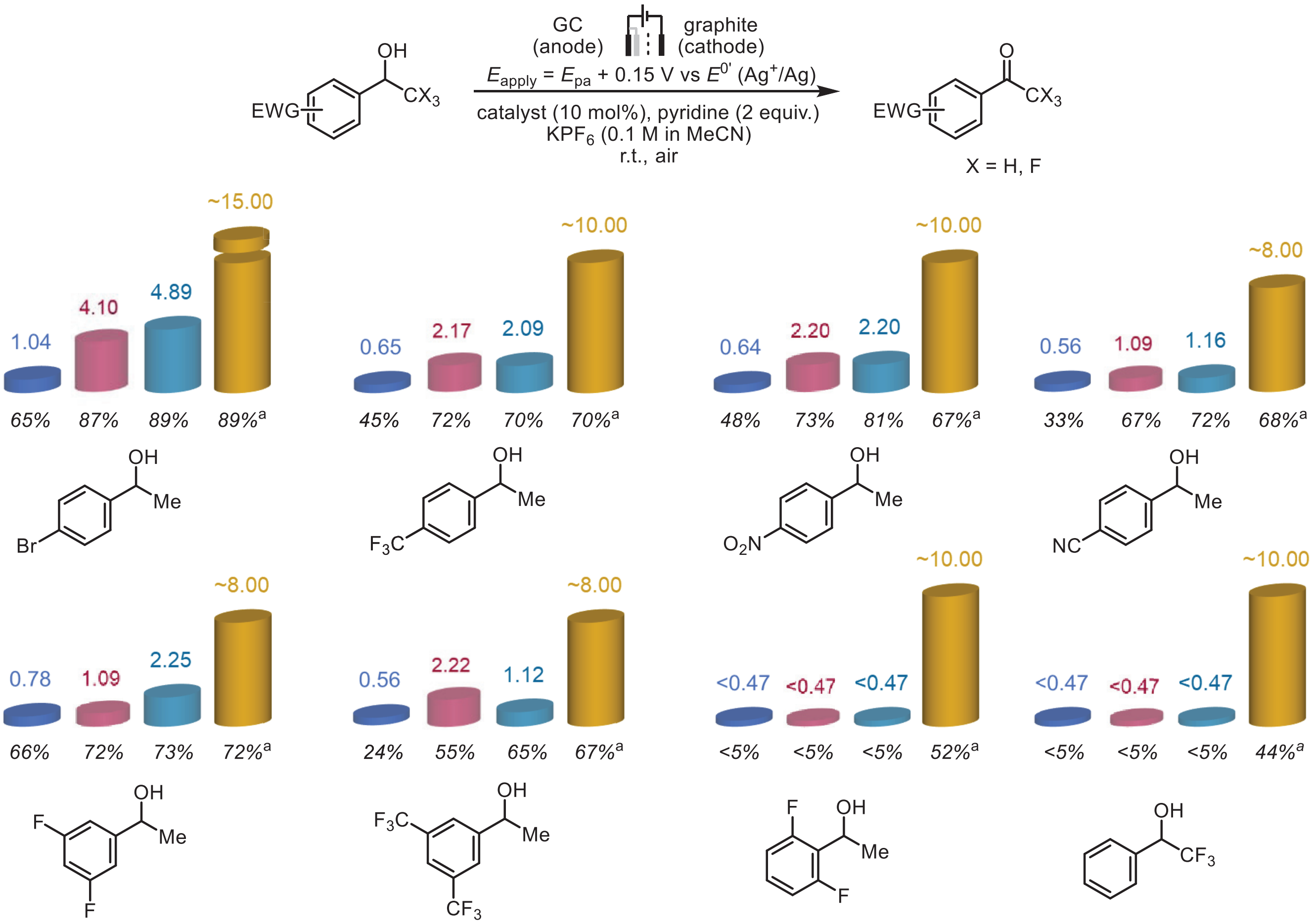

Figure 6. Electrocatalytic performance of NHPI, NHS, Cl_4NHPI, and Cl_6NHS. Relative rate constants are reported relative to using k_{HAT} for the reaction between PINO and 1-phenylethanol; PINO in dark blue, SINO in red, Cl_4NHPI in light blue, Cl_6NHS in yellow. For NHPI, NHS, and Cl_4NHPI, electrolysis experiments were stopped after 3 h, and products were isolated to compare yields and efficiency. [a] For Cl_6NHS, electrolysis experiment were stopped after 1 h.

reported relative to k_{HAT} for the reaction between PINO and benzylic alcohol derivatives as a reference. Expectedly, PINO activated electron-deficient alcohols at considerably lower rates compared to 1-phenylethanol. In comparison, SINO and Cl_4PINO could promote HAT reactions of these less-activated substrates efficiently. Cl_6SINO showed exceedingly fast k_{HAT}. In order to compare their catalytic performance, all substrates were subjected to potential-controlled conditions for electrolysis for 3 h, and their yields were used to represent reaction efficiencies. The reactions were stopped after 3 h to compare yields. All catalysts showed high HAT selectivity and only gave ketone as the product. The yields of the SINO- and Cl_4PINO-catalyzed reactions were generally 20% higher than those catalyzed by PINO under equivalent conditions, but did not have a quantitative correlation with the relative HAT rate constants.[39] For Cl_6SINO, 1 h was sufficient to give similar yields as SINO or Cl_4PINO in 3 h. These bulk electrolysis observations are consistent with the k_{HAT} values determined by cyclic voltammetric titration.

■ DISCUSSION

The data presented above contrasts existing notions about NHS/SINO – specifically its lack of synthetic utility for HAT catalysis. Rather, the system is of both practical and fundamental value. Our results highlight the efficiency of SINO-catalyzed oxidation of alcohols and other substrates, when assessed appropriately, and the potential benefit of SINO for targeting a broader range of C–H bonds which are not readily activated by PINO. Additionally, NHS is a promising backbone for designing new catalysts with a much greater enthalpic driving force compared to NHPI derivatives. As a proof-of-concept, we introduced Cl_6SINO as a superior HAT species, characterized by a 20-fold increase in HAT reactivity relative to PINO in the oxidation of model substrate 1-phenylethanol, and similarly impressive results for other tested substrates. To the best of our knowledge, Cl_6SINO is the most reactive *N*-oxyl type HAT catalyst that has been reported to date.

The enhanced reactivity of Cl_6SINO derives from a marrying of the enthalpically prodigious HAT of SINO with the enhanced polarization of the electron-deficient Cl_4PINO. These properties are both worthwhile considerations when optimizing for greater k_{HAT}; while BDE is a useful measure of the former, E_{PA} could serve as a convenient parameter for gauging TS polarization. Other mechanistic considerations that have been previously discussed, such as the formation of a charge transfer complex preceding HAT facilitated by π–π^* interactions of the aromatic substrate and PINO, may contribute to HAT catalysis, but are likely to be more substrate-specific (such as to phenols or electron-rich benzylic alcohols).[28,40]

While we have been able to provide insight into the intrinsic reactivity of NHS/SINO, and have built on that to arrive at Cl_6NHS/Cl_6SINO, it will be interesting to see if more suitable/effective homogeneous oxidations can be designed to further leverage these insights. Nevertheless, the examples presented herein may serve as an exhibition of the modularity of heterogeneous electrochemical oxidation, not only for quantitative catalyst evaluation, but also as a practical synthetic tool. We believe this methodology can facilitate greater access to very active *N*-oxyl catalysts and accelerate catalyst discovery, potentially in a high-throughput format. Research to this effect is currently underway within our research groups.

CONCLUSIONS

In summary, this work demonstrates that SINO is a potent HAT catalyst, despite claims to the contrary. Recognizing the hidden value in this known scaffold together with a more comprehensive interpretation of the factors affecting HAT reactivity of *N*-oxyl species can lead to research and innovation on the basis of rational design. The potential-controlled electrochemical approach employed here could enable further re-examinations of other potential catalysts that may also have been prematurely dismissed or overlooked.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c00688.

Cyclic voltammetry, electrolysis, computational studies, compound characterization (PDF)

AUTHOR INFORMATION

Corresponding Authors

Derek A. Pratt − *Department of Chemistry and Biomolecular Sciences, University of Ottawa, Ottawa, Ontario K1N 6N5, Canada;* orcid.org/0000-0002-7305-745X; Email: dpratt@uottawa.ca

Stephen Maldonado − *Willard Henry Dow Laboratory, Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109, United States; Program in Applied Physics, University of Michigan, Ann Arbor, Michigan 48109, United States;* orcid.org/0000-0002-2917-4851; Email: smald@umich.edu

Corey R. J. Stephenson − *Willard Henry Dow Laboratory, Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109, United States;* orcid.org/0000-0002-2443-5514; Email: crjsteph@umich.edu

Authors

Cheng Yang − *Willard Henry Dow Laboratory, Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109, United States*

Luke A. Farmer − *Department of Chemistry and Biomolecular Sciences, University of Ottawa, Ottawa, Ontario K1N 6N5, Canada*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.4c00688

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Recupero, F.; Punta, C. Free Radical Functionalization of Organic Compounds Catalyzed by *N*-Hydroxyphthalimide. *Chem. Rev.* **2007**, *107*, 3800−3842.

(2) Bosque, I.; Magallanes, G.; Rigoulet, M.; Kärkäs, M. D.; Stephenson, C. R. J. Redox Catalysis Facilitates Lignin Depolymerization. *ACS Cent. Sci.* **2017**, *3*, 621−628.

(3) Rafiee, M.; Wang, F.; Hruszkewycz, D. P.; Stahl, S. S. *N*-Hydroxyphthalimide-Mediated Electrochemical Iodination of Methylarenes and Comparison to Electron-Transfer-Initiated C−H Functionalization. *J. Am. Chem. Soc.* **2018**, *140*, 22−25.

(4) Horn, E. J.; Rosen, B. R.; Chen, Y.; Tang, J.; Chen, K.; Eastgate, M. D.; Baran, P. S. Scalable and Sustainable Electrochemical Allylic C−H Oxidation. *Nature* **2016**, *533*, 77−81.

(5) Grochowski, E.; Boleslawska, T.; Jurczak, J. Reaction of Diethyl Azodicarboxylate with Ethers in the Presence of *N*-hydroxyimides as Catalysts. *Synthesis* **1977**, *1977*, 718−720.

(6) Zhang, Q.; Chen, C.; Ma, H.; Miao, H.; Zhang, W.; Sun, Z.; Xu, J. Efficient Metal-free Aerobic Oxidation of Aromatic Hydrocarbons Utilizing Aryl-tetrahalogenated *N*-Hydroxyphthalimides and 1,4-diamino-2,3-dichloroanthraquinone. *J. Chem. Technol. Biotechnol.* **2008**, *83*, 1364−1369.

(7) Nechab, M.; Einhorn, C.; Einhorn, J. New Aerobic Oxidation of Benzylic Compounds: Efficient Catalysis by *N*-Hydroxy-3,4,5,6-tetraphenylphthalimide (NHTPPI)/CuCl Under Mild Conditions and Low Catalyst Loading. *Chem. Commun.* **2004**, 1500−1501.

(8) Yang, C.; Arora, S.; Maldonado, S.; Pratt, D. A.; Stephenson, C. R. J. The Design of PINO-like Hydrogen-Atom-Transfer Catalysts. *Nat. Rev. Chem.* **2023**, *7*, 653−666.

(9) Moeller, K. D. Using Physical Organic Chemistry to Shape the Course of Electrochemical Reactions. *Chem. Rev.* **2018**, *118*, 4817−4833.

(10) Bard, A. J.; Faulkner, L. R. *Electrochemical Methods: Fundamentals and Applications*, 2nd ed.; Wiley Global Education: New York, 2001.

(11) Ishii, Y.; Nakayama, K.; Takeno, M.; Sakaguchi, S.; Iwahama, T.; Nishiyama, Y. A Novel Catalysis of *N*-Hydroxyphthalimide in the Oxidation of Organic Substrates by Molecular Oxygen. *J. Org. Chem.* **1995**, *60*, 3934−3935.

(12) Cecchetto, A.; Minisci, F.; Recupero, F.; Fontana, F.; Pedulli, G. F. A New Selective Free Radical Synthesis of Aromatic Aldehydes by Aerobic Oxidation of Tertiary Benzylamines Catalysed by N-hydroxyimides and Co(II) Under Mild Conditions. Polar and Enthalpic effects. *Tetrahedron Lett.* **2002**, *43*, 3605−3607.

(13) Liu, S.; Liu, A.; Zhang, Y.; Wang, W. Direct C_α-heteroarylation of Structurally Diverse Ethers via a Mild *N*-Hydroxysuccinimide Mediated Cross-dehydrogenative Coupling Reaction. *Chem. Sci.* **2017**, *8*, 4044−4050.

(14) Yang, S.; Zhu, S.; Lu, D.; Gong, Y. Formylation of Fluoroalkyl Imines Through Visible-Light-Enabled H-Atom Transfer Catalysis: Access to Fluorinated α-Amino Aldehydes. *Org. Lett.* **2019**, *21* (7), 2019−2024.

(15) Wang, J.; Zhang, C.; Ye, X.; Du, W.; Zeng, S.; Xu, J.; Yin, H. An Efficient and Practical Aerobic Oxidation of Benzylic Methylenes by Recyclable *N*-Hydroxyimide. *RSC Adv.* **2021**, *11*, 3003−3011.

(16) Arnaud, R.; Milet, A.; Adamo, C.; Einhorn, C.; Einhorn, J. Hydrogen Abstraction from Ethylbenzene by Imide-*N*-oxyl Radicals

with and without O_2: a DFT Theoretical Study. *J. Chem. Soc., Perkin Trans. 2* **2002**, *2*, 1967−1972.

(17) Hermans, I.; Jacobs, P.; Peeters, J. Autoxidation Catalysis with *N*-Hydroxyimides: More-reactive Radicals or Just More Radicals? *Phys. Chem. Chem. Phys.* **2007**, *9*, 686−690.

(18) Yang, C.; Farmer, L. A.; Pratt, D. A.; Maldonado, S.; Stephenson, C. R. J. Mechanism of Electrochemical Generation and Decomposition of Phthalimide-*N*-oxyl. *J. Am. Chem. Soc.* **2021**, *143*, 10324−10332.

(19) The scan rate of 0.1 V s^{-1} is commonly used and corresponds to an experimentally relevant time scale (~20 s).

(20) In this experiment, the initial current of a mediated electrolysis represents how fast the mediator can be regenerated, i.e., the kinetics of HAT.

(21) NBu_4PF_6 was chosen for voltammetric experiments because it is highly soluble in acetonitrile, and its concentration can be easily changed when necessary, making it a good option for analytical purposes. However, alkyl ammonium salts are very soluble in organic solvents and difficult to remove. Thus, we chose KPF_6 for preparative experiments as it can be easily removed by column chromatography.

(22) Equal amounts of pyridinium tetrafluoroborate (acid) and pyridine (base) were added to investigate the stability of the *N*-oxyls. Because the redox event of *N*-hydroxyl/*N*-oxyl couple at a glassy carbon electrode is a proton-coupled electron transfer process, the electron transfer event is dependent on three components: redox couple, electrode, and acid/base. In order to determine formal standard potential ($E^{0\prime}$) and/or peak current ratio (i_{pc}/i_{pa}), both acid and base should be buffered. We also found that conjugate acids (pyridinium salts) have minimum impact on the desired oxidation reaction. Thus, pyridinium salts were not used during bulk electrolysis to avoid purification issues.

(23) Costentin, C.; Savant, J.-M. Multielectron, Multistep Molecular Catalysis of Electrochemical Reactions: Benchmarking of Homogeneous Catalysts. *ChemElectroChem* **2014**, *1*, 1226−1236.

(24) We also attempted to experimentally study the decomposition of succinimide-*N*-oxyl under electrochemical conditions. Besides minor ring-opening products, we observed the deoxygenation product as the major decomposition product. This is possibly due to an oxygen abstraction by the electrode surface.

(25) Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06-Class Functionals and 12 Other Function. *Theor. Chem. Acc.* **2008**, *120*, 215−241.

(26) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. A Consistent and Accurate *ab initio* Parameterization of Density Functional Dispersion Correction (DFT-D) for the 94 Elements H-Pu. *J. Chem. Phys.* **2010**, *132*, No. 154104, DOI: 10.1063/1.3382344.

(27) The smaller difference in k_{HAT} (4-fold) between PINO and either SINO or Cl_4PINO compared to what is suggested by the calculated $\Delta\Delta G^{\ddagger}$ at 25 °C (~29-fold) may be due to a greater tunneling contribution in reactions of PINO. Substantial primary KIEs ($k_H/k_D > 19$) for PINO-catalyzed HAT from benzylic substrates at 25 °C have been reported by both Annunziatini et al. and Cai et al. indicating tunneling is playing a role in this reactivity (see ref 28 and 29). It was also noted that more electron-rich derivatives of PINO (such as that derived from 3,6-MeO_2-NHPI) benefitted from a greater tunneling contribution compared to more electron-poor derivatives.

(28) Annunziatini, C.; Gerini, M. F.; Lanzalunga, O.; Lucarini, M. Aerobic Oxidation of Benzyl Alcohols Catalyzed by Aryl Substituted N-Hydroxyphthalimides. Possible Involvement of a Charge-Transfer Complex. *J. Org. Chem.* **2004**, *69*, 3431−3438.

(29) Cai, Y.; Koshino, N.; Saha, B.; Espenson, J. H. Kinetics of Self-Decomposition and Hydrogen Atom Transfer Reactions of Substituted Phthalimide N-Oxyl Radicals in Acetic Acid. *J. Org. Chem.* **2005**, *70* (1), 238−243.

(30) The polar effect reported for NHPI has been shown with multiple substrates in addition to benzylic alcohols (*N*-alkylamides, tertiary benzylamines, toluene, cyclohexane, *N*-benzyl acetamides, phenols). See refs 12 and 31−35.

(31) Minisci, F.; Punta, C.; Recupero, F.; Fontanaa, F.; Pedullia, G. F. A New, Highly Selective Synthesis of Aromatic Aldehydes by Aerobic Free-radical Oxidation of Benzylic Alcohols, Catalysed by *N*-hydroxyphthalimide Under Mild Conditions. Polar and Enthalpic Effects. *Chem. Commun.* **2002**, 688−689.

(32) Minisci, F.; Punta, C.; Recupero, F.; Fontana, F.; Pedulli, G. F. Aerobic Oxidation of N-Alkylamides Catalyzed by N-Hydroxyphthalimide under Mild Conditions. Polar and Enthalpic Effects. *J. Org. Chem.* **2002**, *67*, 2671−2676.

(33) Minisci, F.; Recupero, F.; Cecchetto, A.; Gambarotti, C.; Punta, C.; Faletti, R.; Paganelli, R.; Pedulli, G. F. Mechanisms of the Aerobic Oxidation of Alcohols to Aldehydes and Ketones, Catalysed under Mild Conditions by Persistent and Non-Persistent Nitroxyl Radicals and Transition Metal Salts − Polar, Enthalpic, and Captodative Effects. *Eur. J. Org. Chem.* **2004**, *2004*, 109−119.

(34) Bietti, M.; Forcina, V.; Lanzalunga, O.; Lapi, A.; Martin, T.; Mazzonna, M.; Salamone, M. Kinetic Study of the Reaction of the Phthalimide-*N*-oxyl Radical with Amides: Structural and Medium Effects on the Hydrogen Atom Transfer Reactivity and Selectivity. *J. Org. Chem.* **2016**, *81*, 11924−11931.

(35) Bietti, M.; Cucinotta, E.; DiLabio, G. A.; Lanzalunga, O.; Lapi, A.; Mazzonna, M.; Romero-Montalvo, E.; Salamone, M. Evaluation of Polar Effects in Hydrogen Atom Transfer Reactions from Activated Phenols. *J. Org. Chem.* **2019**, *84*, 1778−1786.

(36) DiLabio, G. A.; Franchi, P.; Lanzalunga, O.; Lapi, A.; Lucarini, F.; Lucarini, M.; Mazzonna, M.; Prasad, V. K.; Ticconi, B. Hydrogen Atom Transfer (HAT) Processes Promoted by the Quinolinimide-*N*-oxyl Radical. A Kinetic and Theoretical Study. *J. Org. Chem.* **2017**, *82*, 6133−6141.

(37) Many collected voltammograms did not appear to have a simple logistic (i.e. S-shaped) form. This point suggests that the operative processes were likely more complex than a simple E-C mechanism. The *N*-oxyl species have competing reactions with some substrates, for example olefin addition to the allylic compounds. It is difficult to perform foot-of-the-wave analysis (FOWA) or simulation since we do not know the complete mechanisms or their rates. Nevertheless, we believe that the presented analysis still provides a useful means to compare the reactivity of these catalysts, and a range of their kinetics for reaction development.

(38) Although the initial reaction current is proportional to $k_{HAT}^{1/2}$, the overall reaction efficiency is not solely dependent on the HAT reactivity, as HAT is not the only reaction going on. We think at least catalyst decomposition can complicate the reaction.

(39) D'Alfonso, C.; Bietti, M.; DiLabio, G. A.; Lanzalunga, O.; Salamone, M. Reactions of the Phthalimide N-Oxyl Radical (PINO) with Activated Phenols: The Contribution of π-Stacking Interactions to Hydrogen Atom Transfer Rates. *J. Org. Chem.* **2013**, *78*, 1026−1037.

(40) Mazzonna, M.; Bietti, B.; DiLabio, G. A.; Lanzalunga, O.; Salamone, M. Importance of π-Stacking Interactions in the Hydrogen Atom Transfer Reactions from Activated Phenols to Short-Lived N-Oxyl Radicals. *J. Org. Chem.* **2014**, *79*, 5209−5218.