

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

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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. We put forth an example where a potential-controlled electrochemical analysis reveals that succinimide-*N*-oxyl (SINO) compares favorably to PINO as a hydrogen atom transfer catalyst – in contrast to previous claims based on other approaches. Furthermore, our efforts to understand the basis for the greater reactivity of SINO relative to PINO have shed further light on the interplay of thermodynamic and kinetic factors in these HAT reactions and suggest that transition state (TS) polarization is a particularly important consideration. This is illustrated by the essentially identical reactivity of tetrachloro-PINO and SINO despite the significantly greater thermodynamic driving force in the reactions of the latter. Such measures of HAT TS polarization (i.e., proton affinity of the *N*-oxide anion) may be useful parameters in predicting and/or rationalizing reactivity in addition to reaction energetics (i.e., O-H bond dissociation enthalpy of the *N*-OH moiety). Building on these insights, we report the design and initial characterization of a chlorinated SINO derivative that has significantly greater reactivity as a HAT catalyst than either PINO or its chlorinated derivative.

Introduction

Phthalimide-*N*-oxyl (PINO) is an appealing hydrogen atom transfer (HAT) catalyst, enabling the direct generation of open-shell intermediates from fairly activated starting materials.¹ Recent developments of selective lignin oxidation,² benzylic iodination,³ and allylic C-H oxidation,⁴ all rely on the use of PINO or its derivatives. Since the first use of PINO as HAT reagent for organic synthesis in 1978,⁵ there has been an effort to identify and/or design improved structures. Although many candidates have been evaluated from several individual reports, only modest improvements have been realized.^{6,7,8}

In addition to the challenges associated with the design of new catalysts, a lack of consistent and robust approaches to measure catalytic efficiency has hampered the identification of superior alternatives to PINO. In most reports, PINO-type catalysts are generated by a chemical oxidant from parent *N*-hydroxyphthalimides (NHPIs).^{1,8} Their catalytic efficiency is then a function of the rates of PINO generation, the subsequent HAT, and all subsequent chemical steps (**Figure 1A**). Although an experimentally measured low catalytic efficiency could indicate a natively slow rate of PINO generation, low reactivity of HAT, or both, a conclusion that the catalyst under study is intrinsically ‘poor’ without further assessment can be misleading. This point is particularly important when the catalyst is evaluated under conditions where catalyst generation is performed at a single driving force. A more meaningful approach to evaluate the catalytic efficiency of PINO-type catalysts has yet to be established to facilitate identification and/or design of next-generation 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

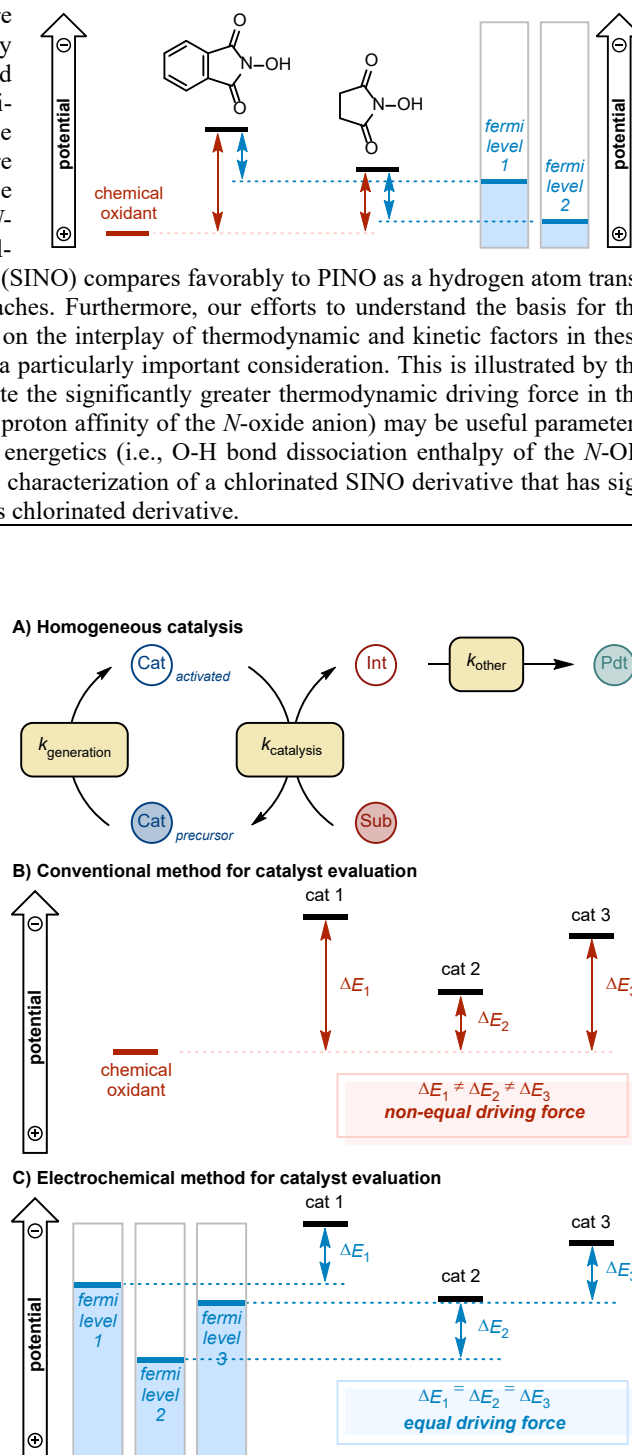


Figure 1. Approaches of assessing catalytic efficiency of redox-promoted homogeneous catalysis. Cat = catalysts; Sub = substrate; Int = intermediate; Pdt = product.

latter have discrete chemical potentials (**Figure 1B**), electrons at an electrode surface have an electrochemical potential (i.e., fermi level)¹⁰ that can be easily and arbitrarily varied over the entire range 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 of catalyst generation, affording more direct insight on the catalytic reaction and subsequent chemical steps. Although routinely applied in the fields of energy storage, CO₂ reduction, and many others,¹¹ heterogeneous oxidations have generally remained on the fringe in organic chemistry.

In the present work, we provide a robust exhibition of this approach by comparing a previously maligned^{3,4,12} hydrogen atom transfer (HAT) catalyst, succinimide-*N*-oxyl (SINO), to PINO. As we show below, SINO has higher activity than PINO when assessed appropriately, and as such, is attractive in the context of HAT catalysis. On one hand, the succinimide species can be easily derived from Diels-Alder reactions between maleic anhydride and a variety of dienes, providing opportunities for innovative catalyst design. On the other hand, SINO is expected to activate a broader range of substrates compared to PINO on the basis of thermodynamic driving forces.^{13,14} However, the current understanding is that SINO is an inferior HAT mediator compared to PINO,^{3,4,12} ascribed mostly to a 'likely' lower stability.^{3,4} Consequently, use of the NHS/SINO redox couple in reaction development has been rarely reported.¹⁵⁻¹⁷ This work provides new insights on the merits of SINO and possible reaction methodologies where it is ideally suited.

Results

Evaluation of *N*-oxyls by a potential-controlled approach.

Our strategy to compare the catalytic efficiency between PINO and SINO aims to interrogate each of the key steps in the mechanism of *N*-oxyl mediated C-H abstractions (**Figure 2**).¹⁸ The anodic oxidation of *N*-hydroxy precursors and the key HAT step were investigated by cyclic voltammetry and voltametric titration, respectively. The overall catalytic performance of HAT and the subsequent chemical steps were studied under potential-controlled conditions.

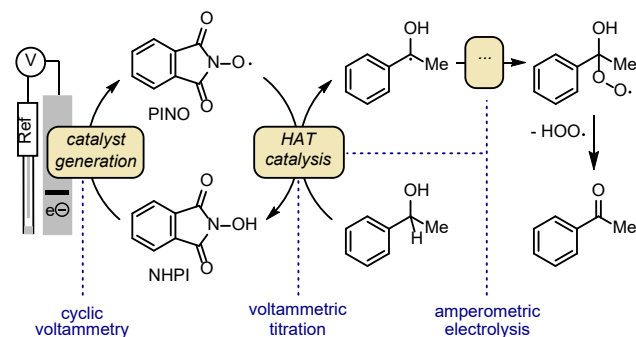
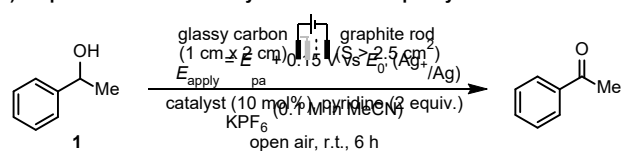
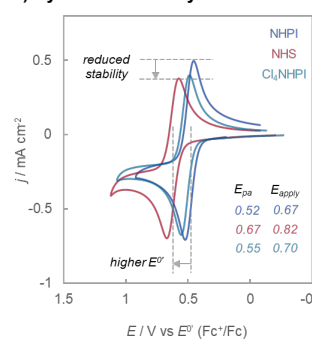


Figure 2. Potential-controlled electrochemical approach for assessment of *N*-oxyl HAT catalysts.

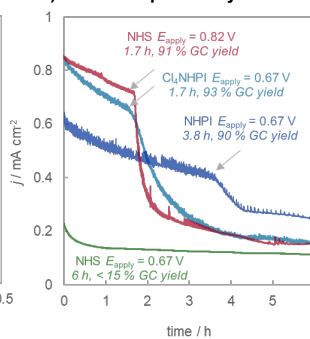
A) Amperometric electrocatalytic oxidation of 1-phenylethanol



B) Cyclic voltammetry



C) Chronoamperometry



D) Cyclic voltametric titration with 1-phenylethanol

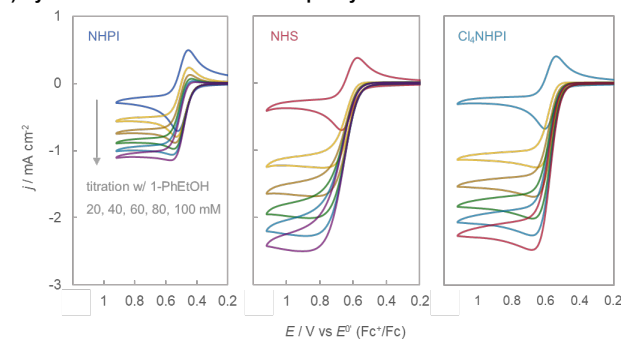


Figure 3. Evaluation between NHPI/PINO and NHS/SINO. **A)** Amperometric oxidation of 1-phenylethanol (20 mM) catalyzed by electrochemically generated nitroxides. Divided cell. **B)** Cyclic voltammetry for oxidation of 2 mM *N*-hydroxy compounds in the presence of 0.1 M NBU₄PF₆,²² 0.2 M pyridine, 0.2 M pyridinium tetrafluoroborate²³ at the scan rate of 0.1 Vs⁻¹. **C)** Bulk electrolysis *i*-*t* curve for 6 h. **D)** Cyclic voltametric titration of NHPI or NHS (2 mM) with 1-phenylethanol (20, 40, 60, 80, and 100 mM).

The key experiment demonstrating SINO as a more efficient HAT catalyst than PINO was demonstrated by 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 type of 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 Vs⁻¹ (**Figure 2B**).¹⁹ The larger initial current density in reactions with NHS than with NHPI (0.8 vs 0.6 mA/cm²) 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 Fc⁺⁰) with a 91% yield by gas chromatography-mass spectroscopy, while the PINO-

promoted reaction required 3.8 h (0.82 V vs $\text{Fc}^{+/0}$) to provide the oxidized product in a similar yield (90%). In a comparative experiment, SINO exhibited lower efficiency than PINO when the optimized potential of NHPI oxidation (0.67 V vs $\text{Fc}^{+/0}$) was applied (90 vs. <15% 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) between these two catalysts (Figure 3B), the previously reported low efficiency of SINO-catalyzed HAT reactions is likely due to a slow oxidation that is rate-limiting for the entire reaction.

To support our bulk electrolysis observation, a series of electroanalytical experiments were conducted to understand the kinetic and thermodynamic aspects of the catalytic reaction. Cyclic voltammetric titration within the kinetic regime²¹ 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 $\text{M}^{-1}\text{s}^{-1}$ and 97.2 $\text{M}^{-1}\text{s}^{-1}$, respectively (Figure 3D). Furthermore, the persistence of each of the *N*-oxyl radicals was evaluated by determination of the cathodic/anodic peak current ratio ($i_{\text{pc}}/i_{\text{pa}}$) at the scan rate of 0.1 Vs^{-1} . Consistent with previous hypotheses,^{3,4} SINO was indeed less persistent than PINO ($i_{\text{pc}}/i_{\text{pa}} = 0.93$ vs 0.86) (Figure 3B). Similar to the PINO-PINO charge transfer decomposition mechanism proposed by our laboratories,¹⁸ our calculation suggests that SINO also reacts with itself to open the ring. Differently, the barriers for SINO-SINO are lower (SI), and the product is much more thermodynamically stable, which provides theoretical basis for the lower persistence/stability of SINO compared to PINO. However, the bulk electrolysis under potential-controlled conditions suggested that catalyst stability was not the determining factor in the prior assessment of SINO's utility (or lack thereof) as an HAT catalyst. These data suggest that when evaluated at 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 touted as a more potent alternative to PINO,^{4,6} we measured corresponding k_{HAT} values to compare with SINO. Our voltammetric data suggested that the kinetics of Cl_4PINO promoted HAT reaction with 1-phenylethanol was nearly identical to SINO (98.1 vs 97.2 $\text{M}^{-1}\text{s}^{-1}$). Additionally, SINO and Cl_4PINO seemed to have similar stability according to their almost identical $i_{\text{pa}}/i_{\text{pc}}$ (SI). Use of Cl_4NHPI in potential-controlled oxidations of 1-phenylethanol gave very similar performance to NHS (1.7 h, 91% vs. 1.7, 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 ($\Delta\text{BDE}_{\text{O-H}} = +4.8$ kcal/mol).¹³ These computational results were corroborated by Hermans et al, but were interpreted more cautiously.¹⁴ Our own higher accuracy CBS-QB3 calculations predict that the $\text{BDE}_{\text{O-H}}$ of NHS (88.1 kcal/mol) is indeed significantly greater than 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 re-actions should be consider-

ably smaller. Indeed, when we mapped out the energy surface for HAT from 2-phenylethanol to each of SINO and PINO

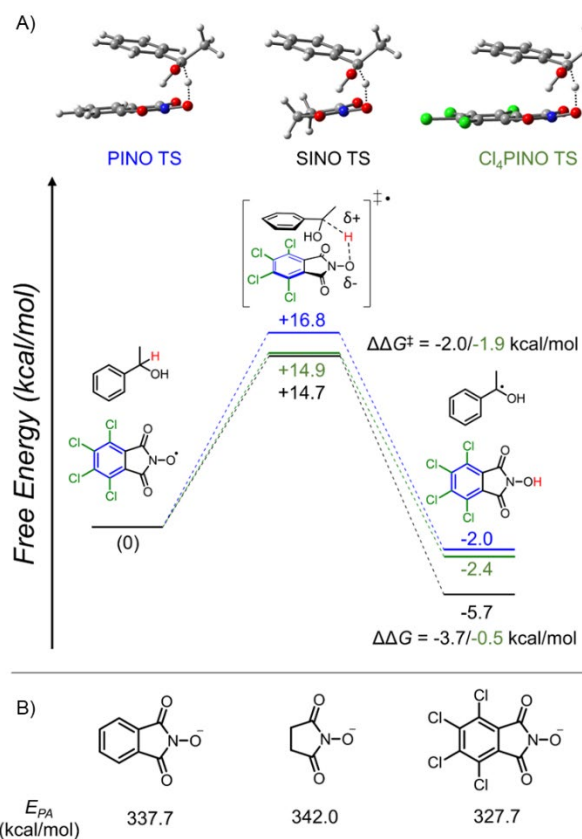


Figure 4. A) Energetics of HAT between PINO, SINO, and Cl_4PINO and 2-phenylethanol determined by M06-2X/cc-PVTZ with IEFPCM solvation (acetonitrile) and GD3 empirical dispersion corrections. B) Proton affinities (E_{PA}) of PINO⁻, SINO⁻ and Cl_4PINO^- determined by CBS-QB3.

using M06-2X/cc-PVTZ while applying solvation (IEFPCM/MeCN) and dispersion (GD3) corrections,^{24,25} we found a much smaller difference in the barriers ($\Delta\Delta G^\ddagger = -2.0$ kcal/mol), as shown in Figure 4A. Since these reactions are exergonic, the difference in BDEs would not be 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 may play a role. Both reactions are predicted to proceed via TS structures wherein the substrate alcohol is H-bonded to a carbonyl oxygen atom and the substrate phenyl ring is oriented over top of the aryl backbone of PINO and the two-carbon back-bone of SINO. As such, the PINO TS would uniquely benefit from the interaction of the π orbitals of the electron poor PINO and electron-rich substrate, as has been suggested in the reaction of PINO with toluene and phenol.²⁶

Alternatively, it is possible that the TS for HAT from 1-phenylethanol to PINO benefits from greater polarization. In principle, the pK_a 's of NHPI and NHS could inform on the ability of PINO and SINO to stabilize negative charge density in the TS. However, since these values (6.3 and 6.0, respectively)²⁷ have been recorded in water where extensive H-bonding interactions are likely to obscure the intrinsic stabi-

ties of the anions, we determined the proton affinities (E_{PA}) of PINO⁻ and SINO⁻ using CBS-QB3 (Figure 4B). The difference in the calculated proton affinities ($\Delta E_{PA} = +4.3$ kcal/mol) is consistent with the notion that PINO can better stabilize negative charge density than SINO and would therefore enable a more polarized TS.

Consistent with the observed reactivity of Cl₄PINO, the $\Delta\Delta G^\ddagger$ for HAT from 1-phenylethanol was determined to be -1.9 kcal/mol relative to PINO (Figure 4A). This difference is essentially identical to that determined for SINO relative to PINO, although the reaction with Cl₄PINO is not nearly as exergonic ($\Delta\Delta G = -0.5$ kcal/mol). At first glance, the increased k_{HAT} values for Cl₄PINO over PINO may arise due to either the modest increase in reaction enthalpy ($\Delta BDE_{O-H} = +0.6$ kcal/mol, as determined by CBS-QB3) or a stronger interaction of the π orbitals of the more electron-poor Cl₄PINO and electron-rich substrate. Given that the k_{HAT} values for Cl₄PINO and SINO follow similar trends regardless of whether the substrate has a pendant aromatic ring, the interaction of the π orbitals on Cl₄PINO (and therefore PINO) with those of the substrate do not seem to be a particularly important determinant of their reactivity. Instead, their propensity to engage in a more polarized TS (as suggested by their lower proton affinities) may be key. Therefore, while Cl₄PINO and SINO both possess similarly enhanced activity over PINO, the underlying factors appear to be different, and clearly not based solely on the BDE_{O-H} values of their precursors – as is often assumed.⁶

Building on the SINO scaffold. Since electronegative halogen atoms have been demonstrated to improve the HAT reactivity of *N*-oxyls (i.e., Cl₄PINO vs. PINO), we investigated the reactivity of a chlorinated SINO derivative. Catalyst precursor Cl₆NHS 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 Cl₆NHS (both determined by CBS-QB3) suggest a thermodynamically and kinetically more favorable HAT reaction of Cl₆SINO relative to SINO. Indeed, voltammetric titration suggested that Cl₆SINO promoted HAT reaction was greater than one order of magnitude (~20 times) faster than that promoted by

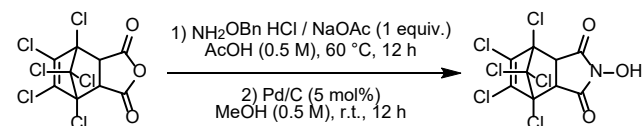
PINO (Figure 5B). Accordingly, when using Cl₆-NHS to perform electrocatalytic oxidation of 1-phenylethanol, it required much shorter reaction time to give similar yields to NHPI (0.7 h, 88% vs 3.8 h, 91%) (Figure 5B).

The ability of SINO-derived catalysts to activate a wider range of substrates than PINO derivatives was demonstrated over 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 specifically evaluated. In addition to 1-phenylethanol, PINO reacted with cyclohexene at a rate of 24.3 M⁻¹s⁻¹, and diphenylmethane at a slow rate of 11.6 M⁻¹s⁻¹. However, reactions between PINO and a variety of more challenging substrates including toluene, isopropanol, tetrahydropyran, tetrahydrofuran exhibited rate constants < 11 M⁻¹s⁻¹. These HAT reactions were too slow to promote high enough current increases at the scan rate of 0.1 Vs⁻¹ for the determination of k_{HAT} . In contrast, SINO reacted with these substrates at faster rates. When using diphenylmethane, toluene, ethanol, tetrahydrofuran, tetrahydrofuran as substrates, the HAT rate constants were measured as 32.6, 13.5, 15.6, 47.3 and <11 M⁻¹s⁻¹, respectively. Cl₄PINO showed very similar HAT reactivity to SINO among these substrates. Cl₆SINO exhibited 5 to 20 times faster HAT than PINO. These results suggest that SINO is, in fact, a promising scaffold for *N*-oxyl HAT catalyst development. During these voltammetric studies, we note that the shape of the catalytic current vs potential profile for each substrate were subtly different (SI), suggesting possible differences in the mechanisms of each HAT reaction,²⁸ an observation which will be explored in future work.

Table 1. Measured k_{HAT} values between *N*-oxyls and various substrates by cyclic voltammetric titration. ^a Unable to determine due to potential overlap.

substrate	k_{HAT} (M ⁻¹ s ⁻¹)			
	PINO	SINO	Cl ₄ PINO	Cl ₆ SINO
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) Synthesis of Cl₆NHS



B) Comparisons on PINO- vs SINO- scaffolds

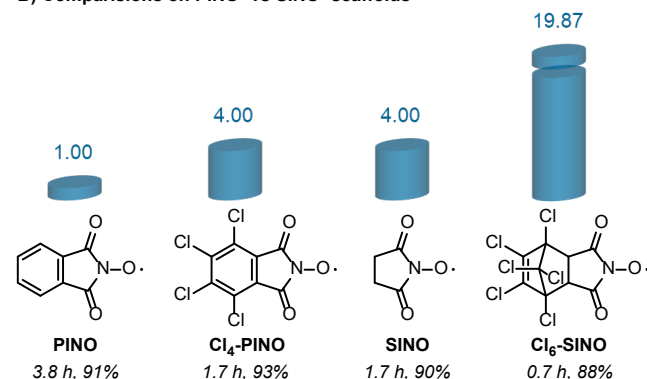


Figure 5. The reactivity of Cl₆SINO.

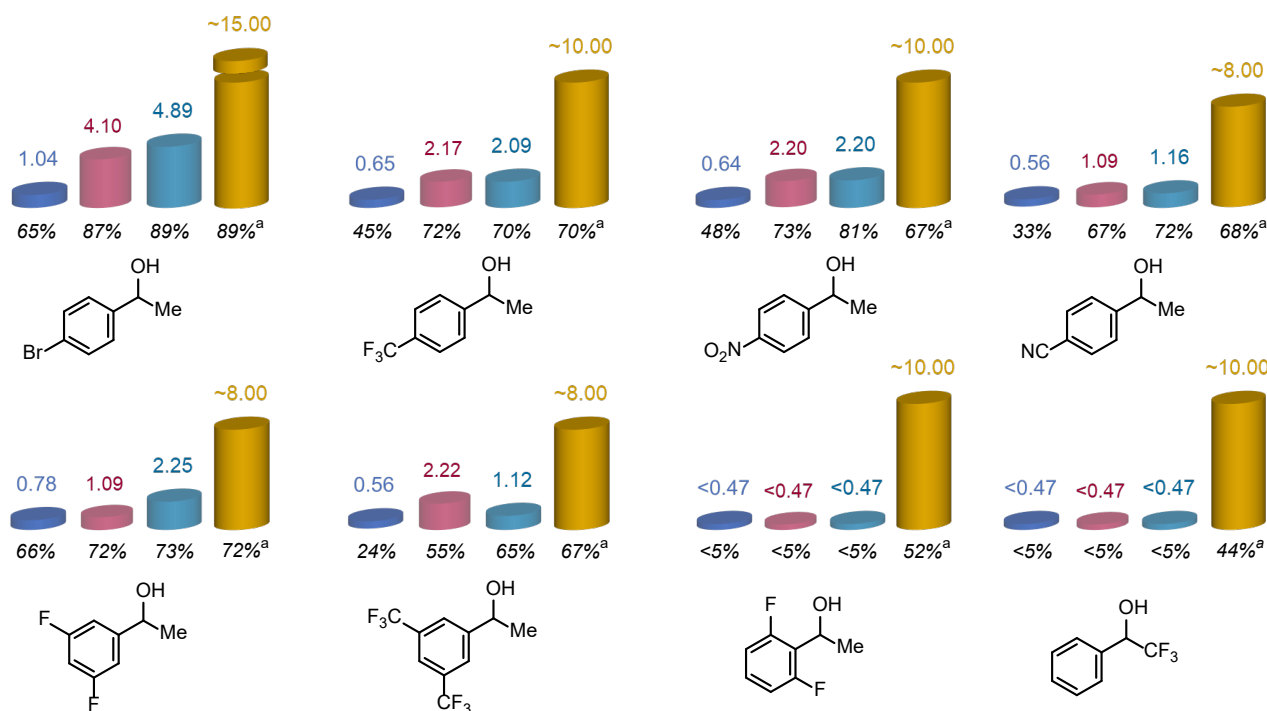
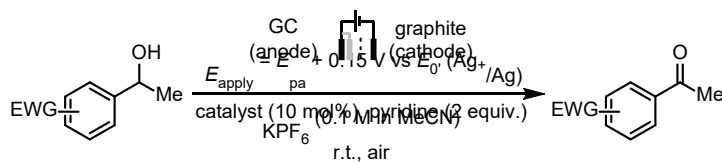


Figure 6. Electrocatalytic performance of NHPI, NHS, Cl_4NHPI , and Cl_6-NHS . Relative rate constants are reported using k_{HAT} for the reaction between PINO and 1-phenylethanol as a reference; PINO in dark blue, SINO in red, Cl_4NHPI in light blue, Cl_6-NHS in yellow. For NHPI, NHS, Cl_4NHPI , electrolysis experiments were stopped after 3 h, and products were isolated to compare yields and efficiency. ^a For Cl_6-NHS , electrolysis experiment was stopped after 1 h.

The catalytic performance of PINO, SINO, Cl_4PINO , and Cl_6SINO were further compared during oxidations of several electron-deficient benzylic alcohols (**Figure 6**). Their k_{HAT} values were measured by cyclic voltammetric titration and reported as relative values using k_{HAT} for the reaction between PINO and 1-phenylethanol as a reference. We found that PINO was able to activate electron-deficient alcohols at considerably lower rates compared to 1-phenylethanol. In comparison, SINO and Cl_4PINO could promote HAT reactions towards most 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 previously demonstrated 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 SINO- or Cl_4PINO -catalyzed reactions were generally 20% higher than PINO under equivalent conditions, but do not have a quantitative correlation with the relative HAT rate constants.²⁹ For Cl_6SINO , it only required 1 h instead of 3 h to give similar yields that SINO or Cl_4PINO could achieve. These bulk electrolysis observations are in reasonable agreement with the k_{HAT} values determined by cyclic voltammetric titration.

Discussion

Overall, the data presented above markedly contrast the popular view that NHS/SINO is not synthetically useful for HAT

catalysis. Rather, this system has tremendous potential value for HAT catalysis both fundamentally and practically. Our results demonstrate the higher efficiency of SINO-catalyzed alcohol oxidation as opposed to PINO, and the potential utilization of SINO to target a broader range of C-H bonds which PINO is unable to activate. On the other hand, succinimide provides a promising backbone to design new catalysts by simple derivatization. We demonstrate Cl_6SINO as a superior HAT species with a 20-fold increase in HAT relative to PINO in the oxidation of model substrate 1-phenylethanol. To the best of our knowledge, this is the most reactive *N*-oxyl type HAT species to date. This aspect facilitates expansion of the current library of *N*-oxyl catalysts, potentially accelerating catalyst discovery in a high-throughput format. Research on these directions within our research groups is ongoing.

The definition of an efficient organic electrocatalyst must be understood comprehensively to avoid overlooking potentially useful compounds. The example presented herein also serves as an example to the organic synthetic community of the merits and benefits of catalyst evaluation through heterogeneous electrochemical generation. Although cumbersome evaluation of a potential HAT catalyst through a series of homogenous oxidations featuring distinct molecular oxidants with different electrochemical potentials is also possible, the convenience, speed, and precision afforded by heterogeneous oxidation with a biased electrode are clearly advantageous.

Our comparison of SINO, PINO and Cl₄-PINO as HAT catalysts has revealed how important TS polarization is in the reactivity of these *N*-oxyl radicals and that the proton affinities of the corresponding *N*-oxide anions can be used to rationalize its contribution. This may be a useful consideration in future design of significantly improved HAT catalysts since efforts to date have been based almost exclusively on consideration of reaction energetics (i.e., O-H BDE of the *N*-hydroxy moiety).

Conclusions

In summary, this work illustrates that the NHS/SINO redox pair is a potent HAT catalyst despite repeated claims to the contrary. Recognizing the 'hidden' value in this known succinimide scaffold together with a more comprehensive interpretation of the factors affecting HAT reactivity of *N*-oxyl species can quickly lead to research in several new directions. The potential-controlled electrochemical approach can motivate further re-examination of other potential catalysts that may also have been erroneously dismissed.

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- (23) 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 ($E^{0'}$) 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 being used during bulk electrolysis to avoid necessary purification issues.

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(29) Although the initial reaction current is proportional to $k_{\text{HAT}}^{1/2}$, 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.