nature reviews chemistry

https://doi.org/10.1038/s41570-023-00511-z

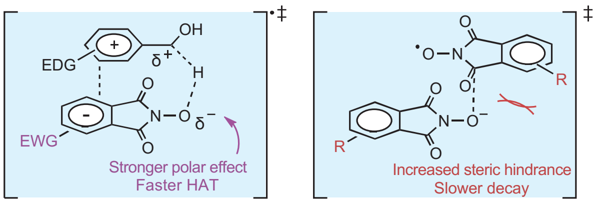
Review article

The design of PINO-like hydrogen-atom-transfer catalysts

Cheng Yang[1], Sahil Arora[1], Stephen Maldonado[1,2] ✉, Derek A. Pratt[3] ✉ & Corey R. J. Stephenson[1] ✉

Abstract

Phthalimide-*N*-oxyl (PINO) is a valuable hydrogen-atom-transfer (HAT) catalyst for selective C–H functionalization. To advance and optimize PINO-catalysed HAT reactions, researchers have been focused on modifying the phthalimide core structure. Despite much effort and some notable advances, the modifications to date have centred on optimization of a single parameter of the catalyst, such as reactivity, solubility or stability. Unfortunately, the optimization with respect to one parameter is often associated with a worsening of the others. The derivation of a single catalyst structure with optimal performance across multiple parameters has therefore remained elusive. Here we present an analysis of the structure–activity relationships of PINO and its derivatives as HAT catalysts, which we hope will stimulate further development of PINO-catalysed HAT reactions and, ultimately, lead to much improved catalysts for real-world applications.



Sections

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[1]Willard Henry Dow Laboratory, Department of Chemistry, University of Michigan, Ann Arbor, MI, USA. [2]Program in Applied Physics, University of Michigan, Ann Arbor, MI, USA. [3]Department of Chemistry and Biomolecular Sciences, University of Ottawa, Ottawa, Ontario, Canada. ✉e-mail: smald@umich.edu; dpratt@uottawa.ca; crjsteph@umich.edu

Introduction

The synthetic chemistry community is becoming increasingly aware of the potential for hydrogen-atom-transfer (HAT) catalysis to enable direct homolytic bond activations[1,2]. Phthalimide-*N*-oxyl (PINO) (Fig. 1) is a type of HAT catalyst that allows functionalization of relatively activated C–H bonds (for example, benzylic[3] and allylic[4]) at room temperature and even unactivated C–H bonds[5] (for example, cyclohexyl and adamantyl) at elevated temperatures. The selectivity of PINO arises from the relatively low bond dissociation enthalpy ($BDE_{O–H}$) in *N*-hydroxyphthalimide (NHPI) (Fig. 1) of around 88 kcal mol^{-1} (versus $BDE_{C–H}$ of about 100 kcal mol^{-1})[6], which makes reactions of all but relatively activated substrates endergonic. The development of PINO-catalysed reactions is now well documented in many review articles[5,7–27]. For example, Recupero and Punta previously prepared a comprehensive review on the use of PINO for HAT reactions[5].

Although PINO is an attractive HAT catalyst for industrial applications, there are very few examples of its usage in practice[5]. The three main obstacles to this are[11]: PINO is generally not sufficiently reactive for abstractions of unactivated C–H bonds, its insolubility in hydrocarbons limits its applications in a wide range of reactions, and decomposition of both PINO and NHPI can be rapid during the reaction. Thus, research efforts have focused on functionalization of the phthalimide core structure to optimize either reactivity, solubility or stability. Although important, an emphasis on PINO-derived HAT catalyst design has rarely appeared, with two notable exceptions: Xie and co-workers have discussed multi-*N*-oxyl organocatalysts[28] and Luan and co-workers recently compiled reports on functionalization of the phthalimide core structure[29]. Nevertheless, a unifying discussion of structure–activity relationships to guide HAT catalyst design is lacking.

The purpose of this Review is to capture and distill the wealth of strategies and information associated with this first-in-class catalyst. We review the advances on catalyst development from a structure–reactivity perspective, presenting the relationships and discussing their implications to enable future efforts to discover PINO-type HAT catalysts that are optimized across multiple parameters. The goal in many of the works cited in this Review is to perform a narrow range of specialized reactions. This Review covers these efforts by highlighting the relationship between structural modification and catalyst behaviour while providing possible hypotheses for some observed trends. Given that the majority of the previous efforts are based on the phthalimide core structure, this Review is focused on the functionalization of the NHPI backbone and its influence on its activities as a HAT agent. Related structures such as *N*-hydroxybenzimidazole[30] and *N*-hydroxyimide[31], synergistic combination of NHPI analogues[32], and solid-material-supported NHPI catalysts[33,34] are not included in this Review.

Generation of PINO-type catalysts

PINO-type radicals have lifetimes in the range of seconds to minutes[6] and therefore are generally generated in situ by oxidation of their precursor NHPIs. Thus, the design of PINO-type catalysts necessarily involves the development of synthetic approaches to NHPI-type catalyst precursors and oxidation methodologies to access their corresponding catalytic species. The generation of PINO-type species is typically performed in one of the following three ways.

First, organic oxidants are used to generate PINO. Historically, PINO was (re)generated by the organic reagent diethyl azodicarboxylate (DEAD) **1** for use in amination reactions[35] (Fig. 1a). Other examples of organic oxidants include *meta*-chloroperbenzoic acid (*m*-CPBA)[36] and anthraquinone[37], which behave as electron and/or proton shuttles to promote the formation of PINO.

Second, PINO-type catalysts are also effectively (re)generated using the inorganic species[36] nitric oxide (NO), nitric dioxide (NO_2) and nitric acid (HNO_3), as well as metals[38]. This aspect was pioneered by Ishii and co-workers, together with the Daicel Chemical Company, to address industrially relevant problems, such as oxidation of a mixture of cyclohexanone/cyclohexanol (ketone–alcohol oil)[38]. The most extensively studied metal salt for this purpose is cobalt(II) acetate. Under aerobic conditions, Co(II) (**2**) combines with O_2 to form $Co(III)OO^{\bullet}$ (**3**), which abstracts an H-atom from NHPI to generate PINO and Co(III)OOH (**4**) (Fig. 1b). The role of Co beyond initiation is not particularly clear.

Third, the oxidation of NHPI can also be operated at an anode, as first demonstrated by Masui and co-workers[39]. This approach needs additional pyridine-derived bases to enable a multiple-site concerted proton–electron transfer (MS-CPET) to form the catalytic PINO species[40] (Fig. 1c). Experiments carried out via electrochemical generation of PINO have provided mechanistic insights to PINO-catalysed HAT reactions[41], and this process also has potential for the development of environmentally benign processes.

Besides the three major oxidation methods, direct photochemical approaches[42] and enzymatic catalysis[43] can also be used to generate PINO-type species, but since most efforts on PINO-type catalyst development start with these three methods, they are emphasized in this Review.

Improving catalyst reactivity

Thermodynamic considerations in PINO reactivity

The HAT reactivity of PINO-type radicals is strongly dependent on the thermodynamics of the reaction. The thermodynamic driving force can be derived from the difference between the $BDE_{O–H}$ in the *N*-hydroxy derivative and the $BDE_{C–H}$ of the substrate, given that entropic changes in HAT processes are usually very small[44]. The often-observed linear relationship between reaction rate and BDE is a manifestation of the Bell–Evans–Polanyi relation[44]. This relation states that the difference in activation energy between a reaction of interest (E_a) and a reference reaction of the same class (E_0) is proportional to the enthalpy of reaction (ΔH), that is, $E_a - E_0 = \alpha\Delta H$, where α characterizes the position of the transition state along the reaction coordinate. Thus, an *N*-oxyl radical derived from an *N*-hydroxy compound with a larger $BDE_{O–H}$ is expected to undergo a HAT reaction more quickly than a similar radical from a compound with a smaller $BDE_{O–H}$. The Bell–Evans–Polanyi model assumes that the pre-exponential factor of the Arrhenius equation and α are the same for the reactions of the same type. In reality, these factors may vary slightly for different reactants. Nonetheless, the Bell–Evans–Polanyi model is an extremely valuable conceptual tool, and provides a simple way to estimate activation energies for a given type of HAT reaction.

Pedulli and co-workers have performed electron paramagnetic resonance measurements to understand the effects of adjacent carbonyl substituents on $BDE_{O–H}$ for various *N*-hydroxy compounds[6] (Fig. 2a). A typical hydroxylamine, such as **5** and **6**, without any electron-withdrawing groups (EWGs) has a $BDE_{O–H}$ of about 70 kcal mol^{-1} (ref. 5). The presence of one proximal carbonyl (in the hydroxamic acids **7** and **8**) leads to an increase of approximately 10 kcal mol^{-1} in $BDE_{O–H}$, while two adjacent carbonyls (NHPIs) raise the $BDE_{O–H}$ by around 20 kcal mol^{-1}. Among *N*-hydroxy derivatives, hydroxylamines have comparatively low BDEs, and are therefore poor precursors for developing HAT catalysts. One notable subtype (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) has been extensively used to catalyse oxidation reactions, but operates by a

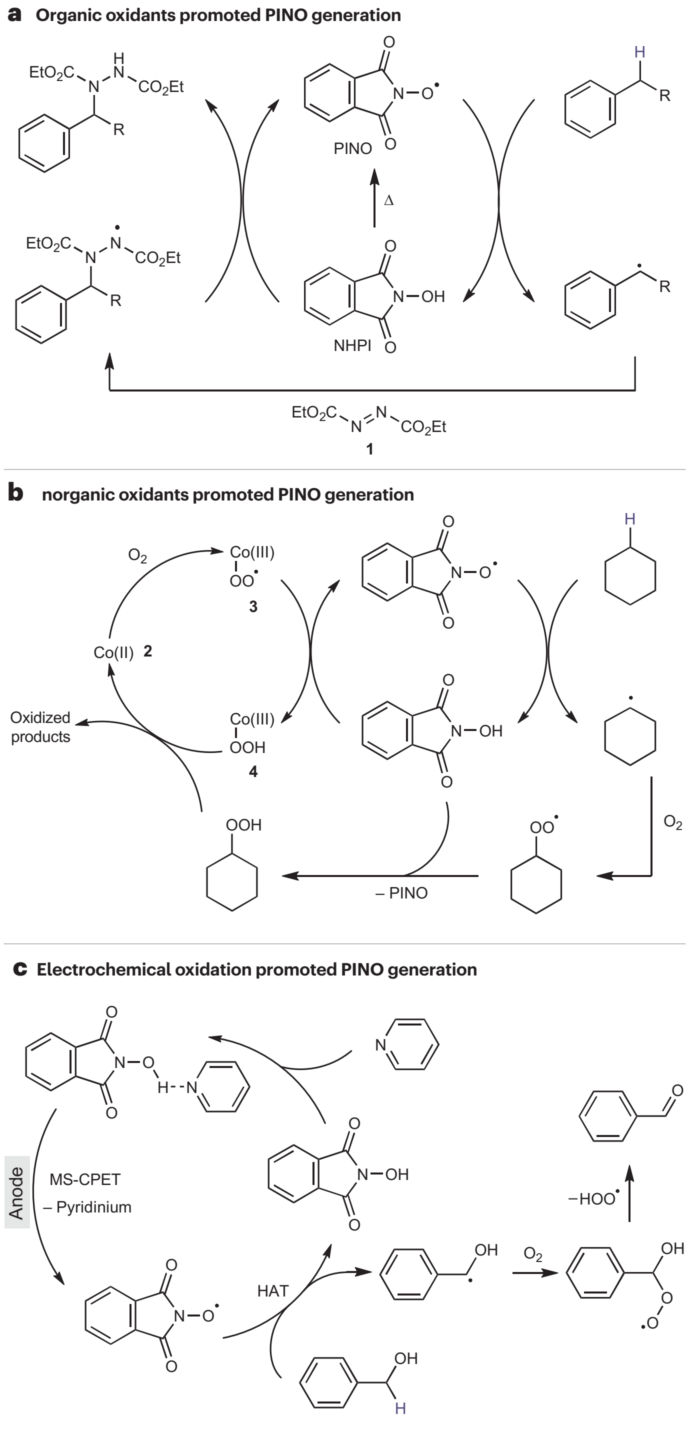


Fig. 1 | Three strategies of PINO generation from oxidation of NHPI. **a**, Organic oxidants promoted phthalimide-*N*-oxyl (PINO) generation: *N*-hydroxyphthalimide (NHPI)/diethyl azodicarboxylate-promoted benzylic amination of ethylbenzene. R, alkyl groups. **b**, Inorganic oxidants promoted PINO generation: NHPI/Co(II) catalysed oxidation of cyclohexane. **c**, Electrochemical oxidation promoted PINO generation: PINO-catalysed electrochemical oxidation of benzylic alcohol. HAT, hydrogen atom transfer; MS-CPET, multiple-site concerted proton–electron transfer.

completely different mechanism, which involves an oxoammonium ion as the active catalytic species[45]. Hydroxamic acids have both low $BDE_{O–H}$ values and poor stability[46], which restricts their application to the oxidation of very weak C–H bonds, such as those in polyunsaturated fatty acids[47]. By comparison, PINO-type HAT catalysts act on several substrates including benzyl alcohol (**9**), cumene (**10**), ethylbenzene (**11**), toluene (**12**), cyclohexane (**13**) and adamantane (**14**). The general trend of their HAT kinetics is that the stronger their C–H bonds, the slower the HAT reactions[6] (Fig. 2b).

Understanding the influence of peripheral carbonyl groups on $BDE_{O–H}$ values of hydroxylamines remains an active area of interest. Pedulli and co-workers have provided three possible explanations[6]. They rely on the $BDE_{O–H}$ value being a direct measure of the enthalpy difference between the *N*-oxyl species and the parent hydroxylamine, so that any factors affecting the stability of either the hydroxylamine or *N*-oxyl radical can affect the strength of the O–H bond. The higher $BDE_{O–H}$ values with adjacent carbonyls can then be understood as reflecting resonance stabilizations by charge separation and intramolecular hydrogen bonding (Fig. 2c). Furthermore, the presence of the carbonyl group in PINO reduces the importance of the mesomeric structure owing to its electron-acceptor character, thus implying a destabilization of these species with respect to alkyl nitroxides (Fig. 2c).

Accordingly, a straightforward hypothesis is that the introduction of EWGs on the phthalimide core structure will lead to a further increase in $BDE_{O–H}$ and therefore result in a more reactive *N*-oxyl radical. However, such modifications have resulted in only minor perturbations of $BDE_{O–H}$ (ref. 48), perhaps a manifestation of the 'law of diminishing returns', given that two carbonyls already have such a large effect. Lucarini and co-workers found that introducing an EWG scarcely increases $BDE_{O–H}$: for example, the addition of an ester group increases the $BDE_{O–H}$ by less than 1 kcal mol^{-1}[48] (Fig. 2a). Similarly, introducing a methoxy substituent—an electron-donating group (EDG)—caused a <1 kcal mol^{-1} decrease of $BDE_{O–H}$[48] (Fig. 2a). These marginal perturbations are not sufficient to substantially influence the rate of HAT from a hydrocarbon substrate. When these functionalized NHPIs were used to catalyse the oxidation of 1-(4-methoxyphenyl) ethanol, and the initial rate of formation of 4-methoxyacetophenone was measured, the NHPI-mediated reaction was found to be $(10 \pm 1) \times 10^{-3}$ mmol min^{-1}, whereas the 2-ester-NHPI-mediated reaction was $(12 \pm 1) \times 10^{-3}$ mmol min^{-1} and the 2-methoxy-NHPI-mediated reaction was $(6 \pm 0.6) \times 10^{-3}$ mmol min^{-1}. These kinetic experiments suggest that EWGs can activate the catalysts whereas EDGs can deactivate the catalysts.

An alternative strategy to adding EWGs to the phthalimide ring to boost the reactivity of PINO-type compounds is the replacement of the carbonyls with other electron-deficient functionalities. In 2003, Sheldon and co-workers investigated saccharin *N*-oxyl as a HAT catalyst for selective aerobic oxidation of cycloalkanes[49] (Fig. 2d). They proposed that replacing one carbonyl with an even more electron-deficient sulfonyl group could increase $BDE_{O–H}$ and thus enhance its reactivity for H-atom abstraction. The catalyst was used together with the metal salt cobalt(II) acetylacetonate ($Co(acac)_2$) under aerobic conditions. Their results suggested that the *N*-hydroxysaccharin **15**/$Co(acac)_2$ combination was more reactive than NHPI/$Co(acac)_2$ in the autoxidation of cycloalkanes. Oxidation of cyclododecane (**16**) using the catalyst **15**/$Co(acac)_2$ for 4 h gave a total conversion of 35% with 64% selectivity towards the ketone oxidation product **17**, while NHPI only gave a 23% conversion after 8 h. However, NHPI offered higher conversion than

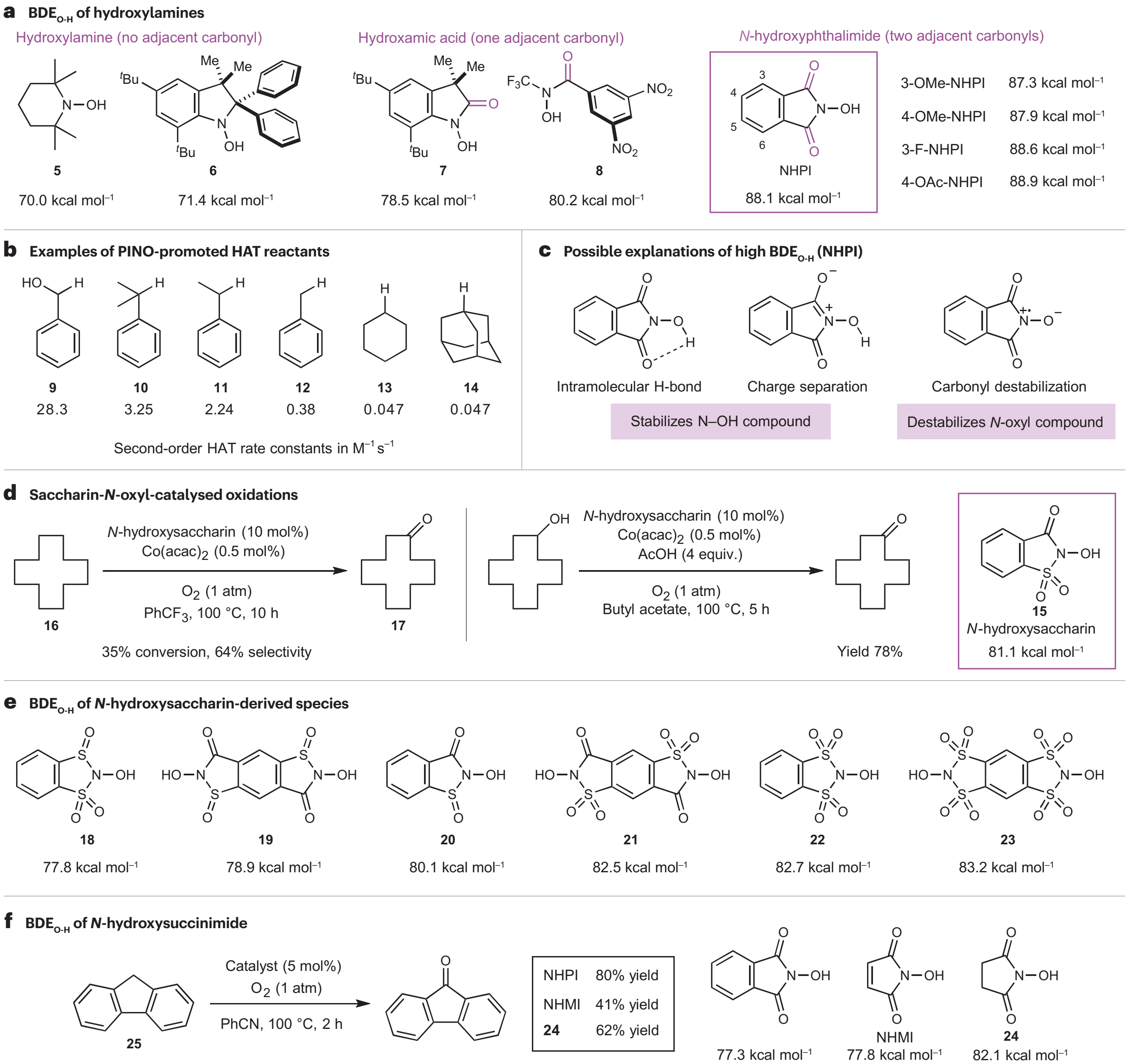


Fig. 2 | Thermodynamic aspects (BDE analysis) of PINO-type HAT mediators. **a**, Bond dissociation enthalpies (BDE$_{O-H}$ values) of representative hydroxyamines bearing no or one or two carbonyls. Electron-withdrawing carbonyls are responsible for the increase of BDE$_{O-H}$ in *N*-hydroxyphthalimide (NHPI). **b**, Rate constants for phthalimide-*N*-oxyl (PINO) abstracting a variety of different substrates, measured in benzene + 10% acetonitrile at 25 °C. The relatively low BDE$_{O-H}$ of NHPI results in a limited substrate scope for hydrogen-atom-transfer (HAT) reactions. **c**, Explanations for the high BDE$_{O-H}$ of NHPI. **d**, Saccharin-*N*-oxyl-catalysed oxidations. acac, acetylacetonate; AcOH, acetic acid; PhCF$_3$, α,α,α-trifluorotoluene. **e**, BDE$_{O-H}$ values of *N*-hydroxysaccharin-derived species. Sulfonyl and sulfinyl groups are not efficient electron-withdrawing groups to increase BDE$_{O-H}$. **f**, *N*-hydroxysuccinimide-mediated oxidations. NHMI, *N*-hydroxymaleimide; PhCN, benzonitrile.

N-hydroxysaccharin (**15**) when operating reactions to 24 h (43% versus 32%), possibly owing to greater stability relative to the catalyst **15**. Sheldon and co-workers then expanded the reaction scope to other hydrocarbons and alcohols in a follow-up report[50] (Fig. 2d).

Chen and co-workers followed up this work and computed the BDE$_{O-H}$ values for a set of NHPI analogues (**18**–**23**) bearing a combination of carbonyl, sulfonyl and sulfinyl groups to better understand the structure–BDE relationships[51] (Fig. 2e). Incorporation of both sulfinyl and sulfonyl groups resulted in a decrease in planarity of both the starting *N*-hydroxy compounds and derived *N*-oxyl radicals. However, neither sulfinyl and sulfonyl groups lead to increases in the BDE$_{O-H}$ (and the associated increased HAT rate). Density functional theory

(DFT) calculations suggested that none have a BDE_{O-H} larger than that of NHPI, with some exhibiting values smaller by around 5 kcal mol^{-1}, which implies that these radicals are better stabilized. This may be due to the availability of a lone pair of electrons in the sulfinyl case. However, because this does not apply for the sulfonyl, yet sulfonyl's BDE_{O-H} is still lower, another effect may be more important—perhaps a weaker H-bond resulting, at least in part, from the non-planar structure.

Besides NHPI and its derivates, *N*-hydroxysuccinimide (**24**) has been investigated to probe the possibility of using **24** as a HAT mediator in catalysis. In 1995, Ishii and coworkers reported the PINO-catalysed C–H oxidation of benzylic substrates[52] (Fig. 2f). They found that NHS was inferior to NHPI in the oxidation of fluorene **25** (61% versus 80% yield). Subsequent computational studies suggested that the succinimide *N*-oxyl should be more reactive than PINO as a HAT species on the basis of BDE calculations and effective activation energies reacting with ethylbenzene at 0 K (9.5 kcal mol^{-1} versus 13.3 kcal mol^{-1})[53,54]. However, many experimental studies demonstrated inferior performance of NHS compared to NHPI[4,55]. In contrast, Xu has recently shown that NHS performed better than NHPI when oxidizing biomass-derived hydroxymethylfurfural[56], suggesting that there may be more opportunities for using this simple catalyst.

Kinetic considerations in PINO reactivity

Polar effects play an important part in the HAT reactivity of *N*-oxyl radicals because the HAT transition state (TS) structure is highly polarized for electron-poor *N*-oxyl radicals, including PINO[57] (Fig. 3a). The strength of the polar effect is dependent on the extent to which the substrate and the *N*-oxyl radical can stabilize the partial positive and negative charges, respectively, in the TS. As such, EWGs on PINO-type catalysts and EDGs on reaction substrates will lower the energy barrier and accelerate the kinetics of the reaction[57]. Decoupling of enthalpic (thermodynamic) effects from polar (kinetic) effects can be challenging, because they operate in the same direction in most cases.

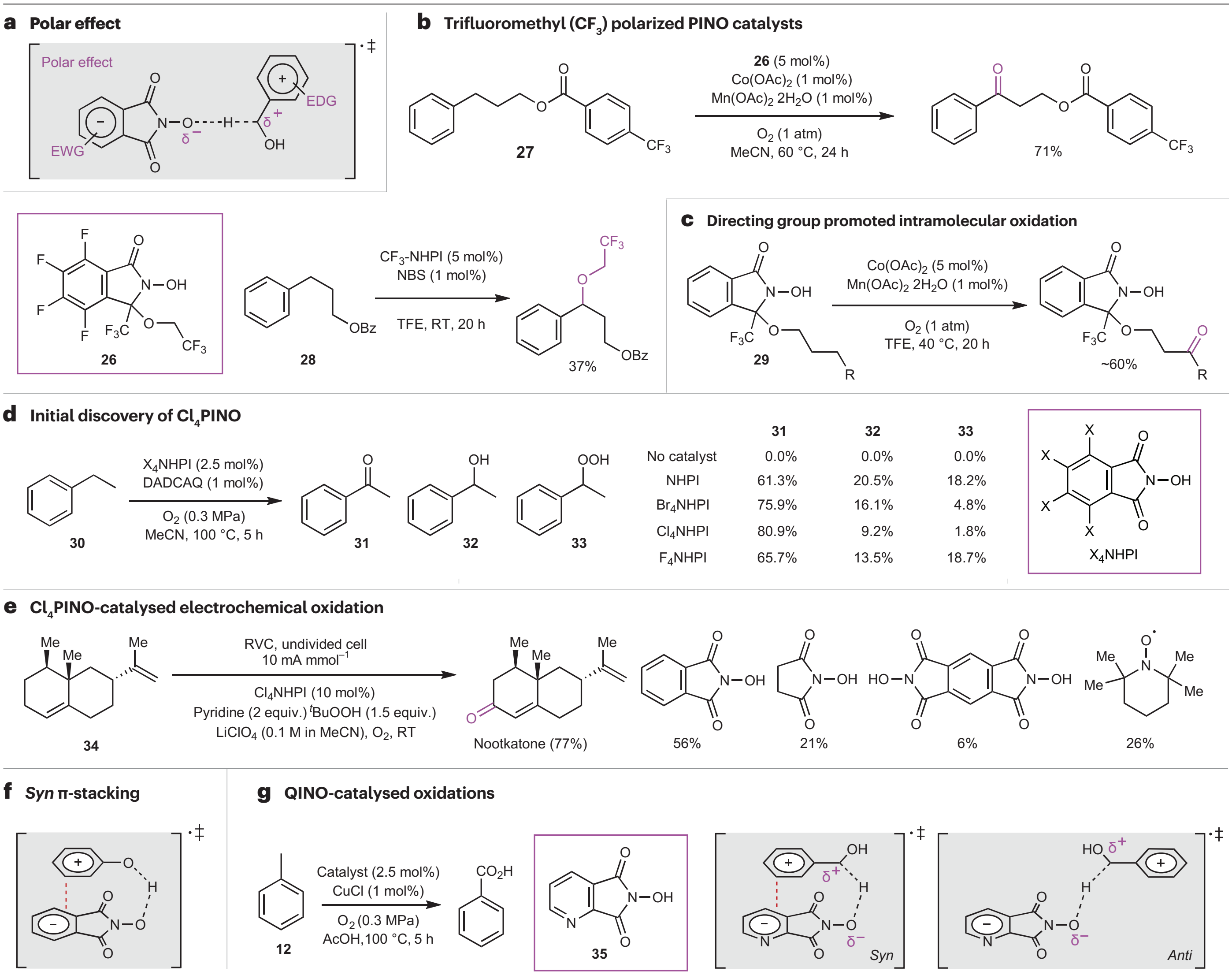
In 2016, Kanai and co-workers evaluated the kinetic effect of inclusion of an adjacent trifluoromethyl (CF_3) group on the PINO structure[58] (Fig. 3b). They hypothesized that replacing one carbonyl group with a CF_3-substituted sp^3-hybridized carbon would generate an additional tunable site (R group) and a nonplanar backbone, while retaining the desirable electron-withdrawing properties. Catalysts bearing trifluoroethoxy or benzoyl groups afforded higher yields than the methoxy-substituted analogues. The introduction of EWG on the phthalimide ring also improved the yield. The best-performing catalyst (**26**) featured a combination of trifluoroethoxy as the R group and perfluorination of the aromatic ring. Using catalyst **26** together with cobalt and manganese salts, oxidation of the benzylic substrate **27** gave a 71% yield. Benzylic substitution on substrate **28** occurred in 37% yield when used in conjunction with *N*-bromosuccinimide. Despite the promising results, evaluation of a range of CF_3-substituted catalysts on benzylic C–H oxidation indicated that all CF_3-substituted catalysts had less efficient activity than NHPI (91% yield). Kanai and co-workers later built upon this system to include a covalently bound directing group in substrate **29** in order to activate more inert C–H bonds[59] (Fig. 3c). Besides the fairly activated C–H bonds (such as benzylic, propargylic and tertiary), even very challenging acyclic methylene $C(sp^3)$–H bonds could be converted to corresponding ketones or alcohols using their method. The reactions proceeded regioselectively at the γ- and/or δ-positions, whereas the α-, β-, and other positions beyond the δ-position remained intact. The observed reactivity and regioselectivity could be rationalized by the intramolecular conformational accessibility of the *N*-oxyl radical and the electronic characteristics of $C(sp^3)$–H bonds. Based on the reported reaction times and yields, these analogues probably had lower BDE_{O-H} values than NHPI.

A considerable improvement in reactivity was achieved by chlorinating the phthalimide core. These halogenated analogues were first developed by Xu and co-workers in 2008 when studying the aerobic oxidation of ethyl benzene (**30**)[60] (Fig. 3d), with the goal of improving their previously developed reaction[37]. The proposed mechanism starts with a spontaneous HAT process between 1,4-diamino-2,3-dichloroanthraquinone (DADCAQ) and *N*-hydroxy-tetrachlorophthalimide (Cl_4NHPI) to generate the tetrachlorophthalimide-*N*-oxyl (Cl_4PINO) catalyst and a ketyl radical. The Cl_4PINO can then abstract a hydrogen atom from ethylbenzene to produce its corresponding benzylic radical, which is rapidly trapped by oxygen. The benzylic peroxyl radical formed can then undergo HAT with the ketyl radical to regenerate the quinone and benzylic hydroperoxide, which releases water to form the product, acetophenone **31**. Some other oxidation products included 1-phenylethanol (**32**) and benzylic hydroperoxide (**33**). Their results suggested that Cl_4PINO was a more efficient HAT catalyst than PINO (80% versus 61% yield), presumably as a result of the modest increase in the BDE_{O-H}.

The more reactive catalyst precursor Cl_4NHPI is commercially available from many chemical manufacturers, and therefore its use in electrochemical systems has been investigated. In 2016, Baran and co-workers reported the electrochemical generation of Cl_4PINO from Cl_4NHPI to mediate allylic C–H oxidations[4] (Fig. 3e). They evaluated a variety of possible oxidation electrocatalysts on allylic oxidation of valencene (**34**). Specifically, they observed that electrochemical oxidation of Cl_4NHPI more efficiently oxidized the target substrate than oxidation of NHPI (77% versus 56% yield). Their optimized C–H oxidation strategy exhibited broad substrate scope and high chemoselectivity. Furthermore, their method was scalable and could be demonstrated on a 100-gram scale. Although halogenation of PINO produces a more reactive *N*-oxyl radical, Cl_4PINO also decomposes more readily than PINO (see subsection 'Increasing catalyst stability').

Secondary orbital overlap (or π-stacking) may also contribute to the reactivity of PINO-type catalysts. In 2014, Lanzalunga and co-workers introduced the importance of the π effect in HAT reactions between *N*-oxyl radicals and phenols[61]. Using computational methods, they showed that (Fig. 3f) from the pre-reaction complex, the reaction proceeds by a HAT process through a π-stacked (*syn*) activated complex in which the phenol's aromatic ring and that of PINO can interact through space, thereby providing for charge transfer from the electron-rich phenolic ring to the electron-poor aromatic ring of PINO.

To demonstrate the π-stacking effect further, Lanzalunga and co-workers performed a kinetic study of HAT reactions from quinolinimide-*N*-oxyl (QINO), a catalyst generated from *N*-hydroxyquinolinimide (**35**), to a series of organic compounds[62]. The catalyst **35** and similar heterocyclic analogues were initially proposed by Xu and co-workers in 2011 for the purpose of enhancing complexation between PINO derivatives and copper(I) chloride (CuCl) for oxidation of toluene (**12**)[63] (Fig. 3g). Consistent with Xu's observations, Lanzalunga observed that the HAT rate constants of QINO are higher than those observed with PINO. The relevance of polar effects is supported by calculations conducted for the reactions of the two *N*-oxyl radicals with toluene. These calculations indicated that the HAT process was enabled by a substantial degree of charge transfer, from the π-stacking that occurred between the toluene and the aromatic rings of the *N*-oxyl species in the TS. When QINO or PINO interacted with toluene, the free energies of the *syn* TS structures



	31	32	33
No catalyst	0.0%	0.0%	0.0%
NHPI	61.3%	20.5%	18.2%
Br$_4$NHPI	75.9%	16.1%	4.8%
Cl$_4$NHPI	80.9%	9.2%	1.8%
F$_4$NHPI	65.7%	13.5%	18.7%

Fig. 3 | Design of a more reactive PINO-type catalyst through EWG polarization effect. a, Demonstration of polar effect in phthalimide-*N*-oxyl (PINO)-catalysed hydrogen-atom-transfer (HAT) reactions. EDG, electron-donating group; EWG, electron-withdrawing group. **b**, Trifluoromethyl group polarized PINO catalysts. Adding the trifluoromethyl group leads to the decrease of BDE$_{O–H}$ of *N*-hydroxyphthalimide (NHPI). NBS, *N*-bromosuccinimide; RT, room temperature; TFE, trifluoroethanol. **c**, Chemo- and regioselective oxygenation of aliphatic C(sp^3)–H bonds using a covalently bound directing activator. R, alkyl groups. **d**, Tetrahalogenated PINO species promoted oxidation of ethyl benzene. Br$_4$NHPI, *N*-hydroxytetrabromophthalimide; Cl$_4$NHPI, *N*-hydroxytetrachlorophthalimide; DADCAQ, 1,4-diamino-2,3-dichloroanthraquinone; F$_4$NHPI, *N*-hydroxytetrafluorophthalimide. **e**, Tetrachlorophthalimide-*N*-oxyl-mediated electrochemical oxidation of olefins. LiClO$_4$, lithium perchlorate; RVC, reticulated vitreous carbon; ^{t}BuOOH, *tert*-butyl hydroperoxide. **f**, Demonstration of secondary overlap in PINO-mediated HAT reactions. **g**, Quinolinimide-*N*-oxyl (QINO)-catalysed oxidation of toluene. AcOH, acetic acid. The double dagger indicates a possible transition state.

were about 3.2 kcal mol^{-1} smaller than those of the *anti*-structures in the gas phase, and about 2.2 kcal mol^{-1} smaller after solvent correction (Fig. 3g). These calculations all showed pronounced structural effects of the *N*-oxyl on the charge transfer occurring in the π-stacked conformation.

Of course, making the *N*-oxyl radical more electron-poor to boost its reactivity towards C–H bonds means that it will require greater oxidizing power to generate it (that is, a stronger chemical oxidant or more positive electrochemical potential). Lepretre, Saint-Aman, and co-workers observed a positive linear correlation between the redox potentials of substituted NHPI derivatives and the Hammett parameters σ of the substituents[64]. In other words, EWGs shift the redox potential towards more positive values. These larger driving forces can affect overall catalytic performance and potentially limit substrate scope.

Installing functionality to improve selectivity

Kato and co-workers developed the bowl-shaped PINO analogues **36** to **39** to realize site-selective radical reactions[65,66] (Fig. 4a). They used the geometry of these catalysts to achieve site-selective amination of 1-cyclohexyl-4-ethylbenzene. When starting with NHPI as the catalyst, benzylic amination occurred at both secondary and tertiary positions in a normalized ratio of 53 to 47. When using the bowl-shaped catalysts **36** to **39** under the same reaction conditions, derivative **39** showed superior performance and gave complete regioselectivity for secondary C–H abstraction (a normalized ratio of 100 to 0) (Fig. 4a). They showcased the synthetic utility of their method in a site-selective functionalization of estrone 3-methyl ether and a range of benzylic C–H bonds in an intermolecular competition featuring two different benzylic ether substrates.

In addition to regioselectivity, PINO-catalysed asymmetric HAT reactions have also been attempted with the chiral PINO species **40**. In 1999, Einhorn and co-workers first reported this strategy[67], using a bulky R-group to block the substrate approach from one face to realize an enantioselective transformation (Fig. 4b). However, the test reaction—desymmetrization of 2-substituted indanes (**41**)—gave only 8% enantiomeric excess. In subsequent studies, the same authors developed C_2-symmetric analogues of PINO (**42**) and used them for the kinetic resolution of various *N*-acyl oxazolidines[68]. Efforts to optimize reaction conditions suggested that the selectivity was highly dependent on the substitution pattern of the catalyst. In the presence of copper(I) chloride and O_2, the reaction catalysed by catalyst **42** resulted in 80% conversion and 99% enantiomeric excess. Comparatively, their previous chiral catalyst **40** gave 75% conversion and only 28% enantiomeric excess, which was much lower than the C_2-symmetric analogue **42**. Although encouraging, the general applicability of these catalysts towards asymmetric reactions was limited to the kinetic resolution.

Tan and co-workers prepared a series of anthrone-containing analogues of PINO and investigated their abilities for asymmetric oxidation of benzylic alcohols and diols[69] (Fig. 4c). Specifically, the aerobic oxidation of acenaphthene in the presence of optically enriched anthrone-NHPI (**43**) (10 mol%) and $Co(OAc)_2$ (5 mol%) gave rise to the alcohol in 42% yield albeit in low enantiomeric excess (4%). Poor chemoselectivity was also observed, as indicated by the formation of the over-oxidized lactone in 35% yield. Similar results were obtained with other benzylic alcohols and diols.

It should be emphasized that PINO-catalysed asymmetric oxidations are theoretically challenging. First, even if the chiral PINO-type catalysts were exceptionally good for stereoselective abstraction of a hydrogen atom, the resulting carbon-centred radical will generally either exhibit planar geometry or have a very small barrier to inversion. Second, since O_2 is a linear diatomic molecule and reacts at nearly diffusion-controlled rates with most carbon-centred radicals[70], it is expected that its reaction will be only mildly influenced by sterics. Although oxygen addition is reversible, this is unlikely to be competitive with HAT from NHPI unless the carbon-centred radical intermediate is extremely stable. Even if it were, the chiral NHPI would need to be able to distinguish between the two enantiomeric peroxyl radicals, which would be even more difficult than between the original C–H bonds because of the intervening dioxygen moiety.

Widening solvent compatibility

NHPI is poorly soluble in most hydrocarbons, necessitating the use of polar solvents such as acetic acid or acetonitrile for most C–H oxidation reactions. To perform aerobic oxidations of alkanes without any solvent, Ishii and co-workers developed alkylated NHPI derivatives derived from trimellitic anhydride with high solubility in nonpolar hydrocarbons[71] (Fig. 5a). The *n*-dodecyl ester substituted catalyst **44** afforded the best catalytic performance for the oxidation of alkanes without solvent at 100 °C. Oxidation of cyclopentane with catalyst **44** yielded cyclopentanone, cyclopentanol and glutaric acid in yields of 41%, 13% and 46%, respectively. During the reaction, the measured turnover number of catalyst **44** was 20. In comparison, the measured turnover number was only 9 with NHPI. The same trend was observed when oxidizing large ring cycloalkanes such as cyclooctane and cyclododecane.

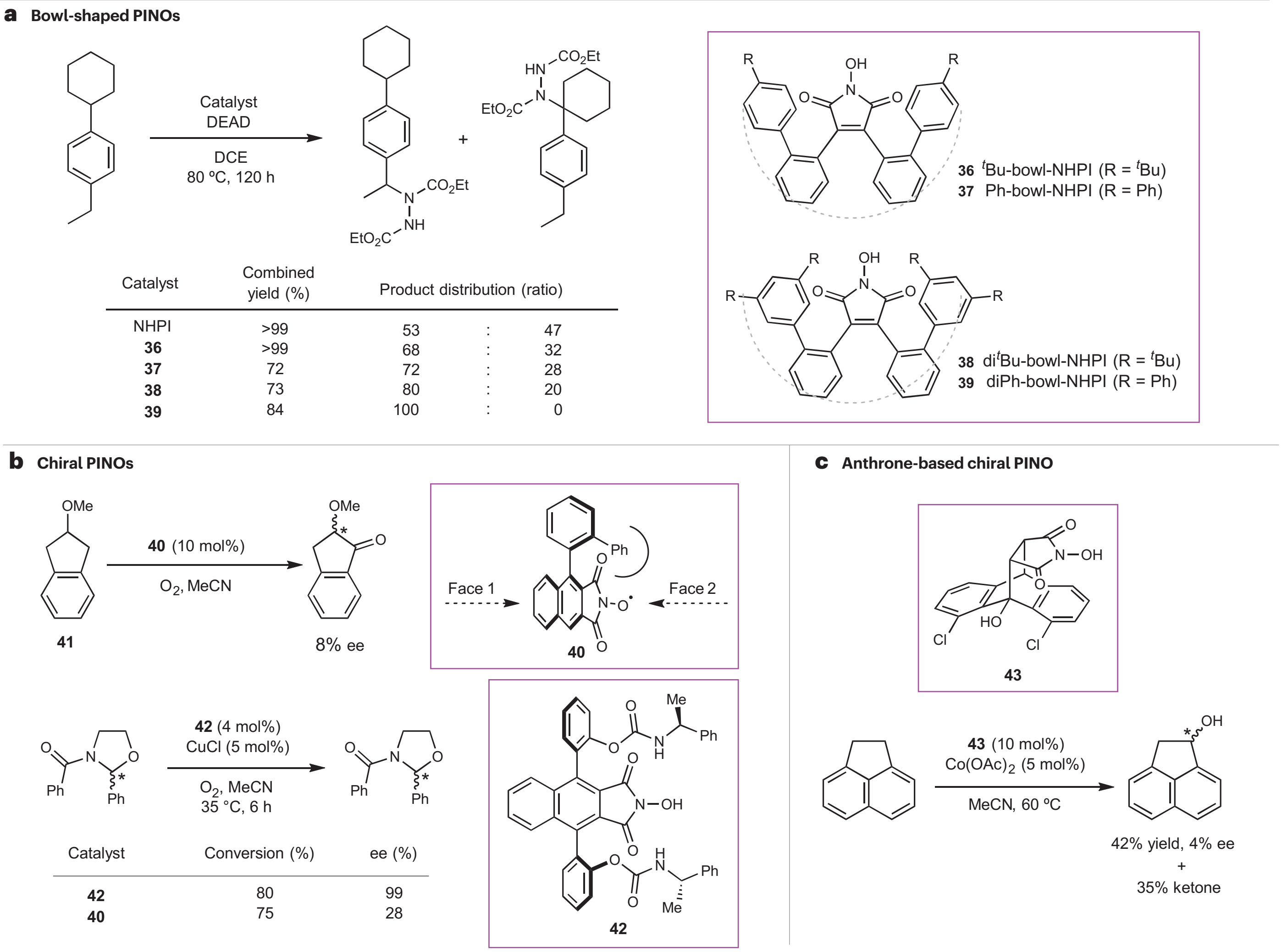
In a subsequent report, the same group prepared two different types of fluoroalkylated ester-NHPI derivatives, F_{15}-NHPI **45** and F_{17}-NHPI **46**[72] (Fig. 5b). The aerobic oxidation of cyclohexane was carried out under air (10 atm) in the presence of the NHPI derivatives $Co(OAc)_2$, and $Mn(OAc)_2$, at 100 °C for 14 h. While NHPI gave a turnover number of 19.0, the fluorinated analogues showed better performance with a higher turnover number (up to 45.6).

Besides the ester functionality, Punta and co-workers demonstrated that an ether group could also improve lipophilicity[73,74] (Fig. 5c). Using ether-substituted derivative **47** and **48**, the presence of a polar solvent is no longer required to guarantee complete solubilization of the catalyst, enabling oxidation of cumene **10** under neat conditions. Catalyst **47** showed higher reactivity and stability and gave 54% conversion of cumene after 6 h. Their results also reveal the unexpected necessity of using small amounts of acetonitrile to fully promote the HAT process and prevent the catalyst from detrimental hydrogen-bond-driven aggregation.

Increasing catalyst stability

High loadings of NHPI (>10–20 mol% in most reports) are generally required to achieve high conversions, possibly owing to the short lifetime of PINO[5,7–27]. The potential for decomposition makes the strategic design of more persistent PINO-type catalysts particularly important. PINO decomposition was first studied under electrochemical conditions by Masui and co-workers in 1987 (ref. 41). Here, they reported that electrolysis of NHPI in acetonitrile in the presence of pyridine yielded a trimeric species (**49**), which was isolated in 71% yield (Fig. 6a). Small amounts of other compounds were also detected, including phthalic anhydride (**50**) (8%), phthalic acid (**51**) (3.5%), and phthalimide (**52**) (2.5%). Whether the small amounts of hydrolysed products came from the reaction itself or the work-up was unclear. Two mechanistic hypotheses have been advanced to account for the formation of the trimer **49**. Masui originally proposed that the electrochemically generated PINO first underwent disproportionation to form the corresponding oxoammonium **53** and the NHPI anion **54**, which combined to generate a dimer (**55**)[41] (Fig. 6b). Subsequent homolytic cleavage of the acyl nitroso species **55** would liberate nitric oxide and yield an acyl radical that could be trapped by a third equivalent of PINO. In 2003, Pedulli proposed an alternative pathway whereby PINO underwent C–N bond cleavage to form an acyl radical intermediate **56**, which could react with a second molecule of PINO to yield the dimer **55** and ultimately trimer **49**[6] (Fig. 6b).

Masui's mechanistic hypothesis was not only built on the corresponding disproportionation chemistry that occurs with TEMPO and related persistent dialkylnitroxides, but also their kinetic measurements. To determine reaction order, Masui and co-workers monitored the decomposition of PINO spectroelectrochemically and observed a second-order process characterized by $k_d = 24.1\ M^{-1}\ s^{-1}$ at 25 °C (ref. 41) (Fig. 6a). Masui's initial study was supported by several independent reports. For example, Espenson and co-workers chose lead(IV) acetate ($Pb(OAc)_4$) as a chemical oxidant to generate PINO from NHPI and



a Bowl-shaped PINOs

Catalyst	Combined yield (%)	Product distribution (ratio)		
NHPI	>99	53	:	47
36	>99	68	:	32
37	72	72	:	28
38	73	80	:	20
39	84	100	:	0

b Chiral PINOs

Catalyst	Conversion (%)	ee (%)
42	80	99
40	75	28

c Anthrone-based chiral PINO

Fig. 4 | Efforts towards developing regio- or enantioselective PINO species. **a**, Design of bowl-shaped phthalimide-*N*-oxyl (PINO) derivatives **36** to **39** for site-selective hydrogen-atom-transfer reactions. DCE, 1,2-dichloroethane; DEAD, diethyl azodicarboxylate; NHPI, *N*-hydroxyphthalimide. **b**, Attempt to develop NHPI-based chiral PINO analogues. ee, enantiomeric excess. **c**, Anthrone-based chiral PINO species.

monitored its decomposition[75]. Their data also suggested that PINO decay occurred by a second-order process in acetic acid at 25 °C, but operated at a slower rate of 0.61 $M^{-1}\,s^{-1}$ (Fig. 6a). Baciocchi, Lanzalunga and co-workers later independently measured a rate constant of 0.4 $M^{-1}\,s^{-1}$ under very similar conditions[76]. They also determined second-order decomposition rate constants of 0.9, 4.0 and 0.4 $M^{-1}\,s^{-1}$ in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), carbon tetrachloride (CCl_4), and acetonitrile in the presence of 1% acetic acid, respectively (Fig. 6a). It is important to note that the reported lifetime of PINO under acidic conditions is longer than in basic solutions. An electroanalytical study of PINO-catalysed alcohol oxidation has showed a different redox response in sulfuric acid[77]. Other applications, including attempts to use the NHPI/PINO couple as anolytes in redox flow batteries, have also shown promise[78]. Although the majority of reactions promoted by PINO-type catalysts have been carried out in the presence of base, further studies of the NHPI/PINO coupling in acids could provide more opportunities for organic catalysis.

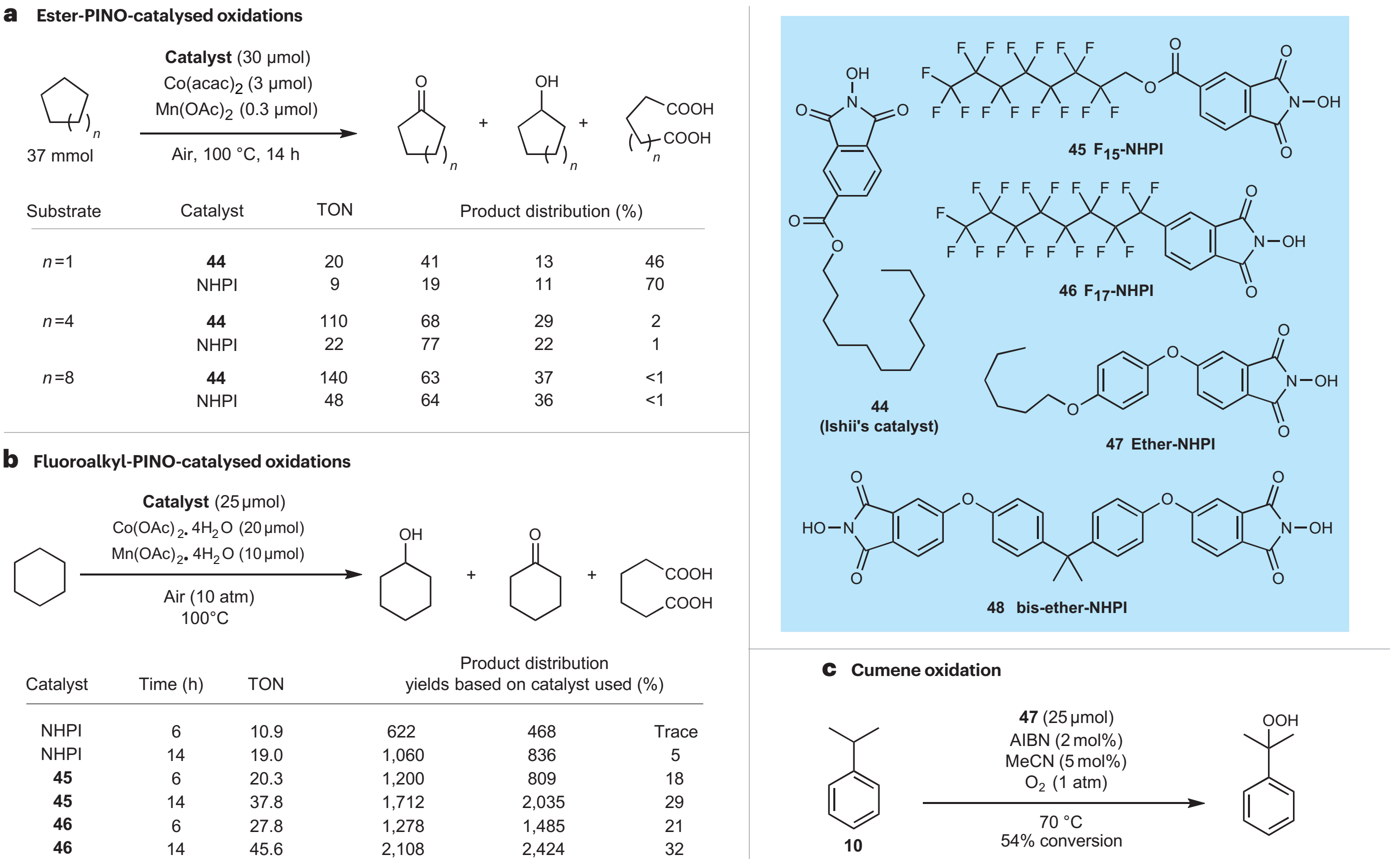
In contrast, Pedulli and co-workers reported evidence for a first-order decay of PINO in a benzene/acetonitrile (9:1) solution[6] (Fig. 6a). In their experiments, PINO was generated photochemically and monitored by electron spin resonance spectroscopy. Following Pedulli's work, Kushch and co-workers also investigated the kinetics of a series of PINO derivatives[79] (Fig. 6a). They used hypervalent iodine oxidants ((diacetoxyiodo)benzene, bis(trifluoroacetoxy)]iodobenzene) and cerium(IV) ammonium nitrate to generate PINO. Monitoring its decay by ultraviolet–visible spectroscopy, they obtained $k_d = 5.0 \times 10^4\ s^{-1}$. Their data also suggested that the stability of PINO derivatives was dependent on electronic effects: electron-donating groups stabilized PINO, while electron-withdrawing groups destabilized PINO. It is worth mentioning that Cl_4PINO, although proficient at catalysing oxidation, decomposed more readily ($26.0 \times 10^4\ s^{-1}$) than PINO. In addition, steric effects also had a role in PINO's stability, with bulky groups attached to the phthalimide ring seeming to enhance the stability. For example, the measured decay rate constant of tetraphenylphthalimide-*N*-oxy (Ph_4PINO) was $1.4 \times 10^4\ s^{-1}$.

The more persistent Ph_4PINO species derived from *N*-hydroxytetraphenylphthalimide (Ph_4NHPI) (**56**) was first described by Einhorn and co-workers in 2004[80] (Fig. 6c). The intent was to improve the lifetime of PINO via substitution of the phthalimide ring as a way to decrease catalyst loading. They discovered that catalyst precursor **56** in combination with CuCl could catalyse benzylic oxidation using only 1 mol% catalyst precursor. Using ultraviolet–visible spectroscopy to track the reaction, the kinetic data yielded a second-order rate constant $k_d = 0.16\ M^{-1}\ s^{-1}$ at 35 °C. When the initial concentration was 0.5 mM, the measured half-life $t_{1/2}$ was 205 min. For comparison, decay of PINO under the same conditions gave $k_d = 0.8\ M^{-1}\ s^{-1}$ and $t_{1/2} = 43$ min (that is, 4.7 times longer than PINO). Since steric effects can influence the stability of PINO, these data suggested that a second-order decay was more likely. Einhorn and co-workers then developed synthetic methods to expand the scope of Ph_4NHPI to investigate in a follow-up study[81]. Another report described the synthesis of 3,6-disilylated NHPI[82], but kinetic data have not been reported yet.

As mentioned above, a synthetically useful catalyst should satisfy multiple criteria. Although manipulating the steric environment surrounding the key *N*-oxyl moiety should improve radical persistence, this approach may cause a simultaneous decrease in HAT activity. For example, Lanzalunga and co-workers determined that the rate constant of HAT from phenols to PINO was significantly influenced by steric effects[76]. According to their report, ortho-dimethylated phenols are more than an order of magnitude more reactive to PINO than ortho di-*tert*-butylated phenols, even though the former reactions are approximately 1.7 kcal mol^{-1} less exothermic. For the same reaction, although adding phenyl groups to the phthalimide core (that is, Ph_4PINO) is functional in terms of prolonging PINO's lifetime, it is questionable whether this modification has an overall beneficial influence on reaction efficiency.

The quantitative accuracy of these published kinetic studies is influenced by several practical experimentation limits, confounding the determination of the reaction order. These measurements were performed under different conditions (for example, temperatures, solvents and concentrations) using different instruments/technologies. The formation of PINO was achieved using different approaches, which may also affect the decomposition mechanisms. To date, a standard method to study PINO decay has not been implemented.

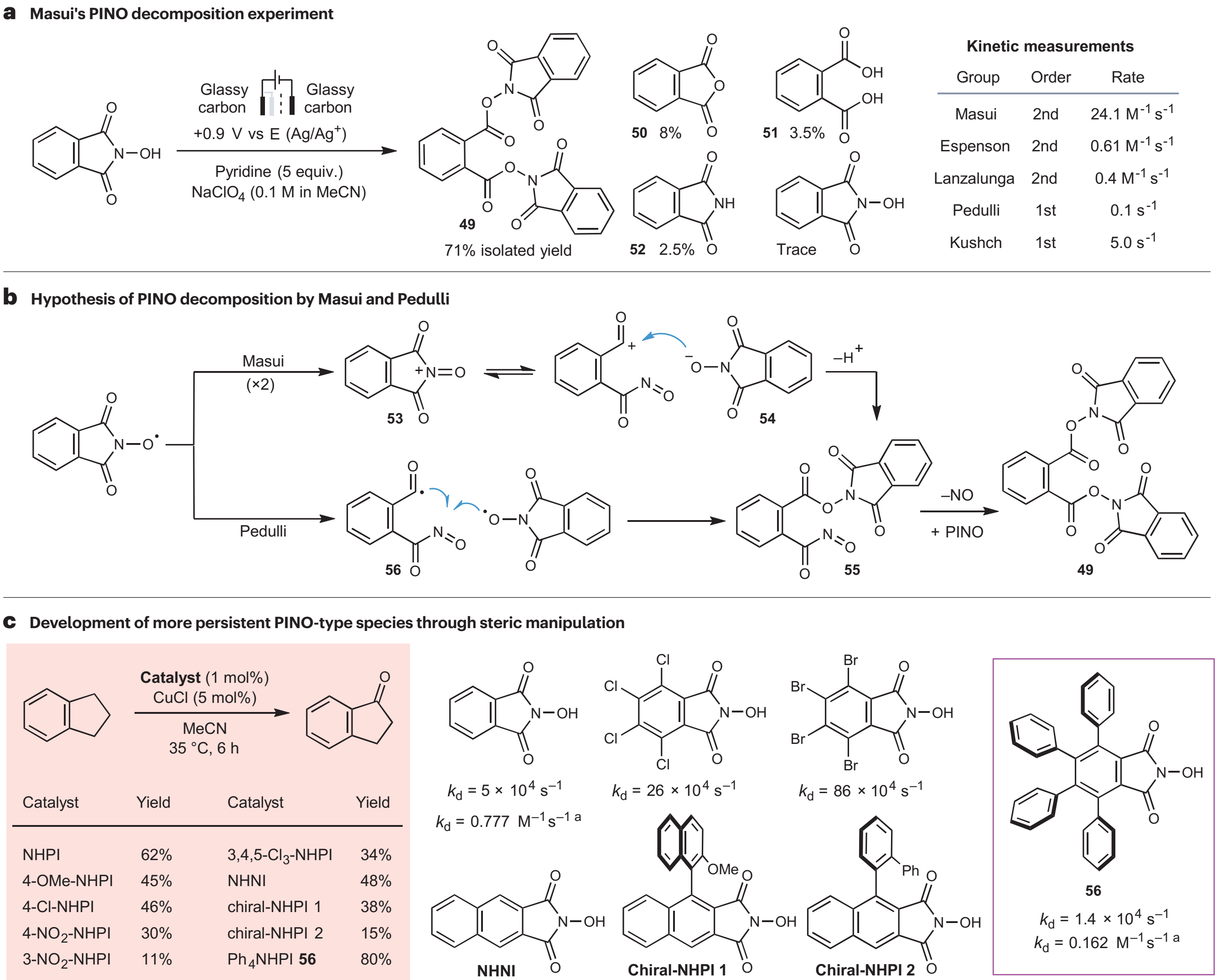
Electroanalytical studies of the NHPI/PINO redox couple have offered new insights into this catalytic system. Besides using voltametric titration to determine HAT rates, the persistence of electrochemically generated PINO can be quantitively analysed via the



Substrate	Catalyst	TON	Product distribution (%)		
n=1	**44**	20	41	13	46
	NHPI	9	19	11	70
n=4	**44**	110	68	29	2
	NHPI	22	77	22	1
n=8	**44**	140	63	37	<1
	NHPI	48	64	36	<1

Catalyst	Time (h)	TON	Product distribution yields based on catalyst used (%)		
NHPI	6	10.9	622	468	Trace
NHPI	14	19.0	1,060	836	5
45	6	20.3	1,200	809	18
45	14	37.8	1,712	2,035	29
46	6	27.8	1,278	1,485	21
46	14	45.6	2,108	2,424	32

Fig. 5 | Development of more lipophilic PINO catalysts. The solubility of both *N*-hydroxyphthalimide (NHPI) and phthalimide-*N*-oxyl (PINO) in organic solvents can be improved by introduction of long alkyl chains to the phthalimide core. **a**, The ester-PINO **44** mediated oxidation of cyclo hydrocarbons. $Co(acac)_2$, cobalt(II) acetylacetonate; $Mn(OAc)_2$, manganese(II) acetate. **b**, Fluoroalkyl-PINOs **45** and **46** catalysed oxidation of cyclohexane. TON, turnover number. **c**, Ether-PINO species **47** and **48** catalysed cumene oxidation. AIBN, azobisisobutyronitrile.



Group	Order	Rate
Masui	2nd	24.1 $M^{-1}s^{-1}$
Espenson	2nd	0.61 $M^{-1}s^{-1}$
Lanzalunga	2nd	0.4 $M^{-1}s^{-1}$
Pedulli	1st	0.1 s^{-1}
Kushch	1st	5.0 s^{-1}

Catalyst	Yield	Catalyst	Yield
NHPI	62%	3,4,5-Cl_3-NHPI	34%
4-OMe-NHPI	45%	NHNI	48%
4-Cl-NHPI	46%	chiral-NHPI 1	38%
4-NO_2-NHPI	30%	chiral-NHPI 2	15%
3-NO_2-NHPI	11%	Ph_4NHPI **56**	80%

Fig. 6 | Development of more stable PINO-type species. a, Masui's PINO decomposition experiment in 1987. Kinetic results of phthalimide-*N*-oxyl (PINO) decay reported by Masui[41], Espenson[75], Lanzalunga[76], Pedulli[6] and Kushch[79]. Masui's experiment is critical to advance the catalytic performance of PINO but received very little attention in the design of improved PINO-type catalysts. Ag/Ag$^+$, silver/silver ion reference electrode; $NaClO_4$, sodium perchlorate. **b**, Hypothesis of PINO decomposition by Masui and Pedulli. **c**, Development of more persistent PINO-type species through steric manipulation[80]. [a]Kinetics measured by Einhorn[80]. k_d, rate constant of decay; NHNI, 2-hydroxy-1H-benzo[f]isoindole-1,3(2H)-dione; NHPI, *N*-hydroxyphthalimide; Ph_4NHPI, *N*-hydroxytetraphenylphthalimide.

cathodic/anodic current ratio (i_{pc}/i_{pa}). Although Masui stated that the rate of decomposition was not affected by the base (pyridine) concentration[41], Rafiee and co-workers observed that the decay of PINO increased with the basicity of the (aqueous) solution[83]. A recent voltametric study by Stephenson and co-workers on a similar system suggested that PINO decay occurred significantly faster ($i_{pc}/i_{pa} \ll 1$) in the presence of strong bases ($pK_a > 15$ in acetonitrile, 3 units higher than for pyridine, about 12)[40] (Fig. 7a). When benzylic alcohol oxidations were attempted with these strong bases, no desired reactivity was observed, because PINO decomposition outcompeted the HAT reaction. Moreover, tetrabutylammonium phthalimide-*N*-oxide (TBA^+PINO^-) was found to be irreversibly oxidized. Even a full equivalent of TBA^+PINO^- could not achieve benzylic oxidation under electrochemical conditions. These results indicate that PINO decomposition operates by at least two mechanisms and can be accelerated by strong bases.

The observation of base-promoted PINO decay motivated computational studies to investigate the mechanism of PINO decomposition[40]. By calculating the energies of possible intermediates, both Masui and Pedulli's hypotheses were rejected, because they were either thermodynamically unfavoured or kinetically inaccessible. An alternative, base-dependent, second-order decomposition mechanism was proposed (Fig. 7b). In the presence of weak bases ($pK_a < 15$), a weakly nucleophilic PINO can attack a carbonyl group of a second PINO to generate a dimeric species (**55**), which leads to trimer **49** via C–N homolysis and combination of the resultant acyl radical with a third PINO. In the presence of strong bases ($pK_a > 15$), the more nucleophilic NHPI anion **54** predominates, which leads to a significantly faster decomposition ($i_{pc}/i_{pa} \ll 1$). By calculation, the activation energy of the anionic decomposition was 14.8 kcal mol^{-1} lower than the other radical path. The data indicated that the PINO decomposition was enabled by the electrophilic nature of the two carbonyls. This mechanistic insight may explain the stabilities of different PINO derivatives in the literature. For example, adding electron-withdrawing groups renders carbonyls more electrophilic and destabilizes the corresponding PINOs. The elucidation of the major decomposition path provides new viewpoints towards advancing PINO-type catalysts by improving reactivity and stability simultaneously.

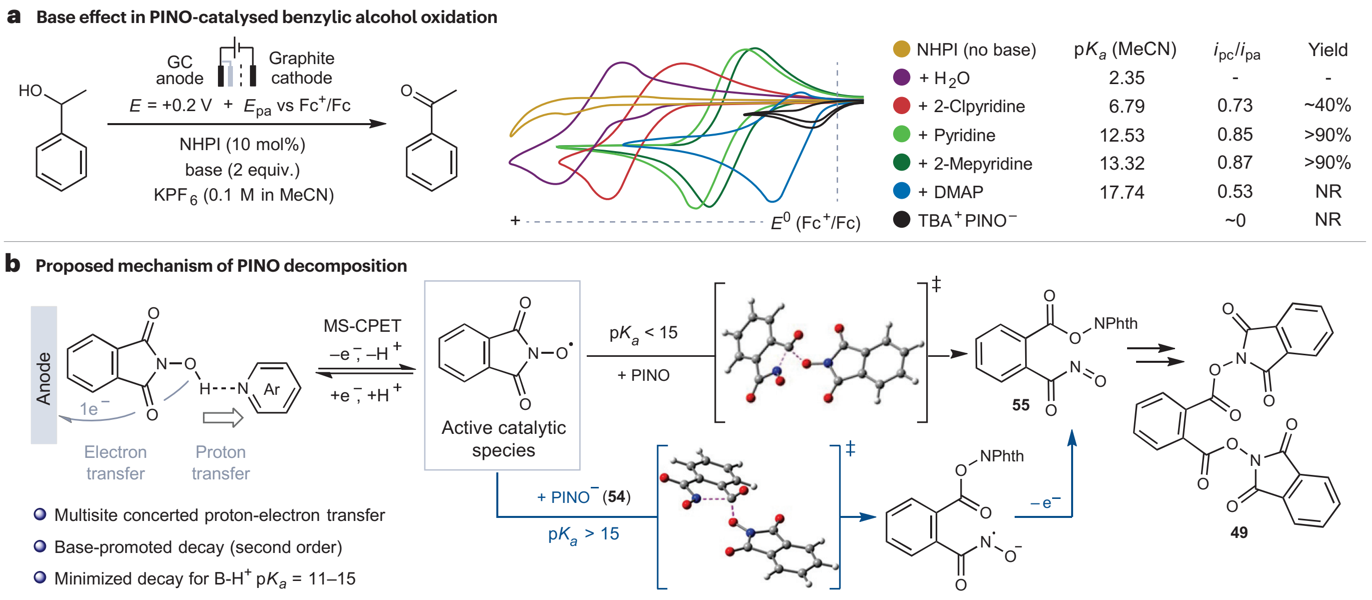
Conclusion and outlook

PINO-type compounds are promising HAT catalysts for selective C–H functionalization. Although several advances have been made, it could be argued that we remain a long way from an optimal catalyst. Indeed, there is still substantial room for improvement. Most efforts have focused on improving a single characteristic of the catalyst—particularly by maximizing the BDE$_{O-H}$ of the catalyst precursor, improving radical persistence via steric effects, or improving solubility in hydrocarbon substrates. The ideal catalyst would satisfy four criteria simultaneously. First, an ideal catalyst must exhibit high reactivity and include at least one functional handle for tuning BDE and electronic properties. Second, the catalyst should be sufficiently persistent under the reaction conditions to minimize off-cycle (decomposition) pathways. Third, the catalyst should allow easy functionalization to achieve desired regio- or stereoselectivity. Fourth, the design of the structure should be modular and compatible with widely accessible building blocks.

Given the importance of catalytic efficiency in chemical reactions, improving HAT reactivity and persistence to off-cycle decomposition pathways should be considered in concert moving forward. For the former, the current method of enhancing reactivity was achieved by BDE tuning or increasing polarization via introduction of electron-withdrawing substituents (Fig. 8). Since these two methods typically render the two carbonyls even more electrophilic, these approaches strengthen the driving force for catalyst decomposition by nucleophilic substitution (among other possible pathways), therefore intertwined with decreasing stability. That is, these approaches render a catalyst that is more potent but with a shorter operational lifetime. For the latter, manipulating sterics can simultaneously preclude access to other molecules, thus not only preventing deleterious interactions but also desirable reaction pathways (Fig. 8). As such, the catalyst is more persistent but less reactive. These considerations should lead to new strategies that can uncouple radical persistence to off-cycle reactions without compromising HAT reactivity. To this end, future work could enhance our current understanding in the following principal ways.

First, the fundamental details of these catalytic reactions with PINO-type catalysts should be better understood. As the HAT reactions are strongly dependent on BDEs, we suggest that the BDE$_{O-H}$ values of all newly designed NHPI derivatives should be reported. Furthermore, the generation of PINO-type catalysts can also influence the overall catalytic performance, and the difference among various catalyst initiation methods should be considered during catalyst design. The importance of possible radical chain processes should be evaluated.

Next, the development of practical syntheses for substituted hydroxylamine compounds should be explored. Most existing syntheses rely on condensation between anhydrides and hydroxylamines. Very few direct oxidations of amines have been reported. The usual oxidants are limited to *m*-CPBA[84], sodium tungstate (Na_2WO_4)[85], and dioxiranes[86]. Given that amines are widely accessible, the development



	pK_a (MeCN)	i_{pc}/i_{pa}	Yield
● NHPI (no base)			
● + H_2O	2.35	-	-
● + 2-Clpyridine	6.79	0.73	~40%
● + Pyridine	12.53	0.85	>90%
● + 2-Mepyridine	13.32	0.87	>90%
● + DMAP	17.74	0.53	NR
● TBA$^+$PINO$^-$		~0	NR

Fig. 7 | The base effect on PINO-catalysed benzylic alcohol oxidation and revised mechanism of its decomposition. a, Phthalimide-*N*-oxyl (PINO)-catalysed oxidation of 1-phenylethanol. E_{pa}, anodic peak potential; Fc, ferrocene; Fc$^+$, ferrocenium; GC, glassy carbon; i_{pc}/i_{pa}, cathodic/anodic current ratio. Cyclic voltammetry for oxidation of *N*-hydroxyphthalimide (NHPI) in the presence of different bases. 2-Clpyridine, 2-chloropyridine; 2-Mepyridine, 2-methylpyridine; DMAP, dimethylaminopyridine; E^0, standard potential; NR, no reaction; TBA$^+$PINO$^-$, tetrabutyl ammonium phthalimide-*N*-oxide. **b**, Proposed mechanism of PINO decomposition. The electrophilicity of the carbonyls is responsible for the decomposition of PINO. MS-CPET, multiple-site concerted proton–electron transfer; Phth, phthalimide; PINO$^-$, phthalimide-*N*-oxide.

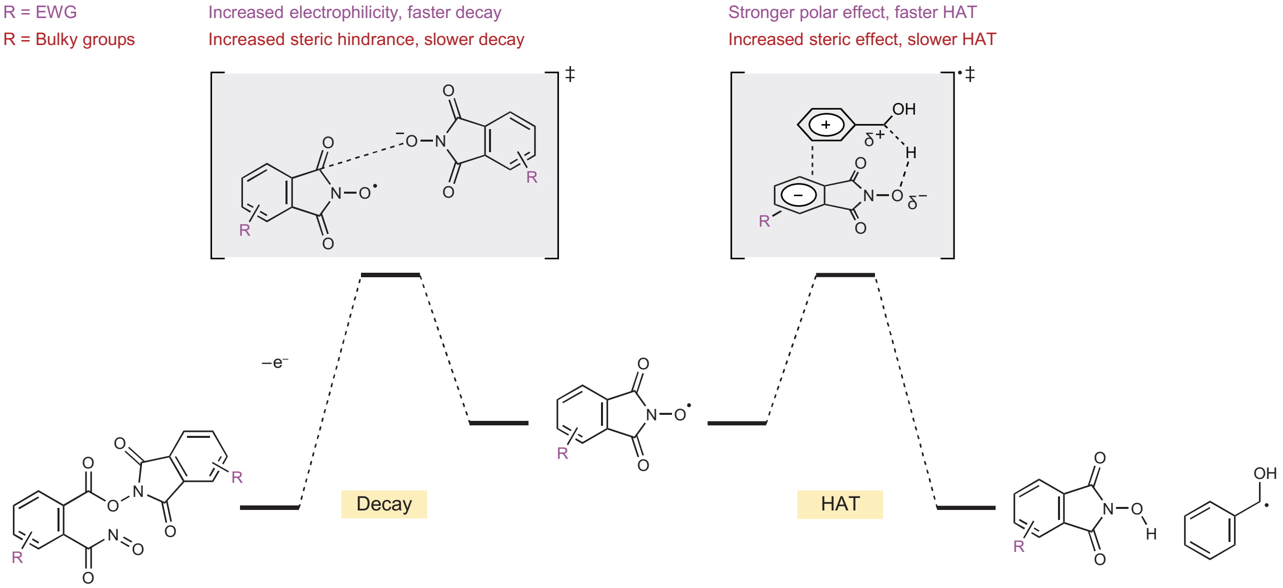


Fig. 8 | Key considerations for optimization of PINO-catalysed oxidations. Electron-withdrawing group (EWG) polarization gives enhanced reactivity but decreased stability, while steric manipulation leads to improved stability but diminished reactivity. Improving both the reactivity and the stability of phthalimide-*N*-oxyl (PINO) in concert is challenging. HAT, hydrogen atom transfer.

of new direct oxidation methods could expand the scope of possible catalyst analogues and could accelerate structure–activity relationship elucidation for *N*-hydroxy compounds of greater structural diversity.

Additionally, a standardized benchmark for catalyst evaluation is necessary. The overwhelming majority of reports use different measurements, metrics or units to evaluate a catalysts's properties of interest. Although general trends are (more or less) clear, quantitative comparisons between studies are challenging. Developing a benchmark for PINO derivatives is also important. Without defined metrics, systematic and head-to-head catalyst comparisons cannot be performed, impeding the recognition and valuation of useful strategies.

Finally, PINO-type catalysts with core structures beyond phthalimides must be more widely considered. From the literature it is clear that functionalization of phthalimide cores overall yields modest improvements. The possibility remains that there are other fruitful structures to pursue.

In summary, advancing PINO-type catalysts remains a promising and exciting endeavour.

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Acknowledgements

C.R.J.S. and S.M. acknowledge the financial support from the National Science Foundation (CBET-2033714), and the University of Michigan. D.A.P. acknowledges the financial support from the Natural Sciences and Engineering Research Council of Canada (RGPIN-2022-05058). C.Y. acknowledges a Rackham pre-doctoral fellowship from the University of Michigan.

Author contributions

C.Y., S.M., D.A.P. and C.R.J.S. contemplated the topic and structure of the Review. C.Y. conducted the literature research. All authors contributed to the discussion of the content and wrote or edited the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Peer review information *Nature Reviews Chemistry* thanks Jie Wu, Osvaldo Lanzalunga, Giorgio Olivio and the other anonymous reviewer(s) for their contribution to the peer review of this work.