Radical Polarity

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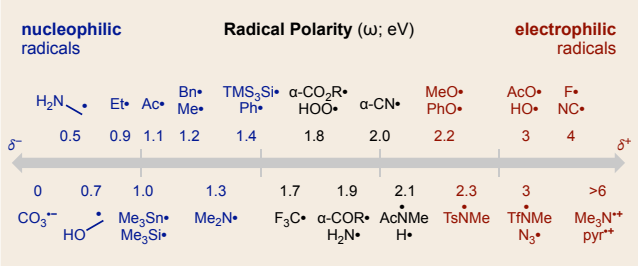
Supporting Information Placeholder

ABSTRACT: The polarity of a radical intermediate profoundly impacts its reactivity and selectivity. To quantify this influence and predict its effects, the electrophilicity/nucleophilicity of >500 radicals has been calculated. This database of open-shell species entails frequently encountered synthetic intermediates, including radicals centered at sp^3, sp^2, and *sp* hybridized carbon atoms or various heteroatoms (O, N, S, P, B, Si, X). Importantly, these *computationally* determined polarities have been *experimentally* validated for electronically diverse sets of >50 C-centered radicals, as well as N- and O- centered radicals. High correlations are measured between *calculated* polarity and *quantified* reactivity, as well as within parallel sets of competition experiments (across different radical types and reaction classes). These multi-pronged analyses show a strong relationship between the computed electrophilicity, ω, of a radical and its relative reactivity (k_{rel} vs Δω slopes up to 40; showing mere Δω of 0.1 eV affords up to 4-fold rate enhancement). We expect this *experimentally validated database* will enable reactivity and selectivity prediction (by harnessing polarity-matched rate enhancement) and assist with troubleshooting in synthetic reaction development.



Introduction

Radical chemistry is often taught and understood primarily via *thermodynamic* factors, such as the strength of bonds formed and broken, as in the case of radical C-H chlorination. However, *kinetic* effects, such as polarity, also play an important role in dictating the efficiency and selectivity of radical-mediated chemistry – sometimes even overriding thermodynamic effects.[1–3] Crucially, the *polarity* (i.e., *nucleophilicity* or *electrophilicity*) of a radical (sometimes referred to as *philicity* or *polar effects*) – and its proper matching – often dictates its viability (and chemoselectivity) in key radical mechanisms, such as π-addition or H-atom transfer (HAT) reactions (**Figure 1**).

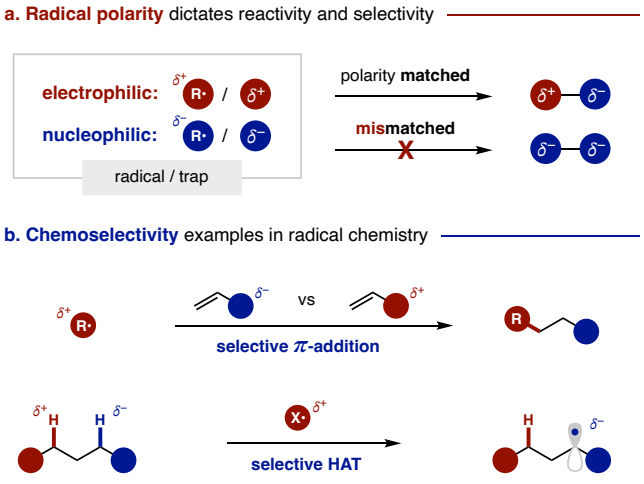


Figure 1. Radical polarity effects in organic synthesis.

Notably, *nucleophilic* radicals (blue) are superior in both Giese π-additions to electron-deficient alkenes[4] and Minisci aryl substitutions of pyridiniums[5] (**Figure 2**). Conversely, *electrophilic* radicals (red) are better suited for (anti-Markovnikov) Kharasch π-additions to electron-rich alkenes,[6] as well as homolytic aromatic substitutions (S_HAr) of electron-rich arenes.[7] Similarly, homolytic substitution (S_H2) reactions are strongly influenced by polarity. For example, HAT of hydridic C-H bonds are best mediated by an electrophilic radical (N•, O•),[8–10] while abstraction of electrophiles by either group- (e.g., xanthate) or halogen atom transfer (XAT) are often facilitated by nucleophilic radicals (Sn•, Si•).[11,12] Notably, these kinetic effects have been harnessed to enable polarity-reversed catalysis with thiols,[13,14] chemoselective π-additions,[15,16] and C-H functionalization of complex molecules.[17–23] Given these important possibilities (and a renaissance in developing tools to harness radical chemistry),[24–28] we reasoned that rapid determination of radical polarity is essential to understanding radical mechanisms and developing synthetic methodologies based on these open-shell intermediates.

To improve chemists' familiarity with this important kinetic effect, we sought to create a readily accessible database that quantifies and compares the polarity of a wide range of synthetically relevant radicals. In this effort, we were inspired by the pioneering *resource collections* of data for pKa (Bordwell),[29] BDE (Luo),[30] redox potentials (Nicewicz),[31] and especially, nucleophilicity (Mayr),[32] of closed-shell intermediates. Throughout our pursuits in the areas of reaction development and synthetic troubleshooting, we often consult these invaluable resources, and thus, we sought to generate a similarly useful database for radical polarity.

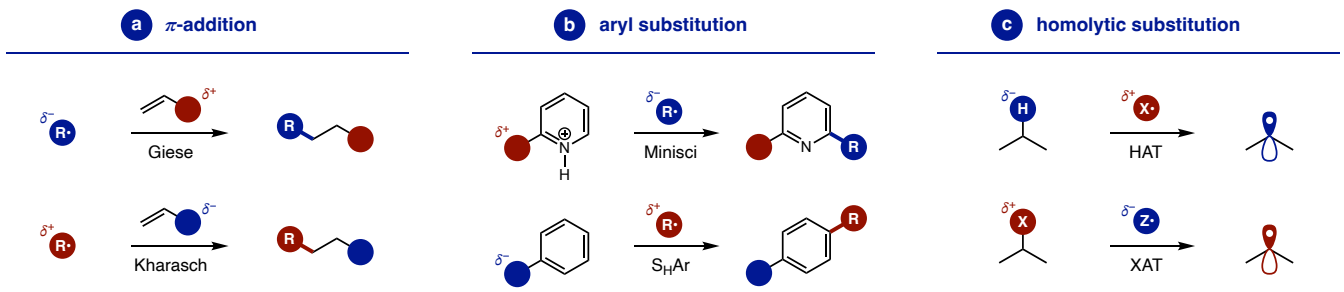


Figure 2. Key mechanisms in radical chemistry and examples of polarity effects in each.

Strategy and Approach

Initially, we were drawn to the electrophilicity/nucleophilicity index developed by De Proft and coworkers.[33] In this seminal work, the electrophilicity of 35 radicals was computed using **Equation 1**.

$$\omega = \frac{\chi^2}{2\eta} = \frac{1}{8}\frac{(I+A)^2}{(I-A)} \qquad (1)$$

In this formula, first defined by the groups of Maynard and Parr for atoms and closed-shell molecules,[34,35] global electrophilicity, ω, is related to the square of Pauling electronegativity, χ, divided by twice the chemical hardness, η. This relationship ($\chi^2/2\eta$) is analogous to electrical power, $P = V^2/R$ (V, voltage; R, resistance). Importantly, these absolute properties (χ and η) are easily calculated from vertical ionization energy, I, and electron affinity, A, as shown in the second half of the equation above. As a practical consideration, it is notable that these values are readily accessible by simple DFT calculations according to the computational workflow shown in **Figure 3**. This figure also includes a simple 'rule of thumb' for *qualitatively* predicting radical polarity, wherein nucleophilic radicals are more easily oxidized to stabilized cations, while electrophilic radicals are readily reduced to their anions.[1,13]

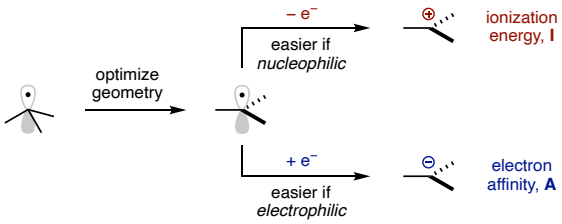


Figure 3. Computational workflow (B3LYP-D3/6-311+G**).

As another key design element, De Proft and coworkers established that this theoretical electrophilicity scale does not require adjustment by additional reaction data (experimental or theoretical). In fact, nearly half of the radicals they studied (15 of 35) afforded similar qualitative results to a theoretical study based on principal component analysis (PCA). In that earlier investigation,[36,37] Héberger and Lopata performed transition state energy calculations and compared them with experimental radical reactivity data (rate constants of radical additions to alkenes) to identify a high correlation between experimental rate constant data and these key descriptors: electron affinity, ionization potential. Despite this strong foundation, there is limited direct experimental validation for computed radical electrophilicity.[38]

At the outset, we identified three major goals for this study:

(1) To build a *comprehensive database* of radical polarity for many common synthetic intermediates (to facilitate reaction discovery and optimization),
(2) To *experimentally validate* this computational data set, and
(3) To derive a *practically meaningful* understanding of this property within the context of synthetic reactivity.

Towards these goals, we *calculated electrophilicities* (ω) for >550 radicals frequently encountered in synthesis (both carbon- and heteroatom-centered). This data set represents a >10x expansion of known radical polarities (>95% previously unknown). Toward our second aim, we include a strong *experimental validation* of these global electrophilicities by evaluating the rates of reactivity for an electronically diverse set of >50 C-centered radicals. As shown below, we observed a high correlation ($R^2 > 0.7$) between these calculated polarities and the quantified reactivity of these radicals in HAT reactions. Finally, we include a series of experiments to show how a difference in electrophilicity (Δω) between radicals relates to their competitive reactivity with nucleophilic traps (0.1 eV ~ 4-fold rate enhancement).

Results and Discussion

In a comprehensive effort to assess a broad range of reaction mechanisms, we compiled a list of the most common radicals encountered in organic synthesis and calculated their electrophilicity (ω) at the B3LYP-D3/6-311+G** level of theory (see SI for details of benchmarking and method selection). The underlying rationale in selecting these radicals was to evaluate a variety of key effects, including atom hybridization (sp^3, sp^2, *sp*) and diverse steric and

electronic substitution – within a wide range of motifs typically found in synthetically and biologically relevant molecules. To showcase the depth and breadth of these selected radicals, a pair of summaries are included below featuring the electrophilicity of diverse classes of radicals centered on **carbon** (**Figure 4**) and various **heteroatoms** (O, N, S, P, B, Si, X) (**Figure 5**). Across the bottom, the electrophilicity scale (in eV) is indicated with increasing electrophilicity from left to right. To calibrate each chart, **H•** (~2 eV) is shown along a central vertical line. Different classes of radicals are clustered and separated vertically for rapid identification, with the simplest and most archetypal shown atop, progressing downward to greater complexity. Then, within each row, the effects of substituent variation are highlighted graphically by including key structures, while each data point (presented in more detail to follow) is indicated by a point on the line.

The first summary graphic, **Figure 4**, depicts sixteen **alkyl** radicals (whose full structures and ω values appear as first two lines of Table 1) on the top line as sixteen red dots (~1 eV). The structures of five representative alkyl radicals are shown to illustrate the observed trend that greater substitution at the C-centered radical decreases electrophilicity (or increases nucleophilicity). On the next line, **allyl** and **benzyl** radicals are represented (in blue), with key substituent effects shown for para-substituted benzyl radicals, as well as five and seven-membered rings whose oxidations would afford aromatic or anti-aromatic molecules, respectively. For comparison, **vinyl** (green) and **alkynyl** (black) radicals are included in this row, with the latter highlighting the vastly greater electrophilicity of an *sp*-hybridized radical (>3 vs 1 eV; see also **nitrile** below).

Heteroatom-substituted C-radicals are then shown for **oxygen** substitutions at varying positions – proximal to alcohols, ethers, or esters, as with **α,β,γ,δ-oxy** (purple). These are often more nucleophilic than their aliphatic equivalents. Notably, **acyl** (orange) radical nucleophilicity is clearly illustrated, contrasting with the electrophilicity of **α-carbonyls** (blue) and especially **β-dicarbonyls** (red). Next, a broad range of **nitrogen** substitution is illustrated, including for nucleophilic **α,β,γ,δ-amino** (green) and **α-amide** (orange) C-radicals, versus electrophilic **α-cyano** (purple) ones.

Next, **aryl** radicals (red) of increasing electron-deficiency highlight the greater innate electrophilicity of aromatic sp^2 radicals relative to aliphatic sp^3 radicals (>1.5 vs <1 eV). Then, a set of diverse **heteroaryl** radicals (blue) illustrate the influence on C-radical electrophilicity of inductively withdrawing (but poorly resonance-donating) atoms (S > O > N), as well as their quantity (2 > 1) and placement within the ring.

Lastly, other **heteroatom** substituents are shown for comparison, including **halogens** (green), **sulfur** in different oxidation states (**thiyls**; purple), as well as **α-silyl** (red) and **α-boryl** (blue) C-radicals. Importantly, common **charged** and neutral radicals that are commonly employed as single-electron reductants – due to their nucleophilicity – are included for reference at the left (e.g., formate (top), and those from Hantzsch ester or dicyanobenzene (bottom).

In **Figure 5**, key **heteroatom-centered** radicals quantified in this study are also summarized. Notably, the incorporation of atoms that are more electronegative than carbon (N, O) affords greater electrophilicity, as illustrated by a much wider scale (20 vs 3 eV for carbon). Conversely, less electronegative atoms (B, Si) yield more nucleophilic radicals (<1.5 eV). This summary chart is similarly arranged in a purposeful manner with more commonly encountered radical classes shown above. For example, ten distinct classes of **nitrogen**-centered radicals are included in the first five rows (**aminyl**, **azido**, **isocyanato**, **aminium radical cations**, **iminyl**, **hydroxy aminyl**, **amidyl**, **imidyl**, **sulfonamidyl**, **hydrazinyl**) along with their respective clusters (1–5 eV), illustrating the greater importance of the atom, hybridization, or functional group identity on the radical's polarity, rather than its substituents.

Notably, and perhaps counterintuitively, *neutral* N-centered radicals are mostly *nucleophilic* (<2 eV) when substituted with alkyl groups, such as **aminyl** (red) or **iminyl** radicals (blue). α-Heteroatoms (N, O) also afford *nucleophilicity*, as with **hydroxy aminyl** (green) and **hydrazinyl** radicals (blue). Otherwise, any withdrawing substituent that increases p-character of the N-centered radical yields the expected *electrophilic* (>2 eV) character. For example, **azido** and **isocyanato** radicals (black), as well as N-radicals with carbonyl or sulfonyl substitution are nearly all to the right of **H•** (more electrophilic).

The third row of this chart illustrates a key takeaway that can be quickly gleaned from this type of graphical depiction; namely, all **imidyl** radicals (orange; 4 eV) are more electrophilic than **amidyl** or carbamyl ones (purple; 2 eV), regardless of substitution. However, **sulfonamidyl** substitution (red; 2–5 eV) greatly impacts ω, yielding either radicals that are more electrophilic (Tf_2N•; 5 eV) than *all* imides (4 eV) or others less electrophilic (TsMeN•; 2.3 eV) than even some amides and carbamates (2.4 eV). At the top right, several examples of *charged,* **N-radical cations** (red) – commonly employed as single-electron oxidants or HAT-mediators – are included (8–17 eV; note broken axis, included for scale) to illustrate the enormous influence of a formal charge. It is notable that each of these radical cations is more electrophilic than even the most electronegative element, F• (>8 vs 4 eV).

Rows 6-9 (**Figure 5**) next highlight 14 distinct classes of **oxygen**-centered radicals, wherein the O-atom is covalently bound to a C, O, N, P, S, Si, acyl, aryl, or sulfonyl group. As expected, nearly all of these O-centered radicals are more electrophilic than hydrogen (>2 eV) – with TfO• (5 eV) and 2,4,6-$(NO_2)_3$-PhO• (5 eV) each being more electrophilic than F• (4 eV). Interestingly, a few outliers showcase the α-heteroatom substitution effect, where O-bound heteroatoms are electron-releasing, as in the cases of **O_2** (neutral or anionic; black), **peroxyl** (purple) and **hydroxyl amine** (green), which are each less electrophilic than **H•** (<2 eV). In contrast, C, Si, or S substitution merely tune (or enhance) the expected electrophilicity, as with **hydroxyl** (green), **siloxyl** (orange), **acyloxyl** (red), **phenoxyl** (blue), **sulfinoxyl** (purple), **phosphoryloxyl** (orange), and **sulfonyloxyl** (purple) radicals. Again, charged cases, as in **O-radical cations** (green or black) are most electrophilic and beyond the broken scale (>8 eV).

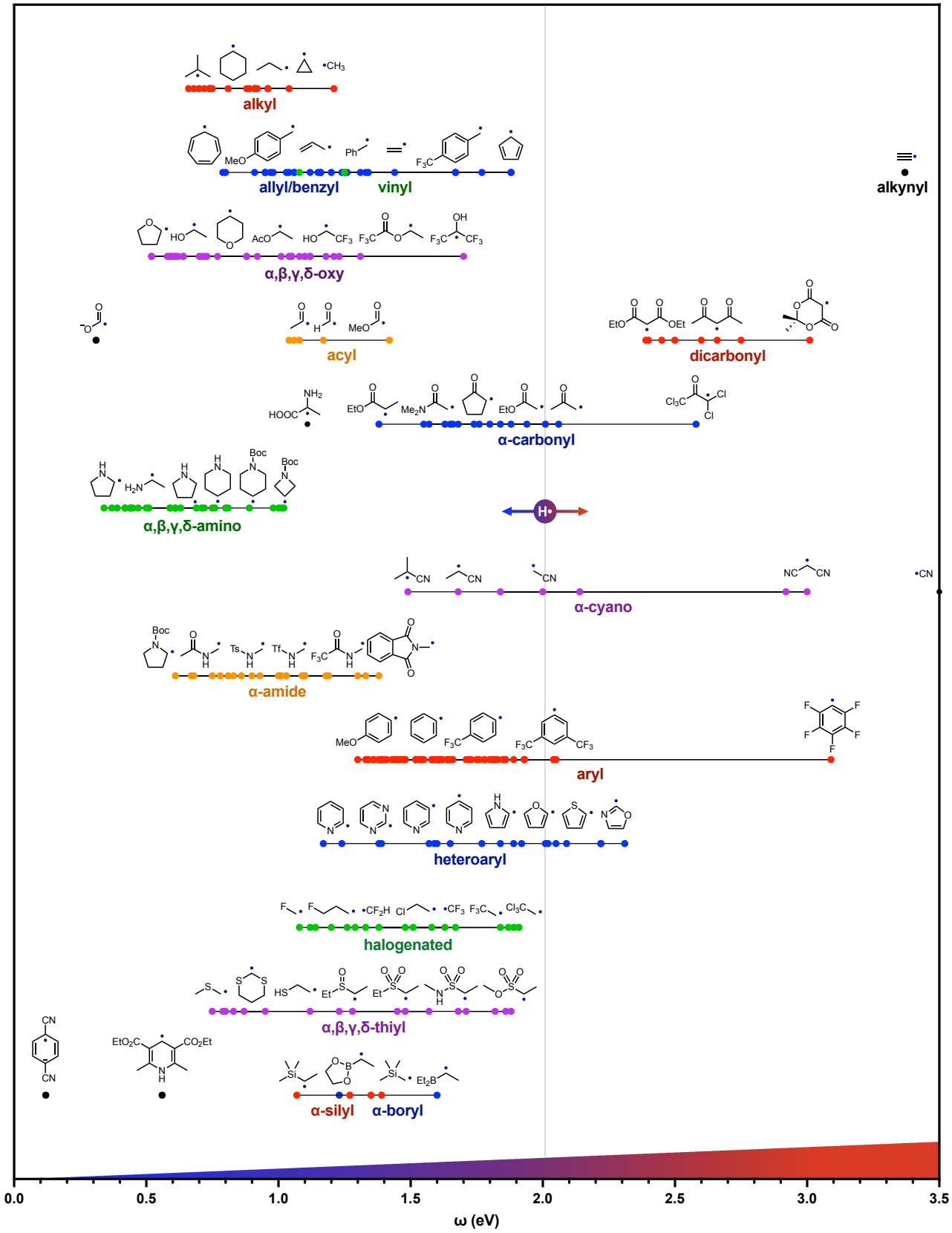


Figure 4. Carbon-centered radical polarity (Summary); nucleophilic (left) to electrophilic (right).

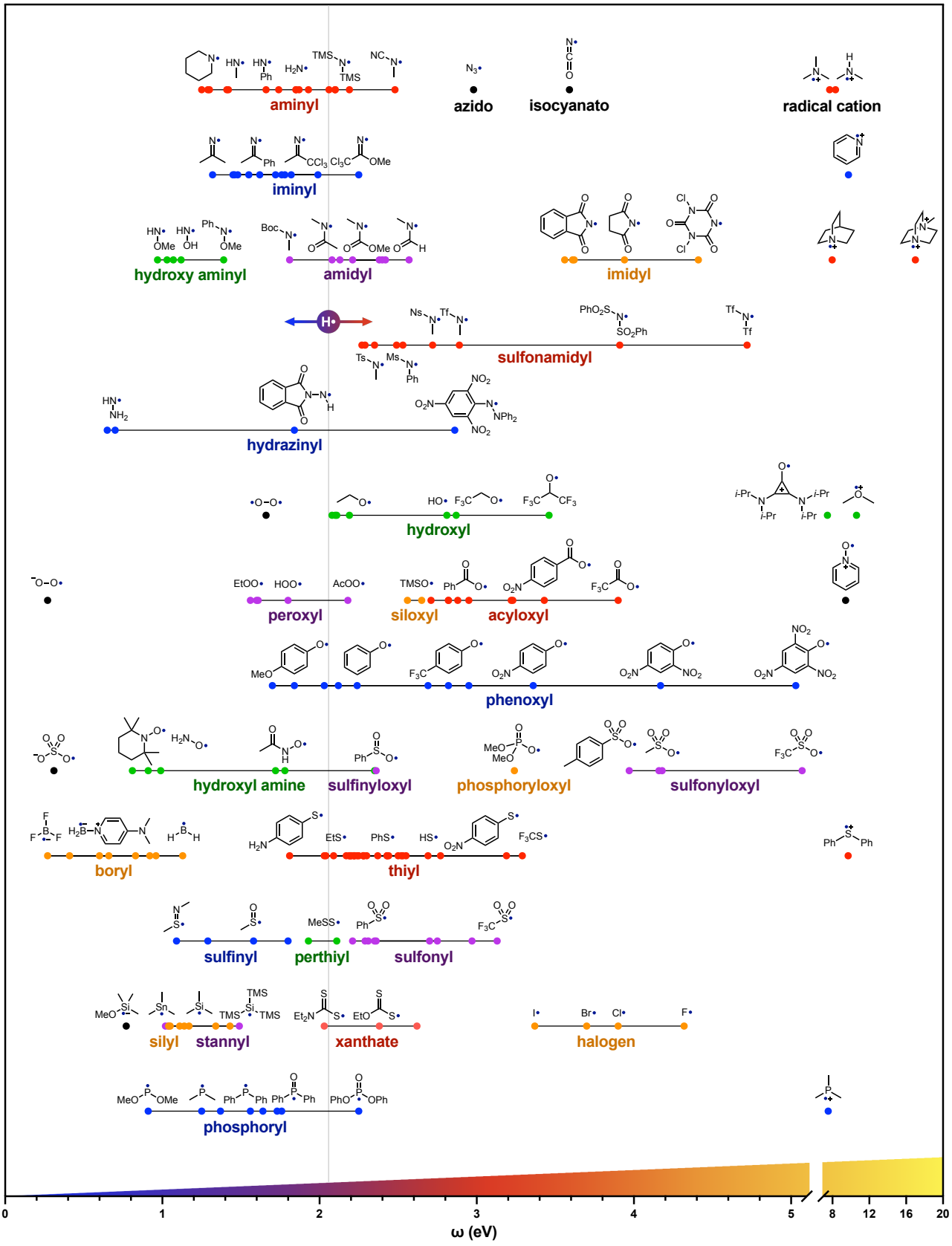


Figure 5. Heteroatom-centered radical polarity (Summary); nucleophilic (left) to electrophilic (right).

The final four rows then illustrate other common **heteroatom radicals** frequently employed in synthesis, including those centered on boron (**boryl**; orange), sulfur (**thiyl**; red) including in different oxidation states, such as **sulfinyl** (blue), **perthiyl** (green), **sulfonyl** (purple), **xanthate** (red), as well as silicon (**silyl**; orange), tin (**stannyl**; purple), and phosphorus (**phosphoryl**; orange). Interestingly, all these heteroatom-centered radicals (S, Si, Sn, P) are less electrophilic (<3 eV) than those of **halogens** (>3 eV). Again, **radical cations** (on S or P, like N and O above) are highly electrophilic outliers (>8 eV) that are oxidizing, while **radical anions** (on O, B, or Si) are highly nucleophilic (<0.8 eV) and can instead be used as single-electron reductants.

Carbon-centered Radicals

Zooming in from this global overview of generic radical classes, each table below provides more granular insights about substituent effects on discreet radicals within each category. To start, **Table 1** catalogs an array of **aliphatic radicals**. All these alkyl radicals are more nucleophilic than hydrogen (<2 eV), yet key trends may still be gleaned from this table. For instance, simple **alkyl** (sp^3) radicals are all quite nucleophilic (<1 eV), regardless of substitution pattern or **cyclic/acyclic** arrangement (red/blue). Then, to varying extents, **methyl** (red), **allyl** (green), **benzyl** (purple), and **vinyl** (orange) radicals are less nucleophilic, but still more so than hydrogen (<2 eV). Within this data, notable observations include:

- *Substitution effects:* An increase in nucleophilicity from methyl radical (1.2 eV) to primary (0.9 eV) and secondary/tertiary (0.7 eV) radicals illustrates the influence of hyperconjugation/induction in increasing electron density at the radical carbon.[1] Similar substitution effects are found within the benzyl series (nucleophilicity: 3° > 2° > 1° ; 1.0, 1.1, 1.2 eV), as well as the allyl series of radicals: 3°/2° > 1° ; 1.0, 1.2 eV).
- *Strain effects:* Within the family of cyclic alkyl radicals, nucleophilicity decreases with ring strain. For examples, carbocycles with five (0.7 eV), four (0.8 eV), or three (1 eV) atoms are sequentially less nucleophilic. The outliers, cyclohexyl (0.8 eV), adamantyl (0.7 eV), and bicyclopentane (0.9 eV) are less nucleophilic than expected – perhaps due to overlap with adjacent antibonding orbitals (e.g., $\sigma^*_{C\text{-}H}$ or $\sigma^*_{C\text{-}C}$).
- *Resonance effects:* Electronic delocalization also decreases nucleophilicity. Instructive pairs include: (*i*) propyl (0.9 eV) vs allyl (1.2 eV), (*ii*) cyclohexyl (0.8 eV) vs cyclohexadienyl (1 eV), and (*iii*) benzyl (1.1 eV) vs bibenzyl/tribenzyl (1.4 eV).

Table 1. Aliphatic Carbon Radicals

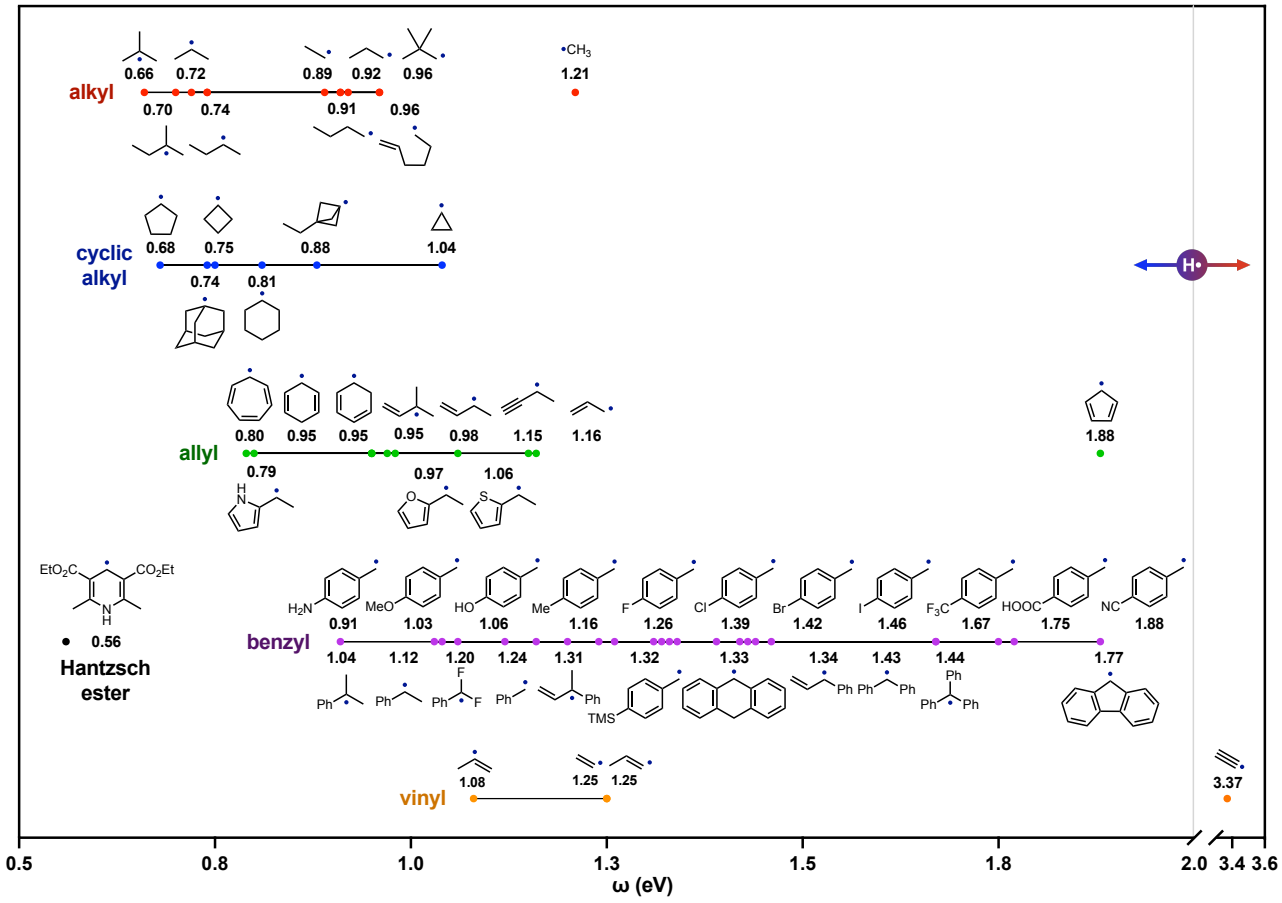
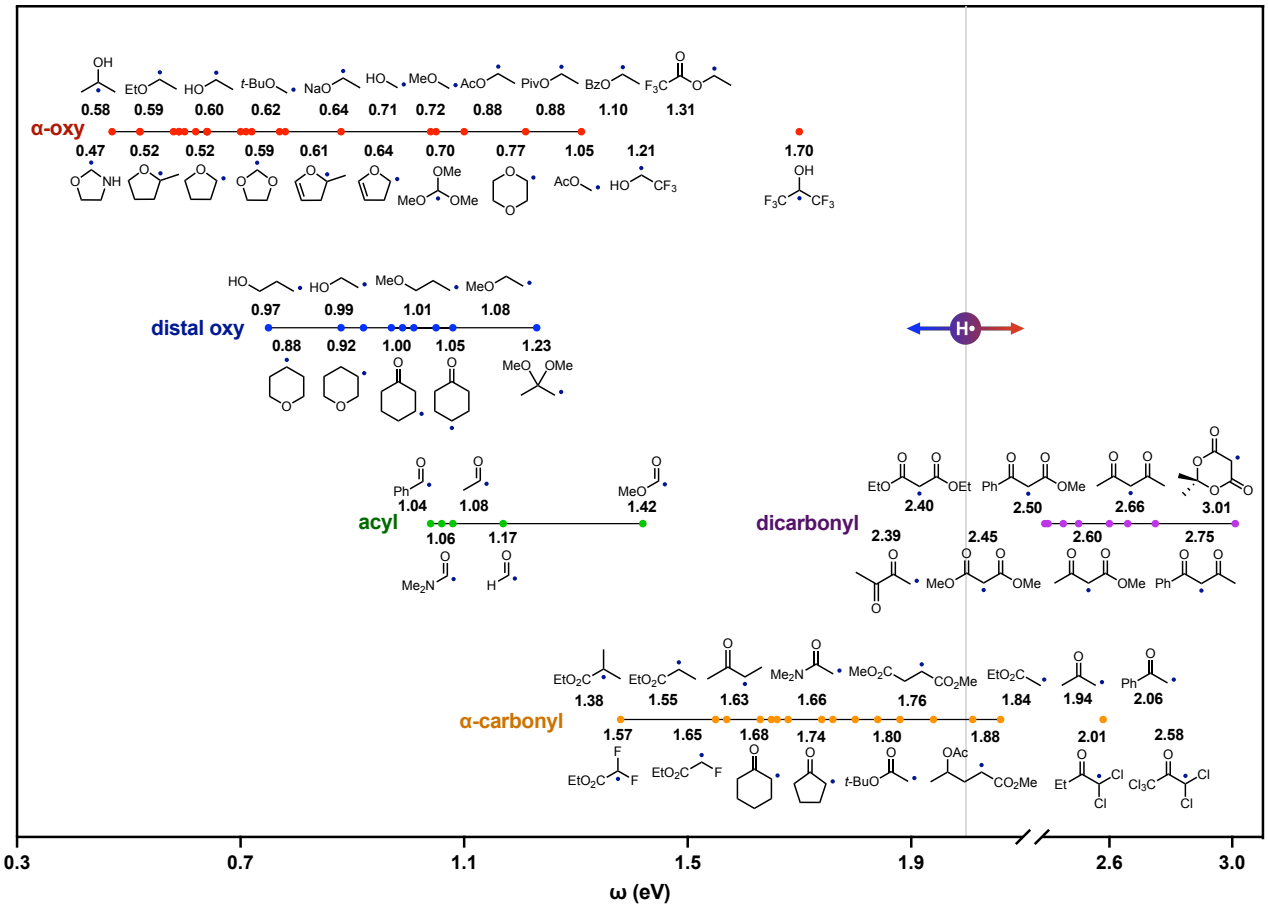


Table 2. Oxygen-substituted Carbon Radicals



- *Aromaticity:* A useful mnemonic for understanding polarity entails the observation that nucleophilic radicals may be easily oxidized to stabilized cations, while electrophilic radicals are readily reduced to stabilized anions.[1,13] An exemplary pair for this model includes cycloheptadienyl (0.8 eV), a *nucleophilic* radical, whose oxidation yields an aromatic (stabilized) cation, versus cyclopenadienyl (1.9 eV), an *electrophilic* radical, whose reduction yields an aromatic anion. Notably, pro-aromatic radicals, which are easily oxidized and nucleophilic (e.g. cyclohexadienyl, 1.0 eV; Hantzsch ester, 0.6 eV), are frequently employed in synthesis.[39]

- *Benzyl substituents:* To relate this database to other resources, we calculated the electrophilicity of benzyl radicals with varying para-substituents, whose Hammett constants (σ_p) have been rigorously measured experimentally (albeit, for two-electron systems) and are widely available.[40] To our delight, a plot of calculated electrophilicity, ω, versus experimental σ_p affords a strong correlation ($R^2 = 0.94$) (see **Fig 12** below). Notably, benzyl radicals with *para*-**donor** groups: NH_2 (0.9 eV), OMe (1.0 eV), Me (1.16 eV) are more nucleophilic than unsubstituted phenyl, H (1.2 eV) and have negative σ_p values (< 0). Conversely, those with *para-acceptor* groups: F (1.3 eV), CF_3 (1.7 eV), CN (1.9 eV) are more electrophilic, correlating with their respective, positive σ_p values (> 0).

- *Hybridization:* Increasing *s*-character of the radical SOMO correlates with higher electrophilicity. For example, an sp^3 radical (ethyl: 0.9 eV) is more nucleophilic than sp^2 vinyl radicals (internal, 1.1 eV; terminal, 1.3 eV), which are much more nucleophilic than an *sp* radical (ethynyl: 3.4 eV).

- *Effects are additive*: It is noteworthy that these effects are preserved and may be combined, as in the cases of tertiary/secondary/primary alkyl (3° > 2° > 1°), which are more nucleophilic than the analogous allyl or benzyl trios that follow the same trends within each grouping.

Given the importance of oxidations in organic synthesis, we next investigated the polarity of **oxygen-substituted** carbon-centered radicals, **Table 2**. In comparison with non-heteroatom-substituted alkyl radicals, these oxy analogs are typically more nucleophilic with **α-** and **multi-** substitution (red) affording greater influence than **distal-** (β, γ) or **mono-** substitution (blue). As demonstrated in Roberts' pioneering contributions,[13] **acyl** radicals (green) are more nucleophilic than **α-carbonyl** analogs (orange). And the greater electrophilicity of **dicarbonyl** radicals (purple) again demonstrates how these effects are additive. Notable observations also include:

- *Resonance:* Nucleophilicity is greater when **α-oxy** substitution

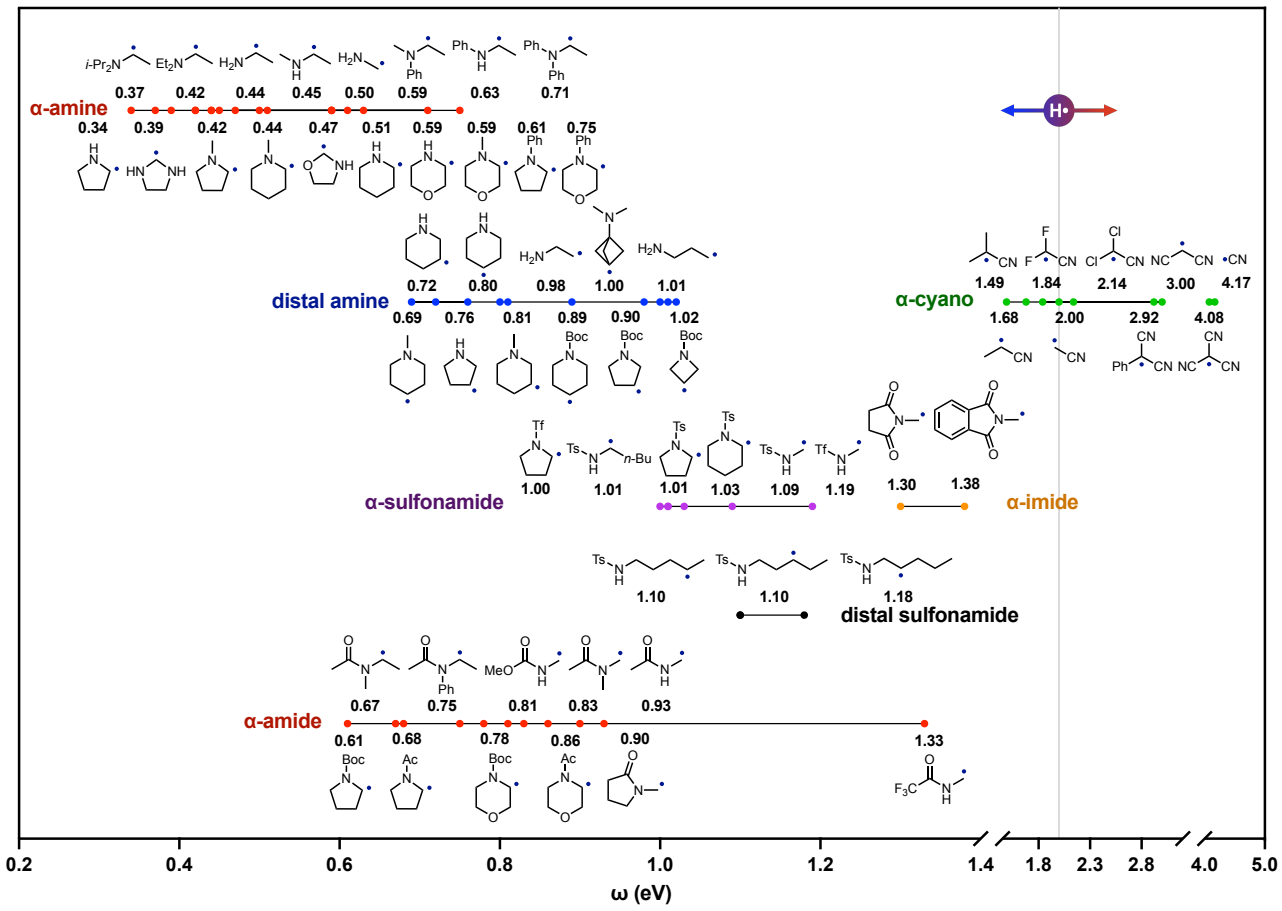
allows for resonance donation of the oxygen lone pair to the radical. For examples, tetrahydrofuranyl (THF; 0.5 eV) > cyclopropyl (0.7 eV), and α-diethyl ether (0.6 eV) > 2° butyl (0.7 eV). In comparison, substituents on THF are less important than resonance effects for 3° vs 2° (both 0.5 eV), but they are more evident for 2° vs 1° (0.6 vs 0.7 eV). Notably, α-acetals are *less* nucleophilic than simple α-ethers (0.6 vs 0.5 eV), likely due to inductive effects, which complicate polarity effects.[41]

- *Induction:* Conversely, **distal** oxygens *decrease* nucleophilicity since their inductive effects are not balanced by resonance. For example, among both cyclic and acyclic pairs (0.9-1.0 eV), the β-oxy radical is slightly less nucleophilic than the γ-oxy (by <0.1 eV) – and both are much less nucleophilic than the α-ether (0.6 eV; by >0.3 eV). Interestingly, an acetal (bearing two β-oxy-groups) is the most electrophilic of this set (1.2 eV).
- *Ketyl radicals:* Given our ongoing interest in harnessing ketyl radicals,[16,42] we were interested to learn of the slightly attenuated nucleophilicity of the ketyl radical anion (0.64 eV) relative to its protonated or alkyl counterparts (0.59-0.60 eV). Although both remain more nucleophilic than a simple alkyl radical (0.72 eV), we anticipate the associated acid or cation greatly impacts polarity – as observed for their catalytic generation.[43,44]
- *Dicarbonyls:* The α-radical of a 1,4-di-ester is more electrophilic than its mono-ester analog (1.8 vs 1.6 eV) due to inductive effects. Yet, stronger resonance effects are apparent in the much greater electrophilicity of a 1,3-di-ester (2.5 eV), where the α-radical is flanked by two carbonyls. Similarly tracking acidity, electrophilicity increases in this (all-Me) series: β-di-ester < β-di-ketones < β-ketoester (2.5, 2.6, 2.7 eV).

Given the privileged role of amines in medicinal chemistry,[45] we next investigated the polarity of **nitrogen-substituted** carbon-centered radicals (**Table 3**). The **α-amino** (red) radicals are more nucleophilic than even α-oxy variants due to increased N lone pair donation (versus electronegative O). In fact, they are the most nucleophilic of all C-centered radicals we investigated. Amines show a decreased inductive effect for **distal** (β, γ) amine substitution (blue). Similarly, **α-cyano** radicals (green) mirror α-carbonyls, while **α-sulfonamide** (purple), **α-imide** (orange), and **α-amide** (red) radicals parallel their α-oxy analogs. Key observations:

- *Amines:* Like alcohols and ethers, where α-OH and α-OR radicals are alike, α-NH_2, α-NHR, and α-NR_2 radicals have similarly high nucleophilicity (0.4 eV), which explains their efficient reactivity with electron-poor alkenes.[46,47] Yet, within heterocyclic structures, the radicals on rings with free amines (α, β, or γ) are consistently more nucleophilic than N-alkyl (by 0.1

Table 3. Nitrogen-substituted Carbon Radicals



eV) or N-Boc (by 0.2 eV) analogs. Recently, the elevated nucleophilicity of α-amino radicals was harnessed to enable Sn-free abstraction of electrophilic halides via XAT.[48]

- *Amides:* Common protecting groups, such as carbamates, amides, and sulfonamides, decrease nucleophilicity of α-amino radicals in the order: NH > NMe > NBoc > NAc > NTs ~ NTf; as shown in the pyrrolidine series (0.3, 0.4, 0.6, 0.7, 1.0 eV; in various rows). While sulfonamides are quite withdrawing – even at distal β, γ, or δ positions (as in remote HAT pathways)[49] – they are not as electrophilic as the double carbonyls of imides, as shown in the protected methyl amine series: α-NTs < α-NTf < α-succinimide < α-phthalimide (1.1, 1.2, 1.3, 1.4 eV).
- *Distal:* The inductively withdrawing effect of a **distal sulfonamide** (black) explains why β (1.2 eV) is more electrophilic than γ or δ (1.1 eV). Yet resonance donation competes: α (1.0 eV).
- *Nitriles:* The strongly additive effect of an α-cyano group is especially evident in the acetonitrile series, where electrophilicity increases: α-CN < α-di-CN < α-tri-CN (2.0, 3.0, 4.1 eV).

Table 4. Aryl Radicals

Substituent	para ω	meta ω	ortho ω
–NH_2	1.33	1.30	1.47
–*t*-Bu	1.38	1.34	1.34
–Me	1.39	1.36	1.38
–OMe	1.40	1.39	1.61
–H	1.41	1.41	1.41
–OH	1.45	1.43	1.78
–NHAc	1.46	1.39	1.75
–Ph	1.48	1.44	1.48
–OAc	1.52	1.52	1.36
–SMe	1.53	1.45	1.59
–SH	1.54	1.55	1.61
–F	1.58	1.60	1.85
–Cl	1.62	1.66	1.81
–Br	1.64	1.71	1.83
–Ac	1.64	1.52	1.65
–I	1.64	1.76	1.82
–CO_2H	1.65	1.60	1.61
–CF_3	1.73	1.72	1.80
–CN	1.86	1.85	1.93
–NO_2	1.93	1.89	2.04

We next quantified the polarity of **aryl** and **heteroaryl** radicals. For the aryl radical data set (**Table 4**), we chose 20 electronically diverse benzene substituents and varied their positions *ortho, meta,* and *para* to the radical. Notably, the positions mattered much less than the electronics of the substituent. Relative to the unsubstituted **phenyl** radical (1.4 eV), those with **donor** groups (NH_2, *t*Bu, OMe) were only mildly less electrophilic (1.3-1.4 eV) or even more electrophilic in some cases (OH, Ph, SH: 1.5 eV) – regardless of substitution pattern. On the other hand, **acceptor** groups ranged from slightly (halides, acyl: 1.6 eV) to significantly (CF_3, CN, NO_2: 1.7-2.0 eV) more electrophilic. Notable observations include:

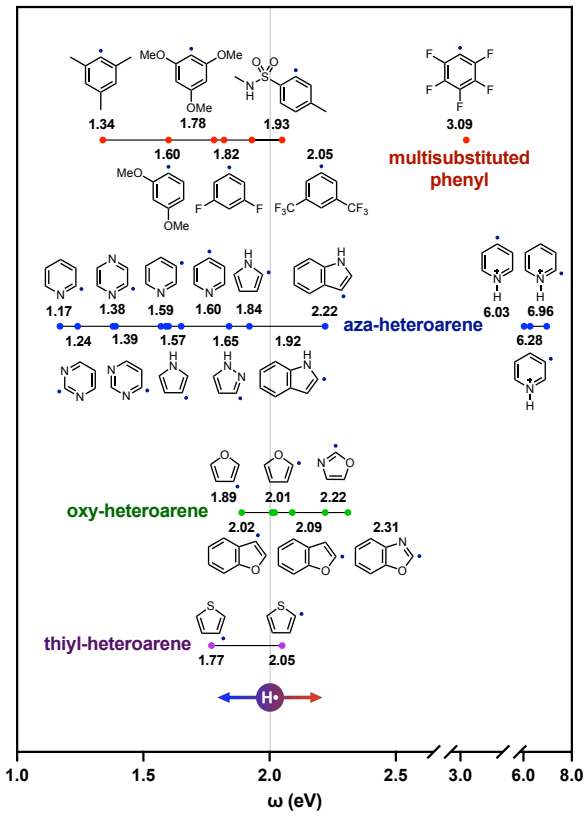
- *Phenyl:* The phenyl radical (1.4 eV) is more electrophilic than a methyl (1.2 eV), allyl/benzyl (1.2 eV), or vinyl (1.3 eV) radical, but is still less electrophilic than a *para*-CF_3 benzyl radical (1.7 eV), which is coincidentally similar to CF_3-aryl radicals (1.7-1.8 eV). This electrophilic character, as well as the strong aryl C-H bond, explains why aryl radicals are best suited among C-centered radicals to enable C-H functionalization by HAT.[50]
- *Substitution:* Groups at the *ortho* position generally have a stronger impact on polarity than *meta* or *para*, as in the case of *p*-Cl (1.6 eV), *m*-Cl (1.7 eV), and *o*-Cl (1.8 eV).
- *Hammett:* The graph of Hammett constants (σ_p and σ_m) against these electrophilicities again yields strong trends, with a correlation coefficient of $R^2 = 0.85$ for the para position and $R^2 = 0.86$ for the meta position (see later section).

To complement these aryl radicals, we also included arenes with multiple heteroatom substitutions, as well as **aza**-, **oxy**-, and **thiyl-heteroaryl** radicals (**Table 5**). While the electrophilicity of these radicals is similar to the aryl set, there are instructive trends and outliers. For example, tri-Me and mono-Me are alike (1.3-1.4 eV), yet electrophilicity increases with **OMe** substitution (mono < bis < tri: 1.4, 1.6, 1.8 eV), illustrating the additive inductive effect. Other withdrawing groups show similar increases in electrophilicity, such as **CF_3** (mono < bis: 1.7, 2.1 eV) and **F** (mono < bis < pent: 1.6, 1.8, 3.1 eV). Notably, the observation that **C_6F_5** radical is so much more electrophilic than even a **bis-CF_3** aryl affords an opportunity to selectively harness these intermediates in organic synthesis.[51]

Notable observations of the **heteroarene** radicals include:

- *Heteroatoms:* **Aza**-heteroaryl radicals (blue), such as 2-pyridine, 2-pyrimidine, and 2-pyrazine (< 1.4 eV), are more nucleophilic than phenyl radicals (1.4 eV), while **oxy**- and **thiyl**- heteroaryl radicals (green/purple) are more electrophilic (1.8-2.3 eV). **Five**-membered heteroarenes (> 1.8 eV) are also more electrophilic than **six**-membered heteroarenes (< 1.8 eV).
- *Nucleophilicity:* The **2-pyridyl** (1.2 eV) radical is the most nucleophilic of any aryl radical measured (even aniline), explaining how it has been harnessed as a nucleophile in Giese additions to acrylates.[15]
- *Radical cations:* Conversely, upon protonation by an acid, the nucleophilic 2-pyridyl radical (1.2 eV) becomes highly electrophilic (7.0 eV), explaining how it was harnessed as an electrophile in Kharasch additions to electron-rich alkenes.[15]

Table 5. Heteroaryl Radicals



Last among the carbon-centered radicals, we probed the following substituents: **Halogen-, Sulfur-, Silicon-** and **Boron** (**Table 6**). Importantly, we noted these effects are similarly additive. For example, in the **α-Cl** series, more chloride substituents lead to greater electrophilicity (mono < bis < tri: 1.1, 1.3, 1.5 eV). This effect is also observed in the **α-F** series, where fluorines also increase electrophilicity (mono < bis < tri: 1.1, 1.2, 1.7 eV). However, like other heteroatoms, opposing electronic effects of halogen substituents (resonance donor, but inductive acceptor) result in an **α-F** radical being less electrophilic than the **β-F** radical (induction only) by a significant gap (1.1 vs 1.5 eV). A distal **β-Cl** is similarly more electrophilic than the **α-Cl** radical (1.6 vs 1.1 eV). Mixed halide or carbonyl and halide substitution yield progressively more electrophilic radicals, as in the cases of Cl_5-acetone (2.6 eV) and Cl_2-acetonitrile (2.1 eV), which are each more electrophilic than even a **perfluorobutyl** radical (1.9 eV). Other notable observations include:

- *Resonance vs Induction:* Whereas an **α-F** substituent increases nucleophilicity by resonance donation, the other halides, which have sequentially larger orbitals that are less suitable for resonance mixing, instead exhibit greater electrophilicity due to greater inductively withdrawing effects. Thus, mono **α-halides** afford more electrophilic radicals in the following order: I > Br > Cl > F. Again, di- and tri- substitution increase these effects.
- *Sulfur:* Similarly, the more polarizable **sulfur** atom increases electrophilicity relative to oxygen substituents. For example, **α-SH** and **α-SMe** radicals are more electrophilic than α-OH or α-OMe radicals (0.8 vs 0.7 eV). Distal thiol induction similarly exceeds distal ether effects (1.1-1.2 vs 1.0-1.1 eV).

Table 6. Halogen-, Sulfur-, Silicon- and Boron-substituted Carbon Radicals

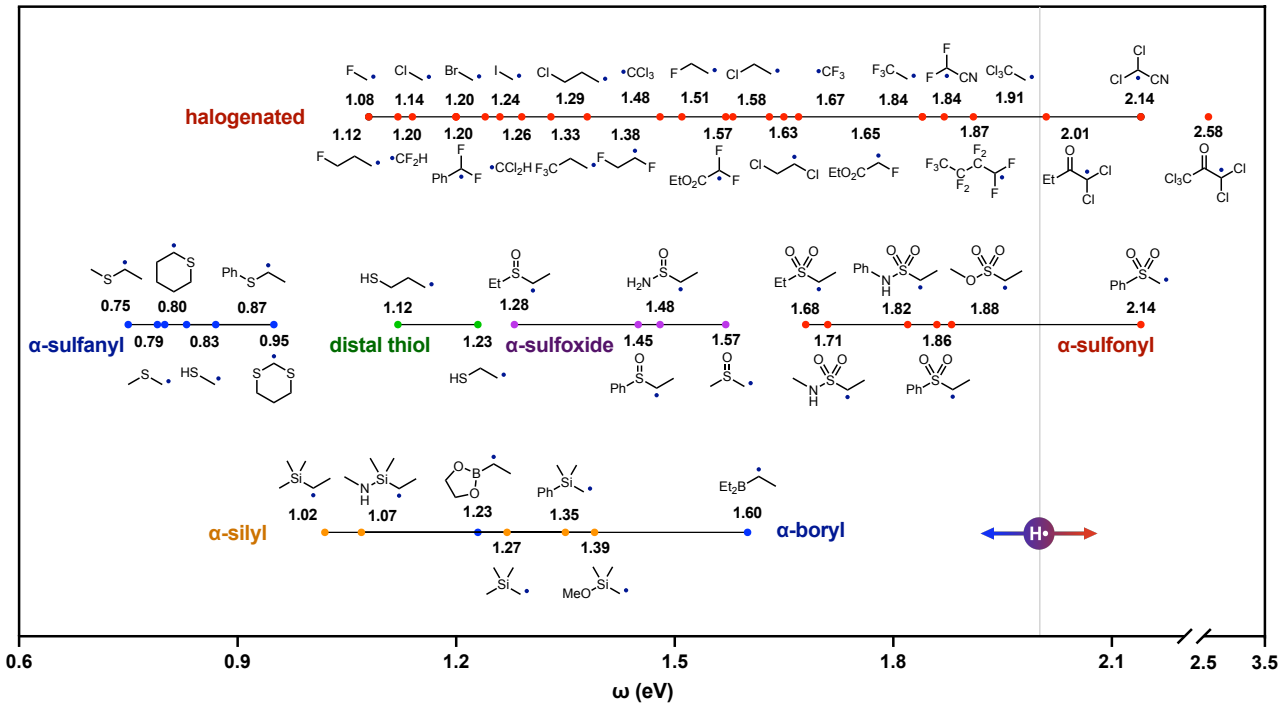
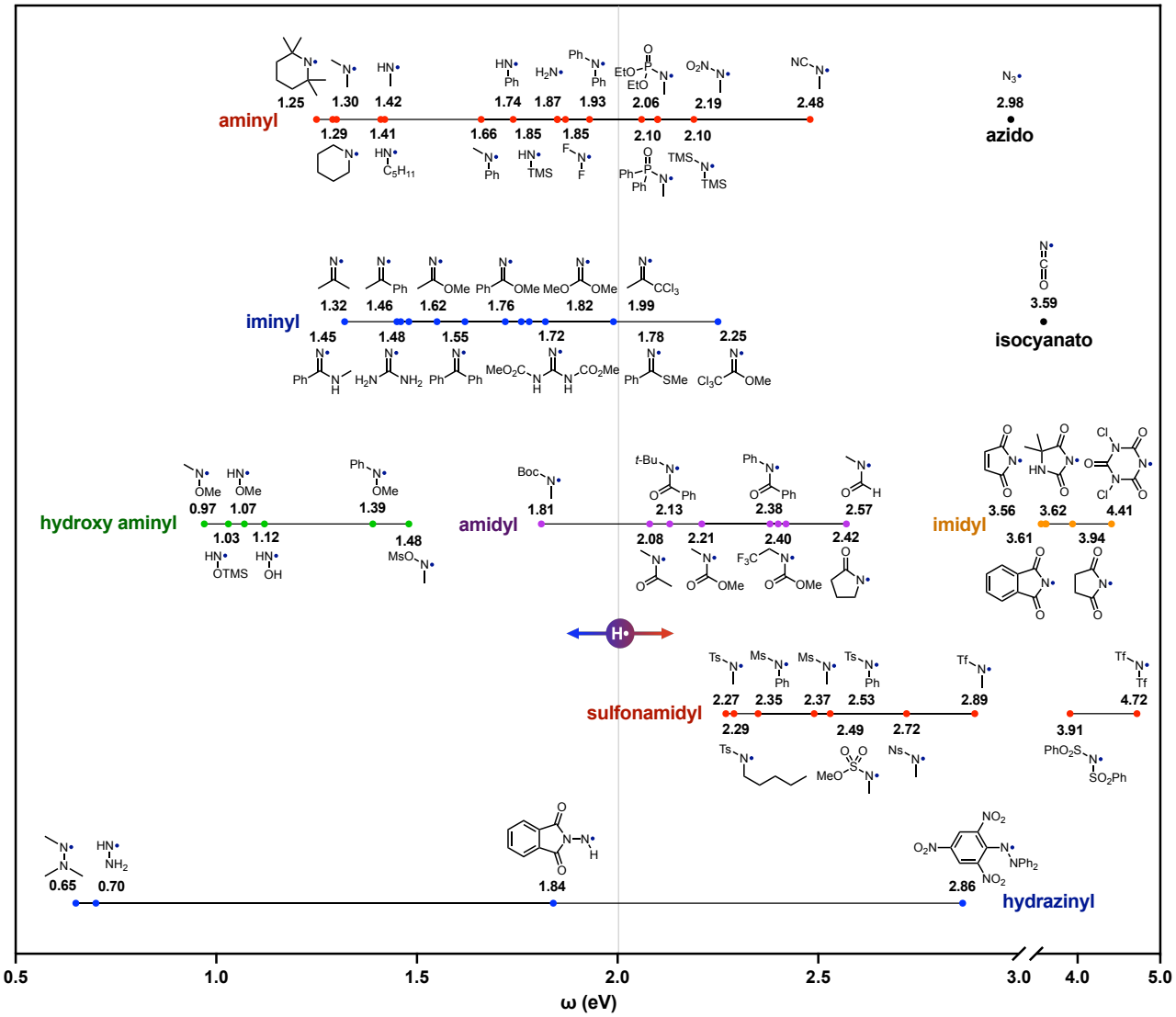


Table 7. Nitrogen Radicals



- *Sulfonyl:* Whereas **α-sulfoxide** radicals (S=O: 1.3 eV) are less electrophilic than α-carbonyls (C=O: 1.6 eV), further oxidized **α-sulfonyl** radicals ($S(=O)_2$: 1.7-2.1 eV) are much more electrophilic. We have recently shown such α-sulfonyl radicals are uniquely suited to enable kinetically challenging C-to-C HAT, unlike the less electrophilic α-carbonyl radicals.[52]

- *Silicon/Boron:* Continuing the observed trend of greater electrophilicity due to poor orbital mixing (and greater induction vs resonance effects; e.g.: Cl > F), **silicon** and **boron** atoms afford more electrophilic **α-silyl** and **α-boryl** radicals (1.0-1.6 eV) than even α-sulfur radicals (0.8 eV) (ω: B > Si > S > O > N) – perhaps explaining the utility of **α-silyl** radicals in remote HAT.[53,54]

Heteroatom-centered Radicals

Alongside these carbon-centered radicals, we also interrogated heteroatom-centered radicals, including at **nitrogen** (**Table 7**). These open-shell intermediates provide a valuable tool for forging C-N bonds frequently found in biologically relevant molecules.[55,56] Given the higher electronegativity (χ) of nitrogen (3.0) versus carbon (2.6) – and that ω is proportional to χ^2 – it is not surprising that most N-centered radicals are more electrophilic than the C-centered radicals described above. Notably, the scale guide (ω: H ~ 2) is now at the center, rather than towards the right as in previous tables. As expected, electrophilicity increases with inclusion of adjacent protecting groups. For example, within the **aminyl** series (red), ω increases for these NH-**R** radicals: -Me, -Ph, -P(O), $-NO_2$, -CN (ω: 1.4, 1.7, 2.1, 2.2, 2.5 eV). Interestingly, this wide range contrasts *nucleophilic* aminyl radicals versus *electrophilic* amidyl and imidyl radicals (or EWG-substituted aminyls: -CN, $-N_2$). Other key observations, aside from those discussed with **Figure 5**, include:

- *Orbital hybridization:* The rightward shift of the **iminyl** series (blue) – and **azido** (black) – versus simple N-alkyl aminyls also illustrates an increase in electrophilicity with more s-character ($sp^3 < sp^2 < sp$), as seen with alkyl, vinyl, and alkynyl radicals.

- *α-Heteroatom effect*: Further probing N-substituents, the electron-releasing lone pair on the α-oxygen of **hydroxy aminyl** (green) and **hydrazinyl** (blue) radicals replicates the α-effect observed with peroxy and hydroxyl amine radicals, resulting in more nucleophilic radicals than typical aminyl (<1.1 vs 1.4 eV).
- *Protecting groups:* Conversely, withdrawing groups increase electrophilicity in the following trend: aminyl < carbamate < **amide** (purple) < **sulfonamide** (red) < **imide** (i.e., a bis-amide; orange) < bis-sulfonamide (red). These electron-withdrawing groups are strong enough to overcome the nucleophilic α-heteroatom effect, as in the case of hydrazine (0.7 eV), substituted with a phthalimide (1.8 eV) or tri-NO_2-Ph (2.9 eV).
- *H-atom transfer*: It is noteworthy that most N-centered radicals used in selective HAT are more electrophilic than H• (center).[10] Namely, bis-sulfonamides (4 eV)[57] and amides (2 eV)[58] are frequently employed in *inter*-molecular HAT. Yet, less nucleophilic imines,[59] imidates,[60] or mono-sulfonamides[61] (>1.4 eV) are also often found in *intra*-molecular HAT.[9]

Another key heteroatom class includes **oxygen**-centered radicals (**Table 8**). Unlike oxygen-substituted C-centered radicals (e.g., α- or β-alcohols), in which oxygen's impact was dictated by polarizability rather than electronegativity, these heteroatom-centered radicals are more influenced by the latter. Thus, with a higher electronegativity of oxygen versus carbon or nitrogen (χ: 3.4 vs 2.6, 3.0), O-centered radicals are more highly electrophilic (ω > 2) than most others investigated. Notably, **hydroxy** radicals (red) are uniformly more electrophilic than their aminyl analogs. Exemplary pairs include: MeO• (2.2 eV) vs Me(H)N• (1.4 eV); PhO• (2.2 eV) vs Ph(H)N• (1.7 eV); and even HO• (2.8 eV) vs H_2N• (1.9 eV). In general, these O-centered radicals are strongly electrophilic, making them well-suited for HAT[62] – often affording high chemo-selectivity,[63] or even *opposite* site-selectivity than Me•, as in the C-H functionalization of ibuprofen.[64] This electrophilicity is further enhanced with addition of acceptor groups, such as carboxyl or sulfonyl. Further observations include:

- *α-Heteroatoms*: As above, the presence of an adjacent electron-releasing lone pair increases nucleophilicity, as seen in **peroxy** (blue) and **hydroxyl amine** (red) radicals. Substituent effects of note in these sets, include:
  EtOO• (1.6 eV) < HOO• (1.8 eV) < AcOO• (2.2 eV)
  Me_2NO• (0.9 eV) < AcN(H)O• (1.7 eV) < PhthNO• (2.4 eV)

Table 8. Oxygen Radicals

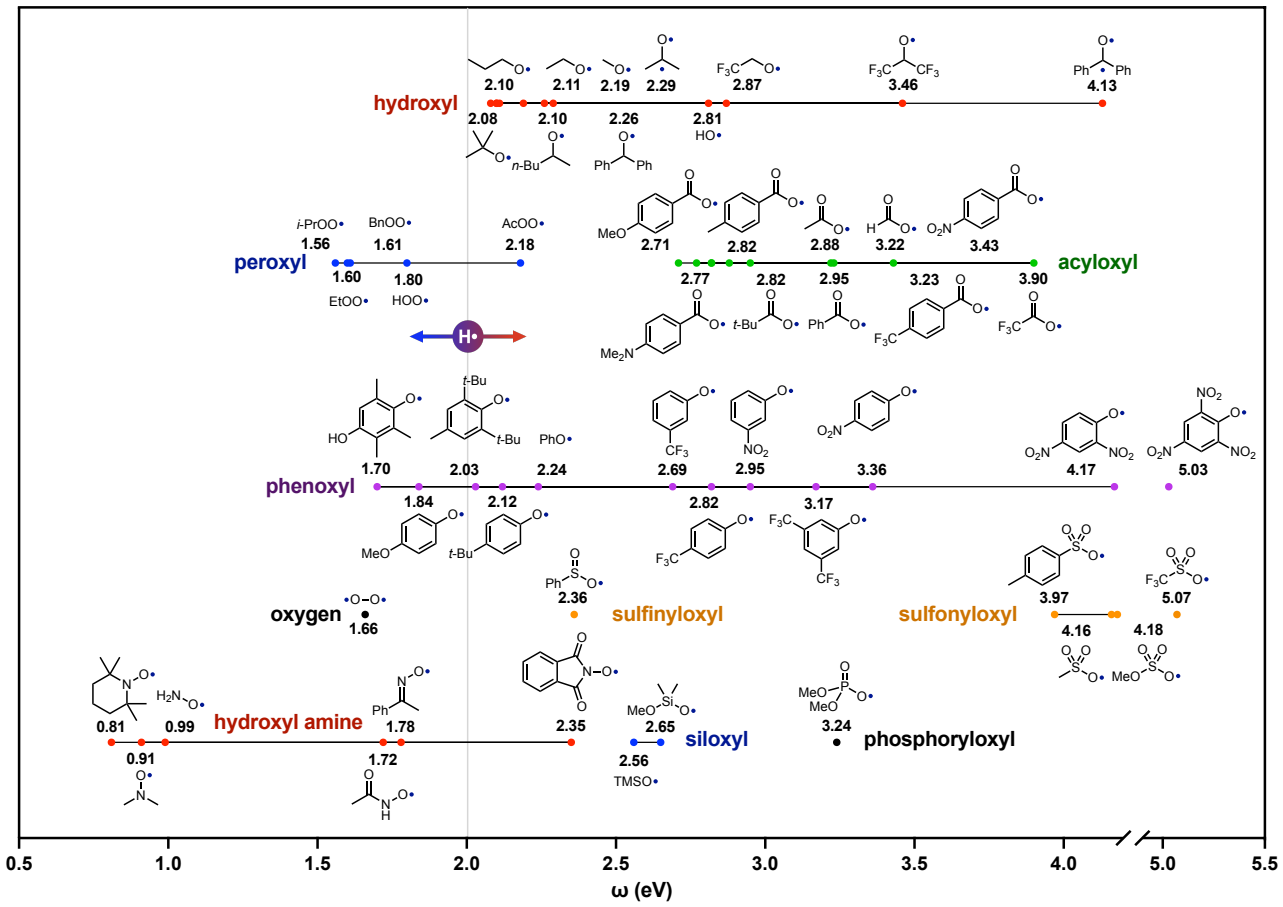
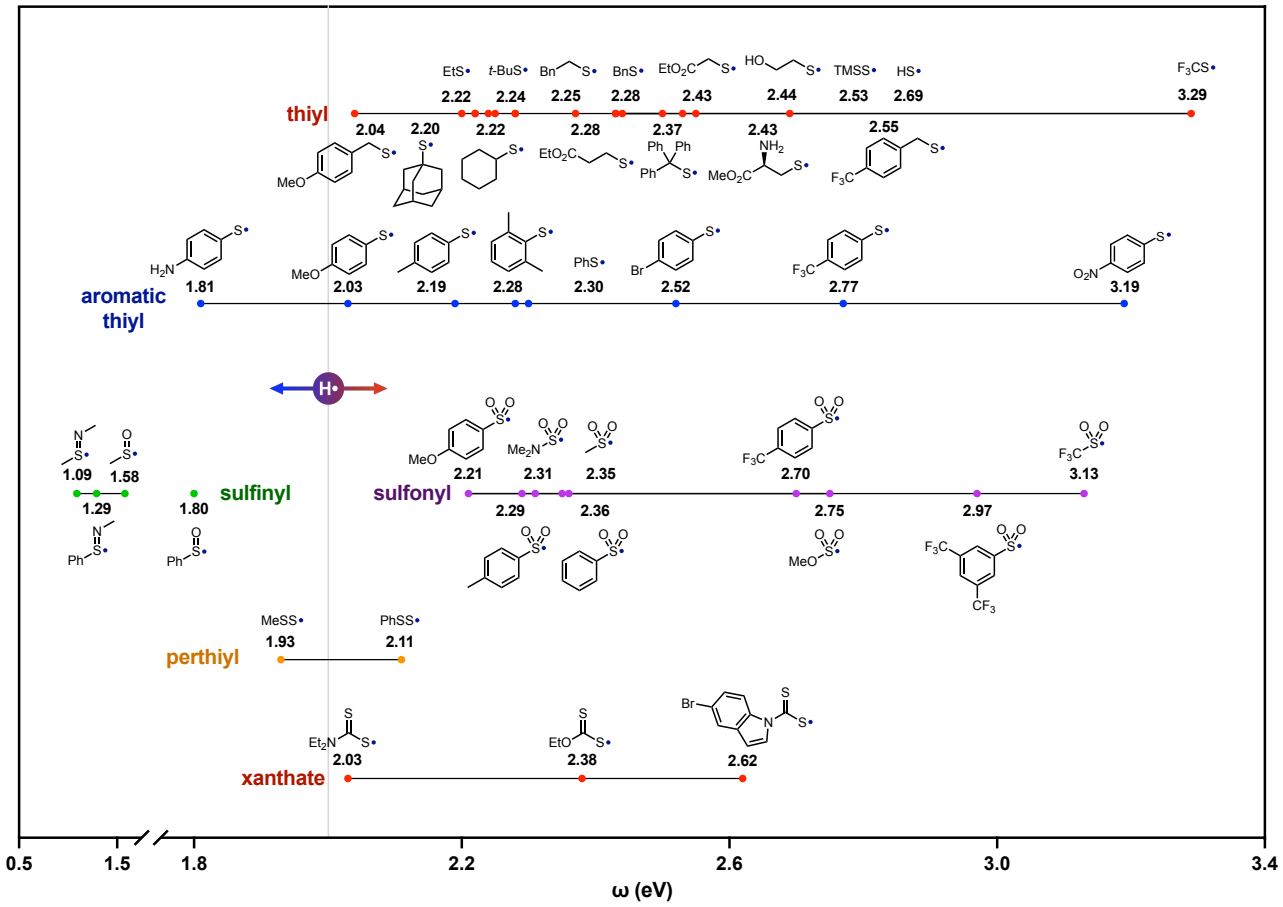


Table 9. Sulfur Radicals



- *Acetoxy:* As a class, **carboxyl** radicals (green) are among the most electrophilic, such as AcO• (2.9 eV) or BzO• (3.0 eV), which are tunable by *donors* – PivO• (2.8 eV), pMeOBzO• (2.7 eV) – or *acceptors* – TFA• (3.9 eV) or pNO$_2$BzO• (3.3 eV). For this reason, the AcO• derived from PhI(OAc)$_2$, and its analogs, have served as useful HAT reagents – especially when a non-polar solvent is employed to suppress β-scission (i.e., loss of CO$_2$ by AcO• to form Me•), which is less capable of HAT.[65]

- *Phenoxy tunability:* **Phenoxy** radicals (purple) are much more susceptible to electronic tuning by substitution, as evidenced by the wider ω window (1.7-5.0 eV) compared with carboxyl radicals (2.7-3.9 eV). For examples, ω increases with the following *para*-substituents: -OMe, -H, -CF$_3$, -NO$_2$ (ω: 1.8, 2.2, 2.8, 3.4 eV). Useful variants also include BHT, *para*-substituents, and *bis*-CF$_3$ or *tri*-NO$_2$ analogs, which further widen the range. Coincidentally, the exceptionally high electrophilicity of phenoxy radicals has recently been harnessed to enable nucleophilic aromatic substitution of halophenols.[66]

- *Benzophenone:* We were intrigued to find the triplet biradical of benzophenone is more electrophilic (4.1 eV; top) than nearly all other O-centered radicals, including those with strongly withdrawing groups (carboxyl, sulfonyloxy), which shows the significant influence of a neighboring open shell. Synthetically, this amplified electrophilicity of biradicals (easily accessed by photoexcitation of aryl ketones) has been harnessed to enable direct HAT – without additional HAT mediators.[67,68]

- *Oxygen:* Triplet **oxygen** (black), like peroxy radicals, is less electrophilic than H• (1.7 eV). Such ambiphilic character allows O$_2$ to react with either nucleophilic or electrophilic species. For this reason, synthetic chemists often make great efforts to exclude atmospheric oxygen from radical reactions.

- *TEMPO:* The hydroxyl amine radical, **TEMPO**, is much more nucleophilic than most heteroatom-centered radicals. With an ω (0.8 eV) closer to alkyl radicals (0.7 eV), it is less polarity-matched to trap such radicals. Thus, users should note that the absence of TEMPO-adducts does not always exclude the presence of nucleophilic radicals in a reaction mechanism – and other indirect detection methods may be more suitable.[69]

- *Protected oxygen:* Given the high electrophilicities of **siloxy** (blue), **sulfinyloxy**, and especially, **sulfonyloxy** (orange) radicals, it is expected these species may also mediate HAT reactions well – if made synthetically accessible. However,

oxidation of a triflate anion to its O-centered radical may prove challenging. Instead, **phosphoryloxy** (black) radicals are accessible by photoinduced oxidation of phosphates – to facilitate C-H functionalizations under quite mild conditions.[70,71]

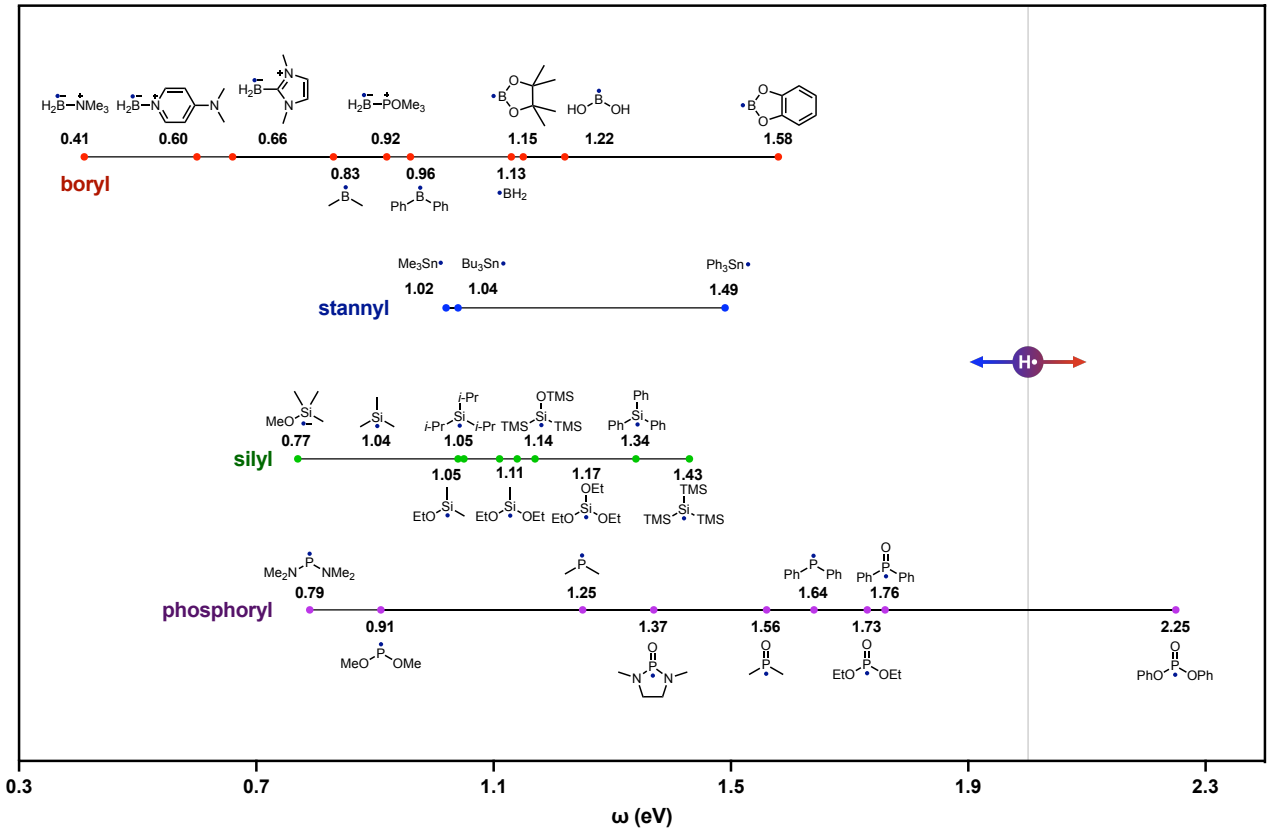
Next, we probed **sulfur**-centered radicals (**Table 9**) since they are common intermediates in radical chemistry. One of the most important roles of thiol radicals is to enable polarity-reversed catalysis in HAT reactions.[13] Although the S-H bond is much weaker than an O-H bond (BDE: 88 vs 96 kcal/mol),[30] the resultant thiyl radical is slightly more electrophilic (ω: 2.2 vs 2.1 eV) – due to the larger size (and poor orbital overlap) of sulfur. Thus, an HAT transition state where a nucleophilic C-radical abstracts H• from a thiol to generate an electrophilic RS• is also kinetically favored by this polarity match (in addition to the thermodynamic benefit afforded by the weak S-H bond). The electrophilic nature of thiyl radicals also enables their utility as a "click reaction" via the rapid addition to alkenes, as in the thiol-ene reaction.[72] Elemental sulfur was recently added to nucleophilic acyl radicals to harness this polarity inversion to electrophilic reativity.[73]

Given the broad utility of thiyl radicals in such mechanisms, we determined the polarity of a wide range of **alkyl** (red) and **aryl** (blue) **thiyl** radicals. Most thiyl radicals were found to be more electrophilic than H• (2 eV), spanning a range of 2-3 eV. Surprisingly, more oxidized sulfur variants, **sulfonyl** (purple) and **xanthate** (red) radicals also fall within this narrow range, which may explain the similar behavior and utility of such electrophilic intermediates in facilitating group transfer reactions, as either radical leaving groups[74,75] or by nucleophilic catalysis.[76,77] The only S-centered radicals consistently less electrophilic than H• (< 2 eV) are **sulfinyl** (green) radicals, which resemble acyl radicals and are similarly nucleophilic (see Table 2). Interestingly, **persulfide** (orange; 1.9-2.1 eV) radicals have a similar polarity to H•, and have been described as ideal HAT reagents, given their weaker RSS-H bond (70 kcal/mol) and 10^4 greater reactivity than thiyl radicals.[78]

In contrast with other heteroatom-centered radicals described above (N, O, S), which are mostly electrophilic (> 2 eV), radicals centered at **boron**, **tin**, **silicon**, and **phosphorus** are nearly all nucleophilic (**Table 10**). This nucleophilicity renders them better suited to generate C-radicals by halogen atom transfer (XAT) of C-X bonds, since electrophilic halides are more easily abstracted by nucleophilic B, Sn, Si or P-centered radicals.[11,12] Atom-specific observations include:

- *Boron:* Among **boryl** radicals (red), the nucleophilicity of BH_2 (1.1 eV) increases upon addition of a donor group, such as: NMe_3 > DMAP > NHC > $P(O)(Me)_3$ (0.4, 0.6, 0.7, 0.9 eV). This superior nucleophilicity explains why NHC-boranes have been employed as a tin-free alternative for reductions by atom- or group- transfer.[79]

Table 10. Boryl, Stannyl, Silyl, and Phosphoryl Radicals



- *Tin:* Although traditionally used more commonly, **stannyl** radicals (blue) are similarly nucleophilic to less toxic alternatives, **silyl** (green) and **boryl** (red). Thus, given modern methods of accessing such radicals without thermal homolysis, the same types of reactivity are accessible in a tin-free fashion.

- *Silicon:* In the **silyl** radical (green) series, we were interested to find the frequently used supersilyl radical[80] is actually least nucleophilic among (less accessible) $R_3Si\bullet$ radicals, according to this trend: $(TMS)_3Si\bullet < Ph_3Si\bullet < (EtO)_3Si\bullet < (Me)_3Si\bullet$ (1.4, 1.3, 1.2, 1.0 eV). Moreover, the neutral $(Me)_3Si\bullet$ radical can be made more nucleophilic by methoxide addition, as in the $(MeO)(Me)_3Si\bullet$ radical anion (0.8 eV) – a key proposed intermediate in the KOtBu-catalyzed silylation of indoles.[81]

- *Phosphorus:* Oxidation state and substituents ensure that the **phosphoryl** radicals (green) span a wide range of polarity. For example, P(V) phosphonyl radicals, such as those generated from phosphine oxides are highly electrophilic (up to 2.3 eV), and have been chemoselectively intercepted by nucleophiles in multicomponent cascades.[82] Conversely, P(III) phosphinyl radicals ($R_2P\bullet$), especially with heteroatom substitution, are highly nucleophilic (< 1 eV), and have been used to facilitate XAT of aryl halides.[83]

Importantly, **charged** radicals (**Table 11**) span the widest range of all radical polarities investigated (0-17 eV). All **radical anions** (left of H•), including *heteroatom*-centered borates, silanoates, carbonates, and sulfates, as well as *carbon*-centered α-borates, ketyls, dienyls, and formates, are significantly more nucleophilic than their neutral counterparts. Striking examples include fluorine-substituted **radical anion**, $BF_3\bullet^-$ (0.3 eV; orange), which is much more nucleophilic than even non-fluoro BH_2 (1.1 eV; Table 10), and the *neutral* C-radical bearing an **α-BF_3 anion** (0 eV; red), which is also significantly more nucleophilic than its non-fluoro counterpart, α-BEt_2 (1.6 eV; Table 6). This may illuminate the mechanisms of oxidative activation and reactivity of **α-borate**[84] and **α-silanoate**[85] radical precursors, including in additions to electrophiles.[86] On the opposite end of the redox spectrum, mild 1-e^- reduction of deficient arenes affords **di-CN-dienyl radical anion** (0.1 eV; from DCB), a synthetically useful nucleophilic radical.[87–89]

Even highly electrophilic O-centered radicals are rendered quite nucleophilic by the presence of a **nearby anion** (blue), whether by resonance ($O_2\bullet^-$; 0.3 eV) or simply inductive (**persulfate**; 0.1 eV) effects. A recent competition experiment supports this nucleophilicity of a **formate** radical anion (0.3 eV) via chemoselective hydrocarboxylation of an electron-deficient alkene.[90] And nucleophilic boryl radical addition to imides has been proposed as a key chain propagation step in the metal-free decarboxylative borylation of carboxylic acids.[91]

Conversely, **radical cations** are extremely electrophilic (significantly right of H•, or even F•, 4 eV; note broken axis). Key classes used in synthesis include radical cations centered at:

- *Nitrogen:* **Aminium** (green) radical cations, generated by N-Cl homolysis of protonated amines (8-9 eV), have enabled either selective: remote C-H amination by 1,5-HAT,[9] or aryl C-H amination of electron-rich arenes by S_HAr.[23] The bridged bicyclic aminium of quinuclidine (8 eV), which is stable to α-elimination, selectively promotes intermolecular HAT of nucleophilic α-amino,[21,22] or α-oxy,[92] C-H bonds. And bis-cationic DABCO analogs, such as from Selectfluor, are *vastly* more electrophilic (17 eV), affording highly *para*-selective aryl C-H amination[20] – even more than pyridinium (10 eV)[93] or aminium (8 eV).[23]

- *Oxygen:* The non-stabilized radical cation of Me_2O (10.6 eV; blue) is too reactive for synthetic utility, but an O• appended to an aromatic, bis-amino-**cyclopropenium** cation (7.5 eV) is a persistent radical,[94] which may be useful as a highly electrophilic, TEMPO analog.

- *Carbon:* Protonated **pyridyl** radicals (6-7 eV; red) are significantly more electrophilic than their neutral analogs (1-2 eV; Table 5). This feature has been exploited to enable chemoselective π-addition to electron-rich alkenes over deficient ones.[15] If the electron hole is within the aromatic π-system (versus on the pyridyl periphery), the resulting **dienyl radical cation** is even more highly electrophilic (11 eV) – affording a valuable mechanism for nucleophilic aromatic substitutions.[95–97] Radical cation intermediates also facilitate anti-Markovnikov additions of mineral acids to alkenes[98] and inverse-demand Diels-Alder cycloadditions.[99,100]

For comparison, an array of common radicals found in **biology** were also investigated (**Table 12**). This functionally rich (and computationally more expensive) data set follows the trends seen above and illustrates how smaller, idealized fragment properties can be extrapolated to more complex systems. For example, the α-amino acid radical of **alanine** (1.1 eV; orange) falls between α-amino (0.4 eV) and α-acid (1.6 eV) values, and the less nucleophilic NAc variant (1.5 eV) reflects its more electrophilic α-amido (0.9 eV) group. Similarly, the anomeric radical of **pyranose** (0.9 eV; red) is nucleophilic, although not as much as the simpler five-membered acetal (0.6 eV; Table 2). Conversely, heteroatom-centered radicals are more electrophilic. Although the complex N-centered radicals (**furanose** and **adenosine**) are more electrophilic than their simpler Me(H)N• and Ph(H)N• variants (by 0.6 and 1 eV; Table 7), the O-centered radicals (**serine** and **guanosine**) are nearly as electrophilic as their simpler EtO• and *p*NO_2PhO• analogs (within 0.3eV; Table 8). Given the similar set of S-centered radicals in Table 9, it is interesting to deconstruct the components of **cysteine** (2.5 eV) that make it more electrophilic than its methyl ester and non-amino version (2.4 eV each) or simply EtS• (2.2 eV). Methionine, a highly electrophilic radical cation (9 eV), also appears in Table 11. Lastly, as expected, **Eosin Y** (green)[67] is highly nucleophilic (and reducing) as a radical anion (0 eV), but highly electrophilic (and oxidizing) as a di-radical (5 eV) – similar to $O_2\bullet^-$ (0.3 eV; Table 11) and benzophenone di-radical (4 eV), respectively.

Table 11. Charged Radicals

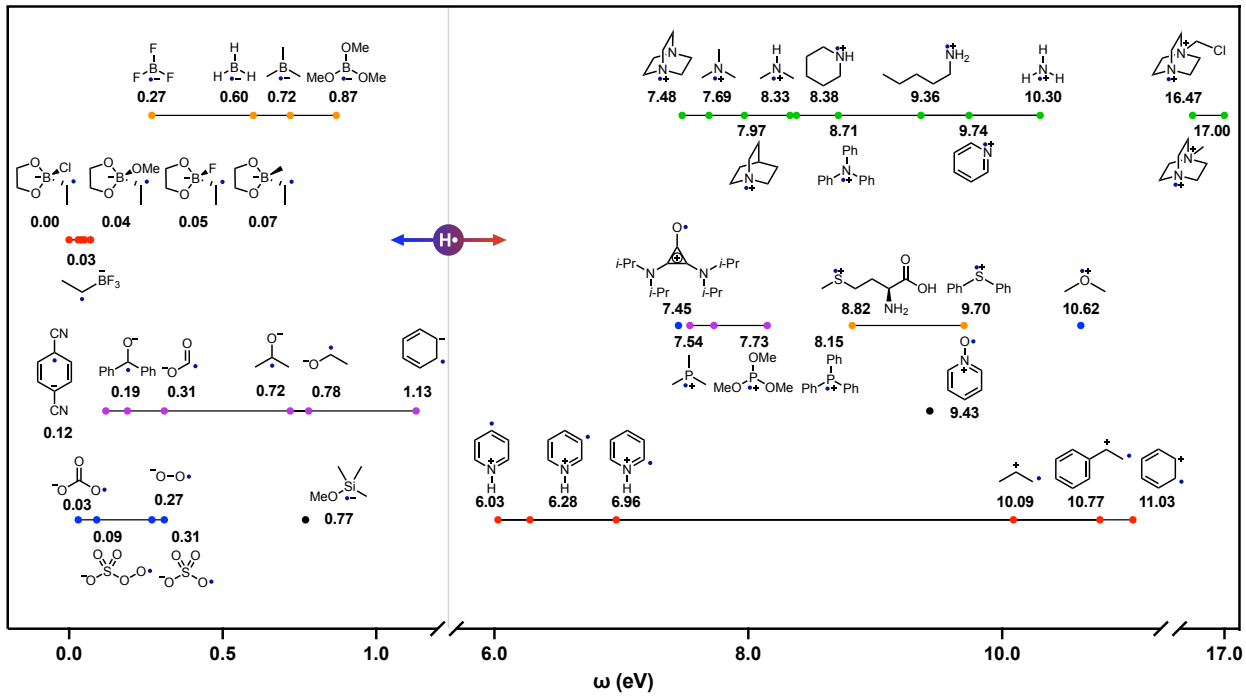


Table 12. Biological Radicals

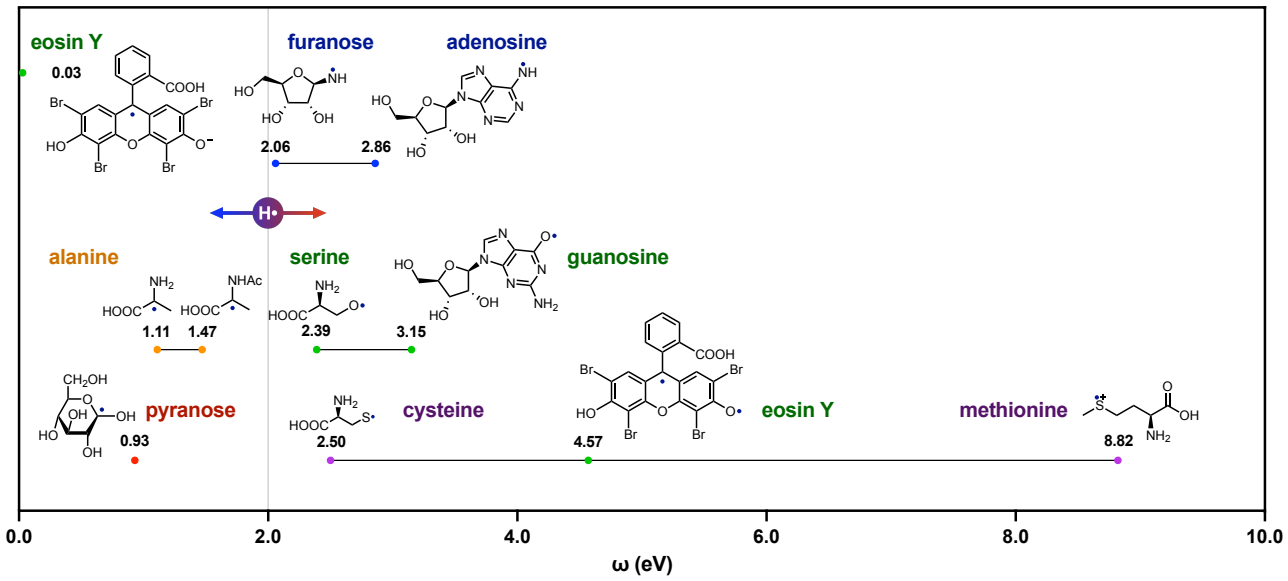
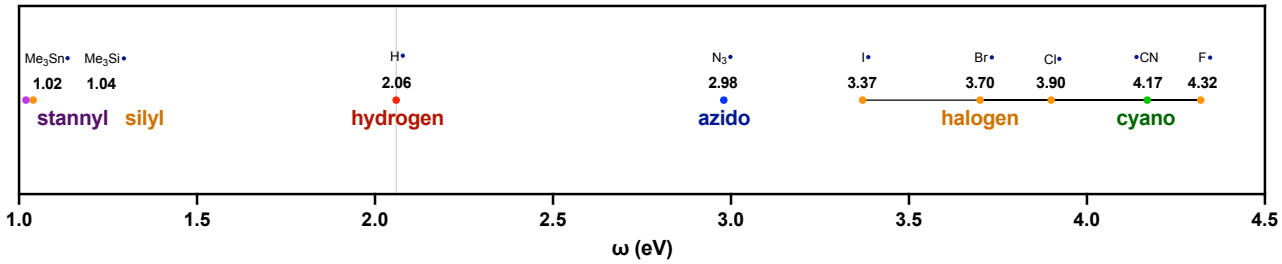


Table 13. Inorganic Radicals (Halides and XAT-mediators)



Finally, select **inorganic** radicals (**Table 13**) were investigated since these are frequently employed intermediates in radical chemistry. Notably, **silyl** and **stannyl** radicals are nucleophilic (1 eV) and often engage in abstraction of halides (XAT). Instead, **azido**, **halogen**, and **cyano** radicals are highly electrophilic (>3 eV), and often react with nucleophilic partners. For example, HAT reactions are well-known with Br• or Cl•[8–10] and azido radicals.[18] Interestingly, the *sp* cyano radical is more electrophilic than *all* of the halogen atoms except fluorine. Most importantly, in contrast with C-centered radicals, which track polarizability of substituents, these halide-centered radicals are instead governed by electronegativity ($\chi \propto \omega$), where: F• > Cl• > Br• > I•. Perhaps less intuitive though, there are several N- and O- centered radicals (and many radical cations) that are more electrophilic than F• (see **Figure 5**).

Experimental Validations

Towards our second goal of experimentally validating this newly calculated radical polarity database, we sought to design a practical set of experiments that could be conducted in a typical synthetic lab. Radical kinetic experiments typically require pulse irradiation techniques and a fast detection spectrometer to obtain rate constants with nanosecond-resolution (e.g. by laser flash photolysis).[78,101] In contrast, we questioned if a simpler, *indirect* kinetic method could be designed, employing standard GC or NMR tools to determine product ratios or reagent concentrations.[102] This approach offers the dual benefits of not requiring special instrumentation or techniques, and can be easily reproduced by other synthetic chemists looking to extend these studies in their own labs.

Validation 1: HAT to C-centered radicals

Our proposed validation experiments are described in **Figure 6**. They are predicated on the hypothesis that a *nucleophilic* H• donor would react faster with polarity-matched *electrophilic* radicals, k_1, versus mismatched nucleophilic radicals, k_2, (**Fig 6a**). Supersilane (TMS_3SiH) was selected as the nucleophilic H• donor, as the H-atom was quantitatively assigned as hydridic via NBO electron populations (partial charge of -0.1 vs Et_3SiH: -0.2; see SI). Moreover, we expected a weak Si-H bond of 83 kcal/mol (vs Et_3SiH: 92 kcal/mol) would overcome any thermodynamic effects.

Yet, we recognized a key challenge remained for generation of the radicals in a consistent and rapid manner. To this end, we predicted the radicals (R•) could be most readily accessed by purchasing or synthesizing their respective iodides (R-I) and photolyzing with UV light, 370 nm (**Fig 6b**). Although this approach addressed the issue of accessibility of radicals, it introduced the new challenge of accounting for radical propagation. Specifically, upon radical initiation (k_{init}) by R-I photolysis, capture of R• by R_3SiH via HAT (k_{HAT}) also generates R_3Si• that may abstract I• from R-I to form another R• in a propagation step (k_{prop}).

However, we reasoned the relative rates (k_1/k_2) of *electrophilic* (k_1) vs *nucleophilic* (k_2) radical trapping would still be meaningful, since the rate of HAT by R_3Si• (k_{HAT}; 10^5 $M^{-1}s^{-1}$) is slower – and thus more rate-determining – than propagation with R-I (k_{prop}; 10^9 $M^{-1}s^{-1}$).[12] Moreover, if propagation (k_{prop}) is also dictated by polarity (*nucleophilic* Si• preferentially abstracts more *electrophilic* R-I), then the effect might be compounded. Thus, this simple, *indirect* kinetic method would yield a meaningful validation of relative rates of radical reactivity (k_1/k_2).

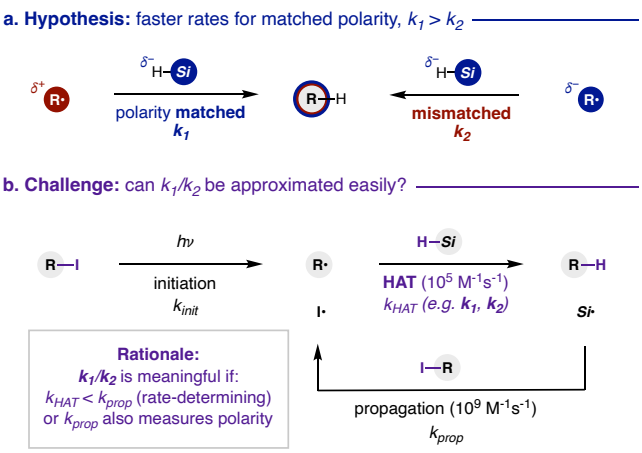


Figure 6. Proposed experimental validation.

To our delight, the results of these practical measurements of *relative* rates were highly correlated with radical electrophilicity (ω), as shown in **Figure 7**. In these experiments, all commercially available (or easily synthesized) carbon-centered radical (R•) precursors (alkyl and aryl iodides) were directly photolyzed with UV light (370 nm) in the presence of supersilane, TMS_3SiH. Upon quenching these reactions after 3, 6, or 10 minutes, the remaining silane concentration was quantified by gas chromatography versus a calibrated internal standard to measure reaction progress via reagent consumption (i.e., % conv). This approach yielded greatest precision among data (collected in triplicate or greater) – likely due to volatility of many products, R-H (e.g., see SI for comparison of ArI and *Si*H consumption *vs* ArH formation). Notably, a graph of silane reagent conversion (y-axis) versus electrophilicity (x-axis) for all carbon-centered radicals affords a strong correlation between these experimental (% conv) and calculated (ω) values. The data collected at 10 minutes was found to best capture the widest range of reactivity (see SI for other times and standard deviation analysis) and is shown in four ways within **Figure 7**.

First, the data is represented with chemical structures beside each point (**Fig 7a**). This graph best illustrates the higher reactivity of polarity-matched *electrophilic* radicals (k_1) versus mismatched *nucleophilic* radicals (k_2) with nucleophilic R_3SiH. Specifically, the top right quadrant entails mostly aryl radicals or highly deficient (α-CF_3, α-CN) alkyl radicals, which were computed to be the most **electrophilic** among C-centered radicals (ω > 1.5). They typically yield >75% conversion within 10 minutes. Conversely, the **nucleophilic** alkyl radicals (ω < 1) afford <40% conversion in the same period. In addition to depicting the **key trend** that alkyl radicals are more nucleophilic, while aryl radicals are more electrophilic, the structures also illustrate how substitution patterns affect this relationship (or not). In contrast, two major outliers (*t*-butyl, pyrazole) highlight factors not accounted for, such as *major* sterics (weaker C-I bonds) or *multiple* heteroatoms (repulsive electrons). Next, the data is represented with error bars for each data point, instead of chemical structures, illustrating the precision of the collected data (**Fig 7b**). On this plot of reactivity vs ω, we also included the trendline, whose fit shows a high correlation ($R^2 = 0.7$; $R = 0.83$).[103]

Given the clustering of aryl radicals at the top right quadrant, we included two additional graphs, which separately comprise either alkyl *or* aryl radicals alone. In the case of only alkyl radicals, the trendline correlation ($R^2 = 0.7$) remains strong (**Fig 7c**). While the aryl-only radical plot suggests these sp^2 radicals are too reactive for a strong trend ($R^2 = 0.1$) (**Fig 7d**). Data collected at shorter durations yielded similar observations (see SI). The full tables with complete population standard deviation calculations for each data point may be found in the SI, along with a colored gradient visualization for easily identifying outliers and 'best fit' structures.

An initial survey of reactivity with a radical trap of inverted polarity (butylated hydroxytoluene, BHT) was also conducted (see SI). However, given the significantly lower reactivity of this electrophilic H-donor entailing an O-H bond (< 20% conv in 1 hr, vs 10 min data shown in data **Fig 7**), no strong trends were observed. Alkenes were also explored, but these multi-component systems afforded intractable complexity.

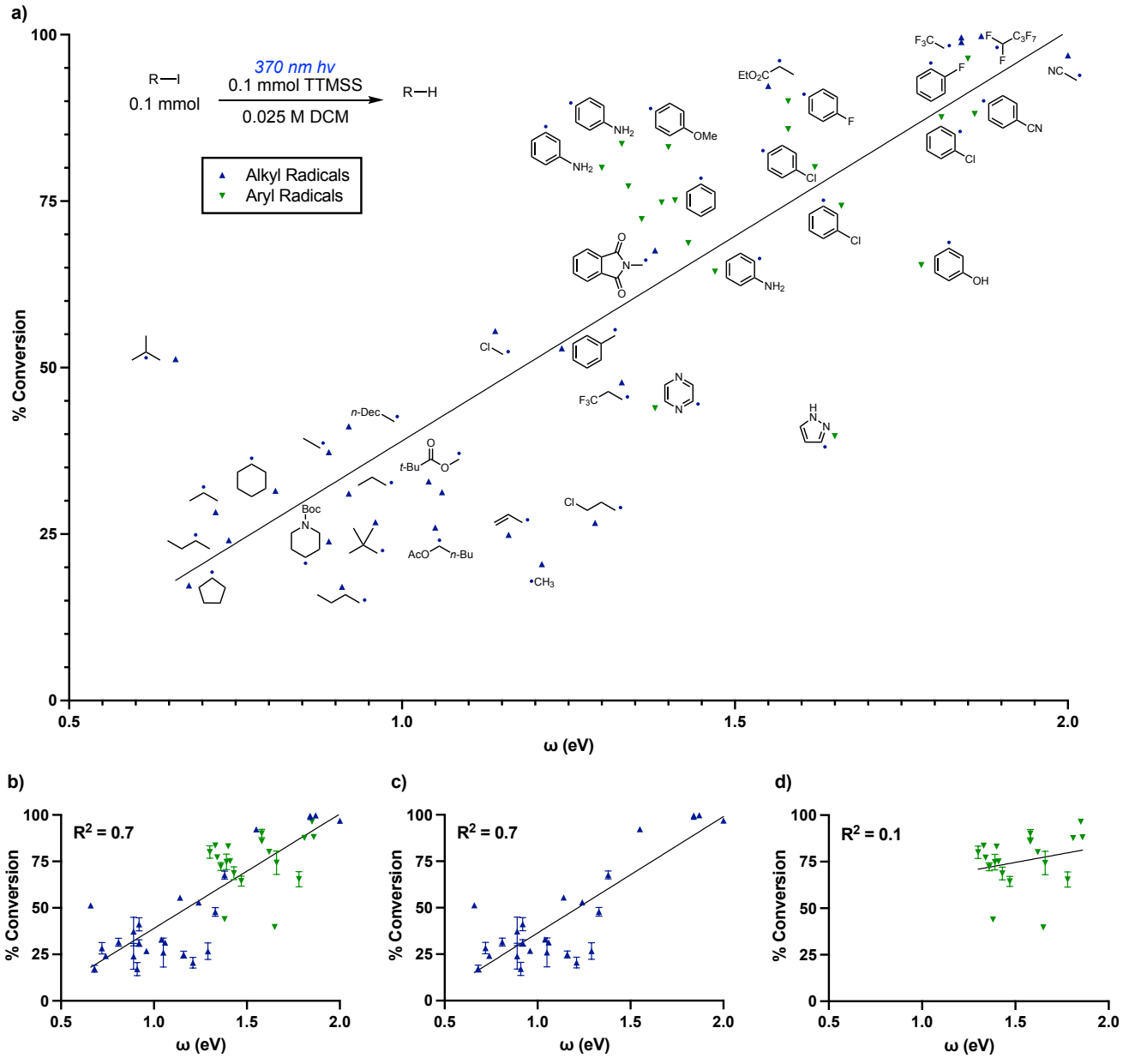


Figure 7. Experimental validation of radical electrophilicity, ω. Carbon-centered radical precursors (alkyl or aryl iodides) were directly photolyzed with supersilane, TMS_3SiH. Reaction conversion (y-axis) vs electrophilicity (x-axis) for all carbon-centered radicals – with (a) structures or (b) error bars. Data also graphed separately for (c) alkyl radicals and (d) aryl radicals. See SI for full tables.

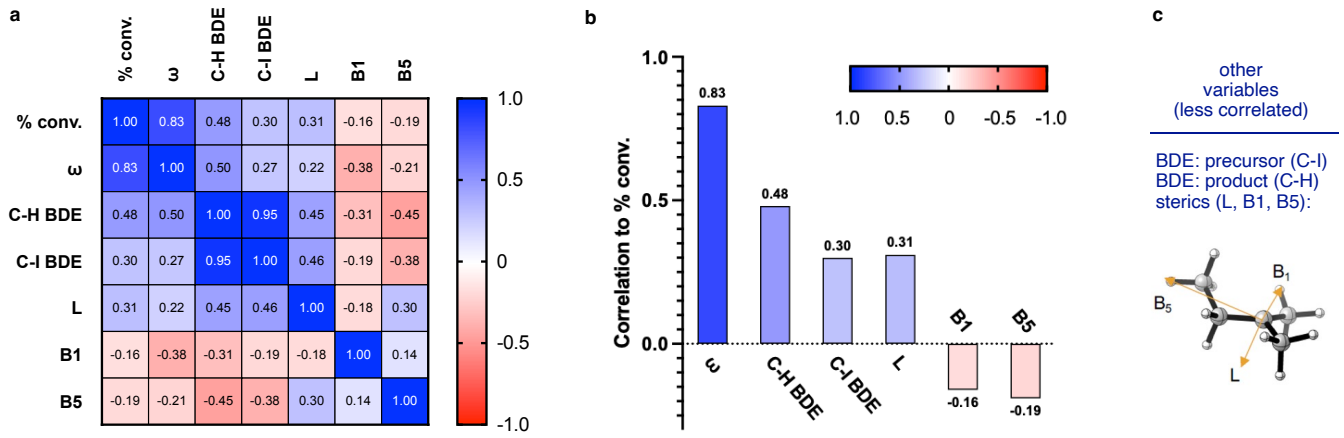


Figure 8. Correlation analysis – as a matrix (a) or bar graph (b) – confirms radical polarity is the most important factor influencing experimental reactivity (% conv). Variables include electrophilicity (ω, eV), bond dissociation energy (BDE) of either product (C-H) or reactant (C-I), and steric parameters (Sterimol), L (distance along axis of radical), B1 (shortest length from radical), B5 (longest length from radical).

To further test the meaningfulness and validity of this correlation between *calculated* radical electrophilicity (ω) and *experimental* kinetic data (% conv), we considered other factors that might also correlate with radical reactivity. For example, we examined thermodynamic parameters, including bond strengths (BDE) of the radical precursors (C-I) and products (C-H), as well as steric parameters (L, B1, B5) that might influence reactivity (see SI for full definitions). As shown in the Pearson-type correlation matrix of **Figure 8**, a statistical analysis of the relationship between each of these variables (where perfect correlation = 1) indicates ω is only correlated highly (dark blue: >0.8) with our experimental data (% conv). Alternatively, bond strength (C-H or C-I BDE) and steric parameters (Sterimol; L, B1, B5) afford only weak correlations (purple: ≤ 0.5, or inversely, light red: ≤ –0.5). The only other high correlation observed in this full matrix analysis is between C-H and C-I bond strengths (0.95), which are each related to radical stability. Yet, the absence of any other high correlation with our calculated electrophilicity or experimental data provides further support that this relationship is significant and meaningful. A two-dimensional bar graph representation is also included (**Fig 8b**) to illustrate the higher correlation of experimental reactivity with polarity over other factors.

For comparison, a correlation analysis of the terms that *comprise* electrophilicity (**Eq 1**; $\omega = \chi^2/2\eta$) yields a very different picture (**Figure 9**). As expected, this data table is instead populated by many more blue squares, indicating the components of ω are also better related to reactivity than other factors. The top row of **Fig 9** shows radical polarity (ω: 0.83) is most correlated with reactivity, followed closely by electron affinity (A: 0.82), which is a measure of electrophilicity. The next closest correlated components with experimental reactivity are electronegativity (χ: 0.77) and ionization energy (I: 0.64). Lastly, chemical hardness (η: 0.08) is the least predictive of reactivity.

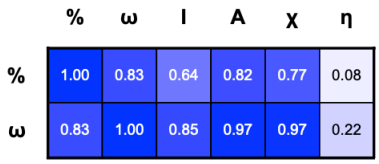


Figure 9. Correlation analysis of experimental reactivity (% conv) versus radical polarity (ω) – and its components – shows reactivity is most correlated with polarity. Less correlated parameters include electron affinity (A) electronegativity (χ), ionization energy (I), and chemical hardness (η).

In further analysis, the bottom row of **Fig 9** shows there is strong correlation between radical polarity (ω) and the terms that comprise it (e.g. I, A, χ, η) – especially between ω and A or χ (both 0.97; see SI for full two-dimensional analysis). Yet, no individual term is as correlated to experimental reactivity (exp) as polarity (ω; 0.83). We note that A may provide a reasonable substitute to ω, since the data for this simplified parameter may be more freely available in the literature for many radicals (precluding a need for computation).

Validation 2: HAT to N-centered radicals

Next, we supplemented this C-centered radical data with experiments to validate the *heteroatom*-centered radicals. As shown in **Figure 10**, N-chloro-butyl amines were synthesized with varying protecting groups (Boc, Ts, Tf). In this informer set, the calculated polarity (ω) again corresponds well to reactivity –across a wide range of electron-withdrawing character.

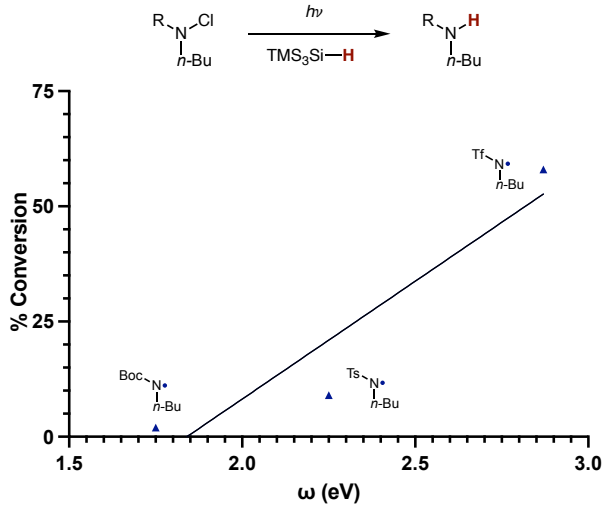


Figure 10. Experimental validation with Nitrogen-centered radicals.

Validation 3: HAT to O-centered radicals

Similarly, an electronically diverse set of O-centered radicals were synthesized. As shown in **Figure 11**, these phenoxy radicals, whose electronics were varied by para-substituents (*p*-OMe, *p*-tBu, *p*-CF_3), further demonstrated that radical reactivity correlates with polarity – even in these heteroatom-centered cases.

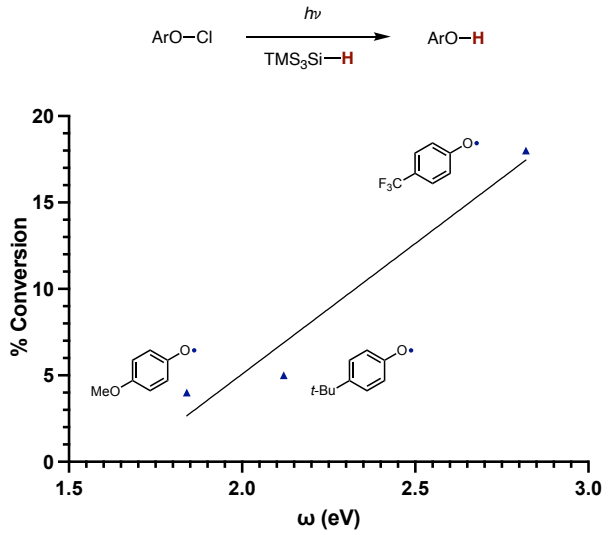


Figure 11. Experimental validation with Oxygen-centered radicals.

Hammett Correlations

As noted in the computational data discussion above, we also sought to relate this radical polarity database to other readily available data collections (including for closed-shell species). To this end, we constructed several Hammett plots, as shown in **Figure 12**.

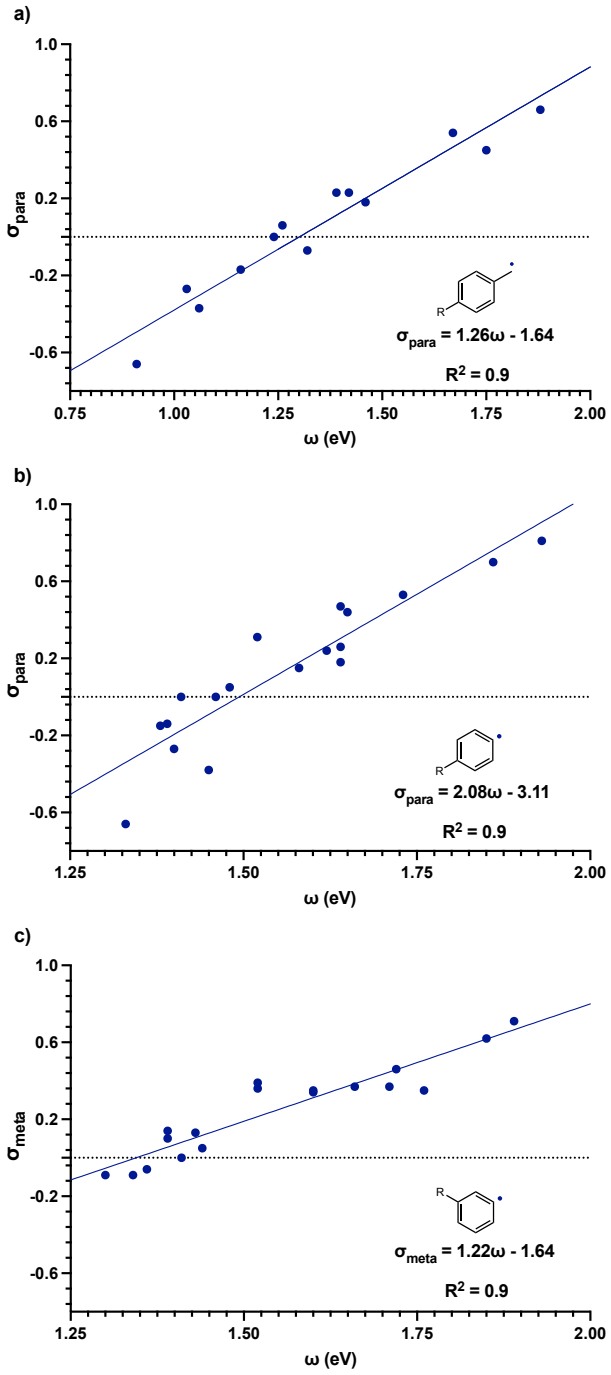


Figure 12. Hammett plot (σ vs ω) for (a) benzyl radicals (para, σ_p), or aryl radicals with (b) para, σ_p, or (c) meta, σ_m, substituents.

In these cases, when the substituent constants of para-substituted benzyl radicals (σ_p) are plotted versus electrophilicity (ω), a trendline is nicely fit – with a slope of 1.26 and strong correlation ($R^2 > 0.9$; **Fig 12a**). Similarly, when substituent constants for the aryl radicals are plotted against electrophilicity, both the para (σ_p; **Fig 12b**) and meta (σ_m; **Fig 12c**) parameters are again well correlated, ($R^2 > 0.9$ for both), albeit with varying slopes (m = 2.1 vs 1.2). This strong relationship between our computed *radical* polarity data and experimental data for *closed-shell* species affords further experimental validation of this extensive ω data set.

Competition Experiments

Competitions 1: HAT to C-centered radicals

Lastly, and perhaps most importantly, we wished to determine a practical interpretation of the units for radical polarity, ω (eV), so users could anticipate the synthetic outcomes that correspond with these values. To this end, we designed a series of competition experiments to measure the relative rates of reactivity for varying radicals (**Figure 13**). Three non-volatile radical precursors were chosen to allow for redundant quantification of mass balance by measuring each reaction component, including the pair of radical precursors remaining, as well as the radical trap consumed. Upon reacting a 1:1 mixture of each radical precursor (R-I) and irradiating in the presence of TMS_3SiH for 30 seconds, the ratio of products formed was evaluated across four trials for each competition.

To our delight, a significant difference in reactivity was observed in each pair of alkyl radicals examined, as shown in **Fig 13b**. For example, the α-phthalimidyl radical (black; 1.4 eV) was found to react eight times *slower* (with a nucleophilic silane trap) than the more electrophilic α-acyl radical (red; 1.6 eV). In this scenario, an ω difference of only +0.2 eV yields an 8-fold increase in reactivity – or more simply: Δω of 0.1 eV affords 4-fold faster reactivity. In another pair of experiments, α-phthalimidyl radical (black; 1.4 eV) was found to react 17 times *faster* than the more *nucleophilic* α-acyloxy radical (blue; 1.0 eV). In this case, a doubled ω difference of 0.4 eV results in a nearly doubled reactivity difference of 17 (vs 0.2 eV = 8). Here, the simplified ratio (0.1 eV ~ 4) is again a useful, predictive mnemonic. Finally, in the most extreme pair of partners, *electrophilic* α-acyl radical (red; 1.6 eV) reacts 44-fold faster than *nucleophilic* α-acyloxy radical (blue; 1.0 eV) – an even larger difference than would be expected using the predictive formula (0.1 eV ~ 4; or 0.6 eV ~ 24). Thus, our simplified rule of thumb that 0.1 eV affords 4-fold faster rates (k_1/k_2) is a useful *lower* bound for predicting improved reactivity upon switching synthetic intermediates for radicals with better matched polarity.

Although pairs of *aryl* radicals were also evaluated (see SI), their differences were too small (< 3-fold) to extrapolate meaningful trends. This is consistent with the data shown in **Fig 7d**, indicating that aryl radicals react too quickly with silanes for useful evaluation of kinetic data by this simplified, indirect method.

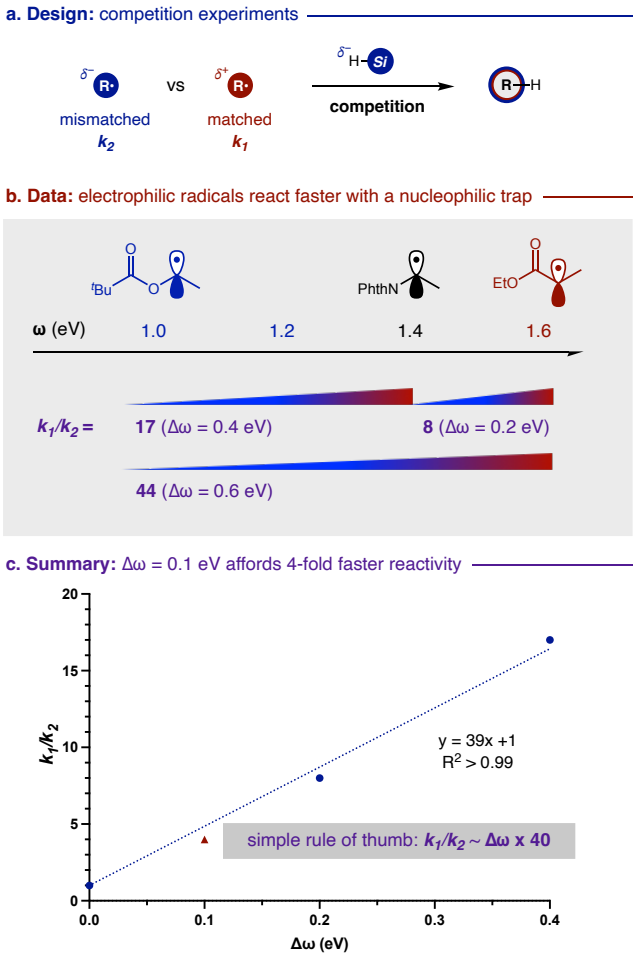


Figure 13. Competition Experiments 1: HAT to C-centered radicals. (a) Design. (b) Data. (c) Summary: results, trend, and predictive mnemonic.

Upon plotting the results of the first two alkyl radical competitions (as k_1/k_2 vs Δω), a trendline was cleanly fit with a slope of ~ 40 (**Fig 13c**). This slope is consistent with the simplified predictive formula noted above (Δω: 0.1 eV corresponds to a 4-fold rate increase). In fact, substitution of 0.1 eV into the full equation (y = 39x + 1) yields a 4.9-fold increase per 0.1 eV, while the simplified value (from Δω x 40; shown as a red triangle) is 4-fold. Moreover, if the third, most extreme pair of radicals ($k_1/k_2 = 44$) is included in the plot, the resultant trendline (y = 60x + 1) predicts a 7-fold increase per 0.1 eV (see SI). Yet, given the sizable difference in polarity of this radical pair (well beyond likely synthetic exchanges), we expect the simplified mnemonic (0.1 eV ~ 4-fold; or $k_1/k_2 = \Delta\omega$ x 40) to be more useful in comparing similar radical pairs. Thus, users of this database may simply locate any two radicals of interest in the previous tables and *predict* their reactivity difference by merely multiplying Δω by 40. We expect this would give a lower bound for the actual reactivity difference expected, and thus it would greatly enable the design and troubleshooting of synthetic applications of radical chemistry.

Competitions 2: HAT to N-centered radicals

To further establish the *predictive* power of this polarity database, we then probed additional experimental kinetic data across a *broad range of reactions*. To facilitate these studies, we assessed reported experimental data, emphasizing competition experiments with *heteroatom*-centered radicals. For example, Mosher measured relative rates (k_{rel}) of HAT by an N-centered, isocyanato radical for various para-substituted benzyl C-H bonds.[104] As shown in **Figure 14**, the difference in polarity (Δω) between substituted aryl radicals is predictive of the rate difference (k_{rel}) measured for HAT reactions from their respective benzylic C-H bonds.

In this graph, where the competitive rate of HAT is expressed as the higher rate of reactivity for the nucleophile over the electrophile (k_{nuc}/k_{el}), an upward trend is apparent where more electrophilic radicals are much less reactive than unsubstituted ones (with an electrophilic N-radical). For example, the most electrophilic radical (p-NO_2: 2.2 eV) is least reactive (k_{rel} > 4 vs parent benzyl radical). In contrast, the nucleophilic tolyl radicals (1.2 eV) more rapidly engage in HAT with the electrophilic N-radical (k_{rel} > 2 favoring the substituted benzyl radical instead). This qualitative prediction is borne out across all six competitive benzyl radical pairs (vs unsubstituted). An analysis of this plot of relative rates (k_{nuc}/k_{el}) versus polarity gap (Δω) indicates a high correlation (R^2=0.6). Notably, this HAT of C-H bonds by N-radicals (Δω: 0.1 eV corresponds to a 2-fold rate increase) shows a more modest influence of polarity (slope of only ~2.5) compared to the HAT of Si-H bonds by C-radicals (slope of 40; see **Fig 13c**). Nonetheless, both quantitatively and qualitatively, there is a strong influence of polarity in this HAT reaction too – with the electrophilic isocyanato radical more rapidly abstracting the hydridic, or more nucleophilic, H-atom.

Competitions 3: HAT to O-centered radicals

Next, we probed the competitive HAT reactions of O-centered radicals (to benchmark against the C- and N- centered ones above). In this study (**Figure 15**), we compiled the experimental data of five different classes of competition experiments (see SI for full details) to assess the electrophilicity of O-centered radical reactivity. The data for this meta-analysis includes *inter-* and *intra- molecular* HAT competitions for five C-H bond pairs: aliphatic vs α-oxy C-H bonds (dioxane vs cyclohexane), α-oxy vs α-trioxy (ortho-ester), α vs β to a nitrogen (amide), N-H vs α-amino (amine), and different functional groups (ketones vs ethers).[105] By selecting examples with minimal steric difference, we could probe the electronic influence of the electrophilic *t*-butoxy radical. In other words, these C-H pairs were specifically evaluated to minimize other effects (e.g. BDE, sterics) and better probe the isolated role of polarity. As expected, the more nucleophilic H-atoms are more rapidly abstracted in all cases. Interestingly, when plotting relative rates (k_a/k_b) versus the polarity gap (Δω), a steeper slope is observed (m >20) showing a stronger influence on these less related HAT pairs. And most importantly, trendline analysis indicates an even higher correlation (R^2=0.8) for these O-centered radical experiments.

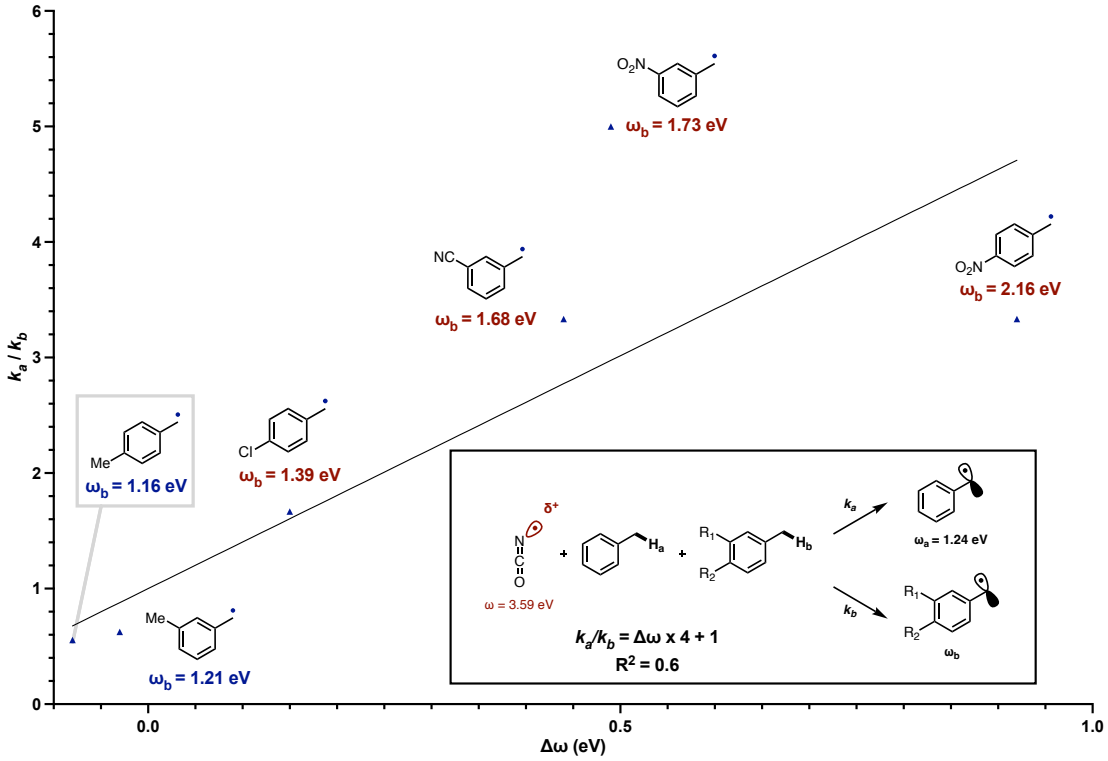


Figure 14. Competition Experiments 2: HAT to N-centered radicals. The difference in polarity (Δω) is predictive of the rate difference (k_{rel}) in HAT of various para-substituted benzyl C-H bonds by an isocyanato radical.

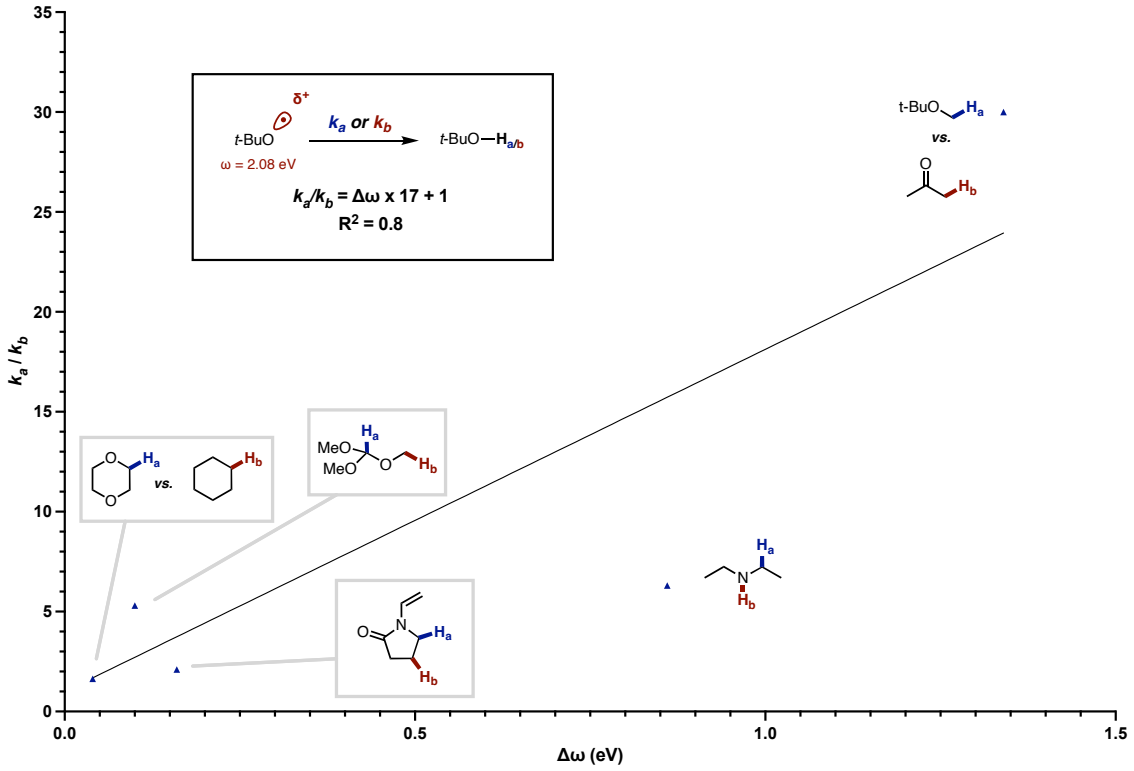


Figure 15. Competition Experiments 3: HAT to O-centered radicals. The difference in polarity (Δω) is predictive of the rate difference (k_{rel}) in HAT of various classes of C-H bonds by a tert-butoxy radical.

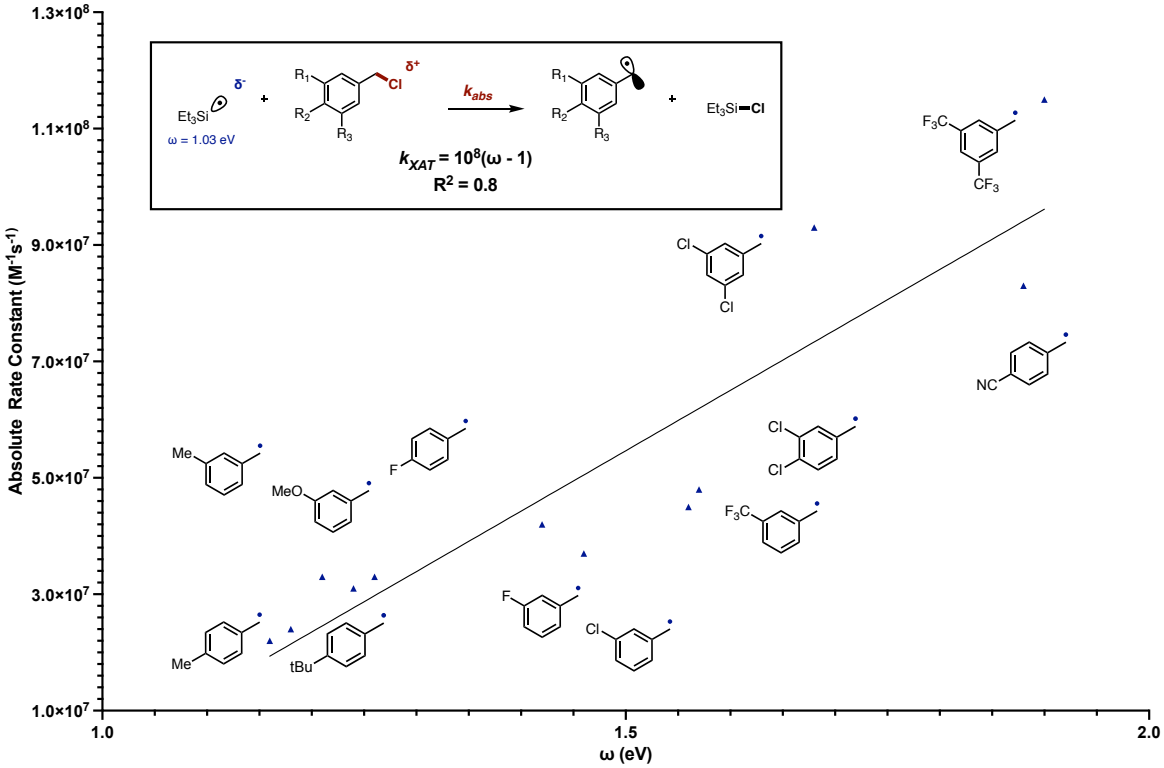


Figure 16. Competition Experiments 4: Halogen atom transfer (XAT) of benzyl chlorides by Si-centered radicals. The rate (k) of chloride-abstraction by nucleophilic silyl radicals with benzyl chlorides of varying electronics correlates strongly to the polarity (ω) of the ensuing radical.

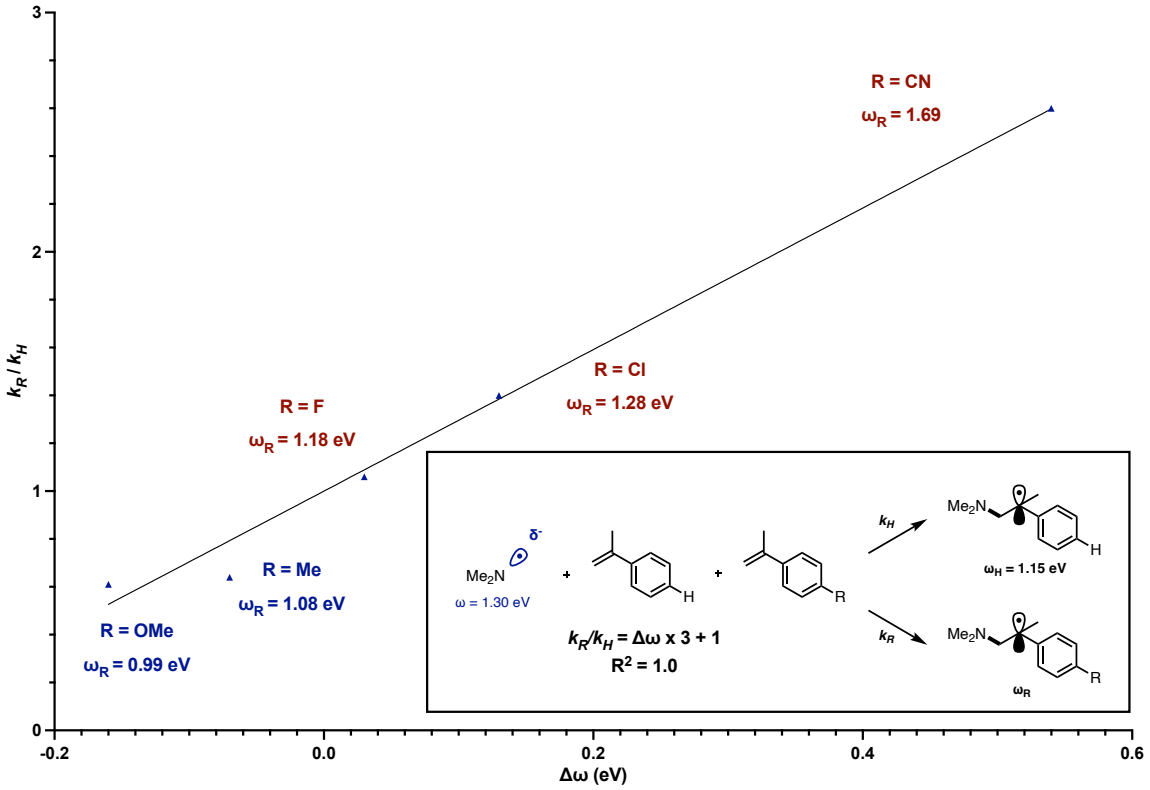


Figure 17. Competition Experiments 5: π-additions of N-centered radicals. The difference in polarity (Δω) is predictive of the rate difference (k_R/k_H) in π-additions of nucleophilic, amino radicals to styrenes of varying electronics.

Like our own competition experiments, the observed trend across these five competitive probes is notable because they elucidate reactivity preferences *across different substrates classes*.

Competitions 4: XAT to Si-centered radicals

To complement these experimental validation data for HAT of C-, N-, and O-centered radicals, we also sought to investigate the impact of radical polarity on halogen-atom transfer (XAT) reactions. To this end, we turned to the absolute rate constants for chlorine abstraction by a triethylsilyl ($Et_3Si\bullet$) radical that were measured by Chatgilialoglu, Ingold, and Scaiano.[106] This polarity model predicts a nucleophilic silyl radical will abstract electrophilic chlorine atoms more rapidly. Thus, the polarity (ω) of the resulting benzyl radicals was calculated (as a measure of substrate electrophilicity) and plotted against the experimentally measured absolute rates (**Figure 16**). Once again, a strong correlation (R^2=0.8) was found between the rate constants and ω – providing another experimental validation of this database.

Competitions 5: π-additions

Lastly, we sought to assess this impact of radical polarity on *an entirely different reaction class*. Thus, we probed competition experiments entailing radical π-additions. For this analysis, we employed the study by Michejda and Campbell on the relative rates of addition of dimethylaminyl radical to styrenes with varying para substituents.[107] To our delight, these competitive π-additions of N-centered radicals again showed a clear relationship between polarity (Δω) and relative rate (k_{rel}) (**Figure 17**). In this reversed case, the nucleophilic amine is predicted to react with more electrophilic alkenes at a faster rate. Indeed, in all five competition experiments (substituted vs unsubstituted styrenes), addition to the electron-deficient alkene – and ensuring formation of the more electrophilic radical – is favored. Again, trendline analysis indicates a very high correlation (R^2>0.99) between the polarity gap (Δω) and relative rates of reactivity of the aryl vs phenyl substituted styrenes (k_R/k_H) for this distinct reaction class (π-addition vs atom transfer).

Broader Interpretation, Application, and Caveat

It is important to note that radical polarity is one of many factors that may impact reactivity. For instance, radical reactions, such as H-atom transfers, are also influenced by solvent effects, sterics, secondary orbital interactions, triplet repulsion, H-bonding, and of course, thermodynamics (e.g. C-H bond strengths). The value of this study is to illustrate the utility of radical polarity (ω) as a tool to complement those others and potentially simplify reactivity prediction in this complex environment.

Conclusions

In summary, we have developed a radical polarity database by computationally determining the global electrophilicity (ω) of over 500 radicals that are frequently encountered in organic synthesis. Importantly, this *computational* dataset has also been

experimentally validated for a sterically and electronically diverse set of radicals. Statistical analyses of this correlation demonstrate this *kinetic* parameter of radical polarity is a better predictor of reactivity than typical *thermodynamic* values (e.g., BDE). Importantly, based on several, complementary, competition experiments, we have also introduced a simple mnemonic to predict the reactivity difference between radicals with varying polarity (k_1/k_2 = up to 40 x $\Delta\omega$). Ultimately, we expect this extensive, *quantitative* database of carbon- and heteroatom- centered radicals, as well as the validated interpretation of these values, will serve as a resource to many chemists interested in harnessing radical intermediates in organic synthesis.

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge on the ACS Publications website at DOI:

Printable poster summary of radical polarities (PDF)
Experimental procedures and computational details (PDF)
Coordinates for each radical, as txt files (ZIP)
Computed energies and electrophilicity values (XLS)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank the National Institutes of Health (R35 GM119812) and National Science Foundation (2400304) for financial support. Computational resources provided by the Ohio Supercomputer Center.

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