N-Ammonium Ylide Mediators for Electrochemical C–H Oxidation

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ABSTRACT: The site-specific oxidation of strong C(sp^3)-H bonds is of uncontested utility in organic synthesis. From simplifying access to metabolites and late-stage diversification of lead compounds to truncating retrosynthetic plans, there is a growing need for new reagents and methods for achieving such a transformation in both academic and industrial circles. One main drawback of current chemical reagents is the lack of diversity with regards to structure and reactivity that prevent a combinatorial approach for rapid screening to be employed. In that regard, directed evolution still holds the greatest promise for achieving complex C–H oxidations in a variety of complex settings. Herein we present a rationally designed platform that provides a step towards this challenge using *N*-ammonium ylides as electrochemically driven oxidants for site-specific, chemoselective C(sp^3)–H oxidation. By taking a first-principles approach guided by computation, these new mediators were identified and rapidly expanded into a library using ubiquitous building blocks and trivial synthesis techniques. The ylide-based approach to C–H oxidation exhibits tunable selectivity that is often exclusive to this class of oxidants and can be applied to real world problems in the agricultural and pharmaceutical sectors.

Introduction

The area of C–H oxidation has experienced a dramatic increase in attention from the organic chemistry community stemming from a strategic simplification of retrosynthesis,[1] a desire for late-stage functionalization in discovery settings,[2] and as a means to access valuable metabolites.[3] Methods to achieve such functionalizations, specifically C(sp^3)–H to C–O, have a rich history in organic synthesis.[4] In an industrial setting, biochemical approaches are the most oft-applied methods of achieving such transformations in a chemo- and position-selective manner using a toolkit of CYP-enzymes or whole cell approaches (Figure 1A).[5] These methods are popular due to their mild nature, catalyst-controlled selectivity (rather than substrate control), and their ability to tune and modulate selectivity through directed evolution.[6,7] In an effort to emulate these features, a myriad of reactive species have been described for the direct conversion of C(sp^3)–H to C–O bonds. Among the tactics explored, direct hydrogen abstraction by reactive radicals[4,8,9] (including metal-oxo[10] and dioxirane[11] that are known to generate reactive radicals transiently) has been established as an effective approach for this purpose (Figure 1A). The mainstream approach for metabolite synthesis/late-stage oxidation involves a combination of trial-and-error together with a careful evaluation of critical chemical features such as sterics and electronics to control innate selectivity. This is illustrated in Figure 1B with three different commercially used pharmaceuticals (**1**[12,13], **3**[14] and **4**[15]) and one agrochemical (**2**)[16]. With the native metabolic sites highlighted in red,[17-20] one observes similar selectivities using metal-oxo species that can be tuned to some extent using engineered enzymes such as **5** for the oxidation of buspirone (**1**). Although the screening of chemical reagents such as **5**-**8** on these commercial products (**1**-**4**) can also furnish natural metabolites, this trial-and-error approach is limited. To be sure, each reagent or catalyst requires a separate laborious synthesis that makes rapid tunability challenging. In contrast, the extraordinary utility of directed evolution approaches is a consequence of the sheer number of enzymatic catalysts that can be empirically screened (hundreds to millions). Our attempts to improve electrochemical C–H oxidation using quinuclidine **11** as the hydrogen atom transfer (HAT) based mediator (Figure 1C) was emblematic of this problem.[21] Thus, several analogs of quinuclidine (**12**-**17**) were either prepared (4–6 steps)[22] or purchased, yet no improvement in efficiency or selectivity was observed in the oxidation of sclareolide **9**. Each designed quinuclidine analog generally required a de novo total synthesis requiring weeks or months of effort. To even begin to compete with any

biochemical approach, a combinatorial array of simple, tunable, and easily accessed mediators/reagents/catalysts is needed so that synthesis is no longer a bottleneck. Herein we present such an approach using a new class of mediators that have rarely been employed in organic synthesis: *N*-alkyl ammonium ylides. These mediators, designed based on first principles and triaged through *in-silico* screening, form the basis of a simple chemical approach to C–H oxidation as they are easily prepared, stable, modular, and exhibit unique selectivity.

Results and Discussion

This study was launched with a structure-agnostic approach guided by a postulated mechanism. As such, instead of starting with a plausible mediator structure, the desired catalytic cycle was modeled, and thermodynamic descriptors were evaluated computationally. To perform such an *in-silico* screen logically, deprotonation of protonated species **MH** to regenerate the precursor to this radical $\mathbf{M}^{-}$, and 3) oxidative regeneration of $\mathbf{M}^{\bullet}$. Accordingly, three thermodynamic parameters were chosen to estimate the efficacy of each elementary step: hydrogen binding free energy ($\Delta G_{H\text{-}bind}$), deprotonation free energy (DPFE) and oxidation potential (E_{ox}). The ideal reactive radical needs to have a large negative $\Delta G_{H\text{-}bind}$ (kJ/mol) to readily facilitate hydrogen abstraction, low DPFE (kJ/mol) for mild deprotonation, and low E_{ox} (V/SHE) for facile oxidation. We initially evaluated the oxidation potentials (E_{ox}) and hydrogen binding energies ($\Delta G_{H\text{-}bind}$) for numerous potential mediator structural classes (**11**, **12**, **18-24**) using first principle density functional theory (DFT) calculations along with chemical intuition and literature precedent[23-27] (see SI for details regarding the calculation methodology). This allows for a targeted search of effective mediator candidates. Boundaries for furthering the search ($\Delta G_{H\text{-}bind} \leq -$

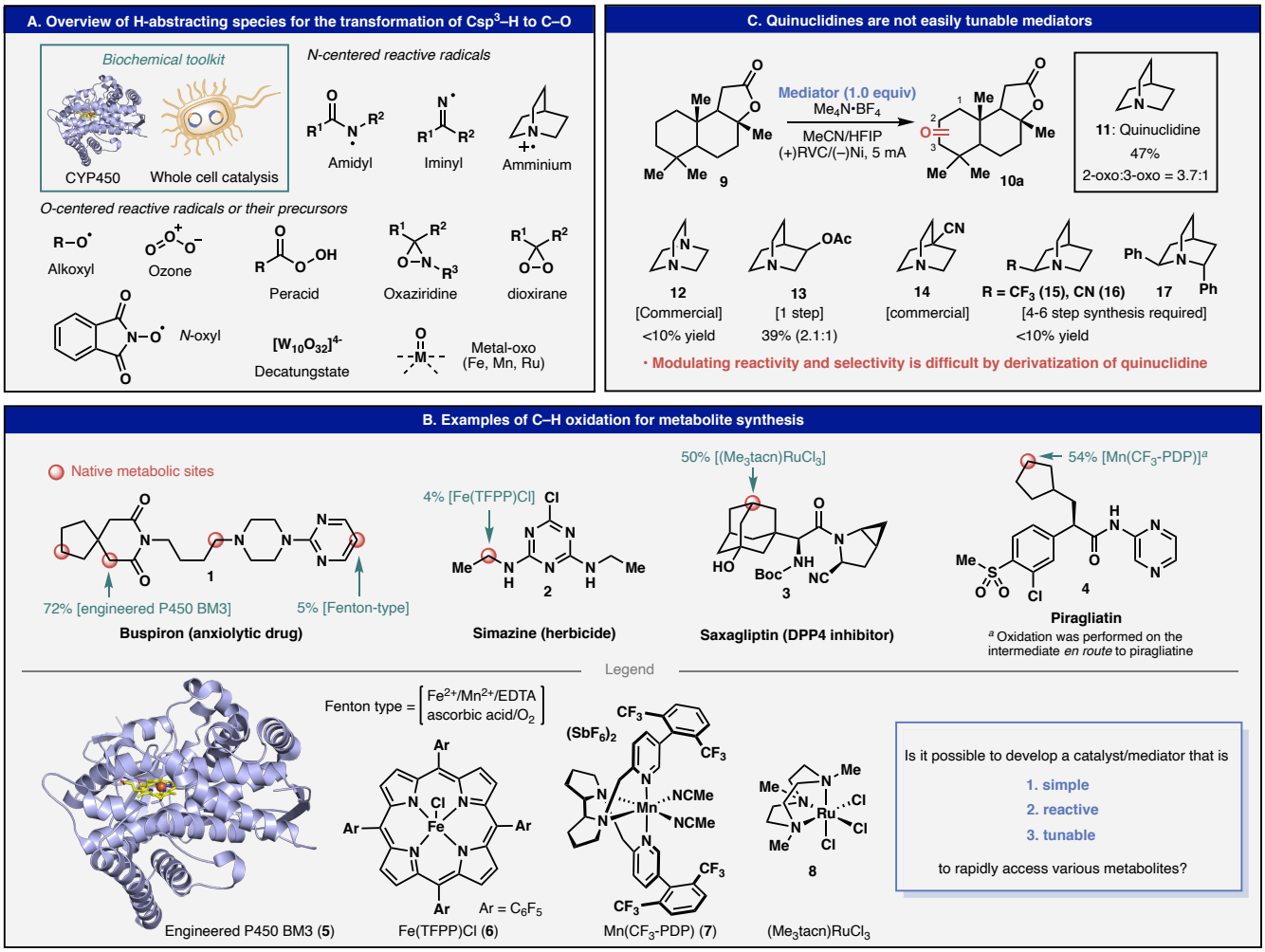

Figure 1. Overview of known reactive species for strong C(sp^3)–H bond oxidation, current state of the art in metabolite synthesis, and challenges for further innovation. (A). Summary of representative reactive species or precursors that were previously used for C(sp^3)–H oxidation. (B). Sophisticated reactive species are used in recent examples for metabolite synthesis, illustrating the potential of simple and tunable mediators to enable access to various metabolites. (C). Our attempt to develop tunable quinuclidine-based mediators were concluded difficult due to synthetic inefficiency for analog preparation and unsatisfactory change in reactivity/selectivity.

parameters were chosen to evaluate reactive radicals based on the cycle depicted in Figure 2A. This general catalytic cycle was modeled from the mechanism of quinuclidine-mediated C–H oxidation[21] and consists of three elementary steps: 1) hydrogen abstraction by the reactive mediator-centered radical $\mathbf{M}^{\bullet}$, 2) 180 kJ/mol, $E_{ox} \leq 1.7$ V vs. SHE) were set based on the $\Delta G_{H\text{-}bind}$ for the quinuclidinium radical $\mathbf{11}^{\bullet}$ ($\Delta G_{H\text{-}bind}$ = –183 kJ/mol) which has shown demonstrated reactivity for the desired transformation (Figure 2A), as well as readily achievable oxidation potential within common solvent electrochemical window (E_{ox}

≤ 1.7 V). Within these boundaries (highlighted in blue), three promising mediator candidates (**11**•, **22**•, **23**•) were identified, effectively ruling out the unpromising ones. For example, the quinuclidine analog **12** (Figure 1C), which is not effective in C–H oxidation, lies far outside the promising area. Among the promising candidates, the imidazolium mediator **23** was considered less attractive due to its high DPFE values (673 kJ/mol, experimental pK_a = 23[28]), making regeneration of such species difficult under mild conditions. Quinuclidine scaffolds based on **11** were excluded due to low tunability demonstrated previously (Figure 1C). The result of this analysis thus led to the identification of the *N*-ammonium amminium radical **22**• as a possible candidate for experimental study: low DPFE (600 kJ/mol), highly negative hydrogen binding energy ($\Delta G_{H\text{-}bind}$ = –229 kJ/mol), moderate oxidation potentials (E_{ox} = 1.7 V vs. SHE) and excellent tunability as discussed below. To our knowledge,

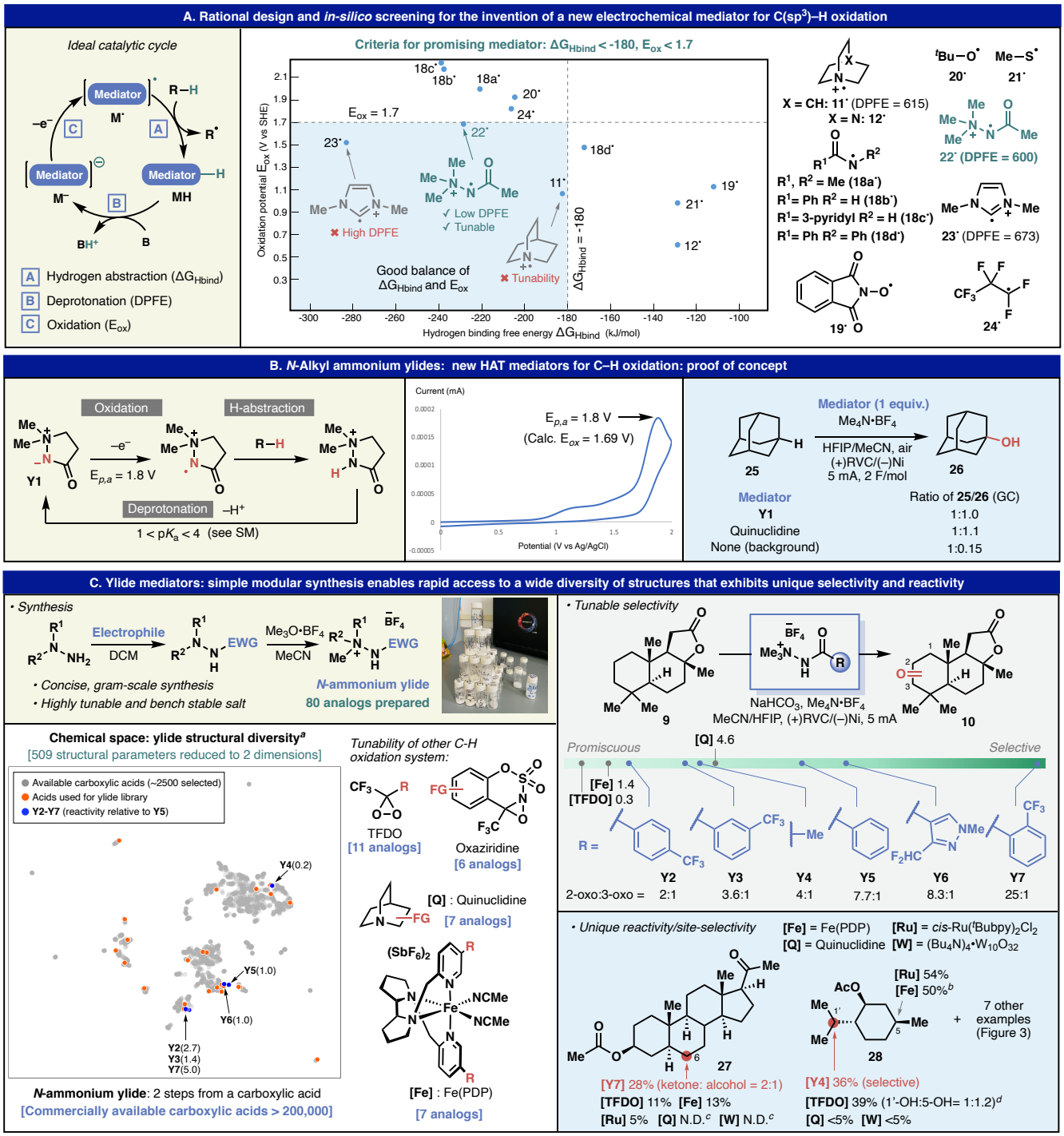

Figure 2. Design, proof of concept and library construction of new electrochemical mediator N-ammonium ylides (A). Design of ideal catalytic cycle and evaluation of thermodynamic parameters (E_{ox}, $\Delta G_{H\text{-}bind}$, DPFE) of reactive species in order to perform in-silico screening logically and efficiently. (B). The preliminary results to confirm predicted parameters, which were proven to be in good agreement with experimental results. (C). Synthesis of N-ammonium ylides, their unparalleled diversity and unique tunability to rapidly modulate their reactivity/selectivity. [a] Possible chemical space constructed by 2419 acids shown in grey, screened mediators are highlighted orange, and **Y2**-**Y7** are highlighted blue. [b] Reference 34. [c] Product distribution was too complex to analyze. [d] Reference 42.

N-ammonium ylides (the precursor to such radicals) have not been studied in the realm of C–H functionalization, with the closest example being a triazolium betaine for activated C–H bond functionalization.[29]

The simple cyclic *N*-ammonium ylide **Y1** was synthesized to confirm these calculated results (Figure 2B). Indeed, the measured oxidation potential matched with the calculated value, and the predicted basicity (less basic than quinuclidine) was experimentally confirmed (see SI for basicity study). Most excitingly, it was experimentally proven that an *N*-ammonium ylide can be effective for unactivated C–H bond oxidation. This finding led to an extensive investigation of *N*-ammonium ylides as a new class of tunable and easily accessed mediators for electrochemical C–H bond oxidation. The simple, modular gram-scale synthesis of *N*-ammonium ylide salts enabled rapid construction of a library, carrying various electron-withdrawing groups (EWG) and alkyl groups (R^1, R^2) (Figure 2C). Most of the ylide salts are stable and handled without any precaution to atmospheric oxygen and moisture. The free ylides can be conveniently generated in situ with a mild base ($NaHCO_3$) or separately isolated and employed in the reaction. The tunability of *N*-ammonium ylides is unparalleled to other classes of reactive species; even if the EWG is limited to carboxylic acids, more than 200,000 carboxylic acids are commercially available, demonstrating a huge window of structural variation. With a small library of ylides in hand (80 members), a reactivity screening was performed across the entire library (see SI for details), leading to the identification of ylides **Y2**-**Y7** as better mediators than **Y1** based on reactivity, ease of preparation and structural diversity. In particular, to highlight the remarkable structural diversity, visualization of the chemical space for readily available carboxylic acids, building unit for ylide mediators, was attempted.[30] In order to provide a reasonably sized dataset for the analysis of carboxylic acid chemical space (see SI for details), the list of acids from a Reaxys® substructure search (>2.78 million) was filtered based on commercial availability, functionality and available data, resulting in 2419 acids for which two- and three-dimensional Mordred descriptors were calculated.[31] Uniform Manifold Approximation and Projection (UMAP), a non-linear dimensionality reduction technique that preserves global structure, was applied to the data to enable visualization of the chemical space (Figure 2C, UMAP).[32,33] Qualitative analysis indicated that the preliminary screening campaign covered a large region of chemical space, but the possibilities for further exploration are vast. In contrast, other species known to be useful for direct C–H oxidation such as dioxirane, oxaziridine, quinuclidine, and iron-oxo complexes have much fewer derivatives reported in the literature to date despite many decades of precedent (see SI for detailed references used for counting derivatives). The tunable selectivity of these mediators was vividly demonstrated in the oxidation of sclareolide **9**, in which the ratio of 2-oxo and 3-oxo products varied from 2:1 to 25:1 simply by changing substituents on the ylides. Moreover, these ylides provided improved reactivity and differing site-selectivity in C–H oxidation relative to other methods. For example, isopregnanolone acetate (**27**) and menthol acetate (**28**) gave poor conversion when quinuclidine was used as a mediator, whereas ylides **Y4** and **Y7** afforded the oxidation products in synthetically useful yields in these cases. Notably, site-selectivity and reactivity for these substrates were either superior (in the case of **27**) or orthogonal (in the case of **28**) to known oxidation systems (Fe-[34], Ru-[35], and W-based[36], TFDO[37,38], and quinuclidine[21]) demonstrating that *N*-alkyl ammonium ylides are a distinct class of reactive species with high tunability. To aid the practitioner and understand the contextual selectivity of ylides, all substrates in this study were subjected to this comparative panel of oxidants.

Figure 3 illustrates the scope of ylide-mediated electrochemical C–H oxidation with a broad range of substrates and unveils their unusual and often singularly selective nature. **Y7** was found to be the most effective across various substrates; in some cases **Y4** and **Y6** were found superior to **Y7**, demonstrating rapid reaction optimization through this combinatorial approach. Two general protocols employing either hexafluoroisopropanol (HFIP)/CH_3CN or water/CH_3CN solvent mixtures. The latter solvent combination often resulted in a cleaner reaction, albeit with slower product formation. Although the oxidation of unactivated C–H bonds are routinely carried out in the presence of a large excess of substrates in the literature, all screening was performed with the substrate as limiting agent, to accurately represent real-world applications. Ylide-based C–H oxidations generally fell into two categories: unique selectivity and enhanced reactivity not readily achievable with other known chemical oxidants (Class I) and selectivity in line with that observed previously (Class II). In general, substrates falling into Class I are more complex and likely better representations of the types of molecules encountered in medicinal and natural product chemistry. The ability of ylide-mediators to oxidize unactivated methylene positions in these settings where all other commonly employed chemical reagents fail is notable (e.g., **27**, **29**-**32**). This selectivity stems from a strong affinity of the *N*-ammonium amidyl radical to hydrogen along with steric guidance of such radical, as corroborated by DFT calculations which model the transition state of the oxidation of **29** (see SI for details). The same calculations can rationalize why quinuclidine has unique methine selectivity on the same molecule. In fact, one of the only methine-oxidations observed in this work was on the isopropyl group of menthol acetate (**28**). In this case, the methylene positions are less sterically accessible by the bulky ylide mediator resulting in the tertiary alcohol product derived from C1 oxidation. This result is especially unusual given that, of the productive oxidants screened, all favored C5-oxidation. Another unique attribute of the ylide platform is its tendency to afford significant quantities of secondary alcohol rather than ketone products (**27**, **32**, **33**).[39]This stands in stark contrast to quinuclidine-mediated electrochemical oxidation, where only ketone products were observed. Although a precise reason for this observation remains elusive, the literature supports a Russell-type mechanism for disproportionation of the intermediate hydroperoxy radical leading to carbonyl and alcohol products.[24] Oxidation of an amide to an imide could also be achieved in good yield relative to other chemical oxidants screened (**34).** Dealkylation, a process that is often observed in drug metabolism, was observed when imide formation was structurally impossible (**35**).

Class II substrates are simpler systems that are often found within the scope tables of other methodologies and provide a good baseline comparison to existing protocols. In general, ylides delivered similar site-selectivity to other systems involving homolytic hydrogen abstraction. Namely, distal C–H bonds that are more than two carbon atoms away from an electron-withdrawing group are susceptible to oxidation, and C–H bonds in cyclic structures are more reactive than acyclic ones.[40] Estrone derivative **44** did display some unique reactivity using **Y7** as it cleanly furnished benzylic ketone (C6), whereas other oxidants gave mixtures of overoxidized products (C6 and C9) or the unusual olefin product (likely stemming from dehydration of C9–OH). As mentioned above, a subtle difference between ylides and other oxidants was noticeable when a substrate contains tertiary C–H bond (**37** and **38**). Although low conversion or yield was indeed observed in some cases, this appears to be the trend for all oxidants screened and is a general challenge in this field.

Figure 4 depicts specific applications of the ylide-platform for the preparation of valuable metabolites and derivatives thereof. For instance, Penconazole **45** (Figure 4A) is a widely used fungicide with a primary metabolite profile in humans stemming from enzymatic oxidation on the propyl chain.[41] When this compound was subjected to ylide-mediated electrochemical C–H oxidation (**Y4**), the propyl group was successfully oxidized to afford the ketone products **46** in 26% yield in a 2:1 ratio (the

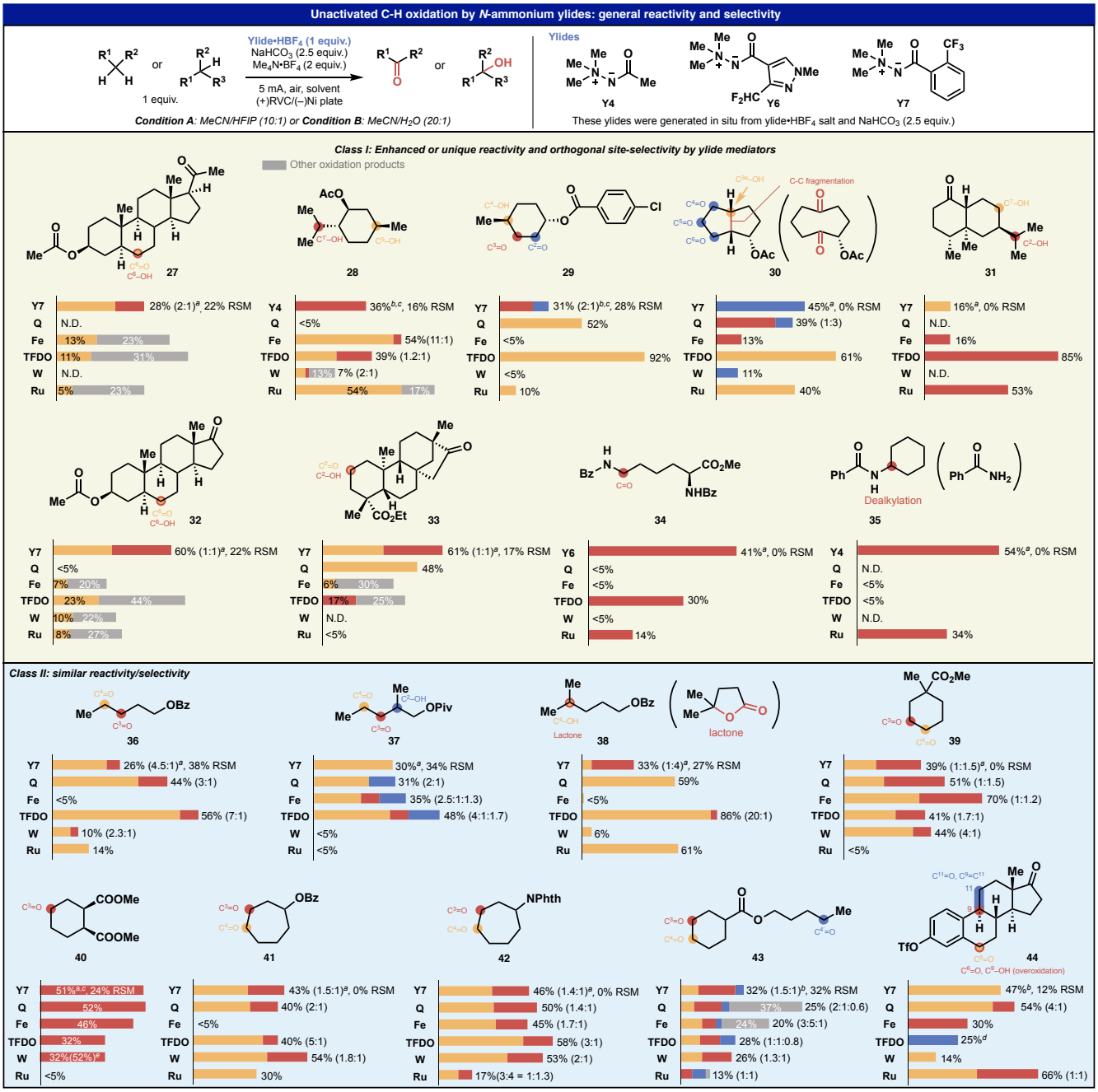

Figure 3. Ylide-mediated electrochemical C(sp^3)–H oxidation. See SI for the detailed conditions for each reaction. N.D. indicates that product distribution was too complex to analyze. RSM: recovered starting material (%). [a] Condition A was used. [b] Condition B was used. [c] Recovered starting material was recycled once. [d] See SI for detailed product distribution. [e] Yield with flow system (Reference 36).

alcohol corresponding to **46a** being the natural metabolite). Notably, other known oxidation conditions gave either poor conversion or different oxidation products, again demonstrating the unique chemoselectivity of the ylide protocol in the presence of the Lewis-basic triazole. In contrast, non-enzymatic routes to such derivatives required a de novo total synthesis (6 steps each from 2,4-dichlorophenylacetic acid). Another interesting application is the short synthesis of compound **50**, which is a common intermediate for metabolites of buspirone and tiospirone (Figure 4B).[42] In this case the remote oxidation of **52** to **53** was performed using **Y7** without affecting the alkyl bromide and imide functionality (The starting material was recycled three times). The success of this key oxidation allowed us to access **53** in two steps from readily available material as opposed to a known 8-step synthesis from expensive, pre-oxidized **54.**[42]

The reaction was also robust enough for preparative scale as demonstrated with the 10-gram scale oxidation of **41** in batch, delivering 40% yield of ketone **55** (Figure 4C). For this larger scale run, a less expensive stainless steel cathode could be used in place of the Ni-plate.

Mechanistically, it is hypothesized that ylide mediators achieve C–H oxidation through the canonical electrochemical pathway outlined in Figure 2A (analogous to quinuclidine). The intramolecular experiment outlined in Figure 4D using ylide **56** demonstrates a clear directing effect that is unique to this system as most oxidants employed for sp^3 C–H oxidation will engage an olefin preferentially (see **58**). Further evidence for this mechanism (see SI for an extensive discussion) stems from the use of both labeled $^{18}O_2$ and $H_2{}^{18}O$ showing conclusively that the source of oxygen comes from air (Figure 4E).[24]

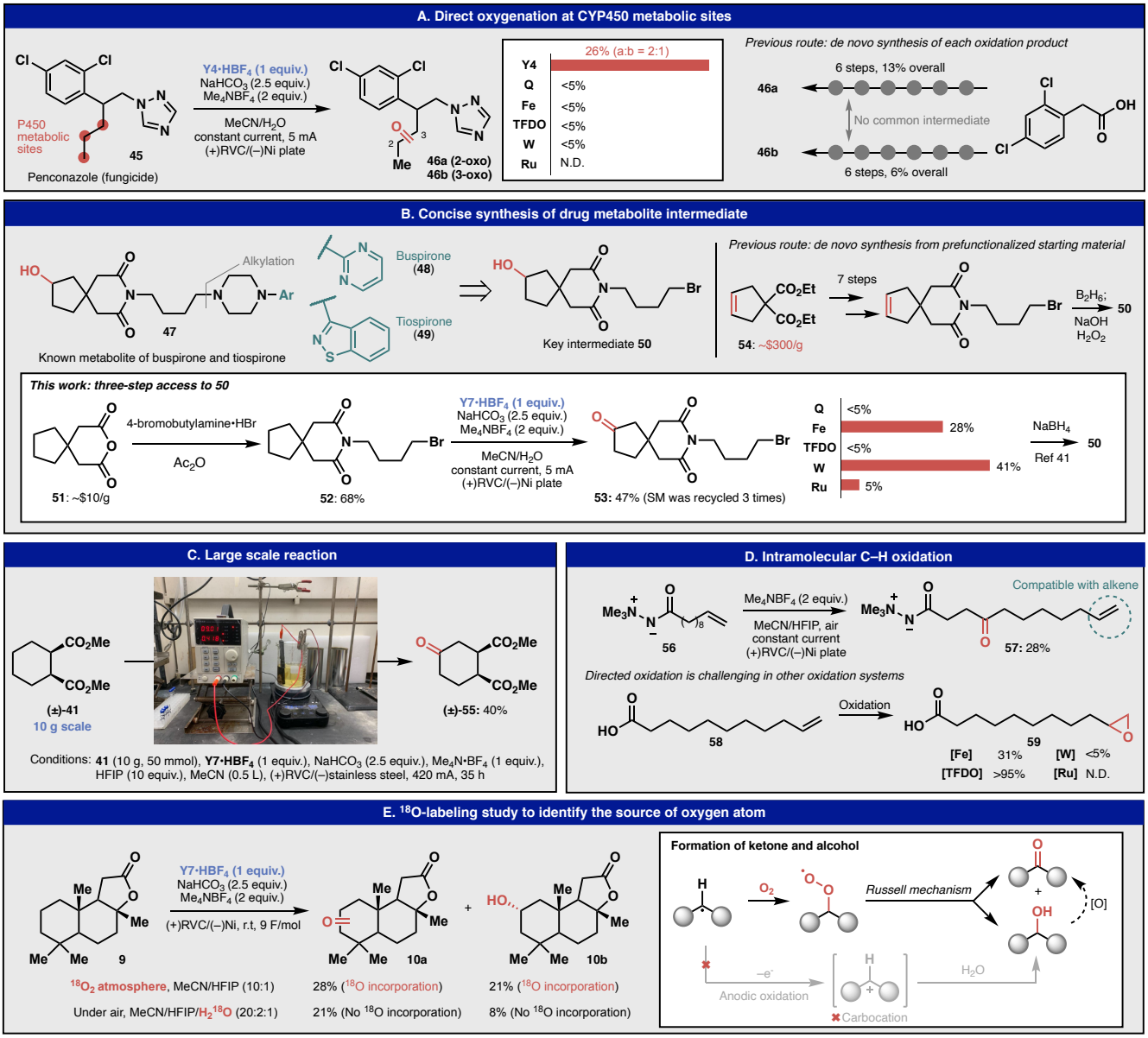

Figure 4. Practicality of ylide-mediated electrochemical C–H oxidation in various contexts and mechanistic study. (A). Ylide mediated oxidation as uniquely effective approach for direct oxidation of P450 metabolic sites on Penconazole. (B). Short synthesis of a key intermediate for drug metabolites without prefunctionalization. (C). 10 gram-scale reaction was performed without the need of expensive reagents. (D). Intramolecular C–H oxidation is directed and tolerates alkene. (E). ^{18}O-labelled experiments to identify the source of oxygen in the products.

Conclusion

A new class of reactive radicals with tunable reactivity and selectivity for unactivated C–H oxidation has been disclosed. Although the reactions presented in this work were performed under electrochemical conditions, the utility of *N*-ammonium ylides may not be limited to electrochemical oxidation; it is possible that such species can also be employed in other (photo)chemical C–H functionalization processes under suitable conditions. Since various ways to intercept the resulting carbon radical after C–H abstraction are known, the unique tunability of such ylides will have an impact on various aspects of C–H functionalization chemistry.

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures, additional experimental data, the detail of DFT calculation (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. †‡These authors contributed equally to this work.

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