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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Communication

Regiospecific Alkene Aminofunctionalization *via* an Electrogenerated Dielectrophile

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Cite This: *J. Am. Chem. Soc.* 2023, 145, 8299–8307
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ABSTRACT: Modular strategies to rapidly increase molecular complexity have proven immensely synthetically valuable. In principle, transformation of an alkene into a dielectrophile presents an opportunity to deliver two unique nucleophiles across an alkene. Unfortunately, the selectivity profiles of known dielectrophiles have largely precluded this deceptively simple synthetic approach. Herein, we demonstrate that dicationic adducts generated through electrolysis of alkenes and thianthrene possess a unique selectivity profile relative to more conventional dielectrophiles. Specifically, these species undergo a single and perfectly regioselective substitution reaction with phthalimide salts. This observation unlocks an appealing new platform for aminofunctionalization reactions. As an illustrative example, we implement this new reactivity paradigm to address a longstanding synthetic challenge: alkene diamination with two distinct nitrogen nucleophiles. Studies into the mechanism of this process reveal a key alkenyl thianthrenium salt intermediate that controls the exquisite regioselectivity of the process and highlight the importance of proton sources in controlling the reactivity of alkenyl sulfonium salt electrophiles.

Oxidative alkene functionalization reactions are a fundamental class of synthetic transformations and represent a premier tactic to rapidly increase molecular complexity.[1−3] However, modular and regioselective alkene heterofunctionalization strategies, which introduce two distinct functional groups across the π-bond, remain fundamentally limited despite their clear synthetic value. In principle, if an alkene could be transformed into a dielectrophile that is susceptible to a single regioselective substitution by one nucleophile, diverse heterofunctionalized products could be readily obtained through addition of a second, distinct nucleophile (Figure 1, top). Unfortunately, although alkenes can be transformed into vicinal dielectrophiles (e.g., dihalides or halonium intermediates), none of these species offer the necessary selectivity profile to enable this idealized platform. Specifically, use of these conventional dielectrophiles for intermolecular alkene heterofunctionalization has been stymied by a series of inextricable problems:[4−8] (1) competitive elimination pathways; (2) poor substitution regioselectivity; and (3) uncontrolled sequential addition of the same nucleophile (Figure 1, middle). Circumventing these limitations has been a longstanding synthetic goal and pioneering advances have exploited π-acidic metals or main group organocatalysts and reagents to formally engage alkenes as dielectrophiles.[9−13] However, each established strategy requires substantial compromises relative to an idealized dielectrophile approach. For example, hypervalent iodine and selenium promoted alkene heterofunctionalization reactions rely on bifunctional nucleophiles to enforce selectivity for heterofunctionalization over homofunctionalization.[14−16] While effective, this design strategy fundamentally limits the range of accessible products to a subset of heterocyclic compounds. As a consequence, multistep procedures based on initial alkene epoxidation followed by iterative stoichiometric activation and substitution steps remain the most commonly employed synthetic workaround to formally replicate the potential reactivity of dielectrophiles.[17,18] Overall, identification of a new dielectrophile that undergoes a single regioselective substitution is poised to dramatically expand the pool of readily accessible, vicinally substituted molecules.

Recent advances have revealed diverse and unique electrophilic reactivity from C(sp^2) and C(sp^3) thianthrenium salts.[19−33] Among these efforts, our group has introduced an oxidative alkene aziridination strategy that relies on the generation of dicationic adducts derived from electrolysis of an alkene and thianthrene. In all reported studies regarding the reactivity of these dielectrophiles, both carbon−sulfur bonds were displaced either through substitution or elimination pathways.[33,34] Indeed, nothing is known about selective manipulation of just one of the electrophilic sites of these adducts. We recognized that selective substitution at one site of this dielectrophile would represent a fundamentally new reactivity paradigm for alkene-derived dielectrophiles. We suspected this might be feasible based on two key hypotheses: (1) the dicationic species would be more electrophilic than the nascent monocationic sulfonium salt, preventing homofunctionalization and (2) differential reactivity at each site of the dicationic adduct would allow for regioselective substitution. If correct, the dicationic adducts would meet all the prerequisites

Received: January 31, 2023
Published: April 6, 2023

https://doi.org/10.1021/jacs.3c01137
J. Am. Chem. Soc. 2023, 145, 8299−8307

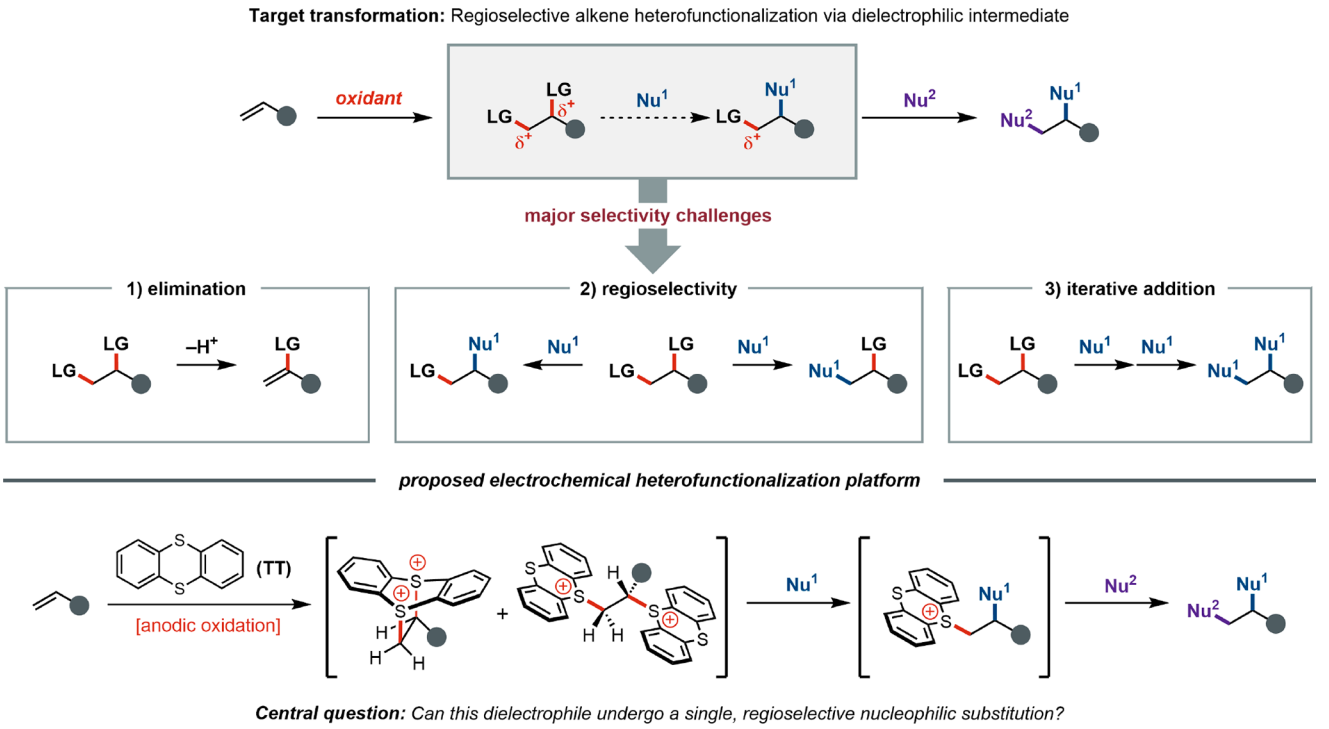


Figure 1. Electrochemical heterofunctionalization platform. Target alkene heterofunctionalization transformation using dielectrophiles and major challenges (top). Proposed platform for alkene heterofunctionalization exploiting electrochemically generated dielectrophiles (bottom).

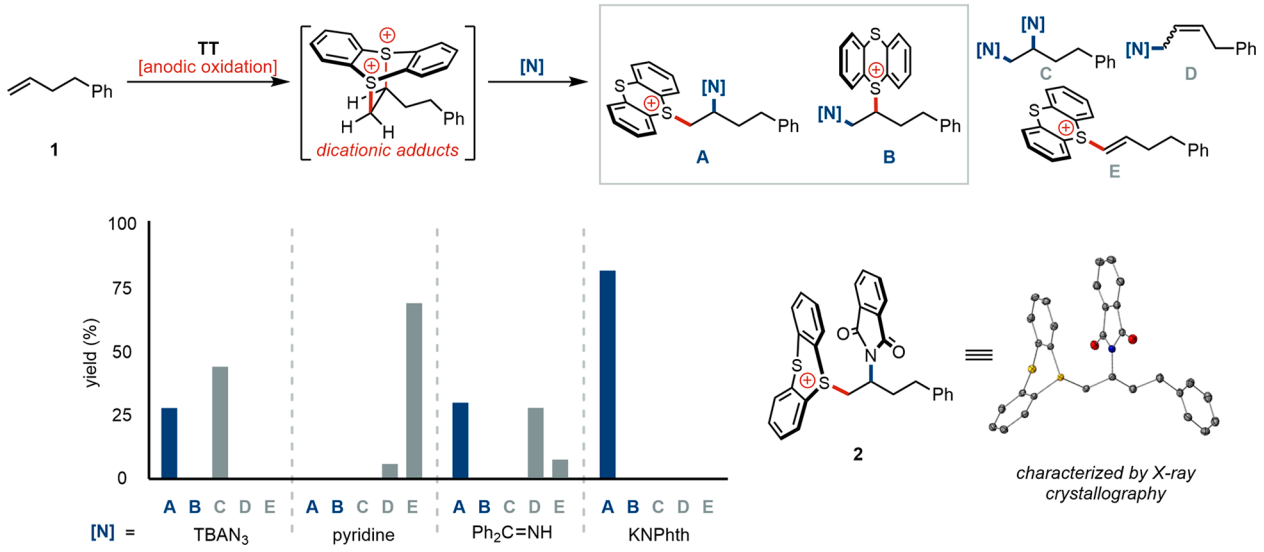


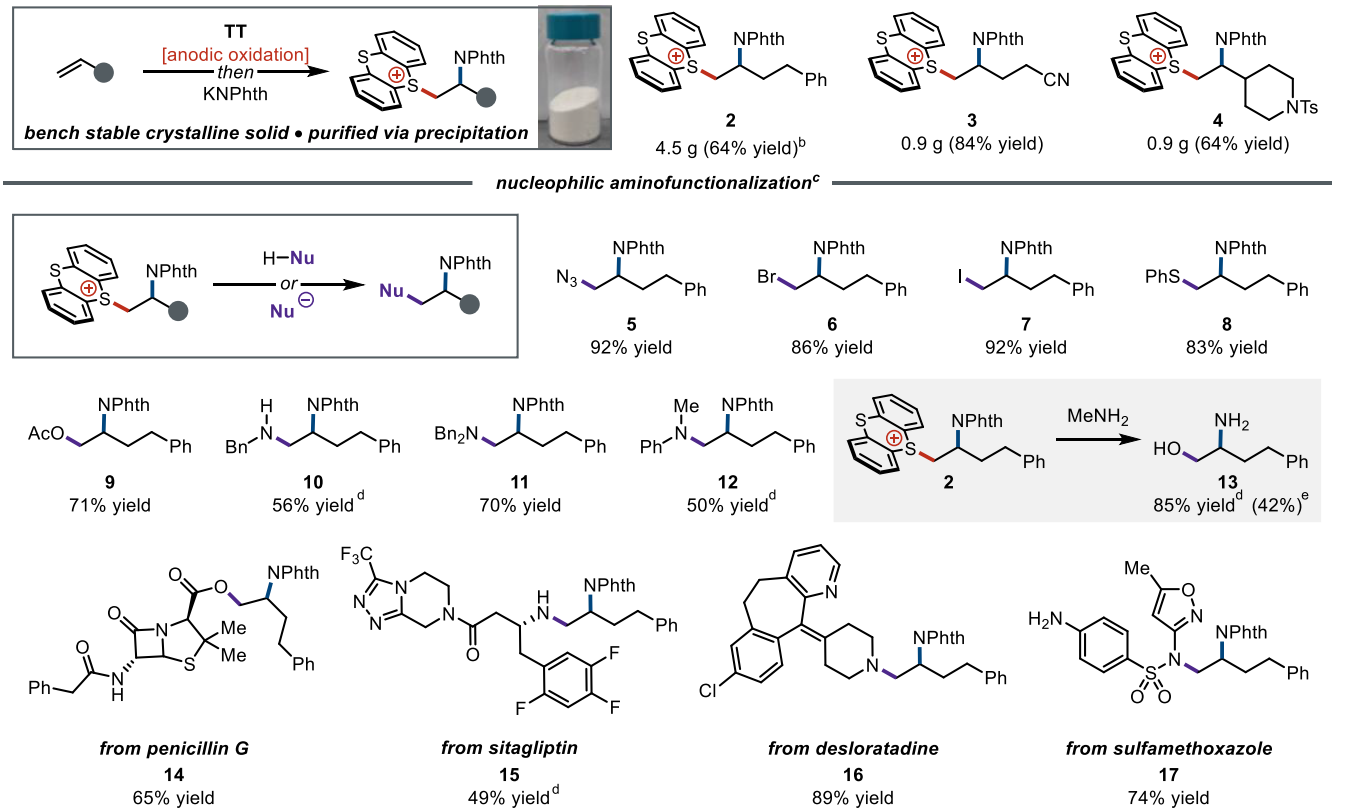
Figure 2. Strategy validation. Substitution of electrogenerated dicationic adducts with various ammonia surrogates and X-ray structure of selective internal addition.

for an idealized dielectrophile approach to modular alkene heterofunctionalization (Figure 1, bottom).

We selected the development of oxidative aminofunctionalization reactions as a specific context to explore the prospect of substituting the dicationic adducts with two distinct nucleophiles. This important class of reactions introduce one carbon−nitrogen bond alongside a distinct, second new carbon-heteroatom bond. In principle, alkene aminofunctionalization reactions represent an appealing approach to prepare important nitrogen-containing compounds; however, they remain limited to using established approaches.[35,36] Rather than employing dielectrophilic intermediates, important recent advances have instead focused on a nitrogen umpolung strategy through either the use of presynthesized electrophilic nitrogen reagents[37−51] or *in situ* oxidation of nitrogen nucleophiles.[52−57] Of particular relevance to the proposed strategy, pioneering parallel efforts from Morandi, Leonori, and Fu have introduced distinct platforms for alkene aminofunctionalization that leverage new catalytic approaches to prepare β-chloroamines from alkenes.[37,38,41,52] These approaches exploit the versatile substitution chemistry of the alkyl chloride, which can be displaced by numerous nucleophiles. However, these processes typically proceed through transient aziridine or aziridinium intermediates, which can complicate substitution regioselectivity. We envisioned that regioselective single substitution of the

https://doi.org/10.1021/jacs.3c01137
J. Am. Chem. Soc. 2023, 145, 8299−8307

Table 1. Scope of Selective Single Addition and Further Substitution[a]



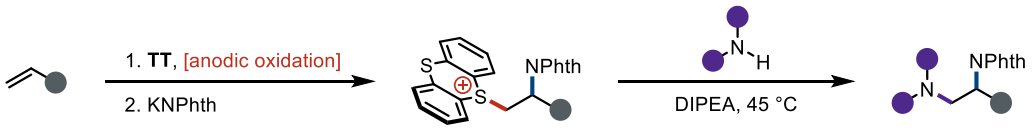
[a]Reactions were conducted using alkene (1.8 mmol), **TT** (1.5 equiv), 18 mL MeCN (0.2 M KPF_6), I = 65 mA, 2.23 h (3 F/mol alkene), 30 °C. After electroylsis, potassium phthalimide (5 equiv) is added and stirred for 2 h. Yields are of the purified product. See the SI for further experimental details. [b]Reaction run on an 11 mmol scale. [c]Reactions were conducted using 2 (0.45 mmol), nucleophile (1–2 equiv), base if necessary (1–2.5 equiv), MeCN or DMF (1–3 mL), 45 °C. Yields are of the purified product unless otherwise noted. Products isolated as 1:1 mixtures of diastereomers when applicable. [d]Yield determined by 1H nuclear magnetic resonance analysis of the crude reaction mixture. [e]Product isolated as a Boc-protected amine. See SI for further experimental details.

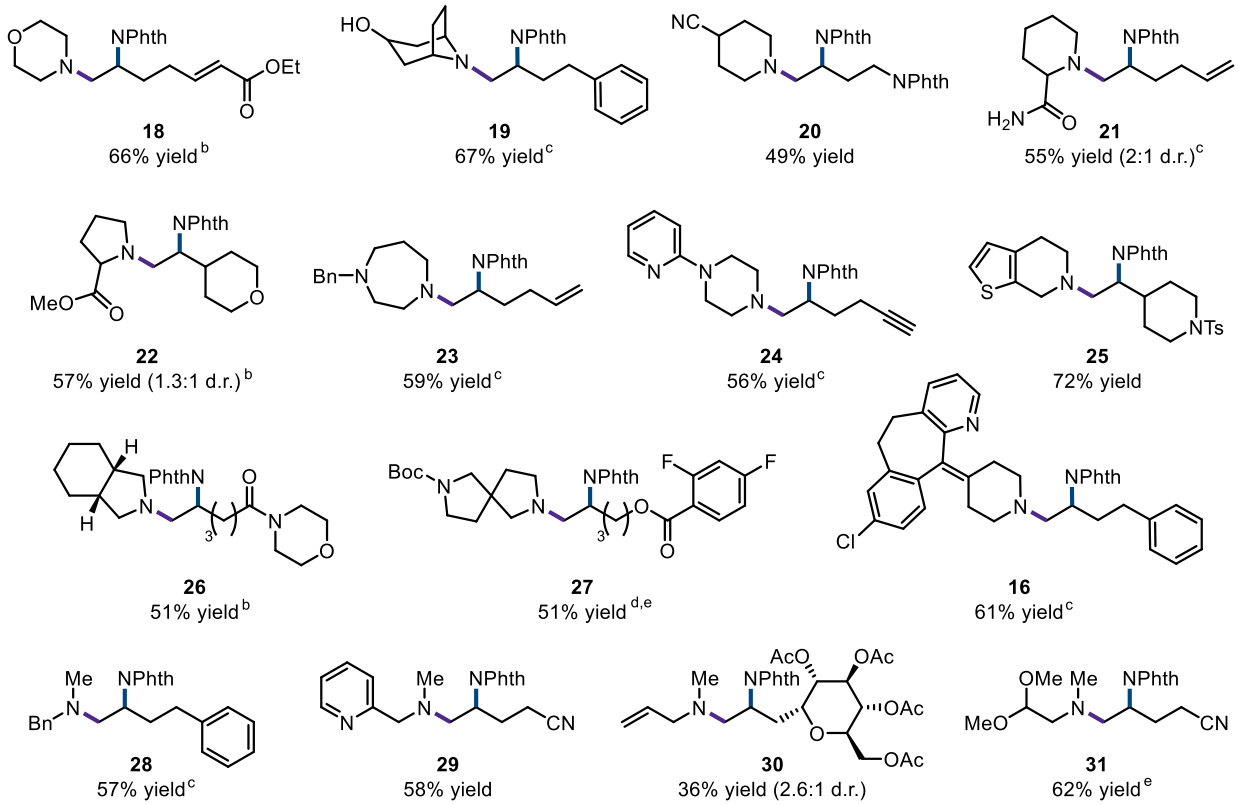
dicationic adducts using a simple nitrogen nucleophile to produce a protected β-aminothianthrenium salt would unlock a powerful and potentially generalizable platform for oxidative alkene aminofunctionalization.

To commence our studies, we surveyed the reactivity of a range of ammonia surrogates with electrochemically generated dicationic adducts derived from alkene **1** as a representative model substrate (Figure 2). We reasoned that addition of any of these formal ammonia sources would enable a general approach to access complex aminofunctionalized products. At the outset, we anticipated a series of potential reactivity pathways: (1) desired single nucleophilic displacement to provide constitutional isomers **A** or **B**; (2) iterative substitution of the dielectrophile by the nitrogen-nucleophile to provide homofunctionalization product, **C**; (3) elimination-substitution pathways to provide allylic substituted products, **D**;[23] and (4) elimination of the dicationic adducts to provide alkenyl thianthrenium salt **E**.[21] Initially, we tested azide, a classic anionic nucleophile and ammonia surrogate. We found that treatment of **1** with tetrabutylammonium azide resulted in the formation of azidosulfonium salt **A** with no evidence of the constitutional isomer, **B**. While the exquisite regioselectivity of this substitution was promising, we observed a significant amount of the diazide product **C**. We questioned whether weaker nucleophiles could accentuate the difference in reactivity between the initial adduct and the desired monosulfonium salt product to mitigate the formation of homofunctionalization product **C**. We found that pyridine was insufficiently nucleophilic and resulted in predominant elimination to alkenyl thianthrenium species, **E**, which did not continue to convert under the reaction conditions. In contrast, treatment of the adducts with benzophenone imine and diisopropylethylamine resulted in the generation of sulfonium salt **A**, again as a single constitutional isomer. In this case, although homofunctionalization **C** was not observed, the yield was nonetheless diminished by formation of the allylic product **D** in roughly a 1:1 ratio with the desired product. Excitingly, potassium phthalimide, however, possessed the appropriate balance of nucleophilicity and basicity to deliver monosulfonium salt **A** in quantitative yield from the dicationic adducts as a single constitutional isomer. Formation of homofunctionalization product **C** was completely suppressed; the 1,2-phthalimidosulfonium salt does not undergo measurable substitution by excess potassium phthalimide even if given an extended 80 h reaction time (see the Supporting Information). The formation of terminal sulfonium salt **2** was unambiguously verified *via* X-ray crystallography. Excitingly, regioselective monosubstitution was not limited to alkene **1**, and electrolysis of thianthrene in the presence of various alkenes followed by treatment with potassium phthalimide enabled preparative generation of an array of substituted sulfonium salts (**2**–**4**) (Table 1, top).[58] Each salt could be readily purified by precipitation from the reaction mixture. In each case, these salts were sufficiently stable to storage on the

https://doi.org/10.1021/jacs.3c01137
J. Am. Chem. Soc. 2023, 145, 8299–8307

Table 2. Scope of Electrochemical One-Pot Unsymmetrical Diamination Reaction[a]





[a]Reactions were conducted using alkene (0.4 mmol), **TT** (1.5 equiv), 8 mL MeCN (0.2 M n-Bu_4NPF_6), I = 14.4 mA, 2.23 h (3 F/mol alkene). After electrolysis, potassium phthalimide (5 equiv) is added and stirred for 2 h, then amine (2.5 equiv), DIPEA (5 equiv), 12−24 h, 45 °C. Yields and diastereoselectivity are of the purified product unless otherwise noted. See the SI for further experimental details. The major diastereomer was not determined. [b]3.5 equiv amine was used. [c]I = 12 mA, 2.5 F/mol alkene. [d]1.6 equiv amine was used. [e]Yield determined by 1H nuclear magnetic resonance analysis of the crude reaction mixture.

benchtop and exhibited no measurable decomposition for over half a year. Overall, these results establish that the thianthrene-derived dicationic adducts possess a unique selectivity profile relative to other dielectrophiles, enabling exclusive and regioselective monosubstitution.

We next investigated whether these modestly hindered 1,2-phthalimidosulfonium salt products could be substituted with a second nucleophile without deleterious elimination pathways (Table 1, bottom). Selective second substitution constitutes the last key requirement to enable a diverse array of net alkene aminofunctionalization protocols. Classic strong nucleophiles such as halides, azide, and thiolate each efficiently substituted the thianthrenium salt electrophile and delivered vicinally heterofunctionalized compounds **5**−**8** in high yield. Of note, while *N*-halophthalimide reagents have been developed, phthalimide addition into halonium intermediates is unselective and use of these reagents with unactivated alkenes provides 1:1 mixtures of constitutional isomers.[5] Weaker nucleophiles, such as carboxylates, amines, and anilines, similarly could be employed as nucleophiles, generating products **9**−**12** in good yield. Interestingly, treatment of 1,2-phthalimidosulfonium salt **2** with methylamine directly afforded the free 1,2-aminoalcohol **13**, presumably *via* cyclization of an intermediate hemiaminal followed by full deprotection of the phthalimide (see the Supporting Information for detailed mechanistic proposal). We next probed whether pharmaceutically relevant molecules—which typically bear multiple potentially problematic functional groups—could be selectively engaged using this amino-functionalization protocol. Excitingly, diverse nucleophiles such as penicillin G, sitagliptin, desloratadine, and sulfamethoxazole could each be employed to afford complex, vicinally substituted products **14**−**17** in high yield. These substitution reactions each selectively engaged the most nucleophilic functional group on the bioactive molecules, tolerating other functional groups such as amides, anilines, and basic heterocycles. Additionally, subsequent deprotection of the phthalimide unit to reveal an unprotected primary amine could be carried out in a one-pot procedure without any intermediate purification (see the Supporting Information for details). This new reactivity platform provides a means to bypass the aziridine intermediates that would be conventionally employed

https://doi.org/10.1021/jacs.3c01137
J. Am. Chem. Soc. 2023, 145, 8299−8307

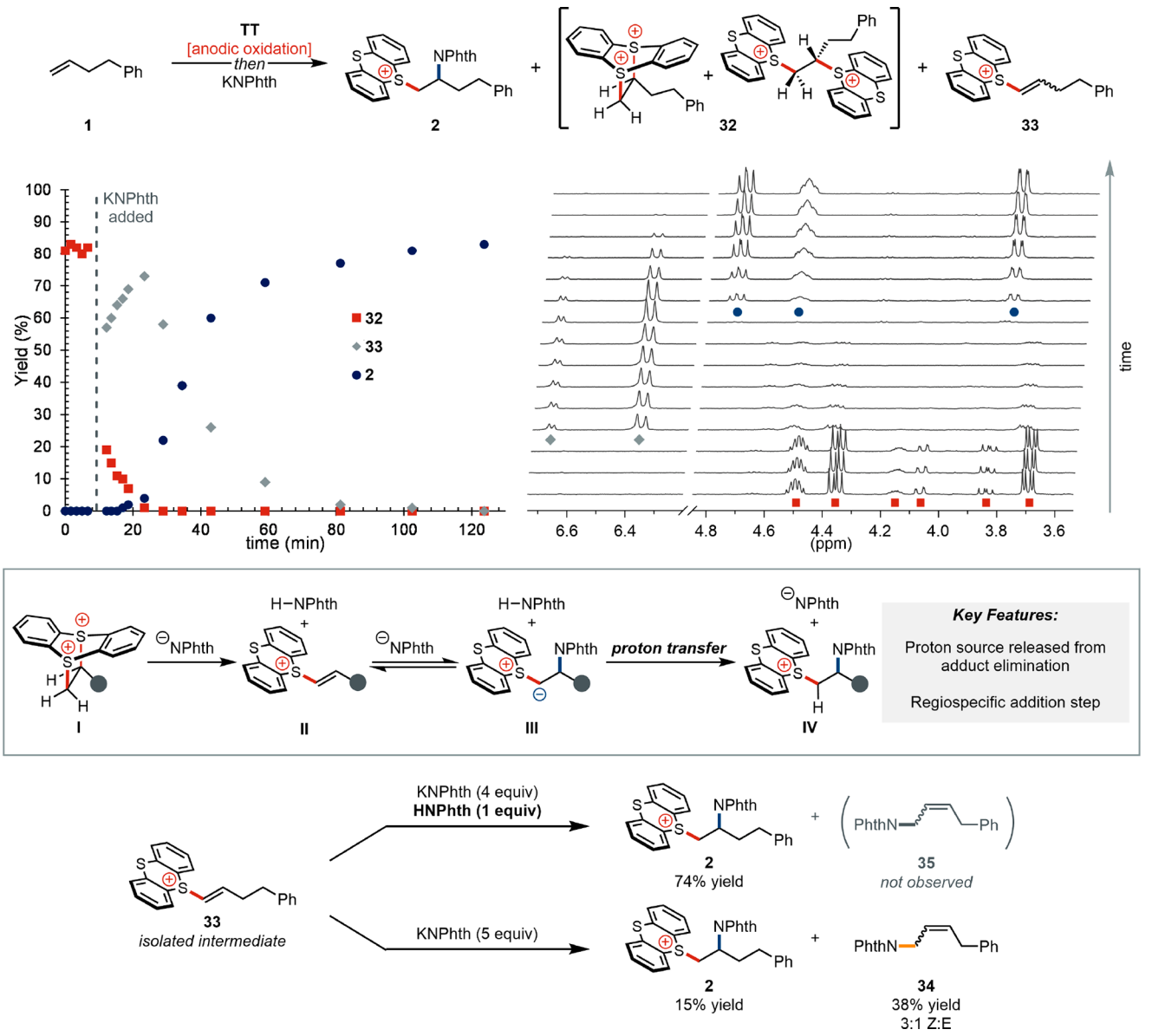


Figure 3. Mechanistic details of the regioselective single substitution into the dicationic adducts. Time course analysis of the reaction profile (top). Working mechanistic model to rationalize regioselective phthalimide anion addition (middle). Validation of the importance of proton source on the observed 1,2-phthalimidosulfonium salt formation (bottom). Yields determined by ^{1}H nuclear magnetic resonance analysis. See the SI for further experiment details.

to prepare analogous products from alkenes. Accordingly, it circumvents the challenges encountered in aziridine-based strategies such as the poorly controlled regiochemistry and oligomerization pathways endemic to unactivated N–H aziridine opening[59,60] and harsh removal of sulfonyl protecting groups that enable controlled ring opening.[61]

We envision that these studies lay the foundation for the development of a diverse array of one-pot alkene hetero-functionalization protocols. To this end, we targeted one-pot alkene diamination with two distinct nitrogen nucleophiles as a case study given the classic challenges associated with unsymmetrical alkene diamination.[41,62−75] In principle, a series of diamines could be synthesized by the addition of an amine nucleophile and base to the reaction mixture following phthalimide substitution (Table 2). First, we targeted the use of cyclic amines as second nucleophiles. Construction of diversely substituted nitrogen heterocycles would be particularly interesting for medicinal chemistry efforts, as saturated nitrogen heterocycles are among the most common nitrogen-containing functional groups in pharmaceutical compounds.[76] We found that a series of functionalized cyclic amines, including piperidines (**16**, **19**, **20**, **21**, **25**), pyrrolidines (**22**, **26**, **27**), piperazines (**24**), diazepanes (**23**), and morpholines (**18**) were competent nucleophiles for this alkene diamination reaction. Nucleophiles bearing functional groups such as esters (**22**), nitriles (**20**), pyridines (**16**, **24**), tertiary amines (**23**), and carbamates (**27**) were each well-tolerated. Excitingly, amines bearing potentially competitive nucleophilic functional groups, such as free amides (**21**) and alcohols (**19**) underwent selective diamination. We found that desloratadine, a complex nucleophile that worked well in the two-pot functionalization sequence, could also be leveraged using the streamlined one-pot procedure (**16**) at slightly diminished yield relative to the two-pot protocol. Various terminal alkenes of differing steric

https://doi.org/10.1021/jacs.3c01137
J. Am. Chem. Soc. 2023, 145, 8299−8307

and electronic environments underwent net diamination. These substrates could contain functional groups such as esters (**18**, **27**), alkynes (**24**), phthalimides (**20**), sulfonamides (**25**), and amides (**26**). Substrates containing more than one alkene were exclusively functionalized at the most electron rich site (**18**, **21**). Acyclic secondary amines were also amenable to this one-pot diamination protocol and provided the heterofunctionalized compounds in high yield (**28**−**31**). Again, diverse functional groups were tolerated across both alkene and amine reaction components, including acetals (**31**), alkenes (**30**), nitriles (**29**, **31**), and acetyl-protected carbohydrates (**30**).

We next turned our attention to elucidating the origin of the exquisite regioselectivity that underpins each of these new aminofunctionalization processes. Indeed, across each alkene studied, only a single constitutional isomer of the 1,2-phthalimidosulfonium salt was obtained. Curiously, previously reported intramolecular competition experiments studying sulfonium salt electrophiles suggest that, at best, only modest selectivity for the more substituted position should be observed.[77] This discrepancy suggested that displacement of the thianthrene-based dicationic dielectrophiles may proceed through a distinct, regiospecific mechanism rather than simple nucleophilic substitution. To probe the substitution mechanism, we conducted a time course analysis of the reaction of dicationic adducts with potassium phthalimide using ^{1}H NMR (Figure 3, top). Following addition of potassium phthalimide to the reaction mixture after electrolysis, we observed rapid elimination of the adducts **32** to form an alkenyl thianthrenium salt **33**. This intermediate is subsequently consumed as the 1,2-phthalimidosulfonium salt **2** is formed. Taken together, these data suggest that the alkenyl thianthrenium salt **33** may be on pathway to the desired product. Overall, we suspect that the regioselective substitution by potassium phthalimide occurs *via* the following sequence of steps (Figure 3, middle): (1) the phthalimide anion initially eliminates the dicationic adduct **I** to the corresponding alkenyl thianthrenium salt **II**; (2) remaining phthalimide anion nucleophile adds into the alkenyl thianthrenium salt **II** at the internal, β-position to generate a stabilized sulfur ylide **III**; (3) the sulfur ylide **III** is protonated by phthalimide formed during the first step to furnish the ultimate monosulfonium salt product **IV**. This working mechanistic model offers a plausible explanation for the observed regioselectivity in the dielectrophile substitution, given that alkenyl sulfonium salts are far more electrophilic at the β-position than α.[78]

While vinyl and alkenyl sulfonium salts have been employed as electrophiles for diverse transformations,[21,24−29,79−89] they have not been leveraged for single substitution as proposed herein. Indeed, selective single nucleophilic addition into these species to form a monosulfonium salt has only been observed in a handful of isolated instances as an undesired byproduct.[78,85,90,91] Accordingly, we sought to validate that this species was indeed kinetically competent in the reaction. To this end, we prepared and isolated the proposed alkenyl sulfonium salt intermediate, **33**, and directly subjected it to substitution conditions (Figure 3, bottom). Importantly, the proposed substitution mechanism involves an equivalent of the corresponding nucleophile conjugate acid, which is formed through elimination of the electrogenerated dicationic adducts to form the alkenyl thianthrenium species (**I** to **II**). Based on the working mechanistic model, this conjugate acid should be crucial as it is required to protonate the ylide species **III** and deliver the final monosulfonium salt product **IV**. Consistent with this hypothesis, reaction of isolated alkenyl thianthrenium salt, **33**, with a mixture of potassium phthalimide and an equivalent of phthalimide results in the formation of the 1,2-phthalimidosulfonium salt **2** as the exclusive product. Furthermore, omission of the phthalimide proton source results in poor yield of the 1,2-phthalimidosulfonium salt **2** and instead results in a new major allylic substitution byproduct **34**, similar to recently reported alkenyl thianthrenium salt allylation processes.[23,27,28] These experiments illustrate that proton balance is a crucial parameter that controls the reactivity of alkenyl sulfonium salt substitution. Since recent efforts from Ritter et al. have introduced general and operationally simple methods to prepare alkenyl thianthrenium salts,[21] we leveraged these mechanistic observations to develop an adapted protocol for one-pot diamination from these species for researchers without access to electrochemical equipment (see the Supporting Information). Overall, these data are consistent with alkenyl thianthrenium salt, **33**, as a key intermediate that explains the observed regiospecificity.

In summary, we have illustrated that dicationic adducts derived from anodic oxidation of thianthrene and alkenes present a unique selectivity profile relative to more conventional dielectrophiles. This observation enabled an operationally simple and modular alkene aminofunctionalization platform. Specifically, we show that potassium phthalimide formally displaces the internal electrophilic position of the dicationic adducts to furnish a monosulfonium salt. This key intermediate can then be substituted with a series of different nucleophiles to synthesize diverse vicinally functionalized molecules with exquisite regioselectivity. Mechanistic studies revealed that *in situ* elimination of the dicationic adducts to generate an alkenyl thianthrenium salt is the key step that controls the ultimate regioselectivity of the formal substitution by potassium phthalimide. Overall, we anticipate that the unique selectivity profile of these unusual dielectrophiles lays the foundation for the development of a wide array of heterofunctionalization reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c01137.

Discussions of general methods and materials, electrochemical methods and materials, mechanistic investigations, substrate preparation, scale-up batch electrolysis set-up and procedure, general experimental procedures, product isolation and characterization, X-ray diffraction data, and crystal data, figures of large divided cell with electrodes, potential mechanism for aminoalcohol and byproduct formation, deprotection of aminofunctionalized product, diamination sequence starting from vinyl thianthrenium salt, implication of vinyl thianthrenium salt **33** as an intermediate in the reaction, attempted aminofunctionalization of an internal alkene, large-scale divided cell with electrode assembly, LCMS data, molecular drawings, and NMR spectra, and tables of reaction optimization for ammonia surrogate screening, substitution profile of potassium phthalimide addition into dicationic adducts, full time course data, and crystal data and structure refinement (PDF)

https://doi.org/10.1021/jacs.3c01137
J. Am. Chem. Soc. 2023, 145, 8299−8307

Accession Codes

CCDC 2238455 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank Prof. Alison Wendlandt and Prof. Mark Levin for helpful suggestions and manuscript proofreading. The authors thank the Weix, Stahl, Yoon, and Schomaker groups for sharing their chemical inventory. Dr. Blaise J. Thompson is acknowledged for his assistance with power supply design and fabrication. Tracy Drier is acknowledged for electrochemical glassware fabrication. The authors also acknowledge that the invaluable support and helpful suggestions from all Wickens group members throughout the investigation of this project. The authors acknowledge generous support from the Alfred P. Sloan Foundation for funding this project. Support for this research was provided by the UW-Madison Office of the Vice Chancellor for Research and Graduate Education with funding from the Wisconsin Alumni Research Foundation. Spectroscopic instrumentation was supported by a generous gift from Paul. J. and Margaret M. Bender, NSF (CHE-1048642, CHE-2017891), and NIH (1S10OD020022-1). The Bruker D8 VENTURE Photon III X-ray diffractometer was partially funded by NSF Award #CHE-1919350 to the UW−Madison Department of Chemistry.

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