Electrochemical Synthesis of Allylic Amines from Alkenes and Amines

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ABSTRACT: Allylic amines are valuable synthetic targets en route to diverse biologically active amine products. Current allylic C–H amination strategies remain limited with respect to the viable *N*-substituents. Herein we disclose a new electrochemical process to prepare aliphatic allylic amines by coupling two abundant starting materials: secondary amines and unactivated alkenes. This oxidative transformation proceeds via electrochemical generation of an electrophilic adduct between thianthrene and the alkene substrates. Treatment of these adducts with aliphatic amine nucleophiles and base provides allylic amine products in high yield. This synthetic strategy is also amenable to functionalization of feedstock gaseous alkenes at 1 atmosphere. In the case of 1-butene, remarkable Z-selective crotylation is observed. This strategy, however, is not limited to the synthesis of simple building blocks; complex biologically active molecules are suitable as both alkene and amine coupling partners. Preliminary mechanistic studies implicate vinylthianthrenium salts as key reactive intermediates.

Aliphatic amines are prevalent in pharmaceuticals, natural products, and other biologically active molecules.[1–3] Thus, the development of strategies to rapidly construct C–N bonds is of longstanding synthetic importance. Allylic amines are particularly valuable building blocks due to their synthetic versatility.[4–8] A deceptively simple strategy to prepare alkyl allylic amines would be the oxidative coupling of alkenes and aliphatic amines (Fig. 1, top). Such a reaction would be an attractive complement to classic amine allylation strategies such as S_N2[9–16] and π-allyl substitution reactions[17–24] that rely on prefunctionalized electrophiles. However, successful realization of such a transformation requires a strategy to promote the desired oxidative C–N bond-forming process without undesired oxidation of the aliphatic amine starting materials or the aliphatic allylic amine products (0.8 – 1.1 V *vs* SCE).[25] As a consequence, generation of aliphatic allylic amines by oxidative coupling of alkenes and amines has remained elusive.[26–35] Instead, pioneering reports have established powerful C–H functionalization protocols to construct allylic C–N bonds using oxidatively stable nitrogen sources.[36–39] These reaction manifolds primarily take advantage of electronically deactivated nitrogen pronucleophiles[40–50] and nitrene precursors.[51–65] As a direct result, these established approaches offer limited access to aliphatic allylic amine products and instead furnish products with electron-deficient nitrogen atoms, such as allylic sulfonamides and carbamates (Fig. 1, middle).

Despite the significant progress in other oxidative amination reactions,[66–71] to date, there is a single intermolecular allylic C–H amination reaction that directly furnishes aliphatic allylic amine products.[26] This strategy, reported by Ritter and co-workers in 2020, exploits photochemically-activated sulfilimine reagents as nitrogen sources. While this is a landmark report in allylic C–H amination, installation of different *N*-substituents in the product requires preparation of unique electrophilic reagents. Additionally, this reagent design strategy is not readily amenable to tertiary amine synthesis.

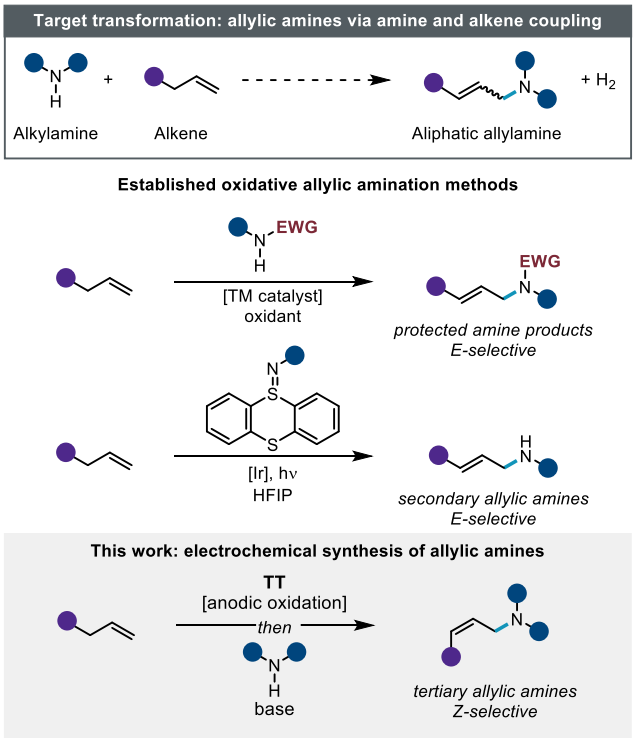
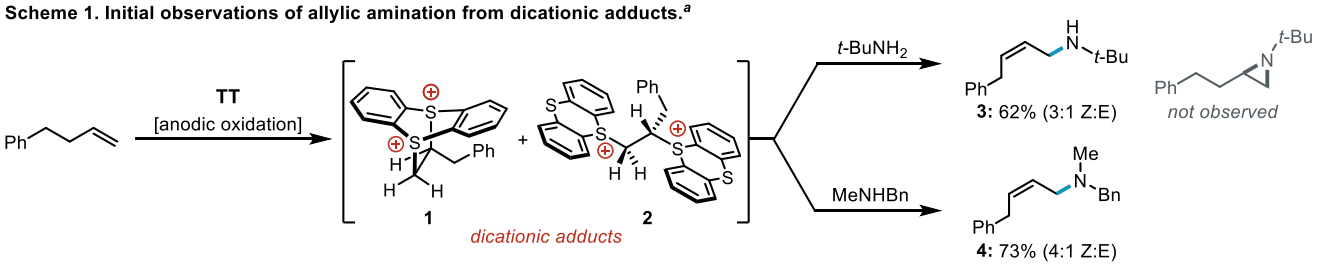


Figure 1. Project overview. Idealized transformation to access alkyl allylic amines (top); representative established allylic C–H amination reactions (middle); schematic overview of this work (bottom). TT = thianthrene.

Accordingly, a complementary synthetic technology that generates allylic amines via an oxidative coupling of unactivated amine nucleophiles and alkenes remains poised to have a significant impact on organic synthesis. Such an approach would directly translate the >4 million commercially available aliphatic amines into versatile allylic amine building blocks.[72]

Scheme 1. Initial observations of allylic amination from dicationic adducts.[a]

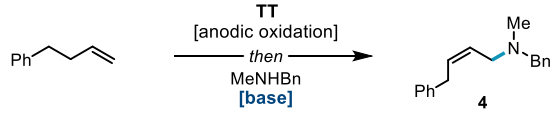


[a]Reactions were conducted using alkene (0.15 mmol), **TT** (0.23 mmol), 3 mL MeCN (0.2 M n-Bu_4NPF_6), I = 4.0 mA, 2.5 h (2.5 F mol^{-1} alkene); then amine (1.2 mmol), 16 h. Yields and Z:E ratios were determined by ^1H NMR analysis. See the Supporting Information (SI) for details.

We recently developed an electrochemical strategy to engage oxidatively sensitive nucleophiles in net oxidative alkene difunctionalization reactions.[71] Our approach draws inspiration from Yoshida's pioneering cation pool work[73–75] and contributes to a rapidly growing body of literature exploiting oxidized thianthrene derivatives as synthetic intermediates.[76–83] Specifically, we leveraged electrochemistry to cleanly generate dicationic adducts between unactivated alkenes and thianthrene (**TT**),[84,85] a safe[86] and inexpensive[87] reagent. This strategy circumvents the need for oxidatively stable coupling partners in net oxidative alkene functionalization reactions; the oxidative alkene activation event is decoupled from nucleophilic substitution. In our first report, we leveraged this approach to enable the formal coupling of primary amine nucleophiles with alkenes to furnish aziridine products through a one-pot, two-operation process. Herein, we report an electrochemical strategy to prepare linear, tertiary allylic amine products with Z-selectivity from aliphatic amines and alkenes. This is accomplished by diverting the reactivity of the dicationic alkene-thianthrene adducts down a formal substitution-elimination pathway.

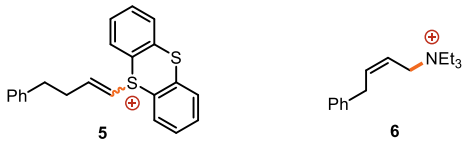
Our development of an allylic amination process began with an unexpected observation during the study of our dication pool aziridination reaction. We found that, upon exposure to excess tert-butylamine, the electrogenerated mixture of dicationic electrophiles **1** and **2** was transformed into the linear allylic amine product **3** in 3:1 Z:E ratio rather than the expected *N-tert*-butylaziridine (Scheme 1). We suspected this net substitution-elimination process may be a consequence of the increased steric bulk about the nitrogen nucleophile. This rationalization suggested that secondary amine nucleophiles may proceed down an analogous allyic amination pathway rather than forming aziridinium intermediates. Such a reaction would furnish tertiary (Z)-allylic amine products and serve as an ideal complement to the recent secondary (E)-allylic amine synthesis developed by Ritter and co-workers.[26] To probe this hypothesis, we exposed an electrogenerated mixture of **1** and **2** to an excess of *N*-methylbenzylamine. To our delight, this resulted in conversion of the adduct to the corresponding allylic amine product **4** with 4:1 Z-selectivity. Next, we aimed to identify a suitable stoichiometric base to lower the necessary equivalents of amine (Table 1). We surveyed a range of bases and found *i*-Pr_2NEt promoted the desired allylic functionalization in 79% yield with a 1:1 stoichiometry of amine and alkene starting materials. Increasing the steric bulk of the amine base to triisobutylamine resulted in formation of a vinyl thianthrenium salt **5** alongside a reduced yield of allylic amine product (entry 2). Smaller amine bases, such as triethylamine, also resulted in reduced yield (40%) of the desired allylic amine product **4** due to competitive formation of an allylic ammonium salt **6** derived from the triethylamine base (entry 3). Alternative bases, such as Cs_2CO_3, promoted the desired allylic functionalization albeit in diminished *Z*-selectivity (entry 4). Weaker inorganic bases, such as $NaHCO_3$, provided vinyl thianthrenium product alongside traces of the desired allylic amine (entry 5). Overall, this method provides an appealing one-pot synthesis of allylic amine building blocks.

Table 1. Base evaluation for the allylic amination reaction.[a,b]



entry	base	yield **4** (Z:E)	yield **5**
1	*i*-Pr_2NEt	79% (6:1)	n.d.
2	*i*-Bu_3N	27% (5:1)	52%[c]
3	Et_3N	40% (3:1)	n.d.
4	Cs_2CO_3	61% (3:1)	n.d.
5	$NaHCO_3$	<5%	67%[d]

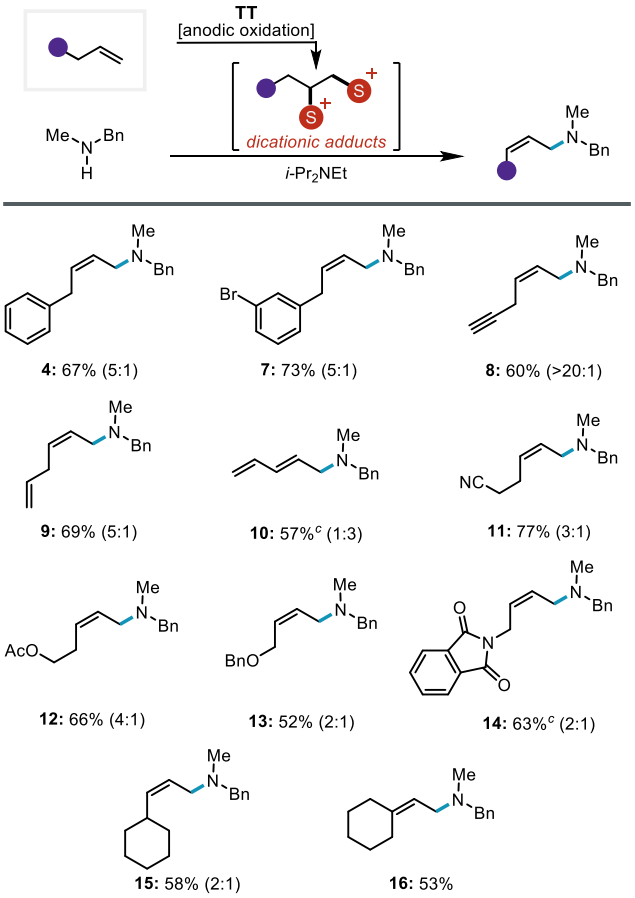
Observed side products



[a]Reactions were conducted using alkene (0.15 mmol), **TT** (0.23 mmol), 3 mL MeCN (0.2 M n-Bu_4NPF_6), I = 4.0 mA, 2.5 h (2.5 F mol^{-1} alkene); then base (1.1 mmol), amine (0.30 mmol), 16 h. Yields and Z:E ratios were determined by ^1H NMR analysis. See the Supporting Information (SI) for details. [b]n.d. = not detected. [c]5:1 E:Z ratio. [d]6:1 E:Z ratio.

With optimized conditions in hand, we next investigated the alkene scope for this allylic amination process, employing *N*-methylbenzylamine as a model secondary amine nucleophile (Table 2). Allylic amination of 4-phenyl-1-butene and an aryl bromide derivative provided the desired (Z)-allylic amine products (**4**, **7**) without detectable arene thianthrenation. Likewise, selective alkene functionalization in the presence of an unconjugated alkyne was obtained with high Z-selectivity (**8**). This result, alongside with tolerance of aromatic substrates (**4, 7**), illustrates the exquisite chemoselectivity for adduct formation between oxidized thianthrene and alkene over previously observed thianthrenation of arenes[76] and alkynes.[88] Unconjugated dienes underwent selective monofunctionalization to provide a (Z)-skipped diene **9** and (E)-conjugated diene **10** building blocks. Alkenes bearing a variety of proximal functional groups, such as nitrile (**11**), acetate (**12**), ether (**13**), and phthalimide (**14**) each efficiently delivered the desired allylic amine products. These examples illustrate the viability of accessing allylic amine building blocks with a secondary homoallylic (**11, 12**) or allyic (**13**, **14**) functional group handle for further elaboration. Allylcyclohexane underwent allylic

Table 2. Scope of alkenes for allylic amination via dication pool strategy.[a,b]



[a]Reactions were conducted using alkene (0.4 mmol), **TT** (0.6 mmol), 8 mL MeCN (0.2 M n-Bu_4NPF_6), I = 12.0 mA, 2.2 h (2.5 F mol^{-1} alkene); then i-Pr_2NEt (2.8 mmol), amine (0.8 mmol), 16 h. Yields and Z:E ratios are of the purified product unless otherwise noted. See the SI for further details. [b]Isolated yield (Z:E). [c]NMR yield. [d]Reactions were conducted using alkene (1 atm), **TT** (1.0 mmol), 4 mL MeCN (0.2 M n-Bu_4NPF_6), I = 60.0 mA, 45 min (1.7 F mol^{-1} **TT**); then i-Pr_2NEt (3.2 mmol), amine (0.4 mmol), 3 h.

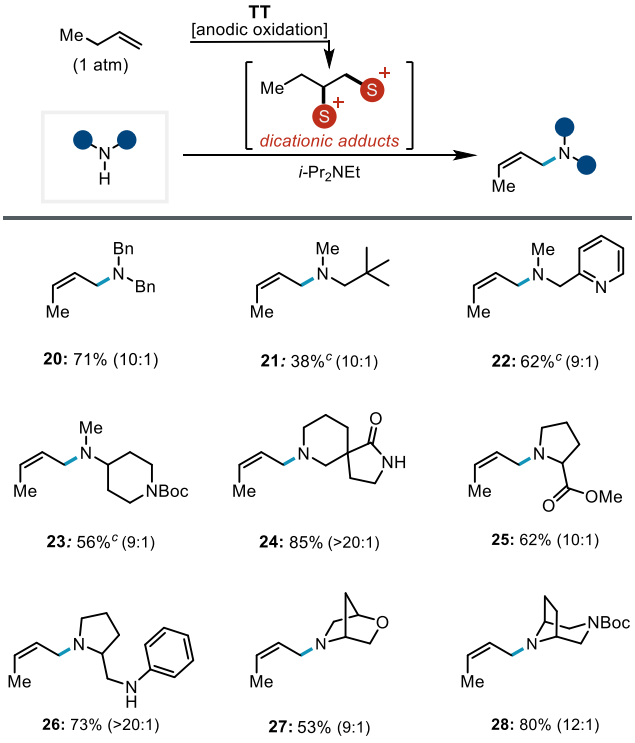
amination to furnish the sterically hindered vinylcyclohexane product **15**.[89] Finally, vinylcyclohexane underwent allylic amination to form trisubstituted allylic amine **16**.[90]

We next probed whether this oxidative coupling strategy is also amenable to functionalization of commodity feedstock alkenes derived from steam cracking and related petroleum refinery processes (Table 2).[91,92] Electrolysis of thianthrene under one atmosphere of propene and isobutene each generated the desired dicationic adducts. Treatment of these reaction mixtures with i-Pr_2NEt and N-methylbenzylamine resulted in allyl- and methallylamine products (**17, 18**) in high yields relative to the amine starting material. Traditional methods to produce these products rely on S_N2 displacement of the corresponding allylic halides, which are industrially derived from the same feedstock alkenes through a multistep oxidation-halogenation sequence.[93] In contrast, this electrochemical method offers an appealing alternative protocol that produces H_2 gas as the stoichiometric byproduct since thianthrene can be recycled and reused.[94] Notably, 1-butene—the simplest alkene to form stereoisomeric allylic amine products—gave allylic amine **19** in high Z-selectivity. This highlights the value of this new transformation beyond a green chemistry context; crotylhalides are only readily available as an €-dominant mixture.

Next, we probed the scope of the amine nucleophile, employing 1-butene as the alkene coupling partner (Table 3). These transformations furnish synthetically attractive Z-crotylamine building blocks that are not straightforward to access using conventional alkylation chemistry. Simple, acyclic dialkylamines **(20–23)** resulted in high yields and Z-selectivity. Of note, even sterically hindered amines delivered the corresponding Z-crotylamine product **21**, albeit with a diminished yield. Heteroaromatic and saturated heterocycles are tolerated both as pendant functional groups (**22**, **23**) or as the nucleophile itself (**24–28**). Amine nucleophiles bearing potential competing nucleophiles were also selectively transformed into (Z)-allylic amine products (**24, 26**), preserving the unprotected functional groups for further derivatization. In addition to spirocyclic piperidine **(24)**, other bicyclic heterocycles with morpholine **(27)** and piperazine **(28)** cores underwent Z-selective crotylation.

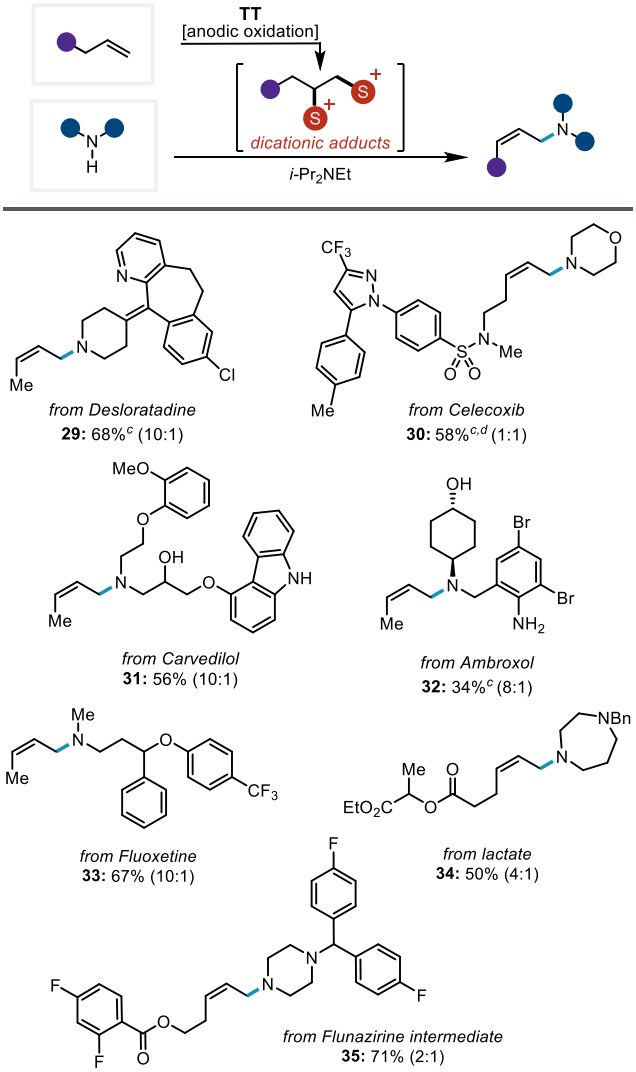
In addition to the efficient formation of simple, allylic amine building blocks, we envisioned that this newly realized oxidative allylic amination methodology would also streamline the synthesis of more complex amine products (Table 4). With this in mind, we next evaluated a range of drug-

Table 3. Scope of Z-crotylamine building blocks.[a,b]



[a]Reactions were conducted using butene (1 atm), **TT** (1.0 mmol), 4 mL MeCN (0.2 M n-Bu_4NPF_6), I = 60.0 mA, 45 min (1.7 F mol^{-1} **TT**); then i-Pr_2NEt (3.2 mmol), amine (0.4 mmol), 3 h. Yields and Z:E ratios are of the purified product unless otherwise noted. See the SI for further experimental details. [b]Isolated yield (Z:E). [c]NMR yield.

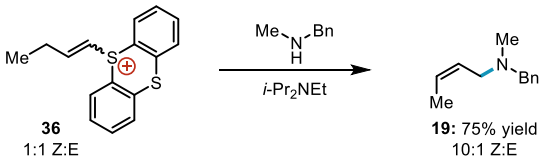
Table 4. Oxidative coupling of complex bioactive molecules.[a,b]



[a]Limiting amine reactions were conducted using alkene (1 atm), **TT** (1.0 mmol), 4 mL MeCN (0.2 M n-Bu_4NPF_6), I = 60.0 mA, 45 min (1.7 F mol^{-1} **TT**); then i-Pr_2NEt (3.2 mmol), amine (0.4 mmol), 3 h. Limiting alkene reactions were conducted using alkene (0.4 mmol), **TT** (0.6 mmol), 8 mL MeCN (0.2 M n-Bu4NPF_6), I = 12.0 mA, 2.2 h (2.5 F mol^{-1} alkene); then i-Pr_2NEt (2.8 mmol), amine (0.4 mmol), 16 h. Yields and Z:E ratios are of the purified product unless otherwise noted. See the SI for further details. [b]Isolated yield (Z:E). [c]NMR yield. [d]0.8 mmol amine.

like compounds as both alkene and amine coupling partners. Due to their structural complexity, these substrates each contain numerous functional groups expected to be labilities for typical oxidative allylic amination procedures. Lewis basic heterocycles, such as pyridine (**29**) and pyrazole (**30**) as well as oxidatively sensitive electron-rich aromatic systems (**31–33**),[25] each delivered the desired allylic amine products. Additionally, allylic amines could be obtained from substrates bearing a variety of saturated heterocycles, including piperidine (**29**), morpholine (**30**), homopiperazine (**34**), and piperizine (**35**). Of note, the homopiperazine (**34**) and piperizine substrates (**35**), each contain a competent tertiary amine nucleophile yet produce the desired allylic amine products in synthetically useful yield. This chemoselectivity extended to other nucleophilic functional groups; unprotected alcohols and arylamines (**31**, **32**) did not compete with the secondary amine under these allylation conditions, leaving them as synthetic handles for further functionalization. An array of different aryl halides were well tolerated, including both medicinally relevant fluorinated groups (**30**, **33**, **35**) as well as aryl bromides (**32**) and chlorides (**29**) that readily participate in cross-coupling reactions.

Next, we aimed to provide some preliminary mechanistic insight into this new process. Monitoring the transformation of dicationic adducts to allylic amine over time revealed that the adducts are rapidly consumed and a vinylthianthrenium salt is generated. Given the basic conditions, we suspected that the vinylthianthrenium salt was likely a key intermediate en route to the observed allylic amine product rather than an off-cycle reservoir. To probe this specific question, we directly prepared vinylthianthrenium salt **36** by base-induced elimination of the electrochemically generated dicationic adducts between 1-butene and thianthrene. We then subjected this isolated vinylthianthrenium **36** to otherwise standard substitution conditions (see SI for experimental details). Under these conditions, the allylic amine product **19** was formed in 75% yield and identical stereoselectivity to what is observed under standard conditions (Eq. 1). This is consistent with the vinyl thianthrenium salt serving as an on pathway intermediate. Based on these data, we have constructed a working mechanistic model wherein the vinylthianthrenium salt undergoes a base-induced isomerization to an allylic thianthrenium intermediate. This species is then rapidly trapped with the amine nucleophile. Indeed, there is a single report of vinylsulfonium salts being converted to allylic amines.[95] Studies are underway to clarify the mechanistic details of this reaction, particularly the stereodetermining step for the process. Beyond the mechanistic implications, however, these data also indicate that vinylthianthrenium salts prepared through chemical means[77] can be engaged as an electrophile for this transformation. We envision this may be valuable for practicing synthetic chemists in a small-scale research and development setting where electrochemistry offers a less significant advantage relative to more traditional synthetic tactics.



36
1:1 Z:E

19: 75% yield
10:1 Z:E

(1)

Overall, we developed an electrochemical synthesis of allylic amines from terminal alk enes and secondary amines. This represents the first example of a formal C–H functionalization approach to furnish tertiary aliphatic allylic amines as well as the first example of a strategy for Z-selective oxidative allylic C–H functionalization. This linear-selective process exhibits good functional group tolerance and is attractive for substrates ranging from feedstock gas functionalization to derivatization of complex molecules. Furthermore, the conditions are operationally simple; no precautions to exclude air or moisture are necessary. Preliminary mechanistic studies indicate that vinylthianthrenium salts are key intermediates. We anticipate that this new electrochemical transformation will find immediate application in organic synthesis given the established synthetic utility of allylic amine building blocks. Moreover, we anticipate that the results reported herein set the stage for the development of a wide range of Z-selective allylic functionalization reactions that remain challenging to accomplish via more conventional approaches.

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures, characterization data, and spectra (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank Prof. Mark Levin for helpful discussions regarding this manuscript. We thank the Weix, Stahl, Yoon and Schomaker groups for sharing their chemical inventories. In addition, we would like to thank Sam Gellman and the entire Gellman group for hosting the authors of this work during a temporary closure of our labs. Along this line, we also thank the staff of the Paul Bender Chemistry Instrumentation Center for enabling NMR and MS sample analysis during building construction. B. J. Thompson is acknowledged for his assistance with the design and fabrication of the power supply. T. Drier is acknowledged for the fabrication of electrochemical glassware. We also acknowledge support and suggestions from all members of the Wickens group throughout the investigation of this project. This work was financially supported by the Office of the Vice Chancellor for Research and Graduate Education at the University of Wisconsin-Madison, with funding from the Wisconsin Alumni Research Foundation. This material is based upon work supported by the National Science Foundation Graduate Research Fellowship Program under Grant No. DGE-1747503 (K.T.). Any opinions, findings, and conclusions or recommendations expressed in this material are those of the author(s) and do not necessarily reflect the views of the National Science Foundation. Spectroscopic instrumentation was supported by a generous gift from Paul J. and Margaret M. Bender, the National Science Foundation (CHE-1048642), and the National Institutes of Health (S10OD012245 and 1S10OD020022-1).

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