Mechanism of *Z*-Selective Allylic Functionalization *via* Thianthrenium Salts

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ABSTRACT: A detailed mechanistic study of the *Z*-selective allylic functionalization *via* thianthrenium salts is presented. We have leveraged kinetic analysis and deuterium labeling to concretely determine each of the elementary steps involved and used computational methods to establish a high-resolution mechanistic model to rationalize the observed reactivity and selectivity. We find that the reaction proceeds *via* a rate- and stereodetermining allylic deprotonation of an alkenylthianthrenium species. The *Z*-configuration of the resultant allylic ylide is translated into the final *Z*-allylic amine product through a sequence of subsequent fast and irreversible steps: protonation to form a *Z*-allylic thianthrenium electrophile followed by regioselective substitution by the nucleophile. In the stereodetermining deprotonation step, computational studies have identified a series of stabilizing non-bonding interactions in the *Z*-alkene forming transition state that contribute to the observed stereoselectivity.

Stereoselective methods to make alkenes have proven to be valuable tools for the synthesis of complex molecules.[1,2] However, established approaches to prepare alkenes are skewed towards *E*-selective methods and preparation of *Z*-alkenes remains generally more challenging. Indeed, *Z*-alkenes cannot be generated selectively *via* thermodynamically-controlled processes since the *E*-stereoisomer is often more thermodynamically favorable due to minimization of steric interactions.[3] This restriction can be circumvented by kinetically-controlled processes, but successful approaches must either offset the energetic penalty from 1,3-allylic strain in the *Z*-alkene-forming transition structure or introduce new impediments to the *E*-alkene-forming pathway.[4] While several *Z*-selective methods to prepare alkenes have been established (*e.g.* Wittig olefination and semi-hydrogenation), the development of new protocols to access *Z*-alkenes remains an area of considerable contemporary interest.[5–8] As new distinct approaches to synthesize *Z*-alkenes continue to emerge, elucidating the origin of stereocontrol in these processes is of significant importance.[9–14] In addition to establishing a fundamental mechanistic understanding of these new transformations, identification of the factors that control reactivity and selectivity in these reactions can, in turn, provide a blueprint for rational improvements to reaction conditions.[15,16]

Recently, independent reports from our group alongside Shu and co-workers introduced a new class of transformations to prepare an array of *Z*-alkene products (Figure 1).[17,18] In these methods, alkenes are first transformed into thianthrenium electrophiles[19–21] which are then treated with base and a nucleophile to furnish allylic functionalized products with exquisite regioselectivity and surprising *Z*-selectivity. More recently, Soós and Varga cleverly exploited this allylic functionalization reactivity to introduce a new method to prepare *Z*-enals in the context of natural product synthesis.[22,23] Taken together, these advances suggest this new reactivity manifold will ultimately lead to a general platform for formal *Z*-selective allylic C(sp^3)–H functionalization. However, the mechanism of this process remains unknown. Confoundingly, the minimal mechanistic data presented to date are consistent with multiple mechanisms because the focus of the experiments has been establishing kinetic competence of thianthrenium species that could potentially interconvert. Consequently, the elementary steps of the reaction remain opaque which precludes the elucidation of the origin of stereocontrol.[24,25] Overall, we posit that constructing a detailed mechanistic model for this transformation will be a requisite step to translate the reactivity into a broadly-applicable strategy in *Z*-alkene synthesis.

Herein, we present an experimental and computational mechanistic investigation that uncovers the elementary

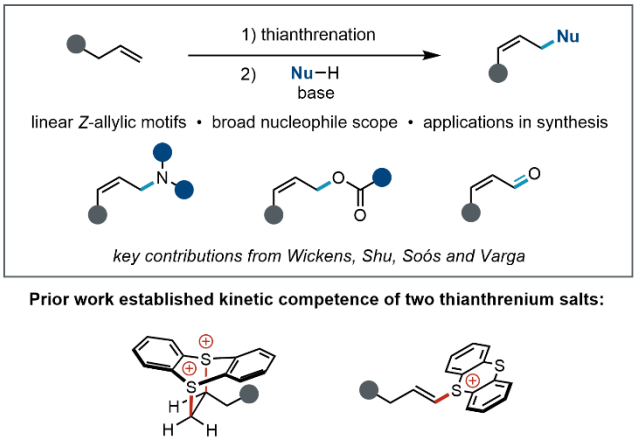


Figure 1. *Z*-Selective allylic functionalization from thianthrenium salts.

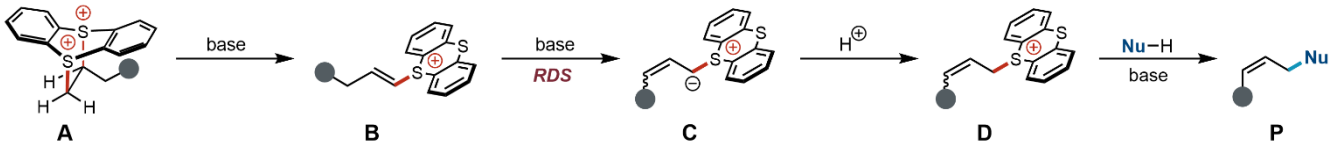


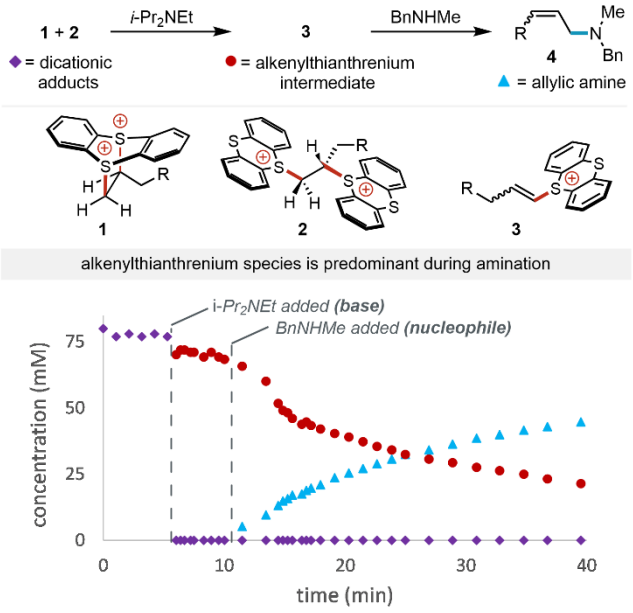
Figure 2. Overview of the experimentally determined elementary steps involved in the transformation of thianthrenium salts into *Z*-allylic products.

steps involved in transforming thianthrenium salts into allylic amine products using amine nucleophiles. A complete mechanism that is consistent with these new experimental and computational findings (*vide infra*) is presented in Figure 2. The reaction proceeds through an isolable alkenylthianthrenium intermediate **B** that is generated upon base-induced elimination of dicationic adduct **A**.[17,20,26–28] Next, **B** undergoes an allylic transposition to allylic thianthrenium electrophile **D** *via* rate determining formation of allylic ylide **C**. These steps are rendered irreversible through rapid and exergonic substitution of **D** by the nucleophile to afford the final linear *Z*-allylic product (**P**). Below, we will delineate the experimental and computational data that lead to the conclusion of these outlined elementary steps.

Since both dicationic adducts and alkenylthianthrenium salts have been established as kinetically competent for allylic functionalization,[17,18] our first task was to determine which thianthrenium species to employ for our subsequent mechanistic studies. To this end, we electrochemically-generated a pool of metastable dicationic adducts **1** and **2** using 4-phenyl-1-butene and thianthrene (Scheme 1). Upon treatment with base in the absence of amine nucleophile, we observed rapid and quantitative elimination of dicationic adducts **1** and **2** to a solution-stable alkenylthianthrenium intermediate **3**.[29] Upon subsequent addition of *N*-methylbenzylamine nucleophile, we observed that the conversion of **3** corresponded to the formation of allylic amine product **4**. Furthermore, alkenylthianthrenium salt **3** was the only thianthrenium species detected by ^{1}H NMR spectroscopy during the allylic amination reaction. No detectable steady-state concentration of other thianthrenium species was observed (*e.g.* dicationic adduct **A** or allylic thianthrenium salt **D**). Crucially, however, these data do not exclude that transient thianthrenium electrophiles may be generated during allylic amination. These observations are consistent with the alkenylthianthrenium salt being a convergent intermediate as proposed in previous mechanistic hypotheses.[17,18] With these initial mechanistic insights, we opted to skip the highly exothermic elimination step (ΔH = –27.0 kcal/mol; see Fig. S76) of dicationic precursors to simplify the reaction conditions.[30,31] Thus, we conducted our experimental investigations using bench-stable alkenylthianthrenium salt **3** to streamline subsequent mechanism analyses (Scheme 2).

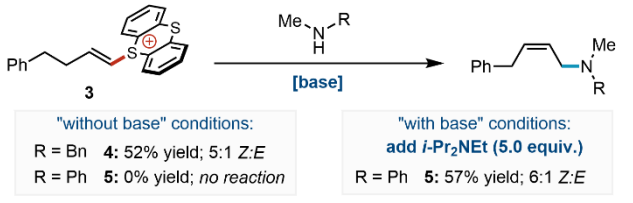
We next set out to identify the model amine nucleophile that would enable the clearest mechanistic analysis. We recognized that a secondary aliphatic amine, employed in our initial disclosure of this reactivity, could complicate kinetic analysis by serving as not only the nucleophile but also the base.[32] Indeed, when alkenylthianthrenium salt **3** was treated with *N*-methylbenzylamine in the absence of exogenous base, we observed allylic amine product **4** in 52% yield and 5:1 *Z:E* (Scheme 2). We hypothesized that an arylamine would be an insufficient base for the reaction, deconvoluting the kinetic analysis with respect to the amine

Scheme 1. Monitoring speciation of thianthrenium salts.[a]



[a]Electrogenerated adducts were prepared using 4-phenyl-1-butene (0.2 mmol), thianthrene (0.3 mmol), 2 mL MeCN-d_3 (0.4 M KPF_6), I = 6.0 mA, 2.2 h (2.5 F mol^{-1} alkene); then *i*-Pr_2NEt (1.6 mmol); then amine (0.3 mmol). CH_2Br_2 was used as an internal standard. R = Bn. See SI for details.

Scheme 2. Model amine selection for mechanistic studies of *Z*-selective allylic amine synthesis from thianthrenium salts.[a,b]



[a]Reactions conducted using alkenylthianthrenium salt (0.05 mmol), nucleophile (0.05 mmol), 0.5 mL MeCN, 6 h. [b]yields and *Z:E* determined by ^{1}H-NMR.

nucleophile. To test this hypothesis, we treated **3** with *N*-methylaniline, with and without amine base (*i*-Pr_2NEt).[17] These experiments revealed that in the absence of exogenous base, no conversion of **3** was observed. However, in the presence of *i*-Pr_2NEt base, we obtained a 57% yield of the desired product, **5**, with 6:1 *Z:E* selectivity (Scheme 2). Taken together, these results indicate that aniline acts only as a nucleophile in this process. Overall, we identified the simplest components necessary for a mechanistic study of the reaction: alkenylthianthrenium salt, *N*-methylaniline nucleophile,[33] and base (*i*-Pr_2NEt).[34]

With a model reaction in hand, we set out to elucidate the elementary steps of the amination reaction using kinetic experiments. We found zero-order dependence of the initial reaction rate on the concentration of the *N*-methylaniline nucleophile (Figure 3A). Thus, we conclude that the rate-determining step occurs prior to nucleophilic substitution.

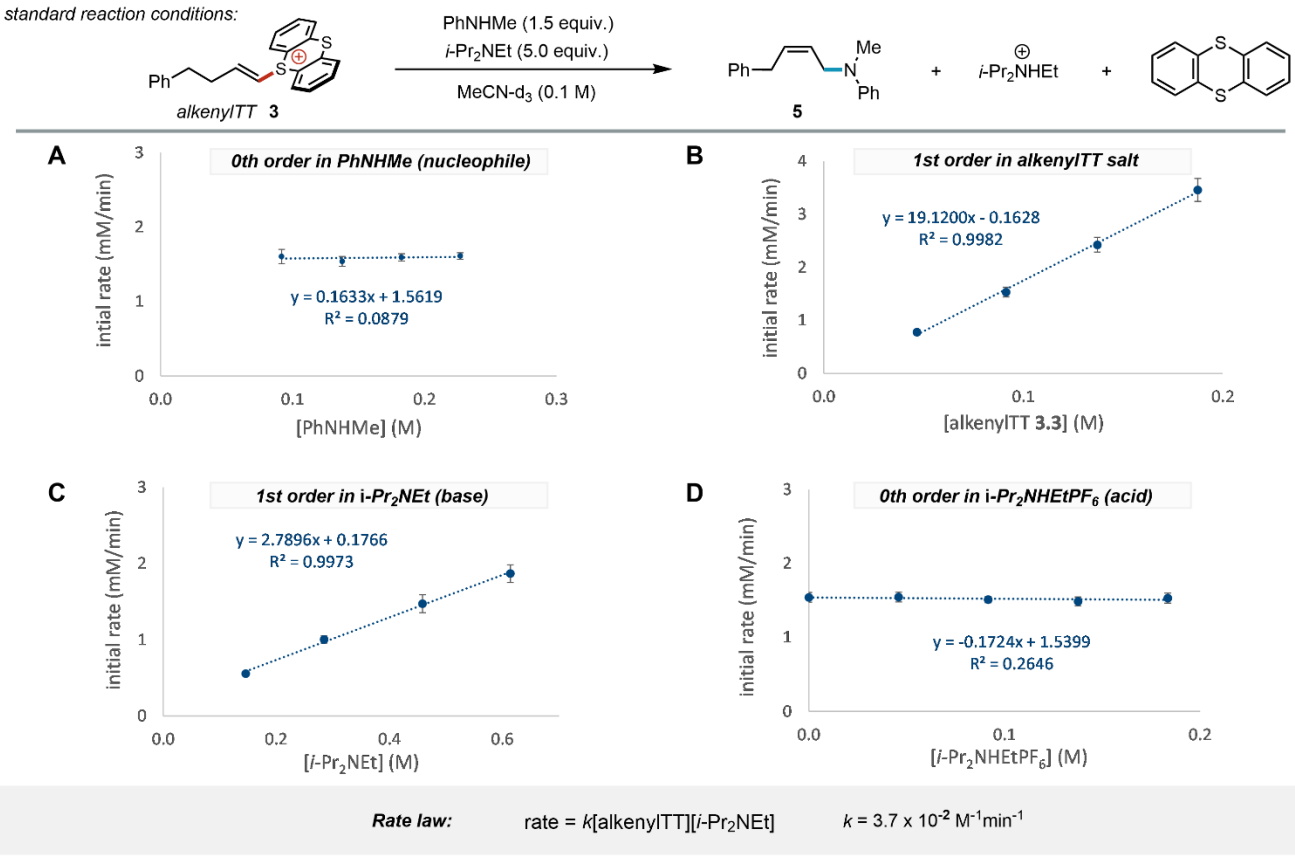
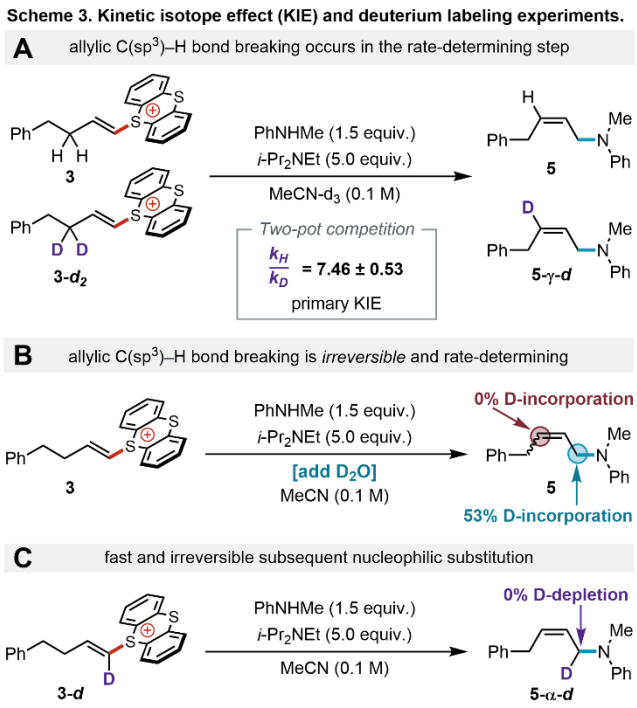


Figure 3. Reaction kinetics for amination of alkenylthianthrenium salt and summary of rate law. (A) 0th order in aniline nucleophile, (B) 1st order in alkenythianthrenium salt, (C) 1st order in trialkylamine base, (D) 0th order in conjugate acid of amine base. See SI for experimental details.

Next, kinetic experiments revealed a first-order dependence on the alkenylthianthrenium salt **3** (Figure 3B) as well as a first-order dependence on trialkylamine base (*i*-Pr_2NEt) (Figure 3C). These data are consistent with rate-determining allylic deprotonation of the alkenylthianthrenium salt. Lastly, we questioned if the conjugate acid of *i*-Pr_2NEt, which is formed throughout the reaction, plays any kinetic role through protonation of a thianthrenium ylide intermediate. Thianthrenium ylides have been postulated as key intermediates in both the mechanistic model presented herein as well as those previously suggested in the literature. When varying the concentration of exogenous *i*-$Pr_2NHEtPF_6$, we observed no impact on the initial rate of allylic amine **5** formation (Figure 3D). These observations are inconsistent with previously proposed mechanisms in which a dicationic adduct is transiently formed from alkenylthianthrenium salts followed by nucleophilic substitution or elimination.[35] The kinetic analyses afford an experimental rate constant of 3.7±0.8 x 10^{-2} $M^{-1}min^{-1}$ for this reaction (see Table S13). Overall, these data support deprotonation of the alkenylthianthrenium species being involved in the rate-determining step and exclude an array of alternative scenarios (see SI for details).

Next, we conducted deuterium labeling experiments to support the rate-determining allylic deprotonation of the alkenylthianthrenium species by the base. As expected, a primary kinetic isotope effect (KIE) of 7.46±0.53 was observed in a two-pot competition experiment between **3** and **3-*d*$_2$** (Scheme 3A). This large primary KIE was consistent with the KIE of 7.31±1.26 obtained in a one-pot competition experiment (Table S18). These results support that allylic C(sp^3)–H/D bond breaking is involved in the rate-determining step for the transformation of alkenylthianthrenium salts into allylic functionalized products.[36] These KIEs combined with reactant orders are inconsistent with rate-determining conjugate-addition-type mechanisms, which have been observed with alkenylthianthrenium salts in other synthetic context (see SI).[37,38] To probe the irreversibility of

Scheme 3. Kinetic isotope effect (KIE) and deuterium labeling experiments.



this key allylic deprotonation step, the reaction was conducted with an excess of deuterium oxide as a deuterium source (Scheme 3B).[39,40] We reasoned that an irreversible allylic deprotonation would give no deuterium incorporation into the corresponding alkenyl position of the allylic amine product. Experimentally, no deuterium was detected in the site of initial C(sp^3)–H bond breaking, consistent with the allylic deprotonation being irreversible in the presence of a nucleophile (Scheme 3B). Furthermore, this result is inconsistent with a Curtin-Hammett scenario involving rapid and reversible isomerization between the alkenylthianthrenium salt and an allylic thianthrenium tautomer.[41]

Having identified the rate-determining step, we next probed each subsequent elementary step to establish a complete mechanistic picture. First, to validate the formation of the ylide **D** intermediate, we examined the allylic amine product formed with the addition of deuterium oxide to the reaction conditions. The site that corresponds to the proposed allylic thianthrenium ylide intermediate exhibited 53% deuterium incorporation (Scheme 3B).[42] This *ca.* 50% value corresponds to incorporation of a single deuteron and is consistent with irreversible ylide **C** protonation due to fast nucleophilic substitution of the resultant allylic thianthrenium electrophile **D**. To further support this proposal, we subjected α-deuterated alkenylthianthrenium salt **3-*d*** to the amination conditions (Scheme 3C). Allylic amine product **5-α-*d*** derived from deuterium-labeled alkenylthianthrenium salt **3-*d*** shows no deuterium depletion at the corresponding position. Taken together, these results are consistent with transient formation of a non-stabilized allylic thianthrenium salt[43] followed by rapid and irreversible trapping of this species by the amine nucleophile.

The elementary steps outlined thus far in this mechanistic study invoke the substitution of an allylic thianthrenium electrophile despite no observation of branched allylic amines that are common side products for allylic halide substitution reactions.[44,45] Notably, transformation of thianthrenium salts under these conditions is consistently regioselective for linear products, with only isolated exceptions with thianthrenium salts derived from sterically hindered alkene precursors.[46] To evaluate whether substitution behavior of the proposed allylic thianthrenium species is consistent with these observations,[47] we conducted dispersion-corrected density functional theory (DFT) calculations. These calculations indicated that the *Z*-allylic electrophile undergoes substitution with high regioselectivity for

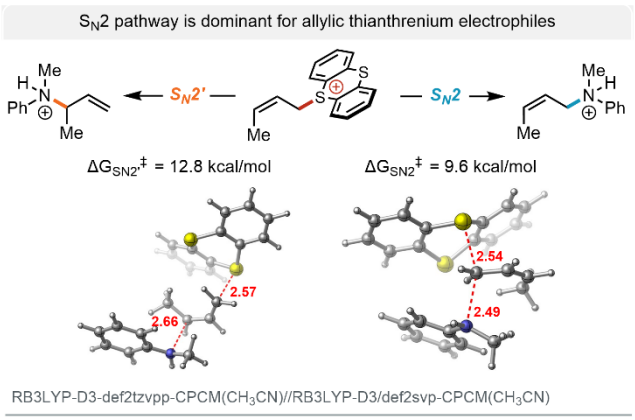


Figure 4. Computations to probe the nucleophilic substitution of postulated allylic thianthrenium intermediate.

S_N2 over S_N2' (Figure 4, $\Delta\Delta G^‡$ = 3.2 kcal/mol).[48,49] These computational data are consistent with the experimental observations and, accordingly, support the intermediacy of an allylic thianthrenium intermediate.

With a complete sequence of elementary steps established,[50] we wanted to build and validate a computational model of the process with the ultimate goal of identifying the stereodetermining step. Our computational studies predict that the allylic deprotonation has the highest energetic barrier, consistent with experimental data that assign this as the rate-determining step (Figure 5). After deprotonation, the subsequent elementary steps are each downhill in energy and ultimately rendered irreversible by highly exergonic nucleophilic displacement of the allylic thianthrenium intermediate. Notably, consistent with experimental observations, these calculations indicate that the deprotonation to form the allylic thianthrenium ylide occurs with *Z*-selectivity ($\Delta\Delta G^‡$ = 2.3 kcal/mol, see SI for details). While the computational model appears to identify ylide formation as stereodetermining, we recognized that this would be an unusual scenario because it requires that the allylic anion is configurationally stable. However, in stark contrast to the low rotational barriers of simpler allylic anions, our calculations predict an unsurmountable barrier (~56 kcal/mol, Fig. 5 inset) for *Z/E*-isomerization of the allylic thianthrenium ylides. This high rotational barrier precludes isomerization between **C_Z** and **C_E** at room temperature (Figure 5). The origin of this high barrier is the direct consequence of localized alkene and ylide character as opposed to the anion being fully delocalized through the π-system (see Fig. S71). Overall, these data indicate that allylic deprotonation of the alkenylthianthrenium species sets the stereochemistry of the final allylic functionalized product. This stereodetermining step is a rare example of *Z*-selective deprotonation that enables *Z*-alkene synthesis.

To establish the origin of *Z*-selectivity, we next took a closer look at the stereodetermining allylic deprotonation step (*i.e.* formation of **C_Z** and **C_E** intermediates). Given that the key deprotonation step is highly endergonic (~15 kcal/mol uphill in energy), we reasoned that, according to Hammond's postulate, the energy of the late transition state would be controlled more by the factors influencing the allylic ylide stability than the alkenylthianthrenium starting material. As shown in Figure 5, calculations show a slight preference for the *Z*-isomer (~0.4 kcal/mol) of the allylic thianthrenium ylide in comparison to the *E*-allylic ylide.[51] This energetic preference for the *Z*-isomer reflects the conformational preference of simpler, freely-rotating allylic anions, which have an established preference for the *Z*-conformation.[52–57] Previous studies into allylic anion systems have put forward various explanations for this preference based on either electrostatic considerations[58] or non-bonding interactions,[59–62] although other possibilities have not been ruled out.[63] Regarding the formation of allylic thianthrenium ylides, natural bond orbital (NBO) analysis of the competing allylic deprotonation transition states (**TS1_E** and **TS1_Z**) revealed that the *Z*-forming transition state has more overall stabilizing interactions than the *E*-forming transition state (see Fig. S75). Specifically, we identified several C–H σ to C–C σ* or C–C π* non-bonding interactions that are present only in the transition structure that

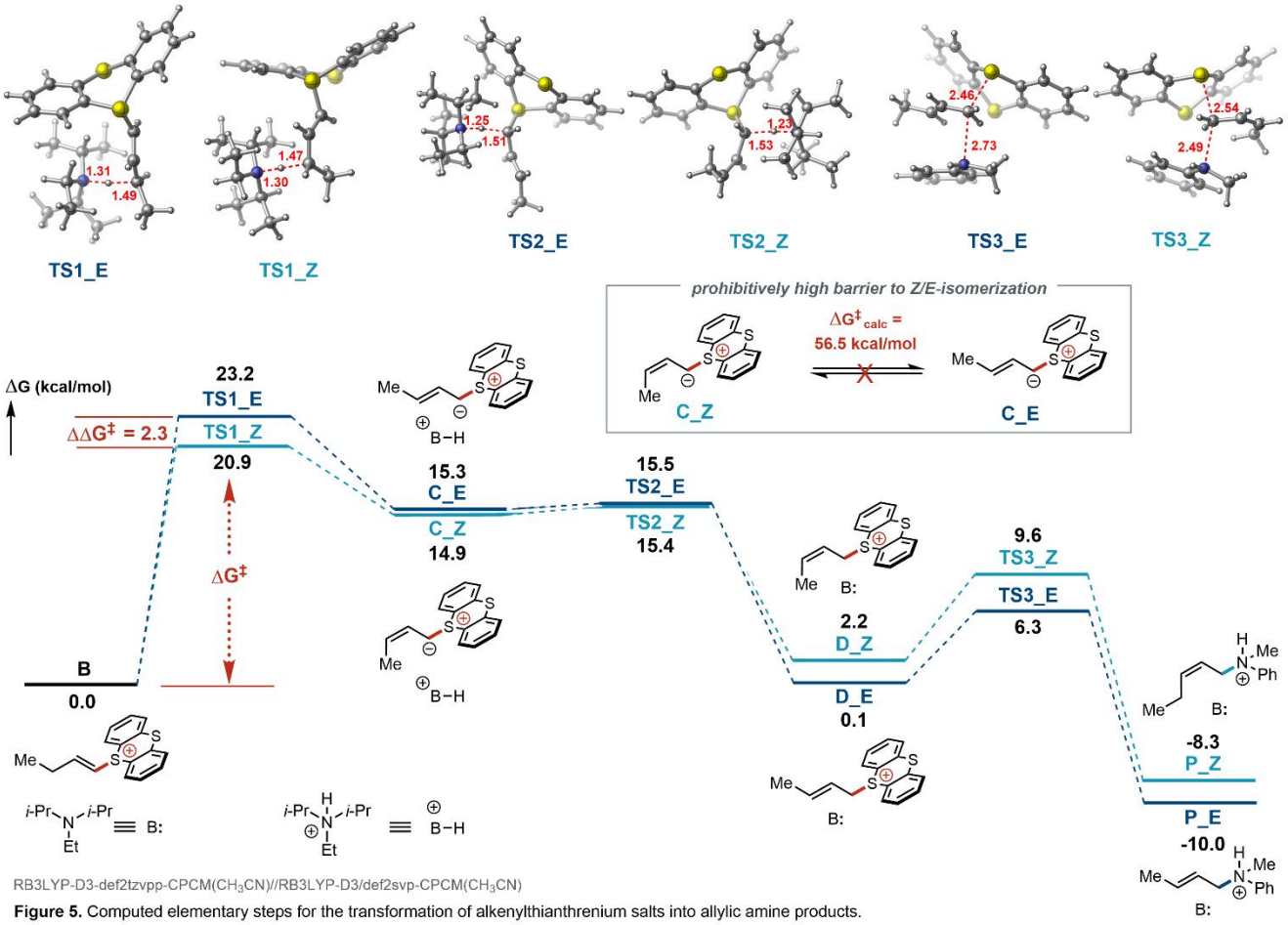


Figure 5. Computed elementary steps for the transformation of alkenylthianthrenium salts into allylic amine products.

leads to the *Z*-allylic ylide. Furthermore, the resultant *Z*-allylic ylide product still possesses the majority of these NBO interactions. This suggests that the kinetic selectivity for *Z*-allylic ylide formation is tied to the factors that influence stability of the *Z*-allylic thianthrenium ylide.

In conclusion, we have outlined a detailed mechanistic model of the *Z*-selective allylic functionalization in the context of amine nucleophiles and thianthrenium salts derived from aliphatic alkenes. For the first time, the elementary steps of this reaction and the corresponding energetic landscape have been elucidated. Upon rate- and stereodetermining allylic deprotonation of the alkenylthianthrenium salt, a *Z*-allylic thianthrenium ylide is generated. In contrast to all-carbon allylic anions, the allylic thianthrenium ylide stereochemistry is locked by a prohibitively high barrier for C–C double bond rotation. Protonation of the *Z*-allylic thianthrenium ylide affords an allylic thianthrenium electrophile that is regioselectively substituted by a nucleophile. We anticipate these findings can lead to design of allylation methodologies that improve the selectivity for other alkenes and nucleophile classes. More broadly, this study uncovered a new mechanism to enforce *Z*-selectivity in alkene synthesis that relies on key stabilizing interactions rather than steric clashes.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, supporting characterization data and spectra, computational procedures and coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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(29) These results are consistent with qualitative observations in our previous work wherein we isolated and re-subjected the alkenylthianthrenium species to support its kinetic competence.

(30) For example, we recognized that one-pot allylic functionalization from dicationic adducts would result in inaccurate quantification of base concentration necessary for kinetic analyses. See ref. 31.

(31) Kim, M. J.; Wang, D. J.; Targos, K.; Garcia, U. A.; Harris, A. F.; Guzei, I. A.; Wickens, Z. K. Diastereoselective Synthesis of Cyclopropanes from Carbon Pronucleophiles and Alkenes. *Angew. Chem. Int. Ed.* **2023**, *62* (21), e202303032.

(32) We found that the initial rate of the reaction exhibited a first-order dependence on the secondary amine concentration (see Fig. S15).

(33) Allylic amination with PhNHMe and 4-Ph-1-butene-derived alkenylTT salt also enables in situ monitoring of *Z:E* ratios.

(34) In addition to *i*-Pr_2NEt being a suitable homogeneous base for monitoring in situ reaction kinetics, our group and others have observed superior *Z*-selectivity with trialkylamine bases than with heterogeneous bases such as carbonate.

(35) Consistent with our prior work, we observe rapid and quantitative elimination of dicationic adducts to alkenylthianthrenium salt. The rate of elimination is significantly faster than that of allylic amination.

(36) Simmons, E. M.; Hartwig, J. F. On the Interpretation of Deuterium Kinetic Isotope Effects in C□H Bond Functionalizations by Transition-Metal Complexes. *Angew. Chem. Int. Ed.* **2012**, *51* (13), 3066–3072.

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(39) We expect exchange between deuterium from D_2O and the conjugate acid of the amine base would be rapid where complete scrambling is to be observed. Under these conditions, deuteration of anionic intermediates should be feasible.

(40) Perrin, C. L.; Dwyer, T. J.; Baine, P. Two-Dimensional NMR Exchange Spectroscopy Study of Proton Exchange in Aqueous Ammonium Ion: H/D Primary Kinetic Isotope Effect for Direct Nitrogen-to-Nitrogen Proton Transfer. *J. Am. Chem. Soc.* **1994**, *116* (9), 4044–4049.

(41) Our data are inconsistent with a plausible Curtin-Hammett explanation for the origin of *Z*-selectivity recently suggested by Soós and coworkers. See ref. 23.

(42) Deuterium incorporation is close to 50% for *Z*-isomer of the allylic product. Curiously, lesser %D-incorporation was observed for the *E*-isomer product. We tentatively attribute this discrepancy to contributions from molecular dynamics. See Fig. S42 and S77 for details.

(43) Stabilized allylic sulfonium and thianthrenium salts have been made but not with *Z*-stereochemistry. We suspect that non-stablized aliphatic allylic thianthrenium species are too reactive electrophiles to be isolated under the basic conditions used for their generation.

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(45) Hansen, T.; Vermeeren, P.; de Jong, L.; Bickelhaupt, F. M.; Hamlin, T. A. SN2 versus SN2′ Competition. *J. Org. Chem.* **2022**, *87* (14), 8892–8901.

(46) For regioselectivity with sterically hindered alkenylthianthrenium salts, see ref. 23.

(47) To probe the formation of a transient allylic thianthrenium electrophile, we aimed to alter the energentic landscape of allylic amination by using a bulky trialkylamine base as the nucleophile. In situ monitoring under these modified conditions revealed a new allylic intermediate during the allylic amination. We postulate the identity of this transient intermediate as the allylic thianthrenium tautomer (see Fig. S53 for details), consistent with the mechanism put forward.

(48) A similar energy difference was observed between the S_N2 and S_N2' transition states leading to the *E*-allylic product (See Fig. S74).

(49) We reasoned that the nucleophilic substitution is stereoretentive in the pathways calculated given they are stereoretentive in allylic substitution with other allylic electrophiles. See refs. 44 and 45.

(50) We considered a diverse array of possible alternative mechanisms, including each of those previously proposed in literature. None of the other mechanisms are consistent with new experimental details disclosed in this study. See SI for details.

(51) This is counter to the well-established thermodynamic preference for the *E*-configuration of neutral alkenes. Indeed, the alkenylthianthrenium starting material, allylic thianthrenium intermediate, and allylic products were more stable in the *E*-configuration.

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(63) For example, the energy difference may also involve changes in the relative contribution of allylic $A^{1,2}$ and $A^{1,3}$ strain (for a computational analysis, see Fig. S69).

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