Electrogenerated thianthrenium conjugate enables (Z)-selective allylic amination

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CellPress

Spotlight

Electrogenerated thianthrenium conjugate enables (*Z*)-selective allylic amination

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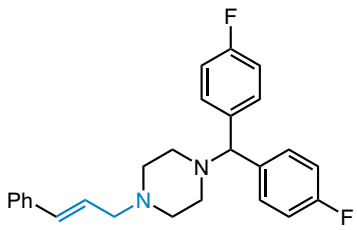
Developing straightforward methodologies to access allylic amines is of contemporary importance in drug development and natural product synthesis. Recently, Wickens *et al.* developed an electrochemical approach with thianthrene adducts as reactive functional intermediates to transform terminal olefins and secondary amines into tertiary allylic amines in high yields and distinct *Z*-selectivity.

Aliphatic allylic amines are found in several natural products and biologically active molecules and are prime building blocks when it comes to synthetic planning (Figure 1A). Therefore, developing efficient and robust amine allylation strategies is of high synthetic interest and has been the quest of several research groups over the past decades. It has been envisioned that a simple oxidative coupling between ubiquitous alkyl amines and alkenes would be an attractive counterpart to existing allylation pathways. However, the low oxidation potentials of both the alkyl amine coupling partner and the desired alkyl allylic amine product hampered the development of such methods. Alternatively, as exemplified in Figure 1B, transition metal catalyzed C–H functionalization procedures have flourished. Those transformations even require the use of oxidatively stable deactivated nitrogen pronucleophiles that can undergo intermolecular amination reactions (see Stahl example) [1] or nitrene precursors (see Dauban and White examples) [2,3]. While these reaction conditions allowed for a broad array of molecules to be synthesized, they do not readily afford the desired alkyl allyl amines but rather the corresponding carbamates or sulfonamides, respectively.

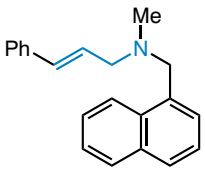
It was not until 2020, and a study published by the Ritter group, that the first allylic C–H amination reaction that directly furnished alkyl allyl amines was reported [4]. This breakthrough was enabled by the reaction of thianthrenylidene amines with alkenes under photoirradiation using an iridium sensitizer. Both terminal and internal olefins are tolerated under the reaction conditions and (*E*)-allylic amine products are selectively obtained. More recently, the Wickens group developed a complementary approach where an electrochemically generated electrophilic adduct reacted with aliphatic amine nucleophiles in the presence of base to provide (*Z*)-allylic amine products in excellent yields [5]. Interestingly, while both protocols clearly share common features, such as the use of thianthrene as starting material, they also differ in the way maneuvers are conducted. Under Ritter's conditions, the activated thianthrene reacts with the amine to form the thianthrenylidene intermediate, whereas Wickens' protocol is based on the formation of key dicationic adducts issued from the reaction between thianthrene and the olefin. Both protocols lead selectively to either the formation of the (*E*)- or the (*Z*)-allylic amine products. Finally, employing exclusively primary amines in Ritter's work and secondary amines in Wickens' work, respectively, adds another layer of complementarity to the described procedures. It is a remarkable feature that photochemical and electrochemical synthesis enables this complementarity, thus both rendering sustainable alternatives to conventional activation modes.

The reaction of thianthrenium cations with ubiquitous alkenes or alkynes to afford dicationic conjugates in a 1:1 or 2:1 stoichiometry was first described mechanistically in 1979 [6]. Thianthrene by itself is a readily available and biocompatible reagent [7] that can be recycled within the process, as previously described by the same research group [8]. However, it took several decades until synthetic organic chemists recognized the potential of this powerful redox reagent and decided to repurpose its use in recent methodology. In the study published by the Wickens group, the dicationic intermediates between thianthrene and alkenes reacted with secondary amines in the presence of a strong base, like di-*iso*-propyl ethylamine (DIPEA), delivering the desired tertiary allylic product in short reaction times. The protocol is highly selective towards the coupling of terminal olefins with secondary amines, as other unconjugated internal alkenes or alkynes are tolerated within the same substrates (Figure 2A). Also, gaseous alkenes like propene or butene smoothly undergo the adduct formation at ambient pressure (1 atm) and directly form allylic amines without further modifications. Other nucleophilic functional groups, such as amides, alcohols, anilines, or arylamines, are unreactive under these conditions and remain untouched for postfunctionalization, demonstrating the high selectivity of this protocol towards secondary amines. Complex drug molecules such as carvedilol or ambroxol were successfully coupled, highlighting the compatibility of the developed methodology in the context of late-stage derivatization of pharmacologically relevant targets. It is important to note that these reaction conditions feature a distinct *Z*-selectivity of the final allylic amine products (commonly 2:1 or 10:1). A key intermediate is the vinylthianthrenium (Figure 2B), which was also observed by the Ritter group [9] and can be readily generated from the dicationic adducts through elimination. No matter what initial *E*:*Z* ratio of the vinylthianthrenium intermediate was used, the product always yields high *Z*-selectivity (usually 10:1) of the final allylic amine. However, the nature of this selectivity remains elusive at this point. The treatment of the cationic

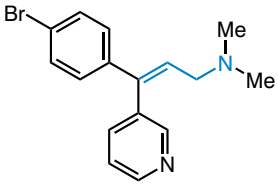
(A) Abundance of allylic amines in natural product and pharmaceutics



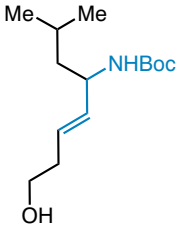
Flunarizine



Naftifine



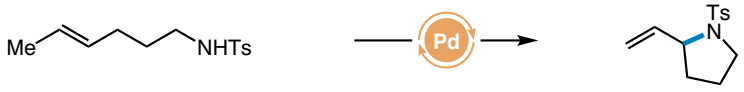
Zimelidine



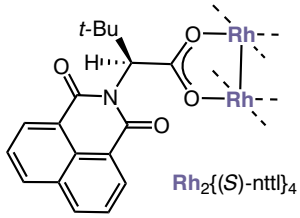
Gramicidin S intermediate

(B) Transition metal-based oxidative allylic amination methodologies

Stahl, **2002** - *Direct dioxygen-coupled palladium catalysis*

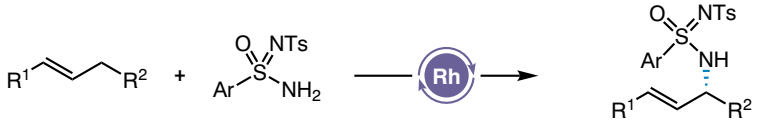


Simple catalytic system — Atom-economical alternative



$Rh_2\{(S)\text{-nttl}\}_4$

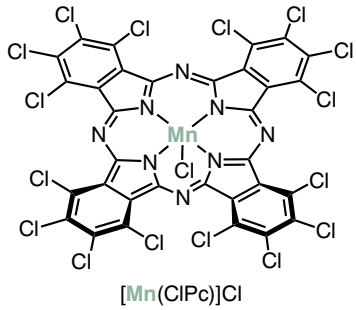
Dauban, **2008** - *Hypervalent iodine-mediated in situ generation of chiral nitrene*



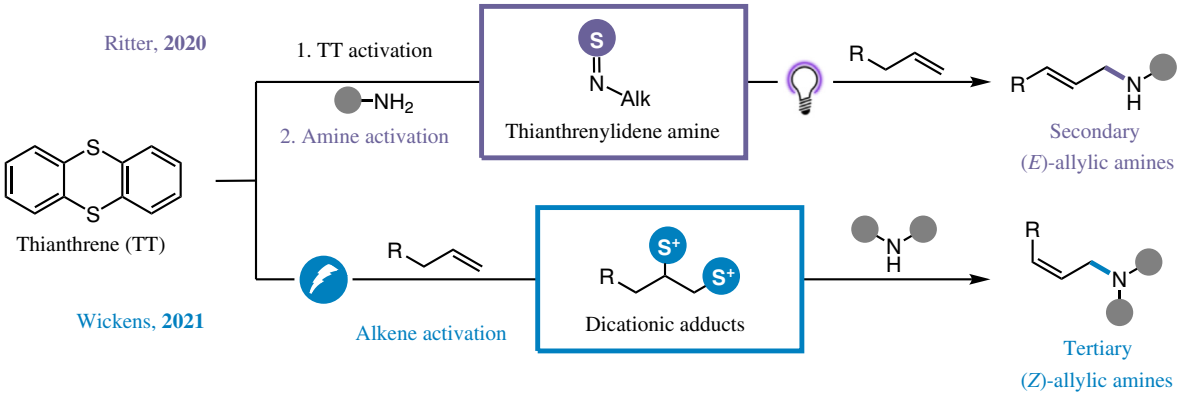
In-situ nitrene generation — Excellent stereoselectivities

White, **2021** - *Sustainable manganese perchlorophtalocyanine catalysis*

Excellent selectivities — Mechanistic understanding



(C) Direct access to allyl allylamines using photochemical and electrochemical complementary approaches



Alkylamines starting materials — Good functional group tolerance — Complementary (*E*) or (*Z*) selectivities

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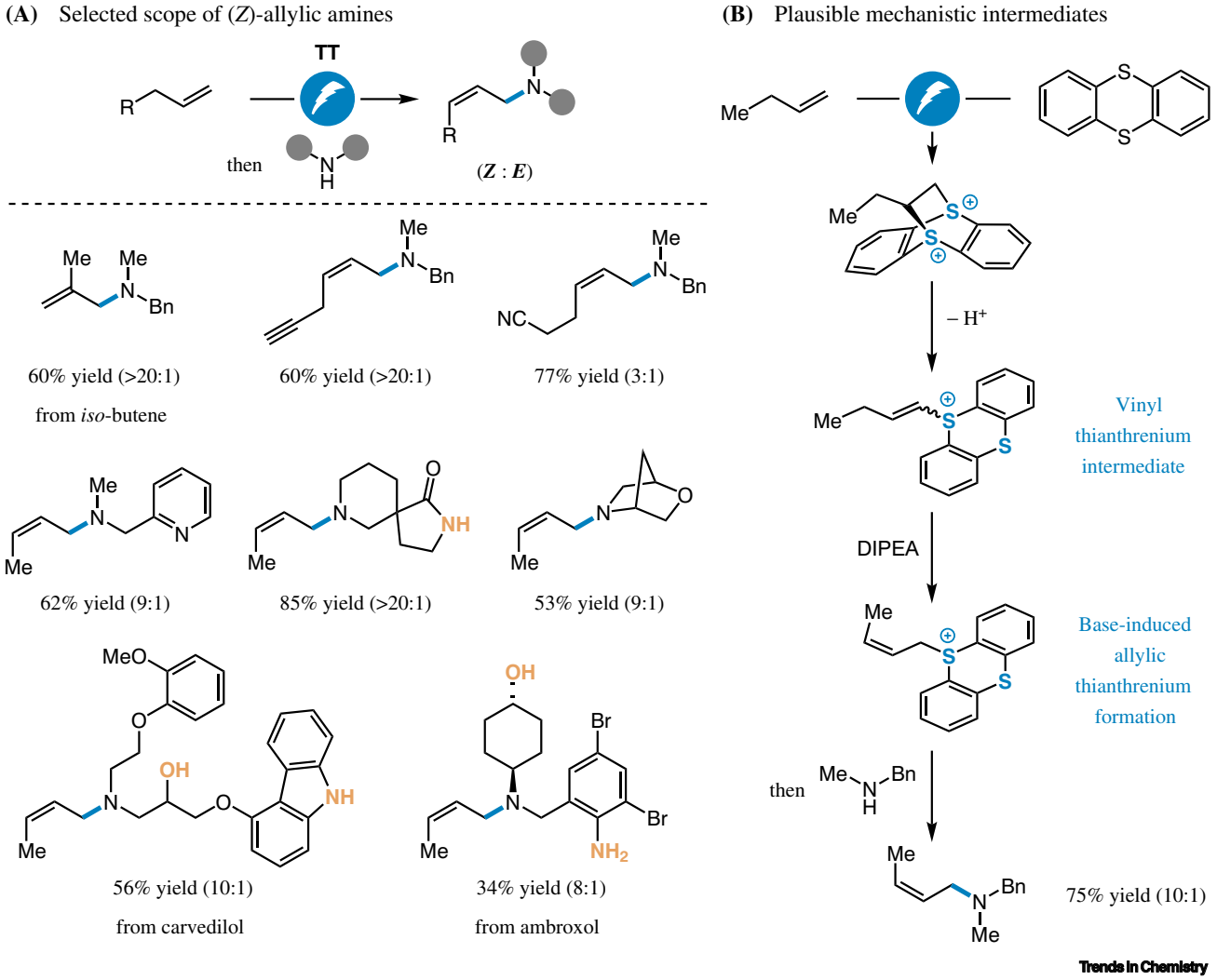

Figure 2. Selected scope of the thianthrenium-derived activation of terminal olefins and the synthesis of *Z*-allylic amines (A). Initial mechanistic proposal based on plausible reaction intermediates (B).

vinylthianthrenium species with base induces the isomerization towards the (*Z*)-allylic thianthrenium salt [10], allowing the trapping by the secondary amine, thus enabling the overall reaction towards the tertiary amine allylic product.

The work by Wickens and coworkers reinforces the synthetic utility of thianthrenium adducts as valuable building blocks and functional groups in organic chemistry. Either independently or merged with first-row transition metals catalysis, this motif will certainly allow for future breakthroughs in method developments where sensitive functional groups are introduced into more complex molecules.

Declaration of interests

No interests are declared.

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Figure 1. Allylic amines are privileged examples in drug molecules (A). Common strategies employ sophisticated transition-metal catalysis to obtain the allylic amine products (B). Recently, Ritter and Wickens developed complementary conditions to obtain (*E*)- and (*Z*)-allylic amines in great selectivity from either photochemical or electrochemical functionalization (C). See [4,5].

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