A TALE OF TWO STEREOISOMERS: THIANTHRENE-MEDIATED ALLYLIC AMINATION

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INTRODUCTION

Amines are among the most common functionalities found in bioactive compounds, ranging from complex natural products to various classes of drugs. In particular, allylic amines are a motif that has attracted much attention due to their presence in antifungals, antihistamines, and opioid receptor antagonists.[1] Traditional methods to afford allylic amines from pre-functionalized olefins include nucleophilic substitution, the Overman rearrangement, reductive amination, and the Tsuji-Trost reaction.[2] However, the necessity of these methods to pre-functionalize the olefin, usually at the allylic position, increases the amount of steps to access the amine and thus decreases the efficiency of a synthetic route.

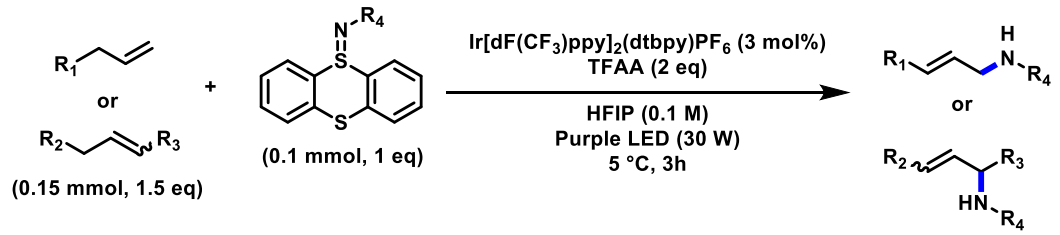
Several methods have been developed to directly aminate the allylic C-H bond. Sharpless and coworkers discovered a direct allylic C-H amination by using selenium diimide reagents in a manner akin to the Riley oxidation.[3] More recently, insertions of nitrenes into allylic C-H bonds have proven to be effective, especially in the late-stage functionalization of complex natural products.[4] Powerful methods to directly couple the wide libraries of commercially available olefins and amines have largely relied on transition metal catalysis, which, until recently, has historically suffered from the need to mitigate the reactivity of Lewis basic amines in order to prevent poisoning of the catalyst.[1] Therefore the development of alternative coupling methods that do not primarily rely on transition metals has been attractive, resulting in the utilization of thianthrene, an inexpensive and safe reagent, to mediate allylic aminations.

E-SELECTIVE ALLYLIC AMINATION

Ritter and coworkers developed an allylic amination strategy that leverages iminothianthrenes, olefins, an iridium photocatalyst, light (400 nm), and acidic conditions to afford secondary allylic amines with predominantly *E* stereoselectivity (**Scheme 1**).[5] This method chemoselectively involves allylic amination at the most electron rich olefin and broad functional group tolerance. However, free amino acids, allylic alcohols, electron poor olefins, and conjugated olefins are notably unreactive in this method.

Mechanistic studies demonstrated that the photocatalyst is likely not participating in any redox processes. Instead, the photocatalyst serves as an energy transfer catalyst, quenched by the iminothianthrene species in order to liberate a nitrogen-centered radical that can add into the olefin's pi system and ultimately yield the *E* allylic amine. While this method can leverage both internal and terminal olefins as coupling partner without any pre-functionalization, this reaction is notably air sensitive and still requires the synthesis of the iminothianthrene precursor before conducting the actual allylic amination.

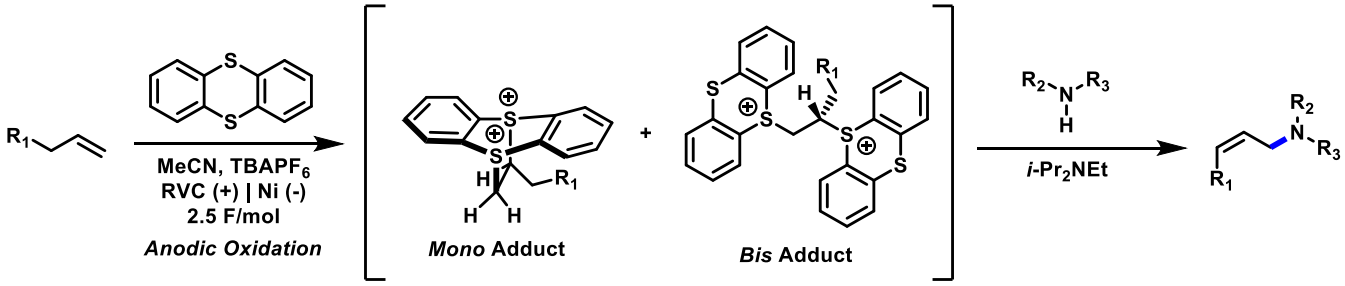
Scheme 1. Photochemical *E*-Selective Allylic Amination



Z-SELECTIVE ALLYLIC AMINATION

While developing an electrochemical method to form *N*-alkyl aziridines, Wickens and coworkers discovered that anodic oxidation of thianthrene in the presence of an olefin will form dicationic adducts (**Scheme 2**).[6] Treatment of these adducts with secondary amines allows for the formation of tertiary allylic amines with *Z* stereoselectivity via a vinyl thianthrenium intermediate.[6] This method complements Ritter's method in accessing the opposite stereoselectivity and being mediated by thianthrene. Like most olefin-amine couplings to afford allylic amines, this method suffers from a lack of applicability to internal olefins.

Scheme 2. Electrochemical *Z*-Selective Allylic Amination



CONCLUSION AND FUTURE DIRECTIONS

These complementary thianthrene-based methods can synergize with recent developments in electrophilic metal catalyzed amine-olefin couplings, which feature *E*-selectivity in forming tertiary allylic amines.[1] In spite of these advances, further improvements remain to be seen in increasing the stereoselectivity, potentially achieving stereospecificity, and applying thianthrene mediation to the allylic functionalization of other groups.

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