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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.0c06997 • Publication Date (Web): 10 Sep 2020

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Catalytic Metal-free Allylic C-H Amination of Terpenoids

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ABSTRACT The selective replacement of C–H bonds in complex molecules, especially natural products like terpenoids, is a highly efficient way to introduce new functionality and/or couple fragments. Here, we report the development of a new metal-free allylic amination of alkenes that allows the introduction of a wide range of nitrogen functionality at the allylic position of alkenes with unique regioselectivity and no allylic transposition. This reaction employs catalytic amounts of selenium in the form of phosphine selenides or selenoureas. Simple sulfonamides and sulfamates can be used directly in the reaction without the need to prepare isolated nitrenoid precursors. We demonstrate the utility of this transformation by aminating a large set of terpenoids in high yield and regioselectivity.

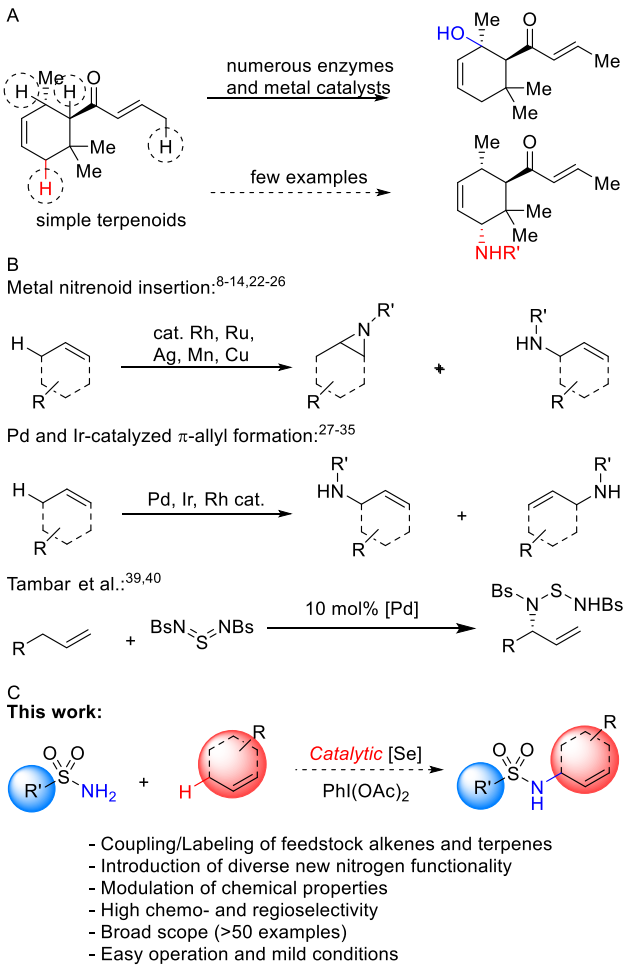
INTRODUCTION

The selective replacement of C–H bonds in complex organic molecules is a powerful tool for the efficient construction of new molecular species. As such, this important problem has received significant attention over the last century, resulting in many new methods for the formation of new C–O, C–N, and C–C bonds.[1-6] Considering the well-documented importance of nitrogen in biologically active compounds, the formation of new C–N bonds via C–H amination reactions is a particularly promising application of this technology.[7-14]

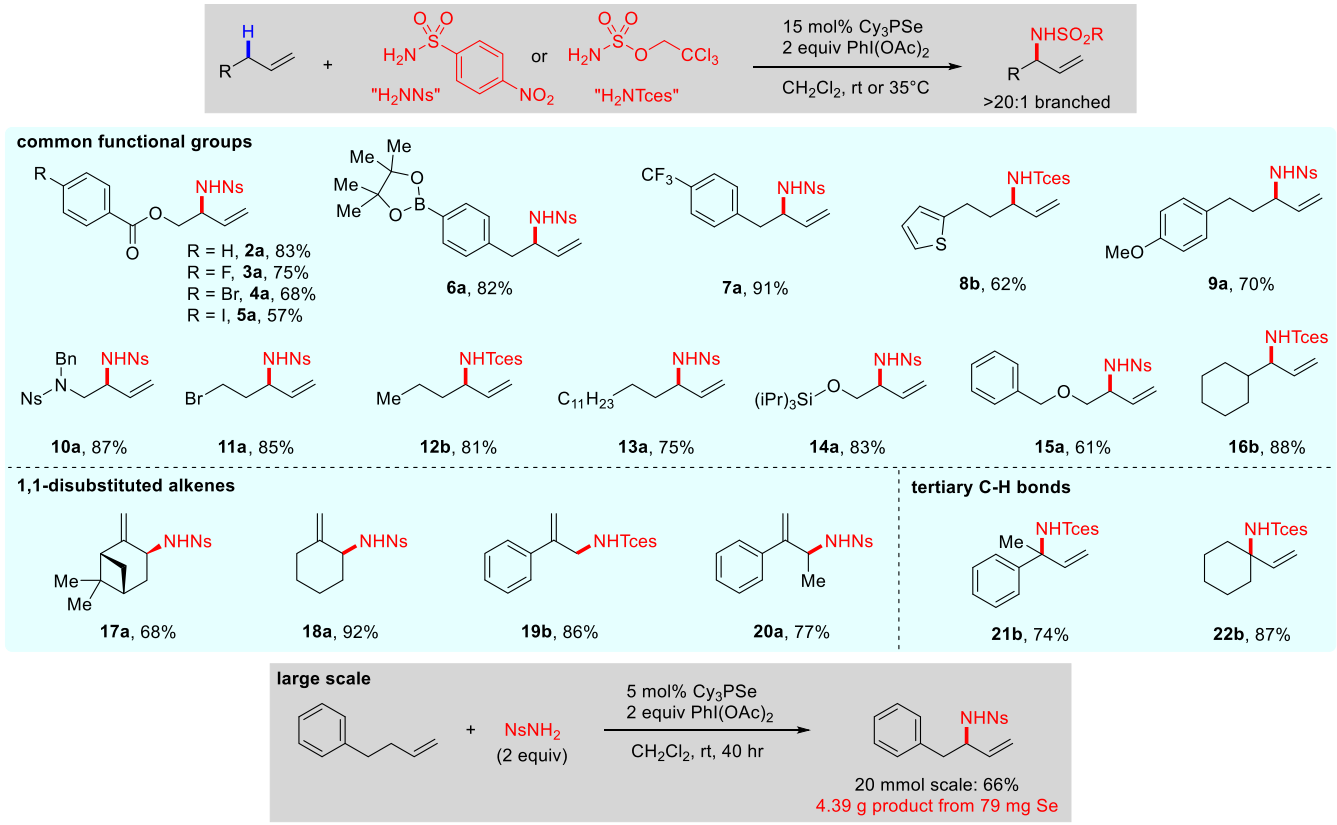
Inspired by nature, we were drawn to a particular synthetic challenge: can new classes of potentially bioactive nitrogen-containing compounds be generated by combining the naturally-occurring structural complexity of terpenes with a general allylic C–H amination method (Scheme 1A)? In synthesizing terpenoid natural products, organisms generate structural complexity in the carbon backbone by cyclizing acyclic isoprenoid precursors.[15] They then add functional complexity using C–H oxidation reactions of exquisite selectivity to introduce new C–O bonds in well-defined locations, often in allylic positions.[16] This approach has been successfully mimicked in the laboratory by several groups carrying out total syntheses of natural products and late-stage functionalizations.[17-20] We imagined that an analogous allylic C-H amination reaction could enable the synthesis of a wide variety of previously unknown nitrogen-containing bioactive compounds using the pre-existing structural diversity of terpenoids. Furthermore, such a method would also allow the selective labeling of terpenoids with functional reagents via the extra valence on the nitrogen atom.

The primary challenge in C–H amination of complex substrates is achieving predictable site selectivity, as highlighted by recent attempts to use C–H amination to selectively label complex biologically active molecules.[9,13,14] In this context, the presence of carbon-carbon double bonds in terpenoids presents both a prime underexplored opportunity and a difficult problem. As a consequence of the weakened C–H bond in the allylic positions, alkenes ought to provide a convenient reactive handle for introducing new functionality.[21] However, the high reactivity of the C–C π bond itself poses special challenges for known C–H amination methods (Scheme 1B). Existing nitrenoid-[11-14,22,23] or radical-based[8-10,24-29] approaches to C–H amination result in competing aziridination and/or alkene addition reactions rather than allylic amination. Methods that involve the formation of π-allyl complexes[30-38] avoid

Scheme 1. C-H Amination of Terpenoids.



Scheme 2. Terminal alkene substrate scope.



aziridination but are prone to problems with alkene transposition and regioselectivity, and are thus often limited to a narrow range of alkene substitution patterns. Furthermore, each of these systems are optimized to introduce only a single nitrogen substituent, or require special pre-made nitrogen sources, hampering their use as a means of introducing new functionality.

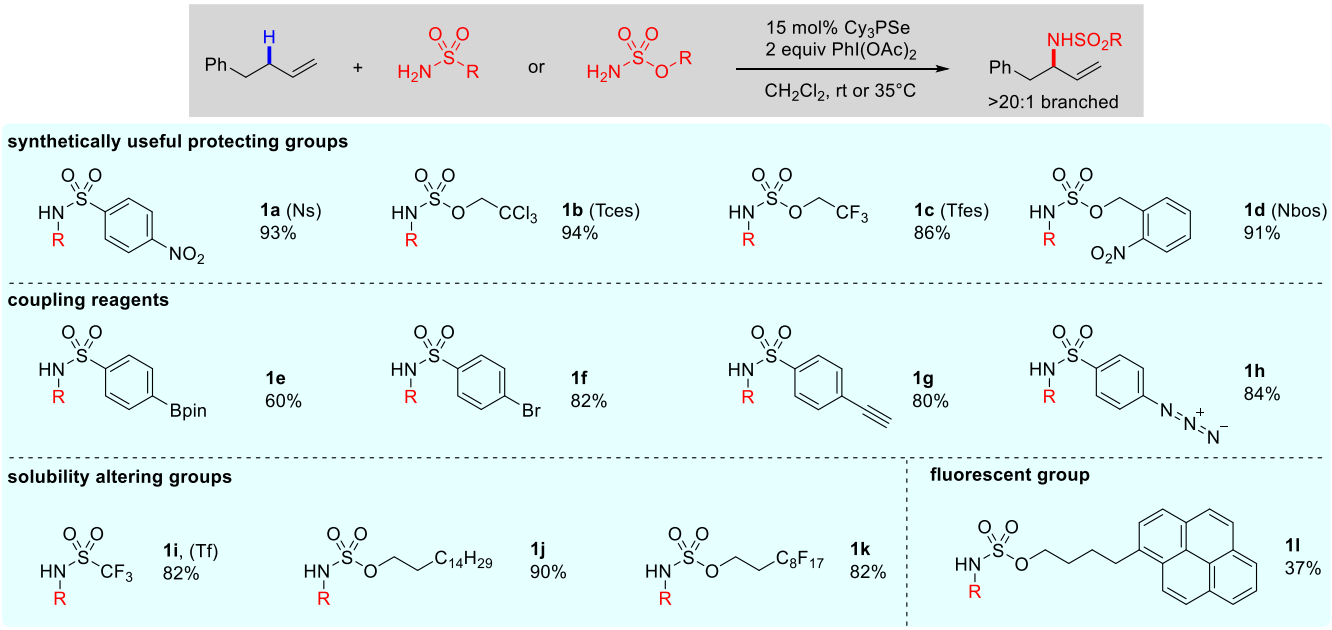
To achieve our goal of selective terpenoid amination, we needed to develop a new, more versatile solution to the general problem of allylic C–H amination; one that gives good reactivity and predictable regioselectivity for all alkene substitution patterns without alkene transposition and that allows the introduction of a wide range of functional groups via the nitrogen substituent (Scheme 1C). This new method would serve as a selective coupling reaction between sulfonamides/sulfamates and alkenes via the adjacent C–H bond.

In 1976, Sharpless and coworkers determined that a stoichiometric selenium reagent derived from anhydrous TsNClNa (Chloramine-T) could achieve highly selective allylic C–H amination of a range of simple alkenes.[39-41] Unfortunately, development and application of this exciting reaction has remained largely dormant (with the notable exception of an enantioselective sulfur variant)[42-45] since this initial report due to its moderate yields, the need for an inconvenient and potentially explosive nitrogen source, and the use of stoichiometric quantities of selenium. We reasoned that we could solve these problems by using a catalytic quantity of a selenium catalyst and regenerating the active selenium bis(imide) in situ with a milder, more convenient nitrenoid source, thereby greatly expanding the utility of this underexplored reaction. For this purpose, we targeted the use of simple sulfonamides and sulfamates as nitrogen sources, which in combination with inexpensive $PhI(OAc)_2$, would allow maximum flexibility in directly introducing a wide variety of nitrogen substituents. In the process, we discovered that introduction of a ligand for selenium was critical for high reactivity of the selenium catalyst.

RESULTS AND DISCUSSION

We started by treating a test alkene (4-phenyl-1-butene, **1**) with $PhI(OAc)_2$ and 4-nitrobenzenesulfonamide ($NsNH_2$) in the presence of catalytic Se powder. Disappointingly, no coupling product was formed under these conditions. At this stage, we reckoned that the use of a selenium source bearing an appropriate ligand would be more effective. In transition metal catalysis, phosphine and *N*-heterocyclic carbene (NHC) ligands are commonly used to improve the solubility and stability of the active metal center and to control its reactivity. In a similar manner, analogous complexes of these ligands with selenium, i.e. phosphine selenides and selenoureas, which are trivial to generate from the corresponding phosphines and imidazolium salts, might also serve as more effective catalysts. Indeed, we and others have recently shown that these complexes can be used to control the selectivity of selenium-catalyzed reactions.[46-48] Gratifyingly, phosphine selenide catalysts did afford the desired allylic amination product, with 15 mol % tricyclohexylphosphine selenide (Cy_3PSe) proving to be the most convenient and effective catalyst. The quantity of catalyst could be reduced further to 5 mol % with only a moderate drop in yield. No trace of any alkene transposition products was detected, nor was any competing amination of the benzylic position observed. The procedure is operationally simple, requiring only addition of the selenium catalyst and the stoichiometric oxidant to a mixture of the alkene and sulfonamide or sulfamate to be coupled.

Scheme 3. Alkene labeling with functional sulfonamides/sulfamates.



We tested a variety of terminal and 1,1-disubstituted alkenes (Scheme 2) and found that a wide range of functional groups, including esters, protected alcohols and amines, electron-rich aromatics, aryl boronates, and alkyl and aryl halides were well-tolerated. Amination of protected homoallylic alcohol and homoallylic amine groups generates synthetically important 1,2-aminoalcohols and 1,2-diamines. Importantly, primary, secondary, and tertiary C–H bonds could all be effectively aminated using this procedure. The reaction can be easily run on large scale with no diminution of yield; at 5 mol % catalyst loading 4.39 grams of product 1a can be generated using less than 80 mg of elemental selenium (Scheme 2). Notably, two of the most conveniently removed protecting groups for amines, the 4-nitrobenzenesulfonyl (Ns) and 2,2,2-trichloroethoxysulfonyl (Tces) groups, generally gave high yields.

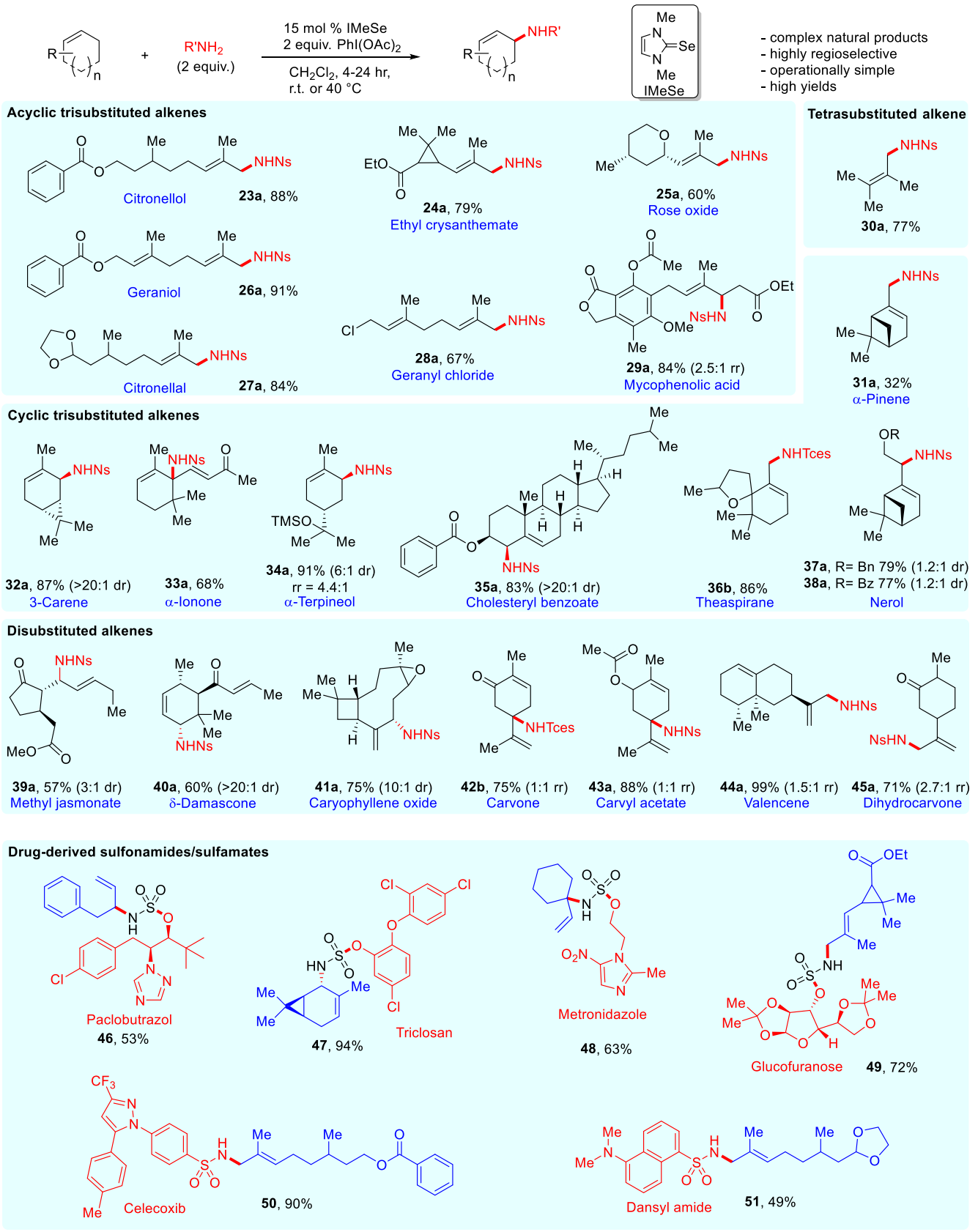
To illustrate the full potential of this reaction as a labeling method, a wide range of sulfonamides and sulfamates were coupled with our test alkene (Scheme 3). Several types of synthetically useful amine protecting groups were introduced in high yields, including groups that are cleaved using mild nucleophilic substitution (Ns), Zn reduction (Tces), hydrolysis (Tfes), and photolysis (Nbos). Groups that can undergo further coupling reactions can also be reliably introduced, including aryl halides and boronates for cross-coupling (**1e**, **1f**) and alkynes and azides for Cu-catalyzed cycloaddition (**1g**, **1h**). The polarity and/or solubility of the alkene substrate can be modified by appropriate choice of amination partner, including groups with strongly acidic N–H bonds (TfNH, pKa ~ 7 in H_2O), long hydrocarbon chains for hydrophobicity (**1j**), and perfluorocarbon chains for fluorous separation (**1k**). This coupling procedure could also be used to label substrates with fluorescent groups (**1l**).

We then tested our allylic amination procedure on more highly substituted alkenes and found that these gave disappointing yields with the Cy_3PSe catalyst. However, a screen of ligands revealed that simply changing the catalyst to the *N*-heterocyclic carbene-derived selenourea IMeSe gave us high yields for these more active substrates. These two catalysts were generally orthogonal: IMeSe gave high yields for more electron rich alkenes whereas Cy_3PSe was required for less electron rich alkenes.

Having successfully developed a broadly applicable allylic C–H amination reaction, we returned to the original question of whether this method could be used to generate new nitrogen-containing compounds based on terpenoid scaffolds. A variety of terpenoid natural products were subjected to the optimum reaction conditions (Scheme 4). We were able to obtain good yields of allylic amination products for every alkene substitution pattern from monosubstituted to tetrasubstituted, and in most cases a single regioisomer was formed. Acyclic trisubstituted alkenes, e.g. those derived from uncyclized terpenoids like citronellol and geraniol, reliably gave amination at the more substituted end of the alkene, trans to the third substituent, giving a single alkene stereoisomer (**23a**-**29a**). Mycophenolic acid, for example, was preferentially aminated beta to the ester according to this rule, rather than at the weaker benzylic/allylic C-H bond. In compounds with multiple C=C bonds, the most electron-rich alkene reacted preferentially.

Exploration of cyclic substrates revealed that trisubstituted alkenes typically provided endocyclic substitution products (**32a**-**34a**), most notably at the highly sterically hindered tertiary position in α-ionone. If the endocyclic site was blocked, as in cholesterol, theaspirane, nerol, and pinene, exocyclic substitution took place instead (**31a**, **35a**-**38a**). High diastereoselectivity was usually observed in cyclic alkene substrates, with amination occurring at the stereoelectronically required axial C–H bond (**32a**, **34a**, **35a**, **40a**, **41a**). Interestingly, the 1,2-disubstituted alkenes methyl jasmonate and δ-damascone reacted regioselectively (**39a**, **40a**), as did 1,1-disubstituted alkene caryophyllene oxide (**41a**). The most challenging substrates were those bearing an exocyclic isopropenyl group (**42b**-**45a**). Although these gave high overall yields of products, selectivity between a CH_3 group and a CH group was sometimes low. It is important to note that in almost all cases, the regioselectivity observed in this selenium-catalyzed protocol was different from that observed in nitrenoid, radical, and

Scheme 4. Amination of terpenoids and tagging of biologically active sulfonamides and sulfamates.



π-allyl amination reactions, which usually aminate on the less-substituted end of the alkene, providing unique access to these amination products.

To demonstrate the ability of this reaction to easily couple complex partners, a collection of sulfamates and sulfonamides derived from biologically active compounds was reacted with

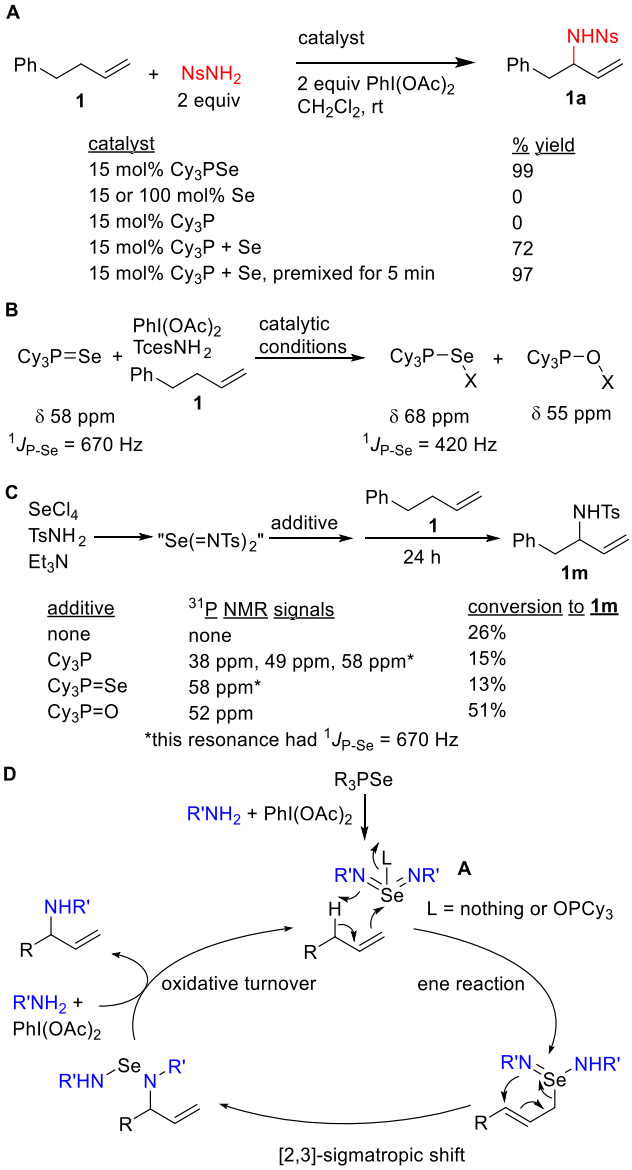
several different alkene partners (Scheme 4). Sulfamates were easily prepared in a single step from biologically active alcohols like the antifungal paclobutrazol, antibiotics triclosan and metronidazole, as well as a glucofuranose derivative. These sulfamates were then coupled to a range of alkenes in good yields, generating alkene/drug conjugates (**46**-**49**). The sulfonamide analgesic celecoxib (**50**) and the fluorescent group dansyl amide (**51**) also could be coupled to terpenoids in good yields.

The observed regio- and stereoselectivities are consistent with the sequential ene reaction/[2,3]-sigmatropic rearrangement mechanism originally proposed by Sharpless (Scheme 5D) and are similar to those observed in the stoichiometric reactions of sulfur and selenium bis(imide)s. Specifically, steric and electronic bias in the initial ene reaction generally determines the observed product. Similar to SeO_2 oxidations,[49] development of partial positive charge at the internal carbon explains why amination at the more substituted end of the most electron rich alkene is observed. A complex interplay between steric and electronic effects is responsible for the observed order of substitution pattern reactivity (CH_2 > CH ~ CH_3). More substituted C-H bonds result in a more exothermic ene reaction because they give more substituted alkene products, but steric hinderance at more substituted C-H bonds inhibits activation of highly substituted methine centers. The observed preference for activation of the axial hydrogen is due to the fact that only the axial hydrogen has proper stereoelectronic overlap with the pi system to undergo the ene reaction.

To test the role of the ligand, several mechanistic experiments were performed (Scheme 5A). Neither commercial Se powder nor Cy_3P alone gives any product. Adding Se and Cy_3P to the reaction mixture separately does give the desired product, but these two reagents also react with each other to generate Cy_3PSe under these conditions. Indeed, pre-mixing of Se and Cy_3P for just 5 minutes before adding the other reagents results in yields that are nearly the same as using premade Cy_3PSe, indicating that in situ formation of the phosphine selenide is a viable alternate protocol.

In situ ^{31}P NMR spectroscopy of the catalytic reaction mixture revealed the immediate disappearance of the signal for Cy_3PSe with concomitant formation of two new species (Scheme 5B, see Supporting Information for details). Both new species persisted for the duration of the catalytic reaction, and the same NMR spectrum was obtained in the presence or absence of alkene **1**. One new resonance at 68 ppm had clear satellites from coupling to ^{77}Se, whose coupling constant ($J_{P\text{-}Se}$ ~ 425 Hz) is substantially smaller than that of Cy_3PSe. The downfield shift and reduced coupling constant of this species are both consistent with substantial weakening of the P-Se bond via coordination at Se. Similar values have been observed for metal complexes of Cy_3PSe.[50] The other resonance at 56 ppm is somewhat broad and has no ^{77}Se satellites. Addition of an authentic sample established that this resonance is due to Cy_3PO, but its downfield shift relative to free phosphine oxide (~56 vs 49 ppm) is consistent with coordination of the oxygen to a Lewis acid and/or hydrogen bond donor.[51,52] Unfortunately, further NMR investigations did not allow conclusive identification of the exact species to which Cy_3PO and Cy_3PSe are coordinated.

Scheme 5. Mechanistic experiments and proposed catalytic cycle



Isolation or characterization of the putative selenium bis(imide) has not been reported, frustrating our efforts to establish it as a key intermediate. Instead, we focused our study on the active aminating reagent previously prepared by Sharpless from $SeCl_4$ and $TsNH_2$ in the presence of Et_3N (Scheme 5C).[39] This mixture was then treated with an equivalent of Cy_3P, Cy_3PSe or Cy_3PO and a ^{31}P NMR spectrum was obtained. Then, 1 equiv of alkene **1** was added to each of these mixtures and allowed to react for 24 h. Addition of Cy_3P resulted in three new ^{31}P NMR resonances, none of which corresponds to free Cy_3P. We can assign these as Cy_3PNTs (38 ppm), Cy_3PO (49 ppm) and Cy_3PSe (58 ppm), indicating that free phosphine is rapidly oxidized by the putative selenium bis(imide) and unlikely to persist under the reaction conditions. Addition of Cy_3PSe to selenium bis(imide) resulted in no change in the ^{31}P NMR for Cy_3PSe. However, addition of Cy_3PO to this mixture resulted in a significant change in the ^1H NMR resonances of the tosyl substitutents, accompanied by a shift of the Cy_3PO ^{31}P NMR resonance to 52 ppm. Notably, conversion of alkene **1** to amination product **1m** was only moderate for the putative free selenium bis(imide), as well as for the mixtures with Cy_3P and Cy_3PSe added. However, addition of Cy_3PO resulted in a substantial increase in conversion

to 51%. This is identical to the yield of **1m** under our standard catalytic conditions (51%).

We propose that selenium bis(imide) is generated by oxidation of the phosphine selenide by $PhI(OAc)_2/RSO_2NH_2$ and that phosphine oxide formed in the process (and possibly phosphine selenide) may coordinate to the bis(imide) under the reaction conditions (Scheme 5D).[52] Coordination of phosphine oxide to the selenium bis(imide) is predicted to be moderately exergonic by DFT calculations (ΔG ~ -10 kcal/mol, see Supporting Information for details) and may help stabilize the selenium bis(imide) and/or promote its regeneration. Furthermore, these calculations identify a transition state ($\Delta G^{\ddagger}$ = +18 kcal/mol) for the ene reaction to take place on the adduct **A** with simultaneous displacement of the phosphine oxide. We note that we are unable to rule out the possible intermediacy of free selenium bis(imide) under the reaction conditions.

CONCLUSIONS

In conclusion, we have developed a new broadly applicable selenium-catalyzed allylic C–H amination of alkenes. Alkene substitution patterns from mono- to tetrasubstituted can be directly coupled with a wide range of sulfonamides and sulfamates with high, predictable regioselectivity in an operationally simple, metal-free reaction. This reaction has been used to introduce new C–N bonds in an assortment of terpenoid natural products, thereby generating a new class of potentially bioactive products.

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures, spectral characterizations, and additional data. (PDF)

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ACKNOWLEDGMENT

We thank the University of Washington and the National Science Foundation (CHE-1764450) for funding.

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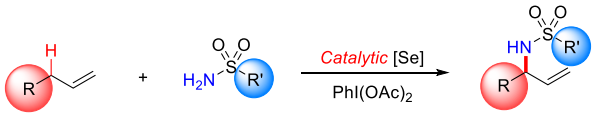

- Coupling/Labeling of alkene feedstocks
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