Allylic C–H Amination for the Preparation of syn-1,3-Amino Alcohol Motifs

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Abstract: A highly selective and general Pd/sulfoxide-catalyzed allylic C–H amination reaction en route to syn-1,3-amino alcohol motifs is reported. Key to achieving this reactivity under mild conditions is the use of electron-deficient N-nosyl carbamate nucleophiles that are thought to promote functionalization by furnishing higher concentrations of anionic species in situ. The reaction is shown to be orthogonal to classical C–C bond-forming/reduction sequences as well as nitrene-based C–H amination methods.

Introduction

A diverse range of natural products and pharmaceuticals include syn-1,3-amino alcohols as dominant motifs. Important advances have been made in asymmetric C–C and C–N bond-forming reactions to generate β-amino ketones and β-hydroxy imines. Complementary methods that furnish 1,3-amino alcohols with minimal oxidation-state manipulations would provide strategic advantages in streamlining their syntheses. Although metal nitrene systems for aliphatic C–H aminations provide direct routes for accessing syn-1,3-amino alcohols, analogous allylic C–H aminations face challenges in chemoselectivity and/or reactivity, particularly with terminal olefins. Such reactions would be highly valuable in synthetic planning due to the latent functionality preserved in the unsaturated moiety (vide infra). We have recently discovered Pd(II)/sulfoxide catalyst systems that effect predictably selective allylic C–H esterifications, alkylations, and aminations, and demonstrated their strategic use in streamlining complex molecule synthesis. Notably, our group recently reported an intramolecular allylic C–H amination reaction of homoallylic N-tosyl carbamates to generate 5-membered vinyl oxazolidinones en route to syn-1,2-amino alcohol motifs. We now report that the use of a more electron-deficient N-nosyl carbamate nucleophile enables a mild Pd(II)/sulfoxide-catalyzed allylic C–H amination reaction with extraordinary chemoselectivities that furnishes vinyl syn-1,3-amino alcohol precursors from terminal olefins.

Results and Discussion

Design Principles. Mechanistic studies indicated that intramolecular allylic C–H amination to form 5-membered vinyl oxazolidinones proceeds via Pd(II)/sulfoxide-mediated hetero-


A. Electrophilic C–H Cleavage

\[ \text{R} - \text{H} + \text{O} = \text{R} + \text{R} \]

B. Nucleophilic Functionalization

\[ \text{NH} \rightarrow \text{N} \]

C. Catalyst and Endogenous Base Regeneration

\[ \text{L} \text{Pd}(0) + \text{O} \rightarrow \text{L} \text{Pd(OAc)}_2 + \text{AcOH} \]

Figure 1. Design principles for intramolecular C–H amination.

Table 1. Allylic C–H Amination Reaction Optimization

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time</th>
<th>Isolated Yield</th>
<th>(\delta^c)</th>
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<tbody>
<tr>
<td>1</td>
<td>(p)-Tol</td>
<td>72 h</td>
<td>15%</td>
<td>5:1</td>
</tr>
<tr>
<td>2</td>
<td>(p)-ClPh</td>
<td>24 h</td>
<td>38%</td>
<td>3:7</td>
</tr>
<tr>
<td>3</td>
<td>(p)-NO(_2)Ph</td>
<td>24 h</td>
<td>67%</td>
<td>4:4</td>
</tr>
<tr>
<td>4</td>
<td>o-NO(_2)Ph</td>
<td>24 h</td>
<td>63%</td>
<td>2:6</td>
</tr>
</tbody>
</table>

\(\text{R}^1 \text{N}\text{H} \text{N=O} \text{R} \)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R(^a)</th>
<th>Isolated Yield</th>
<th>(\delta^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>(\text{Propyl} )</td>
<td>20%</td>
<td>60%</td>
</tr>
<tr>
<td>6</td>
<td>Ethyl</td>
<td>20%</td>
<td>67%</td>
</tr>
<tr>
<td>7</td>
<td>(\text{Butyl} ) (2f)</td>
<td>84%</td>
<td>63%</td>
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\(\text{L} \text{Pd(OAc)}_2 (10 \text{ mol}%) \)

\(\text{PhBQ} (2 \text{ equiv.}) \)

\(\text{BiSO Ligand}^a (5 \text{ mol}%) \)

\(\text{DCE} (0.656 \text{ M}) \)

\(45^\circ \text{C}, 24 \text{ h} \)

\(\text{R}^1 \text{N} \text{H} \text{N=O} \text{R} \)

\(\text{L} \text{Pd(OAc)}_2 (10 \text{ mol}%) \)

\(\text{PhBQ} (2 \text{ equiv.}) \)

\(\text{BiSO Ligand}^a (5 \text{ mol}%) \)

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\(\text{DCE} (0.656 \text{ M}) \)

\(45^\circ \text{C}, 24 \text{ h} \)


11. The inclusion of catalytic amine base, recently discovered to promote intermolecular allylic C–H aminations with N-tosyl carbamate nucleophiles (ref 8b), gave a minor increase in yield for substrate 2a (15% \(\rightarrow\) 37%); however, the diastereoselectivity was significantly diminished (5.1:1 \(\rightarrow\) 1.8:1 syn:anti).


15. Heating the reaction with N-tosyl carbamate substrates to 65 \(^\circ\)C also promoted reactivity; however, the yields were lower, and inconsistent results were observed.


Interestingly, reactivity and selectivity in this system are not strongly impacted by steric bulk adjacent to the carbamate (Table 1, entries 5–7). This is in stark contrast to the allylic C–H amination system furnishing syn-1,2-amino alcohol motifs, where one bulky substituent adjacent to the carbamate (generally a branching element) was deemed important for achieving good diastereoselectivity; a bulky quaternary alkyl substituted carbamate, albeit proceeding with excellent diastereoselectivity, suffered from poor reactivity (\textit{vide infra}).
Allylic C–H Amination toward syn-1,3-Amino Alcohols

Table 2. Allylic C–H Amination Reaction Scope

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Additives: p-nitrobenzoic acid (10 mol %), BisSO ligand (5 mol %). b Reaction run in oxygenated DCE. c Isolated yield of major syn product, >20:1 syn:anti.

Reaction Scope. Significantly, use of this more electron-deficient nitrogen nucleophile proved to be a general solution for the formation of a wide range of 6-membered oxazinanones (Table 2). Substrates derived from secondary alcohols having prochiral allylic C–H bonds show good to excellent levels of diastereoselectivity favoring the syn-1,3-isomer (5, 7–12). The observed stereochemical outcome is consistent with functionalization proceeding via a chair-like transition state.13 No conformational biasing element is required for effecting cyclization as evidenced by efficient generation of oxazinanone 4 (70%) derived from a primary alcohol precursor.25 Even a substrate originating from a sterically hindered tertiary alcohol generated syn-1,3-oxazinanone 6 in good yield.

This method is orthogonal to all other current state-of-the-art methods for generating this synthetically important motif. The complementary nature of this method to C–C and C–N bond-forming/reduction sequences is highlighted by the synthesis of oxazinanones 7 and 8 having reduction-sensitive proximal ketone and ester functionalities. In contrast to nitrene-based systems, perfect chemoselectivity is seen for allylic C–H amination over benzylid and ethereal C–H amination (9, 10; (+)-15 and (+)-16, Scheme 1).13 Strikingly, this allylic C–H amination method shows unprecedented chemoselectivity for C–H amination of terminal olefins (11 and 12). In all cases, syn-oxazinanone products of greater than 20:1 diastereomeric ratio can be obtained in good yields after standard column chromatography (see parenthetical yields in Table 2).

Predictable diastereomeric outcomes are crucial for C–H functionalization methods to find use at late stages of complex molecule synthesis. Gratifyingly, for substrates containing multiple stereogenic centers, the diastereomeric outcome of this reaction is controlled by the stereocenter containing the carbamate (Scheme 1). In substrates containing homoallylic (17, 19) or trishomoallylic (13, 14) stereogenic centers the reaction is consistently syn-selective relative to the N-nosyl carbamate.

Streamlining Synthesis. We have previously demonstrated the ability of predictably selective C–H amination reactions to streamline the synthesis of nitrogen containing molecules by “skipping” oxygenated intermediates that are burdensome to carry through synthetic sequences.7,8 The ability of this allylic C–H amination reaction to efficiently access optically enriched syn-1,3-amino alcohols is highlighted in the synthesis of (+)-alloseedrine 25, a member of the sedum alkaloids that have shown promising memory enhancing properties (Scheme 2).17 Starting from commercially available enantioenriched bis-homoallylic alcohol (+)-21, the nitrogen is introduced at the correct oxidation state via C–H amination in only two steps. Major diastereomer (+)-23 was easily isolated using standard flash column chromatography in 61% yield with >20:1 diastereomeric purity and with no erosion in enantiomeric excess (>99% ee). Notably, the N-nosyl group can be easily deprotected using mild PhSH/K2CO3 conditions to afford the free oxazinanone in 91% yield.18 Alkylation furnished (−)-24 whose terminal olefin moieties could be used to forge the piperdine core via Grubs ring-closing metathesis (RCM).19 Hydrogenation, followed by basic hydrolysis completed the total synthesis of (+)-alloseedrine 25 in six steps and 27% overall yield. By avoiding multiple functional group manipulations and exploiting the terminal

olefin functionality, an allylic C–H amination route affords the shortest and highest-yielding synthesis of (+)-25 to date.20

**syn-1,2-Amino Alcohol Synthesis.** Significantly, the discovery that N-nosylcarbamate nucleophiles lead to improved reactivity for intramolecular allylic C–H aminations could be used to increase the efficiency of our previously reported reaction for generating 1,2-amino alcohol motifs. Homoa allylic N-nosyl carbamates 26b and 26d underwent Pd(II)/sulfoxide 1-catalyzed intramolecular allylic C–H amination to furnish anti-oxazolidinones 27b and 27d in comparable yields and diastereoselectivities and a 3-fold decrease in reaction times (72 h → 24 h) to those reported with the analogous N-tosyl carbamate substrates (Table 3, entries 1, 2). In contrast to the 1,3-amino alcohol system, however, reactivity with sterically congested substrates such as tert-butyl 26f and tertiary alcohol-derived carbamate 26g remained low (entries 3, 4). These results demonstrate a distinct steric limitation for this chemistry in furnishing 5-membered oxazolidinone rings that is not observed in generating 6-membered oxazinanone rings. Gratifyingly, the allylic C–H amination reaction for generating 1,2-amino alcohol motifs also proceeds with outstanding chemoselectivity. This is illustrated in the preferential C–H amination of terminal over internal olefins in the doubly homoa llylic N-nosyl carbamate substrate 26h (entry 5). Interestingly, syn-oxazolidinone 27h is obtained in both good yields and diastereoselectivities despite the lack of an adjacent branching element previously deemed to be crucial for obtaining synthetically useful diastereomeric outcomes with this system.

**Conclusion**

We report herein the discovery that an electron-deficient N-nosyl carbamate nucleophile furnishes a general Pd(II)-sulfoxide-catalyzed allylic C–H amination reaction to generate 6-membered syn-oxazinanones under mild reaction conditions. The extraordinary chemoselectivity of this method is underscored by its demonstrated ability to selectively...
K₂CO₃/H₂O, and 1 x 15 mL of water. The organic layer was collected and dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography. **In general, the major syn-diastereomer can be isolated by flash chromatography (25–35% gradient EtOAc/hexanes) directly from the crude reaction mixture.**

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**Supporting Information Available:** Experimental procedures, full characterization, and additional experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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