Diastereoselective synthesis of unsaturated 1,2-amino alcohols from \( \alpha \)-hydroxy allyl ethers using chlorosulfonyl isocyanate

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Abstract—Diastereoselective synthesis of 1,2-amino alcohols was achieved from a highly diastereoselective allylic amination reaction of \( \alpha \)-hydroxy allyl ethers using chlorosulfonyl isocyanate. Diastereoselectivities varied depending on the stereochemistry of the ethers used and the stability of the carbocation intermediate obtained during the reaction. We propose that this CSI reaction is the results of either a \( \text{S}_2\text{N}_1 \) or \( \text{S}_\text{N}\text{Ar} \) mechanism, according to the stability of the carbocation intermediate.

The stereoselective synthesis of 1,2-amino alcohols has been the focus of recent studies in the synthetic and industrial fields, because of their important roles in organic synthesis as fundamental building blocks, and because of their occurrence in a number of natural products, drugs and chiral auxiliaries or ligands.\(^1\) The common synthetic routes to these compounds include the reduction of \( \alpha \)-amino acids, \( \alpha \)-amino ketones or \( \alpha \)-hydroxy imines,\(^2\) the nucleophilic substitution of 1,2-diols,\(^3\) epoxides,\(^4\) aziridines,\(^5\) cyclic carbonates or cyclic sulfates,\(^6\) the aminoxylation or oxymethylation of olefins,\(^7\) the hydroboration of enamines,\(^8\) nucleophilic addition to N-protected \( \alpha \)-amino aldehyde\(^9\) or to an O-protected \( \alpha \)-hydroxy imine\(^10\) and the coupling of carbanions with imines.\(^11\) Many of these procedures have one or more problems, for example, low stereoselectivity, limited application and the use of heavy metals.

Recently we reported a novel regioselective and diastereoselective synthetic approach using the chlorosulfonyl isocyanate (CSI) reaction for the unsaturated aromatic 1,2-amino alcohols from an epimeric mixture of optically active allylic ethers having a hydroxyl group attached to an allylic chiral center to the \( \pi \)-system (Scheme 1).\(^12\)

Keywords: 1,2-Amino alcohols; Diastereoselective allylic amination; Chlorosulfonyl isocyanate.

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Scheme 1.

Herein, we describe a new synthetic approach to a variety of unsaturated 1,2-amino alcohols 5 from the appropriate stereoisomers, that is, protected \( \text{syn} \)- and \( \text{anti} \)-\( \alpha \)-hydroxy allyl ethers 4,\(^13\) as an extension of the CSI reaction,\(^14\) and describe how to control diastereoselectivity in this reaction (Scheme 2).

Our initial studies examined the diastereoselective effect of the protecting group of the hydroxyl moiety in \( \text{cis}-(1S,2S) \)-2-methoxy-1-phenyl-but-3-ene 4 (\( R^1 = \text{Ph}, \) \( R^2 = \text{H} \)) as shown in Table 1. The treatment of \( \text{syn-TBS} \) protected methyl ether 4a with CSI furnished \( \text{syn-1,2-amino alcohol 5a} \) with high diastereoselectivity.

Keywords: 1,2-Amino alcohols; Diastereoselective allylic amination; Chlorosulfonyl isocyanate.

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Scheme 2.
Table 1. Conversions of protected α-hydroxy allyl ethers to the corresponding 1,2-amino alcohols

<table>
<thead>
<tr>
<th>Entries</th>
<th>Allyl ethers</th>
<th>Allylic amines</th>
<th>Yield (%), ds ratio\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OTBS</td>
<td>NHCOOMe</td>
<td>41, 95:5</td>
</tr>
<tr>
<td>2</td>
<td>OTIPS</td>
<td>NHCOOMe</td>
<td>41, 97:3</td>
</tr>
<tr>
<td>3</td>
<td>OTBS</td>
<td>NHCOOMe</td>
<td>44, &gt;99</td>
</tr>
<tr>
<td>4</td>
<td>OTIPS</td>
<td>NHCOOMe</td>
<td>41, &gt;99</td>
</tr>
<tr>
<td>5</td>
<td>OTBS</td>
<td>NHCOOMe</td>
<td>76, 93:7</td>
</tr>
<tr>
<td>6</td>
<td>OTBS</td>
<td>NHCOOMe</td>
<td>81, &gt;99</td>
</tr>
<tr>
<td>7</td>
<td>OTBS</td>
<td>NHCOOMe</td>
<td>+ NHCOOMe</td>
</tr>
<tr>
<td>8</td>
<td>OTBS</td>
<td>NHCOOMe</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>OTBS</td>
<td>NHCOOMe</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>OTBS</td>
<td>NHCOOMe</td>
<td>+ NHCOOMe</td>
</tr>
<tr>
<td>11</td>
<td>OTBS</td>
<td>NHCOOMe</td>
<td></td>
</tr>
</tbody>
</table>

All the reactions were carried out at 20 °C, except for entries 7, 8 and 10, 11 (−78 °C). Isolated yield of pure material.

\textsuperscript{a} Based on integrals of OCH\textsubscript{3} signals in carbamates.

(95:5) in 41% chemical yield (entry 1). The product (1,4-amino alcohol) derived from attack at the vinylic position was not detected. Using the syn-TIPS protected methyl ethers 4b, the result was similar to that obtained in the TBS case (entry 2). The stereochemistry of major products was confirmed by converting the carbamates by Bu\textsubscript{4}NF and NaH treatment in THF at 0 °C, into the oxazolidinones.\textsuperscript{12} Moreover, the isomeric anti-protected methyl ethers 4c and 4d, under the same reaction conditions, gave anti-1,2-amino alcohols with high dia-
stereoselectivity (>99) (entries 3 and 4). Next, we investigated the substituent effect on the diastereoselectivity by varying the alkyl moiety (R¹ and R²). The results are summarized in Table 1. Using the syn- and anti-TBS protected methyl ethers 4e and 4f, the diastereomeric ratios were similar to that obtained in entries 1 and 3, respectively, except for the increased chemical yields (entries 5 and 6). Contrary to previous results, CSI reaction of 4f afforded a 1:1.4 inseparable mixture of syn-1,2-amino alcohol 5f and the anti-stereoisomer 6 in 89% chemical yield (entry 7). For anti-ether 4g, anti-1,2-amino alcohol 5g was obtained as a sole product in 84% yield with high diastereoselectivity (>99) (entry 8). In the cases of entries 9–11, the results were similar to those obtained in entries 1–8, except for the formation of 1,4-amino alcohol, (4S)-methyl N-[4-(tert-butyldimethylsilyloxy)pent-2-enyl]carbamate (7) in 6% chemical yield from 4i (entry 9) and a reduction in diastereoselectivity (entry 11).

Furthermore, in order to determine the role of the protected hydroxy group, we introduced a methyl moiety instead of the protected hydroxyl group at the benzylic position. The reaction of the inseparable methyl ethers 9 (erythro:threo = 3.9:1) with CSI produced a 4.0:1 inseparable mixture of the erythro-stereoisomer and the threo-stereoisomer 10 at a yield of 69% and (4R)-methyl N-(4-phenylpent-2-enyl)carbamate (11) in 9% yield (Scheme 3). This result is similar to those shown in Table 1.

From the above results, we suggest that the CSI reactions might proceed via SNi and/or SN1 mechanisms, and that the mechanism route depends on the stability of the carbocation obtained during the reaction. Plausible reaction pathways are shown in Scheme 4.

From the results of Table 1 and Scheme 3, in the case of vinyl ethers (R₂ = H), the SNi mechanism predominates to retain the configuration (entries 1–6 and 9 in Table 1) due to the formation of the less stable carbocation intermediate. These results showed that the protecting group, the stereochemistry of starting materials, and the presence of a chiral hydroxyl group have no effect on diastereoselectivity. However, in the case of cinnamyl ethers (R₂ = Ph), the formation of the more stable carbocation intermediate partially drives this CSI reaction via a SN1 mechanism to produce a competitive SNi/SN1 mechanism. Therefore, in the case of syn-ethers (entries 7 and 10), mixtures of diastereomer were obtained, because the SNi mechanism afforded the syn-1,2-amino alcohol and the SN1 mechanism afforded the anti-stereoisomer. This anti-selectivity via a SN1 mechanism may be explained by the Cieplak electronic model during conversion from ethers to carbanions. In the case of anti-ethers (entries 8 and 11), the anti-stereoisomer was produced exclusively by both SNi and SN1 mechanisms (Scheme 5).

**Scheme 3.**

**Scheme 4.**

**Scheme 5.**
In conclusion, we developed a novel diastereoselective synthetic approach to unsaturated 1,2-amino alcohols from the corresponding 3-hydroxy allyl ethers using the CSI reaction. The diastereoselectivity of this approach was investigated by varying the alkyl substituents. Based on these results, we confirm that both the synthetic approach to unsaturated 1,2-amino alcohols and/or a SN1 mechanism, the balance from the corresponding intermediate.

Acknowledgements
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Supplementary data

References and notes
13. The preparations of optically active compounds 4 are as follows: Compounds 4a and 4b were prepared using Brown methodology and protection of the hydroxyl moiety (Scheme 5) 4c and 4d were prepared from 13 by Mitsunobu inversion and protection of the hydroxyl moiety. Compounds 4g and 4h were prepared from 4a and 4c by oxidation of the double bond (OsO4, NaIO4, 2,6-lutidine) and by using the HWE reaction using diethyl benzylphosphonate in the presence of NaHMDS, respectively. Preparations of 4e–4k are similar to the above synthetic methodology.