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Diastereoselective synthesis of unsaturated 1,2-amino alcohols from α-hydroxy allyl ethers using chlorosulfonyl isocyanate

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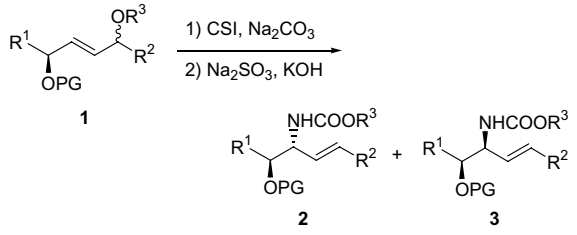
Abstract—Diastereoselective synthesis of 1,2-amino alcohols was achieved from a highly diastereoselective allylic amination reaction of α-hydroxy allyl ethers using chlorosulfonyl isocyanate. Diastereoselectivities varied depending on the stereochemistry of the ethers used and the stability of the carbocation intermediate obtained during the reaction. We propose that this CSI reaction is the results of either a S_Ni or S_N1 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 α-amino acids, α-amino ketones or α-hydroxy imines,[2] the nucleophilic substitution of 1,2-diols,[3] epoxides,[4] aziridines,[5] cyclic carbonates or cyclic sulfates,[6] the aminohydroxylation or oxymecuration of olefins,[7] the hydroboration of enamines,[8] nucleophilic addition to N-protected α-amino aldehyde[9] or to an O-protected α-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.

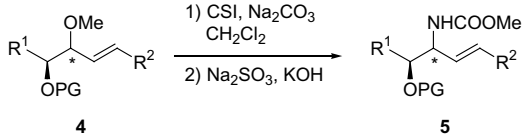
Recently we reported a novel regioselective and diastereoselective synthetic approach using the chlorosulfonyl isocyanate (CSI) reaction for the unsaturated aromatic 1,2-amino alcohols from an epimeric mixture of optically active allylic ethers having a hydroxyl group attached to an allylic chiral center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



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 *syn*- and *anti*-α-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 (1*S*,2*S*)-2-methoxy-1-phenyl-but-3-ene **4** (R^1 = Ph, R^2 = H) as shown in Table 1. The treatment of *syn*-TBS protected methyl ether **4a** with CSI furnished *syn*-1,2-amino alcohol **5a** with high diastereoselectivity



Scheme 2.

Keywords: 1,2-Amino alchohols; Diastereoselective allylic amination; Chlorosulfonyl isocyanate.
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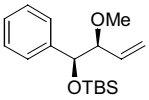
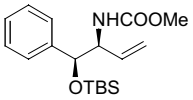
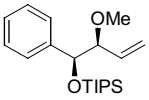
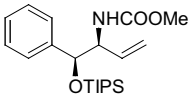
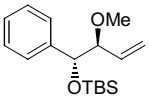
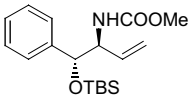
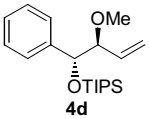
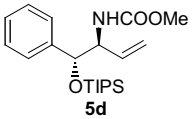
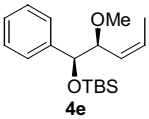
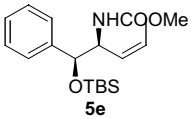
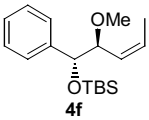
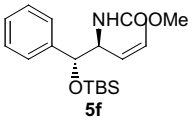
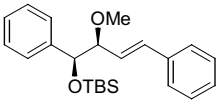
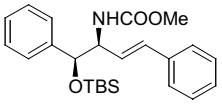
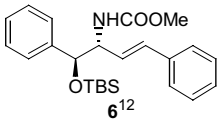
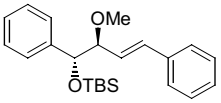
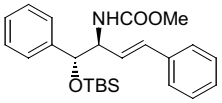
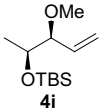
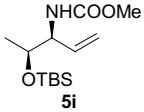
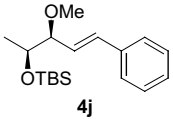
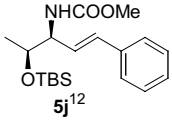
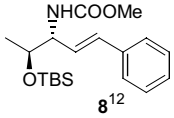
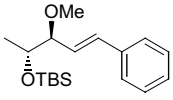
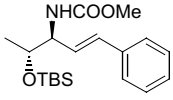
Table 1. Conversions of protected α-hydroxy allyl ethers to the corresponding 1,2-amino alcohols

Entries	Allyl ethers	Allylic amines	Yield (%), ds ratio[a]
1	 **4a**	 **5a**	41, 95:5
2	 **4b**	 **5b**	41, 97:3
3	 **4c**	 **5c**	44, >99
4	 **4d**	 **5d**	41, >99
5	 **4e**	 **5e**	76, 93:7
6	 **4f**	 **5f**	81, >99
7	 **4g**	 **5g** +  **6**[12]	89, 1:1.4
8	 **4h**	 **5h**	84, >99
9	 **4i**	 **5i**	34, 94:6
10	 **4j**	 **5j**[12] +  **8**[12]	82, 1:1.7
11	 **4k**	 **5k**	84, 91:9

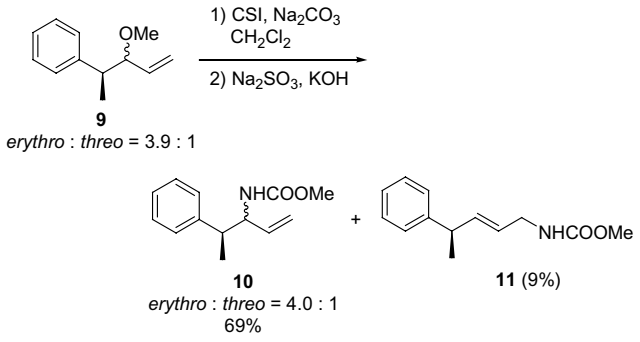
All the reactions were carried out at 20 °C, except for entries 7, 8 and 10, 11 (−78 °C). Isolated yield of pure material.
[a] Based on integrals of OCH_3 signals in carbamates.

(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_4NF and NaH treatment in THF at 0 °C, into the oxazolidinones.[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 (R^1 and R^2). 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 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**[12] 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, (4*S*)-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).

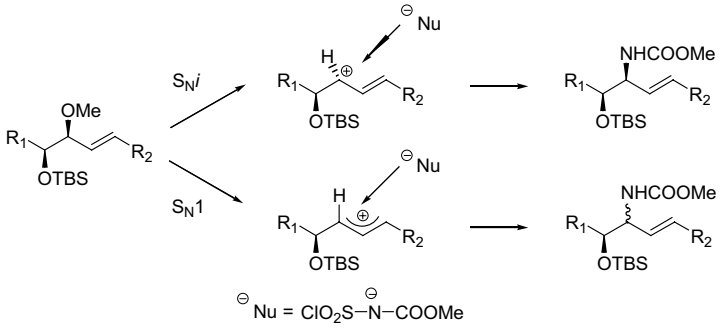
Furthermore, in order to determine the role of the protected hydroxy group, we introduced a methyl moiety instead of the protected hydroxyl group at the benzylic position. The reaction of the inseparable methyl ethers **9** (*erythro*:*threo* = 3.9 : 1) with CSI produced a 4.0:1 inseparable mixture of the *erythro*-stereoisomer and the *threo*-stereoisomer **10** at a yield of 69% and (4*R*)-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 S_Ni and/or S_N1 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.

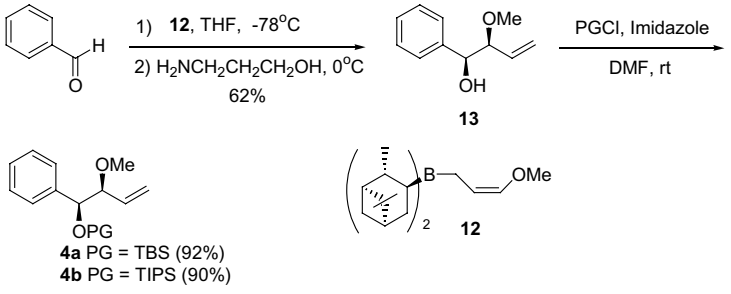


Scheme 3.

From the results of Table 1 and Scheme 3, in the case of vinyl ethers (R_2 = H), the S_Ni 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 (R_2 = Ph), the formation of the more stable carbocation intermediate partially drives this CSI reaction via a S_N1 mechanism to produce a competitive S_Ni/S_N1 mechanism. Therefore, in the case of *syn*-ethers (entries 7 and 10), mixtures of diastereomer were obtained, because the S_Ni mechanism afforded the *syn*-1,2-amino alcohol and the S_N1 mechanism afforded the *anti*-stereoisomer. This *anti*-selectivity via a S_N1 mechanism may be explained by the Cieplak electronic model during conversion from ethers to carbamates.[12] In the case of *anti*-ethers (entries 8 and 11), the *anti*-stereoisomer was produced exclusively by both S_Ni and S_N1 mechanisms (Scheme 5).



Scheme 4.



Scheme 5.

In conclusion, we developed a novel diastereoselective synthetic approach to unsaturated 1,2-amino alcohols from the corresponding α-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 stereochemistry of the protected hydroxyl moiety and the stability of the carbocation intermediate affect the diastereoselectivity. Moreover, our results establish that the described CSI reaction is a competitive reaction that proceeds via a S_Ni and/or a S_N1 mechanism, the balance of which depends on the stability of the carbocation intermediate.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.12.100.

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13. The preparations of optically active compounds **4** are as follows: Compounds **4a** and **4b** were prepared using Brown methodology[15] and protection of the hydroxyl moiety (Scheme 5) **4c** and **4d** were prepared from **13** by Mitsunobu inversion[16] and protection of the hydroxyl moiety. Compounds **4g** and **4h** were prepared from **4a** and **4c** by oxidation of the double bond (OsO_4, $NaIO_4$, 2,6-lutidine)[17] and by using the HWE reaction[18] using diethyl benzylphosphonate in the presence of NaHMDS, respectively. Preparations of **4e**,**f**,**i**–**k** are similar to the above synthetic methodology.
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