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Regioselective and Diastereoselective Allylic Amination Using Chlorosulfonyl Isocyanate. A Novel Asymmetric Synthesis of Unsaturated Aromatic 1,2-Amino Alcohols

Ji Duck Kim, Ok Pyo Zee, and Young Hoon Jung*

College of Pharmacy, Sungkyunkwan University, Suwon 440-746, Korea

yhjung@skku.ac.kr

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Abstract: The diastereoselective synthesis of unsaturated aromatic 1,2-amino alcohols can be achieved on an epimeric mixture of optically active allylic ethers having a hydroxyl group attached to an allylic chiral center to the π-system using chlorosulfonyl isocyanate. These reactions produced the unsaturated *anti*-1,2-amino alcohols either exclusively or predominantly only for aromatic derivatives. The anti-selectivity may be explained by the Cieplak electronic model during the conversion from ethers to carbamates.

The synthesis of chiral 1,2-amino alcohols has been an area of intense study in the synthetic and industrial fields because of their important roles in organic synthesis as fundamental building blocks and their occurrence in a number of natural products, drugs, and chiral auxiliaries or ligands.[1] General methods for the synthesis of these compounds can be divided into two large categories: functional group transformations and the C−C or the C−N bond formations. Of these two methods, the former has been used widely so far, including 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] and the hydroboration of enamines.[8] The latter involves the addition of an organometallic reagent to the N-protected α-amino aldehydes[9] or to the O-protected α-hydroxy imines[10] and coupling of carbanions with imines.[11] Many of these procedures sometimes have one or more problems, for example, low stereoselectivity, limited applications, and the use of heavy metals.

These facts prompted us to find a milder and widely applicable method for the synthesis of the 1,2-amino alcohols, especially the unsaturated 1,2-amino alcohols, which can be easily converted to β-hydroxy-α-amino acids. Since we have developed the novel synthetic methods for N-protected allylic amines from allyl ethers using chlorosulfonyl isocyante (CSI),[12] we found that the reaction of 1,4-diphenylbut-2-enyl methyl ether (**1**) with CSI gave only one product, methyl *N*-(1-benzylcinnamyl)-carbamate (**2**), due to the electronical repulsion of the phenyl ring and the formation of a stable conjugated product (Scheme 1).[12c]

Herein, we now describe a new approach to a variety of unsaturated 1,2-amino alcohols by the control of the stereocenters by asymmetric induction as an extension of the CSI reactions and how to control the diastereoselectivity in this reaction (Scheme 2).

Our initial studies examined the diastereoselective effect of the protecting group of the hydroxyl moiety in 5-methoxy-5-phenylpent-3-en-2-ol **3** (R^1, R^3 = Me, R^2 = Ph) as shown in Table 1. The treatment of **3a** with CSI at −78 °C furnished a 7:1 inseparable mixture of **4a** and **5a** in 55% chemical yield (entry 1). As the size of the silyl moiety of the protecting groups increased, the formation of the anti-isomer of the 1,2-amino alcohols decreased (entries 2−4). However, for the acetyl- or methyl-protected case (entries 5 and 6), a high diastereoselectivity was obtained despite the small bulkiness.

The anti-stereochemistry as a major product was confirmed by converting the inseparable mixture of carbamates, **4b** and **5b**, upon treatment with Bu_4NF and NaH, into the oxazolidinones **6a** and **6b** which are separable. The planar nature of the five-membered ring induced an eclipsing interaction of C_4−C_5 substituents. Thus, the trans-substitution provides a shielding envi-

* To whom correspondence should be addressed. Fax: 8231-290-5403. Tel: 8231-290-7711.

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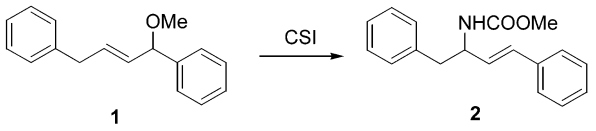
SCHEME 1



SCHEME 2

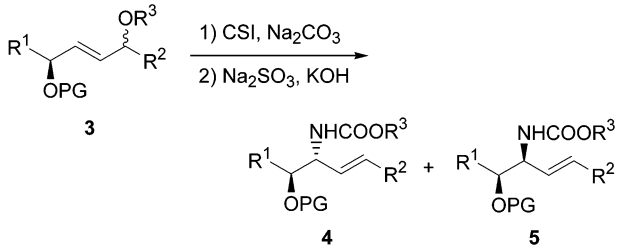
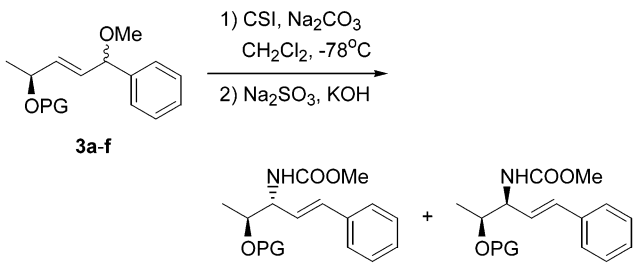


TABLE 1. CSI Reaction of Allyl Ethers by Varying the Protecting Groups of the Hydroxyl Moiety (R^1, R^3 = Me, R^2 = Ph)



	PG	ratio[a] (**4**/**5**)	yield[b] (%)
1	TMS (**3a**)	7.0:1	55[c]
2	TBS (**3**b)	6.2:1	83
3	TIPS (**3c**)	4.5:1	83
4	TBDPS (**3d**)	2.5:1	76[c]
5	Ac (**3e**)	7.4:1	77[d]
6	Me (**3f**)	5.1:1	81[e]

[a] Based on integrals of OCH_3 signals in carbamates. [b] Isolated yield of pure material. [c] Yield determined after deprotection of the hydroxy group with TBAF in THF at 0 °C, due to the difficulty in obtaining the pure material from column chromatography. [d] Yield determined after deprotection of the hydroxy group with K_2CO_3 in MeOH−H_2O at 0 °C. [e] Yield determined after deprotection of the hydroxy group with BBr_3 in CH_2Cl_2 at 0 °C.

ronment for both C_4 and C_5 methine hydrogens. The chemical shifts of H_4 and H_5 are substantially upfield compared to their cis-substituted oxazolidinones. Additionally, the coupling constants J_{ab} for the trans-substituted oxazolidinones are slightly smaller than those observed for the cis-isomers.[13] Therefore, the chemical shift of H_a and J_{ab} value between H_a and H_b of **6a** after decoupling of the methyl moiety indicated that the major product is **4b**, which has the anti-stereochemistry in the CSI reaction (Scheme 3).

To find the role of the solvent in this reaction, we investigated the CSI reaction of TBS-protected ether (**3b**) with various solvents. The results are summarized in Table 2. The treatment of **3b** with CSI in CH_2Cl_2 furnished a 6.2:1 inseparable mixture of **4b** and **5b** in

SCHEME 3

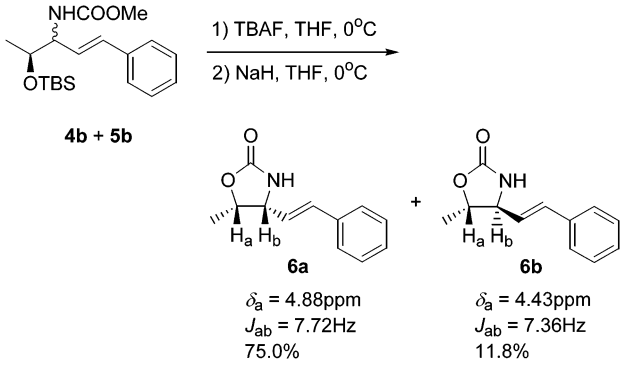
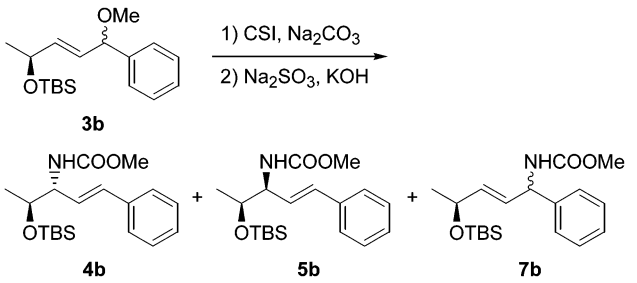


TABLE 2. CSI Reaction of 3b with Various Solvents[a]



	solvent	ratio[b] (**4b**/**5b**)	yield[c] (%) (**4b** + **5b**)	yield[c] (%) (**7b**)
1	CH_2Cl_2	6.2:1	83	*d*
2	$CHCl_3$	5.7:1	77	9
3	Et_2O	5.6:1	53	8
4	hexane	5.2:1	57	23

[a] All the reactions were carried out at −78 °C, except for entry 2 (−60 °C). [b] Based on integrals of OCH_3 signals in carbamates. [c] Isolated yield of pure material. [d] Not detected.

83% chemical yield (entry 1). However, the reaction in $CHCl_3$ gave a 5.7:1 mixture of 1,2-amino alcohol in 77% yield and 1,4-amino alcohol (**7b**) in 9% yield (entry 2). As the polarity of solvent decreased, the proportion of 1,4-amino alcohol increased via tight ion pair, due to the decrease of the ability to stabilize allyl carbocation by solvation. However, the ratios of anti-isomer and syn-isomer of the 1,2-amino alcohols were similar to that obtained in CH_2Cl_2. Therefore, these results suggested that a free allyl carbocation[12b,14] may be involved in formation of the 1,2-amino alcohol and solvent should not affect the diastereoselectivity but regioselectivity of the process.

Next, we investigated the substituent effect on the diastereoselectivity by varying the R^1 moiety (R^1 = Me, Et, *i*-Pr, Ph, R^2 = Ph, R^3 = Me) and protecting groups (TBS and TIPS) as shown in Table 3. The treatment of **3g** with CSI at −78 °C furnished a 6.5:1 inseparable mixture of **4g** and **5g** in 75% chemical yield (entry 3). As the size of R^1 increased, the formation of the anti-isomer of the 1,2-amino alcohols increased (entries 4−8). When R^1 is phenyl and the protecting group is TBS (**3k**), the highest diastereoselectivity (>99) was obtained in an 83% chemical yield (entry 7). In all cases, the formation of

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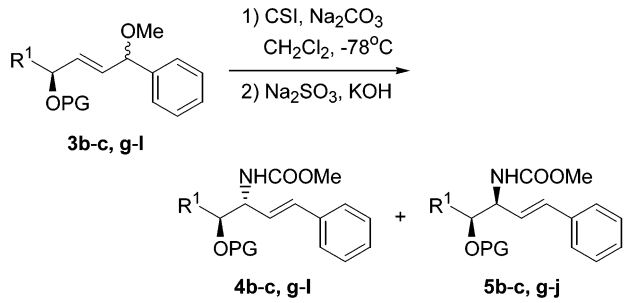
TABLE 3. CSI Reaction of Allyl Ethers by Varying R^1 (R^2 = Ph, R^3 = Me)



	R^1	PG	ratio[a] (**4**/**5**)	yield[b] (%)
1	Me	TBS (**3b**)	6.2:1	83
2		TIPS (**3c**)	4.5:1	83
3	Et	TBS (**3g**)	6.5:1	75[c]
4		TIPS (**3h**)	5.6:1	72[c]
5	*i*-Pr	TBS (**3i**)	11:1	68[c]
6		TIPS (**3j**)	9.4:1	77[c]
7	Ph	TBS (**3k**)	>99	83
8		TIPS (**3l**)	98:2	85

[a] Based on integrals of OCH_3 signals in carbamates. [b] Isolated yield of pure material. [c] Yield determined after deprotection of the hydroxy group with TBAF in THF at 0 °C, due to the difficulty in obtaining the pure material from column chromatography.

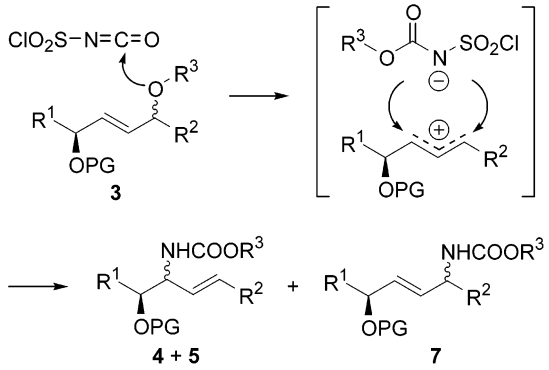


FIGURE 1. Possible model of regioselective nucleophilic attack on the allyl carbocation.

the anti-isomer in TBS protected compounds was slightly increased as compared to the case of the TIPS-protected ones. A similar method was used for the structural determination of **4k** through the formation of oxazolidinone (**6c**).

One plausible mechanism for these regioselective allylic aminations is shown in Figure 1. The stable allyl carbocation is formed by the cleavage of the C−O bond of the ether followed by nitrogen anion attack to produce the unsaturated 1,2-amino alcohol or 1,4-amino alcohol according to the steric hindrance of R^2. When R^2 is phenyl, the unsaturated 1,2-amino alcohol **4** is a major product due to the steric hindrance and the formation of a stable conjugated product.

The diastereoselectivity of **4** may be explained by the Felkin−Anh model or the Cieplak model. These models for a kind of Michael acceptor are based on the steric or electronic factors of the substituents around the site where the nucleophile attacks (Figure 2). From these models, a syn-isomer should be the major product through model A, in which a less bulkier group (R^1) orients inside

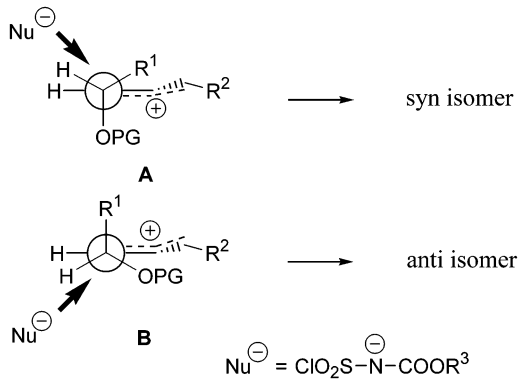


FIGURE 2. Felkin−Anh model (A) and Cieplak electronic model (B) of nucleophilic attack on the allyl carbocation.

and a more bulkier group (OPG)[15] takes up an anti position to the nucleophile attack.[16] However, from our results shown in Tables 1 and 3, the predominant formation of the anti-isomer in the CSI reactions was observed. Thus, our results cannot be explained by the steric factors of substituents such as model A. Instead, these results can be accounted for by the Cieplak electronic model (model B).[17] In intermediates of these CSI reactions, the π bond becomes electron deficient. Therefore, σ-donor substitutions stabilize the transition state. When the σ-donating group (R^1) is in the anti position and CO is inside, overlap of σ-donating σ_{CH} and σ_{CR} orbitals with the π orbital is maximized and overlap of σ^*_{CO} with π is minimized. So, the transition state is stabilized. Therefore, the alkyl moiety becomes anti, the OPG group orients inside, and the nucleophile attacks the less hindered outside position, as shown in Figure 2. This kind of model has been used for explanation of the diastereoselectivity during nitrile oxide cyclization to chiral allyl ethers (the "inside alkoxy" effect)[17b,18] and conjugate addition of nucleophiles to γ-alkoxy α,β-unsaturated carbonyl derivatives.[17c] It is clear from these models that an increase in the steric bulk at the OPG group produced a low anti-diastereoselectivity and an increase in the steric bulk at the alkyl moiety enhanced the anti/syn isomer ratio.

Another substituent effect on the diastereoselectivity by varying the R^2 moiety was examined as shown in Table 4. The treatment of **3m** with CSI at 20 °C furnished a 9.2:1 inseparable mixture of **4m** and **5m** in 29% chemical yield and the 1,4-amino alcohol (**7m**) (45%) (entry

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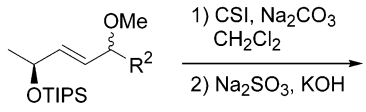
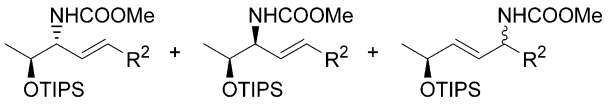
TABLE 4. CSI Reaction of Allyl Ethers by Varying R^2 [a]



3c, **m-s**



4c, **m-s** **5c**, **m-r** **7m-r**

	R^2	ratio[a] (**4**/**5**)	yield[b] (%) (**4** + **5**)	yield[b] (%) (**7**)
1	H (**3m**)	9.2:1	29	45
2	Me (**3n**)	9.2:1	13	76
3	Et (**3o**)	9.4:1	12	74
4	*i*-Pr (**3p**)	7.7:1	14	69
5	Bn (**3q**)	7.5:1	12	76
6	Ph (**3c**)	4.5:1	83	*c*
7	*t*-Bu (**3r**)	5.6:1	22	63
8	2-mesityl (**3s**)	98:2	82	*c*

[a] All the reactions were carried out at 20 °C, except for entries 6 and 8 (−78 °C). [b] Based on integrals of OCH_3 signals in carbamates. [c] Isolated yield of pure material. [d] Not detected.

1). For the **3n** and **3o** cases, a similar formation of the anti-isomer was obtained as compared to the **3m** case (entries 2 and 3). As the size of R^2 increased, the formation of the anti-isomer of the 1,2-amino alcohols decreased but not much due to the negligible steric repulsion between OTIPS and R^2 itself (entries 3−7).[19] However, for **3s**, a very high diastereoselectivity (anti/syn = 98:2) was observed unexpectedly in 82% chemical yield. From the data in Table 4, it appears that the factor controlling the site of the substitution (1,2-amino alcohol or 1,4-amino alcohol) depends more on the formation of a stable conjugated product than on any steric effect.

The diastereoselectivity in entry 8 can be explained by the modified Felkin-Anh model **C**,[20] in which the steric repulsion between OTIPS and the mesityl group, and Me and the mesityl group is minimized even though they are far from each other (Figure 3).

Finally, we changed the R^3 from Me to benzyl group (**3t**) in order to understand how the variation exerts an influence upon the diastereoselectivity. This result (**4t**/**5t** = 4.0:1, 87% yield) is similar to the Me case.

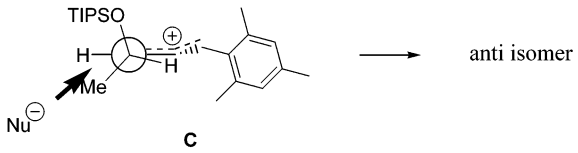


FIGURE 3. Modified Felkin−Anh model of nucleophilic attack on the allyl carbocation.

In conclusion, we have developed a novel regioselective and diastereoselective synthetic approach to the unsaturated aromatic 1,2-amino alcohols from the epimeric mixture of optically active allylic ethers having a hydroxyl group attached to an allylic chiral center to the π-system using the CSI reaction. The diastereoselectivity of this approach was investigated by varying the protecting group of the hydroxyl moiety and alkyl substituents. In all cases, an anti-stereoselectivity has been either exclusively or predominantly observed. An increase in the steric bulk at the OPG group produced a low anti-diastereoselectivity and an increase in the steric bulk at the alkyl moiety (R^1) produced a high excess of the anti-isomer. Treatment of **3k** with CSI furnished the anti-stereoisomer **4k** in 83% chemical yield. The anti-selectivity can be explained by the Cieplak electronic model **B**. For **3s**, the anti-stereoisomer **4s** was obtained as the sole product, which can be explained by the modified Felkin−Anh Model **C**.

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Supporting Information Available: Experimental procedure, characterization data, and spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) One of reviewers suggested that steric interaction between R_2 and CHR_1OTIPS in allyl cations cannot be responsible for anything by geometry optimization with the PM3 Methodol. We deeply appreciated this comment.

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