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Diastereoselective Synthesis of Unsaturated 1,4-Amino Alcohols as a Biologically Important Moiety

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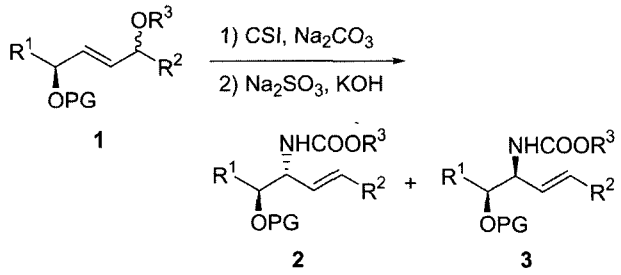
The diastereoselective synthesis of unsaturated 1.4-amino alcohols can be achieved using chial allylic ethers with a hydroxyl group attached to the π-system and chlorosulfonyl isocyanate. The enantioselectivity of the CSI reaction with the chiral allylic and benzylic ethers was examined in various solvents and temperatures. Based on these results, it was proposed that the CSI reaction is a competitive reaction of a S_Ni (retention) and a S_N1 mechanism (racemization) according to the stability of the carbocation intermediate. This means that there is a greater proportion of retention with the less stable the carbocation intermediate and vise versa.

Key words: Chlorosulfonyl isocyanate, Chiral allyl ether, Chiral benzyl ether, 1,4-Amino alcohols, Carbamates

INTRODUCTION

The synthesis of allylic amines has been an area of intense research in the synthetic and industrial fields, owing to their important roles in organic synthesis as fundamental building blocks and their occurrence in a large number of natural products (Johannsen and Jorgensen, 1998). Recently we reported a novel method for synthesizing *N*-allylcarbamates from allyl ethers using chlorosulfonyl isocyanate (CSI) (Jung and Kim, 2000, 2001; Kim *et al.*, 2000, 2001, 2005), and developed a novel regioselective and diastereoselective synthetic approach using the 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 the allylic chiral center of the π-system (Kim *et al.*, 2003) (Scheme 1).

Furthermore, we have found a novel technique for comparing directly the stability of carbocations in the solution phase and have established the stability order of the various carbocations under our reaction conditions



Scheme 1. The reaction of *trans*-allyl ethers with CSI

(Kim *et al.*, 2002), and we have reported the extension of CSI under new reaction condition to the cleavage of various benzyl and *p*-methoxybenzyl protecting groups of alcohols and phenols in the presence of other functional groups (Kim *et al.*, 2003). Also, we carefully suggested that the CSI reaction of allyl ethers is a competitive reaction of S_Ni and S_N1 mechanism according to the stability of the carbocation by the reaction of *p*-substituents in *p*-substituted cinnamyl methyl ethers and 1-(*p*-substituted phenyl)allyl methyl ethers with CSI (Jung and Kim, 2003).

As previously reported, 1,2-amino alcohol derivatives were synthesized by the chiral induction and its mechanism was rationalized in terms of the Cieplak electronic model and modified Felkin-Anh model (Kim, *et al.*, 2003). In papers reporting these models (Cieplak *et*

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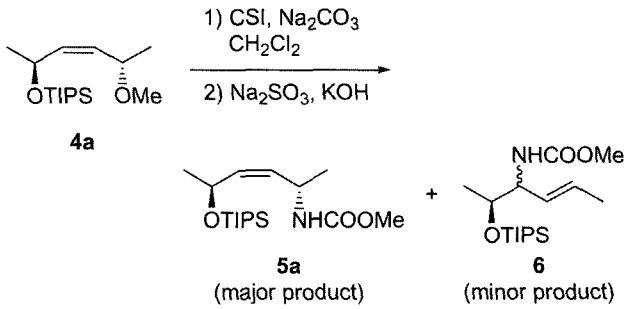


Scheme 2. The reaction of (2*S*, 5*S*)-*cis*-allyl methyl ether with CSI

al., 1981; Houk *et al.*, 1984; Yamamoto, 1992), it was found that the transition state in these mechanisms depends on the geometric configuration of the double bond. Therefore, the initial studies examined the reaction (2*S*,5*S*)-*cis*-allyl methyl ether **4a** with CSI, in order to confirm the effect of the geometric configuration on the diastereoselectivity under the reaction condition. In contrast to previous results, this reaction gave a mixture of (1*S*,4*S*)-1,4-amino alcohol **5a** as a major product and 1,2-amino alcohol **6** (Kim *et al.*, 2003) as a minor product (Scheme 2).

MATERIALS AND METHODS

Commercially available reagents were used without additional purification, unless otherwise stated. All anhydrous solvents were distilled over CaH_2 or P_2O_5 or Na/ benzophenone prior to reaction. All reactions were performed under an inert atmosphere of nitrogen or argon. Melting points were measured on a Gallenkamp melting point apparatus or Electrothermal IA9300 melting point apparatus and were not corrected. Nuclear magnetic resonance spectra (^{1}H- and ^{13}C-NMR) were recorded on a Varian Unity Inova 500 MHz spectrometer for $CDCl_3$ solutions and chemical shifts are reported as parts per million (ppm) relative to, respectively, residual $CHCl_3$ δ_H (7.26 ppm) and $CDCl_3$ δ_C (77.0 ppm) as internal standards. Resonance patterns are reported with the notations s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). In addition, the notation br is used to indicate a broad signal. Coupling constants (*J*) are reported in hertz (Hz). IR spectra were recorded on a Nicolet 205 Infrared spectrophotometer or Bruker Vector 22 Infrared spectrophotometer and are reported as cm^{-1}. Optical rotations were measured with a Jasco P1020 polarimeter. Thin layer chromatography was carried out using plates coated with Kieselgel $60F_{254}$ (Merck). For flash column chromatography, E. Merck Kieselgel 60 (230-400 mesh) was used. High-resolution mass spectra (HRMS) were recorded on a JEOL, JMS-505 or JMS-600 spectrometer using the chemical ionization (CI) method.

General procedure for the preparation of ethers. (2*S*,5*S*)-(*Z*)-2-Methoxy-5-(triisopropylsilyloxy)hex-3-ene (4a)

To a suspension of NaH (0.30 g, 7.22 mmol, 60% in mineral oil) in THF (30 mL) was added ethyl diphenylphosphonoacetate (1.82 g, 5.67 mmol) at -78°C under N_2. After 15 min later, (2*S*)-2-(triisopropylsilyloxy) propionaldehyde (1.19 g, 5.16 mmol) was added and stirred at -78°C for 1 h, then warmed to room temperature. The reaction mixture was quenched with saturated NH_4Cl aqueous solution and extracted with EtOAc (30 mL). The organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (Hexane/ EtOAc = 50: 1) to afford 1.06 g (68%) of (4*S*)-(*Z*)-ethyl 4-(triisopropylsilyloxy) pent-2-enoate as a colorless oil. To a solution of (4*S*)-(*Z*)-ethyl 4-(triisopropylsilyloxy)pent-2-enoate (1.05 g, 3.49 mmol) in benzene (10 mL) was added DIBAL-H (6.99 mL, 6.99 mmol, 1.0 M in toluene) at 0°C under N_2. The reaction was stirred at 0°C for 1 h. Saturated NH_4Cl aqueous solution (20 mL) was added and stirred at 0°C for 1 h, then 1 N HCl (10 mL) was added and extracted with EtOAc (20 mL × 2). The organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (Hexane/EtOAc = 6:1) to give 0.86 g (95%) of (4*S*)-(*Z*)-4-(triisopropylsilyloxy)pent-2-en-1-ol as a colorless oil. To a solution of $(COCl)_2$ (0.31 mL, 3.62 mmol) in CH_2Cl_2 (13 mL) was added DMSO (0.51 mL, 7.24 mmol) at -78°C under N_2. The reaction mixture was stirred at -70 °C for 15 min, a solution of (4*S*)-(*Z*)-4-(triisopropylsilyloxy) pent-2-en-1-ol (0.85 g, 3.29 mmol) in CH_2Cl_2 (3 mL) was added at -70°C and stirred at -60°C for 30 min. NEt_3 (2.29 mL, 16.44 mmol) was added, stirred at -60°C for 30 min and EtOAc (30 mL) was added, then warmed to room temperature. The organic was washed with saturated $NaHCO_3$ aqueous solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (Hexane/EtOAc = 50: 1) to give 0.80 g (95%) of (4*S*)-(*Z*)-4-(triisopropylsilyloxy) pent-2-enal as a colorless oil. To a solution of (4*S*)-(*Z*)-4-(triisopropylsilyloxy)pent-2-enal (0.38 g, 1.48 mmol) in Et_2O (3 mL) was added MeMgBr (0.60 mL, 1.78 mmol, 3.0 M in Et_2O) at -78°C under N_2. The reaction mixture was stirred at -78°C for 1 h and at 0°C for 1 h, then quenched with saturated NH_4Cl aqueous solution and extracted with EtOAc (10 mL). The organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (Hexane/ EtOAc = 10:1) to give 0.21 g (52%) of (2*S*,5*S*)-(*Z*)-5-(triisopropylsilyloxy)hex-3-en-1-ol as a colorless oil and 0.18 g (45%) of (2*R*,5*S*)-(*Z*)-5-(triisopropylsilyloxy)hex-3-en-1-ol as a colorless oil. To a solution of (2*S*,5*S*)-(*Z*)-5-

(triisopropylsilyloxy)hex-3-en-1-ol (0.15 g, 0.55 mmol) in THF (2 mL) was added NaH (33 mg, 0.83 mmol, 60% in mineral oil). The reaction mixture was warmed to 45°C under N_2 and MeI (51 μL, 0.83 mmol) was added dropwise. The reaction mixture was stirred at 45°C for 1 h and cooled to room temperature. H_2O (1 mL) was added and the solution was extracted with EtOAc (10 mL). The organic layer was washed with H_2O and brine. The organic was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (Hexane/EtOAc = 50:1) to give 0.14 g (89%) of (2*S*,5*S*)-(*Z*)-2-methoxy-5-(triisopropylsilyloxy)hex-3-ene (**4a**) as a colorless oil. R_f: 0.37 (30:1 Hexane/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.04-1.08 (m, 21H), 1.18 (d, 3H, J = 6.5 Hz), 1.22 (d, 3H, J = 6.5 Hz), 3.27 (s, 3H), 4.06 (dq, 1H, J = 7.5, 6.5 Hz), 4.71 (dq, 1H, J = 7.5, 6.5 Hz), 5.21 (dd, 1H, J = 10.5, 7.5 Hz), 5.62 (dd, 1H, J = 10.5, 7.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 12.99, 18.76, 22.38, 26.32, 56.86, 65.92, 73.41, 130.67, 138.52; IR (neat): 2924, 1459, 1378, 1263, 1092 cm^{-1}; $[\alpha]_D^{27}$ +18.5 (*c* 1.0, $CHCl_3$); HRMS (CI) calcd for $C_{16}H_{34}O_2Si$+H $(M+H)^+$ 287.2406. Found: 287.2414.

(2*R*,5*S*)-(*Z*)-2-Methoxy-5-(triisopropylsilyloxy)hex-3-ene (4b)

The similar procedure for **4a** was followed using (2*R*,5*S*)-(*Z*)-5-(triisopropylsilyloxy)hex-3-en-1-ol (0.12 g, 0.44 mmol), NaH (26 mg, 0.66 mmol, 60% in mineral oil) and MeI (41 μL, 0.66 mmol) in THF (2 mL). The reaction mixture was purified by column chromatography (Hexane/EtOAc = 50:1) to give 0.12 g (95%) of (2*R*,5*S*)-(*Z*)-2-methoxy-5-(triisopropylsilyloxy)hex-3-ene (**4b**) as a colorless oil. R_f: 0.33 (10:1 Hexane/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.01-1.06 (m, 21H), 1.20 (d, 3H, J = 6.5 Hz), 1.26 (d, 3H, J = 6.0 Hz), 3.22 (s, 3H), 4.02 (dq, 1H, J = 8.5, 6.5 Hz), 4.70 (dq, 1H, J = 8.5, 6.0 Hz), 5.11 (dd, 1H, J = 11.5, 8.5 Hz), 5.58 (dd, 1H, J = 11.5, 8.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 12.98, 18.762, 18.73, 21.77, 25.81, 56.53, 65.75, 73.39, 129.66, 138.89; IR (neat): 2924, 1458, 1374, 1262, 1094, 1022 cm^{-1}; $[\alpha]_D^{27}$ +0.3 (*c* 0.5, $CHCl_3$); HRMS (CI) calcd for $C_{16}H_{34}O_2Si$-H $(M-H)^+$ 285.2250. Found: 285.2255.

(1*R*,4*S*)-(*Z*)-1-Methoxy-1-phenyl-4-(triisopropylsilyloxy) pent-2-ene (4c)

The similar procedure for **4a** was followed using (1*R*,4*S*)-(*Z*)-1-phenyl-4-(triisopropylsilyloxy) pent-2-en-1-ol (0.15 g, 0.45 mmol), NaH (27 mg, 0.67 mmol, 60% in mineral oil) and MeI (42 μL, 0.67 mmol) in THF (2 mL). The reaction mixture was purified by column chromatography (Hexane/EtOAc = 50:1) to give 0.14 g (90%) of (1*R*,4*S*)-(*Z*)-1-methoxy-1-phenyl-4-(triisopropyl-silyloxy) pent-2-ene (**4c**) as a colorless oil. R_f: 0.34 (30:1 Hexane/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.07-1.13 (m, 24H), 3.31 (s, 3H), 4.84 (dq, 1H, J = 8.0, 7.0 Hz), 4.89 (d, 1H, J = 8.5 Hz), 5.52 (ddd, 1H, J = 11.0, 8.5, 1.0 Hz), 5.62 (ddd, 1H, J = 11.0, 8.0, 1.0 Hz), 7.27-7.36 (m, 5H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 13.03, 18.75, 18.38, 25.41, 56.92, 66.22, 80.08, 127.52, 128.39, 128.77, 129.28, 138.29, 142.17; IR (neat): 2926, 2866, 1463, 1366, 1258, 1188, 1093 cm^{-1}; $[\alpha]_D^{27}$ +103.5 (*c* 0.5, $CHCl_3$); HRMS (CI) calcd for $C_{21}H_{36}O_2Si$+H $(M+H)^+$ 349.2563. Found: 349.2558.

(1*S*,4*S*)-(*Z*)-1-Methoxy-1-phenyl-4-(triisopropylsilyloxy) pent-2-ene (4d)

The similar procedure for **4a** was followed using (1*S*,4*S*)-(*Z*)-1-phenyl-4-(triisopropylsilyloxy) pent-2-en-1-ol (0.10 g, 0.23 mmol), NaH (18 mg, 0.45 mmol, 60% in mineral oil) and MeI (28 μL, 0.45 mmol) in THF (1 mL). The reaction mixture was purified by column chromatography (Hexane/EtOAc = 50:1) to give 99 mg (95%) of (1*S*,4*S*)-(*Z*)-1-methoxy-1-phenyl-4-(triisopro-pylsilyloxy)pent-2-ene (**4d**) as a colorless oil. R_f: 0.34 (30:1 Hexane/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.95-1.03 (m, 21H), 1.34 (d, 3H, J = 6.5 Hz), 3.27 (s, 3H), 4.80 (dq, 1H, J = 8.0, 6.5 Hz), 4.86 (d, 1H, J = 8.5 Hz), 5.49 (dd, 1H, J = 11.5, 8.5 Hz), 5.66 (dd, 1H, J = 11.5, 8.0 Hz), 7.27-7.35 (m, 5H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 12.92, 18.66, 18.71, 25.75, 56.69, 66.18, 80.21, 127.69, 128.31, 128.49, 129.14, 139.22, 141.83; IR (neat): 2940, 2867, 1459, 1377, 1088, 1012 cm^{-1}; $[\alpha]_D$ -60.1 (*c*=1.0, $CHCl_3$, 26°C); HRMS (CI) calcd for $C_{21}H_{36}O_2Si$+H $(M+H)^+$ 349.2563. Found: 349.2563.

(2*S*)-1,4-Diphenyl-2-methoxybut-3-ene (7a)

To a solution of L-phenylalanine (5.00 g, 30.27 mmol) in 1 N H_2SO_4 (50 mL) was added a solution of $NaNO_2$ (3.13 g, 45.40 mmol) in H_2O (17 mL) at 0°C. The reaction mixture was stirred at 0°C for 24 h. The solution was saturated with $(NH_4)_2SO_4$ and extracted with Et_2O (50 mL×3). The organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was used for further manipulation without purification. The residue was treated with CH_2N_2 in Et_2O at 0°C. The reaction mixture was purified by column chromatography (Hexane/EtOAc = 3:1) to give 4.42 g (81%) of (2*S*)-methyl 2-hydroxy-3-phenylpropionate as a white solid. The similar procedure for **4a** was followed using (2*S*)-methyl 2-hydroxy-3-phenylpropionate (4.00 g, 22.20 mmol), NaH (1.07 g, 26.64 mmol, 60% in mineral oil) and MeI (2.07 mL, 33.30 mmol) in THF (44 mL) at room temperature. The reaction mixture was purified by column chromatography (Hexane/EtOAc = 6:1) to give 3.19 g (74%) of (2*S*)-methyl 2-methoxy-3-phenylpropionate as a colorless oil. To a solution of (2*S*)-methyl 2-methoxy-3-phenylpropionate (2.50 g, 12.87 mmol) in CH_2Cl_2 (15 mL) was added DIBAL-H (9.00 mL, 13.51 mmol, 1.5 M in toluene) at -78

°C under N_2. The reaction mixture was stirred at -78°C for 1 h and quenched with saturated NH_4Cl aqueous solution (20 mL), then extracted with EtOAc (30 mL). The organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (Hexane/EtOAc = 6:1) to give 1.81 g (86%) of (2*S*)-2-methoxy-3-phenylpropionaldehyde as a colorless oil. The similar procedure for **8e** was followed (2*S*)-2-methoxy-3-phenylpropionaldehyde (1.00 g, 6.09 mmol), NaHMDS (6.70 mL, 6.70 mmol, 1.0 M in THF) and diethyl benzylphosphonate (1.40 mL, 6.70 mmol) in THF (12 mL). The reaction mixture was purified by column chromatography (Hexane/EtOAc = 30:1) to give 1.23 g (85%) of (2*S*)-1,4-diphenyl-2-methoxybut-3-ene (**7a**) as a white solid. R_f: 0.40 (15:1 Hexane/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.89 (dd, 1H, J = 14.0, 6.0 Hz), 3.04 (dd, 1H, J = 14.0, 7.0 Hz), 3.30 (s, 3H), 3.97 (ddd, 1H, J = 7.5, 7.0, 6.0 Hz), 6.12 (dd, 1H, J = 16.0, 7.5 Hz), 6.49 (d, 1H, J = 16.0 Hz), 7.21-7.39 (m, 10H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 43.22, 57.23, 84.08, 126.93, 127.21, 128.43, 128.92, 129.30, 130.29, 133.18, 137.27, 138.93; IR (CH_2Cl_2): 3037, 2928, 1700, 1609, 1460, 1337, 1093 cm^{-1}; mp: 36~38°C; $[\alpha]_D$ +50.9 (c=1.0, $CHCl_3$, 27°C); HRMS (CI) calcd for $C_{17}H_{18}O$-H $(M-H)^+$ 237.1280. Found: 237.1278.

(2*S*)-2-Methoxy-1-phenylbut-3-ene (7b)

To a suspension of methyltriphenylphosphonium bromide (0.96 g, 2.68 mmol) in THF (6 mL) was added LDA (1.34 mL, 2.68 mmol, 2.0 M in heptane/THF/ethylbenzene) at 0°C under N_2. The reaction mixture was stirred at 0°C for 2 h. A solution of (2*S*)-2-methoxy-3-phenylpropionaldehyde (0.40 g, 2.44 mmol) in THF (2 mL) and the reaction mixture was stirred at room temperature for 1 h, quenched with saturated NH_4Cl aqueous solution, then extracted with EtOAc (20 mL). The organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (Hexane/EtOAc = 15:1) to give 0.23 g (59%) of (2*S*)-2-methoxy-1-phenylbut-3-ene (**7b**) as a colorless oil. R_f: 0.30 (15:1 Hexane/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.78 (dd, 1H, J = 14.0, 6.5 Hz), 2.95 (dd, 1H, J = 14.0, 7.5 Hz), 3.30 (s, 3H), 3.79 (ddd, 1H, J = 7.5, 7.5, 6.5 Hz), 5.14 (dd, 1H, J = 17.5, 1.0 Hz), 5.18 (dd, 1H, J = 10.5, 1.0 Hz), 5.69 (ddd, 1H, J = 17.5, 10.5, 7.5 Hz), 7.21-7.24 (m, 3H), 7.26-7.32 (m, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 42.85, 57.11, 84.53, 118.12, 126.87, 128.85, 130.25, 138.73, 139.02; IR (neat): 2928, 1440, 1348, 1339, 1237, 1095 cm^{-1}; $[\alpha]_D$ -6.0 (c=1.0, $CHCl_3$, 27°C); HRMS (CI) calcd for $C_{11}H_{14}O$+H $(M+H)^+$ 163.1123. Found: 163.1123.

(1*S*)-1-Benzyloxy-1-phenylethane (7d)

To a solution of (*S*)-(-)-1-phenylethanol (0.30 g, 2.46 mmol) in THF (12 mL) and DMF (3 mL) was added NaH (0.15 g, 3.68 mmol, 60% in mineral oil) and BnBr (0.44 mL, 3.68 mmol). The reaction mixture was stirred at room temperature for 15 h under N_2, quenched with H_2O (20 mL), then extracted with EtOAc (20 mL). The organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (Hexane/EtOAc = 50:1) to give 0.45 g (87%) of (1*S*)-1-benzyloxy-1-phenylethane (**7d**) as a colorless oil. R_f: 0.43 (15:1 Hexane/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.49 (d, 3H, J = 6.5 Hz), 4.32 (d, 1H, J = 12.0 Hz), 4.47 (d, 1H, J = 12.0 Hz), 4.52 (q, 1H, J = 6.5 Hz), 7.27-7.39 (m, 10H); ^{13}C-NMR (125 MHz, $CDCl_3$ *d* 24.92, 71.01, 77.92, 127.04, 128.17, 128.20, 128.41, 129.06, 129.19, 139.33, 144.42; IR (neat): 2928, 2864, 1494, 1452, 1369, 1305, 1282, 1206, 1096, 1028 cm^{-1}; $[\alpha]_D^{27}$ -94.7 (c 1.0, $CHCl_3$); HRMS (CI) calcd for $C_{15}H_{16}O$-H $(M-H)^+$ 211.1123. Found: 211.1125.

(2*S*)-2-Methoxy-4-*p*-methylphenyl-1-phenylbut-3-ene (7f)

The similar procedure for **8e** was followed using (2*S*)-2-methoxy-3-phenylpropionaldehyde (0.20 g, 1.22 mmol), NaHMDS (1.34 mL, 1.34 mmol, 1.0 M in THF) and diethyl *p*-methylbenzylphosphonate (0.32 g, 1.34 mmol) in THF (3 mL). The reaction mixture was purified by column chromatography (Hexane/EtOAc = 30:1) to give 0.22 g (71%) of (2*S*)-2-methoxy-4-*p*-methylphenyl-1-phenylbut-3-ene (**7f**) ((*E*) : (*Z*) = 4 : 1) as a pale yellow oil.

(2*S*)-(*E*)-2-Methoxy-4-*p*-methylphenyl-1-phenylbut-3-ene
R_f: 0.37 (15:1 Hexane/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.88 (dd, 1H, J = 14.0, 6.0 Hz), 3.02 (dd, 1H, J = 14.0, 7.0 Hz), 3.32 (s, 3H), 3.95 (ddd, 1H, J = 7.5, 7.0, 6.0 Hz), 6.05 (dd, 1H, J = 16.0, 7.5 Hz), 6.46 (d, 1H, J = 16.0 Hz), 7.14 (d, 2H, J = 8.0 Hz), 7.21-7.33 (m, 7H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 21.48, 42.84, 56.71, 83.71, 126.68, 128.45, 128.50, 129.55, 129.87, 132.66, 134.08, 137.85, 138.59; IR (neat): 3026, 2923, 2819, 1604, 1513, 1495, 1453, 1359, 1098 cm^{-1}; HRMS (CI) calcd for $C_{18}H_{20}O$-H $(M-H)^+$ 251.1436. Found: 251.1429.

(2*S*)-(*Z*)-2-Methoxy-4-*p*-methylphenyl-1-phenylbut-3-ene
^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.35 (s, 3H), 2.90 (dd, 1H, J = 14.0, 6.0 Hz), 3.01 (dd, 1H, J = 14.0, 7.0 Hz), 3.19 (s, 3H), 4.36 (ddd, 1H, J = 8.5, 7.0, 6.0 Hz), 5.55 (dd, 1H, J = 11.5, 8.5 Hz), 6.68 (d, 1H, J = 11.5 Hz), 6.91 (d, 2H, J = 7.5 Hz), 7.09 (d, 2H, J = 7.5 Hz), 7.20-7.29 (m, 5H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 21.48, 42.05, 56.11, 83.71, 126.45, 126.55, 128.76, 128.85, 129.11, 129.93, 132.36, 132.88, 137.27.

General procedure for the reaction of alkyl ether with CSI

A suspension of Na_2CO_3 (6.75 mmol) in anhydrous CH_2Cl_2 (12 mL) was adjusted to 20°C or -78°C, then CSI (4.50 mmol) and alkyl ether (3.00 mmol) was added under N_2. The reaction mixture was stirred at 20°C or -78°C, quenched with H_2O (10 mL) when the reaction was completed (TLC monitoring), then extracted with EtOAc (10 mL×2). The organic layer was added to an aqueous solution of Na_2SO_3 (25%) and KOH (10%), and the reaction mixture was stirred at room temperature for overnight. The organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (Hexane/EtOAc).

(1*S*)-Methyl *N*-(1-benzyl-3-phenylprop-2-enyl) carbamate (8a)

The above general procedure was followed using (2*S*)-1,4-diphenyl-2-methoxybut-3-ene (**7a**) (0.10 g, 0.42 mmol), Na_2CO_3 (0.10 g, 0.94 mmol) and CSI (55 μL, 0.63 mmol) in CH_2Cl_2 (2 mL) at -78°C. The reaction mixture was purified by column chromatography (Hexane/EtOAc = 6:1) to give 85 mg (72%) of (1*S*)-methyl *N*-(1-benzyl-3-phenylprop-2-enyl)carbamate (8a) (37% ee) as a white solid. R_f: 0.40 (3:1 Hexane/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.96 (d, 2H, J = 6.5 Hz), 3.68 (s, 3H), 4.61-4.70 (br, 1H), 4.71-4.80 (br, 1H), 6.15 (dd, 1H, J = 16.0, 6.0 Hz), 6.47 (dd, 1H, J = 16.0, 1.0 Hz), 7.21-7.39 (m, 10H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 42.49, 52.92, 54.39, 127.13, 127.39, 128.34, 129.20, 129.26, 130.26, 130.30, 131.07, 137.32, 137.73, 156.99; IR (CH_2Cl_2): 3318, 3027, 1691, 1638, 1537, 1493, 1448, 1321, 1264, 1061 cm^{-1}; HRMS (CI) calcd for $C_{18}H_{19}NO_2$+H $(M+H)^+$ 282.1494. Found: 282.1492.

(1*S*)-Methyl *N*-(1-benzylprop-2-enyl)carbamate (8b)

The above general procedure was followed using (2*S*)-2-methoxy-1-phenylbut-3-ene (**7b**) (0.14 g, 0.89 mmol), Na_2CO_3 (0.21 g, 1.94 mmol) and CSI (0.11 mL, 1.29 mmol) in hexane (4 mL) at 20°C. The reaction mixture was purified by column chromatography (Hexane/EtOAc = 10:1) to give 0.14 g (75%) of (1*S*)-methyl *N*-(1-benzylprop-2-enyl)carbamate (**8b**) (72% ee) as a colorless oil and 10 mg (5%) of methyl *N*-(4-phenylbut-2-enyl)carbamate (**9**) as a white solid. R_f: 0.39 (5:1 Hexane/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.86 (d, 2H, J = 6.5 Hz), 3.66 (s, 3H), 4.40-4.48 (br, 1H), 4.57-4.65 (br, 1H), 5.11 (dd, 1H, J = 10.5, 1.5 Hz), 5.12 (dd, 1H, J = 17.0, 1.5 Hz), 5.81 (ddd, 1H, J = 17.0, 10.5, 5.5 Hz), 7.18-7.32 (m, 5H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 42.06, 52.83, 54.62, 115.72, 127.33, 129.11, 130.21, 137.77, 138.45, 157.01; IR (nujol): 3330, 2954, 2861, 1693, 1539, 1459, 1376, 1255 cm^{-1}; HRMS (CI) calcd for $C_{12}H_{15}NO_2$+H $(M+H)^+$ 206.1181. Found: 206.1182.

(1*S*)-Methyl *N*-(1-phenylethyl)carbamate (8c)

The above general procedure was followed using (1*S*)-1-methoxy-1-phenylethane (**7c**) (0.10 g, 0.73 mmol), Na_2CO_3 (0.18 g, 1.65 mmol) and CSI (96 μL, 1.10 mmol) in hexane (3 mL) at 20°C. The reaction mixture was purified by column chromatography (Hexane/EtOAc = 6:1) to give 0.11 g (85%) of (1*S*)-methyl *N*-(1-phenylethyl) carbamate (**8c**) (66% ee) as a white solid. R_f: 0.34 (3:1 Hexane/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.49 (d, 3H, J = 6.5 Hz), 3.66 (s, 3H), 4.80-4.88 (br, 1H), 4.92-4.98 (br, 1H), 7.25-7.34 (m, 5H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 23.14, 51.32, 52.76, 126.64, 128.01, 129.33, 144.28, 156.93; IR (CH_2Cl_2): 3319, 2974, 2860, 1699, 1532, 1449, 1358, 1252, 1067 cm^{-1}; HRMS (CI) calcd for $C_{10}H_{13}NO_2$+H $(M+H)^+$ 180.1024. Found: 180.1024.

(1*S*)-Benzyl *N*-(1-phenylethyl)carbamate (8d)

The above general procedure was followed using (1*S*)-1-benzyloxy-1-phenylethane (**7d**) (0.30 g, 1.41 mmol), Na_2CO_3 (0.34 g, 3.18 mmol) and CSI (0.19 mL, 2.19 mmol) in hexane (6 mL) at 20°C. The reaction mixture was purified by column chromatography (Hexane/EtOAc = 6:1) to give 0.30 g (84%) of (1*S*)-benzyl *N*-(1-phenylethyl)carbamate (**8d**) (68% ee) as a white solid. R_f: 0.28 (6:1 Hexane/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.49 (d, 3H, J = 6.5 Hz), 4.83-4.90 (br, 1H), 5.07 (d, 1H, J = 12.5 Hz), 5.06-5.10 (br, 1H), 5.12 (d, 1H, J = 12.5 Hz), 7.26-7.36 (m, 10H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 23.18, 51.44, 67.44, 126.64, 128.05, 128.84, 129.22, 129.36, 137.19, 144.17, 156.24; IR (CH_2Cl_2): 3322, 3031, 2974, 1697, 1531, 1453, 1377, 1329, 1245, 1057 cm^{-1}; HRMS (CI) calcd for $C_{16}H_{17}NO_2$+H $(M+H)^+$ 256.1337. Found: 256.1334.

(1*R*)-Methyl *N*-(1-phenylprop-2-enyl)carbamate (8e)

The above general procedure was followed using (1*R*)-1-methoxy-1-phenylprop-2-ene (**7e**) (90 mg, 0.61 mmol), Na_2CO_3 (0.14 g, 1.37 mmol) and CSI (79 μL, 0.91 mmol) in hexane (2 mL) at 0°C. The reaction mixture was purified by column chromatography (Hexane/EtOAc = 10:1) to give 82 mg (71%) of (1*R*)-methyl *N*-(1-phenylprop-2-enyl) carbamate (**8e**) (45% ee) as a white solid and 13 mg (11%) of methyl *N*-(3-phenylprop-2-enyl)carbamate (**10**) as a white solid. R_f: 0.37 (3:1 Hexane/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.68 (s, 3H), 5.10-5.00 (br, 1H), 5.23 (dd, 1H, J = 16.5, 1.5 Hz), 5.24 (dd, 1H, J = 10.0, 1.5 Hz), 5.30-5.38 (br, 1H), 6.00 (ddd, 1H, J = 16.5, 10.0, 6.5 Hz), 7.26-7.36 (m, 5H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 52.96, 57.73, 116.45, 127.71, 128.38, 129.43, 138.35, 141.41, 156.91; IR (CH_2Cl_2): 3320, 2952, 2865, 1701, 1531, 1453, 1243, 1175, 1052 cm^{-1}; HRMS (CI) calcd for $C_{11}H_{13}NO_2$+H $(M+H)^+$ 192.1024. Found: 192.1024.

(1*S*)-Methyl *N*-[1-benzyl-3-(*p*-methylphenyl)prop-2-enyl] carbamate (8f)

The above general procedure was followed using (2*S*)-2-methoxy-4-*p*-methylphenyl-1-phenylbut-3-ene (**7f**) (0.20 g, 0.79 mmol), Na_2CO_3 (0.19 g, 1.78 mmol) and CSI (0.10 mL, 1.19 mmol) in hexane (3 mL) at 0°C. The reaction mixture was purified by column chromato-graphy (Hexane/EtOAc = 10:1) to give 0.17 g (73%) of (1*S*)-methyl *N*-[1-benzyl-3-(*p*-methylphenyl)prop-2-enyl] carbamate (**8f**) (7% ee, (*E*) : (*Z*) = 5 : 1) as a white solid.

(1*S*)-Methyl *N*-[(*E*)-1-benzyl-3-(*p*-methylphenyl)prop-2-enyl] carbamate.

R_f: 0.33 (6:1 Hexane/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.35 (s, 3H), 2.92-2.98 (m, 2H), 3.67 (s, 3H), 4.60-4.65 (br, 1H), 4.68-4.75 (br, 1H), 6.09 (dd, 1H, J = 16.0, 6.0 Hz), 6.45 (d, 1H, J = 16.0 Hz), 7.12-7.36 (m, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 21.41, 42.14, 52.38, 54.00, 126.82, 126.88, 128.78, 129.52, 129.81, 130.59, 134.11, 137.38, 137.69, 156.51; IR (CH_2Cl_2): 3323, 3026, 2921, 1703, 1513, 1453, 1347, 1073, 1035 cm^{-1}; HRMS (CI) calcd for $C_{19}H_{21}NO_2$+H $(M+H)^+$ 296.1650. Found: 296.1649.

(1*S*)-Methyl *N*-[(*Z*)-1-benzyl-3-(*p*-methylphenyl)prop-2-enyl] carbamate.

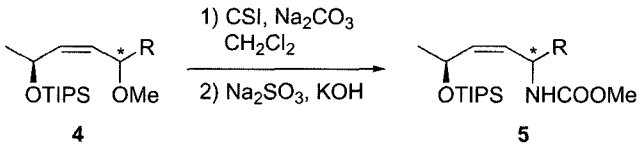
^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.86-2.95 (m, 2H), 3.64 (s, 3H), 4.52-4.60 (br, 1H), 4.87-4.94 (br, 1H), 5.48 (dd, 1H, J = 11.0, 7.0 Hz), 6.58 (d, 1H, J = 11.0 Hz), 7.12-7.36 (m, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 21.41, 41.84, 50.11, 54.00, 126.57, 128.55, 129.26, 129.92, 130.73, 131.34, 134.17, 137.19, 138.00, 156.51.

(1*S*)-Methyl *N*-[1-(*p*-methoxyphenyl)but-3-enyl]carbamate (8g)

The above general procedure was followed using (1*S*)-1-methoxy-1-*p*-methoxy phenylbut-3-ene (**7g**) (0.30 g, 1.56 mmol), Na_2CO_3 (0.37 g, 3.51 mmol) and CSI (0.20 mL, 2.34 mmol) in hexane (6 mL) at 0°C. The reaction mixture was purified by column chromato-graphy (Hexane/EtOAc = 6:1) to give 0.33 g (90%) of (1*S*)-methyl *N*-[1-(*p*-methoxyphenyl)but-3-enyl]carbamate (**8g**) (2% ee) as a white solid. R_f: 0.33 (3:1 Hexane/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.54 (dd, 2H, J = 7.0, 6.5 Hz), 3.65 (s, 3H), 3.81 (s, 3H), 4.72-4.78 (br, 1H), 4.93-5.00 (br, 1H), 5.11 (dd, 1H, J = 10.5, 1.5 Hz), 5.13 (dd, 1H, J = 16.0, 1.5 Hz), 5.69 (ddd, 1H, J = 16.0, 10.5, 7.0 Hz), 6.89 (dd, 2H, J = 8.5, 2.0 Hz), 7.21 (dd, 2H, J = 8.5, 2.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 41.23, 52.34, 54.19, 55.50, 114.19, 116.47, 127.62, 134.19, 134.43, 156.53, 159.05; IR (CH_2Cl_2): 3349, 2956, 2836, 1693, 1612, 1515, 1442, 1249, 1179, 1031 cm^{-1}; mp: 87~88°C; HRMS (CI) calcd for $C_{13}H_{17}NO_3$+H $(M+H)^+$ 236.1286. Found: 236.1286.

RESULTS AND DISCUSSION

Accordingly, the CSI reaction of various *cis*-allyl ethers with methyl and phenyl substituents at carbon where a methoxy group was attached was examined (Scheme 3).



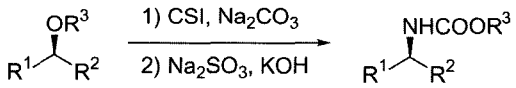
Scheme 3. The reaction of *cis*-allyl methyl ethers with CSI

The treatment of (2*S*,5*S*)-*cis*-allyl ether (R = Me) **4a** with CSI furnished (1*S*,4*S*)-*cis*-1,4-amino alcohol **5a**, with the same stereochemistry as the starting material **4a**, as a major product in 86% chemical yield and 1,2-amino alcohol **6** as a minor product in 4% yield (anti : syn = 1 : 1) (entry 1). In addition, the (2*R*,5*S*)-*cis*-allyl ether **4b** afforded the (1*R*,4*S*)-*cis*-1,4-amino alcohol **5b** in 84% yield and 1,2-amino alcohol **6** (anti : syn = 11 : 1) in 6% yield (entry 2) as shown in Table 1. However, the (1*R*,4*S*)-*cis*-allyl ether substituted by phenyl **4c** gave the (1*R*,4*S*)-*cis*-1,4-amino alcohol **5c** and the (1*S*,4*S*)-*cis*-1,4-amino alcohol **5d** as a 2 : 1 mixture of diastereoisomers (entry 3). In the case of the (1*S*,4*S*)-*cis*-allyl ether **4d**, an inversed product ratio (1 : 2.4) in favor of **5d** appeared (entry 4). In the cases of entries 3 and 4, (2*S*)-methyl *N*-[1-cinnamyl-2-(triisopropylsilyloxy)propyl]carbamate (**7**) (Kim *et al.*, 2003), 1,2-amino alcohol, was obtained in 10% (anti : syn = 1.4 : 1) and 9% (anti : syn = > 99) yield respectively.

Table I shows that the substitution mainly occurred whilst maintaining its stereochemistry, where the alkoxy moiety was attached, to afford the corresponding 1,4-amino alcohols. From these results, it is believed that nucleophilic attack rapidly occurs before the formation of the allylic carbocation hybrid due to the formation of a less stable carbocation intermediate in the *cis*-form than that in the *trans*-form.

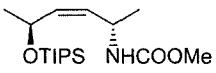
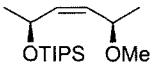
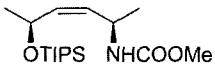
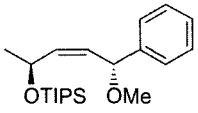
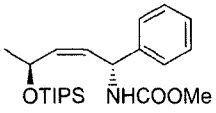
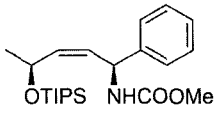
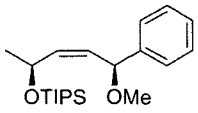
Next, this study tried to investigate the enantioselectivity in the reaction of the chiral allyl ethers with CSI (Scheme 4).

First, an enantiomeric excess of the reaction of (*S*)-1-benzylcinnamyl methyl ether (**7a**) with CSI was observed at various solvents and temperatures. The enantiomeric excess of methyl *N*-(1-benzylcinnamyl)carbamate (**8a**) depended on the solvent and temperature as shown in Table III. The reaction of **7a** with CSI in nitromethane at 0



Scheme 4. The reaction of chiral allyl and benzyl ethers with CSI

Table I. Conversions of *cis*-allyl ethers to the corresponding carbamates[i]

	Allyl Ethers	Allylic amines	Yield[ii] (%) ds ratio
1	 **4a**	 **5a**	86 > 99
2	 **4b**	 **5b**	84 > 99
3	 **4c**	 **5c** +  **5d**	83 2 : 1
4	 **4d**	**5c** + **5d**	87 1 : 2.4

[i] All the reactions were carried out at 20°C except for entries 3 and 4 (-78°C).
[ii] Isolated yield of pure material.

°C afforded **8a** with 10% ee. The same reaction in methylene chloride at 0°C and -78°C gave **8a** with 20% and 37% ee respectively. However, the CSI reaction in hexane at 0°C furnished **8a** with 39% ee. As the polarity of the solvent (Dean, 1972), decreased or the reaction temperature decreased, the enantiomeric excess of the product increased. In each case, the enantiomeric excess of carbamate was determined from the ^{1}H-NMR spectrum of the corresponding Mosher amide which was prepared from **8a** by a treatment with $Ba(OH)_2$ (Wovkulich and Uskokovic, 1985) and Mosher's acid chloride (Truong *et al.*, 2003; Nocholas *et al.*, 2000).

Based on the result shown in Table II, it was found that the proportion of the retention of stereochemistry tends to increase in nonpolar solvents. Therefore, hexane was chosen as a solvent in the reaction of other chiral ethers with CSI. The results are summarized in Table III. A treatment of (*S*)-benzylallyl methyl ether (**7b**) with CSI furnished methyl (*S*)-*N*-(1-benzylallyl)carbamate (**8b**) with 72% ee in 75% chemical yield and methyl *N*-(4-phenylbut-2-enyl)carbamate (**9**) (Kim *et al.*, 2001) in 5% chemical yield (entry 1). Carbamates with 66-68% ee were obtained in the case of the (*S*)-1-phenylethyl ethers (entries 2 and 3). The CSI reaction of **7e** (Fukuzawa *et al.*, 1997) afforded **8e** with 45% ee in 71% chemical yield and *N*-cinnamylcarbamate (**10**) (Takagi and Yamamoto, 1989) in 11% chemical yield (entry 4). However, the results did not exceeded 7% ee under the same reaction conditions

Table II. Results of the reactions of (*S*)-1-benzylcinnamyl methyl ether (**7a**) and CSI conducted with different solvents and temperatures

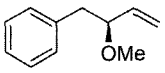
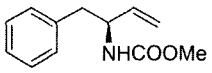
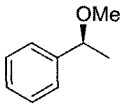
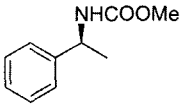
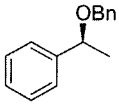
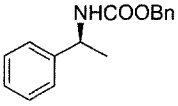
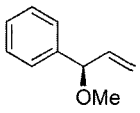
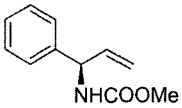
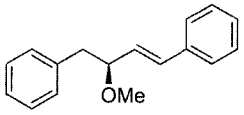
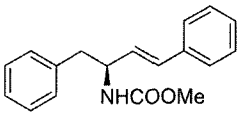
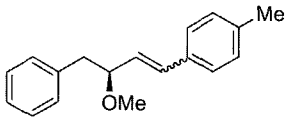
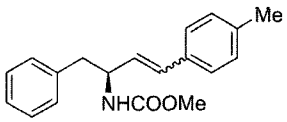
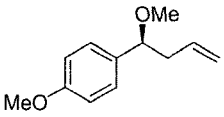
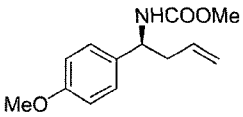
	Solvent	Temperature (°C)	ee (%)[a]	Yield (%)
1	$MeNO_2$	0	10	58
2	CH_2Cl_2	0	20	73
3		-78	37	72
4	$CHCl_3$	0	29	81
5	Et_2O	0	31	72
6		-78	45	76
7	Toluene	0	38	75
8	CCl_4	0	36	65
9	Hexane	0	39	77
10	Pentane	0	38	70

Isolated yield of pure material.
[a] ee was determined from the ^{1}H-NMR spectrum of the corresponding Mosher amide

in the cases of entries 6 and 7.

From the results shown in Table III, it appears that the enantiomeric excess of this CSI reaction profoundly depends upon the stability of the carbocation intermediate (Kim *et al.*, 2002). Therefore, it is proposed that this CSI reaction is a competitive reaction of a S_Ni (retention) (March, 1992; Sykes, 1986) and S_N1 mechanism (racemization) according to the stability of the carbocation intermediate (Fig. 1). In other words, there is a greater

Table III. Conversions of chiral ethers to the corresponding carbamates[i]

	Ethers	Carbamates	ee (%)[a]	Yield[ii] (%)
1	 **7b**	 **8b**	72	75
2	 **7c**[13]	 **8c**	66	85
3	 **7d**	 **8d**	68	84
4	 **7e**	 **8e**	45	71
5	 **7a**	 **8a**	39	77
6	 **7f** (*E*) : (*Z*) = 4 : 1	 **8f**	7	73 (*E*) : (*Z*) = 5 : 1[b]
7	 **7g**[14]	 **8g**	2	90

[i] All the reactions were carried out at 0°C, except for entries 1-3 (20°C).
[ii] Isolated yield of pure material.
[a] ee was determined from the ^{1}H-NMR spectrum of the corresponding Mosher amide.
[b] Isomer ratio determined from the ^{1}H-NMR spectrum

proportion of retention with the less stable the carbocation intermediate and vise versa.

CONCLUSION

A reaction of various chial allylic ethers with a hydroxyl group attached to the π-system and chlorosulfonyl isocyanate afforded the unsaturated 1,4-amino alcohols diastereoselectively. In addition, the enantioselectivity of this CSI reaction with the chiral allylic ethers depends upon the stability of the carbocation intermediate. Overall, it is proposed that this CSI reaction is a competitive reaction involving the S_Ni (retention) and S_N1 mechanism (racemisation).

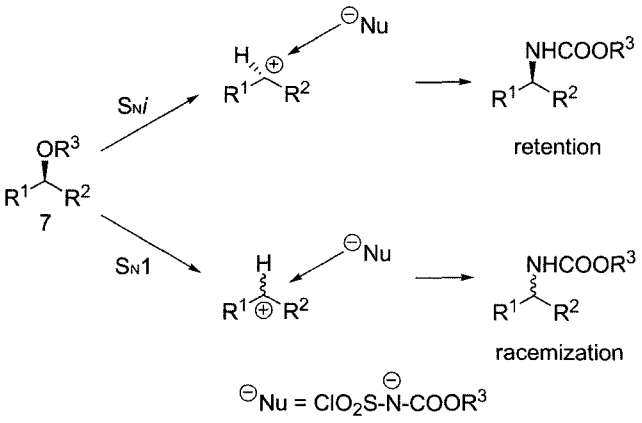


Fig. 1. Proposed mechanism of CSI reaction

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