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SEQUENTIAL CHIRALITY TRANSFER IN INTRAMOLECULAR AMIDOMERCURATION REACTIONS

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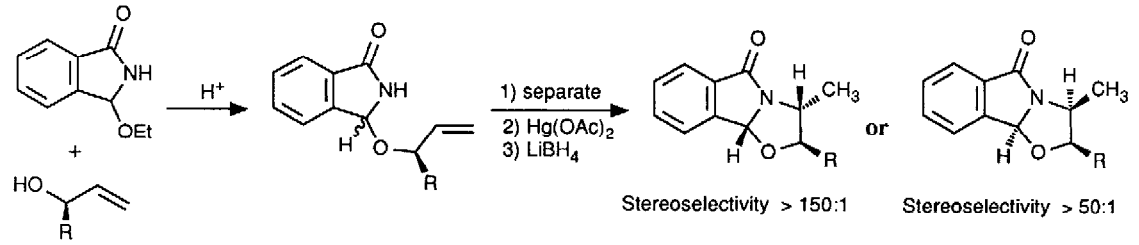
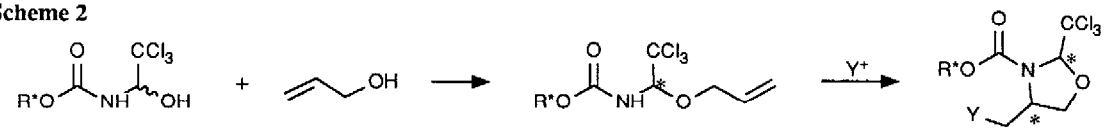
Summary. Control of absolute stereochemistry in the amination of allyl alcohol is effected by transfer of chirality from a chiral auxiliary to the amidal carbon of an N-acylaminomethyl ether derivative, which upon intramolecular amidomercuration results in a second transfer of chirality to the new C-N stereocenter.

Interest in asymmetric synthesis has led to studies of electrophilic heterocyclization reactions in which the substrate contains a removable chiral auxiliary. Although cases where the stereogenic centers are external to the ring formed during the heterocyclization (extraannular) generally result in little asymmetric induction,[1,2] significant asymmetric induction has been found in a few cases where the stereogenic center of proline becomes incorporated into the newly formed heterocyclic ring (intraannular).[3] Very recent studies on intramolecular amidomercuration reactions of substrates containing an intraannular N,O-acetal stereogenic center have shown high levels of stereocontrol in the amination of chiral 2° alcohols (Scheme 1).[4] Hydrolytic cleavage of the auxiliary generates the free amino alcohols. These results, which provide for control of relative stereochemistry, prompt disclosure of our results with related reactions (Scheme 2) that provide for control of absolute stereochemistry in the amination of achiral allylic alcohols by transfer of chirality from an extraannular chiral auxiliary to the intrannular amidal carbon (**B** → **C**) followed by electrophilic heterocyclization to transfer chirality to the new C-N bond (**B** → **C**).

Scheme 1 (Takacs, Helle, and Yang)[4]



Scheme 2

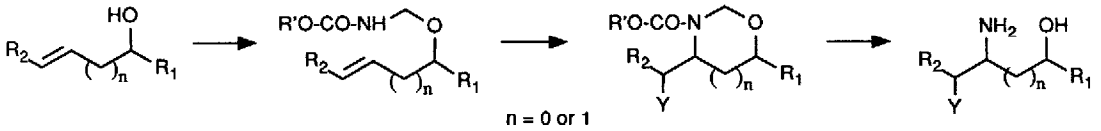


A **B** **C**

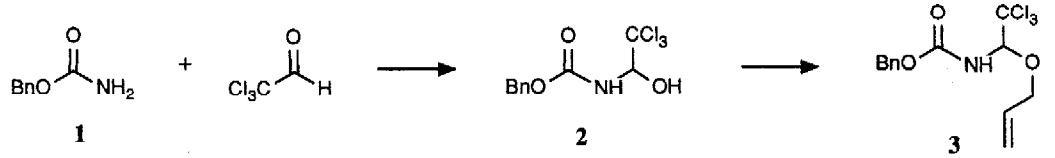
We have previously demonstrated the synthetic utility of N-acylaminomethyl ether derivatives in the stereoselective conversion of allylic or homoallylic 2° alcohols to 1,2- or 1,3-amino alcohols using intramolecular amidomercuration as the key step (Scheme 3).[5] The carbamate functionality allows a chiral auxiliary to be incorporated in R'. However, chirality at such a distance from the reaction site would be expected to result in very low levels of asymmetric induction (see below for confirmation of this assumption). We now show that the technique of sequential chirality transfer from a chiral auxiliary to a stereogenic center in the incipient heterocyclic ring (Scheme 2, **A** → **B**), then to the stereocenter generated in the heterocyclization (**B** → **C**) results in extremely

high stereochemical control in the amination step.

Scheme 3

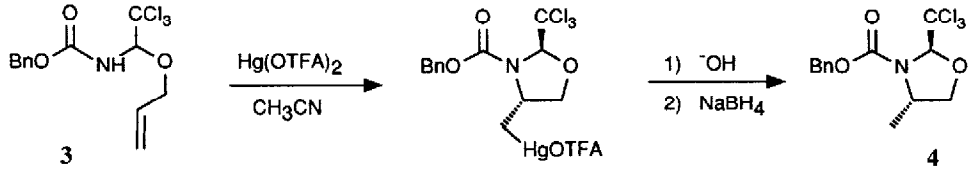


Although earlier studies[6] of electrophilic hetereocyclizations to form *trans*-N-acyl-2,5-dialkylpyrrolidines with excellent stereocontrol (≈98:2) suggested that the chirality at the amidal carbon in structure A (Scheme 2) would result in cyclization to trans oxazolidines, the oxazoldine products formed in Takacs' studies (Scheme 1)[4] have a cis relationship between the substituents at C-2 and C-5 of the oxazolidine ring. The direction and level of stereocontrol exerted by an amidal stereogenic center in an acyclic substrate was tested by cyclization studies with racemic carbamate **3**. Benzyl carbamate was coupled with chloral hydrate in benzene to form adduct **2** in 40% yield. Initial attempts to condense **2** with allyl alcohol under acid or basic conditions proved troublesome. Therefore, alcohol **2** was converted to the corresponding chloride by treatment with thionyl chloride in THF.[7] Addition of triethylamine followed by allyl alcohol resulted in the formation of **3** from **2** in a one-pot procedure in 97% yield.[8]



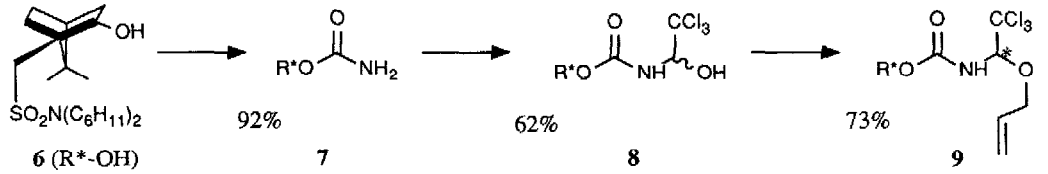
1 **2** **3**

Cyclization of carbamate **3** with mercuric trifluoroacetate in acetonitrile was complete in 30 min. No cyclization was observed using mercuric acetate. *trans*-Oxazolidine **4** was isolated in 60% yield after ligand exchange to hydroxide, reduction with borohydride, and chromatography. Only one stereoisomer could be observed, and the structure and stereochemistry was proven by a single crystal X-ray analysis.[9a] These results suggest that cyclic nature of the substrates shown in Scheme 1 leads to a dramatically different stereochemical outcome from that found with acyclic substrates.



3 **4**

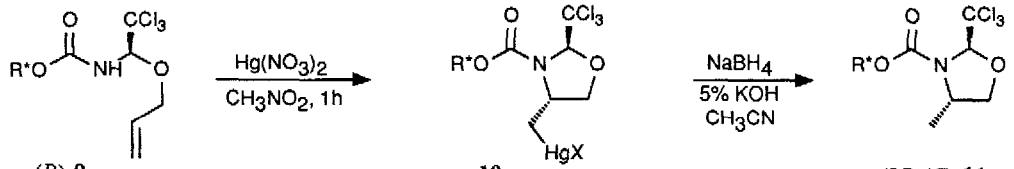
The chiral non-racemic cyclization precursor **9** was prepared by a similar synthetic pathway. Alcohol **6**, previously described by Oppolzer,[10] was used as the chiral auxiliary. This alcohol was converted to the carbamate **7** in 92% yield by reaction with *N*-(trichloroacetyl)isocyanate and hydrolysis on a column of basic alumina. Reaction of **7** with chloral hydrate in refluxing benzene for 20 hr gave, after chromatography, a mixture of **8** (62%, 1.4:1 ratio of isomers) and unchanged **7** (35%). Although the diastereomers of **8** were easily separated by HPLC, results in subsequent reactions using the mixture of isomers were indistinguishable from those using one of the individual diastereomer. Carbamate **9** was obtained in 73% yield by reaction with thionyl chloride followed by allyl alcohol. An 86:14 mixture of diastereomers was formed. The diastereomers were separated easily by chromatography. The major diastereomer of **9** was shown to possess the *R* configuration at the *N,O*-acetal position by single crystal X-ray analysis.[9b,11]



92% 62% 73%

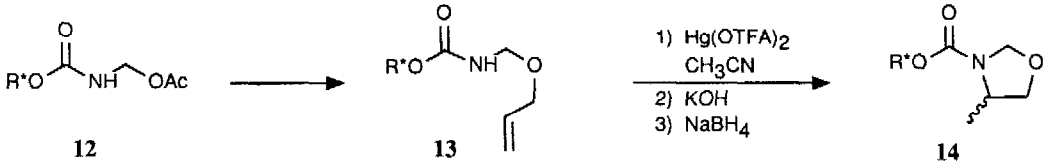
6 (R*-OH) **7** **8** **9**

Cyclization of (*R*)-**9** could be effected with mercuric trifluoroacetate or mercuric nitrate. Cyclization did not occur in acetonitrile, but ^{1}H NMR showed that cyclization to organomercurial **10** was complete in less than 40 min using nitromethane as the solvent. The trifluoroacetate intermediate could not be reduced cleanly to the methyl oxazolidine **11**. However, the solid organomercurial obtained by cyclization with mercuric nitrate and removal of nitromethane under reduced pressure could be reduced with sodium borohydride in acetonitrile to produce (2*R*,4*S*)-**11** in 74% overall yield.[12] The minor diastereomer (*S*)-**9** was also cyclized and reduced according to the same procedure to give (2*S*,4*R*)-**11** in a 70% crude yield. No evidence of diastereomers was observed in either cyclization. The structure and relative stereochemistry of both diastereomers of **11** were confirmed by single crystal X-ray analysis.[9c,d]



(*R*)-**9** **10** (2*R*,4*S*)-**11** 74%

Proof of the assertion that the remote chiral auxiliary alone was not sufficient to effect useful levels of stereocontrol was obtained through cyclization studies of a substrate lacking the trichloromethyl group. Since carbamate **7** did not form an adduct upon treatment with 37% formalin in tetrahydrofuran, the *N*-acetoxymethyl derivative **12** was prepared by reaction of **7** with paraformaldehyde, acetic anhydride, and acetic acid at 78-80 °C for 21 hours. Condensation with allyl alcohol in the presence of *p*-TsOH gave the amidal **13**. Preparation of **13** without purification of **12** gave an overall yield of 50%. Carbamate **13** was found to cyclize equally well using either mercuric trifluoroacetate in acetonitrile or mercuric nitrate in nitromethane. Thus, treatment of **13** with mercuric trifluoroacetate in acetonitrile followed by ligand exchange for hydroxide and reduction with borohydride produced **14** in 86% yield. The diastereomeric ratio was determined to be 40:60 by analytical HPLC. No attempt was made to determine absolute stereochemistry of the major or minor isomers.



12 **13** **14**

These results provide a second system that demonstrates a high level of stereocontrol induced by a stereogenic center at the amidal carbon of *N*-acylaminomethyl ether derivatives of allylic alcohols. Interestingly, the cyclic amidal system shown in Scheme 1[4] provides oxazolidines with stereochemistry opposite that found with the trichloromethyl substituted amidal in our studies. Since our results parallel those found in cyclizations to pyrrolidine systems,[6] the difference may be a result of the conformational constraints placed on the nitrogen nucleophile by the ring system in Takacs' studies.

The results reported in this communication demonstrate the concept of sequential chirality transfer in the

control of absolute stereochemistry of C-N bonds formed by intramolecular amidomercuration. Studies to examine cyclizations of the above type with additional alcohols and to develop efficient methods for cleavage of the oxazolidine ring[13] to generate amino alcohol products and recovered chiral auxiliary are in progress.

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2. One exception is the recent silver-catalyzed cyclization of an allenic amine containing a chiral N-substituent that can complex with the silver ion. Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T., submitted to *J. Chem. Soc., Chem. Commun.* We thank Professor Gallagher for providing a preprint prior to publication.
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7. For examples of synthesis of similar amidoalkylation reagents derived from chloral and reaction with carbon nucleophiles see: Ivanov, C.; Dobrev, A.; Nechev, L.; Nikiforov, T. *Synth. Commun.* **1989**, *19*, 297-306 and references cited therein.
8. The purity and structure of all key compounds were confirmed by chromatography, NMR spectroscopy (both ^{1}H and ^{13}C), and by single crystal X-ray analysis for compounds **4**,**8**,**9**, and both diastereomers of **11**.[9]
9. X-ray data were collected on a Nicolet R3m/V X-ray diffractometer. All crystallographic calculations were carried out using the SHELXTL-PLUS program package (Sheldrick, G. M., Nicolet Instrument Corporation, Madison, WI, USA). The detailed X-ray structural data will be discussed elsewhere. (a) **4**: $C_{13}H_{14}NO_3Cl_3$, M = 338.6 AMU, orthorhombic, space group P $2_12_12_1$ (No. 19), a = 5.962(2)Å, b = 10.644(4)Å, c = 22.975(7)Å, V = 1457.9(8)Å^3, Z = 4, D_x = 1.54 g/cm^3, $F(000)$ = 696 e$^-$, μ = 6.35 cm^{-1}, R = 0.063 (wR = 0.070). (b) **9**: $C_{28}H_{45}N_2O_5SCl_3$, M = 628.1 AMU, orthorhombic, space group P $2_12_12_1$ (No. 19), a = 7.073(2)Å, b = 9.941(3)Å, c = 45.122(11)Å, V = 3172.7(15)Å^3, Z = 4, D_x = 1.315 g/cm^3, $F(000)$ = 1336 e$^-$, μ = 3.89 cm^{-1}, R = 0.086 (wR = 0.079). (c) (2*R*,4*S*)-**11**: $C_{28}H_{45}N_2O_5SCl_3$, M = 628.1 AMU, monoclinic, space group P 2_1 (No. 4), a = 6.576(4)Å, b = 21.048(13)Å, c = 11.448(7)Å, β = 103.88(5)°, V = 1538(2)Å^3, Z = 2, D_x = 1.36 g/cm^3, $F(000)$ = 668 e$^-$, μ = 4.01 cm^{-1}, R = 0.075 (wR = 0.069). (d) (2*S*,4*R*)-**11**: $C_{28}H_{45}N_2O_5SCl_3$, M = 628.1 AMU, monoclinic, space group P 2_1 (No. 4), a = 14.752(15)Å, b = 6.882(11)Å, c = 17.99(2)Å, β = 103.7(1)°, V = 1775(4)Å^3, Z = 2, D_x = 1.171 g/cm^3, $F(000)$ = 664 e$^-$, μ = 3.47 cm^{-1}, R = 0.128 (wR = 0.112).
10. a) Oppolzer, W.; Chapius, C.; Bernardinelli, G. *Tetrahedron Lett.* **1984**, *25*, 5885-5888. b) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969-2004.
11. This result is consistent with other studies of nucleophilic attack on acyliminium ions containing alcohol **6** as the chiral auxiliary. Harding, K. E.; Davis, C. S. *Tetrahedron Lett.* **1988**, *29*, 1891-1894.
12. It was necessary to scrape the organomercurial from the walls of the flask and to suspend the material in acetonitrile before the addition of sodium borohydride to avoid ring opening during the reduction step.
13. For examples of clevage of cyclic acetals of chloral see: Overman, L. E.; Campbell, C. B. *J. Org. Chem.*, **1974**, *39*, 1474-1481.

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