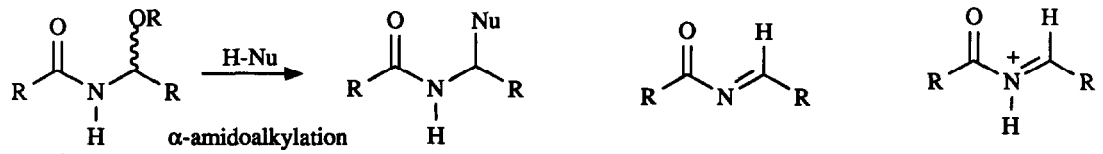
Tetrahedron Letters,Vol.29,No.16,pp 1891-1894,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

# ACYCLIC STEREOSELECTION IN α-AMIDOALKYLATION REACTIONS

Kenn E. Harding* and Clark S. Davis
Department of Chemistry, Texas A&M University, College Station, Texas 77843

The chiral reagent **7** provides the first example of an acyclic α-amidoalkylation reagent that generates a new stereogenic center with excellent stereoselectivity, and the stereochemistry of the resulting products provides evidence that the N-acylimine intermediate reacts through the cisoid conformation **12**.

Reactions of N-acyl N,O-acetals (**1**) with nucleophiles are termed α-amidoalkylation reactions (**1** --> **2**).[1] Reagents of general structure **1** react with a wide variety of carbon nucleophiles including aromatic compounds, alkenes, cyanide ion, isocyanides, enol derivatives, and organometallic reagents.[1,2] The reactive intermediates in these reactions are considered to be N-acylimines (**3a**) or N-acyliminium ions (**3b**). If the imine carbon of **3a** or **3b** is unsymmetrically substituted, reaction with a nucleophile generates a new stereogenic center. Interest in the synthesis of enantiomerically pure compounds[3] has led to recent investigations into the reactions of amidoalkylation reagents that contain chiral directing groups.[4-6] Several α-amidoalkylation reactions of cyclic systems proceed with high diastereoselectivity.[4,5,7] However, previous α-amidoalkylation reactions of acyclic systems have shown much lower stereoselectivity.[5b,6] These recent publications prompt us to report our initial studies that provide the first examples of α-amidoalkylation reactions of <u>acyclic</u> acylimines that proceed with excellent stereoselectivity (> 96% ds).




**1** **2** **3a** **3b**

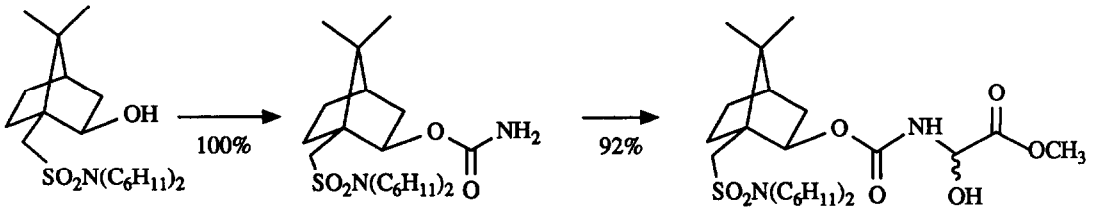
We considered that nucleophilic additions to electrophilic N-acylimine intermediates of the type shown by structure **4** should proceed with high diastereoselectivity when an appropriate chiral alcohol (R*-OH) is used as the chiral auxiliary. Thus, we selected a chiral alcohol previously shown[8] to provide excellent stereofacial selectivity in addition reactions of acrylate and crotonate esters. The intermediate **4** is a hetereosubstituted analog of the crotonate ester system, and the configuration of the newly formed stereogenic center should be determined by the relative accessibility of the two diastereofaces of the imine functionality. Recent experimental and theoretical

**4a** **4b**

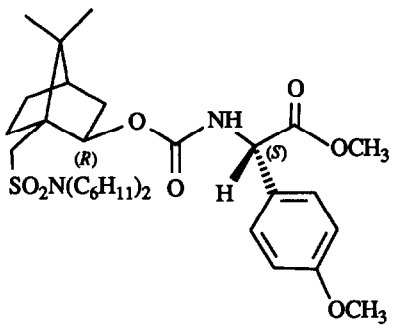
studies on N-acylimines have suggested that the acylimine functionality of intermediates **3** and **4** might exist preferentially in the cisoid conformation shown.[9] The stereochemistry about the C=N bond is predicted to be the

sterically favored (E) configuration as shown.

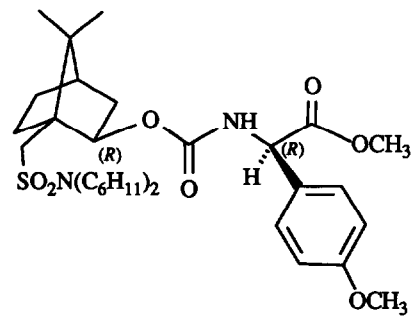
We have now shown that the amidoalkylation reagent **7** generates a reactive acylimine intermediate that undergoes reaction with aromatic rings with extremely high stereoselectivity. The reagent was derived from the known chiral auxiliary **5**.[10] Treatment of the chiral alcohol **5** with trichloroacetyl isocyanate followed by hydrolysis of the resulting N-trichloroacetyl carbamate gave carbamate **6** in quantitative yield.[11] Condensation of carbamate **6** with glyoxylic acid,[12] followed by esterification of the crude reaction mixture with diazomethane, gave the α-hydroxyglycine derivative **7** in 92% yield as a mixture of diastereomers. Treatment of **7** at 0° C with anisole and $BF_3$ etherate provided electrophilic aromatic substitution products in essentially quantitative yield. In addition to products proven to have structures **8** and **9**, the material contains 11% of products that are considered to be the result of ortho substitution on the aromatic ring.




**5** **6** **7**



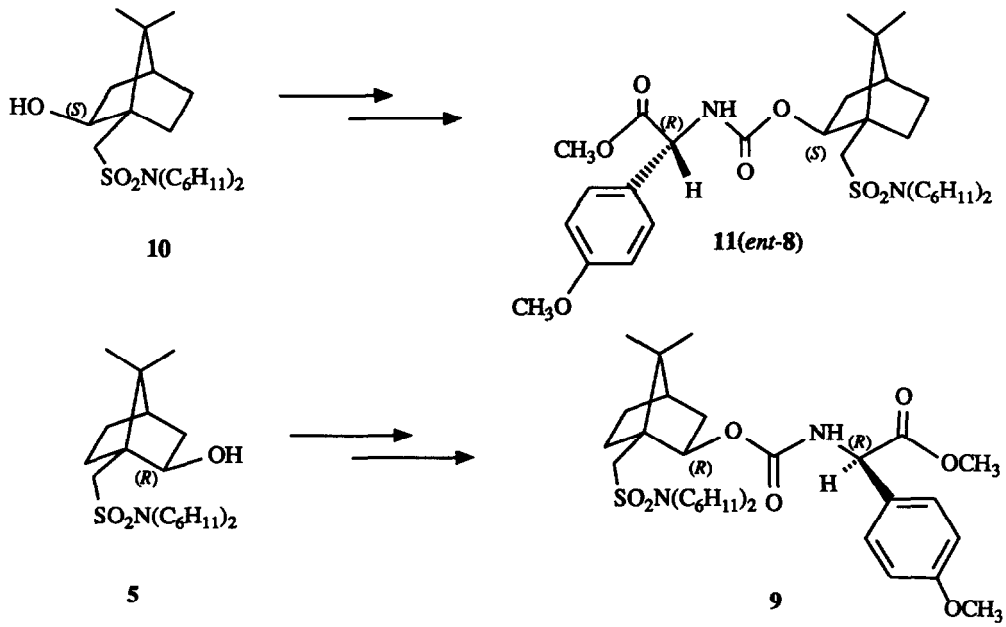

**8**



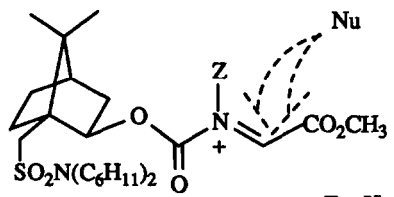

**9**

The ratio of stereoisomers **8** and **9** was determined to be > 96:4 by NMR. A single recrystallization gave product with a diastereomeric purity of > 99%. The stereochemistry of the newly formed stereogenic center in these compounds was established unequivocally by comparison with the spectra for two diastereomeric derivatives prepared from commercially available 2-(*R*)-(4-hydroxyphenyl)glycine. Stereoisomer **8** could not be prepared directly because only the *R* isomer of this amino acid is readily available, but the structure was proven by preparation of its enantiomer **11** (*ent*-**8**). Chiral alcohol **10** (*ent*-**5**)[10] was converted into the chloroformate by treatment with phosgene and pyridine, and reaction with 2-(*R*)-(4-hydroxyphenyl)glycine methyl ester followed by alkylation with MeI gave **11** (*ent*-**8**). The 200 MHz spectrum of **11** showed -OMe signals identical to those of the major product **8** derived from the electrophilic aromatic substitution reaction, thus proving their enantiomeric relationship.

The minor diastereomer was prepared from chiral alcohol **5** and 2-(*R*)-(4-hydroxyphenyl)glycine in an analogous manner to give an authentic sample of **9**. Comparison of the 200 MHz NMR spectra of this sample with the crude α-amidoalkylation mixture provided proof that the crude amidoalkylation product contains less than 4% of diastereomer **9**. Thus, the reaction proceeds with greater than 96% diastereoselectivity.




The proof of stereochemistry of the major product **8** provides evidence that the reaction proceeds through an N-acyl intermediate in the cisoid conformation (see structure **12**). Based on the reasonable assumptions derived from earlier studies with chiral auxiliary **5**[10] that (a) the carbonyl group eclipses the carbinol proton of the chiral auxiliary and (b) the dialkylsulfonamide group shields the front face of the reacting intermediate, and the assumption the two alkoxycarbonyl groups on the C=N bond are trans to each other, the major product **8** must arise from reaction from the *si* face of intermediate **12**. Thus, these studies provide evidence regarding the preferred geometry for reactions of N-acylimine structures.[9] It is noteworthy that the same stereoisomer **8** also predominates when the reaction is conducted in 1:9 sulfuric acid/acetic acid, but the selectivity is slightly lower.[15]




**12**

Z = H or Lewis acid

Although these exploratory studies were made with an α-amidoalkylation reagent that can be considered a chiral electrophilic glycine equivalent,[16] direct cleavage of the chiral auxiliary from **8** without racemization is problematical. However, procedures are available[18] for preparation of intermediates of type **7** with substituents other than carboxylate on the N,O-acetal. Thus, the strategy reported in this paper has greater generality than the previously reported methods,[5a,17] which require a carboxylate equivalent to be incorporated into a cyclic ring system. Studies that apply this strategy to such systems are in progress.[22]

**Acknowledgments.** We thank the Robert A Welch Foundation (Grant A-442) and the National Institutes of Health (Grant GM35793) for support of this research. Initial studies were funded by a NIH Biomedical Sciences Support Grant through Texas A&M University.

## LITERATURE CITED


1. (a) Hellman, H. *Angew. Chem.* **1957**, *69*, 463-471. (b) Zaugg, H. E.; Martin, W. B. *Organic Reactions* **1965**, *14*, 52. (c) Zaugg, H. E. *Synthesis* **1970**, 49-73. (d) Zaugg, H. E. *Synthesis* **1984**, 85-110. (e) Zaugg, H. E. *Synthesis* **1984**, 181-212.
2. For a review of intramolecular amidoalkylation reactions see: Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, 4367-4416.
3. Morrison, J. D.; Mosher, H. S. "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J. **1972**. "Asymmetric Synthesis", Academic Press, Orlando, Florida, Vols. 1-5, **1983-1986**.
4. For a review of EPC synthesis which includes some examples of α-amidoalkylation see: Seebach, D.; Inwinkelried, R.; Weber, T. in"Modern Synthetic Methods", Scheffold, R. Ed., Vol. 4, 125-259 **1986**.
5. (a) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103-1104. (b) Renaud, P.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 843-844. (c) Williams, R. M.; Sinclair, P. J.; Zhai, W. *J. Am. Chem. Soc.* **1988**, *110*, 482-483.
6. (a) Schmidt, R. R.; Machat, R. *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 311. (b) Schmidt, R. R.; Hoffmann, A. *Chem. Ber.* **1974**, *107*, 78. (c) Kober, R.; Papadopoulos, K.; Miltz, W.; Enders, D.; Steglich, W.; Reuter, H.; Puff, H. *Tetrahedron* **1985**, *41*, 1693-1701. (d) Wanner, K. Th.; Kartner, A. *Heterocycles* **1987**, *26*, 921-923.
7. Only amidoalkylation reagents which contain the chirality in a portion of the molecule that has the potential to be removed (transient chiron or chiral auxiliary) are considered here.
8. (a) Oppolzer, W.; Chapuis, C.; Dao, G. M.; Reichlin, D.; Godel, T. *Tetrahedron Lett.* **1982**, *23*, 4781-4784. (b) For a review of asymmetric Diels-Alder and Ene reactions see: Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 876-889.
9. (a) Ben-Ishai, D.; Hirsch, S. *Tetrahedron Lett.* **1983**, 955-958. (b) Bremmer, M. L.; Khatri, N. A.; Weinreb, S. M. *J. Org. Chem.* **1983**, *48*, 3661-3666. (c) Wurthwein, E.-U.; Kupfer, R.; Caliba C. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 252-253.
10. Oppolzer, W.; Chapais, C.; Bernarrdinelli, G. *Tetrahedron Lett.* **1984**, *25*, 5885.
11. Kocovosky, P. *Tetrahedron Lett.* **1986**, *27*, 5521.
12. Zoller, U.; Ben-Ishai, D. *Tetrahedron* **1975**, *31*, 863-866.
13. The reactive intermediate **12** may involve a $BF_3$-N complex as proposed by Weinreb for other N-acyliminium systems generated with $BF_3$ etherate.[14]
14. Scola, P. M.; Weinreb, S. M. *J. Org. Chem.* **1986**, *51*, 3250-3252.
15. The stereoselectivity dropped to 91:9 and regioselectivity was also lower (~ 25% ortho substitution).
16. The system reported in Refs. 5a and 5c is a cyclic N-alkyl N-acyl electrophilic glycinate. The electrophilic glycinate equivalent recently reported by Schollkopf[17] is a masked N-acyl glycinate. For recent examples of reactions of chiral acyclic N-alkyl imino esters as electrophilic glycinates see: Yamamoto, Y.; Ito, W.; Maruyama, K. *J. Chem Soc., Chem. Commun.* **1985**, 1131-1132 and Yamada, T.; Suzuki, H.; Mukaiyama, T. *Chem. Lett.* **1987**, 293-296.
17. Schollkopf, U.; Gruttner, S.; Anderskewitz, R.; Egert, E.; Dyrbusch, M. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 683-684.
18. Examples include the electrochemical oxidation of amides and carbamates,[19] the electrochemical oxidation of α-amidocarboxylic acids,[20] reaction of carbamates with acetals,[21] and protonation of enamides.[6d]
19. For reviews see: Yoshida, K. "Electrooxidation in Organic Chemistry." Wiley-Interscience, 1984, pp. 189-194. Shono, T. "Electroorganic Chemistry as a Tool in Organic Synthesis." Springer, Berlin 1984, pp 63-80. Shono, T. *Tetrahedron* **1984**, *40*, 811-850.
20. Linstead, R. P.; Shephard, B. R.; Weedon, B. C. L. *J. Chem. Soc.* **1951**, 2854. Finkelstein, M.; Ross, S. D. *Tetrahedron* **1972**, 4497. Iwasaki, T.; Horikawa, H.; Matsumonto, K.; Miyoshi, M. *J. Org. Chem.* **1979**, *44*, 1552-1554. Iwasaki, T.; Horikawa, H.; Matsumonto, K.; Miyoshi, M. *Bull. Chem. Soc. Japan* **1979**, *52*, 826-830.
21. Stavrovskaya, A. V.; Protopopova, T. V.; Skoldinov, A. P. *Zhur. Organ. Khim.* **1970**, *6*, 19-24.
22. All new compounds were completely characterized by spectral ($^1H$ and $^{13}C$ NMR, IR) and analytical (HRMS or combustion analysis) methods.


(Received in USA 14 January 1988)