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Diastereoselective protonation of enolates of chiral Schiff bases

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Abstract

Diastereoselective protonation of potassium enolates of chiral Schiff bases prepared from racemic α-amino esters and 2-hydroxypinan-3-one afforded, after mild cleavage of the imine function, optically active α-amino esters.

1. Introduction

Much effort has been devoted to the synthesis of α-amino acids in enantiomerically pure form, and this subject has been covered by several general reviews.[1–3] Amongst the different methods reported in these reviews, asymmetric protonation of enolates is rarely reported; however it is a very efficient method since it permits the conversion of a racemic compound into the desired enantiomer.

Duhamel et al.[4] have centred their research on the deprotonation of Schiff bases of racemic α-amino esters with lithium amides, followed by enantioselective reprotonation of the intermediate prochiral enolate to give optically active products. The reactions can be carried out using simple achiral lithium amide bases, followed by addition of a homochiral proton source (tartrate derivative). However, better results[5] have been obtained by using a combination of homochiral lithium amide bases, for the deprotonation and an optically active acid for the reprotonation (70% ee). A similar result[6] was obtained using LHMDS as the base for deprotonation and adding the more basic chiral secondary amine to the so-formed enolate prior to reprotonation.

Equilibration of Schiff's bases derived from α-amino acids and a chiral carbonyl component via their Cu-chelates followed by hydrolysis, results in moderate enantioselectivity (22–53% ee).[7]

In our laboratory, Daunis[8] et al. used a polyacrylic resin with pendant chirality as the chiral auxiliary. The prochiral ester enolate, reversibly linked to the polymer chain via a Schiff base, is surrounded by

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chiral pendants allowing supramolecular asymmetric induction to occur. Enantioselective protonation depends on the initial configuration of the supported amino acid. Alanine was obtained in 90% ee by repetitive asymmetric protonation.

2. Results

We have developed an efficient method for the synthesis of enantiomerically pure mono and disubstituted α-amino acids,[9] imino acids[10] and functionalized amino acids[11] by diastereoselective alkylation of chiral Schiff bases **1** prepared from 2-hydroxypinan-3-one[12] and α-amino esters. This method has also been extended to the asymmetric synthesis of α-aminophosphonic acids[13] and constituents of natural products: HC toxine[14] leucinostatine.[15] This chiral auxiliary, first used by Yamada,[12b] was then adopted by other teams.[16–18]

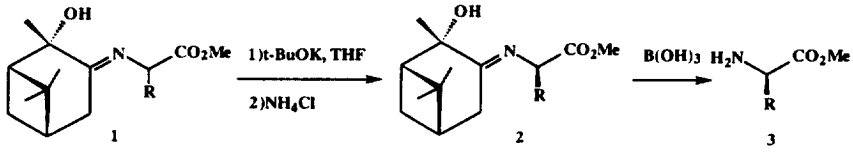
We report here on the use of this readily available chiral auxiliary in the diastereoselective protonation of Schiff bases **1**. For deprotonation several bases have been tested (LDA, Li HMDS, t-BuOK, KHMDS), but t-BuOK was most suitable among the bases examined. Protonation was attempted by different proton sources (H_2O, CH_3CO_2H, NH_4Cl/H_2O, etc); the best results were obtained using a saturated solution of NH_4Cl. The results are reported in Table 1.

Table 1
Protonation of enolates of chiral Schiff bases

Schiff base	R	Yield	de	Aminoester	Yield	ee
2a	C_3H_7	92	79	**3a**	72	>98
2b	i-C_3H_7	95	92	**3b**	80	>98
2c	i-C_4H_9	95	97	**3c**	83	>98
2d	CH_2Ph	96	>98	**3d**	92	>98
2e	2-naphthyl	96	>98	**3e**	94	>98

The Schiff bases were easily cleaved using citric and/or a very mild agent: boric acid. Starting from 2-hydroxypinan-3-one of (S)-chirality, (R)-amino esters were obtained.

In a typical procedure, the Schiff base **1** (1 mmol) was dissolved in dry THF (20 ml) at −78°C under argon, freshly sublimed t-BuOK (2 equiv.) was added and the mixture was stirred for 0.5 h at this temperature. The mixture was quenched with a saturated solution of NH_4Cl and extracted with ether. The organic phase was dried ($MgSO_4$), the solvent evaporated, and the residue was analyzed (diastereomeric excesses were determined by ^1H NMR in C_6D_6 and also by HPLC). For R=CH_2Ph, when the temperature was raised to −50°C, a transesterification reaction occurred but only one diastereomer was detected. Diastereoisomers of Schiff bases **2a**, **2b**, **2c** were separated by column chromatography. The major isomers and the imines **2d**, **2e** were treated with a 15% citric acid solution or boric acid to yield the amino esters **3**.



This work will now be extended to non-natural α-amino esters in order to determine the scope and limitations of this method.

References

1. (a) Isumi, Y.; Chibita, I.; Itoh, T. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 176. (b) Hoppe, D. Nachr. *Chem. Tech. Lab.* **1982**, *30*, 782–783 and 852–853. (c) Kochetkov, K. A.; Belikov, V. M. *Russian Chem. Rev.* **1987**, *56*, 1045–1067. (d) Altenbach, H. J. Nachr. *Chem. Tech. Lab.* **1988**, *36*, 999–1002. (e) O'Donnell, M. J. (Ed.) *Symposia in Print* No. 33, *Tetrahedron* **1988**, *44*, 5253–5614. (f) Haemers, A.; Mishra, L.; Van Assche, I.; Bollaert, W. *Die Pharmazie* **1989**, *44*, 97–109. (g) Mulzer, J.; Altenbach, H.-J.; Braun, M.; Krohn, K.; Reissig, H. U. *Organic Synthesis Highlights*, Verlag Chemie, Weinheim, 1991, pp. 300–305.
2. Williams, R. M. Synthesis of Optically Active α-Amino Acids. In *Organic Chemistry Series*, Baldwin, J. E.; Magm P. D. (Eds); Pergamon Press, Oxford, 1989, Vol. 7.
3. Duthaler, R. O. *Tetrahedron* **1994**, *50*, 11539.
4. Duhamel, L.; Duhamel, P.; Launay, J. C.; Plaquevent, J. C. *Bull. Soc. Chim. Fr.* **1984**, 421.
5. Duhamel, L.; Plaquevent, J. C. *Tetrahedron Lett.* **1980**, *21*, 2521.
6. Duhamel, L.; Fouquay, S.; Plaquevent, J. C. *Tetrahedron Lett.* **1986**, *27*, 4975.
7. Belokon', Yu. N.; Zel'tzer, I. E.; Bakhmutov, V. I.; Saporovskaya, M. B.; Ryzkov, M. G.; Yanovsky, A. I.; Struchkov, Yu. T.; Belikov, V. M. *J. Am. Chem. Soc.* **1983**, *105*, 2010.
8. Calmes, M.; Daunis, J.; Ismaili, H.; Jacquier, R.; Koudou, J.; Nkusi, G.; Zouanate, A. *Tetrahedron* **1990**, *46*, 6021.
9. (a) Bajgrowicz, J. A.; Cossec B.; Pigière, Ch.; Jacquier, R.; Viallefont, Ph. *Tetrahedron Lett.* **1983**, *24*, 3721. (b) Tabcheh, M.; El Achqar, A.; Pappalardo, L.; Roumestant, M. L.; Viallefont, Ph. *Tetrahedron* **1991**, *47*, 4611.
10. Bajgrowicz, J. A.; El Achqar, A.; Roumestant, M. L.; Pigière, Ch.; Viallefont, Ph. *Heterocycles* **1986**, *24*, 2165.
11. El Achqar, A.; Boumzebra, M.; Roumestant, M. L.; Viallefont, Ph. *Tetrahedron* **1988**, *44*, 5319.
12. (a) Schmidt, H. *Chem. Ber.* **1960**, *93*, 2485. (b) Oguri, T.; Kawai, N.; Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1978**, *26*, 803.
13. (a) Jacquier, R.; Ouazzani, F.; Roumestant, M. L.; Viallefont, Ph. *Phosphorus Sulfur* **1988**, *36*, 73. (b) Ouazzani, F.; Roumestant, M. L.; Viallefont, Ph. *Tetrahedron: Asymmetry* **1991**, *2*, 913. (c) Alami, A.; Ouazzani, F.; Roumestant, M. L.; Viallefont, Ph.; El Hallaoui, A. *Amino Acids* **1992**, 189.
14. Jacquier, R.; Lazaro, R.; Ranirisehenо, H.; Viallefont, Ph. *Tetrahedron Lett.* **1984**, *25*, 5525.
15. El Hadrami, M.; Lavergne, J. P.; Viallefont, Ph.; Ait Itto, M. Y.; Hasnaoui, A. *Tetrahedron Lett.* **1991**, *32*, 3985.
16. Minowa, G.; Hirayama, M.; Fuktatsu, S. *Tetrahedron Lett.* **1984**, *25*, 1147.
17. Antoni, G.; Langstrom, B. *Acta Chem. Scand.* **1986**, *40*, 152; *ibid* **1987**, *41*, 511.
18. (a) Solladie-Cavallo, A.; Simon M. C. *Tetrahedron Lett.* **1989**, *30*, 6011. (b) Solladie-Cavallo, A.; Schwarz, J.; Burger, V. *Tetrahedron: Asymmetry* **1994**, *5*, 1621.