Tetrahedron Letters, Vol 32, No 39, pp 5349-5352, 1991
Printed in Great Britain

0040-4039/91 $3 00 + 0
Pergamon Press plc

# Asymmetric Amination of Carboxylic Acids via a Diels-Alder Strategy.**

**Véronique Gouverneur and Léon Ghosez*.**

Laboratoire de Chimie Organique de Synthèse

Université Catholique de Louvain

place Louis Pasteur 1, B - 1348 Louvain-la-Neuve, Belgium

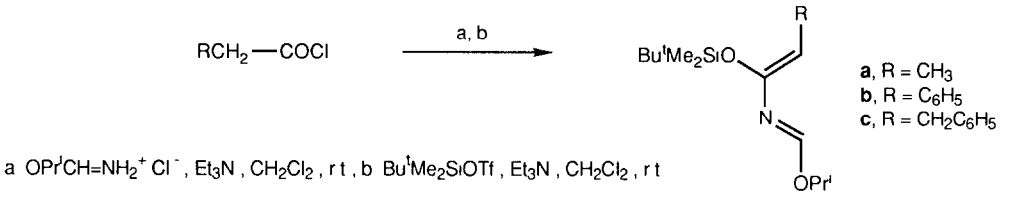
Key Words · amino acids, nitroso compounds, azadienes, cycloaddition, amination

**Abstract :** 2-azadienes **1** which are readily prepared from acyl chlorides react with high facial selectivity with the chiral carbamoyl nitroso dienophile **2** Reduction and hydrolysis of the adducts yield enantiomerically pure amino acids

Few asymmetric syntheses of amino acids by electrophilic amination of carboxylic acid derivatives are known. All the methods reported to date are based on the reaction of chiral enolates with either azodicarboxylate esters or 1-chloro-1-nitroso cyclohexane as electrophilic nitrogen donors.[1]

This communication reports preliminary studies on a new approach towards the asymmetric amination of carboxylic acids using the Diels-Alder reaction of 2-azadienes with chiral nitroso compounds for the stereocontrolled formation of the new C-N bond

The conversion of acid chlorides into 2-azadienes **1** has been reported (Scheme 1) [2] The reaction provided exclusively the E,Z 2-azadienes as determined by the $^{13}C$ and $^{15}N$ spectra.[3] Dienes **1b,c** are new compounds

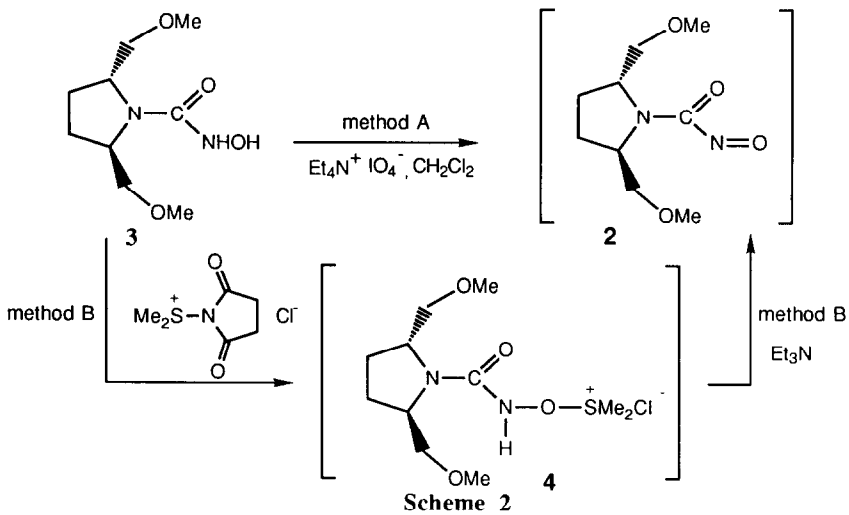



a $OPr^iCH{=}NH_2^+ Cl^-$, $Et_3N$, $CH_2Cl_2$, r t, b $Bu^tMe_2SiOTf$, $Et_3N$, $CH_2Cl_2$, r t

**Scheme 1** **1**

Very few chiral nitroso dienophiles are known. The addition of chiral α-chloronitroso compounds to simple dienes has been studied in detail [4] However these nitroso dienophiles did not yield any cycloadducts with the more nucleophilic 2-azadienes the reaction gave a complex mixture of products We recently observed high facial selectivities in the reaction of cyclic dienes with a carbamoyl nitroso dienophile **2** derived from a 2,5 disubstituted pyrrolidine possessing $C_2$ symmetry.[5] The dienophile was produced *in situ* by oxidation of the corresponding hydroxamic acid **3** with a solution of tetraethylammonium periodate in $CH_2Cl_2$ (Scheme 2, method A).

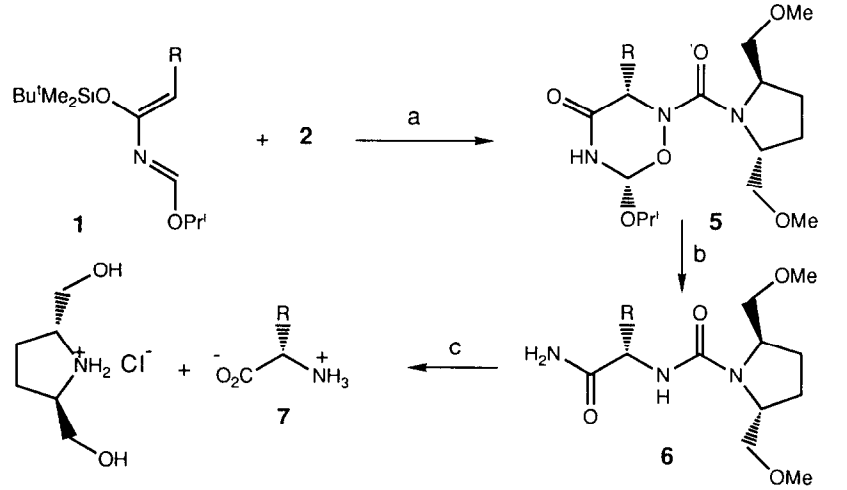
** Dedicated to Professor Kurt Schaffner at the occasion of his 60th birthday.




**Scheme 2**

However, at low temperatures (< 0° C), this oxidation process is too slow and competitive degradation of the azadienes was observed. We have therefore developed a less aggressive method of generating nitroso compounds (Scheme 2, method B). Treatment of compound **3** with the sulfonium reagent developed by Corey[6] for the oxidation of alcohols gave intermediate **4** which upon treatment with triethylamine yielded the desired carbamoyl nitroso compound **2**. Interestingly, we observed no product originating from a carbamoyl nitrene which would have resulted from an α–elimination.

The results of the Diels-Alder reaction of 2-azadienes **1** with **2** generated *in situ* by methods A or B are shown in Scheme 3 and Table 1.




Conditions a. cycloaddition followed by methanolysis at r.t., b $Mo(CO)_6$, $CH_3CN$-$H_2O$, Δ, c 6N HCl , Δ

**Scheme 3**

Table 1 : Reactions of 2-azadienes **1** with nitroso compound **2**

| Entry | R | Method | t° C | Yield % [a] | de (crude) [b] | de (pure) [a] |
|---|---|---|---|---|---|---|
| a | $CH_3$ | A | -25 | 68 | 59 | - |
| b | $CH_3$ | B | -78 | 72 | 90 | ≥98 |
| c | $C_6H_5$ | A | 0 | 68 | 84 | ≥98 |
| d | $C_6H_5$ | B | -78 | 62 | 94 | ≥98 |
| e | $C_6H_5CH_2$ | A | -25 | 70 | 90 | ≥98 |
| f | $C_6H_5CH_2$ | B | -65 | 65 | 93 | ≥98 |

a Yield and de of pure **5** after methanolysis, flash chromatography and recrystallisation from pentane

b Determined by NMR on the crude product of methanolysis

The reactions are regiospecific and proceed with high (≥ 90 %) facial selectivities when conducted at ≤ - 25 ° C. Enantiomerically pure **5** was obtained after flash chromatography and recrystallisation.

Compounds **5** could be readily transformed into the corresponding enantiomerically pure amino acids **7** by a two step sequence. The first step was a reductive cleavage of the N-O bond with molybdenum hexacarbonyl[7] in a refluxing mixture of water / acetonitrile (1/15). Sodium amalgam (4 equiv.) in methanol in the presence of $Na_2HPO_4$ (4 equiv.) gave slightly lower yields of **6**. The second step was the hydrolytic cleavage of the chiral auxiliary (Scheme 3, Table 2)

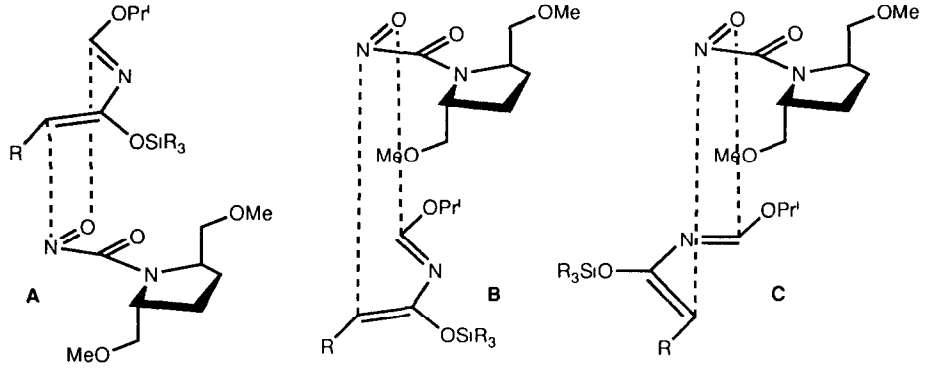
Table 2 : Conversion of **5** into amino acids **7**

| R | Yield % of **6** | Yield % of pure **7** | ee % of **7** | Absolute configuration of **7** |
|---|---|---|---|---|
| $CH_3$ | 78 | 71 | ≥ 98 | 2S |
| $C_6H_5$ | 74 | 74 | ≥ 98 | 2S |
| $C_6H_5CH_2$ | 73 | 78 | ≥ 98 | 2S |

The enantiomeric purity and absolute configuration of the synthetic amino acids **7** were established by comparing the properties of the corresponding Mosher's derivatives with samples prepared from the enantiomerically pure R and S amino esters The enantiomeric purity was determined by capillary GC and NMR

The facial selectivity is consistent with the transition state model depicted in Scheme 4 Calculations carried out earlier[5] by Dr G. Dive predict a more stable syn conformation for the carbamoyl nitroso compound **2**. "Endo" transition state A resulting from an approach from the less hindered side of the dienophile is clearly lower

in energy than the other "endo" transition state B and leads to the observed adduct "Exo" transition state C would also lead to the observed adduct but implies an approach from the more hindered side of the nitroso compound.




**Scheme 4**

In summary we have described a predictable synthetic route to enantiomerically pure amino acids based on a new strategy using the Diels-Alder reaction between 2-azadienes and chiral nitroso compounds The scope of the method has still to be examined We have also described a new mild method of generating of nitroso compounds which should be of general applicability.

## Acknowledgments

This work was generously supported by the Ministère de l'Education et de la Recherche Scientifique de la Communauté Française de Belgique (Action Concertée 86/91-84) and by the University of Louvain (assistantship to V.G.)

## References

1. Gennari, C ; Colombo, L.; Bertolini, G *J Am Chem. Soc* **1986**, *108*, 6394, Evans, D.A , Britton, T.C.; Dorow, R L., Dellaria, J F. *ibid* **1986**, *108*, 6395; *Tetrahedron* **1988**, *44*, 5525, Trimble, L A., Vederas, J.C. *J. Am. Chem Soc.* **1986**, *108*, 6397; Oppolzer, W., Moretti, R.; *Helv Chim Acta* **1986**, *69*, 1923; *Tetrahedron* **1988**, *44*, 5541, Guanti, G ; Banfi, L ; Narisano, E. *ibid* **1988**, *44*, 5553; *Tetrahedron Lett* **1989**, *30*, 5507; Genet, J.P , Juge, S., Mallart, S. *ibid* **1988**, *29*, 6765; Evans, D.A., Britton, T.C. *J Am Chem Soc* **1987**, *109*, 6881, Evans, D A , Ellman, J A. *ibid* **1989**, *111*, 1063, Loreto, M.A.; Pellacani, L., Tardella, P A. *Tetrahedron Lett* **1989**, *30*, 2975; Oppolzer, W.; Tamura, O. *Tetrahedron Lett.* **1990**, *31*, 991.
2. Bayard, P., Sainte, F.; Beaudegnies, R ; Ghosez, L. *Tetrahedron Lett* **1988**, *29*, 3799.
3 Bayard, P.; Gouverneur, V , Hesbain-Frisque, A M., Ghosez, L unpublished results.
4 Gouverneur, V.; Ghosez, L unpublished results
5 Gouverneur, V , Ghosez, L. *Tetrahedron Asymmetry* **1990**, *1*, 363
6 Corey, E.J ; Kim, C.U. *J Am Chem Soc* **1972**, *94*, 7586, *J Org Chem* **1973**, *38*, 1233, *Tetrahedron Lett* **1974**, 287, Corey, E J ; Kim, C.U.; Misco, P F. *Org Synth Coll Vol VI* **1988**, 220
7. Cicchi, S., Goti, A , Brandi, A., Guarna, A., De Sarlo, F. *Tetrahedron Lett* **1990**, *31*, 3351; Guarna, A., Guidi, A ; Goti, A.; De Sarlo, F. *Synthesis* **1989**, 175; Baraldi, P G , Barco, A., Benetti, S , Manfredini, S.; Simoni, D *Synthesis* **1987**, 276

(Received in France 4 July 1991)