Tetrahedron Letters,Vol.30,No.30,pp 3963-3966,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

# PALLADIUM-CATALYZED SYNTHESIS OF DIENIC α-AMINO ACIDS FROM ALLENES

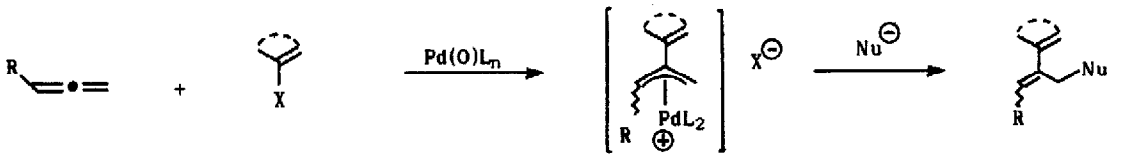
Nina **KOPOLA** , Béatrice **FRIESS** , Bernard **CAZES** and Jacques **GORE** .

Laboratoire de Chimie Organique **I** , associé au CNRS , Université Claude Bernard - LYON I
ESCIL , 43 Bd du 11 Novembre 1918 , 69622 VILLEURBANNE , France.

Summary : 1,3-Dienic or styryl α-amino acid precursors 6 and 10 are easily obtained through the catalytic carbopalladation of allenes followed by the trapping of the intermediate π-allyl complex 3 with either the anion of Schiff base 5 or of acetamidomalonate 9 .

Increasing interest has been recently devoted to the synthesis of non proteogenic unsaturated α-amino acids ; indeed some of these have documented biological activities, especially as suicide enzyme inhibitors (1). Among the possible unsaturations, the introduction of an ethylenic (1b-c, 2), acetylenic (3), or allenic (4) functionality has been studied. As an example, ethynylglycine has been demonstrated to inactivate alanine racemase (5).

Therefore we found it an interesting target to synthesize dienic or styryl α-amino acids which feature an extended unsaturated functionality and could eventually show biological properties. Such compounds seemed to be easily obtained through a palladium-catalyzed synthesis of 1,3-dienic branched systems 4 from allenes 1 and vinyl halides or triflates 2 we described recently (6) ; this one involves a sequential two-step process, namely : i) the carbopalladation of the allenic compound and ii) trapping of the intermediate π-allyl palladium complex 3 by a carbonucleophile.




1 2 3

X = Br , I , O-$SO_2$-$CF_3$

5 $H_2C$ <(N=$CPh_2$ / COOMe)

9 HC(NH-Ac)(COOEt)(COOEt)

4 Nu = CHZZ'
6 Nu = CH(COOMe)-N=$CPh_2$
10 Nu = $CH(COOEt)_2$-NHAc

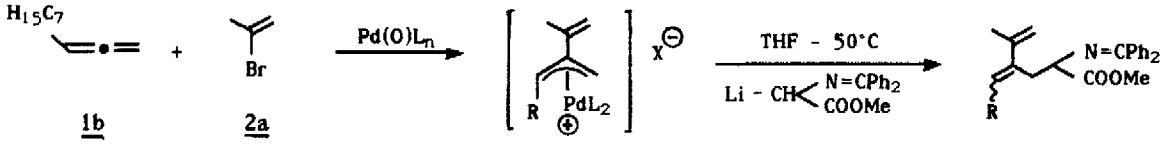
This methodology, coupled with the reported use of the anions of Schiff base 5 (2) and diethyl N-acetylaminomalonate 9 (7) as nucleophiles in palladium-catalyzed allylation, should lead to the anticipated dienic α-amino acid precursors 6 and 10 respectively.

Thus 1,2-propadiene 1a (2 eq.) was treated in an autoclave (THF ; 24 h ; 65-70°C) with a vinyl or aromatic halide 2 (1.3 eq.) and 1 eq. of the lithium enolate of the Schiff base derived from methyl glycinate 5 in the presence of the catalytic system bis(dibenzylideneacetone) palladium - 1,2-bis(diphenylphosphino)ethane [$Pd(dba)_2$ + 1 eq. dppe ; 4% molar].

Our preliminary results are reported in the table together with the following deprotecting transformations to the final α-amino acids 8 .

Vinyl and aryl halides 2a-c lead to the expected alkylated Schiff bases 6a-c in unoptimized 35-56 % yield . Hydrolysis of the imine functionality was realized by treating compounds 6 with aqueous hydrochloric acid . However it came to light that the dienic systems of these imino and amino esters 6 and 7 are quite sensitive to an acidic medium, so that only very mild conditions [2N HCl (10 molar eq.) in ether at 20°C for 0.5 h ] were nearly satisfactory : α-amino esters 7 were then obtained as pure oily compounds which did not need any purification step. Saponification (1.2 eq. of NaOH in methanol, 20°C, 2h) followed by direct ion exchange chromatrography (DOWEX 50WX8 resin ; 20/80 : pyridine/water) afforded the α-amino acids 8 as white solids (8).

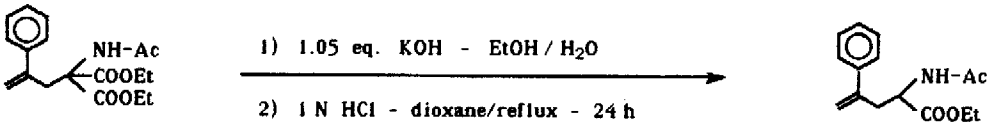
The same procedure was applied to a monosubstituted allene, 1,2-decadiene 1b ; its reaction with isopropenyl bromide gave a stereoisomeric mixture E/Z = 75/25 of the α-imino ester 6d (45 %), showing once more that the palladium-catalyzed sequence is (E)-stereoselective, presumably because of the preferred **anti** configuration of the intermediate π-allyl complex 3 (6).




1b 2a 3 anti 6d E/Z = 75/25

The second α-amino acid precursor, diethyl N-acetylamino malonate 9 , was tested with a very similar experimental procedure, except that the reactions were carried out in dimethylsulfoxide because of the scarce solubility of its sodium salt in tetrahydrofurane. Compounds 10 were obtained in modest yield. Even if the hydrolysis of the acetamidomalonate functionality to an α-amino acid has already been described using strong acidic conditions [6N HCl, MeOH-$H_2O$, reflux](9), our first attemps to realize this transformation from compounds 10 did not succeed in our hands.

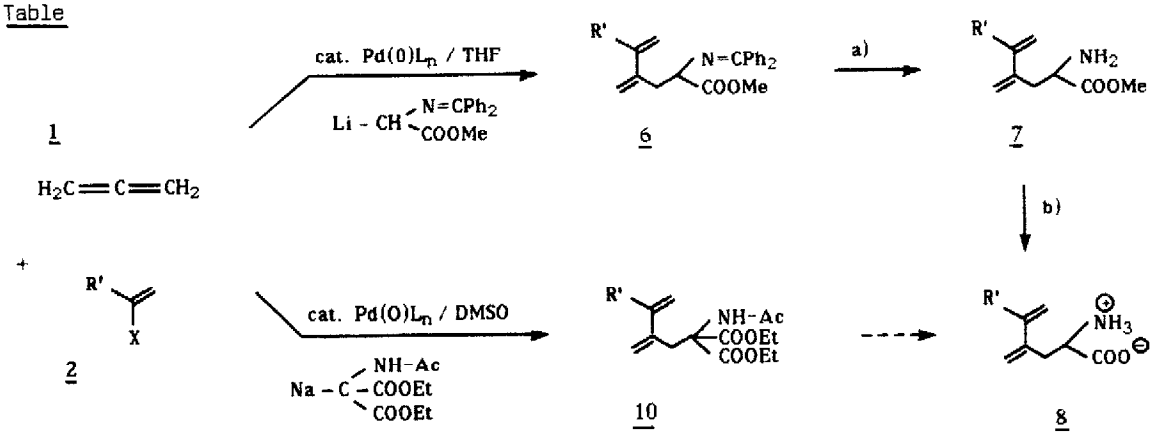
However, a two-step deprotective transformation (3a) could be carried out with the styrenic acetamidomalonate 10c : its saponification followed by decarboxylation leads to acetamido ester 11c in low yield.




10c 11c (30 %)

In conclusion, it has been demonstrated that the carbopalladation of allenes by vinyl or aryl palladium species allows the rapid building-up of the 1,3-dienic or styryl skeletons of unsaturated α-amino acids. Schiff base of methyl glycinate 5 seems more appropriate as carbonucleophile because of an easier deprotection of the α-imino ester 6 to the amino acid 8 ; the biological properties of these compounds are currently under investigation.

Table




a) 2N HCl (10 eq.) , ether , 20°C , 0.5 h.

b) methanolic 1N NaOH (1.2 eq. ) , 20°C , 2 h followed by DOWEX 50WX8 ion exchange chromatography.

| Nucleophile (solvent) | Vinyl halide | 6 or 10 | 7 | 8 |
|---|---|---|---|---|
| Li - CH(N=CPh2)COOMe<br>Li - 5<br>(THF) | 2a  | 6a 52 % | 7a 66 % | 8a 57 % |
| | 2b  | 6b 56 % | 7b 68 % | 8b 68 % |
| | 2c  | 6c 35 % | 7c 64 % | 8c 67 % |
| Na - C(NH-Ac)(COOEt)2<br>Na - 9<br>(DMSO) | 2b  | 10b 50 % | | |
| | 2c  | 10c 40 % | | |

Yields refer to isolated material purified to homogeneity by chromatography except for 7 which were obtained as pure material.

This work was presented at the Seventh IUPAC Conference on Organic Synthesis , July 4-7 1988, NANCY, France [Abstract 4-R10(SC)].

The authors gratefully acknowledge the "Région Rhône-Alpes" for its financial support.

## REFERENCES

1. a) WALSH,C. ; Tetrahedron, 1982, 38 , 871.
b) ANGST,C. ; Pure and Appl. Chem., 1987, 59 , 373.
c) SHEA , R.G. ; FITZNER, J.N. ; FRANKHAUSER, J.E. ; SPALTENSTEIN, A. ; CAPRINO, P.A. ; PEEVERY, R.M. ; PRATT, D.V. ; TENGE, B.J. and HOPKINS, P.B. ; J. Org. Chem. , 1986, 51 , 5243 and references herein.

2. FERROUD, D. ; GENET, J.P. and KIOLLE, R. ; Tetrahedron Lett., 1986, 27 , 23.
FERROUD, D. ; GENET, J.P. and KIOLLE, R. ; Tetrahedron Lett., 1986, 27 , 4573.
GENET, J.P. ; JUGE, S. ; ACHI, S. ; MALLART, S. ; RUIZ MONTES, J.R. and LEVIF, G. ; Tetrahedron, 1988, 44 , 5263.

3. a) SASAKI, N.A. ; MORGAT, J.L. and POTIER, P. ; Int. J. Peptide Prot. Res. , 1986, 27 , 360.
b) ABELES, R. and WALSH, C. ; J. Am. Chem. Soc. , 1973, 95 , 6124.

4. CASARA, P. ; JUND, K. and BEY, P. ; Tetrahedron Lett. , 1984, 25 , 1891.
CASTELHANO, A.L. ; PLIURA, D.H. ; TAYLOR, G.J. ; HSIEH, K.C. and KRANTZ, A. ; J. Am. Chem. Soc., 1984, 106 , 2734.
BLACK, D.K. and LANDER, S.R. , J. Chem. Soc. (C) , 1968, 281 and 283.
BALDWIN, J.E. ; ADLINGTON, R.M. and BASAK, A. ; J. Chem. Soc. Chem. Comm. , 1984, 1284.
CAZES, B. ; DJAHANBINI, D. ; GORE, J. ; GENET, J.P. and GAUDIN, J.M. ; Synthesis, 1988, 983.

5. KURODA, Y. ; OKUHARA, M. ; GOTO, T. ; KOHSAKA, M. ; AOKI, H. and IMANAKA, H. ; J. Antibiotics, 1980, 33 , 132.

6. AHMAR, M. ; CAZES, B. and GORE, J. ; Tetrahedron Lett., 1984, 25 , 4505
AHMAR, M. ; BARIEUX, J.J. ; CAZES, B. and GORE, J. ; Tetrahedron, 1987, 43 , 513.
FRIESS, B. ; CAZES, B. and GORE, J. ; Tetrahedron Lett., 1988 , 33 , 4089.

7. HAUDEGOND, J.P.; CHAUVIN, Y. and COMMEREUC, D. ; J. Org. Chem., 1979, 44 , 3063.
DUNKERTON, L.V. and SERINO, A.J. ; J. Org. Chem., 1982, 47 , 2812.

8. All new compounds exhibited satisfactory spectral data.
The following $^1H$ NMR spectrum ($CDCl_3$ , 300MHz) of $\alpha$-amino acid 8b is given as an example : 2.14 (s, 3H) ; 3.05 (part AB of an ABX system , $J_{AB}$ = 14.6 , $J_{AX}$ = 10 and $J_{BX}$ = 4 Hz , 2H) ; 4.06 ( part X of an ABX system , $J_{AX}$ = 10 and $J_{BX}$ = 4 Hz , 1H) ; 5.2 (s, 2H) ; 5.42 and 5.47 (2s, 2H).

9. a) SAWADA,S. ; NAKAYAMA,T. ; ESAKI, N. ; TANAKA, H. ; SODA, K. and HILL, R.K. ; J. Org. Chem., 1986, 51 , 3385.
b) PAYNES, L.S. and BOGER,J. ; Synth. Comm., 1985, 15 , 1277.

(Received in France 7 March 1989)