Tetrahedron Letters, Vol.31, No.22, pp 3133-3136, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

DOUBLE ASYMMETRIC SYNTHESIS : PALLADIUM CHIRAL COMPLEXES IN THE ALKYLATION OF CHIRAL SCHIFF BASES DERIVED FROM GLYCINE.

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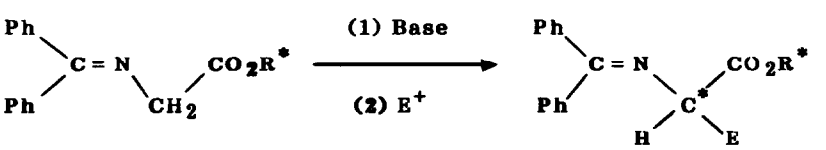
Abstract : A new double asymmetric induction in carbon-carbon bond formation is achieved by the use of palladium chiral complexes in the alkylation of chiral Schiff bases 1 derived from glycine. High diastereoisomeric excesses are obtained (90-99%) using N,N-cyclohexylsulfamoylisobornyl derivatives and DIOP as a matched pair.

The synthesis of enantiomerically pure organic compounds presents a challenge to academic and industrial chemists alike. The notion of (single) asymmetric synthesis is a well known process in which an optically active compound is formed through the reaction of an achiral substrate with a chiral reagent.[1] The double asymmetric induction which concerns the interaction of two chiral reactants is less used.[2]

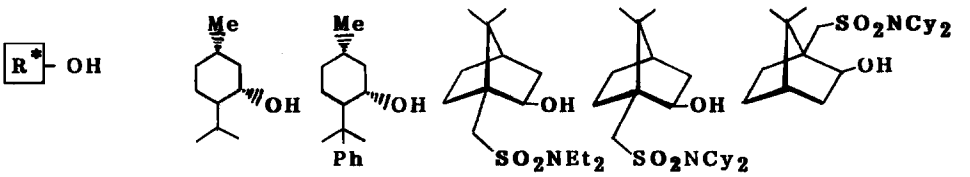
Based on the single asymmetric process, we have reported an efficient catalytic Pd-mediated alkylation derived from glycine giving an enantioselectivity up to 70% ee.[3] A catalytic asymmetric synthesis of amino acids (64 %ee) using phase transfer catalysis has also been recently reported.[4] The alkylation of Schiff base enolates derived from glycine or alanine is presently subjected to extensive investigation especially with chiral imine moiety, and a high diastereoselectivity has been achieved (more than 95%).[5] Only one example of use of a chiral ester of the Schiff base has been very recently reported (60% d.e.),[6] as well as one example of double stereodifferentiation in allylation of ketimines bearing chiral ester group.[7] This prompted us to disclose our results[8] on the alkylation of Schiff bases 1 with ester moiety as chiral auxiliary[9] (single induction) . We wish also to report our studies which are the first example of a double induction in C-C bond formation using a stoechiometric chiral reagent and **catalytic** palladium chiral-complexes as electrophile that provide a good stereoselectivity (90-99% d.e.).[8]

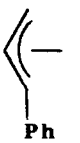


1 R = Chiral alcohol (A-E) 2

Scheme I

First, we studied simple alkylations of Schiff bases series esterified with chiral auxiliary alcohols (R^*OH)[10] and having the stable benzophenone imine as protecting group (scheme I). The results are gathered in table I.[11]



Entry	Electrophile : E^+ / Temp (°C), time	(-) A	(-) B	(-) C	(-) D	(+) E
1	CH_2=$CHCH_2Br$ -40°, 3 h	7[a] (63)[b]	25 (62)	18 (85)	31 (60)	-
2	 Pd (dppe)$_2$ -35°, 2 h	9 (62)	27 (67)	-	35 (67)	
3	 Pd DIOP(+) -35°, 2-3 h	17 (53)	83 (59)	34 (85)	90 (64)	
4	 Pd DIOP(-) -40°, 2 h	53 (56)	69 (70)	-	53 (63)	
5	 Pd DIOP(+) -50°, 4 h	-	-	66 (71)		
6	 Pd DIOP(-) -60°, 6 h	-	-	-	-	90 (75)[12]
7	 Pd DIOP(-) -60°, 6 h	-	-	-	-	97 (60)[13]
8	 Pd DIOP(-) -50°, 4 h	-	-	70 (86)	-	99 (80)[14]

a) Diastereomeric excesses were determined on crude sample by HPLC on silica Zorbax (Dupont) or CSP Bakerbond (Baker) columns (THF/hex. : 5/95).
b) Chemical yields (%).

TABLE I

The electrophile was either allyl bromide (entry 1) or η^3-allylic palladium species generated in situ from allylic acetate and achiral Pd (O) catalyst (entry 2). Under these conditions quite poor diastereoselectivities were obtained (7-35% d.e.) with chiral auxiliaries such as menthol (A), (-)-8-phenylmenthol (B) and sulfonamidoisobornyl derivatives (C) and (D) (entries 1 and 2).

Next, we investigated the double induction process and looked for the matched and mismatched pairs of the two homochiral reagents η^3- allyl species generated with (+) or (-)DIOP and the Schiff bases 1. We performed comparative studies between the different chiral alcohols (A-D)(entries 3-4),and it could be established that the auxiliairies (A and C) did not prove to be very efficient, although an increase in diastereoselectivity could be observed. The diastereomeric excesses remained poor with(-)menthol(A) and with sulfamoylisobornyl alcohol (C): 17%and 34 % d.e. respectively (entry 3), but when using (-)-8-phenylmenthol (B) the diasteroselectivity obtained was remarkably higher (83% d.e. entry 3).The (-)N,N-dicyclohexylsulfamoylisobornyl chiral auxiliary (D) showed a very high and promising effect in this double induction reaction. As expected the diastereoselectivity is very much dependent of the absolute configuration of the ligand (compare entries 3 and 4). When the two chiral components (+) DIOP[15] and alcohol (D), (entry 3) are acting in concert, a diastereoisomeric excess up to 90% is obtained. Therefore we chose the (+)N,N-dicyclohexylsulfamoylisobornyl alcohol (E) and (-)DIOP to prove the effect of combining efficiently the two chiral species. As it can be seen with (-)DIOP as ligand on the allylic palladium electrophile (entries 6-7-8) it is possible to obtain very high diastereomeric excesses (90-99% d.e.).

Although the method developed here is not an economical synthesis of amino acids, this procedure has some advantages in terms of chemoselectivity, since it is known that significant reactivity differences exist between palladium mediated allylic alkylation and classical nucleophilic displacement with an alkyl halide.[16] We would also like to stress the fact that this is the first report of stereodifferentiation using Pd (O)-catalyzed double induction procedure.[17]

Acknowledgements : N. K. thanks the Academy of Finland for financial support ; we also thank Professor W. OPPOLZER for a sample of the alcohols (C-E).

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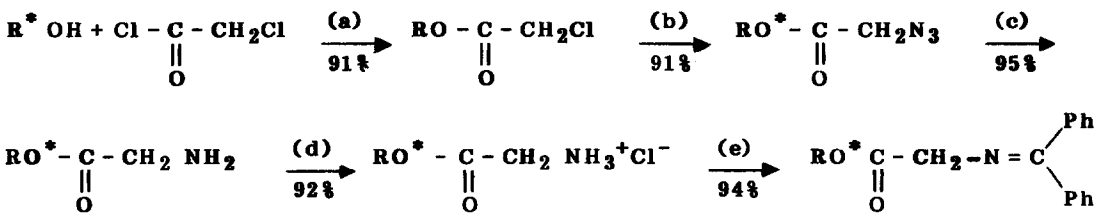
8) Preliminary communication of this work at the 7th IUPAC conference on Organic Synthesis in Nancy (France) July 4-7 1988.

9) The chiral glycine derivatives were prepared starting from the chiral alcohols in five steps in 67 % overall yield according to:



(Reagents : a) $PhNEt_2$, ether reflux, 3-48 h ; b) NaN_3, acetone /H_2O 6:4 reflux (30-40 h) c) H_2, Pd/$BaSO_4$ cat, MeOH (24-48 h); d) HCl gaz, Et_2O, 2 h; e) $Ph_2C{=}NH$, CH_2Cl_2, 24 h, R.T.

10) N,N-Diethyl and N,N-dicyclohexylsulfamolyl isoborneol (C,D,E) were synthetized according to W. OPPOLZER, C. CHAPUIS and G. BERNADINELLI, Tetrahedron Lett., 25, 5885, (1984).

11) For a typical procedure to a mixture of lithium enolate of 1 prepared at -78°C from LDA (0.9 mmol) and Schiff base 1 (1 mmol in THF) was added electrophile system (i.e. allyl bromide or η^3-allyl species generated from allylic acetate or chloride with $Pd(OAc)_2$ and the appropriate chiral ligand). The reaction was monitored by CCM on silica (AcOEt/Hex. 20/80). After hydrolysis with 1 ml of saturated NH_4Cl, the crude was extracted by CH_2Cl_2 and the alkylated derivative 2 isolated by flash chromatography on silica gel (AcOEt/Hex. : 10/90).

12) - oil : ^{1}H-NMR ($CDCl_3$, 250 MHz): 0.8 (s,3H), 1 (s,3H), 1.1-2.2 (m,27H), 2.6 (d,1H, J=12Hz), 2.9 (t,2H J=7Hz), 3.1-3.4 (m,3H), 4.3 (t,1H,J=6Hz), 5 (d,1H,J=6Hz), 6-6.6 (m,2H), 7-7.8 (m,15H) ; I.R. (neat) : 3050, 2940, 1740, 1660 cm^{-1}.

13) oil : ^{1}H-NMR ($CDCl_3$, 250 MHz): 0.9 (s,3H), 1-2.2 (m,20H), 2.6-2.8 (m,2H), 3.1-3.4 (m,4H), 4.2 (dd,1H, J_1=5Hz, J_2=10Hz), 4.7 (d,2H,J=10Hz), 5 (t,1H), 7.1-7.8 (m,10H). ^{13}C-NMR ($CDCl_3$): 171, 169, 139, 113, 79, 64, 57, 44, 22, 20, 19.

14) oil, ^{1}H-NMR ($CDCl_3$, 250 MHz): 0.8 (s,3H), 1.1-2.1 (m,27H), 3-3.4 (m,6H), 4.5 (dd,1H, J_1=4Hz, J_2=10Hz), 5 (d,1H, J=10Hz), 5.2 (d,2H, J=15Hz), 7.1-7.7 (m,10H). ^{13}C-NMR ($CDCl_3$) : 171, 167, 115, 79, 62, 57.

15) DIOP : (4S, 5 S)-4,5-bis-(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane. Commercially available from Merck. This ligand has been found the most efficient in the truly catalytic process, see reference.(3)

16) B.M. TROST and T.R. VERHOEVEN in "Comprehensive Organometallic Chemistry" 8, 825, G. WILKINSON Ed. Pergamon Press (1982).

17) For the recent and first example of stereodifferentiation in the gold (I) : catalyzed reaction see: A. TOGNI, S.D. PASTOR, Helv. Chim. Acta, 72, 1038 (1989).

(Received in France 28 February 1990)