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SYNTHESIS OF α-AMINO ACIDS[1]. SCHIFF BASE OF GLYCINE METHYL ESTER. A NEW AND EFFICIENT PROCHIRAL NUCLEOPHILE IN PALLADIUM CHIRAL CATALYTIC ALLYLATION.

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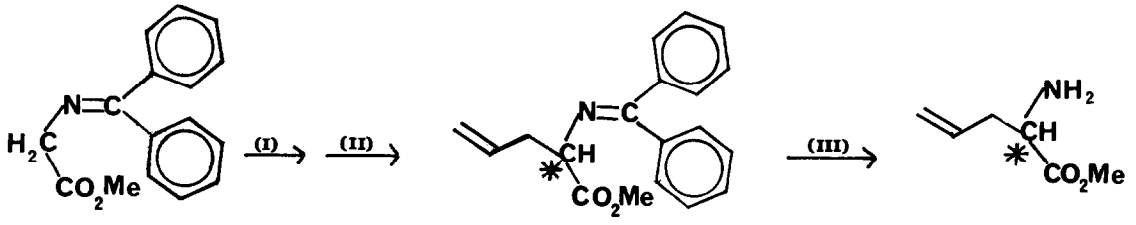
Abstract : Asymmetric carbon-carbon bond formation was obtained in optical yields up to 57 % in allylic alkylations using benzophenone imine of glycine methyl ester 1 as a prochiral nucleophile. Catalytic : (1.5-3 %) palladium-Chiral complexes have been used (12 chiral ligands have been tested) ; (+) or (-) DIOP appeared to be the more efficient. Good chemical yields were also obtained. Catalysis can be performed at low temperature.

Carbon-carbon bond formation[2] is an important process in organic synthesis and increasing research activity for enantioselective C-C bond methods have been developped during the last few years. In reactionsusing palladium complexes[3], two different catalytic systems have been investigated. The first one involves the use of prochiral allylic systems[3] and Bosnish selected an aromatic allylic substrate which gave an 85 % ee with CHIRAPHOS-Palladium catalyst[3b]. Very recently Trost[4] and Hayashi[5] have devised two new ligands for the use in this type of approach which gave ee of 69 % and 92 % respectively. Kagan and Co-workers[6] have proposed a second methodology which involves a prochiral nucleophile with allylic phenoxide in the presence of a Pd-DIOP catalysis, but this approach gives a lower ee (10 %). In the same system Kumada and Hayashi[7] utilized a new chiral ligand containing functional group which permits an enantiomeric excess of 52 % to be obtained.

Recently we reported a practical synthesis of α-amino acids based on Pd-alkylation of Schiff bases derived from glycine[1]. We wish to report the utilisation of this prochiral nucleophile in asymmetric synthesis using Pd-chiral ligands catalysts. In this preliminary study we used the stable benzophenone imine[8] synthon 1 with catalysts bearing different chiral ligands on the palladium[9]. The reaction conditions and results are summarized in Table I.



1 2 3

(I) LDA, THF - 78°C ; (II) CH_2=$CHCH_2OAc$; $Pd(dba)_2$ + L^*

(III) HCl 10 % then K_2CO_3

Table I - Asymmetric allylation of benzophenone imine of glycine methyl ester 1 by Palladium Chiral Ligand complexes[a].

Run	Ligands[10]	Conditions Time (mn)	T, °C	Yields %[b]	ee %[c]	(config)
1	(+) DIOP	60	25	70	3	(R)
2	(+) DIOP	15	-10	80	22	(R)
3	(+) DIOP	15	-35	75	39	(R)
4	(+) DIOP	15	-50	70	52	(R)
5	(+) DIOP	60	-60	60	57[d]	(R)
6	(-) DIOP	15	0	40	12	(S)
7	(-) DIOP	15	-30	62	38.5	(S)
8	(-) DIOP	15	-55	50	55	(S)
9	(-) NORPHOS[12]	40	-35	55	32[e]	(S)
10	(+) NORPHOS[12]	15	-35	70	30	(R)
11	(+) NORPHOS[12]	40	-55	29	31	(R)
12	(-) BINAP[13]	30	-35	84	8	(R)
13	(-) BINAP	40	-55	60	9	(R)
14	(+) PROPHOS[14]	15	-35	64	12	(R)
15	(-) BPPM[15]	15	-35	69	15	(R)
16	DIOXAPHOS[16]	120	-10	45	2	(R)
17	OXAZAPHOS[17]	120	-20	40	6	(R)
18	(-) CHIRAPHOS[18]	15	-35	90	30[f]	(S)
19	PAMP[19]	40	-35	47	17	(R)
20	DIPAMP[19]	15	-35	70	12	(R)
21	DIPMC[20]	15	-35	80	3	(S)

a) *To a mixture of lithium enolate of 1 (prepared at -78°C from LDA (0,9 mmole) and Schiff base 1 (1 mmole in THF) and allylic acetate (1,1 mole) was added preformed[9], palladium catalyst with the appropriate chiral ligand.*

b) *Isolated yield by flash chromatography on silica gel (hexane/ethyl acetate : 4/1).*

c) *Determinated by HPLC with (R) 3,5-dinitrophenylbenzoyl glycine[22] eluent : hex./THF : 98.5/1.5 (Errors within ± 1 % for multi data calculation by integrator D. 2000).*

d,e,f) *The rotations of allylated product were* $[\alpha]_D^{25}$ = +75.1 ; -37.8 ; -34.5 (c = 0.83 ; 0.66 ; 0.62 *in chloroform) respectively.*

The lithium enolate of 1 was very reactive even at low temperature and gave the allylic Schiff base 2. Surprisingly[21] among, the different Pd-chiral phosphines used (see entries 1-21), we found that Pd-DIOP[1] is the most efficient system, giving 39 % ee at -35°C (entry 3). Decreasing the temperature to -50 or -60°C gave acceptable chemical yields with substantially increases of the ee up to 57 % (entries 4,5,8) ; a detailed study of the temperature effect is shown in Table I (compare entries 1-5). NORPHOS[12] gave a lower selectivity than DIOP, under our standard conditions : 30-32 % ee (entries 9-11).

The ligands BINAP[13], PROPHOS[14] and BPPM[15] gave good chemicals yields but relatively poor ee (8-15 %) entries 12-15. Chirality of the phosphorus ligand does not appear to play a crucial role in this system : PAMP[19] and DIPAMP[19] showed poor selectivity (12-17 % ee, entries 19,20). We also investigated the activity of the new chiral ligands DIOXAPHOS[17] and OXAZAPHOS[18] which gave good chemical conversions but low ee (2-6 % entries 16 and 17). The inefficency of these ligands can be explained in terms of steric effects or the lack of functional groups capable[5,7] of interaction with the nucleophile. However, more subtile effects are possible, since DIOP which is reputed to be a very poor ligand (0-10 %)[21] in palladium-catalyzed asymmetric alkylation, has revealed here a high capacity for inducing substantial enrichment. In this study the enantiomeric purity was determined using HPLC with a Pirkle column[22]; the absolute configuguration of 2 was correlated with allylglycine methyl ester[23] easily obtained after acid hydrolysis of 2.

The enantioselectivity achieved here is the highest known for catalytic asymmetric C-C bond formation with a prochiral nucleophile[24].

In this study we have shown that it is possible to obtain acceptable levels of optical purity in asymmetric α-amino acid synthesis using the benzophenone imine of glycine methyl ester as a very simple synthon and readily available ligands such as DIOP.

Modification of the ligand as well as the nature of the prochiral nucleophile should permit to improve selectivity. Obviously, there is a demand for uncommon α-amino acids[25] in organic and bioorganic chemistry ; such studies are currently in progress.

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11 - DIOP : (4S,5S)-(+) and (4R,5R)-(-)-4,5-bis (diphenyl phosphino methyl)-2,2-dimethyl-1,3-dioxolane.

12 - NORPHOS : (2S,3S)-(+)-2,3-bis (diphenyl phosphino)-bicyclo 2.2.1 hept-5-ene. We thank Professor H. Brunner (University of Regensburg) for a gift of (+) and (-) NORPHOS.

13 - BINAP : (S)-(-)-2,2'-bis (diphenyl phosphino)-1,1'-binaphtyl.

14 - PROPHOS : (R)-(+)-1,2-bis (diphenyl phosphino) propane.

15 - BPPM : (2S,4S)-(-)-N-(tert-butoxycarbonyl)-4-(diphenyl phosphino)-2-[(diphenyl phosphino) methyl] pyrrolidine.

16 - DIOXAPHOS : (2S,4S,5R)-(+)-4,5-dimethyl-2-phenyl-4,5-[(2'R,5'S)-1',1',2'-trimethyl-2'-5'-cyclopentylene] -1,3,2-dioxaphospholane ; S. Jugé, Y. Legras, unpublished work.

17 - OXAZAPHOS : (2R,4S,5R)-(+)-3,4-dimethyl-2,5-diphenyl-1,3,2-oxazaphospholidine ; S. Jugé, Europ. Patent 82 057, (1982), (C.A. 99 140162).

18 - CHIRAPHOS : (2S,3S)-(-)-bis (diphenyl phosphino) butane.

19 - PAMP : (S)-(+)-(2-methoxyphenyl) methyl phenyl phosphine, DIPAMP : (R,R)-(-)-1 2-bis [(2-methoxyphenyl) methyl phenyl phosphino] ethane. We thank Dr. P. Potin (SNEA) for a gift of PAMP and DIPAMP.

20 - DIPMC : (1S,2S)-(+)-1,2-bis (diphenyl phosphino methyl) cyclohexane.

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