Ligand Effect on Pd(0)-Catalyzed Allylation of Alkyl (Diphenylmethylene)glycinates

S. GOSIEWSKA, B. GOTOV, and Š. TOMA*

Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University, SK-842 15 Bratislava
e-mail: toma@fns.uniba.sk

Received 27 August 2002

The effect of six different *P,N*-ferrocenyl ligands having both central and planar chirality on the stereoselectivity of Pd(0)-catalyzed allylation of methyl or (1*R*,2*S*,5*R*)-(-)-menthyl (diphenylmethylene)glycinate was studied. Just moderate yields of the allylation products were isolated. The highest stereoselectivity was achieved with the ligand (*R*,p*S*)-BPPFA, namely 25.5 % ee at allylation of methyl glycinate. It was proved that in allylation of (1*R*,2*S*,5*R*)-(-)-menthyl (diphenylmethylene)glycinate the ester chiral auxiliary has a dominant effect.

Transition metal complexes-catalyzed allylic alkylation is one of the most powerful methods for C—C bond formation, for which reason it is very frequently used in organic synthesis [1, 2]. The possibility to use a broad range of chiral ligands makes this reaction even more versatile because allylation can be performed in a stereoselective mode. A special case of this reaction is allylation of glycine methyl ester Schiff bases and especially alkyl (diphenylmethylene)glycinates introduced by *O'Donell* and *Genet* [3—5]. This methodology was extended to allylation of α-isocyanocarboxylates [6] and azlactones [7] and is used for synthesis of α-amino acids. The stereoselective reaction can be achieved using chiral ligands, of which DIOP, BINAP, and CHIRAPHOS type ligands are the most frequently used, or using chiral auxiliaries like menthyl ester of glycine or chiral azlactones [7] or a combination of menthyl glycinate with DIOP [8]. A great progress has been done recently by application of chiral phase-transfer catalysts at allylation of alkyl, especially *t*-butyl (diphenylmethylene)glycinates. As the chiral phase-transfer catalysts (PTC) ammonium salts derived from cinchona alkaloids [9—11] are most frequently used, but C2-symmetrical chiral PTC derived from chiral 1,1′-binaphthalene like spirocyclic tetraalkylammonium salts [12] and sterically hindered ketiminium salts [13] gave also excellent results.

In spite of the fact that chiral ferrocene ligands are frequently used in transition metal-catalyzed reactions (see for example [14, 15]), there was just one paper published describing their use in Pd(0)-catalyzed allylation of alkyl (diphenylmethylene)glycinates. *Dai et al.* [16] have prepared the ferrocene analogues of Trost's "pocket ligands" [17] and reached up to 60 % ee at allylation using allyl ethyl carbonate as the allylation agent. The main aim of this work was to examine the efficacy of different *P,N*-ferrocene ligands having both central and planar chirality in stereoselective Pd(0)-catalyzed allylation of alkyl (diphenylmethylene)glycinates.

EXPERIMENTAL

All reactions were carried out in the solvents which were dried by the usual methods right before the reactions. Benzophenone imine was prepared according to [18], methyl and (-)menthyl *N*-(diphenylmethylene)glycinate were prepared according to [3], $Pd_2(dba)_3.CHCl_3$ was prepared according to [19]. Ferrocene ligands (*S*,p*R*)-*N,N*-dimethyl-1-[1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine ((*S*,p*R*)-BPPFA), (*R*,p*S*)-*N,N*-dimethyl-1-[1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine ((*R*,p*S*)-BPPFA), (*R*,p*S*)-1-[1′,2-bis(diphenylphosphino)ferrocenyl]-*N,N*-diethanolamine ((*R*,p*S*)-BPPFDEA) were prepared as described in [20, 21, 15] and (*S*,p*S*)-1-(4-isopropyl-2-oxazoline-2-yl)-2-(diphenylphosphino)ferrocene ((*S*,p*S*)-iPr-Phosferox), (*S*,p*R*)-1-(4-isopropyl-2-oxazoline-2-yl)-2-(diphenylphosphino)ferrocene ((*S*,p*R*)-iPr-Phosferox), and (*S*,p*S*)-1-(4-*tert*-butyl-2-oxazoline-2-yl)-2-(diphenylphosphino)ferrocene ((*S*,p*S*)-*t*-Bu-Phosferox) were prepared according to [22, 23].

Chromatography was carried out on LOBA 40/100 silica gel or Brockman 90/1 alumina. Melting points were determined on a Kofler hot-stage. ^{1}H NMR spectra were measured on a Varian Gemini 2000 instru-

*The author to whom the correspondence should be addressed.

ment, working frequency 300 MHz in $CDCl_3$, tetramethylsilane was used as internal standard. Ratio of stereoisomers (ee or de values) was determined either by NMR using $Eu(hfc)_3$ shift reagent or by HPLC using Chiracel CD column, eluent being Hex/iPrOH, φ_r = 99.5 : 0.5 or Chiralpack Ad or Ad-H column, eluent being Hex/iPrOH, φ_r = 97 : 3.

Allylation

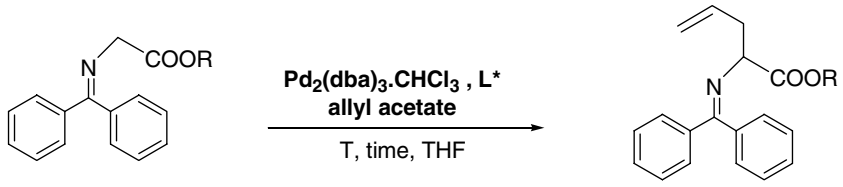
To the cooled to −78 °C solution of lithium diisopropylamide (LDA) (1 mmol) in THF the THF solution of the ester derivative (1 mmol) was added dropwise. After the formation of the enolate (colour change of solution), the temperature of the reaction mixture was allowed to rise up to the temperature of the allylation and the solution of allyl acetate (1.1 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (0.01 mmol; 2 mol % of Pd), and the appropriate ligand (0.04 mmol; 8 mol % of the ligand) in THF was added dropwise. The reaction mixture was stirred for 1 h in case of methyl ester and 3 h in case of menthyl ester. The reaction was quenched with water and extracted with Et_2O. The products were isolated by column chromatography on SiO_2 (methyl ester iHex/AcOEt, φ_r = 5 : 1, menthyl ester iHex/AcOEt, φ_r = 8 : 1). The allylated products were isolated as colourless oils, which is in accord with [4] and [24], respectively, but no NMR spectra of these products are given in that literature.

Methyl ester: ^{1}H NMR (δ, $CDCl_3$): 2.67 (m, 2H, C*HH*C*H), 3.72 (s, 3H, CH_3), 4.16 (dd, 1H, J = 7.7 Hz, 5.4 Hz, C*H*), 5.03 (t, 2H, J = 17.03 Hz, 10.2 Hz, HC=C*HH*), 5.66 (m, 1H, *H*C=CH_2), 7.15—7.18 (m, 2H, Ph), 7.26—7.4 (m, 4H, Ph), 7.34—7.48 (m, 4H, Ph), 7.61—7.64 (d, 2H, Ph). This spectrum is in accord with [25].

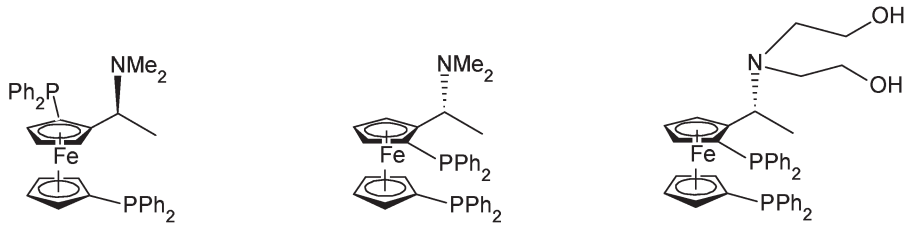
Menthyl ester: ^{1}H NMR (δ, $CDCl_3$): 0.70—2.02 (m, 18H, menthyl), 2.66 (m, 2H, C*HH*C*H), 4.08 (dd, 1H, J = 7.6 Hz, 5.4 Hz, C*H*), 4.7 (dt, 1H, J = 10.7 Hz, 6.6 Hz, COOC*H*), 5.04 (t, 2H, J = 17.5 Hz, 12.1 Hz, CH=C*HH*), 5.71 (m, 1H, *H*C=CH_2), 7.13—7.16 (m, 2H, Ph), 7.26—7.4 (m, 4H, Ph), 7.43—7.48 (m, 4H, Ph), 7.61—7.65 (d, 2H, Ph).

DISCUSSION

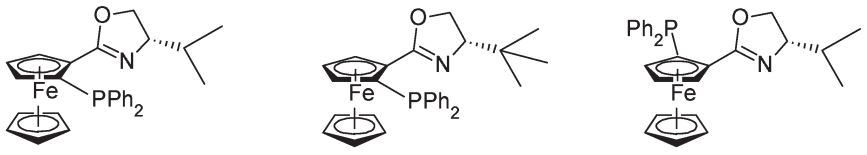
To study the ligand effect on the course of Pd(0)-catalyzed allylation of alkyl (diphenylmethylene)glycinates we decided to use the same conditions as were used by *Genet* [4, 5] with bisphosphine ligand as DIOP, CHIRAPHOS, BINAP, NORPHOS, BPPM, *etc.* (Scheme 1).



Scheme 1



(*S*,p*R*)-BPPFA (*R*,p*S*)-BPPFA (*R*,p*S*)-BPPFDEA



(*S*,p*S*)-i Pr-Phosferox (*S*,p*S*)-*t*-Bu-Phosferox (*S*,p*R*)-i Pr-Phosferox

Chart 1

Table 1. The Results of Pd(0)-Catalyzed Allylation of Methyl (Diphenylmethylene)glycinate[a]

No.	Ligand	Base	Additive	°C	Yield/%	ee/%[b]
1	(*S*,p*R*)-BPPFA	LDA	—	25	54	5(*R*)
2	(*S*,p*R*)-BPPFA	LDA	—	−55	45	6(*R*)
3	(*R*,p*S*)-BPPFA	LDA	—	−55	48	25.5(*S*)[c]
4	(*R*,p*S*)-BPPFA	BSA	—	−55	0	0
5	(*R*,p*S*)-BPPFA	BSA	—	25	38	< 5(*S*)
6	(*R*,p*S*)-BPPFDEA	LDA	—	−55	34	16.2(*R*)[d]
7	(*R*,p*S*)-BPPFDEA	LDA	KOAc[f]	−55	27	16.7(*R*)
8	(*R*,p*S*)-BPPFDEA	LDA	KOAc	−55	23	15.1(*R*)
9	(*S*,p*S*)-iPr-Phosferox	LDA	—	−55	39	11.5(*S*)[e]
10	(*S*,p*S*)-*t*-Bu-Phosferox	LDA	—	−55	37	13.5(*S*)

a) The reaction time was 1 h in all experiments. *b*) Configuration of the main isomer is given and was determined by NMR with chiral shift reagent Eu(hfc)$_3$. *c, d, e*) Specific optical rotation $[\alpha]_D^{24} = -34.2, +22.5, -10.3$ (*c* 0.48, 0.65, 1.06). *f*) 0.5 equivalent.

Chosen ligands are given on Chart 1.

All experiments with methyl ester were carried out at −55 °C using 8 mol % of L* and 2 mol % of Pd, the results are given in Table 1.

From the results given in Table 1 it follows that the best results were achieved with (*R*,p*S*)-BPPFA (48 % yield and 25.5 % ee), which is sterically less demanding than other ligands we have studied. *Genet* [4] has observed similar anomaly, obtaining the best results with small DIOP ligand (60 % yield, 57 % ee). As our results were worse than those of Genet, we decided to add an additive, which can rise the yields in some alkylation reactions [26]. To our surprise, we found that both additives, AcOK as well as $MgBr_2$ had the opposite effect and lowered the reaction yield (No. *7* and *8*). The attempts have been made also to use another base at generating the necessary nucleophile (No. *4* and *5*). No reaction took place when BSA was used as the base at −55 °C, which can be caused by insolubility of the base in the used solvent at such low temperature. The next experiment was carried out in different way. The enolate nucleophile was generated by *N,O*-bis(trimethylsilyl)amide (BSA) at room temperature, the formation of the enolate was detected by colour change of the solution, reaction mixture was then cooled down to −55 °C, but again no reaction was observed. The reaction was then carried out at room temperature, but the result was disappointing.

To check if the change of the ligand chirality has a dominant effect on the stereochemical outcome of the reaction the experiment with (*S*,p*R*)-BPPFA was performed (No. *2*). We have found that the yields of the reactions with both ligands are comparable, but ee was just 6 % in this case and the configuration of the main isomer was *R* in this case. One can speculate that both chiralities are "matched" in the case of (*R*,p*S*)-BPPFA, but "mismatched" in the case of (*S*,p*R*)-BPPFA.

Further on we decided to study if the chiral auxiliary in the ester group can have a great effect on the outcome of allylation. The experiments with (1*R*,2*S*,5*R*)-(-)-menthyl (diphenylmethylene)glycinate were therefore carried out and the results are given in Table 2.

Table 2. Results of Pd(0)-Catalyzed Allylation of (1*R*,2*S*,5*R*)-(-)-Menthyl (Diphenylmethylene)glycinate[a]

No.	Ligand	Yield/%	de/%[b]
1	(*R*,p*S*)-BPPFDEA	23	8
2	(*S*,p*S*)-iPr-Phosferox	16	51
3	(*S*,p*R*)-iPr-Phosferox	26	25
4	(*S*,p*S*)-*t*-Bu-Phosferox	28	29
5	(*S*,p*S*)-iPr-PCy$_2$-Phosferox	26	20
6	(*S*,p*S*)-iPr-Phosferox	26[c]	49
7	DPPF	40	40

a) Reaction time was 3 h, base LDA, and temperature −55 °C in all experiments. *b*) Diastereomeric excess was determined by HPLC on the Chiralpack Ad or Ad-H column, eluent being Hex/iPrOH, $\varphi_r = 97:3$. *c*) 5 mol % of Pd was used in this experiment.

From the results given in Table 2 it follows that the yields of the product are low and comparable with those given in Table 1. The de of the reaction product are low or medium even when the bulkiness of the ligand was changed. This was proved by the exchange of isopropyl group for more bulky *tert*-butyl group (No. *3* and *4*) or diphenylphosphino group for more bulky bis(cyclohexyl)phosphino group (No. *3* and *5*). The yields as well as de rose when higher amount of the Pd catalyst was used (No. *6*). It was of interest to examine what is the effect of chiral auxiliary in the ester group. The experiment with the ligand without both central and planar chirality, that is 1,1′-diphenylphosphinoferrocene (DPPF) was carried out. The results (No. *7*) proved that this auxiliary has a dominant effect on the reaction course because the yields were reasonable (40 %) and de of the product was among the highest (40 % de).

REFERENCES

1. Consiglio, G. and Waymouth, R. M., *Chem. Rev. 89*, 257 (1989).
2. Trost, B. M. and Van Vranken, D. L., *Chem. Rev. 96*, 395 (1996).
3. O'Donell, M. J. and Polt, R. L., *J. Org. Chem. 47*, 2663 (1982).
4. Genet, J. P., Ferroud, D., Juge, S., and Montes, J. R., *Tetrahedron Lett. 27*, 4573 (1986).
5. Genet, J. P., Juge, S., Achi, S., Mallart, S., Montes, J. R., and Levif, G., *Tetrahedron 44*, 5263 (1988).
6. Ito, Y., Sawamura, M., Matsuoka, M., Matsumoto, Y., and Hayashi, T., *Tetrahedron Lett. 28*, 4849 (1987).
7. Trost, B. M. and Ariza, X., *J. Am. Chem. Soc. 121*, 10727 (1999).
8. Genet, J. P., Kopola, N., Juge, S., Ruiz-Montez, J., Antures, O. A. Z., and Tanier, S., *Tetrahedron Lett. 31*, 3133 (1990).
9. Lygo, B. and Wainwright, P. G., *Tetrahedron Lett. 38*, 8595 (1997).
10. Corey, E. J., Noe, M. C., and Xu, F., *Tetrahedron Lett. 39*, 5347 (1998).
11. Chen, G., Deng, Y., Gong, L., Mi, A., Cui, X., Jiang, Y., Choi, M. C. K., and Chan, A. S. C., *Tetrahedron: Asymmetry 12*, 1567 (2001).
12. Ooji, T., Uematsu, Y., Kameda, M., and Maruoka, K., *Angew. Chem., Int. Ed. Engl. 41*, 1551 (2002).
13. Gmouh, S., Jamal-Eddine, J., and Valnot, J. Y., *Tetrahedron 56*, 8361 (2000).
14. Togni, A. and Hayashi, T., *Ferrocenes: Homogeneous Catalysis, Organic Synthesis, Material Science.* VCH, Weinheim, 1995.
15. Kmentová, I., Gotov, B., Solčániová, E., and Toma, Š., *Green Chem. 4,* 103 (2002).
16. You, S. L., Hou, X. L., Dai, L. X., Cao, B. X., and Sun, J., *Chem. Commun. 2000*, 1933.
17. Trost, B. M., Krueger, A. C., Brint, R. C., and Zambrano, J., *J. Am. Chem. Soc. 118*, 652 (1996).
18. Pickard, P. L. and Tolbert, T. L., *Org. Synth. Coll. Vol. V,* p. 520. Wiley, New York, 1973.
19. Ukai, T., Kawazura, H., Ishii, Y., Bonet, J. J., and Ibers, J. A., *J. Organomet. Chem. 65,* 253 (1974).
20. Hayashi, T., Mise, T., Fukushima, M., Kagotami, M., Nagashima, M., Hamada, Y., Matsumoto, A., Kawakami, S., Kanishi, M., Yamamoto, K., and Kumada, M., *Bull. Chem. Soc. Jpn. 53*, 1138 (1980).
21. Hayashi, T., Yamamoto, A., Ito, Y., Nishioka, E., Miura, H., and Yanagi, K., *J. Am. Chem. Soc. 111*, 6301 (1989).
22. Richards, C. J. and Mulvaney, A. W., *Tetrahedron: Asymmetry 7*, 1419 (1996).
23. Ahn, K. H., Cho, C. W., Baek, H. H., Park, J., and Lee, S., *J. Org. Chem. 61*, 4937 (1996).
24. Yaozhong, J., Changyou, Z., and Hury, P., *Synth. Commun. 19*, 881 (1989).
25. Guillena, G. and Najera, C., *J. Org. Chem. 65*, 7310 (2000).
26. Soladie-Cavallo, A. and Simon, M. C., *Tetrahedron Lett. 30*, 6011 (1989).