Enantioselectivity in Organo Transition Metal Chemistry. An Unprecedented Ligand Effect in π-Allyl Palladium Chemistry

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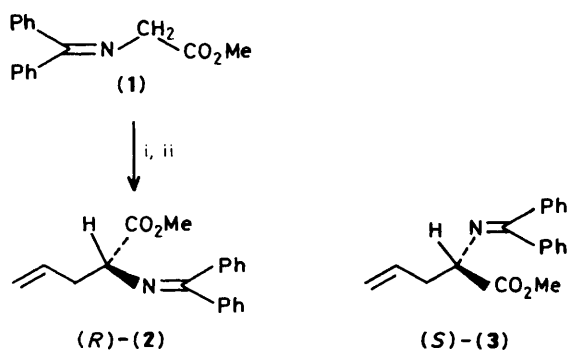
In the palladium catalysed allylic alkylation of Schiff bases derived from glycine methyl ester, using Pd-chiral diphosphine ligands, the enantiomeric excess (e.e.) depends upon the proportion of chiral ligand, showing a maximum effect (e.e. up to 62%) for a molar ratio of 2; a 1 : 1 Pd : diphosphine ligand ratio leads to substantially lower e.e. values and reverses the enantioselection.

Asymmetric carbon–carbon bond forming reactions are of great importance for the synthesis of optically active compounds, and the use of chiral transition metal catalysts for such reactions has attracted considerable attention.[1] Asymmetric induction in the palladium-catalysed allylic alkylation is also of current interest. Among the characteristics investigated, recent work has emphasized the importance of the design of new chiral phosphine[2] or selected allylic substrates[3] in achieving good enantioselectivity. Very few prochiral nucleophiles have been tested; however, we have recently published a practical and efficient synthesis of α-amino acids based on Pd alkylation of Schiff bases derived from glycine.[4] In the search for factors controlling the catalysed enantioselective alkylation of enolates of α-amino ester Schiff bases to maximise efficiency, we have found an unprecedented ligand effect. In this communication we report a maximum enantioselectivity for a diphosphine/Pd ratio = 2. Interestingly, at a lower ratio <2, and for the same ligand, the enantioselection was reversed.

The stable imine (**1**), readily available from methyl glycinate hydrochloride and diphenylmethyleneamine,[5] was used as the substrate in these asymmetric studies (Scheme 1). Treatment of (**1**) with lithium di-isopropylamide (LDA) (0.9 equiv.) in tetrahydrofuran (THF) at −78 °C and subsequent alkylation of the corresponding enolate with allyl acetate in the presence of $Pd(dba)_2$ (dba = dibenzylideneacetone) and the chiral ligand gave the allylated product with some enrichment.

A series of experiments was carried out using $Pd(dba)_2$ (3%) as catalyst, and using different amounts of the chiral ligands: (+)- and (−)-DIOP† [DIOP = 2*S*,3*S*-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane] (Figure 1). In this study at −35 °C, the highest enantiomeric excess[6] (39.2%) for the (*R*)-alkylated product[7] was obtained using 2 equiv. of (+)-DIOP/Pd; no significant



Scheme 1. *Reagents and conditions*: i, lithium di-isopropylamide (LDA), tetrahydrofuran (THF), −78 °C; ii, $Pd(dba)_2$, chiral ligand (L*), CH_2=CH·CH_2OAc.

† Commercially available from Merck and Strem.

Table 1. Enantioselective alkylation of Schiff base (**1**) at −55 °C with 2,3-dichloropropene in the presence of $Pd(dba)_2$ (+)-NORPHOS or (+)-DIOP catalysts.

Entry	Base	$Pd(dba)_2$ (% equiv.)	Ligand (% equiv.)	$[\alpha]_D^{20}$ (°)	% e.e.	% Yield
1	LDA	3	0.5[a]	+15	6	15
2	LDA	3	1[a]	+19.2	7.5	70
3	LDA	3	1.5[a]	−70.8	32.5	81
4	LDA	3	2[a]	−86	45	61
5	NaH	3	2[b]	−127	62	86

[a] (+)-NORPHOS. [b] (+)-DIOP.

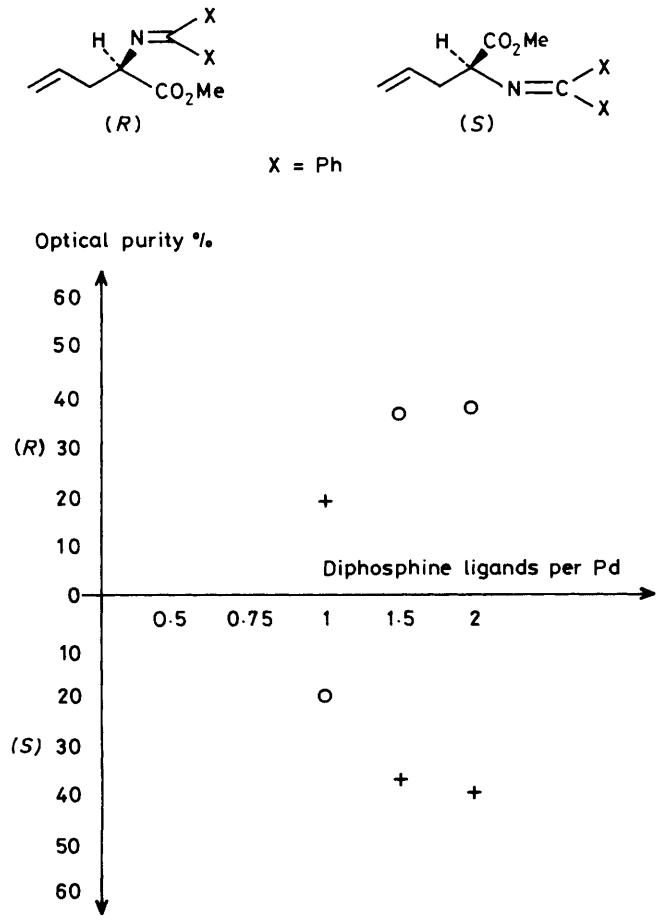


Figure 1. Ligand effect in the asymmetric palladium alkylation of the Schiff base of glycine methyl ester (**1**) at −35 °C in THF: O = (+)-DIOP; + = (−)-DIOP.

decrease of the enantioselectivity (e.e. 38.5%) was observed when 1.5 equiv. of (+)-DIOP per Pd was used, see Figure 1. However, a dramatic ligand effect was observed with 1 equiv. of (+)-DIOP; the e.e. decreased to 20% with formation of the (*S*)-isomer. Similar results were observed with (−)-DIOP with 2 and 1.5 equiv. of the chiral ligand/Pd. The (*S*)-enantiomer was produced in 38.5 and 37.6% e.e., respectively, 62—64% chemical yields. Again, addition of 1 equiv. of (−)-DIOP per Pd reversed the enantioselection and gave the (*R*)-isomer (19.2% e.e.).

This phenomenon has also been observed during the alkylation of (**1**) with 2,3-dichloropropene in the presence of $Pd(dba)_2$, (+)-NORPHOS [NORPHOS = (2*S*,3*S*)-(+)-2,3-bis(diphenylphosphino)bicyclo(2.2.1)hept-5-ene] .[6] Reversed enantioselection was observed with 1.5 equiv. of the bidentate ligand (compare entries 2 and 3, Table 1). In entry 5 a substantial improvement of the e.e. can also be seen, up to 62% with 2 equiv. of (+)-DIOP per Pd using the sodium enolate generated from (**1**) with NaH in THF. We have achieved here one of the highest e.e. values known in π-allyl palladium-allylation with a prochiral nucleophile.

The exact structures of the active species are not known. We believe that it is the structure of the catalyst that changes.[8] The efficiency of the system is a product of its relative distribution with respect to the other catalyst structures in solution.[9]

In conclusion, we emphasize that the present observation, which shows the effect of the Pd/chiral ligand ratio in asymmetric allylic alkylation, is of mechanistic significance and may be of great interest for a better understanding of the enantioselective phenomena.

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