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New Chiral Ligands designed for Palladium-catalysed Asymmetric Allylic Alkylation

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New chiral phosphine ligands containing a chiral functional group remote from the phosphino-groups have been found to be effective in the palladium-catalysed reaction of allyl acetate with the enolate anion of 2-acetylcyclohexanone and give the allylated product in significant enantiomeric enrichment.

Considerable attention has been paid to asymmetric carbon–carbon bond-forming reactions catalysed by chiral transition metal complexes.[1] In 1978, Kagan and coworkers reported[2] that the reaction of prochiral active hydrogen compounds with allylic ethers in the presence of a DIOP–palladium catalyst [DIOP = 2,2-dimethyl-1,3-dioxolan-4,5-bis(methylene)bis(diphenylphosphine)] gave optically active allylated products in up to 10% e.e. The reaction mechanism,[3] in which the nucleophile attacks the face of the π-allyl group opposite to the palladium, suggests that the low stereoselectivity may be ascribed to the large distance between the inducing moiety on the ligand and the developing asymmetric centre (A).[2] We have designed and prepared, for asymmetric allylation, new phosphine ligands which possess a chiral functional group at an appropriate distance from the co-ordinated phosphino-groups. The chiral functional group was expected to interact with the nucleophile forming the asymmetric carbon to bring about higher stereoselectivity (B).

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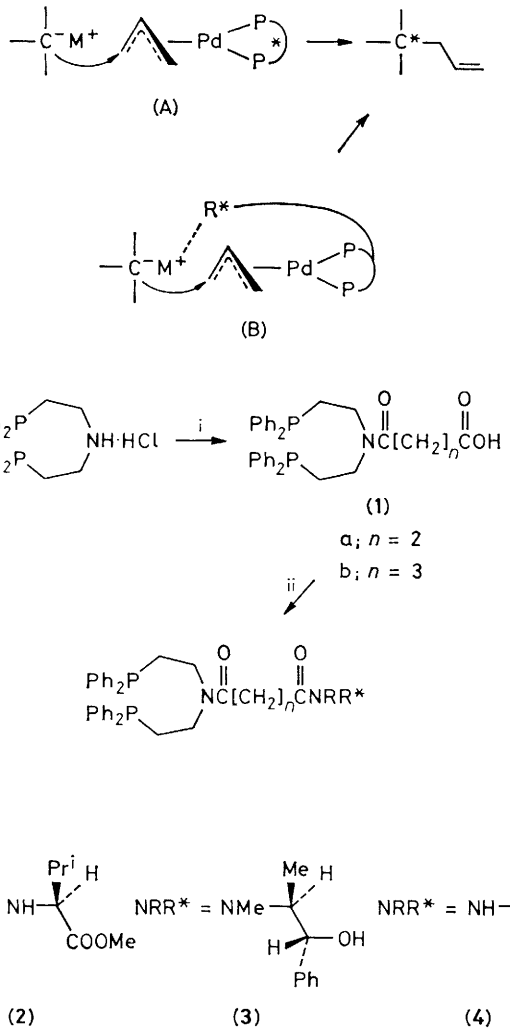
Table 1. Asymmetric allylation.[a]

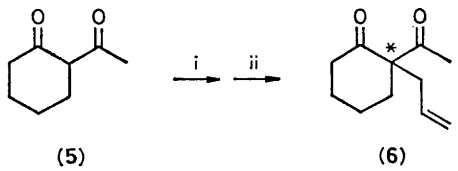
Run	Chiral Ligand	T/°C	% Conversion (% Yield)[b]	$[\alpha]_D^{20}$[c] of (**6**)/°	% e.e.[d]
1	(**2a**)	room temp.	100 (94)	−47.5	19
2	(**2a**)	−30	100 (80)	−115.4	45
3	(**2a**)	−50	89 (52)	−130.9	52
4	(**3a**)	−30	97 (64)	−78.3	31
5	(**4a**)	−30	100 (86)	−38.4	15
6	(**2b**)	room temp.	100 (82)	−12.5	5
7	(**1a**) + Val-OMe[e]	−30	100 (83)	0	0
8	(−)-DIOP	−30	96 (59)	−4.1	2
9	(*S*)-prophos[f]	−30	100 (76)	−28.3	11

[a] To a solution of sodium enolate prepared from 2-acetylcylohexanone (**5**) (5 mmol) and sodium hydride in THF (10 ml) was added a mixture of a ligand (0.04 mmol), di-μ-chlorobis(π-allyl)dipalladium (0.02 mmol), and allyl acetate (7 mmol) in THF (7 ml) at −78 °C. The reaction mixture was kept stirred at a given temperature for 17—20 h. After hydrolysis with dil. HCl and the usual work-up, the product (**6**) was isolated by distillation (74 °C/2 mmHg) or by silica gel preparative t.l.c. (R_f 0.6, hexane/EtOAc = 5/1). [b] Isolated yield. [c] (c 2.5–5.0, chloroform). [d] Determined by ^{1}H n.m.r. spectroscopy using the chiral shift reagent tris[di-(+)-campholylmethanato]europium(III). The maximum rotation of (**6**) is calculated to be 254 ± 7° (chloroform). [e] (*S*)-Valine methyl ester (10 equiv. with respect to Pd). [f] prophos = 1,2-bis(diphenylphosphino)propane.



Scheme 1. i, Succinic or glutaric anhydride, Et_3N, THF; ii, HNRR*, DCC.

Bis(2-diphenylphosphinoethyl)amine was acylated, according to Whitesides' procedure,[4] with succinic or glutaric anhydride to give carboxylic acid (**1**), which was then converted into amides by condensation with optically active amines in the presence of *N*,*N*′-dicyclohexylcarbodi-imide (DCC) (Scheme 1).



i, NaH, THF; ii, CH_2=$CHCH_2OAc$, (π-C_3H_5)PdCl/L*.

The phosphine ligands (**2**—**4**)† were examined for stereoselectivity in the palladium-catalysed reaction of the sodium enolate of 2-acetylcyclohexanone (**5**) with allyl acetate in tetrahydrofuran (THF). The reaction conditions and results are summarised in Table 1, which also contains data obtained with other phosphine ligands, for comparison. An optically active allylated product (**6**) with high enantiomeric purity was obtained in the reaction with phosphine ligands (**2a**) and (**3a**) which contain valine methyl ester and ephedrine, respectively (runs 1—4). The reaction with (**2a**) at −50 °C gave (**6**) in the highest optical purity (52%) (run 3). The high stereoselectivity observed with the ligands (**2a**) and (**3a**) may well be ascribed to their unique structure described above. The amide group and other functional groups such as methoxycarbonyl or hydroxy-groups present in the chiral source of the ligands are expected to co-ordinate to sodium as chelate ligands, and the chelation should increase their ability to differentiate between the enantiotopic faces of the β-diketonate because of the enhanced steric interaction. The lower selectivity of (**4a**), which has the 1-phenylethyl group as a chiral source, supports this theory that high stereoselectivity requires chelation (run 5). The importance of the distance between the chiral functional group and the diphenylphosphino-groups co-ordinated to palladium is indicated by the lower selectivity of (**2b**) which is analogous to (**2a**) but with glutaramide instead of succinamide (run 6). The use of valine methyl ester as solvent (10 equiv. with respect to Pd) resulted in the formation of racemic (**6**) (run 7). The inefficiency of (−)-DIOP[5] and (*S*)-prophos[6] (runs 8 and 9) is as expected. Both of them are chiral ligands which possibly can only control the stereochemistry by orientation of the phenyl rings on the phosphorus (as has been shown in asymmetric hydrogenation)[7] and the phenyl rings are too distant from the developing asymmetric centre in the present asymmetric allylation for this to be possible.

† Optical rotation data for (**2a**): $[\alpha]_D^{22}$ +8.67° (c 3, $CHCl_3$), (**3a**): $[\alpha]_D^{20}$ −41.5° (c 0.5, $CHCl_3$), and (**4a**): $[\alpha]_D^{20}$ −27.2° (c 1, $CHCl_3$).

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