

Enantioselective catalysis with complexes of asymmetric P,N-chelate ligands

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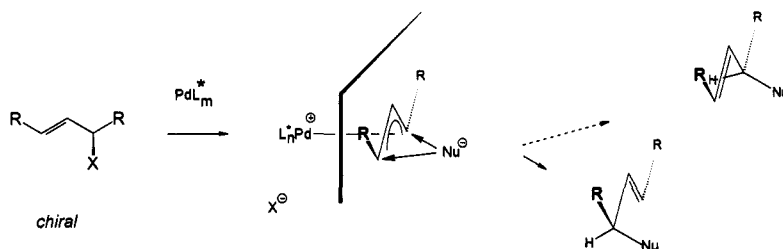
Abstract: Phosphinooxazoline (PHOX) ligands are highly effective in Pd catalyzed asymmetric substitutions of allylic compounds. Amines, malonates, nitronates and other soft nucleophiles were employed. Mechanistic aspects were studied by NMR and x-ray crystal structure analyses. Particular emphasis was placed on highly enantioselective allylic substitutions at cyclic substrates.

INTRODUCTION

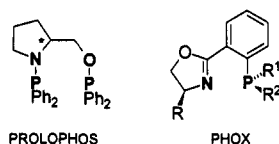
Pd catalyzed asymmetric C-C and C-N bond forming substitutions at allylic compounds are an important area of current research. For a considerable time progress in this area was slow, but over the last few years dramatic improvements were achieved (ref. 1).

The reaction of a chiral, racemic allylic derivative with a Pd⁰ fragment yields the complex of a symmetric allylic cation (Scheme 1). One quite obvious problem associated with this reaction is the long distance between the chiral information provided by L* and the reaction path of the nucleophile. The traditional C₂-symmetric chelate diphosphines are not suited for differentiation of the diastereotopic carbon atoms of the allylic moiety; with diphosphines that gave excellent results in hydrogenations, *i.e.*, CHIRAPHOS, BINAP etc., results were not satisfactory, particularly with cyclic allylic substrates. However, over the last few years it was demonstrated with bisoxazolines (ref. 2) and special diphosphines (ref. 3) that very high enantioselectivity is possible with a proper combination of substrate and ligand.

Scheme 1



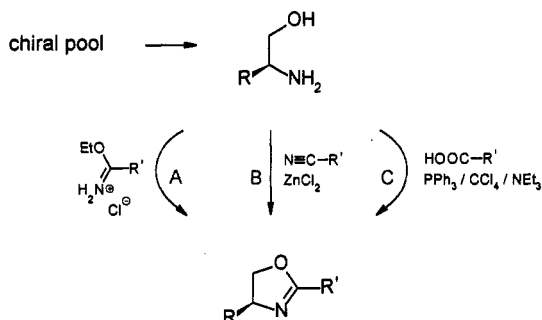
Faller introduced the concept of *electronic differentiation* that was realized in stoichiometric substitutions at molybdenum complexes (ref. 4). A catalytic version of electronic differentiation was apparently first probed by Caesarotti with the ligand PROLOPHOS with two slightly, by bonding to O or N, differentiated P atoms (ref. 5). A fairly low level of enantioselectivity was obtained. We felt that a more pronounced difference in electronic as well as steric properties was required and, therefore, chose the combination of a hard, N, and a soft, P, S or Se, donor. Realization of this proposal made use of the proven usefulness of the oxazoline moiety. Aryl groups were preferred as substituents at P because triarylphosphines are normally stable to air. These considerations led to the phosphinooxazoline (PHOX) ligands (ref. 6). The same concept was independently pursued by the groups of Pfaltz (ref. 7), Williams (ref. 8) and, with a different P-N chelate ligand (QUINAP), J.M. Brown (ref. 9).



PREPARATION OF PHOSPHINOXAZOLINES

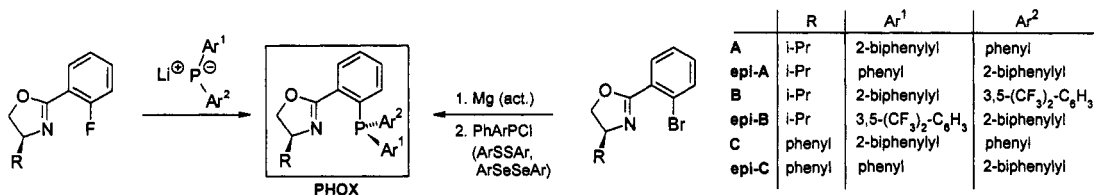
Oxazolines are available from amino alcohols which can be prepared from the chiral pool of natural amino acids. There are many convenient routes from amino alcohols to oxazolines (ref. 10). Usually, one step procedures as described in Scheme 2 are employed (B: ref. 11, 12, C: ref. 13). However, better yields are often achieved with a three step procedure involving (i) formation of an N-acyl amino alcohol, (ii) activation of the OH group and (iii) ring closure with base (ref. 14).

Scheme 2



Introduction of phosphorus is described in Scheme 3 (ref. 14). *Nucleophilic* substitution of fluorine with a diarylphosphide proceeds with 70-90 % yield. In the case of stereogenic phosphorus, with, *e.g.*, Ph and 1-naphthyl or 2-biphenyl, 7:3 mixtures of diastereomers are formed which can be easily separated by flash chromatography or crystallization. *Electrophilic* phosphorus and also sulfur and selenium compounds can be reacted with the Grignard compound obtained from the bromo derivative and activated magnesium. Yields with halophosphines are only 30-50 %, but the P-diastereomers are formed with selectivity of $\geq 85:15$. Configurations at phosphorus were determined by crystal structure analysis.

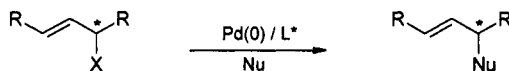
Scheme 3



ACYCLIC SUBSTRATES AND MECHANISTIC ASPECTS

In addition to malonates a variety of nucleophiles were investigated (Scheme 4): amines, N-acylamides (ref. 15), nitro compounds (ref. 16), and sulfonates (ref. 17). These nucleophiles are less reactive than malonates; however, enantioselectivities are very similar and the steric course is independent of the nucleophile.

Scheme 4



R = Me, n-Pr, i-Pr, Ph, CH₂OEt

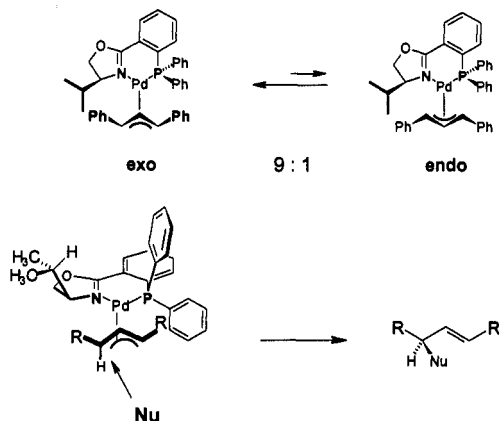
X = OAc, Hal, OCOCH₃, OPO(OR)₂

R = ⁺CH(COOR)₂ (ref. 6, 7, 8), H₂NR (ref. 15), ⁺H₂CNO₂ (ref. 16), ⁺O₂SPh (ref. 17)

Rationalizing the steric course of the nucleophilic substitution is difficult because there are two diastereomeric π -allyl complexes, designated *exo*- and *endo*-isomer here (Scheme 5). The products can be formed via four pathways and the preferred product can arise by reaction at the allylic C *trans* to P of the *exo* or *cis* to P at the *endo* isomer. For the decision between these possibilities, a postulate of Bosnich (ref. 18)

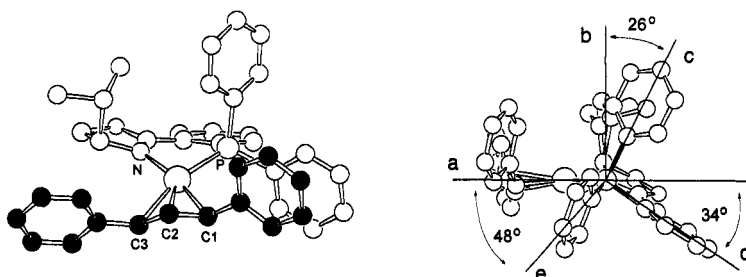
was helpful. This postulate states that the more abundant isomer is the more reactive one (ref. 19). The more abundant is generally the *exo* isomer. According to the known configuration of the products of allylic substitutions the nucleophile preferentially attacks the carbon *trans* to P (ref. 20) (Scheme 5).

Scheme 5




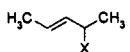
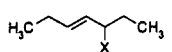
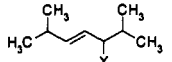
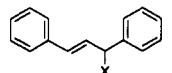
There is so far no direct proof for the mechanism outlined above. There is, however, support by circumstantial evidence from ^{13}C NMR shifts, NMR studies on the interconversion of *exo* and *endo* diastereomers, and x-ray crystal structures (ref. 20, 21).

The crystal structures, for an example see below, also explained why the *exo* are preferred over the *endo* isomers. There are several important general observations: (i) The "inner" chelate cycle PdNCCCCP is non-planar. (ii) A consequence of non-planarity is conformational nonequivalence of the substituents at P, one is axially, the other equatorially arranged. Aryl ring planes are nearly perpendicular to each other, with the axial group pointing its edge, the equatorial its face to the metal. (iii) The substituent of the oxazoline ring occupies an axial position in a way that only the equatorial H can interact with the allylic moiety. The dominating interaction is the one with the equatorial aryl group at P. Minimization of this interaction is the reason for preference of the *exo* over the *endo* diastereomer.

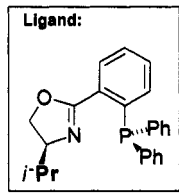


The front view shows quite clearly that the chiral ligand mainly provides interactions at its wings. It appears likely that allylic systems with big substituents, such as phenyl, should display high *exo-endo*- and enantioselectivity, but narrow systems, with small substituents or cyclic, might give low selectivity. This is exactly what was found (cf. Scheme 6). In Scheme 6 substrates are ordered - the isopropyl case is taken from ref. 7 - according to their "broadness" and it is quite remarkable how closely the ee values parallel the steric extension. The importance of this parameter is further underlined by NMR data of the corresponding π -complexes: ratios of 1.8:1, 4:1, and 9:1 for the cyclohexenyl, the 1,3-dimethyl- and the 1,3-diphenylallyl derivative (CDCl_3 solution), respectively. The cause of enantioselectivity though is a kinetic phenomenon, *i.e.*, a function of differing reaction rates at the allylic termini in *exo* and *endo* complexes. Recent results indicate a significant difference of relative reaction rates in acyclic and cyclic substrates with respect to *exo* and *endo* isomers (ref. 21).

Scheme 6

	% ee
	0
	56
	74
	94
	98.5

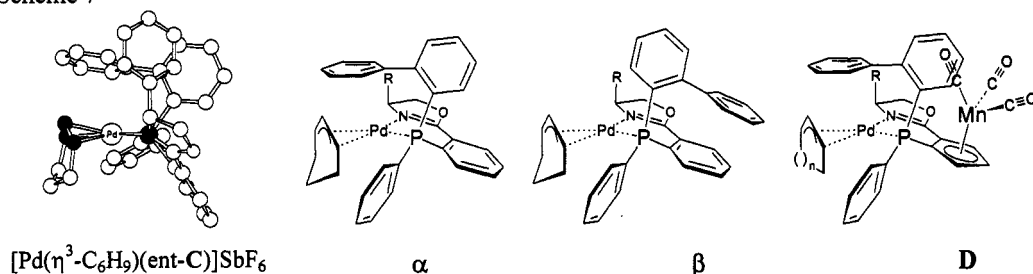
Ligand:



CARBOCYCLIC SUBSTRATES - NEW LIGANDS

The rather clear relationship between the size of the π -allyl moiety and enantioselectivity was very satisfactory as it was in excellent agreement with our mechanistic assumptions. However, the production of racemic product in the case of the cyclic substrate (cf. Scheme 6) was somewhat unsatisfactory from a preparative point of view. Clearly, a ligand was required that would reach into the narrow area directly above or below the allylic sp^2 centers. As such ligands the biphenyl derivatives A-C (Scheme 3) were conceived (ref. 22). We were able to obtain a low resolution x-ray crystal structure of the complex α derived from ligand A ($R = i\text{-Pr}$), and indeed, in the crystal a conformer of the cyclohexenyl π -allyl Pd complex is found in which the phenyl of the 2-biphenyl group is located directly above the allylic moiety as described by formula α (ref. 23) (Scheme 7). Very recently, a high resolution x-ray crystal structure of the similar complex $[\text{Pd}(\eta^3\text{-C}_6\text{H}_9)(\text{ent-C})]\text{SbF}_6$ was achieved, displaying an equivalent conformer (cf. Scheme 7).

Scheme 7

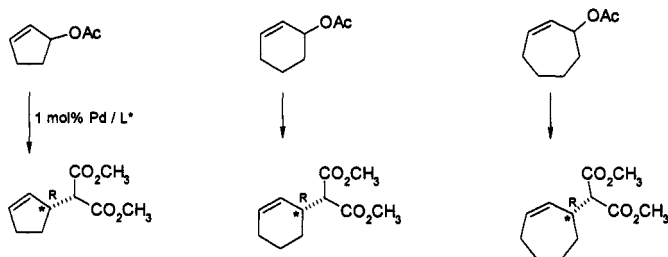


In spite of the favorable conformation in the solid state, enantioselectivities resulting with the ligand A were not satisfactory. Distinct dependence on ring size of the substrate and, to a certain extent, on reaction conditions are apparent from the data given in Scheme 8. In order to enhance electronic effects, the ligand B with electron withdrawing CF_3 groups was prepared. With this ligand improved enantioselectivity was obtained with methylene chloride as solvent (BSA method).

Nevertheless, results were still not satisfactory. A hint towards improvement was gained by an NMR analysis (ref. 21) of the complex α ($R = i\text{-Pr}$) which indicated the existence of several conformers in solution, including the unfavorable conformer β with the crucial phenyl group rotated away from the allylic moiety. In order to destabilize conformers of this type, the cymantrene-based ligand D (Scheme 7) was conceived and could be prepared in a reasonably straightforward way (ref. 24). This ligand induces excellent catalytic activity and displays excellent stability and long shelf life. Conformers analogous to β are

apparently destabilized by interaction with the manganese tricarbonyl group. High enantioselectivity with this new ligand was indeed obtained.

Scheme 8



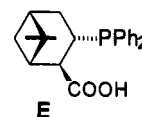
Ligand	Method	5-membered ring [% ee]	6-membered ring [% ee]	7-membered ring [% ee]
A	a	56	51	83
B	a	63	53	83
B	b	64	72	85
D	c	95	93	> 99

Method a: 1.5 eq $\text{LiCH}(\text{COOCH}_3)_2$, dioxane, rt.

Method b: 2.5 eq $\text{CH}_2(\text{COOCH}_3)_2$, BSA method, methylene chloride, 0 °C.

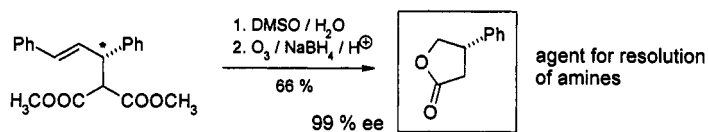
Method c: 1.5 eq $\text{NaCH}(\text{COOCH}_3)_2$, dimethylformamide, -50 °C to 0 °C.

Prior to the development of the new ligand **D**, high enantioselectivities with cyclic substrates were achieved with salts of the easily available β -phosphinocarboxylic acid **E** as chiral ligand (ref. 25): enantiomeric excess of 85, 98 and >99 % ee for the 5-, 6- and 7-membered ring derivatives, respectively [with $\text{LiCH}(\text{COO}-t\text{-Bu})_2$ as nucleophile]. Products with *S*-configuration are formed with **E**.

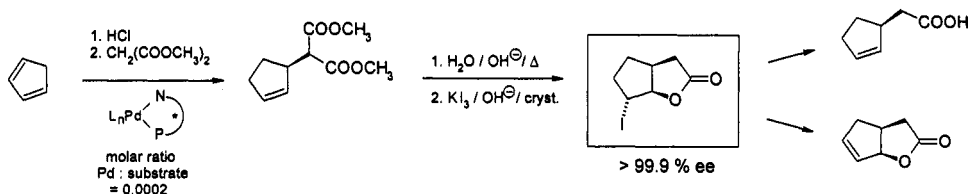


APPLICATIONS

In 1979 this group developed a method for enantiomer resolution of chiral amines which was based on the formation of diastereomeric amides by heating the racemic amine with enantiomerically pure 3-phenylbutyrolactone (ref. 26). At that time there was no convenient way to prepare this compound. It was gratifying that the standard example of allylic alkylation opened a straightforward access (ref. 20b):



Cyclic, in particular 5-membered allylic derivatives, are starting materials for many EPC syntheses. Practicality demanded a high turnover frequency of the catalyst and enantiomerically pure compounds. These problems were solved (ref. 22):



Use of the highly reactive chloride instead of the acetate allowed the amount of catalyst to be reduced from the customary 1-3 mol% to a really satisfactory 0.02 mol% (ca. 5000 turnovers per ca. 3 hours). Furthermore, saponification, decarboxylation and reaction with iodine gave the iodolactone which is obtained

enantiomerically pure with remarkable ease by recrystallization. This iodolactone can be transformed into a variety of useful compounds; for example, cyclopentenyl acetic acid that has been used for a synthesis of chaulmoogric acid (ref. 27).

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