D-76344 Eggenstein-Leopoldshafen (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de) on quoting the depository number CSD-408943.

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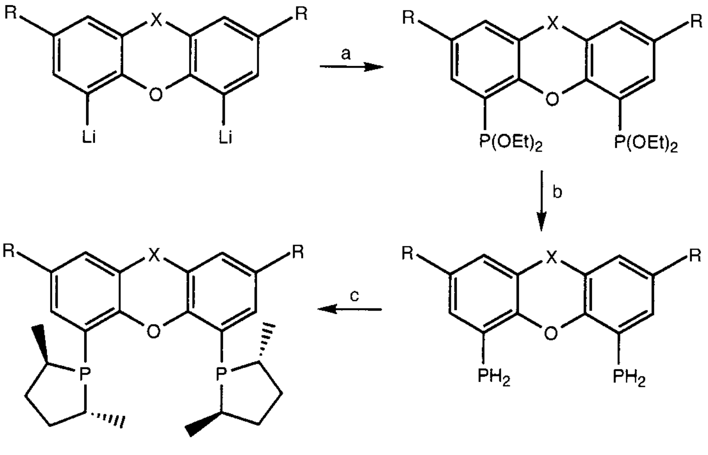
Versatile Ligands for Palladium-Catalyzed Asymmetric Allylic Alkylation[**]

Peter Dierkes, Shailesh Ramdeehul, Laurent Barloy, Andre De Cian, Jean Fischer, Paul C. J. Kamer, Piet W. N. M van Leeuwen, and John A. Osborn[*]

The search for chiral ligands for asymmetric allylic substitution reactions with Pd complexes as catalysts continues apace.[1] High enantiomeric excesses (*ee*) were found for carbon-centered and other nucleophiles with *O*-acetyl-1,3-diphenyl-2-propen-3-ol as the model substrate. Much lower product *ee* values are generally observed for substrates with small substituents[1a] and with less sterically demanding cyclic substrates,[2] although for one family of diphosphane ligands the opposite appears to be true.[2b] The origin of enantioselectivity in these catalytic processes is still under debate, and several parameters are involved. It is generally accepted that in the attack of the nucleophile on the intermediate cationic (η^3-allyl)Pd^{II} complex, the repulsive interactions in the transition state[3] between the chiral ligand and the organic entity bound to the Pd center are an important factor which can largely determine the selectivity. To intensify these repulsive interactions at the Pd center, we synthesized rigid chelating chiral ligands with a large bite angle. Xanthene (dibenzo[*b*,*d*]pyran) and phenoxathiin (dibenzo-1,4-thioxin) were selected as rigid backbones, since 4,5 substitution of the former (older, nonsystematic numbering) and 4,6 substitution of the latter by phosphorus-containing groups leads to a large bite angle (>100°), as in Xantphos complexes.[4]

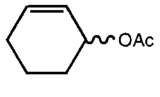
By attaching the chiral (2*R*,5*R*)-2,5-dimethylphospholano groups that were originally used in DUPHOS,[5] a family of several duxantphospholane-type chiral ligands are accessible. The new ligands were obtained in four steps by dilithiation of the backbone, reaction with diethyl chlorophosphonite, reduction with $LiAlH_4$, and treatment of the resulting phosphane with the cyclic sulfate of (2*S*,5*S*)-2,5-hexanediol. This is illustrated by the synthesis of the (*R*,*R*)-duthixantphospholane **A** (Scheme 1). The related chiral ligand, (*R*,*R*)-duxantphospholane **B**, in which the bridging S atom of **A** is formally replaced by a $C(CH_3)_2$ group, was prepared by the same method.[6]



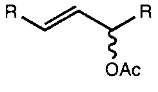
A: R = CH_3, X = S
B: R = H, X = $C(CH_3)_2$

Scheme 1. Synthesis of the chiral P ligand **A**. a) $ClP(OEt)_2$; b) 1) 6 equiv $LiAlH_4$/TMSCl; 2) 30 equiv MeOH; c) 1) 2.0 equiv *n*BuLi; 2) cyclic sulfate of (2*S*,5*S*)-hexane-2,5-diol; 3) 2.2 equiv *n*BuLi. TMS = trimethylsilyl.

The effectiveness of such ligands in Pd-catalyzed allylation reactions was tested by employing dimethyl malonate as the nucleophile and three racemic allyl acetates possessing different steric properties: *O*-acetylcyclohex-2-enol (**1**), *O*-acetylpent-2-en-3-ol (**2**), and *O*-acetyl-1,3-diphenylprop-1-en-2-ol (**3**). Typically a 1 mol% solution of the catalyst was prepared by the addition of one equivalent of **A** (or **B**) to 0.5 mol of $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$ and stirring under nitrogen for 15 min before adding the reactants (Table 1). The catalytic reactions are rapid with the less sterically hindered substrates **1** and **2**



rac-**1**



rac-**2** R = CH_3
rac-**3** R = C_6H_5

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Table 1. Results of alkylation reactions with different substrates.[a]

Entry	Ligand	Substrate	Solvent	Base	T [°C]	t	ee [%]
1	A	**1**	THF	NaH	20	5 min	87 (S)[b, d]
2	A	**1**	THF	NaH	20	30 min	81 (S)
3	A	**1**	THF	BSA	20	30 min	80 (S)
4	A	**1**	THF	BSA	0	2 h	87 (S)
5	A	**1**	THF	BSA	−20	4 h	93 (S)
6	A	**1**	CH_2Cl_2	BSA	20	50 min	82 (S)
7	B	**1**	THF	BSA	20	3 min	77 (S)
8	A	**2**	THF	BSA	20	< 1 min	24 (S)[b, d]
9	A	**2**	CH_2Cl_2	BSA	20	35 min	54 (S)
10	A	**2**	CH_2Cl_2	BSA	0	3 h	68 (S)
11	B	**2**	THF	BSA	20	30 min	66 (S)
12	B	**2**	THF	BSA	0	3 h	82 (S)
13	A	**3**	THF	BSA	0	16 h	83 (R)[c, d]
14	A	**3**	CH_2Cl_2	BSA	0	24 h	97 (R)

[a] The ratio of subtrate to catalyst was 100/1 in each case except entry 2 where it was 500/1. The yield (%) was determined by gas chromatography with a chiral column (β-cyclodextrin capillary column (30 m × 0.25 mm, SGE 25QCE2) by using dodecane as internal standard. [b] The enantiomeric excess was determined by 1H NMR spectroscopy ($CDCl_3$/0.1 M solution of [Eu(hfc)$_3$]). [c] The % *ee* value was determined by HPLC with a chiral column (CHIRALPAK AD, Diacel, 250 × 4.6, flow rate 1 mL min^{-1}, *i*PrOH/*n*-hexane 9:1). [d] The configurations were assigned by comparing optical rotations with literature values.[7]

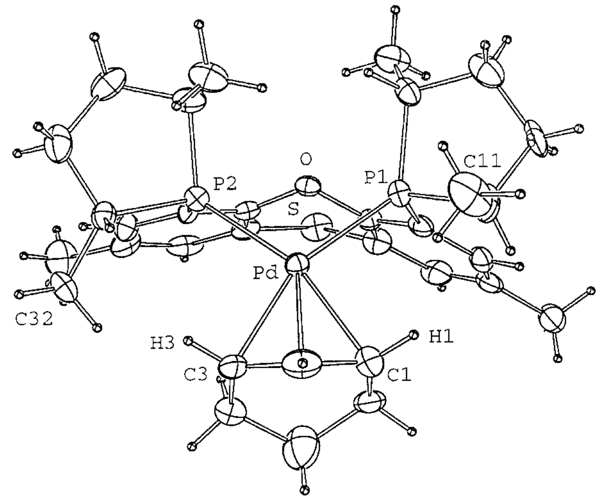


Figure 1. ORTEP view of the [Pd(**A**)(C_6H_9)]$^+$ ion. The BF_4^- ion is omitted for clarity.

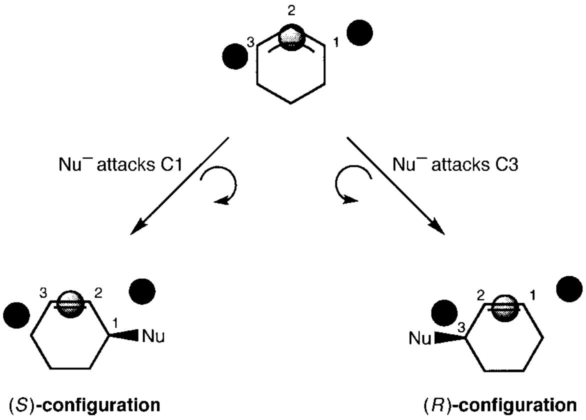
but slower for the more sterically demanding **3**. All reactions gave quantitative yields. With **A** as ligand, *rac*-**1** as substrate, and NaH as base in THF (entry 1), 100 turnovers are converted within 5 min at 20 °C with a product *ee* of 87% (S)[7]. Even 500 turnovers can be attained within 30 min with a small decrease in *ee* (entry 2). Similarly rapid reactions were observed with BSA[8] and KOAc (1 equiv) in THF (entry 3), which allows the reaction to be carried out conveniently at lower temperatures (entries 4 and 5) with 93% *ee* (S) in 4 h for 100 turnovers. The reaction is somewhat slower in CH_2Cl_2 (entry 6) but gives a similar *ee* value. With **B** as ligand, the reaction rates are even higher, but the *ee* values are somewhat lower (entry 7).

For substrate **2** with NaH/THF and ligand **A** (entry 8), the reaction is extremely rapid (complete conversion in less than 1 min) but gives a low *ee* value. With BSA/KOAc in CH_2Cl_2 (entry 9), the reaction is slower but the *ee* value increases, and at 0 °C (entry 10) after 3 h, the S product was obtained in 68% yield. With ligand **B**, the reactions rates were again higher, and the *ee* value increased from 66% at 20 °C to 82% at 0 °C (entries 11 and 12), which is one of the highest values achieved with this sterically undemanding substrate. The reactions of **3** (entries 13 and 14) with **A** as ligand gave the R product with 97% *ee*. Overall, these catalysts appear to be suitable for chiral synthesis with a range of structurally distinct substrates.

We isolated the complex [Pd(**A**)(η^3-C_6H_9)]$^+BF_4^-$ (C_6H_9 = cyclohexenyl) and characterized it by X-ray crystallography (Figure 1).[9] The bonding between the Pd center and the allyl group is essentially symmetric (Pd−C1 2.204(9), Pd−C3 2.200(8), Pd−P1 2.321(2), Pd−P2 2.312(2) Å). The P-Pd-P angle is 104.99(7)°. The closest intramolecular H−H interactions are between the CH_3 groups (C11 and C32) of the dimethylphospholane groups and the the allyl protons H1 (1.99 Å) and H3 (2.19 Å). The backbone of the ligand adopts an envelope conformation on the same side of the P-Pd-P plane as the boat-configured cyclohexenyl group and hence is *exo* to the η^3-allyl moiety. The $^{31}P\{^1H\}$ NMR spectrum of this complex in CD_3CN at 293 K shows an AB pattern with signals at $\delta = 35.9$ (P_A) and 35.4 (P_B) with $J_{P_A,P_B} = 43$ Hz. The $^{13}C\{^1H\}$ spectrum (CD_3CN, 293 K) shows two signals for C1 and C3 at $\delta = 92.9$ and 82.4, both of which are identically coupled to the *trans* P atom ($J_{C,P} = 25$ Hz). No changes are observed down to −40 °C.

These results show that although the C1 and C3 atoms are somewhat different electronically, steric interactions do not cause structural differentiation between these carbon centers in the cationic Pd(η^3-allyl) intermediate, and an early transition state for nucleophilic attack appears very improbable. A simple computer graphics model[10] in which the phospholane ligand is kept frozen, as in the structure of **A**, and the allyl group is replaced by cyclohexene shows that the most stable arrangement has the double bond in the P-Pd-P plane and Pd−C(vinylic) bonds of almost equal length (ca. 2.10 Å). There are notably close contacts between one of the allylic *endo*-CH_2 protons and a CH_3 group (a) of the phospholane (ca. 1.9 Å) and between a vinylic CH proton and the other proximal CH_3 group (b) of the ligand (ca. 2.2 Å); all other interactions are longer than 3 Å. We propose that the CH_3 group (a) will hinder all rotational processes of the organic moiety on Pd in which it would be traversed by an *endo* sp^3 C−H bond; no significant barrier is expected for the passage of sp^2 C−H bonds (Scheme 2).

The reaction of the nucleophile (Nu$^-$) with the (η^3-allyl)Pd cationic intermediate to form the Pd olefin complex must be accompanied by rotation,[11] and attack at C3 requires counterclockwise rotation. Hence, the *endo* sp^3 C3−H bond of the product must pass by the CH_3 group of the ligand, and this raises the barrier for the formation of the R product. No such steric interaction occurs in nucleophilic attack at C1, which involves clockwise rotation. Therefore, the S product should be favored, as is observed experimentally. Hence, a medium to late transition state is involved in the product-determining step. This preferential rotational (PR) concept allows us to understand how the nucleophile can discrimi-



Scheme 2. Preferential formation of the product with *S* configuration. The methyl groups at C11 and C32 are represented by black circles, and the Pd atom by a gray circle.

nated between C1 and C3, which otherwise differ little in their steric and electronic properties.

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[8] BSA = *N*,*O*-bis(trimethylsilyl)acetamide.

[9] a) Crystal data for $C_{32}H_{43}OP_2SPd \cdot BF_4$: $M_r = 730.92$, orthorhombic, space group $P2_12_12_1$, $a = 14.521(4)$, $b = 16.047(5)$, $c = 13.971(4)$ Å, $V = 3255(2)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.49$ g cm^{-3}, $\mu(Cu_{K\alpha}) = 6.65$ mm^{-1}. Data were collected on a Philips PW1100/16 diffractometer with graphite-monochromated $Cu_{K\alpha}$ radiation ($\lambda = 1.5418$ Å) at -100 °C. A yellow crystal of dimensions $0.02 \times 0.30 \times 0.30$ mm was used, and a total of 2270 reflections were collected ($3 < \theta < 54°$); 1931 reflections with $I > 3\sigma(I)$ were used for structure determination and refinement. The structure was solved by direct methods and refined against $|F|$. Hydrogen atoms were introduced as fixed contributors. Empirical absorption corrections, transmission factors: 0.53/1.00. For all computations the Nonius OpenMoleN package[9b] was used. The absolute structure was determined by refining the Flack x parameter: $x = 0.02(2)$. Final results: $R(F) = 0.032$, $Rw(F) = 0.045$, GOF = 1.051, maximum residual electron density 0.69 e Å^{-3}. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101072. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). b) C. K. Fair in MoleN. "An Interactive Intelligent System for Crystal Structure Analysis". Nonius, Delft, The Netherlands, 1990.

[10] A SPARTAN computer graphic programme was used, but in view of the approximate nature of these calculations, more detailed studies are in progress.

[11] The involvement of a rotational motion to explain, in part, the enantioselectivity of catalytic reactions with a P–N ligand was proposed by Brown et al.[3f] See also ref. [3d].

Mechanistic Implications of the Observation of Kinetic Resolution in a Palladium-Catalyzed Enantioselective Allylic Alkylation**

Shailesh Ramdeehul, Peter Dierkes, Rafael Aguado, Paul C. J. Kamer, Piet W. N. M van Leeuwen, and John A. Osborn*

The mechanism of Pd-catalyzed enantioselective allylic alkylation involves two steps which are of major importance in the catalytic cycle.[1] First, the allylic substrate, usually in the

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