The Effect of the Bite Angle of Diphosphane Ligands on Activity and Selectivity in Palladium-Catalyzed Cross-Coupling[+]

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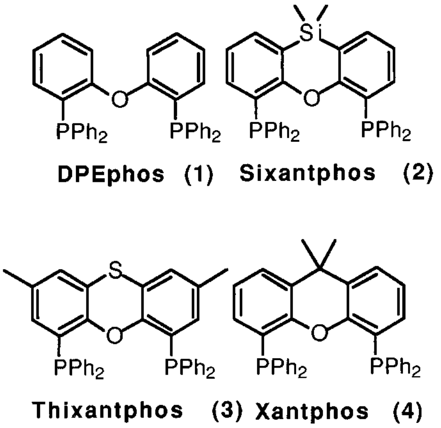
The effect of the natural bite angle (β_n) of diphosphane ligands on catalyst selectivity and activity in the palladium-catalyzed cross-coupling of *sec*-butyl magnesium chloride with bromobenzene was investigated. The calculated natural bite angles range from 78° for dppe (1,2-bisdiphenylphosphanoethane) to 110° for Xantphos. The natural bite angle of diphosphane ligands has a large effect on catalyst selectivity and activity. Both rate and selectivity of the cross-coupling reaction increase with increasing bite angle and reach a maximum value with DPEphos (β_n = 102.7°). Larger bite angles of the diphosphane ligands result in a decreased selectivity and activity.

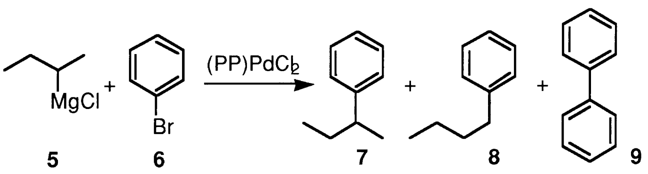
Transition metal catalyzed carbon−carbon bond formation is an important tool for organic chemists and a challenging area of research in homogeneous catalysis. Nickel and palladium catalysts with tailored phosphane ligands have been applied successfully in the cross-coupling reaction. The influence of the type of (di)phosphane used is very large, although the effect is not yet fully understood.[1][2] One of the steric parameters for diphosphanes is the bite angle induced by the ligand.[3] Hayashi et al. found that dppf [1,1′-bis(diphenylphosphanoferrocene)], a diphosphane with a large P−Pd−P bite angle of 99.1° in [dppf]$PdCl_2$, has the highest activity and selectivity of a range of (di)phosphane ligands. Furthermore, comparison of different diphosphanes revealed an increase of selectivity with an increasing bite angle.[4][5]

We have developed a new group of diphosphanes capable of enforcing large bite angles (see Figure 1).[6] According to our calculations, these ligands have natural bite angles varying from 102° to 110° (for palladium complexes). Recent studies on hydroformylation,[6] hydrocyanation,[7] and allylic alkylation[8] showed that changes in the bite angle of these ligands have a strong influence on catalyst selectivity. Since the steric and electronic properties of these ligands are the same, all effects on selectivity or activity can be attributed to the bite angle. Here we present a study on the effect of the bite angle of chelating diphosphanes on the activity and selectivity in the palladium-catalyzed cross-coupling reaction.

Figure 1. Diphosphanes with large bite angles



We prepared mononuclear, *cis*-(P-P)$PdCl_2$ (**1−4a**) complexes of the Xantphos-type ligands (see Figure 1) and the analogous (diphosphane)$PtCl_2$ complexes (**1−4b**). The platinum(II) complexes showed large Pt−P coupling constants of 3640−3800 Hz, indicative of square planar *cis* coordination. The palladium complexes were utilized as catalysts in the coupling of *sec*-butylmagnesium chloride with bromobenzene (see eq. 1, Table 1).[4][5]



Homocoupling, an important competing reaction in the cross-coupling reaction,[9] was not taken into account in Hayashi's study. We therefore applied their best catalytic system, dppf$PdCl_2$, under identical conditions and analyzed the product mixture for the presence of **9**, the homocoupled product. An amount of 3% was observed, which has a small effect on the overall selectivity of this catalyst system. The initial turnover frequency was 79 mol (mol Pd)$^{-1}$ h^{-1}

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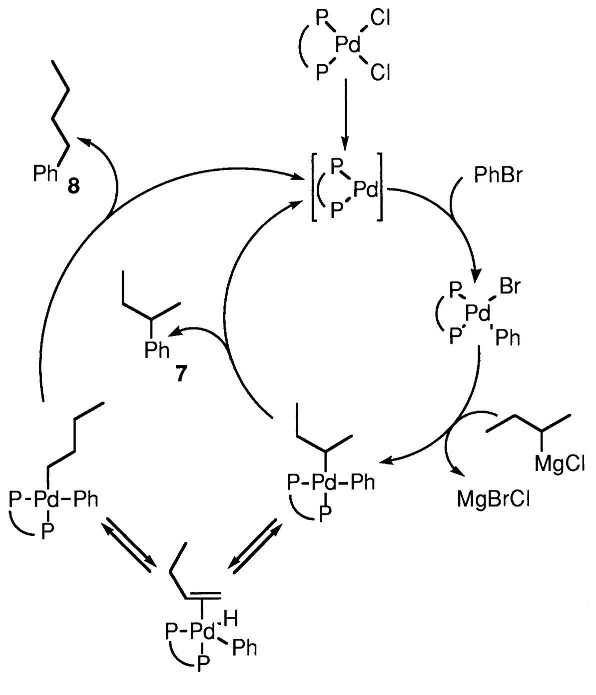
Table 1. Cross-coupling of 2-butylmagnesium chloride with bromobenzene in diethyl ether

Ligand	Bite angle [°]	t.o.f.[a] [mol (mol Pd)$^{-1}$ h^{-1}]	Reaction time [h]	Conversion[b] [%]	7 [%]	8 [%]	9 [%]
dppe [c]	78.1	n.d.	48	4	0	0	n.d.
dppp [c]	86.2	n.d.	24	67	69	31	n.d.
dppb [c]	98.7	n.d.	8	98	51	25	n.d.
dppf	99.07 [d]	79	2	100	95	2	3
DPEphos	102.9	181	2	100	98	1	1
Sixantphos	106.5	36	16	58.8	67	17	16
Thixantphos	107.2	24	16	36.5	51	17	32
Xantphos	110.0	24	16	23.6	41	19	40

Conditions: 0.04 mmol catalyst, 8 mmol **5** and 4 mmol **6** in 20 ml ether, T = 20°C. The 95% confidence interval of the mean measured values is ±1.1%. − n.d.: not determined − [a] Initial turnover frequency, determined after 5 min. of reaction time. − [b] Conversions based on **6**. − [c] Results from reference[5], dppe = 1,2-bis(diphenylphosphano-ethane), dppp = 1,3- bis(diphenylphosphano-propane), dppb = 1,4-bis(diphenylphosphano-butane). − [d] Since we are not able to model the ferrocene-unit accurately, the natural bite angle for dppf is taken as 99.1°, the P−Pd−P angle from the X-ray structure of (dppf)PdCl$_2$[5].

Scheme 1



The catalyst containing DPEphos, β_n = 102.7°, was even more active and selective than the one with dppf. The cross-coupling product **7** was obtained in a selectivity of 98% (compared to 95% for dppf), with only 1% of the homocoupled **9**, and 1% of **8**. The observed initial turnover frequency is 181 mol (mol Pd)$^{-1}$h^{-1}, which is 2.3 times as high as the initial t.o.f. we observed for dppf.

Increasing the β_n of the diphosphane resulted in a decrease of both catalyst activity (an initial t.o.f. of 36 mol/mol/h using Sixantphos) and selectivity. The amount of cross-coupling product **7** decreased, whereas the homocoupled **9** and the sideproduct **8** were formed in larger amounts. At still larger bite angles the amount of homocoupling product **9** increased to a level of 40%.

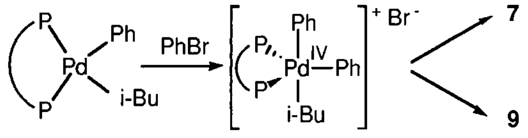
Which step in the catalytic cycle is rate determining, is still under debate. Evidence has been presented that the rate-determining step can be either one of the following steps: the oxidative addition,[10][11] the transmetallation,[12][13] or the reductive elimination step.[14][15]

Brown and Guiry studied the effect of the P−Pd−P bite angle on the rate of reductive elimination. Both experimental work and extended Hückel calculations showed that the P−Pd−P angle increased along the reaction pathway. To investigate this effect they prepared a ruthenium analogue of dppf in order to increase the bite angle to 105−110°. The ruthenium-based ligand exhibited a slightly larger reactivity for reductive elimination than dppf, but the effect was marginal.[16]

An increasing P−Pd−P angle results in a decreasing R−Pd−R′ angle in the intermediate of the catalytic cycle. This smaller R−Pd−R′ angle accelerates reductive elimination. The optimum is reached at a P−Pd−P angle of ca. 102°. The reaction rates of [DPEphos]PdCl$_2$ and [dppf]PdCl$_2$ are similar, which seems to imply that DPEphos still induces a distorted square planar coordination. When the P−Pd−P angle increases further, the Pd(II) species will no longer have a square planar geometry. We propose that this distortion leads to an increasing R−Pd−R′ angle, which results in a decreasing relative rate of reductive elimination. This might explain the decrease of the rate of reaction when going from DPEphos to Xantphos.

An explanation for the formation of *n*-butylbenzene (**8**) can be the increased tendency to form trigonal bipyramidal intermediates with an increasing bite angle. The large bite angle induced by the Xantphos-type diphosphanes stabilize trigonal bipyramidal geometries, and the phosphorus donor atoms will be coordinated in the equatorial plane. This may lead to an increased rate of β-hydride elimination and reinsertion (see Scheme 1). The 1-alkyl palladium intermediate can react further to yield **8**. The ligands that are most suitable for stabilizing trigonal bipyramids, Sixantphos, Thixantphos, and Xantphos give rise to the formation of large amounts of **8**. Additionally, oxidative addition of a second molecule of bromobenzene results in the formation of a trigonal bipyramidal [(diphosphane)Pd^{IV}(Ph)$_2$Bu]$^+$ Br$^-$ complex.[14] Stabilization of this complex by ligands inducing larger bite angles can explain the increasing amounts of homocoupled product **9** (see Scheme 2). The alternative mechanism of transmetallation between isobutylmagnesium chloride and bromobenzene, however, cannot be excluded.

Scheme 2



In conclusion it was found that in the (diphosphane)$PdCl_2$-catalyzed cross-coupling of 2-butylmagnesium chloride with bromobenzene, the selectivity reaches the highest value when the natural bite angle of the diphosphane used is ca. 100°. The rate of the reaction is also maximal at this value. The best selectivity and activity are obtained for DPEphos, a diphosphane with a natural bite angle of 102°. We propose that diphosphanes with larger bite angles stabilize trigonal bipyramidal intermediates leading to 1-butyl-benzene and homocoupled biphenyl.

Experimental Section

Computational Details: All calculations were performed using CAChe WorkSystem software[17] on an Apple Power Macintosh 950 equipped with 2 CAChe CXP coprocessors. The Molecular Mechanics calculations were performed using the MM2 force field.[18] Block-diagonal Newton-Raphson was used as optimization method. Natural bite angle calculations were performed using a method similar to that described by Casey and Whiteker[3] using a Pd−P bond length of 2.288 Å.[5][19]

For the ligands dppe, dppp and dppb, a starting geometry for the chelate ring resembling the appropriate cycloalkane was used. By this procedure, the global minimum resulting from excessive, stabilizing π-stacking interactions (and having a too small a bite angle) was avoided. The geometry obtained in this way is in agreement with geometries observed by X-ray crystallography.[20]

Synthesis: The diphosphane ligands were prepared according to literature procedures.[6]

Complex Synthesis: In a typical experiment, ligand (0.121 g, 0.225 mmol) and $(PhCN)_2PdCl_2$ (0.087 g, 0.225 mmol) ware placed in a Schlenk flask, and flushed with N_2. THF (10 ml) was added, and the reaction mixture was stirred overnight at room temp. The solvent was removed in vacuo, the resulting yellow powder was washed 3 times with 10 ml of diethyl ether, then dried in vacuo.

(DPEphos)$PdCl_2$ (**1a**): Yield: 0.198 g (0.251 mmol, 98%) of yellow powder. − $^{31}P\{^1H\}$ NMR ($CDCl_3$) $\delta = 19.3$.

(DPEphos)$PtCl_2$ (**1b**) Yield: 0.162 g (0.201 mmol, 95%) of yellow powder. − $^{31}P\{^1H\}$ NMR ($CDCl_3$) $\delta = 2.0$ ($J_{Pt-P} = 3795$ Hz).

(Sixantphos)$PdCl_2$ (**2a**):Yield: 0.150 g (0.251 mmol, 86%) of yellow powder. − $^{31}P\{^1H\}$ NMR ($CDCl_3$) $\delta = 24.8$.

(Sixantphos)$PtCl_2$ (**2b**): Yield: 0.161 g (0.187 mmol, 88%) of yellow powder. − $^{31}P\{^1H\}$ NMR ($CDCl_3$) $\delta = 7.6$ ($J_{Pt-P} = 3663$ Hz).

(Thixantphos)$PdCl_2$ (**3a**): Yield: 0.256 g (0.330 mmol, 91%) yellow powder. − $^{31}P\{^1H\}$ NMR ($CDCl_3$) $\delta = 25.3$.

(Thixantphos)$PtCl_2$ (**3b**): Yield: 0.163 g (0.189 mmol, 89%) off-white powder. − $^{31}P\{^1H\}$ NMR ($CDCl_3$) $\delta = 8.4$ ($J_{Pt-P} = 3641$ Hz).

(Xantphos)$PdCl_2$ (**4a**): Yield: 0.140 g (0.185 mmol, 82%) yellow powder. − $^{31}P\{^1H\}$ NMR ($CDCl_3$) $\delta = 22.7$.

(Xantphos)$PtCl_2$ (**4b**): Yield: 0.149 g (0.176 mmol, 83%) pale yellow powder. − $^{31}P\{^1H\}$ NMR ($CDCl_3$) $\delta = 6.6$ ($J_{Pt-P} = 3695$ Hz).

Palladium-Catalyzed Cross-Coupling of Bromobenzene with sec-Butylmagnesium Chloride. General Procedure: The catalyst (0.04 mmol) was placed in a 50 ml Schlenk flask equipped with a stirring bar. Diethyl ether (10 ml)was added, and the reaction mixture was kept at the desired temperature using a water bath (20° C). Bromobenzene (0.42 ml, 4 mmol) and *n*-decane as an internal standard (0.8 ml, 4.1 mmol) were added, followed by 10 ml of a solution of *sec*-butylmagnesium chloride (0.8 M in ether). Samples were hydrolyzed with 10% hydrochloric acid, the organic layer was separated, and analyzed by GC.

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