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

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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 allylic alkylation was investigated. The selectivity and rate of the reaction are mainly determined by steric hindrance induced by the diphosphane ligands. The steric hindrance at the palladium center increases as the natural bite angle of the ligand becomes larger. This results in an increasing selectivity at larger bite angles, but at very large bite angles the rate of the reaction drops. The ligand with the largest calculated bite angle, Xantphos, induced 100% selectivity but the reaction rate became low.

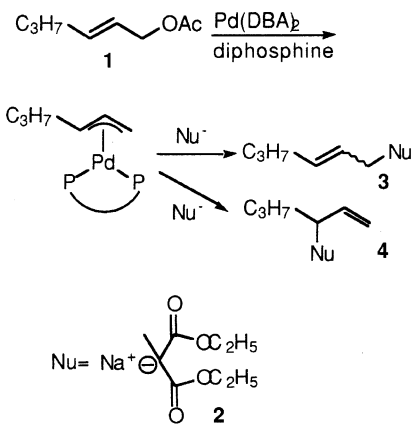
Catalyst selectivity and activity can be influenced by the steric and electronic properties of ligands. Additionally, a third ligand parameter, the bite angle of bidentate ligands,[1] seems to have a crucial effect on reactivity and stability of transition metal complexes. The bite angle can have a tremendous influence on catalyst behavior as shown for the hydroformylation[2][3][4][5] and hydrocyanation[6] reactions.

An intriguing reaction is the palladium-catalyzed allylic substitution reaction. After the discovery by Tsuji[7] further development of this reaction by Trost led to extensive use in organic synthesis.[8] A highly enantioselective palladium diphosphane catalyst was shown to have a large bite angle of 110.5°[9] which indicates that the bite angle can also be of importance in this reaction.

Most studies in this field focused on asymmetric induction and only little attention was paid to regioselectivity. Åkermark and coworkers investigated the influence of the steric bulk of bidentate ligands (substituted phenanthrolines) on the regioselectivity only very recently.[10] A detailed mechanistic and computational study by Bäckvall et al. showed the effect of the electronic properties of ligands on the regioselectivity of the reaction.[11] Steric factors had a large influence on the regioselectivity of this reaction. Recently, both experimental[12][13] and theoretical[14][15] studies were performed on the regioselectivity in the asymmetric allylic substitution, using ligands containing phosphorus and nitrogen donor atoms. Since steric interactions and electronic preferences can induce opposite effects, the involvement of an early or a late transition state remains under debate. All studies mentioned, however, ignored the effect of the bite angle of the ligands, although Trost found that enlarging the bridge of chelating chiral diphosphanes (and consequently increasing the bite angle of the diphosphane) led to higher asymmetric induction.[16]

Here we present a detailed systematic study on the effect of the bite angle of diphosphanes on catalyst activity and selectivity. The catalyst system we employed was prepared in situ using $Pd(DBA)_2$ (DBA = dibenzylidene acetone) and diphosphane in DMF. As a substrate we used 2-hexenylacetate (**1**) and the nucleophile was sodium diethyl methylmalonate (**2**), the same reagent used by Åkermark et al.[10] Only two products were observed: the linear product diethyl 2-(2-hexen-1-yl)-2-methylmalonate (**3**) and the branched product diethyl 2-(1-hexen-2-yl)-2-methylmalonate (**4**). The reaction is depicted in Scheme 1.

Scheme 1



The diphosphane ligands studied as catalyst components were dppe (1,2-bis(diphenylphosphanoethane), dppp (1,3-bis(diphenylphosphanopropane), dppb (1,4-bis(diphenylphosphanobutane), dppf (1,1′-bis(diphenylphosphanoferrocene), DPEphos, Sixantphos, and Xantphos (see Figure 1). The results are summarized in Table 1.

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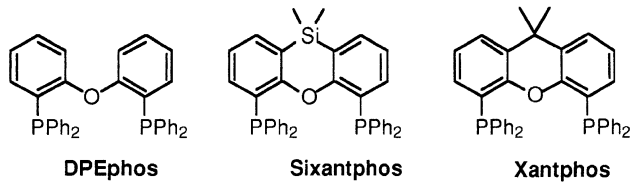
Figure 1. Diphosphanes with large bite angles



The bite angle of the diphosphane used affects both the activity and the selectivity of the catalyst. A sharp increase in catalyst activity (measured in initial turnover frequency) is observed in going from dppe to dppb. A further increase of the bite angle results in a decrease of the t.o.f.

Table 1. Alkylation of 2-hexenylacetate (**1**) with sodium diethyl methylmalonate (**2**) in DMF[a]

Ligand	Bite angle [°]	t.o.f. [mol/mol Pd/hr][b]	Reaction time [h]	Conversion [%][c]	**3** [%]	**4** [%]
dppe	78.1	82	5	98.5	96.2	3.8
dppp	86.2	111	5	97.9	96.6	3.4
dppb	98.6	393	1	98.0	97.7	2.3
dppf	99.07[d]	118	5	97.6	99.0	1.0
DPEphos	102.7	114	5	98.4	99.7	0.3
Sixantphos	106.5	91	20	97.5	99.6	0.4
Xantphos	110.0	22	20	92.1	100.0	0.0

[a] Conditions: 0.01 mmol $Pd(DBA)_2$, 0.02 mmol ligand, 1.0 mmol of **1**, 2.0 mmol of **2** in 3.0 ml DMF, T = 20°C. The 95% confidence interval of the mean measured values is ±0.1%. – [b] Initial turnover frequency, determined after 5 min. reaction time. – [c] Based on **1**; [d] P–Pd–P angle in X-ray of $(dppf)PdCl_2$.[17]

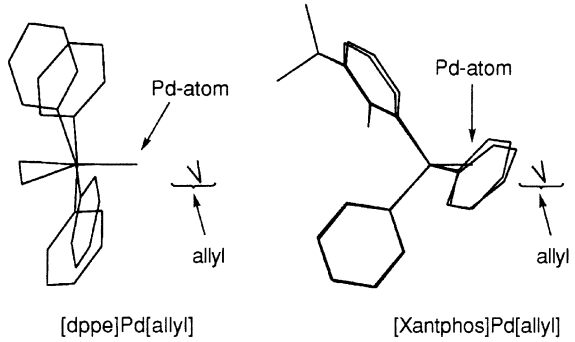
The selectivity of the reaction towards the linear product **3** increases regularly with an increasing bite angle (see Table 1). Using dppe 3.8% of product **4** is obtained, while dppf leads to 1%. When the Xantphos-type ligands are used, less than 1% of **4** is formed. The differences in amounts of **4** formed using Xantphos-type ligands are within the experimental error and will therefore not be discussed. It is noteworthy that when Xantphos is employed, 100% formation of **3** is observed, i.e. without any trace of **4**, which can prevent laborious purification of the desired product.

The selectivities reported were obtained at maximal conversion, which is nearly quantitative.

The formation of **4** is the result of a nucleophilic attack on the substituted carbon atom of the allyl moiety. In the transition state, the hybridization of this carbon atom changes from sp^2 to sp^3, which results in a bending of the R group towards the phosphane. This causes steric interference of the R group with the diphosphane ligand. A larger diphosphane bite angle results in larger steric interference and consequently less **4** is formed.

The steric interference was investigated by molecular modeling. The data from a P_2Pd[allyl] fragment (obtained from a recent X-ray crystal structure[18]) was superimposed on the structures of [dppe]Pd, the ligand with the smallest bite angle, and that of [Xantphos]Pd, the ligand with the largest bite angle (both taken from the natural bite angle calculations). The results are presented in Figure 2.

Figure 2. View through the P···P axes of [dppe]Pd[allyl] and [Xantphos]Pd[allyl]; H atoms were omitted for clarity



[dppe]Pd[allyl] [Xantphos]Pd[allyl]

In [dppe]Pd[allyl], the allyl fragment experiences no steric interference at all from the diphosphane ligand, while in [Xantphos]Pd[allyl] the allyl fragment interacts with the PPh_2 moieties of the ligand. This can be illustrated by the distances between the terminal allyl carbon atom and the *ipso* carbon atom of the phenyl rings. In [dppe]Pd[allyl] the $C\cdots C_{ipso}$ distances are 3.67 and 4.22 Å, whereas in [Xantphos]Pd[allyl] the $C\cdots C_{ipso}$ distances are 3.12 and 3.55 Å.

The increasing embracement of the allyl fragment at large bite angles not only dictates the regioselectivity, but it also hampers the reaction correspondingly. It is therefore not surprising that the initial turnover frequencies decrease when the natural bite angle of the diphosphane used becomes 100° or larger.

Since the ligand is completely symmetric, the regioselectivity cannot be induced by an electronic effect (trans influence).[12][13] The calculated structure of the complex has an approximate C_s symmetry as supported by crystal structure determinations[19] and solution structures[3] of other complexes. It is therefore unlikely that an electronic difference between the two Pd–C bonds results from steric effects, as suggested by Ward.[15] There is probably not much steric hindrance in the starting Pd allyl complex and the effect of increasing bite angle on the selectivity therefore points to a late transition state for this reaction.

In conclusion, the bite angle of a ligand has been shown to be a parameter of utmost importance for catalyst behavior. In the palladium-catalyzed allylic alkylation of 2-hexenyl acetate, regioselectivity increases with an increasing bite angle. The increased selectivity is induced by the increasing embracing of the allyl fragment by the diphosphane. This purely steric interaction inhibits the formation of the branched side product. The best selectivity with reasonably high reaction rates is obtained with DPEphos.

Experimental Section

Computational Details: All calculations were performed using CAChe WorkSystem software[20] on an Apple Power Macintosh 950 equipped with 2 CAChe CXP coprocessors. The Molecular Mechanics calculations were performed using the MM2 force

field.[21] 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[1], using a Pd−P bond length of 2.288 Å.[18][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 a too small a bite angle) was avoided. The geometry obtained this way agrees with geometries observed by X-ray crystallography.[22]

Palladium-Catalyzed Alkylation of Hexenyl Acetate. − General Procedure: To a Schlenk vessel was added $Pd(DBA)_2$, (5.8 mg, 0.01 mmol) and a diphosphane ligand (0.02 mmol), followed by 1 ml of a 1 M solution hexenylactetate (1.0 mmol) and 0.5 M decane (internal standard, 0.5 mmol) in DMF . The Schlenk vessel was kept at 20°C using a water bath and the solution was stirred for 5 min to ensure complete formation of the catalyst. Then 2.0 ml of a 1 M solution of sodium dimethyl malonate in DMF (2.0 mmol) was added. The reaction was monitored with GC at regular time intervals, by working up a small sample in H_2O and ether. The product distribution and the yield were determined using the internal standard.

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