Ligand Bite Angle Effects in Metal-catalyzed C−C Bond Formation

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Contents

I. Introduction

This review will summarize the effect of the bite angle (Figure 1) of bidentate ligands on the catalytic formation of carbon-to-carbon bonds. In the past decade, considerable progress has been made in this area and the effect of bidentates has received a lot of attention. Initially, the effect of bidentate phosphine ligands such as dppe (**1b**,1,2-bisdiphenylphosphinoethane) seemed mainly to stabilize intermediates, and often the catalytic reactions were slower when dppe was used instead of the most common monodentate triphenylphosphine. We will briefly review the history of "ligand effects" in catalysis before discussing a range of reactions for which a notable effect has been observed. It has taken quite some time before the positive effect that bidentates can have on selectivities and rates of catalytic reactions was fully recognized. Most of the established examples of bite angle effects involve diphosphine ligands. Therefore, many important catalysts containing a chelate ligand such as bipyridine and diimine will fall outside the scope of this review. The connecting bridge in these bidentates does play a dominant role in the performance of these catalysts, but systematic studies have not been published.

$Ph_2P-(CH_2)_n-PPh_2$

1 a, dppm, n = 1
b, dppe, n = 2
c, dppp, n = 3
d, dppb, n = 4
e, dpp-pentane, n = 5
f, dpp-hexane, n = 6

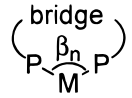

Figure 1. Bite angle: The ligand−metal−ligand angle of bidentate ligands.

The effects of phosphine ligands in catalysis have been known for quite some time. One of the first reports involves the use of triphenylphosphine in the "Reppe" chemistry, the reactions of alkynes, alcohols, and carbon monoxide.[1] It was found that formation of acrylic esters was much more efficient using $NiBr_2(PPh_3)_2$ than $NiBr_2$ without ligand. In the commercial system, though, a phosphine-free catalyst is used. While the reaction was not yet understood mechanistically, the use of phosphines in catalysis attracted the attention of the petrochemical industry worldwide. An early example of a phosphine ligand modified catalytic process is the Shell process for alkene hydroformylation using a cobalt catalyst containing a trialkylphoshine.[2] The reaction requires higher temperatures, but it leads to more linear product as compared to the unmodified catalyst. The general mechanism of the hydroformylation reaction has been known for a long time.[3] Hydrocyanation as used by Du Pont is another early example of an industrially applied catalytic reaction employing ligands.[4] It is a nickel-catalyzed reaction in which aryl phosphite ligands are used for the production of adiponitrile. The development of this process has played a key role in the introduction of the now very common study of "ligand effects" in the field of homogeneous catalysis by organometallic complexes.[5]

While several industries were working on new homogeneous catalysts, important contributions to the new field were made in academia in the early 1960s with the appearance of the first phosphine-modified hydrogenation catalysts. An early example of a phosphine-free ruthenium catalyst was published by Halpern.[6] Triphenylphosphine-modified platinum−tin catalysts for the hydrogenation of alkenes were reported by Cramer from Du Pont in 1963.[7] In the same year Breslow (Hercules) included a few phos-

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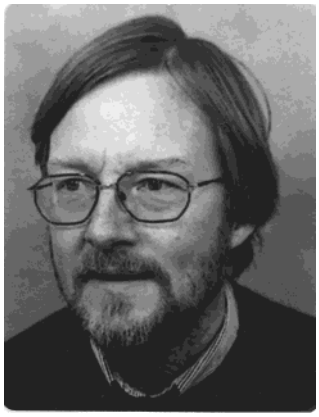

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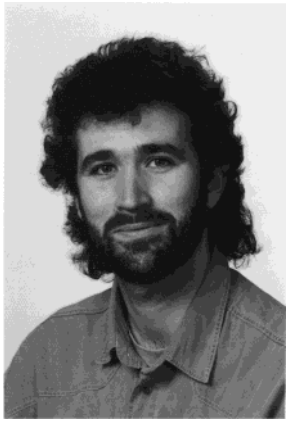


Peter Dierkes has studied chemistry at Münster University and the Imperial College in London. After taking the Ph.D. in Prof. Dehnicke's group in Marburg, Germany, 1994, he spent 2 years as a postdoc in Prof. Osborn's laboratories in Strasbourg and is currently working at the University of Amsterdam toward his Habilitation. His research interests include organometallic chemistry, the preparation of chiral ligands, mechanistic studies of catalytic reactions, and molecular modeling on different levels of theory.

phine complexes of late transition metals in a hydrogenation study employing metal salts reduced by aluminum alkyls, but interestingly the systems containing phosphine were less active![8]

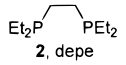
Rhodium-catalyzed hydrogenation was discovered in the mid-1960s by Wilkinson and co-workers.[9] The mechanism of this reaction using $RhCl(PPh_3)_3$ as the catalyst was studied in great detail, which was, without the modern aid of in situ ^{31}P NMR spectroscopy, not an easy task. These studies by Wilkinson and many others have been a major stimulant for workers in this area.

Substitution at the aromatic ring revealed an electronic effect on the reaction rate, electron donors giving higher rates.[10] This was explained assuming that the oxidative addition of dihydrogen is rate-determining. The result might be obscured, however, by influence of the ligands on the position of equilibria between several involved resting states of the catalyst.[10] A few months later Vaska published his first work on the rhodium- and iridium-catalyzed hydrogenation of alkenes.[11] Rhodium-catalyzed hydroformylation using catalysts modified with alkylphosphines and arylphosphines was reported also by Wilkinson's group.[12] The ligands hardly affected the rate and selectivity (70 °C and 100 bar). Pruett found that phosphites had a profound effect on rates and selectivities.[13]

Bidentate ligands have played an important role in the development of catalytic applications of metal organic complexes. The synthesis of dppe (**1b**) was reported as early as 1959.[14] The coordination chemistry of several diphosphines with an ethylene bridge was explored by Chatt and Hieber,[15] but it took a while before it became routinely included in catalysis studies. In the early 1960s diphosphines were mentioned in patents, but specific advantages are not apparent. In their exploration of carbonyl chemistry of cobalt related to carbonylation catalysis, Heck and Breslow[16] reported that $HCo(CO)_4$ gave unidentifiable complexes with dppe. The use of dppe in cobalt-

catalyzed hydroformylation was reported by Slaugh,[17] but compared to PBu_3 it had little effect on either the rate or the selectivity of the ligand free cobalt carbonyl catalyst. Copolymerization of butadiene and propylene oxide using nickel bromide and dppe was published in 1965.[18]

The oldest publication describing specific results for diphosphines we found is by Iwamoto and Yuguchi (1966) who studied the codimerization of ethene and butadiene using iron catalysts containing a range of diphosphines varying in bridge lengths.[19] An incidental use of depe (**2**, 1,2-bis(diethylphosphino)-

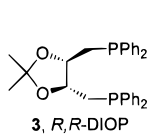


2, depe

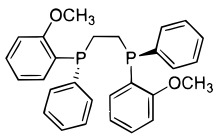
ethane) in $RuHCl(depe)_2$ was reported by Coffey in 1967 who looked at the catalytic decomposition of formic acid by metal complexes.[20] In many instances the activity of catalysts containing dppe instead of PPh_3 is lower. For example, the hydrogenation of styrene using rhodium(I) chloride and dppe is 70 times slower compared to the PPh_3-based system.[21] Similarly, Schrock and Osborn[22] reported in their studies on rhodium-catalyzed hydrogenation that $Rh(dppe)_2^+$, unlike all complexes containing monophosphines, is not active in the isomerization reaction of cyclooctadiene. The strong chelating power of the diphosphine was held responsible for this. Also, for the Wilkinson catalyst, dissociation of one of the monophosphine ligands was part of the reaction sequence. Thus, initially the use of dppe and other bidentate phosphines in catalysis found little support as they were supposed to lead mostly to more stable complexes, rather than more active or selective catalysts.

This was underlined by the theoretical work of Thorn and Hoffmann[23] who explained why migration reactions in complexes containing for instance dppe were slow. The constrained P−M−P angle would slow the migration reaction, since ideally the phosphine ligand coordinated in the position cis to the migrating group would have a tendency to widen the P−M−P angle in the process to "pursue" the migrating group.

A beneficial use of bidentates was discovered in 1971 by Kagan[24] who reported the use of DIOP (**3**) modified rhodium for the hydrogenation of *N*-acetylphenylalanine. Monophosphines for asymmet-



3, *R,R*-DIOP



4, *R,R*-DIPAMP

ric hydrogenation were reported by Knowles,[25] and his discovery of DIPAMP (**4**) led to the commercial application of the asymmetric hydrogenation of the Levodopa precursor. One of the first systematic studies involving a range of diphosphines having various bridge lengths is from Kagan.[21] He studied the room temperature hydrogenation of styrene using rhodium chloride as the catalyst. All diphosphines containing carbon bridge lengths ranging from one to six showed rates lower than the catalysts based on monophosphines, with the exception of dppp (**1c**). This lends further support to the misconception that bidentates lead to slow catalysts, and also perhaps that selective catalysts, such as the enantioselective DIOP ligand, are bound to be slow catalysts. Later it was found that both conceptions are wrong.[26] Sanger[27] has shown that complexation of diphosphines linked by four carbon atoms or more does not lead to simple bidentate behavior but often results in bridged bimetallic complexes.

II. Ligand Parameters

Ligand effects were reviewed for the first time by Tolman.[5] Prior to his studies[28] the effects of phosphorus ligands on reactions or properties of metal complexes were rationalized in terms of electronic effects. Systematic studies had shown, however, that steric effects are at least as important as electronic effects and, in terms of the stability of complexes, can even be dominant. Since then numerous studies have appeared using both the electronic parameter χ and the steric parameter for the cone angle, θ. Alternative methods for the analysis of steric and electronic influences on complex properties have become available,[29,30] but these are not the topic of the present review.

For monodentate phosphorus ligands the cone angle (Figure 2) is defined as the apex angle of a cylindrical cone, centered at 2.28 Å from the center of the P atom, which touches the outermost atoms of the model (actually, this was done using CPK models).

For asymmetrically substituted phosphines an average for the three substituents is taken. Crystal structure determinations have shown that the actual angles in the complexes are smaller than those expressed by the θ-value due to an intermeshing of the substituents. The relative order of cone angles parallels with many properties that have been measured, such as equilibrium and rate constants, NMR chemical shifts, IR frequencies, and molecular structures.

During the 1970s the attention for bidentate phosphines as ligands in catalysis had been growing and so did the need for including them into the electronic and steric mapping. A first ligand parameter was introduced by Tolman; the cone angle for monophosphines was extended for diphosphines and defined as the average cone angle as measured for the two substituents and the angle between the M−P bond and the bisector of the P−M−P angle. Even today,

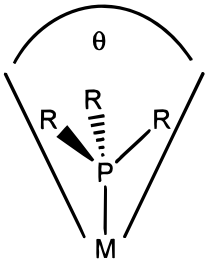


Figure 2. Tolman cone angle, a steric parameter quantifying steric hindrance for monodentate ligands.

this looks like a good approximation for defining a cone angle of a bidentate.

Other parameters for bidentate ligands have been reported, such as the solid angle, pocket angle, repulsive energy, and the accessible molecular surface. The solid angle was introduced by Hirota and co-workers[31a] and extended further by White and Coville.[31b,c] The solid angle Ω is a measure of the "shadow" cast by a group of atoms when placed relative to an apex atom, the metal being the light source on a sphere centered around the metal. Formally,[31b] the solid angle is defined as the integral of the scalar product of the vector **r** with a vector element of surface divided by the cube of the magnitude *r*. This method can be easily applied to systems amenable to molecular mechanics, and polydentate ligands can be treated as well.

The pocket angle was introduced by Barron et al.[32] The pocket angles are calculated from the X-ray structures, allowing free rotation of the substituents at phosphorus, and are used to describe the space available for substrates in a complex containing a bidentate ligand. The pocket angle is defined as the interior cone angle of a bidentate ligand; thus its value is 360° minus Tolman's angle for a bidentate. Since the angle measured in the plane of coordination and perpendicular to the plane can differ substantially, they have been defined independently and their combined use is recommended. A more accurate technique, but also more demanding one, for expressing the steric bulk of ligands was introduced by Brown who calculated the steric congestion of ligands by molecular mechanics calculations.[33] The method concerns the calculation of ligand repulsive energies E_R in energy-minimized structures. Correlation between Tolman's θ-value and Brown's E_R values is good. The AMS approach[34] (accessible molecular surface) seems especially interesting for discussing catalytic properties of complexes. The conformational space of a metal complex is explored with molecular mechanics, which leads to a "pseudodynamic" model of the ligand. Subsequently, the solvent-accessible surface is calculated using a sphere with a diameter of 1.4 Å as a probe. This is known as the Connolly surface in biochemistry for the description of active centers in enzymes.[35] The methods discussed in this paragraph all require extensive studies by MM methods, and comparison of the results requires considerable insight into these techniques.

III. Ligand Bite Angle

In the present study we take a different approach, which is less elaborate than the methods mentioned above. The steric properties of diphosphines are determined by the four substituents at the two phosphorus atoms and the length of the bridge. In general, the most stable complexes are obtained when a five-membered ring can form, i.e., when the bridge between the two phosphorus donor atoms consist of two carbon atoms as in dppe. This is true for octahedral and square-planar complexes in which the "metal-preferred"[36] P−M−P angle is ∼90°. The vast majority of chelate complexes have been synthesized from bidentate ligands possessing relatively short,

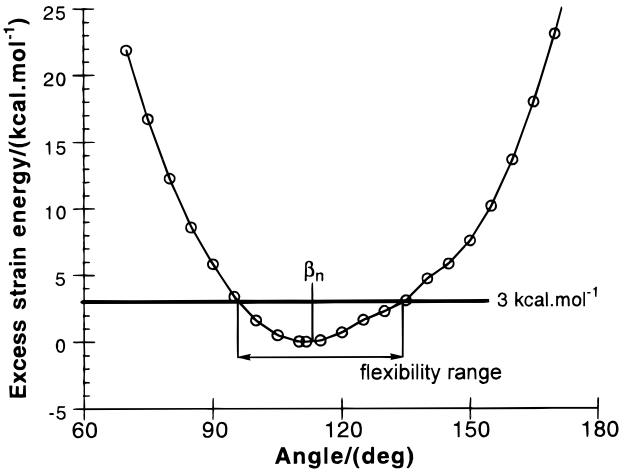


Figure 3. Bite angle and flexibility range in an energy diagram.

bridging backbones. Tetrahedral complexes will prefer P−M−P angles of 109°, and bisequatorial coordination in a trigonal bipyramid requires an angle of 120°. During catalytic processes transitions between different coordination modes may be needed. The "natural" preference of a ligand for a certain coordination mode can influence a reaction of a catalytic cycle in several ways: stabilization or destabilization of the initial, transition, or final state. In addition the flexibility of a bidentate ligand may be important in order to accelerate certain transitions. As we will see, in a one-step reaction the effect of the bite angle may be very clear-cut, but a catalytic cycle involves more steps and equilibria and in many instances the effect on catalysis may not be characteristic of the bite angle.

A means for predicting the "ligand-preferred"[36] P−M−P angle using molecular mechanics has been developed by Casey and Whiteker.[37] They introduced the concepts of natural bite angle (β_n) and flexibility range for diphosphine ligands (Figure 3). Computer modeled geometries can be used to estimate ligand bite angles. The obvious advantage is that no crystal structure is required. The calculations can even be performed before ligands are synthesized. If computer modeling is employed to design new ligands, it is more important to calculate a correct trend rather than perfect geometries. Bite angles of all ligands in a series should thus be modeled with the same program and the same parameter set. The metal center is effectively reduced to a "dummy metal atom". The force constant for the P−M−P bond angle is reduced to 0, and a high-energy constraint fixes the M−P bond to an average length, e.g 2.315 Å for Rh. A dummy metal atom is necessary to pull the lone pairs of electrons and the substituents on the phosphorus atoms in the right direction and to simulate the constraints imposed on the ligand backbone by the metal atom in a complex (see Figure 4).

A second parameter can be used to describe the rigidity of the ligand backbone; Casey defined a "flexibility range", the range of bite angles a ligand can adopt if conformations with energies slightly above that of the minimized structure are considered. It can be estimated from a computed potential energy

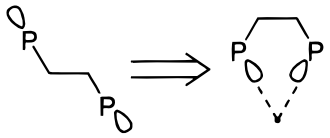


Figure 4. Dummy metal atom used to direct the lone pairs.

diagram. The flexibility range has been defined as the range of bite angles accessible within 3 kcal·mol^{-1} of the minimum energy.

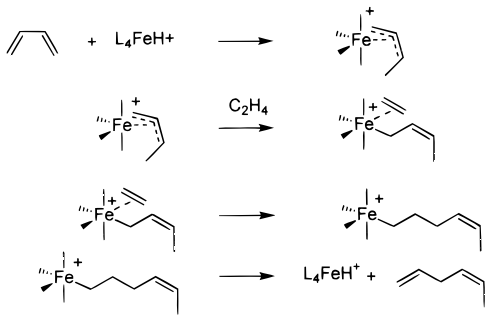
IV. Catalysis

In this review we focus on the effect that bidentate ligands exert on the formation of carbon-to-carbon bonds with special attention focused on the bite angle of the diphosphine. Studies in which series of ligands containing various bridge lengths have been examined will be included in this review. For many reactions a systematic study of the bite angle effect is lacking, but a few of those reactions will be included for which we think that the (large) bite angle plays an important role.

A. 1,4-Hexadiene

Codimerization of ethene and 1,3-butadiene provides 1,4-hexadiene, which is used as a comonomer in ethene−propene−diene elastomers (EPDM).[38] All catalysts for this reaction are based on transition metal hydrides, which react first with butadiene, the most reactive substrate, forming an allyl species. Insertion of ethene is the next step, which is followed by β-hydride elimination. Competing reactions are dimerization and polymerization of butadiene. Du Pont uses a phosphine-free rhodium catalyst for this process. Nickel, iron, and cobalt catalysts, prepared *in situ* using aluminum alkyls are also very active. For nickel−phosphite catalysts it was observed that the initial insertion of butadiene leads to a *syn*-crotyl species which rearranges to the anti-species prior to insertion of ethene (see Scheme 1).[39]

Scheme 1. Co-dimerization of 1,3-Butadiene and Ethene

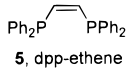


Here we focus on an iron catalyst that was used in conjunction with a series of mono- and diphosphines. The authors[19] considered that the phosphine component would affect the conversion and selectivity for 1,4-hexadiene. A phosphine-free catalyst was reported by Hata[40] from Toyo Rayon Co. in 1964. Iron(III) acetylacetonate reduced by triethylaluminum gave mainly 1,4-*cis*-hexadiene with a turnover frequency (TOF) of 45 mol·(mol of catalyst)$^{-1}$·h^{-1} at room temperature. The effect of bidentate ligands was studied at higher temperatures and pressures (<70 bar, 80 °C) using iron trichloride and triethylaluminum as the catalyst precursor and now TOF's up to 1000 were recorded. *cis*-1,4-Hexadiene is the main product for all catalysts and the main coproduct is polymeric or oligomeric material. Conversions and selectivities are shown in Table 1. We have added the calculated bite angles.[36] A trend to higher selectivities for 1,4-hexadiene and rates is observed for increasing bite angles. Unfortunately, the data correspond to experiments with different metal-to-ligand ratios, which may explain the relatively good result obtained for dpp−ethene (**5**) where a low ligand-to-iron ratio was used. Indeed, high ratios of dppe (**1b**) and iron give low activity and low selectivity for 1,4-hexadiene. A likely composition of the resting state of the catalyst is Fe(diphosphine)$_2$(*anti*-crotyl)$^+$. Later we will see that in square-planar palladium allyl complexes larger bite angles of bidentates lead to a higher proportion of the anti species. As mentioned above, the initial species resulting from the addition of a metal hydride to 1,3-butadiene is also the anti product. A full explanation cannot be given, since the overall selectivities are determined by the products of several rate constants and concentrations of intermediate complexes.

Table 1. 1,4-Hexadiene Formation[a] from $FeCl_3$, TEA, and Diphosphine[19]

ligand	L:Fe	β_n[b] (deg)	conversion % butadiene	selectivity 1,4-hexadiene
dppm (**1a**)	2	72	42.3	6
1,2-dpp−ethene (**5**)	0.5		97.3	66
1,2-dpp−benzene (**6**)	2	83	62.5	49
dppe (**1b**)	1	85	78.2	81
dppp (**1c**)	2	91	100	96

[a] Conditions: chlorobenzene, 20 mL; 0.5−1 mmol of $FeCl_3$; 7.3 mmol of TEA; 60 bar of ethene; 67 g of 1,3-butadiene; 80−85 °C. [b] Natural bite angles β_n are taken from ref 36b.



5, dpp-ethene

B. Platinum-Catalyzed Hydroformylation

Another early example of the effect of the bridge length in a diphosphine on catalytic performance also originates from Japanese workers, namely, the platinum-catalyzed hydroformylation (Scheme 2) of alkenes published by Hayashi and co-workers.[41,42] The system $PtCl_2(PPh_3)_2$−$SnCl_2$ is a good catalyst for the selective hydroformylation of 1-alkenes, as was reported by Orchin.[43] Addition of dppe, however, gave rise to a much slower catalyst.[44] During the 1970s, indeed, dppe (**1b**) (indicated by DPE or DIPHOS in the older literature) was used routinely as the example of a diphosphine, which was a somewhat unfortunate choice, in hindsight, because it often led

Scheme 2. Hydroformylation Reaction

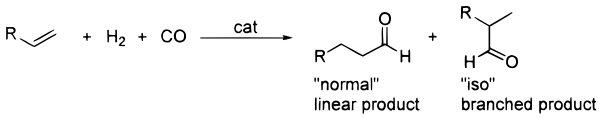
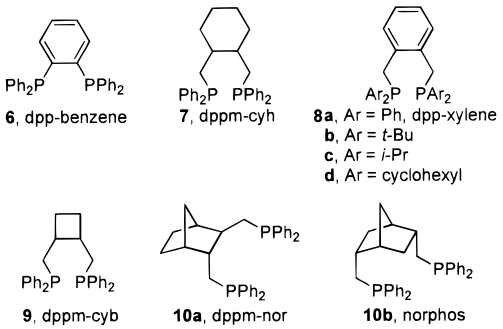


Table 2. Platinum-Catalyzed Hydroformylation[a] of 1-Pentene[41,42]

ligand	β_n[b] (deg)	rel rate	linearity (%)
PPh_3		100	92
dppm	72[b]	0	90
dppe	85[b]	10	90
dppp	91[b]	120	71
dppb	98[b]	400	91
dppm−cyh	90[c]	350	90
dpp−xylene	90[c]	420	91
DIOP	98[b]	1100	96
dppm−cyb	98[c]	1600	99
dppm−nor	97[c]	2100	99

[a] Conditions: benzene solvent; catalyst concentration, 1.4×10^{-4} M; Pt:P:$SnCl_2$ = 1:2:5; 50 bar CO; 50 bar of H_2; 100 °C; platinum as $PtCl_2(PhCN)_2$. [b] Natural bite angles β_n are taken from ref 36. [c] Calculated with Sybyl 6.5 using parameters described in ref 54.

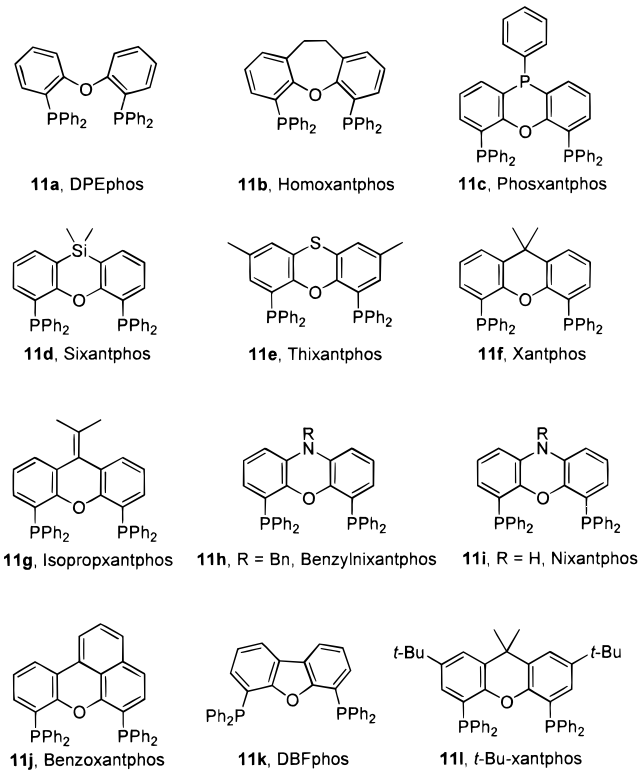
to lower catalyst activity! In the series dppe, dppp, and dppb (**1d**) the latter was by far the fastest catalyst. Interestingly, when the four-carbon bridge was included in a cyclic structure, the rate increased dramatically. The trans-substituted norbornane derivative (**10a**) gave the fastest catalyst. In Table 2



we have collected the relative yields as calculated from the original publications together with the added natural bite angles. As can be seen from the table both the linearity and the rate generally increase with the bite angle. The highest turnover frequency observed is ~700 mol·mol^{-1}·h^{-1}, which is higher than the rate measured for the system based on $HRh(CO)(PPh_3)_3$. It should be borne in mind that a rhodium catalyst shows a rate inversely proportional to the pressure of CO, and thus this rate would be five times higher at 10 bar for rhodium.[45]

In the original work it was suggested that the increased rate can be explained by the intermediacy of a complex in which the bidentate ligand acts as a monodentate. It is known that dppe gives very stable complexes, while for the strained cyclic phosphines dissociation of one arm can easily occur. In this way a coordination site is made available for the incoming alkene. This does not explain why PPh_3 gave much lower rates than bidentates supporting large bite angles, as dissociation of one monophosphine should be an even more facile process. Both their results and more recent work[46] suggest that the reaction of the acyl complex and dihydrogen is rate-determining in platinum hydroformylation. It would seem more likely now that ligands enforcing larger P−Pt−P angles enhance the reaction of the acyl complex with dihydrogen, which might involve trigonal-bipyramidal structures during the reaction or trigonal structures afterward. The detailed mechanism for this reaction is not yet known.

More recently this favorable effect of the bite angle has been further exploited, for the hydroformylation of both internal alkenes[47] and terminal alkenes.[48] Hydroformylation of methyl 3-pentenoate could be accomplished using the newly developed xantphos (**11**) ligands, giving turnover frequencies of ~20 mol·



(mol of catalyst)$^{-1}$.h^{-1} and linearities amounting to more than 90% (Table 3). Both rates and selectivities are remarkable. At lower temperatures the differences between the ligands are more pronounced than at higher temperatures. While DPEphos (**11a**) affords a much faster catalyst, the overall efficiency of sixantphos (**11d**) is higher. Hydroformylation of internal alkenes has been reported before, using cationic platinum complexes[49] or platinum catalysts containing phosphinite ligands.[50]

Table 3. Hydroformylation of Methyl 3-Pentenoate[a]

ligand	β_n[b] (deg)	TOF, hydroformylation	selectivity, *l*:*b*	hydrogenation (%)
DPEphos (**11a**)	102	25.4	1.4	30.4
sixantphos (**11d**)	108	11.5	12	1.9
thixantphos (**11e**)	110	5.6	10	1.8
xantphos (**11f**)	111	3.6	7	1.8

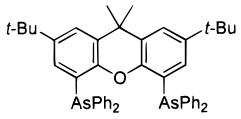
[a] Conditions: 80 °C; 10 bar of H_2/CO; $PtCl_2$:P:$SnCl_2$ = 1:2:2. [b] Natural bite angles β_n are taken from ref 69.

Table 4. Platinum/Tin-Catalyzed Hydroformylation of 1-Octene at 60 °C[a]

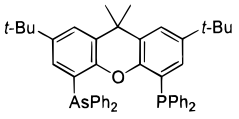
ligand	β_n[b] (deg)	*l*:*b* ratio[c]	*n*-nonanal[c] (%)	isomerization[c] (%)	TOF[c,d]
11*l*	111	230	95	4.5	18
12		>250	92	8.0	210
13		200	96	3.1	350
11b	102	>250	88	12	720

[a] Reactions were carried out in dichloromethane at 60 °C under 40 bar of CO/H_2 (1:1); catalyst precursor $[Pt(cod)Cl_2]$; [Pt] = 2.5 mM; $Pt:SnCl_2$:P:1-octene = 1:2:4:255. [b] Natural bite angles β_n are taken from ref 69. [c] Determined by GC with decane as the internal standard. [d] Averaged turnover frequencies were calculated as moles of aldehyde per mole of Pt per hour.

1-Octene can be hydroformylated with extremely high selectivity for terminal aldehyde product (>99.5%) and very high rates (Table 4) using xantphos-type ligands (**11**).[48] In view of the much milder conditions in these experiments, the turnover frequency of ligand **11b** seems an order of magnitude higher than the ligands reported previously, although the calculated bite angles are only marginally different from the best catalysts reported before. Apparently, ligand **11l**, with a relatively large bite angle, leads to less active catalysts. Surprisingly, the arsine ligands **12** and **13** also result in very active



12, As,As-xantphos



13, P,As-xantphos

catalysts, since usually arsine coordination is very weak. The calculated bite angles of ligands containing arsine as the donor atom are somewhat smaller than those of the corresponding phosphines because the atom radius of arsine is larger than that of phosphorus.

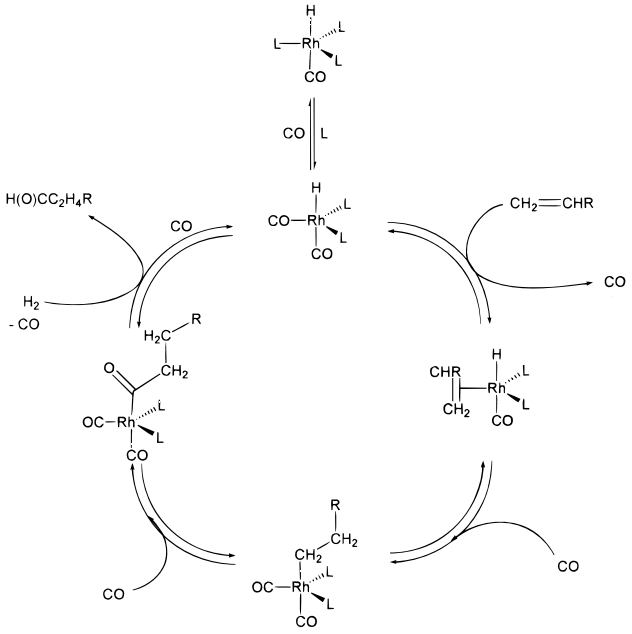
C. Rhodium-Catalyzed Hydroformylation

a. Phosphine-Based Catalysts

Rhodium-catalyzed hydroformylation is one of the most prominent applications of homogeneous catalysis in industry.[38] High selectivities in the hydroformylation of terminal alkenes have been reported for both diphosphine and diphosphite modified catalysts.[51−59] Novel ligands for the selective linear hydroformylation of internal alkenes, which is of great interest in both industry and synthetic organic chemistry, were developed recently.[58,60] Systematic studies of the influence of ligand structure on catalytic performance in the hydroformylation reaction are rare, however, and despite the development of a wide variety of ligands, consistent structure−activity relationships are still lacking.[61]

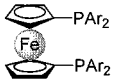
The generally accepted mechanism for rhodium-catalyzed hydroformylation as proposed by Wilkinson in 1968 is shown in Scheme 3.[12] The active catalyst is a trigonal-bipyramidal hydridorhodium complex, which usually contains two phosphorus ligands.

Scheme 3. Mechanism of the Hydroformylation Reaction As Proposed by Wilkinson



According to this mechanism, the selectivity is determined in the step that converts a five-coordinate $L_2Rh(CO)H$(alkene) complex into $L_2Rh(CO)$(alkyl) with either a linear or branched alkyl chain. For the linear alkyl chain this step is virtually irreversible at moderate temperatures and sufficiently high pressures of CO.[62,63] The structure of the alkene complex is therefore thought to play a crucial role in controlling regioselectivity.[65] Contrary to the $L_2Rh(CO)_2H$ complex, the $L_2Rh(CO)H$(alkene) complex has never been observed directly. Brown and Kent[64] have shown that the PPh_3-modified $L_2Rh(CO)_2H$ complex consists of two rapidly equilibrating isomeric structures in which the phosphine ligands coordinate in a diequatorial (ee) and an equatorial−apical (ea) fashion. Their work suggests that perhaps the ee isomer is the one that leads selectively to the linear aldehyde product. Previous studies on electronically modified diphosphine ligands have demonstrated that similar dynamic equilibria between ee and ea complex isomers also exist for diphosphine ligands.[61,65] The ee:ea isomer ratio of the complexes proved to be strongly dependent on phosphine basicity; it increases with decreasing phosphine basicity and a correlation ee:ea with *l*:*b* is implied.

One of the first published, systematic studies involving bidentate phosphines was reported by Unruh and Christenson.[51a] They used substituted dppf ligands (**14**) in order to study the effect of



14 **a**, Ar = Ph
b, Ar = *o*-tolyl
c, Ar = *p*-$MeOC_6H_4$
d, Ar = *p*-ClC_6H_4
e, Ar = *p*-$CF_3C_6H_4$
f, Ar = 3,5-di$CF_3C_6H_3$
g, Ar = 3,5-$F_2C_6H_3$
h, Ar = 2-furyl

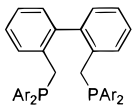
Table 5. Hydroformylation with Substituted Arylphosphines Fe[$C_5H_4P(C_6H_4R)_2$]2 (14)[a]

Ar	χ_i-value (Ar)	rel rate	selectivity (%) linear	branched	isomerization
Ph	4.3	7.2	81	15	4
p-Cl-C_6H_4	5.6	9.3	87	8	5
m-F-C_6H_4	6.0	13.7	89	6	5
p-CF_3-C_6H_4	6.3	13.8	92	2	6

[a] Conditions: 110 °C; 8 bar of CO/H_2 = 1:1; 1-hexene.[51] (χ_i is defined as the Tolman χ-parameter[5] for one substituent in the equation $\chi = \Sigma\chi_i$ for $(R_i)_3P$).

small electronic changes of the ligand on the selectivity of the reaction (Table 5). It is seen that both rate and selectivity increase with increasing χ value, without too much change in the selectivity for isomerization. The effect can be explained along two lines, although this remains speculative in the absence of thorough kinetic data. First, there may be a direct electronic preference for the formation of a higher proportion of the linear alkyl intermediate when the π-back-donation to the phosphine ligand increases. The effectiveness of such an influence, however, will also depend on the kinetics of the catalytic process. Alternatively, the electron withdrawing ligands enhance the formation of ee isomers, since dppf has a relatively large bite angle and it may be able to form intermediates that do not have a purely cis type of configuration for the diphosphine. First, the rate of the hydroformylation reaction increases with increasing χ values. Loss of CO from the complex occurs more readily when arylphosphines having higher χ values (i.e. less electron donating) are applied. Second, a stronger complexation of the alkene donor ligand may be expected to give more electron deficient rhodium complexes. Thus, a higher rate can be explained, because in most phosphine-based systems the step involving replacement of CO by alkene contributes to the overall rate. Kinetic studies show that the reaction rate is indeed first order in alkene concentration and minus first order in CO.

Rhodium catalysts containing diphosphine ligands showing very high selectivity for straight-chain aldehyde formation were reported by Devon et al.[52] at Texas Eastman in 1987. The new bidentate ligand, BISBI (**15a**), gave excellent results in the hydroformylation of propene at 125 °C and 18 bar of synthesis gas compared to other bidentate ligands. A linear-to-branched ratio of 25:1 was obtained, compared to 3.5:1 for dppf and 4:1 for DIOP. The rate for BISBI was the highest as well (3−4000 mol·(mol of catalyst)$^{-1}$·h^{-1}), with a ligand-to-metal ratio of 2.4. Only triphenylphosphine gave a faster reaction, but larger quantities of ligand were needed (TPP:Rh = 124:1), and the linear-to-branched ratio was only 2.4. The ratios found for dppb and dpp−pentane are close to that of TPP, although the bite angles of these ligands are calculated to be quite large, which indicates that the actual complexes are different from the expected bisequatorial complexes. Most likely bridged bimetallic complexes are formed using these ligands.[51b]



15 a, Ar = Ph
b, Ar = 3,5-di$CF_3C_6H_3$

The chemistry and catalysis of BISBI has been studied in detail by Casey and co-workers.[53,63] The natural bite angle calculated for BISBI turned out to be ~120°. The crystal structure of HRh(CO)(BISBI)PPh_3 shows that the P−Rh−P angle in the solid state is 125°. The ligand is quite flexible and accommodates a range of bite angles between 152° in Fe(BISBI)$(CO)_3$ and 104° in Mo(BISBI)$(CO)_4$.[66,67] All spectroscopic measurements support a bisequatorial mode of coordination for BISBI in rhodium hydrido dicarbonyl complexes. Hydroformylation of 1-hexene at 34 °C under 6 bar of CO/H_2 gives the linear and branched aldehyde in a ratio of 66:1. Under the same conditions dppe affords a linear-to-branched ratio of only 2, while the rate is 30 times lower!

When the phenyl groups in BISBI were replaced by strongly electron-withdrawing 3,5-$(CF_3)_2C_6H_3$ substituents (**15b**), a 5-fold rate increase was observed and the linear-to-branched ratio increased to 123:1.[61] The direction of this effect is the same as that discussed above for dppf derivatives.[51]

In 1990 Yamamoto[59,68] reported a new ligand, 2,5-bis(diphenylphosphinomethyl)bicyclo[2.2.1]heptane (**10b**), especially designed and made for its presumably wide bite angle. The calculated natural bite angle is 123° and a high selectivity in 1-alkene hydroformylation using rhodium catalysts was expected. Surprisingly, the linear branched ratio (40 bar, 25−50 °C) does not exceed 59:41. Perhaps the ligand is more flexible than the calculations indicate and the ligand does not have such a strong preference for bisequatorial coordination or bimetallic species are formed. No NMR studies have been published on rhodium hydrido species containing this ligand.

How the bite angle affects the activity and selectivity in the rhodium−diphosphine-catalyzed hydroformylation is the subject of current research.[61] To investigate the exact influence of the natural bite angle of diphosphine ligands on catalytic performance and coordination chemistry in rhodium complexes, van Leeuwen et al. developed a range of new diphosphine ligands based on xanthene-type (**11**) backbones.[54,65,69] Variation of the substituent at the 9-position of the generic backbone structure enables the construction of a series of diphosphine ligands covering a wide range of natural bite angles (Table 6). Moreover, the backbone structure in this type of ligand ensures that variation in electronic properties and in steric size within the series of ligands is minimal. Table 6 shows how the linear-to-branched ratio of the aldehyde product increases with increasing bite angle of the diphosphine. Even for styrene considerable selectivity for the linear product was obtained (*l*:*b* = 2.3:1, at 120 °C, 10 bar, ligand xantphos **11f**).[54]

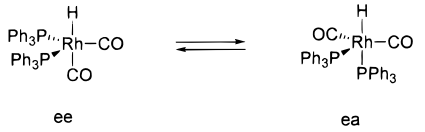
An interesting observation was reported concerning the coordination mode of the diphosphine.[69] Until

Table 6. Results of the Hydroformylation of 1-Octene at 80 °C Using Xantphos Ligands (11)[a]

ligand	β_n[b] (deg)	*l*:*b* ratio[c]	linear aldehyde[c] (%)	isomer[c] (%)	TOF[c,d]	ratio ee:ae
11b	102	8.5	88.2	1.4	36.9	3:7
11c	108	14.6	89.7	4.2	74.2	7:3
11d	108	34.6	94.3	3.0	81.0	6:4
11e	110	50.0	93.2	4.9	110	7:3
11f	111	52.2	94.5	3.6	187	7:3
11g	113	49.8	94.3	3.8	162	8:2
11h	114	50.6	94.3	3.9	154	7:3
11i	114	69.4	94.9	3.7	160	8:2
11j	120.6	50.2	96.5	1.6	343	6:4

[a] Conditions: $CO/H_2 = 1$; $P(CO/H_2) = 20$ bar; ligand/Rh = 5; substrate/Rh = 637; [Rh] = 1.00 mM; number of experiments = 3. In none of the experiments was hydrogenation observed. [b] Natural bite angles β_n are taken from ref 69. [c] Linear over branched ratio, percent linear aldehyde, percent isomerization to 2-octene, and turnover frequency were determined at 20% alkene conversion. [d] Turnover frequency = (mol of aldehyde)·(mol of Rh)$^{-1}$·h^{-1}.

Scheme 4. Equilibrium between the ee and ea Isomers



then it was assumed that a bisequatorial coordination mode was a prerequisite for obtaining high selectivity for linear product. Analyses of the IR spectra and NMR spectra of the putative catalyst resting states, the complexes HRh(diphosphine)$(CO)_2$, have shown that in all complexes the two isomers, ee and ea, (Scheme 4) are in equilibrium. As can be seen in Table 6 the equilibria shift to the side of the ee isomer for ligands with wider bite angles, but nonetheless a substantial amount of the supposedly less selective ea isomer is observed for ligands with smaller bite angles, and these still give reasonably high selectivities. Many details remain unexplained; although the trends are clear, there are quite a few exceptions. Evidently, only for flexible diphosphines having either a relatively narrow natural bite angle (dppe, **1b**) or a relatively wide one (BISBI, **15a**), the natural bite angle controls the chelation mode.[53] The rhodium complexes of the rigid xantphos-type ligands prove to be very sensitive to small changes in the electronic properties and the rigidity of the ligand backbone. In these complexes the chelation mode is only partially imposed by the natural bite angle. The pronounced effect of phosphine basicity on chelation behavior has been demonstrated as mentioned above.[61,65,70]

The natural bite angle does have a clear effect on the selectivity for linear aldehyde formation in the hydroformylation of both 1-octene and styrene, but the ee:ea isomer ratio in the (diphosphine)Rh$(CO)_2$H catalyst resting states is not the key parameter controlling regioselectivity. The expansion of the effective steric bulk of the diphosphine with increasing natural bite angle is the most likely explanation.[61,65] Increasing the steric congestion around the rhodium center will result in more selective formation of the sterically less hindered linear alkyl rhodium species. This is consistent with our model suggested previously, in which the four-coordinate intermediate (diphosphine)Rh(CO)H species that undergoes the alkene attack, plays an important role in the control of regioselectivity.[65]

Table 7. Hydroformylation of Lower Alkenes Using Diphosphites[55]

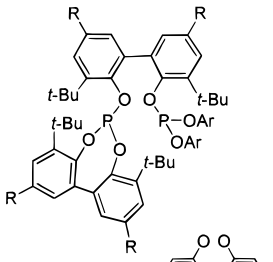
ligand	*T*, °C	$P(CO/H_2)$ (bar)	ratio CO/H_2	alkene	rate,[a] (mol·(mol of Rh^{-1})·h^{-1})	*l*:*b*
16a	70	2.5	1:2	1-butene	2400	50
16a	71	6.7	1:2	1-butene	730	35
20a	70	7	1:2	1-butene	1480	3.2
18	70	7	1:2	1-butene	160	6.3
19	70	4.3	1:1	propene	280	1.2
18	70	4.3	1:1	propene	20	2.1
17a	74	4.5	1:1	propene	402	53
21a	90	7.1	1:1	1-butene	1620	2.3
21b	90	7.1	1:1	1-butene	1320	3.8
21c	90	7.1	1:1	1-butene	1070	2.2
22	90	7.1	1:1	1-butene	3660	2.0
23	90	7.1	1:1	1-butene	1650	9.9
22	90	7.1	1:1	2-butene	1140	0.5
23	90	7.1	1:1	2-butene	65	2.8

[a] Rates were measured in continuous runs or calculated at 30% conversion.

b. Phosphite-Based Catalysts

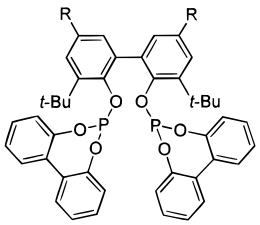
Diphosphites came into focus after the discovery of Bryant and co-workers at Union Carbide Corp. (UCC) that certain bulky diphosphites lead to high selectivities in the rhodium-catalyzed hydroformylation of terminal and internal alkenes.[55] Union Carbide has a long vested interest in hydroformylation. The first publication on the use of phosphites is from UCC's Pruett and Smith.[13] The first exploitation of bulky *mono*phosphites was reported by van Leeuwen and Roobeek,[71] who found high rates for internal and terminal alkenes, but selectivities were low. High selectivities are only obtained when *di*phosphites are used. The advantages of the diphosphite system for propene hydroformylation as compared to the commercial triphenylphosphine system are that less ligand is required and that higher rates can be obtained.

Although a plethora of diphosphites has been tested and recorded in many patents authored by coworkers of several companies,[55,58,72−75] no systematic research has been published about structure−performance relationships. We have not attempted to carry out a complete patent literature search, and unfortunately no comparison of the many structures and the catalytic data is available. The patents included in the references of this review serve only as examples. In Table 7 we have collected a few examples of ligands and their performance in the rhodium-catalyzed hydroformylation reaction taken from one of the early Union Carbide patents.[55] It can be seen that the type of bridge in the diphosphite plays a role, as does the bulkiness of the substituents. There is not a single factor that controls the linearity of the product that is obtained in an evident way. It is noticed that ligands **16** and **17** have a high



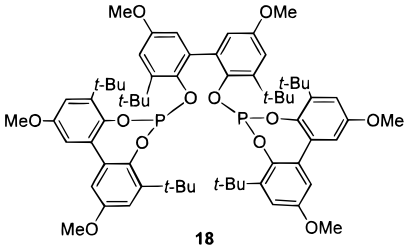
16a R = OMe, $(OAr)_2$ =

b R = *t*-Bu, OAr = 4-C_6H_4-Cl



17a, R = OCH_3
b, R = *t*-C_4H_9,

selectivity for making linear aldehyde. The presence of a bisphenol bridge seems to be important, but it is not enough, because many ligands containing bisphenol backbones fail to give high selectivities. For instance, ligands **18** and **19** give low linearities, even



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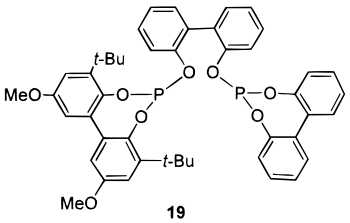

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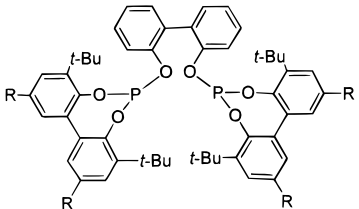
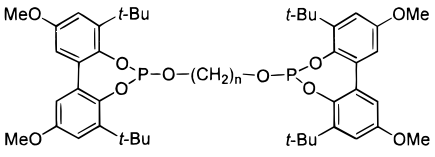
though their structures seem closely related to **16** and **17**. Note an interesting difference between the diphosphites (**21a**−**c**) containing bulky end groups and

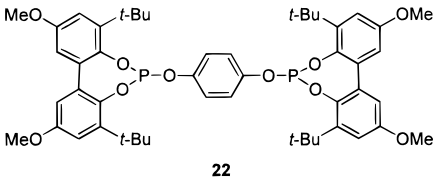


20a, R = OCH_3
b, R = *t*-C_4H_9



21a, n = 2
b, n = 3
c, n = 4

different bridges. In the series 1,2-ethanediol (**21a**), 1,3-propanediol (**21b**), and 1,4-butanediol (**21c**), the propanediol derivative clearly gives the highest linearity. Ligand **22** cannot form bidentate complexes, we presume, and as a result one sees a low selectivity, but the activity is high, reminiscent of the bulky



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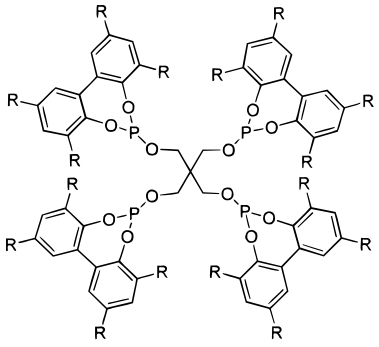
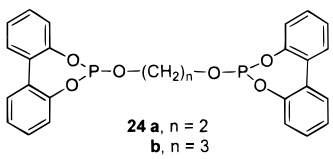
monophosphites. The pentaerythritol derivative (**23**) gives a relatively high linearity, which was exploited



23, R = *t*-C_4H_9

further by Mitsubishi. It also gives a relatively high linearity when using 2-butene, but the rate is very low. Not unexpectedly, the rate of the catalyst containing **22** is high using 2-butene as the substrate, at the cost of a low linearity. From the patents that we have studied no structure−performance relationship can be deduced.

A study by van Leeuwen et al. describes the performance of a few diphosphite ligands (first reported by or related to those reported by Bryant[55]) in the hydroformylation of 1-octene and styrene together with the NMR and IR data of the complexes $HRh(diphosphite)(CO)_2$.[56] Steric bulk plays an important role, as does the bridge linking the two phosphites. In Table 8 we have collected some data showing the selectivities for a few specific diphosphites. High *l*:*b* ratios were obtained with ligands **16** and **17** as reported by Bryant. The ligands are ordered according to the length of the bridge, which may be equivalent to the bite angles. Calculation of the bite angles is usually not straightforward for phosphites due to the large number of conformations with very similar calculated energies. As for **21a**−**c**, we also see for **24a,b** that the propanediol derivative



24a, n = 2
b, n = 3

leads to a slightly higher linearity, with a distinct higher propensity for isomerization for the latter. As was reported by Bryant, a high linearity is obtained when **16** and **17** are used. The former ligand even leads to a high rate (6200 $mol \cdot mol^{-1} \cdot h^{-1}$) and a very high linearity for styrene (84%), which usually has a propensity for giving branched product (120 °C, 5 bar CO, 30 bar H_2).

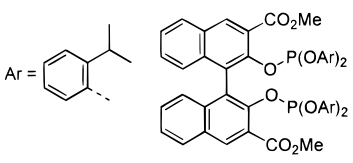
Table 8. Hydroformylation[a] of 1-Octene Using Diphosphites[56]

ligand	TOF	isomerization (%)	*l*/*b* ratio	J_{P-H} (Hz)	CO stretch (cm^{-1})
24a	11 100	0	1.6	72	2028, 1987
24b	1500	20.4	2.2	5	
17a	3600	17.7	>100	4[b]	2074, 2013[b]
17b	6120	26.5	51	9	
16b	3375	0	19	−19, 70	2049, 1966
20b	520	12.9	1.2	4	2070, 2008

[a] Conditions: $T = 80$ °C, [Rh] $= 8 \times 10^{-6}$ M, 20 bar; CO:H_2=1:1; ligand/Rh = 20; T.O.F calculated over 20−30% conversion; initial 1-octene concentration, 1 M. OAr = p-OC_6H_4Cl. [b] Also from ref 78.

As might have been expected, the reaction is much slower when diphosphites are used instead of bulky monophosphites.[76] This is true for both disubstituted and monosubstituted alkenes. The reason for this is that bulky monophosphites form mono−ligand complexes with rhodium hydride carbonyls, which are more active catalysts both for electronic and steric reasons. The kinetics of the hydroformylation of 1-octene using diphosphites show that the reaction is first order in the 1-alkene concentration, that it has an approximate −0.65 order in CO pressure, and that it is virtually independent of the dihydrogen pressure. The linearity decreases with increasing CO partial pressure. This is consistent with a kinetic scheme in which the alkene addition to rhodium is rate-determining.[76] The possibility that a later step is rate-determining is still open (the subsequent hydride migration or acyl formation), in which case coordination of alkene would be involved in a preequilibrium. Gladfelter et al. have found that insertion of alkene is reversible at room temperature. The linearity strongly depended on the precise structure of the ligand and the complexes formed and the conditions applied.

A high proportion of isomerization, which results from the initial formation of secondary alkyl rhodium species, leads to a flattering value of the selectivity for linear product. The coproduction of internal alkenes when using higher alkenes is not very attractive, because this will eventually lead to mainly branched aldehydes. One can also exploit the higher propensity of a catalyst for isomerization, however, to convert internal alkenes to linear products, especially when the selectivity for linear product of a catalyst is very high. For lower alkenes such as 2-butenes UCC has achieved high contents of linear products (see Table 7). Du Pont and DSM have patented the use of ligand (**25**) for the hydroformylation of methyl 3-pentenoate to linear product.[58] Instead of *tert*-butyl groups on the bridge, they use electron-withdrawing ester groups, while the remaining substituents are monophenols,[72,73] rather than diols[74,75] or bisphenols. The efficacy of monophenols containing bulky substituents is described in the patents from Mitsubishi Chemical Corp.[72,73] (**26**).



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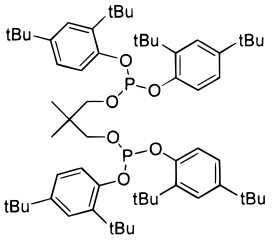

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Table 8 contains a few data concerning spectroscopic properties of the complexes HRh(diphosphite)-$(CO)_2$. Phosphites containing a 1−2-diol bridge give complexes coordinating in an e−a fashion.[56b] The regioselectivity achieved using these complexes is comparable to that achieved using monodentates, linear/branched = ∼2. Ligands such as **24a** lacking the steric congestion in the ligand often give rise to mixtures of complexes, and the selectivities obtained in the catalysis are also low. These complexes are highly fluxional, and a high average J_{P-H} coupling constant is indicative of the e−a coordination mode.[56c] Ligand **24b** clearly affords an e−e complex, but nevertheless the l/b ratio is only 2.2. Diphosphites containing a bisphenol bridge and sufficient steric bulk such as **16** give stable complexes, and usually only one complex is observed attaining an e−e mode of coordination. As mentioned above, these complexes give the highest linear-to-branched ratios. There are, however, exceptions to this rule. Ligand **19** forms selectively e−e-type complexes, as appears from the low coupling constant and the high stretching vibrations in the IR spectrum,[77] but nevertheless the regioselectivity for linear product is only 55%. At room temperature the complexes showed a doublet in the phosphorus NMR spectrum, having a rhodium-to-phosphorus coupling constant in the range of 231−237 Hz. This is typical of an equatorial coordination of the diphosphite. The averaged coupling constant of a ligand that coordinates equatorially axially is smaller, at ∼210 Hz. For both types of coordination only one doublet is observed at room temperature, indicating that a fast interchange occurs.

Complexes having bisequatorial coordination show a small phosphorus-to-hydride coupling constant (cis relationship). Ligand **17a** has also been studied by Gladfelter et al.[78] Typically they show IR absorptions at 2015 ± 5 and 2075 ± 5 cm^{-1}, while axial−equatorial complexes have absorption at 1988 and 2029 cm^{-1}. The latter show the characteristic large coupling constant of phosphorus to hydrogen which averages at high temperature to a triplet of 70−100 Hz. At lower temperatures the exchange on the NMR time scale can be frozen and an AB spectrum can be observed in the ^{31}P NMR spectrum. For the axial−equatorial complexes the phosphorus-to-phosphorus coupling constant ranges from 0 to 70 Hz, but for the bisequatorial complexes the coupling constant is typically 240−235 Hz. This is perhaps larger than one would have expected, and many workers might

have thought they were dealing with a trans-relationship. Interestingly, the exchange process for an e−a bidentate system is an order of magnitude faster than the exchange of an e−e system.[56c] As expected, at low temperature the very large (140−200 Hz) coupling constant of the hydrido to the axial phosphorus atom is observed, while that to the cis phosphorus atom is very small. A detailed explanation of the NMR spectra could be obtained. These spectra are recorded at high concentrations. Using IR spectroscopy at both high and low ("catalytic") concentrations, it was shown that in the catalytic runs the species discussed above are present indeed. In conclusion, high linearities are obtained when the ligands coordinate in an e−e fashion, but the reverse is not true.

Two crystal structures of rhodium complexes containing **16** have been reported;[56a,79] one is a square-planar complex of rhodium acetylacetonate RhAcac(**16**), and the other is the rhodium hydrido dicarbonyl, $HRh(CO)_2$(**16**). The observed P−Rh−P angle in the acac complex is 97°. The compound is highly strained, as can be seen from the large P−O−C angles in the phosphite, which are as large as 140°. The bite angle in $HRh(CO)_2$(**16**) is 116°, and the complex is indeed a trigonal bipyramid with the diphosphite in the equatorial plane. The structure is somewhat distorted; the larger ligands bend toward the small hydride. This explains why the coupling constants for the coupling between phosphorus and hydrogen are sometimes larger (up to 70 Hz) than might be expected in a complex showing a pure cis-relationship between hydride and phosphorus ligand (<10 Hz). This crystal structure confirms the NMR analysis, but so far it is the only X-ray example of a diphosphite rhodium catalyst.

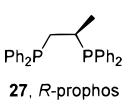
We noted above the differences in stability of the complexes depending on the length of the bridge of the diphosphite and the steric bulk of a diphosphite. Together they determine the preferred bite angle of the bidentate. Obviously, ligands having larger bite angles resist the formation of complexes in which they should coordinate as cis-ligands. This is a clear example of ligands stabilizing or destabilizing the "catalytic" species.

Butadiene Hydroformylation. Hydroformylation of butadiene can be of interest for making several products: linear pentenals, pentanal, and 1,6-hexanedial. In most instances, a broad mixture of product is obtained and getting high selectivity is still a challenge. Hydroformylation using rhodium catalysts based on dppe selectively gives a high proportion of linear monoaldehydes.[80] At low pressures and high temperatures the yield of pentanal can be as high as 95%. Pentenals are most likely intermediates, and longer reaction times give higher selectivities to the saturated product. In this study a large ligand effect was observed; all ligands other than dppe gave much lower yields of pentanal/pentenals (see Table 9). At higher pressures (120 bar) and lower temperatures (80 °C) the main product was (*E*,*Z*)-3-pentenal (96%).[81] Apparently, the hydrogenation reaction is suppressed at higher CO pressure, while the selectivity for the linear C-5 products is retained. Interestingly, *R*,*S*−binaphos (**28**) also gives purely linear pentenals at low temperature (30 °C) and high pressure (100 bar), even though the bite angle should be quite different from dppe.[82]

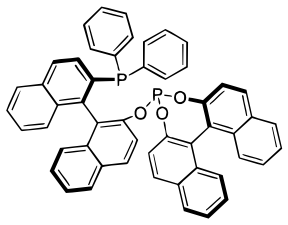
Table 9. Hydroformylation of Butadiene[a]

ligand	β_n[b] (deg)	selectivity pentanal (%)	linearity C_5-aldehydes (%)	rate, (mol·mol^{-1}·h^{-1})
dppm	72			<3
dppe	85	>90[d]	99	250
dpp-ethene		80	98	150
dppf	99	<20	95	500
DIOP	98	15	90	500
dppe[c]	85	>80	98	90
prophos[c]		90	98	200
dppp[c]	91	20		30
dppb[c]	98	<20	80	80

[a] Conditions: 120 °C; 12 bar CO/H_2 (1:1); 20 mmol of 1,3-butadiene; 0.02 mmol of Rh(COD)OAc; 20 mL of toluene; a 100 mL autoclave. [b] Natural bite angles β_n are taken from ref 36b. [c] The remainder is pentenal. [d] At 95 °C.



27, *R*-prophos



28, Binaphos

Ohgomori et al.[83] have studied the bite angle effect on the hydroformylation more recently. They report also a decreasing selectivity for penta(e)nal with increasing bite angle with a concomitant increase of the rate of reaction. Using DIOP, as much as 31% of 1,6-hexanedial has been obtained (90 bar, 100 °C).

Hydroformylation of a 1,3-diene is much slower than the reaction of simple alkenes. The reason for this is probably the formation of η^3-allyl species after the reaction of the diene with rhodium hydrides. These intermediates are more stable than σ-alkyl rhodium species and also undergo the migratory insertion at a much lower rate. Deuterioformylation gave only one isomer of a dideuterio pentenal,[81] showing an irreversible 1,4 addition in the first step. The kinetics of this reaction have not been studied, but the resting state of the catalyst is most likely the allyl species.

The use of bidentate phosphite ligands for rhodium-catalyzed hydroformylation of butadiene has been reported by Packett.[84] The selectivity for C-5 aldehydes was found to be high for most catalysts. The highest selectivity for 1,6-hexanedial (as the acetal of 1,2-ethanediol) was found using ligands **17** as discussed above (e.g. 49%, ligand **17**, 110 °C, 60 bar $CO/H_2 = 4:1$).

D. Alternating Copolymerization of Alkenes and Carbon Monoxide

Thermoplastics with high-performance properties are in increasing demand.[85] In recent years much effort has been devoted to the development of such high-performance plastics which might be produced

at low costs. In the past decade Shell has successfully developed a new family of polymers that will be marketed under the trade name CARILON. They are perfectly alternating copolymers of alkenes and carbon monoxide.

Radical copolymerization of ethene and carbon monoxide has been known for a long time.[86] These polymers had low molecular weights, and the incorporation of CO was usually lower than required for a perfect alternation of ethene and CO. Coordination polymerization for ethene/CO was discovered by Reppe[87a] using nickel cyanide catalysts (this was even before the Ziegler invention[87b−d]). The molecular weights were very low, and the polymers were produced together with diethyl ketone and propionic acid. The first active palladium catalyst (phosphine complexes of $PdCl_2$) was reported by Gough (ICI) in 1967.[88] The rates were promising [300 g/(g of Pd)/h)], but the conditions were harsh (250 °C, 2000 bar). Similar palladium catalysts were used by Fenton (Union Oil)[89] and Nozaki (Shell).[90] High molecular weights were achieved, and the potential of the semicrystalline high-melting polymer was recognized. The polymers, however, contained a considerable amount of catalyst (often as palladium black), and this was deleterious to the stability of the polymer during processing. Hence, considerably more active catalysts were needed.

Catalysis with Diphosphines. In 1982 Sen[91] reported on the use of cationic palladium−(triphenylphosphine)$(BF_4)_2$ species in acetonitrile as catalysts for the copolymerization of alkenes and CO. For ethene/CO he obtained high molecular weights. In the same year, while trying to make methyl propanoate from ethene, CO, and methanol, Drent[92,93] discovered that cationic palladium complexes containing chelating bidentate diphosphine ligands produced alternating polymers of ethene and CO with 100% selectivity, high molecular weight, and yields up to several kilograms per gram of palladium per hour. Under mild conditions (30−60 bar and 80−100 °C) perfectly alternating polymers with melting points of ∼260 °C containing only parts per million quantities of palladium are obtained. The diphosphine catalysts are a few orders of magnitude faster [10 kg/((g of Pd)/h)] than the monophosphine based catalyst [4 ((g/g Pd)/part per million)].

The polymerization reaction is efficiently catalyzed by complexes of the type PdX_2(L−L) (L−L is a chelating bidentate phosphorus or nitrogen ligand—coordinating in a cis fashion—, X is a weakly or noncoordinating anion) in methanol as the solvent. Suitable ligands are dppe, dppp, and dppb, and both triflates and *p*-toluenesulfonic acid provide suitable anions. The catalyst can be made in situ by dissolving palladium acetate and adding ligand and a strong acid. When methanol is the solvent, there is no need to create an active palladium alkyl initiator, as methanol leads to formation of palladium hydride and/or carbomethoxy species.

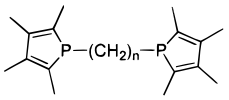
The nature of the bidentate ligand has a strong influence on the rate of reaction and on the molecular weight of the polymer obtained: see Table 10. One clearly sees an increasing rate with increasing bite angle, but for the three widest bite angles the reaction slows down again. For the obtained molecular weight the ratio of the rate of propagation versus the rate of termination or chain transfer is the determining factor. It is seen that the rate of termination increases going down in Table 10, except for the last entry, the dpp−hexane. It should be borne in mind that, in bidentates containing 1,4-butane bridges and larger, the ligands tend to form bimetallic complexes having the phosphines in trans dispositions.[27,94]

Table 10. Copolymerization of CO and Ethene[a]

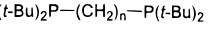
ligand	β_n[b] (deg)	rate mol·(mol^{-1} of catalyst)·h^{-1}	DP[c] (ñ)
dppm	72	1	1
dppe	85	1000	100
dppp	91	6000	180
dppb	98	2300	45
dpp−pentane		1800	6
dpp−hexane		5	2

[a] Conditions: palladium tosylate and diphosphine, 0.7 M in methanol; 85 °C; 45 bar of CO/ethene. [b] Natural bite angles β_n are taken from ref 36b. [c] Average degree of polymerization (ñ) measured by NMR for $H(C_2H_4CO)_nOCH_3$.

Recent work by Doherty[95] et al. confirms the observed trend for rates and bridge lengths in the series of ligands **29a**−**c**. In this instance the effect is even much more pronounced, with polymerization rates for C-2, C-3, and C-4 bridges amounting to 0, 5100, and 46 300 g of polymer/((mol of catalyst)/h, respectively.



29 a n = 1
b n = 2
c n = 3



29 d n = 1
e n = 2
f n = 3

For a complete understanding all mechanistic aspects need to be taken into consideration: initiation modes; propagation; the perfect alternation; chain transfer, or rather the combined result of initiation and termination as a process of chain transfer; resting states of the catalyst; or dormant states of the catalyst. The material published so far on the kinetics comprises only work of stepwise reactions carried out at temperatures of −40 to +25 °C, which is well below the temperature of the catalytic process.

Insertion of carbon monoxide and alkenes into metal-to-carbon bonds requires relative cis positions of the alkyl group and the unsaturated fragment in the reacting complex, which explains the high preference for complexes containing bidentate to form polymers, rather than methyl propanoate.[93] Experimental evidence that the intimate mechanism is indeed migratory insertion rather than an insertion has been presented both for carbon monoxide and alkene insertions for palladium and platinum.[96,97]

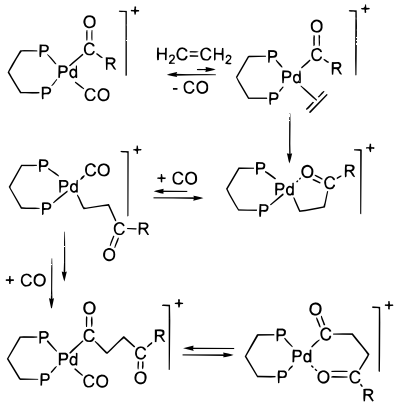
Attempts to measure the rates of insertion of CO and alkenes separately have been undertaken. The rate of CO insertion in the Pd−CH_3 bond has been studied for the complexes (P−P)Pd(CH_3)Cl (P−P = dppe, dppp, dppb, dppf)) and the ionic complexes [(P−

P)Pd(CH_3)(CH_3CN)]$^+SO_3CF_3^-$ (P−P = dppe, dppp, dppb, dppf).[94] The rate was found to decrease in the order dppb ≈ dppp > dppf for the neutral complexes with half-life times ranging from 18 to 36 min at 235 K and 25 bar of CO. The dppe complex reacted much more slowly with a half-life time of 170 min at 305 K. The rate of carbonylation of the Pd−CH_3 bond in the cationic complexes was at least 10 times higher than those of the analogous neutral complexes, the order being dppb ≈ dppp ≈ dppf > dppe with half-life times < 1.5 min at 235 K, except for the dppe complex for which a half-life time of 2.5 min was measured. These studies have clearly shown that the bite angle and backbone flexibility of the ligand strongly influence the rate of migration in methyl−palladium complexes, and the question arises whether this will affect catalytic processes in a similar manner. This is another example which seems to point to a rate-enhancing effect obtained by replacing the two-carbon bridge by a three- or four-carbon bridge in 1,*n*-(diphenylphosphino)alkanes. An example of a cationic palladium complex containing a methyl group and a coordinated CO molecule has been reported.[98] The rate of CO insertion during the copolymerization is not necessarily the same as that of the insertion into the methyl palladium bond, because the intermediate alkyl palladium species is stabilized by an intramolecular ketone to palladium bond, which hampers coordination of carbon monoxide.

Alkene insertions have also been widely studied and many insertion products have been isolated.[99−105] It has been shown that also alkene insertions follow a migratory mechanism in the palladium and platinum square-planar complexes and diphosphorus ligands.[97] The study of the rate of alkene insertions in complexes containing diphosphine ligands turned out to be more complicated than the study of the CO insertion reactions.[94,104] Attempts to carry out reactions on acylpalladium complexes resulted in decarbonylation. When the reaction is carried out under a pressure of CO, the observed rate of alkene insertion depends on the CO pressure. Also, after insertion of the alkene into the acyl species the intermediate decomposes via β-elimination, except when norbornene or norbornadiene are used as the alkene. Therefore most studies on the alkene insertion and isolation of the intermediates concern the insertion of norbornenes.

Insertions of alkenes in the palladium acetyl bond have been studied as a function of the ligand (dppe, dppp, dppb), the alkene, and the anion.[104] The ionic complexes were made to react with a variety of alkenes, giving initially an intermediate in which the ketone is coordinated to the palladium cation. Only a minor bite angle effect was observed, involving a slightly higher rate for dppp as compared to dppe and dppb. In the absence of CO β-hydride elimination took place. Interestingly, this reaction was very fast for the complexes containing dppe. Since insertion was relatively slow for this ligand, we conclude that for dppe the hydride−alkene complex is relatively more stable when the bidentate diphosphine occupies less space (i.e has a smaller bite angle). The same trend in stability of alkyl platinum complexes versus hydride−alkene complexes was observed by Spencer using bis-di(*tert*-butyl)phosphino bidentate ligands.[106]

Scheme 5. Mechanism of the Stepwise Insertion of Alkenes and CO in an Alternating Fashion



The polymerization reaction proceeds via a perfectly alternating sequence of carbon monoxide and alkene insertions in palladium−carbon bonds. Several workers have shown the successive, stepwise insertion of alkenes and CO in an alternating fashion.[93,105] The analysis of final polymers shows that a perfect alternation is obtained. It is surprising that despite the thermodynamic advantage of alkene insertion versus CO insertion nevertheless exactly 50% of CO is built in. The explanation is based on the kinetics and equilibrium constants as reported by Drent and Budzelaar[93] and is depicted in Scheme 5.

The kinetics for the overall reaction have not been reported, but it seems likely that the reaction is first order in alkene and that the order in CO depends on the pressure in such a way that CO suppresses the reaction at very high pressures. Undoubtedly, the rate of chain termination will also depend on the nature of the ligand, which will be the case for ionic mechanisms,[91] but also for mechanisms involving β-hydride elimination and reinsertion.[107] In the latter study it has been reported that the protonation of the alkyl chain end takes place after β-hydride elimination and reinsertion has taken place to give an enolate intermediate. The rate of chain transfer appears to be strongly dependent on the nature of the backbone of the bidentate phoshine.[108]

Before closing this part, we will mention an example of a catalyst system for which the calculated bite angle predicts a result that differs from the actual outcome of the experiment. The natural bite angle calculation for (t-Bu)$_2$P(CH_2)$_3$P(t-Bu)$_2$ gives a value close to that of dppp, and therefore one would expect it to be a good catalyst for polyketone formation, apart perhaps from electronic influences. Instead it was found to give a fast and selective catalyst for the formation of methyl propanoate under the common conditions for making polyketone. Thus, the behavior is more like that of a monophosphine rather than that of a bidentate ligand.[109] Recently it has been shown that this ligand indeed has a tendency to form trans, oligomeric complexes instead of cis chelate complexes.[110] In this instance the steric

Table 11. Hydroxycarbonylation of Styrene[a]

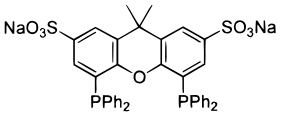
diphosphine	β_n (deg)	conversion (%)	*b*:*l*
dppe	85[b]	<1	47:53
dppp	91[b]	2	23:77
dppb	98[b]	24	17:83
dppf	96[b]	39	16:84
homoxantphos	102[c]	≈90	15:85
DPEphos	103[b]	93	14:86
xantphos	111[c]	96	19:81

[a] Reaction conditions: 10 mL of DME (dimethoxyethane); 75 bar of CO; 150 °C; 2 h; P:Pd = 10:1; 8 mmol of styrene; 0.04 mmol of precursor $PdCl_2(PhCN)_2$; 8 mmol of $H_2C_2O_4$. [b] Natural bite angles β_n are taken from ref 36b. [c] Natural bite angles β_n are taken from ref 69.

hindrance is held responsible. Likewise a series of ligands based on 1,2-xylene (**8a**−**d**) gave fast catalysts for methyl propanoate even though the calculated bite angles are approximately 104°. The authors suggest that it is useful to take into account the "pocket angle", a measure of the available space, rather than the bite angle.[110] Thus, the *tert*-butyl derivatives, having a parallel pocket angle of 128°, give high rates and selectivities for methyl propanoate (99.9%, 12 000 mol·mol^{-1}·h^{-1}), while the ligands carrying the smaller substituents, with pocket angles ≈ 150°, give mainly oligomers at low rates (25%, 200 mol·(mol^{-1} of Pd)$^{-1}$·h^{-1}).

E. Hydroxycarbonylation of Styrene

Hydroxycarbonylation or alkoxycarbonylation of styrene is a potential route to the 2-phenyl or 3-phenyl derivatives of propanoic acid or its esters. Especially the chiral variants of 2-phenylpropanoic esters are of interest since these products are used as antiinflammatory drugs. As yet the enantioselectivities reported are unsatisfactory. Monodentate phosphines give usually the branched product (2-phenylpropanoate) in excess, whereas bidentates give mainly the linear product (3-phenylpropanoate). Monodentates give catalysts that are much faster than bidentate phosphines. Several catalyst systems have been developed. Alper has reported a system consisting of palladium(II) acetate, oxalic acid, CO, and chelating phosphorus ligands.[111] The favorable effect of dppb in this reaction has been known for a long time.[112] Recently a study has been devoted to the bite angle effect on the reaction using the catalyst system developed by Alper.[113] The results are shown in Table 11. The rates of the reaction and the selectivity for the linear product increase with increasing bite angle. The efficacy of xantphos-type ligands was also observed for a water-soluble derivative of this ligand.[114] The mechanism involves an insertion of styrene into a palladium hydride bond. The higher linearity for wide bite angles is explained by the increasing steric hindrance of the ligand with increasing bite angle (see Figure 5).



30, sulfoxantphos

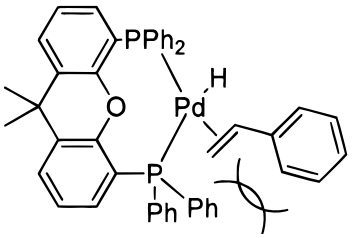


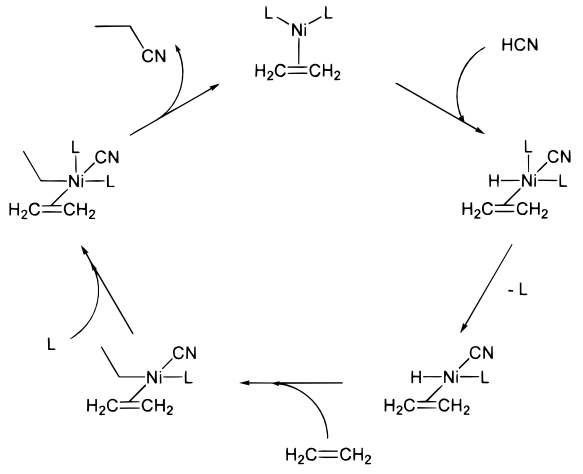
Figure 5. Increased steric hindrance of the ligands with larger bite angles between the styrene substrate and the ligand.

F. Hydrocyanation of Alkenes

The addition of HCN to alkenes is a very useful reaction for the functionalization of organic substrates. Industrially it has a tremendous impact mainly because of the adiponitrile production by Du Pont via hydrocyanation of butadiene using aryl phosphite-modified nickel catalysts.[115] The catalyst consists of a Ni(0) complex stabilized by tris-*o*-tolyl phosphite in the presence of a Lewis acid.[116] The ligand tris-*o*-tolyl phosphite gave the best catalyst performance because of the favorable combination of a large cone angle of 141° and the electronic properties.[117] Recently, bidentate phosphites have been reported to be very effective in the hydrocyanation reaction.[118,119] Bidentate phosphinites based on sugar backbones proved very effective in asymmetric hydrocyanation of vinylarenes; enantiomeric excesses of up to 95% were obtained.[120]

A mechanism for the hydrocyanation according to McKinney[121] is shown in Scheme 6. An oxidative

Scheme 6. Mechanism for the Hydrocyanation of Alkenes according to McKinney[121]

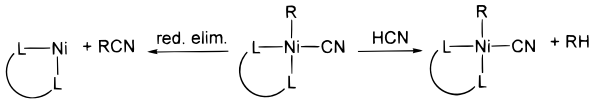


addition of HCN to a three coordinate Ni(0) species takes places, accompanied by ligand dissociation resulting in a square-planer Ni(II) π-olefine complex. The σ-alkyl complex is formed via insertion of the olefin into the metal hydride, assisted by alkene coordination. Subsequent reductive elimination of RCN by an associative process yields the alkyl nitrile and the tetrahedral Ni(0) species.

Whereas phosphites have proven to be versatile ligands in the hydrocyanation reaction, phosphine

ligands, however, lead to catalysts with hardly any activity.[122−125] The explanation is straightforward; the mechanism involves a rate-determining reductive elimination of the alkyl cyanide, which results in the formation of a tetrahedral Ni(0) out of a square-planar Ni(II) compound.[120,121,126,127] This reaction is facilitated by electron-withdrawing ligands such as phosphites, whereas this reaction becomes more difficult when donating ligands such as phosphines are used.[128] Therefore, the reaction proceeds faster when more electron-withdrawing phosphites or phosphinites are employed (Scheme 6). Second, a derailment of the catalytic reaction occurs via a side reaction with HCN, leading to a completely inactive $L_nNi(CN)_2$ species (see Scheme 7). To suppress this

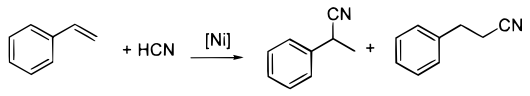
Scheme 7. Reductive Elimination Leading to the Product and the Competitive Side Reaction with HCN



side reaction, the concentration of HCN is kept low in the catalytic process and large excesses of ligand are necessary, even when phosphites or phosphinites are used.[129] Phosphine ligands favoring bite angles of ca. 110°, like the xantphos-type compounds **11**, can destabilize the square-planar Ni(II) species and stabilize the tetrahedral Ni(0) complexes, thus enhancing the reductive elimination and the overall catalysis. Recently Moloy showed that reductive elimination of nitriles from nickel diphosphine complexes was indeed strongly enhanced by ligands that induce large bite angles.[130]

The hydrocyanation of styrene using nickel catalysts containing ligands enforcing large bite angles as catalyst components resulted in remarkable yields and selectivity, especially when compared to common diphosphines (Scheme 8, Table 12).[131] The use of **11a**,

Scheme 8. Hydrocyanation of Styrene



a ligand with a bite angle of 101°, induced a yield (based on HCN) of 35−41%, which is modest but still

Table 12. Nickel-Catalyzed Hydrocyanation of Styrene, Using Diphosphine Ligands[a]

ligand	β_n[b] (deg)	yield[c] (%)	branched (%)
11a	101	35−41	88−91
11d	105	94−95	97−98
11e	106	69−92	96−98
11f	109	27−75	96−99
11k	138	0.7	83
PPh_3		0	
dppe	79	<1	ca. 40
dppp	87	4−11	ca. 90
dppb	99	3−8	92−95
BINAP	85	4	29

[a] Reaction conditions: styrene:Ni = 28.5; HCN:Ni = 17.5; [Ni] = 73.3 mM; T = 60 °C; t = 18 h. [b] Natural bite angles for nickel complexes are taken from ref 131. [b] Yields are based on HCN. Maximum yields based on styrene are 61%.

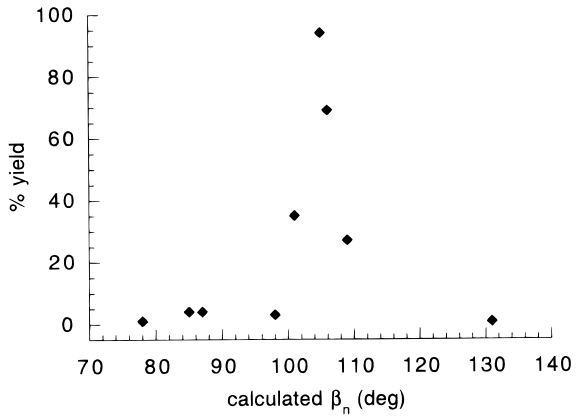
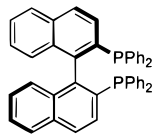


Figure 6. Observed yield versus calculated natural bite angle (β_n) in the nickel-catalyzed hydrocyanation of styrene.

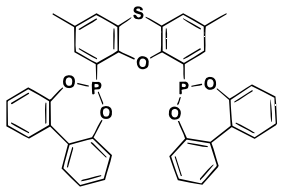
a significant enhancement when compared to PPh_3 or $Ph_2P(CH_2)_nPPh_2$ (n = 2−4). When the bite angle is increased further to 105−106°, using **11d** or **11e**, the yields increased to 95% (see Figure 6). When **11f**, with a calculated bite angle of 109°, was applied, the yield was slightly lower, 75%. Application of **11k**, with β_n = 138°, resulted in virtually no yield. For comparison several well-known common diphosphines were tested as catalyst components under identical conditions. Yields of nitriles were 0−11% (based on HCN), and the formation of large amounts nickel dicyanides was reported.



31, Binap

These results indicate clearly that effective nickel−phosphine-catalyzed hydrocyanation can be achieved when bidentate ligands enhance the reductive elimination step by stabilizing a tetrahedral geometry. Diphosphine ligands with calculated natural bite angles near 106° allow very high conversion and selectivity in the hydrocyanation of styrene. The optimal natural bite angle is 105−106°, while either a slight increase to 109° or decrease to 101° already results in a significant drop in activity (see Figure 6).

The xantphos ligands were also successfully applied in the hydrocyanation of 1-alkenes and ω-unsaturated fatty acid esters.[132] The performance of these xantphos ligands was further improved by changing the electronic properties of the ligands.[133] Electron-donating and -withdrawing substituents were introduced at the para position of the phenyl rings of thixantphos (**11e**). As expected, catalyst activity increased with the electron-withdrawing capacity of the substituents, indicating that reductive elimination probably is still rate-limiting under these conditions. Very high selectivity but unexpectedly low activity was obtained using bisphosphinite **32**, which was caused by the formation of a remarkably stable but inactive nickel bis-chelate complex.[133]



32

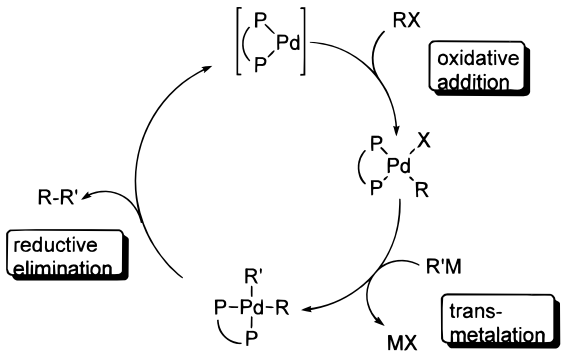
G. Nickel- and Palladium-Catalyzed Cross-Coupling Reactions

Transition metal-catalyzed carbon−carbon bond formation is an important tool for organic chemists and a challenging area of research in homogeneous catalysis. The scope of the reaction is virtually unlimited. The organic electrophiles can be both aryl and vinyl halides or triflates, but also acyl and benzylic halides can be used. These compounds react with a broad range of organic nucleophiles, which are often organometallic compounds.[134] The organic part can again be aliphatic, vinylic, or aromatic, and many metals will provide reactive nucleophiles; most often used are boranes,[135] stannanes,[136] organozinc,[137] and Grignard reagents,[138,139] the latter being one of the first examples in cross-coupling chemistry.

The development of efficient catalysts for this reaction has expanded the scope of this reaction enormously.[138,139] Nickel and palladium catalysts with tailored phosphine ligands have been applied successfully; the influence of the (di)phosphine used is very large, but not yet fully understood. The ligand exerts influence on the metal center and thereby on the course of the catalytic reaction in three ways. The ligand can change the steric bulk around the metal center, the electronic properties of the metal, and enforce the bite angle preferred by the ligand (for diphosphines).[36,37]

The generally accepted mechanism of the catalytic cycle consists of three consecutive elementary steps: oxidative addition, transmetalation, and reductive elimination (Scheme 9). These three reactions will

Scheme 9. Generally Accepted Mechanism of the Cross-Coupling Reaction

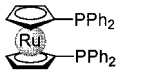


be influenced by ligand modification in a different way, and therefore ligand effects in catalysis are not always straightforward. In recent years, however, a lot of knowledge has been acquired on the individual reaction steps. Although the knowledge obtained from the isolated stoichiometric reactions cannot always be extrapolated to the catalytic system,[140] it has led to more rational catalyst design.

The mechanism of the oxidative addition of aryl iodides to zerovalent palladium was investigated by Fauvarque et al.[141] On the basis of kinetics and on a linear Hammett relationship ($\rho = 2$), they concluded that the mechanism could be best described as an aromatic nucleophilic substitution by the reactive bis-ligated PdL_2. Furthermore, the reaction was assisted by halide coordination. The rate enhancement of electron-withdrawing substituents on oxidative addition of aryl triflates was also found by Jutand and Moshleh.[142] Portnoy and Milstein performed a systematic study of the oxidative addition of aryl chlorides to bidentate phosphine palladium(0) complexes.[143] They also found that the mechanism was an aromatic nucleophilic substitution preceded by ligand dissociation from $Pd(P-P)_2$.[143b] As expected, electron-withdrawing substituents on the aryl chloride and more basic phosphine gave a faster oxidative addition. Furthermore, they studied the effect of the ligand bite angle on the reaction rate by varying the bridge length of the chelating ligand.[143a] Comparison of the rates of oxidative addition was complicated by the formation of different equilibria between mono- and bis-chelated complexes as well as η^1 and η^2 coordination of the ligand depending on the bridge length. Oxidative addition of chlorobenzene to the Pd(0) complex of 1,2-bis(diisopropylphosphino)ethane (dippe) was very slow as a result of the formation of a very stable saturated bis-chelate complex $Pd(dippe)_2$. The oxidative addition to the Pd complexes of 1,3-bis(diisopropylphosphino)propane (dippp) and 1,4-bis(diisopropylphosphino)butane (dippb) showed similar rates, but the distribution between chelating cis and η^1 coordinating trans product differed significantly. These results showed that oxidative addition to the 14e Pd(P−P) complex was faster for dippp than for dippb[143a] as was already predicted by theoretical studies.[144,145] Amatore et al. found the opposite in a comparative study of DIOP, dppf, and binap; binap having the smallest bite angle gave the slowest oxidative addition.[146] This study, however, was complicated by the presence of dba from $Pd(dba)_2$ precursor. Amatore has shown that for monodentate phosphines the presence of labile ligands such as dba,[147] halide ligands,[148] and acetate[149] can change the kinetics of the reaction by coordination to the low-valent palladium intermediates.

Since reductive elimination is in fact the reverse reaction of oxidative addition, ligand effects will often be opposite for this reaction. One of the first indications that reductive elimination is enhanced by ligands that support larger bite angles was the observation by Yamamoto et al. that ethane formation from $NiMe_2(P-P)_2$ was much faster when dppp was used as the ligand instead of dppe.[150] Gillie and Stille showed that ligands with very large bite angles tend to form trans complexes that were reluctant to undergo reductive elimination.[151] Addition of excess alkyl halide provides an alternative pathway via oxidative addition, resulting in a six-coordinate Pd^{IV} complex. This complex did give reductive elimination. For monodentate ligands they suggested a concerted

elimination mechanism from a Pd^{II} complex, preceded by ligand dissociation.[151] Reductive elimination via such a three-coordinate intermediate was also observed by Driver and Hartwig for C−N bond formation, although they found that at higher ligand concentrations reductive elimination via a four-coordinate complex took place.[152,153] Extended Hückel calculations by Calhorda and Brown indicated that if one of the substituents of a $PdR_2(P-P)_2$ complex is sp^2 hybridized, migration prior to dissociation is a likely pathway.[154] This reaction was calculated to be faster when the P−M−P bite angle was allowed to increase. These calculations were experimentally confirmed by Brown and Guiry, who studied the relative rates of reductive elimination from palladium diphosphine complexes.[155]



33, dpp-ruthenocene

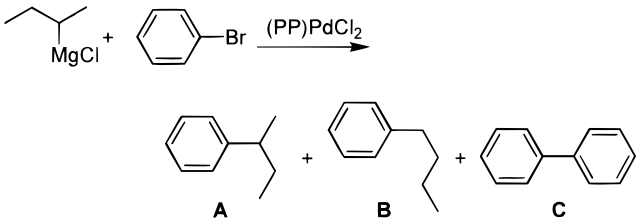
By comparing the elimination rates using dppp, dppf, and dpp−ruthenocene,they showed that the reaction became faster with increasing bite angle. As already mentioned before, this effect was also observed by Marcone and Moloy in the reductive elimination of nitriles from (diphosphine)Pd[R](CN) complexes.[130] DIOP as ligand, having a natural bite angle of 98°, induced a 104-fold faster reductive elimination than dppe having a bite angle of 85°. Furthermore, the same effect is observed in the reductive elimination resulting in carbon-heteroatom formation. For example Hartwig et al. found that carbon−sulfur bond formation via reductive elimination increased dramatically with increasing bite angle.[156] Buchwald et al. showed that the reductive elimination from Pd^{II}-(aryl)(alkyloxy) complexes was initiated by migration of the alkoxide to the aryl.[157,158]

Little is known about the transmetalation step using bidentate ligands. There is ample evidence that for monodentate ligands transmetalation is preceded by ligand dissociation.[159−162] Ligands having very large bite angles probably dissociate more readily and, therefore, enhance the transmetalation step. Facile ligand dissociation might also explain the reversed effect of the ligand bite angle on the amination of aryl bromides as observed by Hartwig.[163] A systematic study of ligand effects on the transmetalation step has not been performed yet.

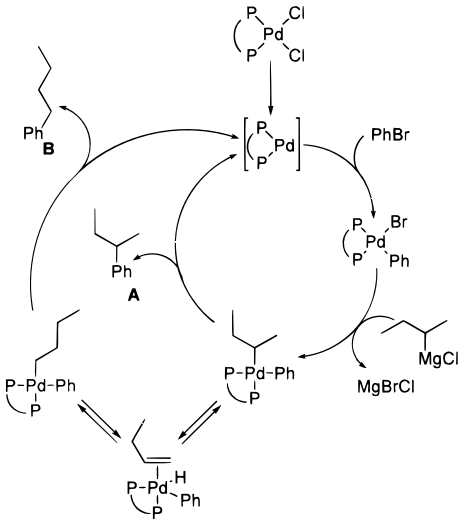
One of the first examples of metal-mediated cross-coupling of two functionalized organic molecules is the Grignard cross-coupling. Hayashi et al. found in a systematic study that dppf, a diphosphine with a large P−Pd−P bite angle of 96° in $(dppf)PdCl_2$, induced the highest activity and selectivity of a range of diphosphine ligands (dppe, dppp, dppb, and dppf). Furthermore, comparison of different diphosphines revealed an increase of selectivity with an increasing bite angle.[164,165]

Van Leeuwen et al. performed a study on the effect of the bite angle of chelating diphosphines on the activity and selectivity in the palladium-catalyzed cross-coupling reactions.[166] The large bite angles induced by these ligands allowed an investigation of

Scheme 10. Cross-Coupling between Bromobenzene and *sec*-Butylmagnesium Chloride, Leading to the Branched Product (A) the Linear Product (B) and the Homo-Coupled Product (C)



Scheme 11. Mechanism of the Cross-Coupling Reaction Using Palladium Diphosphine Complexes



bite angles larger than 100°, a range which was not explored by Hayashi. Since the steric and electronic properties of these ligand atoms are the same, all effects on selectivity or activity can be attributed to the bite angle.

The isolated palladium complexes were utilized as catalysts in the coupling of *sec*-butylmagnesium chloride with bromobenzene (see Schemes 10 and 11). When applying $(dppf)PdCl_2$ as a catalyst in this model reaction, Hayashi and co-workers found A in a yield of 95%.

The effects of the bite angle on catalyst activity and selectivity are summarized in Table 13.

The catalyst containing DPEphos, $\beta_n = 102.7°$, as ligand was more active and selective than the one with dppf. A selectivity of 98% toward the cross-coupling product A was observed (compared to 95% for dppf), with only 1% of the homocoupled C and 1% of B. The observed initial turnover frequency was more than twice as high as that observed for dppf.

Increasing the β_n of the diphosphine to even larger values resulted in a decrease of both catalyst activity and selectivity. The yield of cross-coupling product A decreased, whereas the homocoupled C and the side product B were formed in larger amounts (see Figure 7).

The faster reaction with dppf and DPEphos was explained by faster reductive elimination induced by larger P−Pd−P bite angle.[154] The optimum was found at a P−Pd−P angle of ca. 102° with DPEphos as ligand.[166]

Table 13. Cross-Coupling of 2-Butylmagnesium Chloride with Bromobenzene in Diethyl Ether[a]

ligand	β_n (deg)	TOF[b] (mol·(mol of Pd)$^{-1}$·h^{-1})	reacn time (h)	conversion[c] (%)	% A	% B	% C
dppe[d]	85[e]	nd	48	4	0	0	*f*
dppp[d]	91[e]	nd	24	67	69	31	*f*
dppb[d]	98[e]	nd	8	98	51	25	*f*
dppf	96[e]	79	2	100	95	2	3
DPEphos	103[e]	181	2	100	98	1	1
sixantphos	109[g]	36	16	58.8	67	17	16
thixantphos	110[g]	24	16	36.5	51	17	32
xantphos	111[g]	24	16	23.6	41	19	40

[a] Conditions: 0.04 mmol of catalyst; 8 mmol of 2-butylmagnesium chloride and 4 mmol of bromobenzene in 20 mL of ether; T = 20 °C. [b] Initial turnover frequency, determined after 5 min of reaction time. [c] Conversions based on bromobenzene. [d] Catalytic results from refs 164 and 165. [e] Natural bite angles are taken from ref 36b. [f] Not determined. [g] Natural bite angles are taken from ref 69.

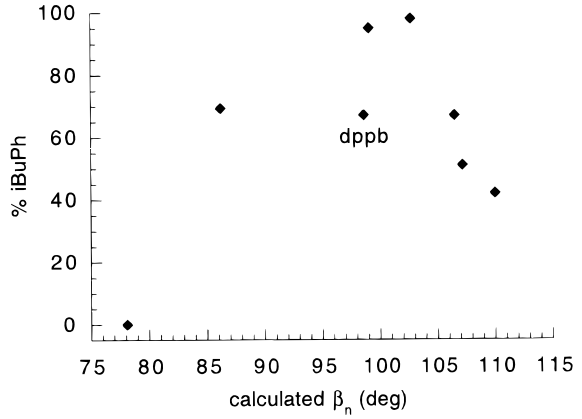


Figure 7. Observed selectivity for cross-coupling versus calculated natural bite angle (β_n).

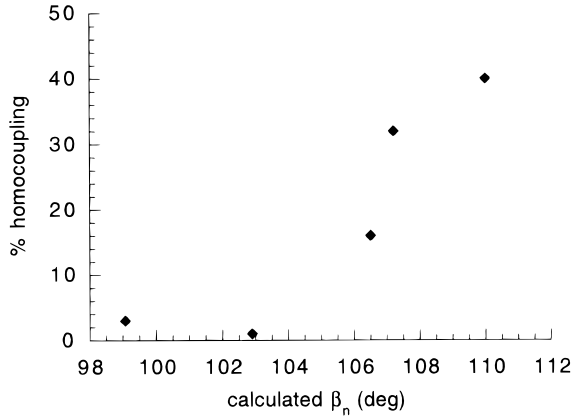
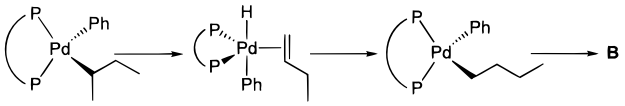


Figure 8. Observed selectivity for homocoupling versus calculated natural bite angle.

Further increase of the natural bite angle of the diphosphine applied might lead to distortion toward tetrahedral coordination. This might explain the decrease of the rate of reaction when going from DPEphos to xantphos. Furthermore, the xantphos ligand is more rigid than DPEphos and dppf, which can enhance this effect.

The formation of B was explained by the increased tendency to form trigonal-bipyramidal intermediates with an increasing bite angle and consequently an increased rate of β-hydride elimination as compared to the reductive elimination from the (diphosphine)-Pd(Ph)(2-Bu) species (Scheme 12). Reinsertion of the

Scheme 12. Isomerization of 2-Butyl to 1-Butyl

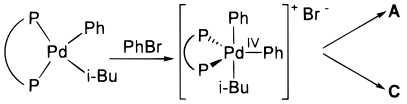


alkene into the Pd−H bond will preferentially lead to the formation of 1-alkyl palladium species

The large amount of homocoupled product C formed when diphosphines with large bite angles (see Figure 8) are employed could be explained by the reductive elimination mechanism of Gillie and Stille.[151]

At very large bite angles the intermediate Pd(II) complex can undergo oxidative addition of a second molecule of bromobenzene forming a five-coordinate Pd(IV) species [(diphosphine)Pd(Ph)$_2$(Bu)]Br, similar to the intermediate proposed by Gille and Stille.[151] The trigonal-bipyramidal complex formed by this reaction is stabilized by ligands with bite angles near 110°, such as sixantphos, thixantphos and xantphos. Subsequent reductive elimination from this Pd(IV) species results in the formation of either C, the homocoupled product, or A, the cross-coupled product (see Scheme 13).[166]

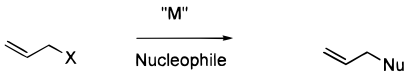
Scheme 13. Cross-Coupling Mechanism via a Five-Coordinate Pd(IV) Species Applying Ligands with Very Large Bite Angles



The alternative mechanism of transmetalation between isobutylmagnesium chloride and bromobenzene, however, could not be excluded.[166]

Miyaura et al. found that the yield of a nickel-catalyzed Suzuki coupling between phenylboronic acid and 3-chlorotoluene increased when ligands inducing larger bite angles were used.[167] The yield increased going from dppe to dppp, and by far the best yields were obtained using dppf as ligand. The only exception in the trend was dppb, which gave poor results; again the formation of bimetallic species[27] can explain this exceptional behavior of dppb. The higher catalytic activity induced by ligands having large bite angles was remarkable because the oxidative addition was rate-limiting. The effect was probably caused by enhanced stabilization of the labile Ni(0) complex formed in the reductive elimination step. The actual effect was therefore not an

Scheme 14. Allylic Alkylation Reaction



actual rate increase of the catalyst but an increased catalyst concentration by preventing decomposition.

H. Allylic Alkylation

The allylic alkylation (Scheme 14) reaction is a classical example of an organometallic reaction that has evolved to a very useful catalytic reaction for synthetic organic chemists.[168] After the initial discovery of the stoichiometric allylic alkylation by Tsuji in 1965,[169] followed by the catalytic variant in the early 1970s[170] extensive research by Trost and others resulted in a detailed insight into the mechanism of the reaction.[171] There is a distinct difference in mechanism using hard nucleophiles (Grignards and alkylzinc reagents) and soft nucleophiles. Hard nucleophiles attack the metal center, whereas the soft ones directly attack the metal bound allyl moiety. Here we only will discuss the alkylation using soft nucleophiles, since in this case the bite angle of the ligand indeed can play a role.

Mechanistic studies of the reaction have been reported but most of the research has focused on the enantioselective alkylation, since this leads to useful applications in organic synthesis.[168] Early reports of moderate asymmetric induction came from the groups of Trost[172] and Bosnich.[173] This induction was achieved under thermodynamical control since a rapid equilibrium between the two diastereomeric π-allyl complexes was involved. In a subsequent paper by Trost[174] an alternative approach was presented in which the selectivity was kinetically controlled. The nucleophile was steered to attack at only one of the two ends of the allyl by creating a chiral pocket around the metal center. The systematic study of this "pocket effect" was based, in fact, on a variation of the "bite angle", although the latter term was not explicitly mentioned. The rationale behind this chiral pocket effect stems from the attack of the nucleophile on the allyl, which is at the opposite site of the metal and its chiral ligands. CPK models showed that a larger bridge of the bidentate ligand would result in a more effective embracing of the allyl group (Figure 9).

Indeed the asymmetric induction increases significantly using the chiral bidentate ligands with larger rings. The same concept, enlarging the bite angle to create a chiral pocket, was used to explain the asymmetric induction of a series of chiral bidentate ligands based on 2-(diphenylphosphino)benzoic acid.[175]

Different diamino scaffolds were used, and it was observed that an increased N−C−C−N dihedral and thus a wider bite angle (see Figure 10) resulted in higher ee's in the allylic alkylation. In a subsequent paper the crystal structure of a palladium allyl complex of such a ligand was reported in which the bite angle was 110.5°.[176] Hayashi et al.[177] used ferrocenylbis(phosphines) and ruthenocenylbis(phosphines) to fine-tune the bite angle (see Figure 11). The X-ray structures of (P−P)$PdCl_2$ complexes of these ligands showed that the bite angles are 98.8 and 100.5°, respectively. Although this seems to be only a small difference, the embracing effect is quite clear; the phenyl groups of the phosphines are 0.2 Å closer to the chlorides. By using chiral analogues of these bidentate ligands in the asymmetric silylations of allylic chlorides, they showed that the wider bite angle indeed gave higher enantioselectivities (10% versus 42% ee).

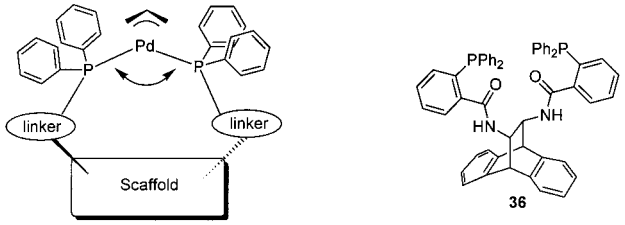


Figure 10. Optimization of the embracing effect of the ligand by changing the scaffold, which results in high enantioselectivity in the allylic alkylation reaction.

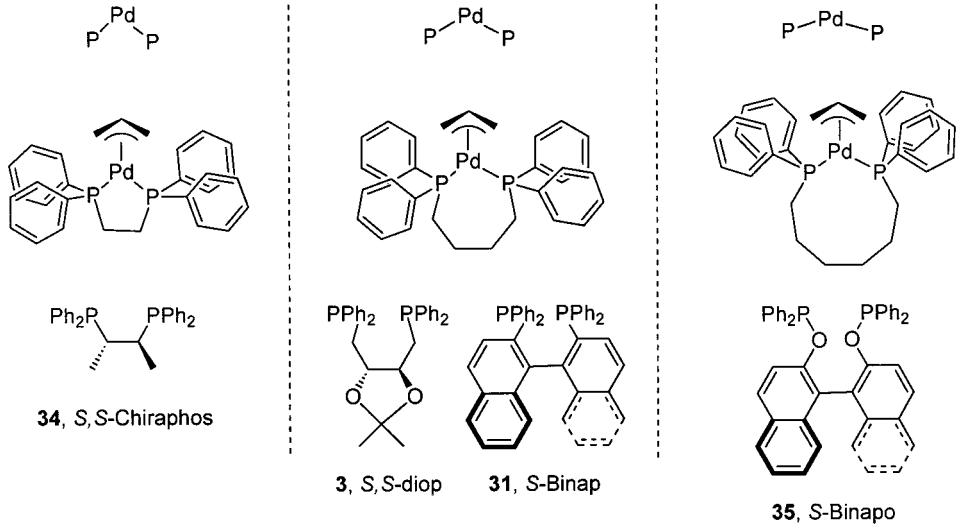


Figure 9. Optimization of the enantioselectivity of the allylic alkylation by changing the bite angle of bidentate phosphine ligands.

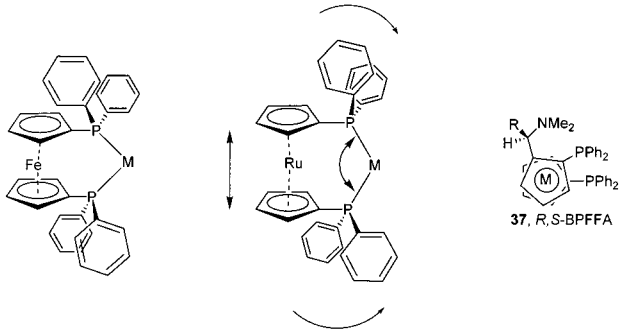
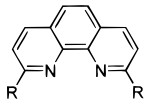


Figure 11. Effect of fine-tuning the bite angle by changing from a ferrocenylbis(phosphine) to a ruthenocenylbis-(phosphine) and a drawing of the chiral analogue **37**.

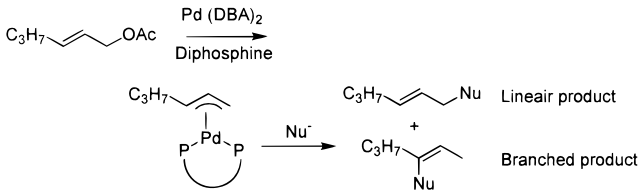
Åkermark showed that the embracing effect of ligands can result in a change of product distribution.[178] Using different 2,9-substituted 1,10-phenanthroline ligands (**38**), the palladium-catalyzed allylic



38a, R = H
b, R = Me

alkylation of terminally substituted allyl acetates was

Scheme 15. Allylic Alkylation of 2-Hexenyl Acetate Yielding the Branched and Linear (E) Product



studied. By fine-tuning the embracing effect, the regioselectivity of the nucleophilic attack was steered. Also, the reaction rate was shown to be strongly dependent on a subtle balance of steric inteactions. They ascribed the increase in reaction rate, observed when using dimethylphenanthroline as the ligand compared to phenanthroline, to steric destabilization of the starting square-planar complex relative to the Pd(0) trigonal intermediate. On further increasing the steric bulk, both the rate and the regioselectivity of the reaction dropped.

The aforementioned results indicate that the bite angle has an effect on the regioselectivity in the allylic alkylation. In a systematic study van Leeuwen et al. investigated the effect of the bite angle on catalyst activity and selectivity in this reaction.[179] In this study diphosphine ligands were studied with bite angles ranging from 85 to 111°: dppe, dppp, dppb, dppf, DPEphos, sixantphos, and xantphos. The substrate and nucleophile used were similar to those of Åkermark et al., i.e., 2-hexenyl acetate and sodium diethyl methylmalonate, respectively. In all the experiments described, only two products were observed: the linear product diethyl 2-(2-hexen-1-yl)-2-methylmalonate and the branched product diethyl 2-(1-hexen-2-yl)-2-methylmalonate (Scheme 15). The selectivity toward the linear product increased using

Table 14. Alkylation of 2-Hexenylacetate with Sodium Diethyl Methylmalonate in DMF[a]

ligand	β_n (deg)	TOF[b] (mol·(mol Pd^{-1}·hr)[b]	reacn time (h)	conversion[c] (%)	linear (%)	branched (%)
dppe	85[d]	82	5	98.5	96.2	3.8
dppp	91[d]	111	5	97.9	96.6	3.4
dppb	98[d]	393	1	98.0	97.7	2.3
dppf	96[d]	118	5	97.6	99.0	1.0
11a	103[d]	114	5	98.4	99.7	0.3
11d	109[e]	91	20	97.5	99.6	0.4
11f	111[e]	22	20	92.1	100.0	0.0

[a] Conditions: 0.01 mmol of $Pd(dba)_2$; 0.02 mmol of ligand; 1.0 mmol of 2-hexenylacetate; 2.0 mmol of sodium diethyl methylmalonate in 3.0 mL of 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 2-hexenyl acetate. [d] Natural bite angles are taken from ref 36b. [e] Natural bite angles are taken from ref 69.

ligands with wider bite angles (see Table 14). Using dppe, a ligand with a small bite angle (85°), 96.2% of the linear product was obtained, whereas the xantphos-type ligands with bite angles larger than 100° resulted in selectivities of 99% or higher. It is noteworthy that when xantphos (**11f**) is employed, a selectivity of 100% can be achieved, which means that the usage of this ligand can prevent laborious purification of the desired product.

Modeling studies clearly confirmed the embracing effect of the ligands with the wider bite angles (Figure 12).[180] These calculations, performed at the PM(tm) level, on the cationic (1-methylallyl)(bisphosphane)palladium complexes also showed that the syn isomer is lower in energy than the anti isomer. The energy differences between these complexes tend to be smaller with increasing bite angle; NMR studies (^1H and ^{31}P) on the isolated complexes revealed a strong correlation between the bite angle and the syn/anti ratio in agreement with these calculations. Stoichiometric alkylation of these complexes with sodium diethyl 2-methylmalonate indicated that this ratio determined the regioselective outcome of the reaction. The syn isomer, dominating in complexes with a small bite angle, results in mainly the linear (E) product, whereas the anti isomer gives more of the branched product. For the catalytic reactions using these complexes the correlation was not as good, due to competitive syn/anti isomerization reaction. These results can be rationalized using a late-transition-state model; i.e., the steric hindrance indirectly induced by the change of hybridization at the C3-position from sp^2 to sp^3. When the preformed complexes were used in the catalytic experiments, the bidentate phosphine ligand with the largest bite angle gave both the highest reaction rate and the highest selectivity toward the linear (E) product. This effect was previously observed by Åkermark for dinitrogen ligands.[178]

Bäckvall[181] and others[182−184] investigated the nucleophilic attack at the central atom of the allyl (Scheme 16). Bidentate σ-donor ligands were found to favor attack at the central position, whereas π-acceptor ligands favor attack at the terminal carbon atom of the allyl. A bite angle effect in steering

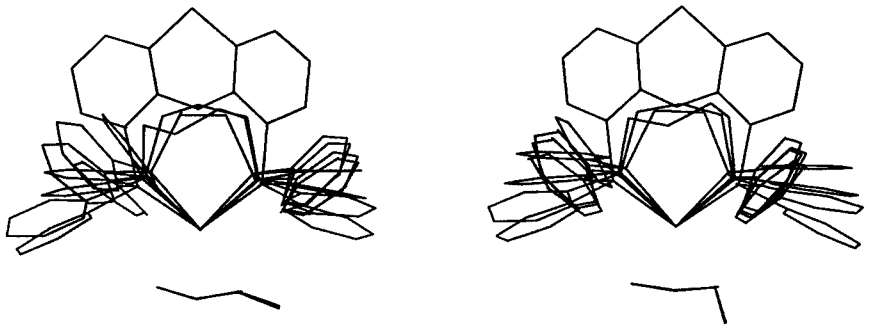


Figure 12. Methyl allyl palladium (ligand) structures (syn and anti) calculated for the bidentate ligands of Table 14, clearly showing the embracing effect of the phenyl groups of the ligands with the wider bite angles. (Reproduced with permission from ref 180. Copyright 1999 Wiley-VCH.)

Scheme 16. Allylic Alkylation of 2-Chloroallyl with the Nucleophilic Attack Either at the Central Carbon or at the Terminal Carbon Atom

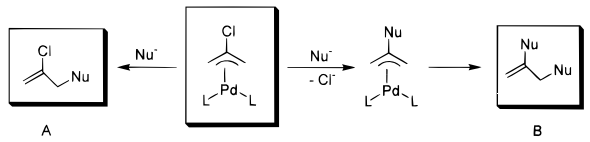


Table 15. Bite Angle Effect on the Selectivity of Nucleophilic Attack at the Terminal Carbon Atom (A) versus the Central Carbon Atom (B) of the Allyl

ligand	bite angle[a]	product ratio A:B
dppe	85	75:25
dppb	98	90:10
dppf	96	99:1

[a] Natural bite angles are taken from ref 36b.

the selectivity was not mentioned, but their results show that diphosphine ligands with wider bite angles suppress attack at the central atom (Table 15). A qualitative explanation based on calculations at the MP level was given by Szabo[185] using an orbital interaction diagram (Figure 13). In the region be-

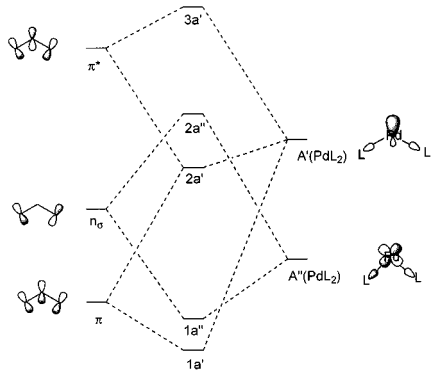
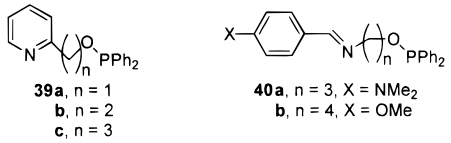


Figure 13. Orbital interaction diagram of allyl(Pd)L_2 (see ref 185).

tween 80° < bite angle < 100° 2a′ is stabilized compared to 2a″, [186] favoring attack at the central position.

From the same study it was concluded that the electronic ligand effect can be large as well. Coordination of π-acceptors results in activation of the allyl moiety. This shows that there is a preferred position of attack when nonsymmetric ligands are used. In the case of P−N ligands, for example, the attack will always take place trans to the phosphorus ligand, since this is the most activated position. Ward[187] also concluded from a theoretical study that soft nucleophiles will attack at the trans-P position. In a set of papers, Togni et al. went a step further[188] and used chiral ferrocene-based P,N ligands for the enantioselective allylic amination. Using these ligands they combined the trans effect with steric effects to steer the nucleophile toward one side of the allyl, yielding the correct isomer. Prétôt and Pfalz obtained high enantioselectivities in the palladium-catalyzed allylic alkylation using phosphite−oxazoline ligands.[189]

A recent paper describes a bite angle effect using PN ligands.[190] Two series of ligands have been prepared, a pyridine/phosphinite (**39**) and an imine/phosphinite (**40**) series with the two ligands connected via a variable alkyl spacer. From stoichiomet-



39a, n = 1
b, n = 2
c, n = 3

40a, n = 3, X = NMe_2
b, n = 4, X = OMe

ric alkylation reactions they found experimental proof for the nucleophilic attack of the malonate taking place solely at the carbon atom trans to the phosphorus. In catalytic experiments these PN ligands resulted in formation of more branched product compared to the previously reported PP ligands (Table 16). The ligands with the longer alkyl bridges between the ligands, and thus the larger bite angles, resulted in an enhanced branched product formation. This bite angle trend observed for these PN ligands indeed is opposite to that found for the PP ligands.

The allylic alkylation reactions mentioned so far were all performed with palladium complexes as the catalyst. In an early report of Cuvigny and Julia[191] this reaction was studied using nickel catalysts. In

Table 16. Catalytic Alkylation of Crotyl Chloride Using PN Ligands[190]

complex	TOF[a] mol·(mol of catalyst)$^{-1}$·h^{-1}	branched (%)	trans (%)	cis (%)
39a	1000	33.3	58.6	8.1
39b	200	41.7	49.6	8.7
39c	1000	55.1	37.8	7.1
40a	900	52.3	39.0	8.7
40b	300	50	41	9

[a] Measured after 5 min.

Table 17. Alkylation of 2-Methyl-2-butenylacetate with Sodium Diethyl Methylmalonate Using $NiCl_2$ in THF

ligand	β_n[a] (deg)	T (°C)	reacn time (h)	yield (%)	linear (%)	branched (%)
dppe	85	65	24	74	62	38
dppp	91	65	24	76	60	40
dppb	98	45	36	87	44	56
dpp−hexane		65	36	55	29	71

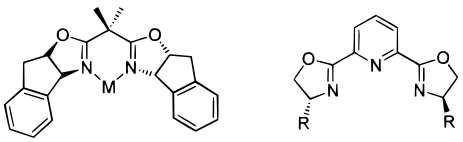
[a] Natural bite angles are taken from ref 36b.

a systematic variation also the bite angle was altered, although this parameter was not explicitly mentioned. In the series dppe, dppp, dppb, dpp−hexane the selectivity toward the branched product increases from 38 to 71% (Table 17). These data show an opposite bite angle trend from that found for the palladium. This suggests a difference in mechanism or transition state compared to the palladium systems.

I. Diels–Alder Reaction

The Diels−Alder reaction has become a standard method for the preparation of six-membered rings.[192] This is mainly due to the development of different types of catalysts, which allows relatively mild reaction conditions and enable enantioselective reactions. Many papers are focused on stereo- and enantioselective Diels−Alder reactions using chiral aluminum catalysts, titanium complexes, boron compounds, lanthanide complexes, and transition metal complexes (Fe, Ru, Cu, V, W, Ni).[193] Evans performed a detailed study using different bis(oxazoline) and bis(oxazolinyl)pyridine ligands in combination with copper and other metals, as Fe, Mg, and Zn, as chiral catalysts for the Diels−Alder reaction.[194]

Davies et al. studied the influence of the bite angle on the enantioselectivity of the copper(II)-catalyzed Diels−Alder reaction also using these type of ligands.[195] For this reason a series of spirobis(oxazolines) has been synthesized (**43**). The number of atoms in the second ring varied from 3 to 6 and determined the bite angle of the complex.



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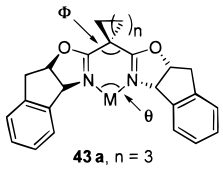
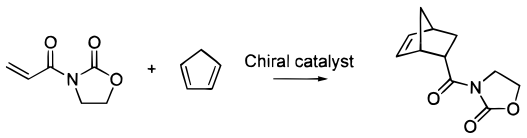


43 a, n = 3
b, n = 4
c, n = 5
d, n = 6

They observed a very clear trend in the enantioselective outcome of the copper catalyzed Diels−Alder reaction (Scheme 17). Ligands with a wider bite angle, resulted in higher ee's. It is likely that a "chiral-pocket effect", similar to that found by Trost in the allylic alkylation, is responsible for the observed bite angle effect. In a subsequent paper Davies and Deeth[196] performed a computational study using cellular ligand field stabilization energy/molecular mechanics confirming the role of the bite angle. These calculations substantiated the previous results, but the bite angle effect was shown to be more complicated than originally suggested. Within a series of structural similar ligands, the correlation between the bite angle and the enantioselective outcome was confirmed.

Scheme 17. Diels−Alder Reaction between Acrylimide and Cyclopentadiene



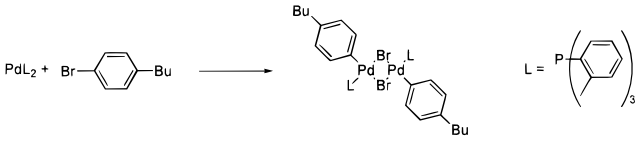
J. Amination of Aryl Halides

Aromatic and aliphatic amines such as aniline and piperidine derivatives are an important class of fine chemicals, which are presently produced via stoichiometric methods. Arylamines are commonly prepared by acidic nitration, followed by an often troublesome reduction and subsequent alkylation of the aniline. A catalytic process can increase both yield and selectivity, as well as eliminate environmentally undesirable reaction steps such as the acidic nitration. Therefore, the recent discovery by Hartwig and Buchwald of a palladium-catalyzed carbon−heteroatom bond formation can be regarded as an important breakthrough.[197] In the following years, extensive research has been devoted to the improvement of this important reaction and extension of the scope.[197] In the search for ligands giving more active catalysts for palladium-catalyzed carbon−nitrogen bond formation, improvements have been made recently using bidentate phosphine[198] and aminophosphine[199] ligands.

The first indications that a catalytic route for the formation of anilines came from the work of Kosugi et al. who showed that palladium *o*-tolylphosphine complexes catalyzed the coupling between aryl bromides and dialkyltin−amides.[200] After the discovery of this first lead it took more than 10 years before a tin-free palladium-catalyzed amination was developed simultaneously by the groups of Hartwig and Buchwald.[201,202] In situ derived catalysts from $Pd_2(dba)_3$ and *o*-tolylphosphine were capable of coupling secondary amines and aryl halides in the presence of strong bases such as sodium *tert*-butoxide or lithium hexamethyldisilazide. Primary amines, however, only showed reasonable reactivity in combination with electron deficient aryl halides.

Mechanistic studies by Hartwig et al. showed that the steric bulk of the *o*-tolylphosphine ligand was the key feature in the catalytic reaction.[161,203] They showed that the oxidative addition product of aryl halides and zerovalent $Pd[P(o\text{-tolyl})_3]_2$ was a palladium dimer containing one phosphine per palladium (Scheme 18). The kinetics of the reaction showed an inverse first order in phosphine ligand, which indicated that the addition of the bromide took

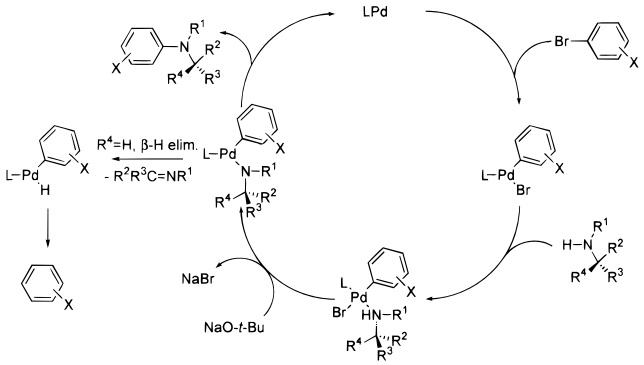
Scheme 18. Oxidative Addition of Aryl Halides to Zerovalent Pd[P(*o*-tolyl)$_3$]$_2$ Yielding a Palladium Dimer



place at monoligated palladium.[204] The formation of this intermediate palladium complex containing only one phosphine is probably enhanced by the steric bulk of tris-*o*-tolylphosphine.

The bimetallic oxidative addition product was converted to the important intermediate palladium amido complex by reaction with an amine and subsequent deprotonation or by direct reaction with a metal amide.[162] The palladium amido complex can undergo product forming reductive elimination (Scheme 19). An important side reaction is β-hydride

Scheme 19. Proposed Mechanism of the Amination Reaction



elimination resulting in imine formation and reduced arene compound. This side reaction is held responsible for the observed low yields for primary amines as substrates using palladium tris-*o*-tolylphosphine as catalyst.

The palladium/*o*-tolylphosphine catalyst developed by Buchwald and Hartwig provided an elegant method for mild and clean production of a wide range of amines, but the system still had several drawbacks. The formation of bisamine complexes[205,206] and the already mentioned β-hydride elimination remained problematic, especially using primary and to a lesser extent acyclic secondary amines.

A tremendous step forward was made simultaneously by the groups of Buchwald[205] and Hartwig[207] by introducing a new generation of palladium catalysts based on bidentate phosphine ligands. Despite the fact that oxidative addition occurs at monoligated palladium in the case of *o*-tolylphosphine,[204] dppf and binap induced higher yields and extended the scope of the catalytic amination reaction.[205,207] This finding was particularly surprising because Buchwald had already found that chelating diphosphines such as dppe, dppp, dppb were inactive in the palladium-catalyzed amination.[202,205,207] The major advantage of the used bidentate ligands was suggested to be caused by reduced β-hydride elimination as a consequence of the higher coordination number of the palladium complexes. Chelating ligands tend to suppress the rate of β-hydride elimination because the required vacant site is blocked. This effect becomes more distinct with increasing bite angle of the ligand.[104,106] Furthermore reductive elimination, the product-forming step of the catalytic reaction, is promoted by chelating ligands with larger bite angles.[130,155] In nickel-catalyzed hydrocyanation this resulted in enhanced reaction rates by ligands enforcing larger bite angles.[131] An additional advantage of the used bidentate ligands mentioned by Buchwald is that they prevent the formation of bisamido palladium complexes, which are inactive in catalysis.[205] This effect is comparable to the diminished formation of catalytically inactive nickel dicyanides reported for diphosphines inducing large bite angles.[131,133] The cooperative beneficial effects of ligands supporting large bite angles probably explain why the first successful bidentate ligands were dppf and binap, whereas small bite angle ligands such as dppe and dppp failed. Both ligands were effective in the palladium-catalyzed amination of aryl halides using primary amines, secondary amines, and anilines. Moreover the scope of feasible aryl substrates was also extended. Next to electron-neutral aryl bromides, also electon-poor, electron-rich, and sterically hindered aryl substrates, including iodides, could now be converted in good yields. The higher yields obtained for primary amines using binap as ligand was mainly due to a reduced amount of diarylated product. The functional group compatibility was further improved by using Cs_2CO_3 as base instead of Na−O−*t*-Bu.[208] By using this procedure, the reaction became tolerant to esters, enolizable ketones, and nitroaromatics.

While the range of amine nucleophiles compatible with the palladium-catalyzed amination was increased enormously, the scope of aryl substrates was still prone to improvement. Hartwig showed by in situ NMR studies that the rate-determining step of the catalytic cycle was most probably oxidative addition of the aryl bromide to L_2Pd^0, in the case in which L_2 was dppf or binap.[198a] This conclusion was supported by the findings of Reddy and Tanaka, who showed that aryl chlorides were active in the palladium-catalyzed amination when tricyclohexylphosphine was used as ligand.[209] Nishiyama et al. showed later that even higher activity could be achieved by *tert*-butylphosphine as a strong donating ligand.[210] The slow oxidative addition of aryl chlorides is accelerated by the strongly electron-donating alkylphosphine.[209,210] Since the oxidative additon was shown to take place at a monoligated LPd^0 complex, Hartwig concluded that the steric bulk of the ligand was needed to promote the required ligand dissociation.[211] The importance of ligand dissociation is supported by the work of Beller, who found that the palladacycle (**44**) was also active in the amination of

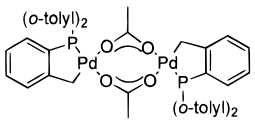


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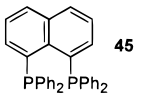
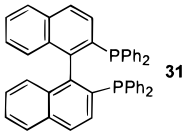
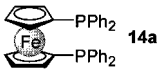
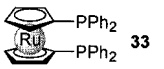
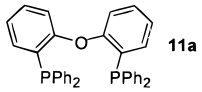
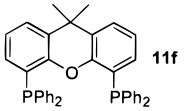
Table 18. Effect of Ligand Bite Angle on Amination of 4-Butylaniline (see Scheme 20)[163]

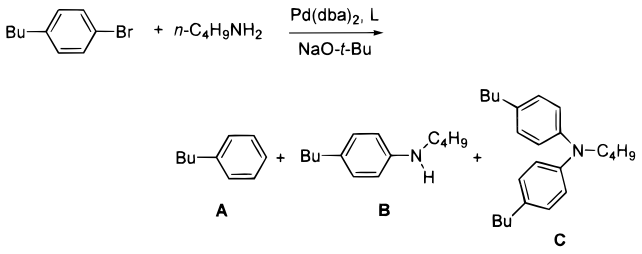
ligand	β_n (deg)	% A	% B	% C
 **45**	82[a]	1.4	78	5.7
 **31**	93[b]	0.9	91	3.0
 **14a**	99[b]	4.4	52	22
 **33**	101[a]	36	12	5.2
 **11a**	103[b]	40	11	3.6
 **11f**	111[c]	24	47	7.0

[a] Natural bite angles are taken from ref 163. [b] Natural bite angles are taken from ref 36b. [c] Natural bite angles are taken from ref 69.

aryl chlorides.[212] Although tris-*o*-tolylphosphine is not a very strong donor like alkylphosphines, the complex forms a monoligated palladium tolylphosphine palladacycle complex, which causes the high reactivity.

The first systematic study on the effect of ligand properties on the outcome of the catalytic reaction was performed by Hamann and Hartwig. They varied electronic properties, steric bulk, and the bite angle of bidentate phosphine and studied the effect on the reaction between aryl bromides and primary amines or anilines.[163] The selectivity of the reaction was determined by the amount of desired monoarylated amine relative to diarylated amine and by the amount of reduced arene product formed (Scheme 20). Surprisingly the selectivity for monoarylated

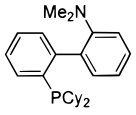
Scheme 20. Amination of 4-Butylaniline (see Table 18)[163]



compared to diarylated product was high for ligands with a small bite angle (see Table 18). This is in contrast with initial studies of Buchwald and Hartwig which showed that ligands with very small bite angles were ineffective in the catalytic amination.[205,207] Furthermore, the effect of changes in the ligand bite angle was opposite to what would be expected. Despite the fact that increasing bite angles enhance the rate of reductive elimination, the ratio of product amine:reduced arene became lower at larger bite angles. Hamann and Hartwig suggested that the rate of β-hydrogen elimination increased because of enhanced ligand dissociation at larger ligand bite angles. Additionally they showed by deuterium labeling studies that there was a second unknown pathway for the formation of reduced arene.[163] The relative amount of arene that was formed by β-hydrogen elimination, however, was higher if ligands with larger ligand bite angles were used. Therefore, they concluded that the bite angle affected the rate of β-hydrogen elimination more strongly than the rate of reductive elimination.

Although the results of Hamann and Hartwig[163] indicated that ligands inducing large bite angles gave poor yields in the palladium-catalyzed coupling of aryl bromides and primary alkylamines, Buchwald reported that DPEphos was a very effective ligand for coupling with anilines.[198b] Both electron-poor and electron-rich substrates provided high yields of coupling products. The reaction also tolerated a large degree of steric congestion of the substrates.

The xantphos ligand (**11f**)[54] induces an even larger bite angle than DPEphos. This ligand was also very effective in the coupling reaction of anilines with aryl bromides.[213] In contrast with the report of Hamann and Hartwig it was found that primary and cyclic secondary amines were active in the palladium-catalyzed amination. In an extensive study to the sequential diarylation of primary amines Buchwald found that xantphos was the superior catalyst when both the *N*-alkylaniline and aryl bromide were electron deficient.[199] For electron-rich *N*-alkylanilines ligand **46** proved to give the better catalyst.[199,214]



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Recently Buchwald reported that xantphos was the only ligand that provided efficient formation of *N*-arylhydrazones. This superior performance in the catalytic formation of arylated hydrazones was attributed to the large bite angle induced by xantphos.[215]

In conclusion, the effect of the ligand bite angle on the palladium-catalyzed amination of aryl halides is not yet fully understood. The influence of the ligand bite angle as well as steric and electronic ligand effects depend very much on the substrates involved. The coupling of primary alkylamines with aryl bromides proceeded best using electron-rich ligands with small bite angles. Several anilines gave high product yields, however, when the ligand bite angle was very large as in the case of xantphos. The existence of several known and unknown side reactions next to the desired catalytic pathway is probably the cause of this unpredictable behavior of the amination reaction.

V. Conclusions

The data summarized in this review show that the bite angle of bidentate ligands is an important

parameter that has a pronounced effect on rate and selectivity of metal-catalyzed reactions. This can be rationalized in terms of stabilization or destabilization of crucial intermediates of the reaction cycle, as was clearly shown for the hydrocyanation. Steric interactions between the ligand and the substrate depend also on the bite angle and thus can play a crucial role. This effect is clearly shown in the palladium-catalyzed allylic alkylation.

Although the bite angle can have dramatic effects on the catalyst performance, the number of systematic studies of bite angle effects is rather limited. This is likely due to a lack of ligands in which the bite angle can be varied in a systematic way without changing other steric and electronic properties. In this view the series of diphosphine ligands based on the xanthene backbone (**11**), in which this angle indeed can be varied systematically without changing properties such as steric bulk and phosphine basicity, is very valuable. Using this series, it has been shown that the bite angle gives unprecedented selectivities and reactivities in several important reactions. The development of other series of bidentate ligands in which the bite angle can be systematically varied is highly interesting and will lead to new insights in several catalytic processes.

VI. Appendix

Ligand-Preferred Bite Angles of Bidentate Ligands

ligand	no. in text	angle	source
dppm	**1a**	72 (2)[a]	X-ray
dppe	**1b**	78[b]	modeled
dppe	**1b**	85 (3)[a]	X-ray
dppp	**1c**	86[b]	modeled
dppp	**1c**	91(4.00)[a]	X-ray
dppb	**1d**	99[b]	modeled
dppb	**1d**	98 (5)[a]	X-ray
DIOP	**3**	98 (90−120)[d]	modeled
Dppen	**5**	89 (4)[a]	X-ray
dpp-benzene	**6**	83 (3)[a]	X-ray
Dppm-cyh	**7**	90[c]	modeled
Dpp-xylene	**8a**	90[c]	modeled
Dppm-cyb	**9**	98[c]	modeled
Dppm-nor	**10a**	97[c]	modeled
NORPHOS	**10b**	123 (110−145)[a]	modeled
DPEphos	**11a**	102 (86−120)[a]	modeled
Homoxantphos	**11b**	102 (92−120)[f]	modeled
Phosxantphos	**11c**	108 (96−127)[f]	modeled
Sixantphos	**11d**	109 (93−130)[f]	modeled
Thixantphos	**11e**	110 (96−130)[f]	modeled
Xantphos	**11f**	111 (97−133)[f]	modeled
Isopropxantphos	**11g**	113 (98−139)[f]	modeled
Benzylnixantphos	**11h**	114 (99−139)[f]	modeled
Nixantphos	**11i**	114 (99−139)[f]	modeled
Benzoxantphos	**11j**	121 (102−146)[f]	modeled
DBFphos	**11k**	131 (117−147)[f]	modeled
dppf	**14a**	96 (4)[g]	X-ray
BISBI	**15a**	123 (101−148)[e] 113 (92−155)	modeled
dppe-Bu	**29e**	87 (1)[a]	X-ray
dppp-Bu	**29f**	99 (1)[a]	X-ray
BINAP	**31**	92 (3)[a]	X-ray
Dpp-rhutenocene	**33**	101[g]	X-ray
DPPN	**45**	82[g]	modeled

[a] These values have been taken from ref 36b. For crystal structure data, the values given in brackets are the standard deviation. For the modeled bite angles, the flexibility range is given (the range of bite angles a ligand can accommodate within a 3 kcal mol^{-1} energy barrier). [b] These values have been taken from ref 179. [c] These values have been calculated for this article. [d] The angle for DIOP has been revised. [e] For BISBI; two conformations with almost identical energies have been found. [f] These values have been taken from ref 69. [g] These values have been taken from ref 163.

Calculation of Bite Angles

By Molecular Modeling. The bite angle calculations are based on the methods used by Casey et al.[37] The Tripos force field implemented in the Sybyl program package has been used for these calculations. A rhodium "dummy atom" has been used to direct the lone pairs of the phosphine ligands. The Dummy−P distances were fixed at 2.315 Å, and the P−Du−P bond angle has a force constant of 0 kcal mol^{-1} deg^{-1} to eliminate any contribution of the metal. Additional force parameters for the Tripos force field are given in the original reference.[54] For some ligands it is of crucial importance to perform a systematic conformer search to make sure the lowest energy conformation is used for the bite angle calculation. The flexibility range has been calculated by fixing the bite angle at given values using constrains (force constant 5000 kcal mol^{-1}).

From X-ray Data. Average P···P distances retrieved from the Cambridge Structural Database are a good starting point to gain more insight into ligand-preferred bite angles, especially for ligands with small bite angles (these are harder to calculate by molecular modeling).[36b] The bite angle is a function of the metal−phosphorous distance. The ligand-preferred bite angles given above have therefore been calculated from P···P distances using a normalized M−P distance of 2.315 Å. P···P distances are average−values obtained from crystal structures (see below) available in the Cambridge Structural Database (CSD). The angles from the crystal structure have been calculated from the P···P distance with M−P distances of 2.315 Å (=2 × ASIN($r_{P\cdots P}$/2/2.315) × 180/PI() with Microsoft Excel 97, $r_{P\cdots P}$ is the P···P distance). If the number of crystal structures is too small for statistical treatment, ligand-preferred bite angles can only be calculated by molecular modeling.

VII. References

(1) Reppe, W.; Schweckendiek, W. J. *Annalen* **1948**, *104*, 560.
(2) Slaugh, L. H.; Mullineaux, R. D. U. S. Pat. 3,239,569 and 3,-239,570, 1966 (to Shell); *Chem. Abstr.* **1964**, *64*, 15745, 19420; *J. Organomet. Chem.* **1968**, *13*, 469.
(3) Breslow, D. S.; Heck, R. F. *J. Am. Chem. Soc.* **1961**, *83*, 4023.
(4) (a) Brown, E. S. In *Aspects of Homogeneous Catalysis*; Ugo, R., Ed.; Dordrecht, Reidel: 1974; Vol. 2, pp 57−78. (b) Drinkard, W. C.; Lindsey, R. V. U. S. Pat. 3,655,723, 1970 (to Du Pont); *Chem. Abstr.* **1972**, *77*, 4986.
(5) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.
(6) Halpern, J.; James, B. R. *J. Am. Chem. Soc.* **1961**, *83*, 753.
(7) Cramer, R. D.; Jenner, E. L.; Lindsey, R. V.; Stolberg, U. G.; *J. Am. Chem. Soc.* **1963**, *85*, 1691.
(8) Sloan, M. F.; Matlack, A. S.; Breslow, D. S. *J. Am. Chem. Soc.* **1963**, *85*, 4015.
(9) Young, J. F.; Osborn, J. A.; Jardine, F. A.; Wilkinson, G. *J. Chem. Soc., Chem. Commun.* **1965**, 131.
(10) O'Connor, C.; Wilkinson, G. *Tetrahedron Lett.* **1969**, *18*, 1375.
(11) Vaska, L.; Rhodes, R. E. *J. Am. Chem. Soc.* **1965**, *87*, 4970.
(12) Evans, D.; Osborn, J. A.; Wilkinson, G. *J. Chem. Soc. A* **1968**, 3133.
(13) Pruett, R. L.; Smith, J. A. *J. Org. Chem.* **1969**, *34*, 327.
(14) Issleib, K.; Müller, D. W. *Chem. Ber.* **1959**, *92*, 3175.
(15) (a) Chatt J.; Hart W. *J. Chem. Soc.* **1960**, 1378. (b) Hieber, W.; Freyer, W. *Chem. Ber.* **1960**, *93*, 462.
(16) Heck, R. F.; Breslow, D. S. *J. Am. Chem. Soc.* **1962**, *84*, 2499.
(17) Cannel, L. G.; Slaugh, L. H.; Mullineaux, R. D. *Chem. Abstr.* **1965**, *62*, 16054; Ger. Pat. 1,186,455 (priority date 1960).
(18) United States Rubber Co. Neth. Appl. 6,507,223, 1965; *Chem. Abstr.* **1965**, *62*, 16013.
(19) Iwamoto, M.; Yuguchi, S. *J. Org. Chem.* **1966**, *31*, 4290.
(20) Coffey, R. S. *Chem. Commun.* **1967**, 923.

(21) (a) Dang, T. P.; Kagan, H. B. *Chem. Commun.* **1971**, 481. (b) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 2567.
(22) Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 3089.
(23) Thorn D. L.; Hoffmann R. *J. Am. Chem. Soc.* **1978**, *100*, 2079.
(24) Poulin, J. C.; Dang, T. P.; Kagan, H. B. *J. Organomet. Chem.* **1975**, *84*, 87.
(25) (a) Knowles, W. S.; Sabacky, M. J. *J. Chem. Soc., Chem. Commun.* **1971**, 481. (b) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D.; Weinkauff, J. *J. Am. Chem. Soc.* **1975**, *97*, 2567.
(26) Kawabata Y.; Hayashi T.; Ogata I. *J. Chem. Soc., Chem. Commun.* **1979**, 462.
(27) Sanger, A. R. *J. Chem. Soc., Dalton Trans.* **1979**, 1971.
(28) Tolman, C. A. *J. Am. Chem. Soc.* **1970**, *92*, 2953, 2956.
(29) Fernandez A.; Reyes C.; Wilson M. R.; Woska D. C.; Prock A.; Giering M. P. *Organometallics* **1997**, *16*, 342.
(30) Joerg S.; Drago R. S.; Sales J. *Organometallics* **1998**, *17*, 589.
(31) (a) Hirota M.; Sakakibara K.; Komatsuzaki T.; Akai, I. *Comput. Chem.* **1991**, *15*, 241. (b) White D.; Taverner, B. C.; Coville, N. J.; Wade, P. W. *J. Organomet. Chem.* **1995**, *495*, 41. (c) White D.; Taverner, B. C.; Leach, P. G. L.; Coville N. J. *J. Organomet. Chem.* **1994**, *478*, 205. (d) White, D.; Coville, N. J. *Adv. Organomet. Chem.* **1994**, *36*, 95.
(32) Koide, Y.; Bott, S. G.; Barron, A. R. *Organometallics* **1996**, *15*, 2213.
(33) (a) Brown, T. L. *Inorg. Chem.* **1992**, *31*, 1286. (b) Choi, M.-G.; White, D.; Brown, T. L. *Inorg. Chem.* **1993**, *32*, 5591. (c) Brown, T. L.; Lee, K. J. *Coord. Chem. Rev.* **1993**, *128*, 89.
(34) Angermund, K.; Baumann, W.; Dinjus, E.; Fornika, R.; Gorls, H.; Kessler, M.; Krüger, C.; Leitner, W.; Lutz, F. *Chem. Eur. J.* **1997**, *3*, 755.
(35) Connolly, M. L. *Science* **1983**, *221*, 709.
(36) (a) Kamer, P. C. J.; Reek, J. N. H.; van Leeuwen, P. W. N. M. *CHEMTECH* **1998**, *28* (9), 27. (b) Dierkes, P.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **1999**, 1519.
(37) Casey, C. P.; Whiteker, G. T. *Isr. J. Chem.* **1990**, *30*, 299.
(38) Parshall, G. W.; Ittel, S. D. *Homogeneous Catalysis*, 2nd ed.; Wiley: New York, 1992.
(39) Tolman, C. A. *J. Am. Chem. Soc.* **1970**, *92*, 6777, 6785.
(40) Hata, G. *J. Am. Chem. Soc.* **1964**, *86*, 3903.
(41) Hayashi, T.; Kawabata, Y.; Isoyama, T.; Ogata, I. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3438.
(42) Kawabata, Y.; Hayashi, T.; Ogata I. *J. Chem. Soc., Chem. Commun.* **1979**, 462.
(43) Hsu, C.; Orchin, M. *J. Am. Chem. Soc.* **1975**, *97*, 3553.
(44) Schwager, I.; Knifton, J. F. *J. Catal.* **1976**, *45*, 256.
(45) van Rooy, A.; De Bruijn, J. N. H.; Roobeek, C. F.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Organomet. Chem.* **1996**, *507*, 69.
(46) Petrosyan, V. S.; Permin, A. B.; Bogdashkina, V. I.; Krut'ko, D. P. *J. Organomet. Chem.* **1985**, *292*, 303.
(47) Meessen, P.; Vogt, D.; Keim, W. *J. Organomet. Chem.* **1998**, *551*, 165.
(48) van der Veen, L. A.; Keeven, P. K.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Chem. Commun* **2000**, 333.
(49) Tang, S. C.; Kim, L. *J. Mol. Catal.* **1982**, *14*, 231.
(50) (a) van Leeuwen, P. W. N. M.; Roobeek, C. F.; Wife, R. L.; Frijns, J. H. G. *J. Chem. Soc., Chem. Commun.* **1986**, 31. (b) van Leeuwen, P. W. N. M.; Roobeek, C. F. *New J. Chem.* **1990**, *14*, 487.
(51) (a) Unruh, J. D.; Christenson, J. R. *J. Mol. Catal.* **1982**, *14*, 19. (b) Hughes, O. R.; Young, D. A. *J. Am. Chem. Soc.* **1981**, *103*, 6636.
(52) Devon, T. J.; Phillips, G. W.; Puckette, T. A.; Stavinoha, J. L.; Vanderbilt, J. J. U. S. Pat. 4,694,109, 1987 (to Eastman Kodak); *Chem. Abstr.* **1988**, *108*, 7890.
(53) Casey, C. P.; Whiteker, G. T.; Melville, M. G.; Petrovich, L. M.; Gavney, J. A., Jr.; Powell, D. R. *J. Am. Chem. Soc.* **1992**, *114*, 5535.
(54) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3081.
(55) Billig, E.; Abatjoglou, A. G.; Bryant, D. R. (to Union Carbide) U.S. Pat. 4,769,498 = EP 214622 U.S. 4668651; Eur. Pat. 213,-639 = U.S. 4748261, 1987; *Chem. Abstr.* **1987**, *107*, 7392r.
(56) (a) van Rooy, A.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J.; Veldman, N.; Spek, A. L. *Organometallics* **1996**, *15*, 835. (b) Buisman, G. J. H.; Vos, E. J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **1995**, 409. (c) Buisman, G. J. H.; van der Veen, L. A.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1997**, *16*, 5681.
(57) Cuny, G. D.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 2066.
(58) Burke, P. M.; Garner, J. M.; Tam, W.; Kreutzer, K. A.; Teunissen, A. J. J. MWO 97/33854, 1997 (to DSM/Du Pont); *Chem. Abstr.* **1997**, *127*, 294939.
(59) Yamamoto, K.; Momose, S.; Funahashi, M.; Ebata, S.; Ohmura, H.; Komatsu, H.; Miyazawa, M. *Chem. Lett.* **1994**, *2*, 189.
(60) van der Veen, L. A.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 336.
(61) Casey, C. P.; Paulsen, E. L.; Beuttenmueller, E. W.; Proft, B. R.; Petrovich, L. M.; Matter, B. A.; Powell, D. R. *J. Am. Chem. Soc.* **1997**, *119*, 11817.
(62) Lazzaroni, R.; Uccello-Barretta, G.; Benetti, M. *Organometallics* **1989**, *8*, 2323.
(63) Casey, C. P.; Petrovich, L. M. *J. Am. Chem. Soc.* **1995**, *117*, 6007.
(64) Brown, J. M.; Kent, A. G. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1597.
(65) van der Veen, L. A.; Boele, M. D. K.; Bregman, F. R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J.; Schenk, H.; Bo, C. *J. Am. Chem. Soc.* **1998**, *120*, 11616.
(66) Casey, C. P.; Whiteker, G. T.; Campana, C. F.; Powell, D. R. *Inorg. Chem.* **1990**, *29*, 3376.
(67) Herrmann, W. A.; Kohlpaintner, C. W.; Herdtweck, E.; Kiprof, P. *Inorg. Chem.* **1991**, *30*, 4271.
(68) Miyazawa, M.; Momose, S.; Yamamoto, K. *Synlett* **1990**, 711.
(69) van der Veen, L. A.; Keeven, P. H.; Schoemaker, G. C.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Lutz, M.; Spek, A. L. *Organometallics* **2000**, *19*, 872.
(70) Casey, C. P.; Paulsen, E. L.; Beuttenmueller, E. W.; Proft, B. R.; Matter, B. A.; Powell, D. R. *J. Am. Chem. Soc.* **1999**, *121*, 63.
(71) van Leeuwen, P. W. N. M.; Roobeek, C. F. *J. Organomet. Chem.* **1983,** *258*, 343; Brit. Pat. 2,068,377, U.S. Pat. 4,467,116, 1983 (to Shell Oil); *Chem. Abstr.* **1984**, *101*, 191142.
(72) Sato, K.; Karawagi, J.; Tanihari, Y. Jpn. Kokai Tokkyo Koho JP 07,278,040 (to Mitsubishi); *Chem. Abstr.* **1996**, *124*, 231851.
(73) Sato, K.; Kawaragi, Y.; Takai, M.; Ookoshi, T. U.S. Pat. 5,235,-113, EP Pat. 518241, 1993 (to Mitsubishi); *Chem. Abstr.* **1993**, *118*, 191183.
(74) Röper, M.; Lorz, P. M.; Koeffer, D. Ger. Offen. DE 4,204,808, 1994 (to BASF); *Chem. Abstr.* **1994**, *120*, 133862.
(75) Lorz, P. M.; Bertleff, W.; Röper, M.; Koeffer, D. EP 472,071, 1992 (to BASF); *Chem. Abstr.* **1992**, *117*, 34513.
(76) van Rooy, A.; Orij, E. N.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 34.
(77) van Leeuwen, P. W. N. M.; Buisman, G. J. H.; Van Rooy, A.; Kamer, P. C. J. *Recl. Trav. Chim. Pays-Bas* **1994**, 1.
(78) Moasser, B.; Gladfelter, W. L.; Roe, D. C. *Organometallics* **1995**, *14*, 3832.
(79) van Rooy, A.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M.; Veldman, N.; Spek, A. N. *J. Organomet. Chem.* **1995**, *494*, C15.
(80) van Leeuwen, P. W. N. M.; Roobeek, C. F. *J. Mol. Catal.* **1985**, *31*, 345; Brit. Pat. Appl. 33,554, 1981 (to Shell Resarch); *Chem. Abstr.* **1982**, *96*, 6174.
(81) Bertozzi, S.; Campigli, N.; Vitulli, G.; Lazzaroni, R.; Salvadori, P. *J. Organomet. Chem.* **1995**, *487*, 41.
(82) Horiuchi, T.; Ohta, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *Tetrahedron* **1997**, *53*, 7795.
(83) Ohgomori, Y.; Suzuki, N.; Sumitani, N. *J. Mol. Catal. A: Chem.* **1998**, *133*, 289.
(84) Packett, D. L. U.S. Pat. 5,312,996, 1995 (to UCC); *Chem. Abstr.* **1995**, *123*, 82828.
(85) Ash, C. E. *J. Mater. Educ.* **1994**, *16*, 1.
(86) Brubaker, M. M. U. S. Pat. 2,495,286, 1950 (to Du Pont); *Chem. Abstr.* **1950**, *44*, 4285.
(87) (a) Reppe, W.; Magin, A. U.S. Pat. 2,577,208, 1951; *Chem. Abstr.* **1952**, *46*, 6143. (b) Ziegler, K.; Gellert, H. G. U.S. Pat. 2695279, 1954 (Cabot, G. L., Inc.), and Pat. 2699457, 1955 (Cabot, G. L., Inc.). (c) Ziegler, K.; Holtzkamp, E.; Breil, H.; Martin., H. *Angew. Chem.* **1955**, *67*, 426. (d) Ziegler, K.; Holtzkamp, E.; Breil, H.; Martin., H. *Angew. Chem.* **1955**, *67*, 541.
(88) Gough, A. Brit. Pat. 1,081,304, 1967 (to ICI); *Chem. Abstr.* **1967**, *67*, 100569.
(89) Fenton, U.S. Pat. 3,530,109, 1970 (to Union Oil); *Chem. Abstr.* **1970**, *73*, 110466; U.S. Pat. 4,076,911, 1978; *Chem. Abstr.* **1978**, *88*, 153263.
(90) Nozaki, K. U.S. Pat. 3,689,460, 1972 (to Shell Oil); *Chem. Abstr.* **1972**, *77*, 152860.
(91) (a) Sen, A.; Lai, T. W. *J. Am. Chem. Soc.* **1982**, *104*, 3520. (b) Lai, T. W.; Sen, A. *Organometallics* **1984**, *3*, 866. (c) Sen, A.; Brumbaugh, J. S. J. *Organomet. Chem.* **1985**, *279*, C5.
(92) (a) Drent, E. Eur. Pat. Appl. 121,965, 1984 (to Shell); *Chem. Abstr.* **1985**, *102*, 46423. (b) Drent, E. *Pure Appl. Chem.* **1990**, *62*, 661. (c) Drent, E. Eur. Pat. Appl. 229408, 1986; *Chem. Abstr.* **1988**, *108*, 6617. (d) Drent, E. Eur. Pat. Appl. 399617, 1990; *Chem. Abstr.* **1991**, *114*, 165108. (e) Drent, E.; van Broekhoven, J. A. M.; Doyle, M. J. *J. Organomet. Chem.* **1991**, *417*, 235.
(93) Drent, E.; Budzelaar, P. H. M. *Chem. Rev.* **1996**, *96*, 663.
(94) Dekker: G. P. C. M.; Elsevier: C. J.; Vrieze, K.; van Leeuwen, P. W. N. M. *Organometallics* **1992**, *11*, 1598.
(95) Doherty, S.; Eastham, G. R.; Tooze, R. P.; Scanlan, T. H.; Williams, D.; Elsegood, M. R. J.; Clegg, W. *Organometallics* **1999**, *18*, 3558.
(96) van Leeuwen, P. W. N. M.; Roobeek, C. F.; van der Heijden, H. *J. Am. Chem. Soc.* **1994**, *116*, 12117.
(97) van Leeuwen, P. W. N. M.; Roobeek, C. F. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 61.
(98) Tóth, I.; Elsevier: C. J. *J. Am. Chem. Soc.* **1993**, *115*, 10388.

(99) Vetter, W. M.; Sen, A. *J. Organomet. Chem.* **1989**, *378*, 485.
(100) Catellani, M.; Chiusoli, G. P.; Castagnoli, C. *J. Organomet. Chem.* **1991**, *407*, C30.
(101) Li, C. S.; Cheng, C. H.; Liao, F. L.; Wang, S. L. *J. Chem. Soc., Chem. Commun.* **1991**, 710.
(102) Ozawa, F.; Hayashi, T.; Koide, H.; Yamamoto, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1469.
(103) Markies, B. A.; Rietveld, M. H. P.; Boersma, J.; Spek, A. L.; van Koten, G. *J. Organomet. Chem.* **1992**, *424*, C12.
(104) Dekker: G. P. C. M.; Elsevier: C. J.; Vrieze, K.; van Leeuwen, P. W. N. M. *J. Organomet. Chem.* **1992**, *430*, 357.
(105) van Asselt, R.; Gielens, E. E. C. G.; Rülke, R. E.; Elsevier: C. J. *J. Am. Chem. Soc.* **1994**, *116*, 977.
(106) Mole, L.; Spencer, J. L.; Carr, N.; Orpen, A. G. *Organometallics* **1991**, *10*, 49.
(107) Zuideveld, M. A.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Klusener, P. A. A.; Stil, H. A.; Roobeek, C. F. *J. Am. Chem. Soc.* **1998**, *120*, 7977.
(108) Zuideveld, M. A.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. Submitted for publication.
(109) Drent, E.; Kragtwijk, E. EP 495,548 (to Shell) 1991; *Chem. Abstr.* **1992**, *117*, 150569.
(110) Clegg, W.; Eastham, G. R.; Elsegood, M. R. J.; Tooze, R. P.; Wang, X. L.; Whiston, K. *Chem. Commun.* **1999**, 1877.
(111) El Ali, B.; Alper, H. *J. Mol. Catal.* **1992**, *77*, 7; **1993**, *80*, 377.
(112) Sugi, Y.; Bando, K. *Chem. Lett.* **1976**, 727.
(113) Del Rio, I.; Ruiz, N.; Claver, C.; van der Veen, L. A.; van Leeuwen, P. W. N. M. Submitted for publication.
(114) Schroeder Goedheijt, M.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Chem. Commun.* **1998**, 2431.
(115) Hutmacher, K.; Krill, S. In *Applied Homogeneous Catalysis with Organometallic Compounds: A Comprehensive Handbook in Two Volumes*; Cornils, B., Herrmann, W. A., Eds.; VCH: Weinheim; New York; Basel; Cambridge, U.K., Tokyo, 1996, p 465.
(116) (a) Seidel, W. C.; Tolman, C. A. U.S. Pat. 3,850,973, 1973 (to Du Pont); *Chem. Abstr.* **1975**, *82*, 97704. (b) King, C. M.; Seidel, W. C.; Tolman, C. A. U.S. Pat. 3,925,445, 1975 (to Du Pont); *Chem. Abstr.* **1976**, *84*, 88921. (c) Rapoport, M. U.S. Pat. 4,371,-474, 1983 (to Du Pont); *Chem. Abstr.* **1983**, *98*, 125452.
(117) (a) Tolman, C. A.; McKinney, R. J.; Seidel, W. C.; Druliner, J. D.; Stevens, W. R. *Homogeneous Nickel-Catalyzed Olefin Hydrocyanation*; *Advances in Catalysis*, Vol. 33; Academic: New York, 1985; Part 1. (b) McKinney, R. J. In *Homogeneous Catalysis*; Parshall, G. W., Ed.; Wiley: New York, 1992; p 42.
(118) (a) Kreutzer, K. A.; Tam, W. U.S. Pat. 5,512,696, 1996 (to Du Pont); *Chem. Abstr.* **1996**, *125*, 114851. (b) Breikss, A. I. U.S. Pat. 5,523,453, 1996 (to Du Pont); *Chem. Abstr.* **1996**, *125*, 114201. (c) Kreutzer, K. A.; Tam, W. U.S. Pat. 5,663,369, 1997 (to Du Pont); *Chem. Abstr.* **1996**, *125*, 114851. (d) Tam, W.; Kreutzer, K. A.; McKinney, R. J. U.S. Pat. 5,688,986, 1997 (to Du Pont); *Chem. Abstr.* **1997**, *127*, 752788.
(119) (a) Baker, M. J.; Harrison, K. N.; Orpen, A. G.; Pringle, P. G.; Shaw, G. *J. Chem. Soc., Chem. Commun.* **1991**, 803. (b) Baker, M. J.; Pringle, P. G. *J. Chem. Soc., Chem. Commun.* **1991**, 1292.
(120) (a) Casalnuovo, A. L.; RajanBabu, T. V.; Ayers, T. A.; Warren, T. H. *J. Am. Chem. Soc.* **1994**, *116*, 9869. (b) RajanBabu, T. V.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 6325.
(121) McKinney, R. J.; Roe, D. C. *J. Am. Chem. Soc.* **1986**, *108*, 5167.
(122) Haenel, M. W.; Jakubik, D.; Rothenberger, E.; Schroth, G. *Chem. Ber.* **1991**, *124*, 1705.
(123) (a) Drinkard, W. C., Jr. Ger. Pat. OLS 1,806,096 1969 (to Du Pont); *Chem. Abstr.* **1969**, *71*, 30093. (b) Drinkard, W. C.; Kassal, R. J. Fr. Pat. 1,529,134, 1969; *Chem. Abstr.* **1969**, *71*, 30092.
(124) Albanese, P.; Benzoni, L.; Carniso, G.; Crivelli, A. It. Pat. 869,-900, 1970 (to Montecatini); *Chem. Abstr.* **1973**, *78*, 135701.
(125) Elmes, P. S.; Jackson, W. R. *Aust. J. Chem.* **1982**, *35*, 2041.
(126) Keim, W.; Behr, A.; Lühr, H.-O.; Weisser, J. *J. Catal.* **1982**, *78*, 209.
(127) Bäckvall, J. E.; Andell, O. S. *Organometallics* **1986**, *5*, 2350.
(128) Collmann, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.
(129) Keim, W.; Behr, A.; Bioul, J. P.; Weisser, J. *Erdöhl, Kohle, Erdgas, Petrochem.* **1982**, *35*, 436.
(130) Marcone, J. E.; Moloy, K. G. *J. Am. Chem. Soc.* **1998**, *120*, 8527.
(131) Kranenburg, M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Vogt, D.; Keim, W. *J. Chem. Soc., Chem. Commun.* **1995**, 2177.
(132) Goertz, W.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M.; Vogt, D. *J. Chem. Soc., Chem. Commun.* **1997**, 1521.
(133) Goertz, W.; Keim, W.; Vogt, D.; Englert, U.; Boele, M. D. K.; Van der Veen, L. A.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **1998**, 2981.
(134) *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, **1998**.
(135) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(136) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.
(137) Knochel, P.; Perea, J. J. A.; Jones, P. *Tetrahedron* **1998**, *54*, 8275.
(138) Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669.
(139) Negishi, E.-i. *Acc. Chem. Res.* **1982**, *15*, 340.
(140) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254.
(141) Fauvarque, J.-F.; Pflüger, F.; Troupel, M. *J. Organomet. Chem.* **1981**, *208*, 419.
(142) Jutand, A.; Moshleh, A. *Organometallics* **1995**, *14*, 1810.
(143) (a) Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1655. (b) Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1665.
(144) Otsuka, S. *J. Organomet. Chem.* **1980**, *200*, 191.
(145) Hofmann, P.; Heiss, H.; Müller, G. *Z. Naturforsch., B: Anorg. Chem. Sci.* **1987**, *42*, 395.
(146) Amatore, C.; Broeker, G.; Jutand, A.; Khalil, F. *J. Am. Chem. Soc.* **1997**, *119*, 5176.
(147) Amatore, C.; Jutand, A.; Khalil, F.; M'Barki, M. A.; Mottier, L. *Organometallics* **1993**, *12*, 3168.
(148) Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, *115*, 9531.
(149) Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M. A.; Meyer, G. *Organometallics* **1995**, *14*, 5605.
(150) Kohara, Tt.; Yamamoto, T.; Yamamoto, A. *J. Organomet. Chem.* **1980**, *192*, 265.
(151) Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4933.
(152) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 4708.
(153) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 8232.
(154) Calhorda, J. S.; Brown, J. M.; Cooley, N. A. *Organometallics* **1991**, *10*, 1431.
(155) Brown, J. M.; Guiry, P. J. *Inorg. Chim. Acta* **1994**, *220*, 249.
(156) Mann, G.; Baranano, D.; Hartwig, J. F.; Rheingold, A. L.; Guzei, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 9205.
(157) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6787.
(158) Widenhoefer, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6504.
(159) Farina, V. In *Transition Metal Alkyl Complexes: Oxidative Addition and Transmetalation in Comprehensive Organometallic Chemistry*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Academic Press: New York, 1995; Vol 12, p 161.
(160) Farina, V.; Krishan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.
(161) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969.
(162) Louie, J.; Paul, F.; Hartwig, J. F. *Organometallics* **1996**, *15*, 2794.
(163) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 3694.
(164) Hayashi, T.; Konishi, M.; Kumada, M. *Tetrahedron Lett.* **1979**, *21*, 1871.
(165) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.
(166) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Eur. J. Inorg. Chem.* **1998**, 155.
(167) Saito, S.; Ohtani, S.; Miyauri, N. *J. Org. Chem.* **1997**, *62*, 8024.
(168) Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*, Wilkinson, G., Ed.; Pergamon: Oxford, U.K., 1982; Vol. 8, p 799.
(169) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, 4387.
(170) Atkins, K. E.; Walker, W. E.; Manyik, R. M. *Tetrahedron Lett.* **1970**, 3821.
(171) (a) Trost, B. M.; Vranken, Van D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089. (c) Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257. (d) Dierkes, P.; Ramdeehul, S.; Barloy, L.; De Cian, A.; Fischer, J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Osborn, J. A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3116. (e) Ramdeehul, S.; Dierkes, P.; Aguado, R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Osborn, J. A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3118.
(172) (a) Trost, B. M.; Dietsche, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 8200. (b) Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1977**, *99*, 1649.
(173) Bosnich, B.; Mackenzie, P. B. *Pure Appl. Chem.* **1982**, *54*, 189.
(174) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143.
(175) Trost, B. M.; Vranken, Van D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327.
(176) Trost, B. M.; Breit, B.; Peukert, S.; Zambrano, J.; Ziller, J. W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2386.
(177) Hayashi, T.; Ohno, A.; Lu, S.; Matsumoto, Y.; Fukuyo, E.; Yanagi, K. *J. Am. Chem. Soc.* **1994**, *116*, 4221.
(178) (a) Sjögren, M. P. T.; Hansson, S.; Åkermark, B.; Vitagliano, A. *Organometallics* **1994**, *13*, 1963. (b) Sjögren, M. P. T.; Hansson, S.; Norrby, P.-O.; Åkermark, B.; Cucciolito, M. E.; Vitagliano, A. *Organometallics* **1992**, *11*, 3954. (c) Åkermark, B.; Hansson, S.; Vitagliano, A. *J. Am. Chem. Soc.* **1990**, *112*, 4587. (d) Oslob, J. D.; Åkermark, B.; Helquist, P.; Norrby, P.-O. *Organometallics* **1997**, *16*, 3015.
(179) Kranenburg, M.; Kamer, P. C. J.; Leeuwen, van P. W. N. M. *Eur. J. Inorg. Chem.* **1998**, 25.
(180) Haaren, van R. J.; Oevering, H.; Coussens, B. B.; Strijdonck, van G. P. F.; Reek, J. N. H.; Kamer, P. C. J.; Leeuwen, van P. W. N. M. *Eur. J. Inorg. Chem.* **1999**, 1237.
(181) (a) Aranyos, A.; Szabó, K. J.; Castaño, A. M.; Bäckvall, J.-E. *Organometallics* **1997**, *16*, 1058. (b) Castaño, A. M.; Aranyos,

A.; Szabó, K. J.; Bäckvall, J.-E. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2551.
(182) Hegedus, L. S.; Darlington, W. H.; Russell, C. E. *J. Org. Chem.* **1980**, *45*, 5193.
(183) (a) Hoffmann, H. M. R.; Otte, A. R.; Wilde, A.; Menzer, S.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 100. (b) Hoffmann, H. M. R.; Otte, A. R.; Wilde, A. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 253. (c) Wilde, A.; Otte, A. R.; Hoffmann, H. M. R.; *J. Chem. Soc., Chem. Commun.* **1993**, 615.
(184) (a) Carfagna, C.; Mariani, L.; Musco, A.; Sallese, G.; Santi, R. *J. Org. Chem.* **1991**, *56*, 3924. (b) Carfagna, C.; Galarini, R.; Musco, A. *J. Mol. Catal.* **1992**, *72*, 19. (c) Carfagna, C.; Galarini, R.; Linn, K.; López, J. A.; Mealli, C.; Musco, A. *Organometallics* **1993**, *12*, 3019.
(185) Szabó, K. J. *Organometallics* **1996**, *15*, 1128.
(186) Albright, T. A.; Burdett, J. K.; Whangbo, M.-H. *Orbital Interactions in Chemistry*; Wiley: New York, 1985, Chapters 1 and 19.
(187) Ward, T. R. *Organometallics* **1996**, *15*, 2836.
(188) (a) Blöchl, P. E.; Togni, A. *Organometallics* **1996**, *15*, 4125. (b) Burckhardt, U.; Gramlich, V.; Hofmann, P.; Nesper, R.; Pregosin, P. S.; Salzmann, R.; Togni, A. *Organometallics* **1996**, *15*, 3496. (c) Togni, A.; Burckhardt, U.; Gramlich, V.; Pregosin, P. S.; Salzmann, R. *J. Am. Chem. Soc.* **1996**, *118*, 1031.
(189) Prétôt, R.; Pfalz, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 323.
(190) Haaren, van R. J.; Druijven, K.; Strijdonck, van G. P. F.; Oevering, H.; Reek, J. N. H.; Kamer, P. C. J.; Leeuwen, van P. W. N. M. *J. Chem. Soc., Dalton Trans.* **2000**, 1549.
(191) Cuvigny, T.; Julia, M. *J. Organomet. Chem.* **1986**, *317*, 383.
(192) Carruthers, W. In *Cycloaddition Reactions in Organic Synthesis;* Tetrahedron Organic Chemistry Series, Vol. 8; Pergamon Press: Elmsford, NY, 1990.
(193) (a) Kagan, H. B.; Riant O. *Chem. Rev.* **1992**, *92*, 1007. (b) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1.
(194) (a) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; Matt, von P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582. (b) Evans, D. A.; Miller, S. C.; Lectka, T.; Matt, von P. *J. Am. Chem. Soc.* **1999**, *121*, 7559. (c) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994. (d) Evans, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 4895. (e) Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3372.
(195) Davies, I. W.; Gerena, L.; Castonguay, L.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Chem. Commun.* **1996**, 1753.
(196) Davies, I. W.; Deeth, R. J.; Larsen, R. D.; Reider, P. J. *Tetrahedron Lett.* **1999**, *40*, 1233.
(197) (a) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046. (b) Hartwig, J. F. *Synlett* **1997**, 329. (c) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (d) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (e) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (f) Belfield, A. J.; Brown, G. R.; Foubister, A. J. *Tetrahedron* **1999**, 11399.
(198) (a) Hamann, B. C.; Hartwig, J. F.; *J. Am. Chem. Soc.* **1998**, *120*, 7369. (b) Sadighi, J. P.; Harris, M. C.; Buchwald, S. L. *Tetrahedron Lett.* **1998**, *39*, 5327.
(199) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.
(200) Kosugi, M.; Kameyam, M.; Migata, T. *Chem. Lett.* **1983**, 927.
(201) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.
(202) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348.
(203) Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030.
(204) Hartwig, J. F.; Paul, F. *J. Am. Chem. Soc.* **1995**, *117*, 5373.
(205) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215.
(206) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 3534.
(207) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217.
(208) Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359.
(209) Reddy, N. A.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807.
(210) (a) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617. (b) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367.
(211) Alcazar-Roman, L. M.; Hartwig, J. F. *Abstr. Pap. Am. Chem. Soc.* 218: 22-INOR.
(212) (a) Beller, M.; Riermeier, T. H.; Reisinger, C.-P.; Herrmann, W. A. *Tetrahedron Lett.* **1997**, *38*, 2073. (b) Riermeier, T. H.; Zapf, A.; Beller, M. *Top. Catal.* **1997**, *4*, 301.
(213) Guari, Y.; van Es, D. S.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron Lett.* **1999**, *40*, 3789.
(214) Harris, M. C.; Geis, O.; Buchwald, S. L. *J. Org. Chem.* **1999**, *64*, 6019.
(215) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251.

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