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Catalysis by palladium complexes: new prospects in amination of aryl and hetaryl chlorides

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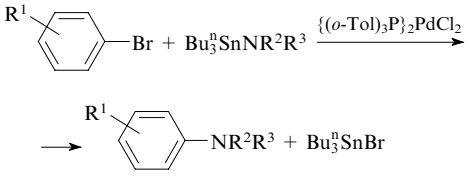
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Abstract. The main achievements in the chemistry of palladium-catalysed amination of chloroarenes are discussed. The general mechanism of the Buchwald – Hartwig reaction and the main types of catalytic systems used for the amination of aryl and hetaryl chlorides are considered. The bibliography includes 122 references.

I. Introduction

The catalysis by metal complexes has long ago exceeded the bounds of laboratory practice; nowadays it is extensively applied in industry. Most (~90%) of the modern industrial processes include at least one catalytic step. Palladium-based catalysts are widely used in the reactions involving the formation of new C – C bonds as well as C – N, C – O and C – S bonds.[1–6]

Palladium-catalysed amination is a relatively new trend in this area. The formation of N-substituted anilines from aryl halides and tin amides in the presence of palladium triarylphosphine complexes was discovered by Buchwald and Hartwig in 1994.[7,8]

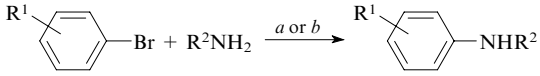


R^1 = Alk, OAlk, NAlk, CO_2Alk; R^2, R^3 = Alk, Ar.

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In 1996, amines and chelate-forming diphosphines replaced toxic tin amides and P(*o*-Tol)$_3$.[9,10] The Buchwald – Hartwig amination has been recognised as a reliable method for the synthesis of aromatic amines due to high yields and good reproducibility.



(*a*) $Pd_2(dba)_3$, BINAP, NaOBu^t, PhMe, 80 °C (Buchwald), for example: R^1 = CN, R^2 = Hex (Hex = n-C_6H_{13}), yield 98%;
(*b*) (dppf)$PdCl_2$, dppf, NaOBu^t, THF, 100 °C (Hartwig), for example: R^1 = R^2 = Ph, yield 94%;
dba is dibenzylideneacetone, BINAP is 2,2′–bis(diphenylphosphino)-1,1′-binaphthyl, dppf is 1,1′-bis(diphenylphosphino)ferrocene.

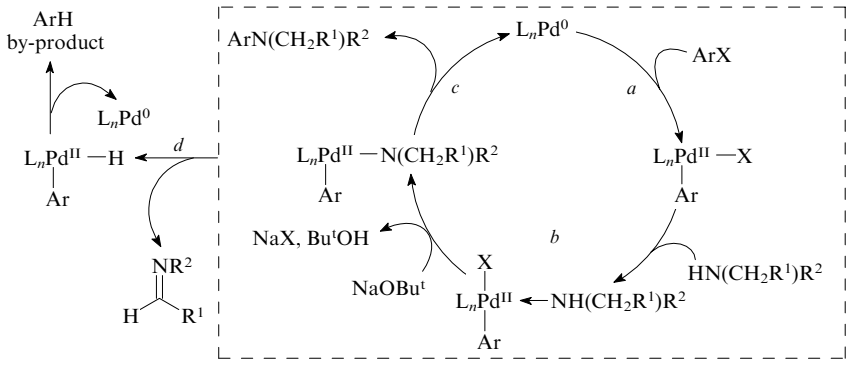
Aryl bromides were most often used as starting compounds in the catalytic amination reactions.[11,12] Readily available chloroarenes turned out to be non-reactive under the classical conditions of the Buchwald – Hartwig reaction (with palladium triphenylphosphine complexes) due to the higher energy of the C – Cl bond in comparison with C – Br:[13]

Ph – X	PhI	PhBr	PhCl	PhF
E_{diss} /kcal mol^{-1}	65	81	96	126

For the first time, the reaction with activated chloroarenes was performed in the presence of a palladacycle (Beller, 1997; see Section V) while that with non-activated chloroarenes, in the presence of palladium complexes with electron-rich trialkylphosphines (Reddy, Tanaka 1997, see Section III). This area has been intensively developed during the following decade mainly by Buchwald's and Hartwig's research groups.[14] The present review describes the main recent developments in this area. As far as a typical synthetic chemist, being restricted by a particular substrate and a reagent, is relatively free only in the choice of the reaction conditions we paid special attention to the latter issue.

The possibility of amination depends on several factors: on the structure of a substrate, on the properties of the amination

Scheme 1



R^1, R^2 = Alk, Ar; L is phosphine; X = Cl, Br, I.

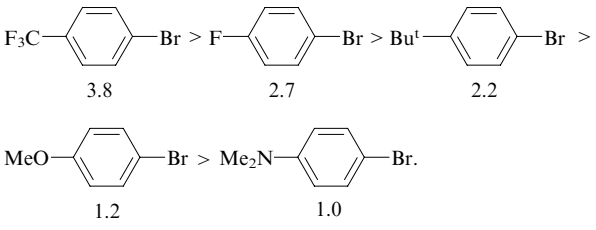
agent, on the nature of a catalyst, particularly the nature of the ligand, on the choice of a base, solvent, temperature, *etc*. From our point of view, the most convenient way to systematise these data is to arrange them according to the type of ligands. Such a classification of catalytic reactions is rarely used,[15] but it is quite appropriate for a synthetic chemist. As the number of papers on reactions of chloroarenes with various N-nucleophilic reagents in the presence of palladium complexes is rather huge (more than 320),[5] only the most popular catalytic systems are discussed in the present review. The data on amination in super-critical media [16] and under microwave irradiation [17–23] are not included and only the reactions that proceed under the conditions similar to those of the classical Buchwald–Hartwig amination are discussed.

II. Mechanism and kinetics of haloarene amination

It was thought originally that the catalytic cycle of amination does not depend on the substrate structure, the nature of the ligand and base and corresponds to the general scheme of cross-coupling including three major steps: oxidative addition of an aryl halide to a Pd^0 complex (*a*); trans-metallation producing an aryl(amide) complex $L_nPd(Ar)N(CH_2R^1)R^2$ (*b*) and reductive elimination of arylamine (*c*). In some cases, a side process of β-hydrogen elimination occurs yielding an imine and aryl hydride palladium complex. The reduction of this complex results in the formation of arenes as the by-products (Scheme 1).

The role of ligands, for example of di- and monophosphines,[24] is the stabilisation of Pd^0. Obviously, electron-enriched phosphines are more efficient in the stabilisation of the metal centre and thus enhance the oxidative addition. The trans-metallation was assumed to be the rate-determining step of the process.[25]

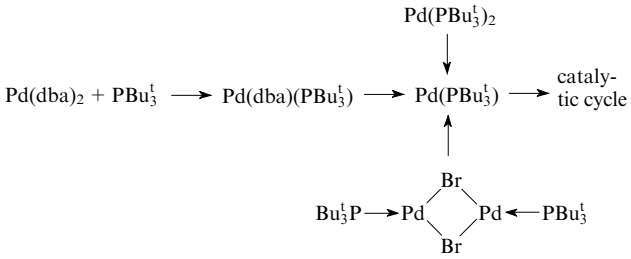
As in other cross-coupling reactions the spatial structure of the substrate and electronic effects of substituents significantly affect the amination rate: the electron-withdrawing groups increase it considerably, while the donating groups decrease the rate.[25] The relative rates of amination of *para*-substituted bromoarenes in the reaction with $Bu^n_3SnNMe_2$ decrease in the series



However, the catalytic cycle is actually much more complicated. The amination mechanism is determined by a number of factors and any stage of the cycle can be rate-determining depending on these factors. Let us discuss in brief the key items of the cycle.

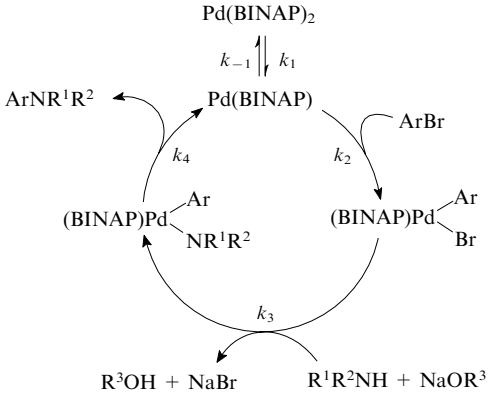
1. Formation of active catalytic species

According to the modern views, the formation of active species Pd^0L, where L is a ligand, for example mono- or diphosphine, is the first and quite often the rate-determining step of the catalytic amination. Thus for PBu^t_3 the amination rate is controlled by the formation of monophosphine complex $Pd(PBu^t_3)$.[26]



In the case of diphosphines, the active species Pd^0L are generated upon dissociation of Pd^0L_2. For instance, $Pd(BINAP)_2$ being in equilibrium with Pd(BINAP) does not participate in the catalytic cycle (Scheme 2).[27] An amine and a base react with Pd(BINAP)Ar(Br) yielding palladium aryl(amide) complex, and reductive elimination from this complex results in arylamine. Thus, the amination in the presence of BINAP is a zero-order reaction with respect to the amine, a

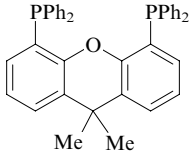
Scheme 2



$$\frac{-d[ArBr]}{dt} = \frac{k_1 k_2}{k_{-1}[L]}[ArBr][Pd]\,.$$

first-order reaction with respect to bromoarene and an inverse first-order reaction with respect to the ligand.

The catalytic cycle for the ligand Xantphos looks similarly: the change in the ligand concentration in the solution significantly affects the reaction rate. The reaction rate decreases sharply at high ligand concentration due to the formation of the complex $Pd(Xantphos)_2$. Low catalytic activity of this complex is caused by its insufficient solubility in common organic solvents and its slow dissociation rate, which inhibit the formation of active species Pd^0(Xantphos) and oxidative addition.[28]



Xantphos

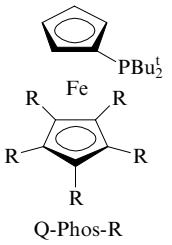
2. Oxidative addition

Under similar conditions the rate of oxidative addition [29] and reductive elimination is determined by steric and electronic characteristics of the ligand.[30–32]

$$L_nM + A{-}B \underset{\text{reductive elimination}}{\overset{\text{oxidative addition}}{\rightleftharpoons}} L_nM\begin{matrix}A\\B\end{matrix}$$

However, their relative contributions and their cumulative effect on the reaction rate are not comprehensively studied yet. Generally, the phosphines with electron-donating substituents, for example, alkyl groups, favour the oxidative addition to a greater extent than triarylphosphines.[30]

In the case of bulky monophosphines Q-Phos-R (R = 4-Tol, 4-$CF_3C_6H_4$) the type of the first step (dissociation or oxidative addition) depends on the nature of the halide.

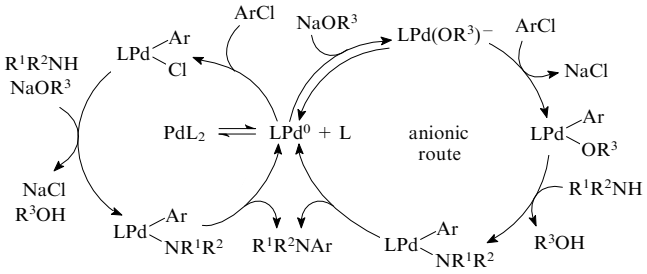


Q-Phos-R

Possible mechanisms of oxidative addition of haloarenes to the complex PdL_2 and the corresponding expressions for the rate constants are presented in Scheme 3. Thus the addition of iodobenzene proceeds as a standard substitution (path *a*). In the case of bromobenzene, the first and rate-determining step is irreversible phosphine dissociation (path *d*). In the case of chlorobenzene, the dissociation is reversible and the oxidative addition is the rate-determining step of the process (path *e*).[33]

Depending on the character of the ligand, the addition may proceed according to two competitive mechanisms. The anionic mechanism includes the formation of the complex $[LPd(OR)]^-$ as the first step of the reaction (Scheme 4).[34] The reactions with bulky diphosphines are of the zero order with respect to the base. On the contrary, the reactions with monophosphines, *e.g.* with PBu^t_3, proceed by two mechanisms simultaneously. Obviously, the formation of the complexes $[LPd(OR)]^-$ will accelerate oxidative addition and transmetallation promoting the reaction on the whole.

Scheme 4



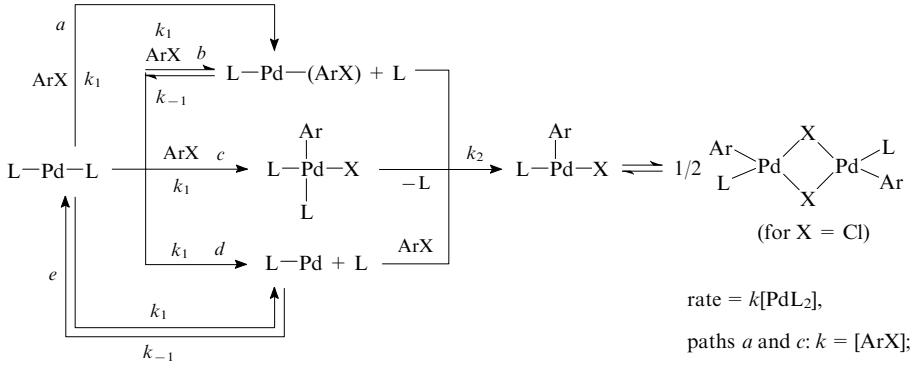
L = PBu^t_3; R^1 = Me, R^2 = Bn; R^3 = Bu^t, 2,4,6-$Bu^t_3C_6H_2$; Ar = Ph.

3. Reductive elimination

The reductive elimination is the most thoroughly studied step of this catalytic cycle.[35–43] In contrast to oxidative addition, the elimination rate is higher for the phosphine complexes containing electron-withdrawing groups. These groups decrease to some extent the electron density on the metal site and thus favour the reduction. The effect of sterically hindered ligands is similar. The chelate-forming ligands favour the reductive elimination and impede the side process of β-hydrogen elimination. The steric factor prevails over the electronic effects.[43] The most remarkable example is the ligand PBu^t_3 possessing a unique combination of properties. On the one hand, the presence of electron-donating alkyl groups promotes oxidative addition but impedes elimination. On the other hand, the steric properties of this phosphine favour the reductive elimination. The combined effect is an extremely high activity of palladium complexes with PBu^t_3.

It is known that the reductive elimination proceeds as a dissociative process accompanied by the formation of three- or

Scheme 3



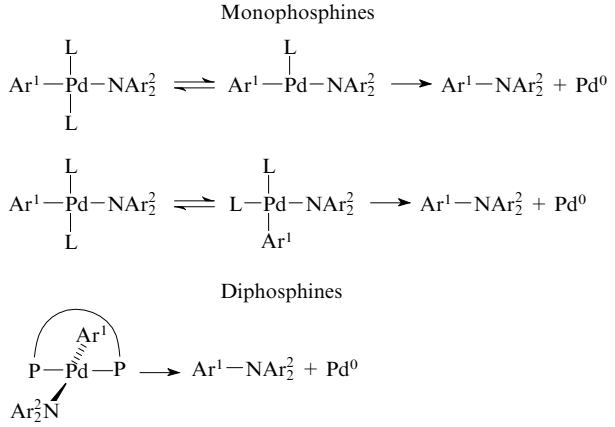
L = Q-Phos-R (R = 4-Tol, 4-$CF_3C_6H_4$); Ar = Ph; X = Cl, Br, I.

rate = $k[PdL_2]$,

paths *a* and *c*: $k = [ArX]$; path *d*: $k = k_1$;

path *b*: $k = \dfrac{k_1k_2[ArX]}{k_{-1}[L] + k_2}$; path *e*: $k = \dfrac{k_1k_2[ArX]}{k_{-1}[L] + k_2[ArX]}$.

four-coordinate amide intermediates, the former reaction rate being higher. Monophosphines at low concentrations yield three-coordinate or T-shaped intermediates, while high concentrations result in four-coordinate intermediates. In the case of diphosphines, for example, dppf, the elimination proceeds directly from the four-coordinate complex.



However, the elimination rate for bidentate ligands may be higher than that for monodentate ligands.[42] The ligands that form a larger 'bite' angle at the central atom (the angle P–M–P, β_n) favour the reductive elimination more effectively.[44,45] During migration, the 'bite' angle β_n, in the phosphine ligands increases, and phosphines with larger angles β_n accelerate the migration.

Ligand	BINAP	Xantphos	dppf
β_n/deg	92	111	99

The choice of a ligand determines not only the rate, but also the selectivity of reaction. Thus in the reaction of bromoarenes with amino derivatives of some NH-heterocycles, coupling can involve either the amino group or the nitrogen atom of the heterocycle depending on the ligand type.[46]

The choice of a suitable base is equally important.[5,47] Sodium *tert*-butoxide is a standard base of the catalytic amination. However, in the case of substrates with labile functional groups (such as COR, COOR, *etc.*) weaker bases are used (K_3PO_4, Cs_2CO_3, K_2CO_3, *etc.*).

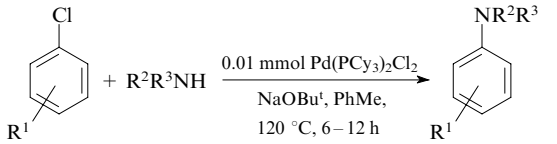
Most often, the amination is carried out in organic solvents that perform several functions simultaneously they dissolve the starting compounds and partially bases, determine the reaction temperature and stabilise intermediates. Toluene is the most frequently used solvent, while dioxane, xylene, dimethoxyethane and THF are less common. In most cases the solvents should be anhydrous and devoid of traces of oxygen. In the presence of oxidation-resistant ligands, the reaction can be carried out under aerobic conditions. Some catalytic systems allow the presence of water in the reaction mixture.

Depending on the solvent and the catalyst, the temperature of amination may vary from 25 °C (for the most active catalysts) up to 140 °C. In most cases, the temperature interval of the process is 70–100 °C.

III. Catalysis by palladium monophosphine complexes

1. Trialkylphosphines

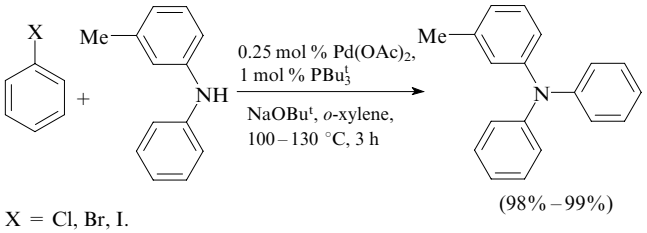
The first report on the amination of non-activated chloroarenes in the presence of trialkylphosphine PCy_3 (Cy is cyclohexyl) was published in 1997.[48] The reaction under described conditions was accompanied by side processes, namely, by amine dehydrogenation and reduction of the starting substrates. No reaction with primary aliphatic amines that can form imines takes place under such conditions.



R^1 = H, 4-Me, 2-Me, 4-CN;

R^2R^3NH = MeN⟨⟩NH, ⟨⟩NH, PhMeNH, Hex_2NH, Bn_2NH.

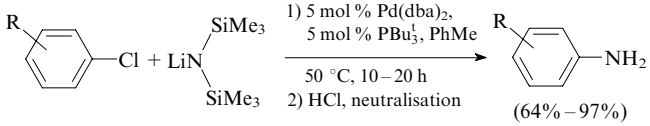
Tri-*tert*-butylphosphine is more efficient in C–N-coupling reactions and equally suitable for amination of aromatic chlorides, bromides and iodides.[49,50] Thus the reaction of chlorobenzene with a substituted diphenylamine proceeds in 3 hours with quantitative yield of the product.



X = Cl, Br, I.

The systems PBu^t_3–$Pd(dba)_2$ and PBu^t_3–$Pd_2(dba)_3$ are reported [51] to be the most efficient in coupling reactions of aryl halides with amines (and with boronic acids and organomagnesium compounds). The PBu^t_3–$Pd_2(dba)_3$ system makes possible the amination of deactivated aryl chlorides including *ortho*-substituted ones, with secondary and primary aromatic and aliphatic amines at 60 °C (Scheme 5).

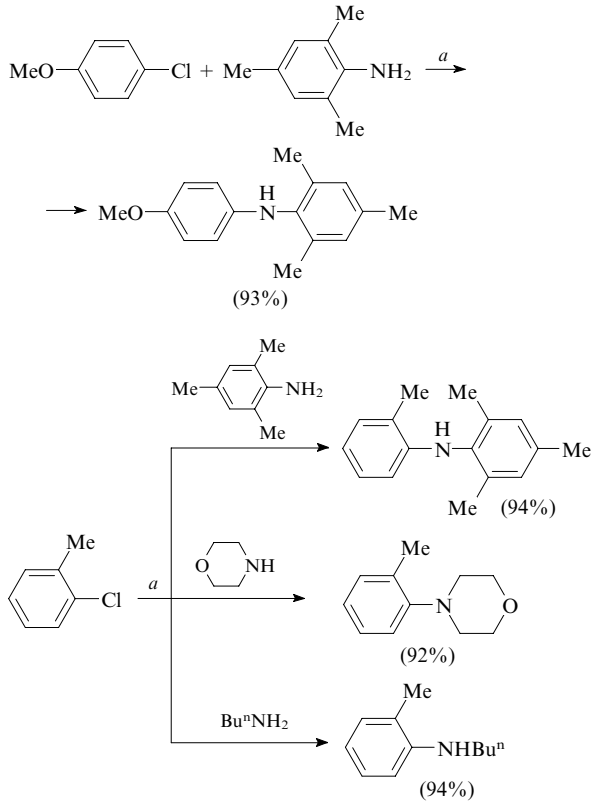
Amides,[52] NH-heterocycles,[53,54] carbamates [53] can also be used as amination agents (Table 1).



R = H, 4-CO_2Me, 4-Bu^n, 4-OMe, 3-OMe, 3-Me, 4-F.

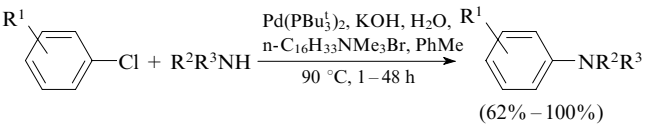
Aqueous potassium or sodium hydroxides in combination with n-$C_{16}H_{33}NMe_3Br$ as a phase-transfer catalyst can be used instead of alkoxides. Being weaker bases, the alkalis make possible the reactions with substrates containing labile functional groups (COOR, NO_2, CN *etc.*). Commercially available

Scheme 5



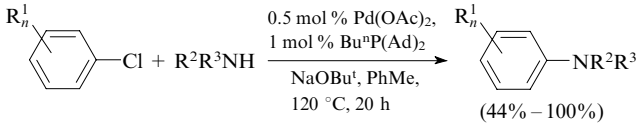
(*a*) 3 mol % $Pd(dba)_2$, 3 mol % PBu^t_3, $NaOBu^t$, dioxane, 60 °C, 18 h.

$Pd(PBu^t_3)_2$ is less active than the catalyst generated *in situ* from a palladium compound and PBu^t_3, but withstands KOH and NaOH.[55]



R^1 = H, 2-Me, 4-CO_2Me, 4-Me, 4-OMe, 4-NO_2, 4-CN, 4-Ac;
R^2 = H, Alk, R^3 = Alk; R^2 = H, Ar, R^3 = Ar.

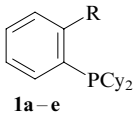
Complete conversion is observed in the reactions of aryl chlorides, including *ortho*,*ortho*-disubstituted ones, with secondary aliphatic and primary aromatic amines in the presence of the palladium complex with bis(1-adamantyl)butylphosphine [$Bu^nP(Ad)_2$, trademark cataCXium® A].[56]



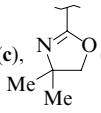
R^1_n = H, 4-Me, 3-Me, 3-OMe, 2-Ac, 2-F, 2,6-Me_2;
R^2, R^3 = Alk; R^2 = H, R^3 = Ar.

2. Dialkylarylphosphines

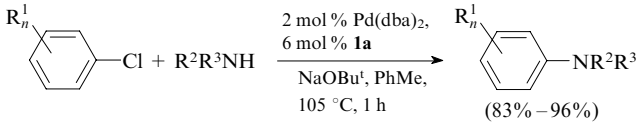
Dicyclohexylarylphosphines **1a**–**e** containing a heteroatom in an *ortho*-substituent with respect to the phosphine group form metal chelates.



1a–**e**

R =  (**a**), $(MeO)_2CH$ (**b**), Me_2NCH_2 (**c**),  (**d**), OMe (**e**).

Ligand **1a** is the most active among compounds **1**; its palladium complexes catalyse reactions of substrates containing bulky *ortho*-substituents with primary and secondary aromatic and aliphatic amines.[57, 58]

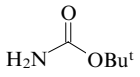
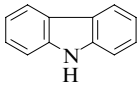


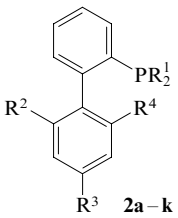
R^1_n = 2-OMe, 4-C(O)Ph, 4-CN, 4-CF_3, 2,5-Me_2, 3,5-Me_2;
R^2, R^3 = H, Alk, Ar.

3. Dialkylphosphinobiphenyls and related biaryls

The so-called Buchwald phosphines **2a**–**k**, **3** are widely used in the cross-coupling reactions (Table 2).[59, 60]

Table 1. The reaction of chloroarenes ($R^1C_6H_4Cl$) with NH-heterocycles and carbamate (R^2R^3NH).

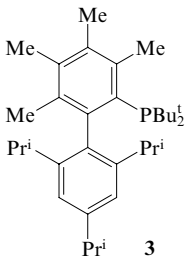
R^1	R^2R^3NH	Catalyst	Conditions	Yield (%)	Ref.
4-Me		5 mol % $Pd(dba)_2$, 5 mol % PBu^t_3	Cs_2CO_3, toluene, 100 °C, 12 h	64	53
4-Me		4 mol % $Pd(dba)_2$, 4 mol % PBu^t_3	NaOPh, toluene, 100 °C, 24 h	59	53
4-CHO		1 mol % $Pd(OAc)_2$, 1 mol % PBu^t_3	K_2CO_3, *o*-xylene, 120 °C, 6 h	71	54



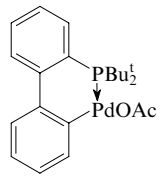
2a – k

Ligand **2**	R^1	R^2	R^3	R^4
a (Cyclohexyl JohnPhos)	Cy	H	H	H
b (MePhos)	Cy	Me	H	H
c (DavePhos)	Cy	NMe_2	H	H
d (X-Phos)	Cy	Pr^i	Pr^i	Pr^i
e (S-Phos)	Cy	OMe	H	OMe
f	Cy	OPr^i	H	OPr^i
g (JohnPhos)	Bu^t	H	H	H
h	Bu^t	Me	H	H
i	Bu^t	NMe_2	H	H
j	Bu^t	Pr^i	H	H
k	Bu^t	Pr^i	Pr^i	Pr^i

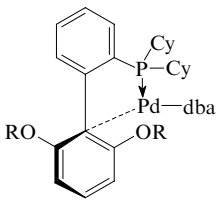
Steric and electronic properties of such ligands can be tuned by varying the substituents in the aromatic rings. The interaction of the biaryl π-system with palladium can result in cyclopalladation, which increases the stability of the catalyst (see Section V for more detailed discussion on the palladacycles). The phosphines containing substituents in positions 2′ and 6′ cannot form palladacycles of type **4**. However, the donor groups (OMe or OPr^i) increase the electron density and the size of the biphenyl moiety thus additionally stabilising Pd complex **5**.



3



4

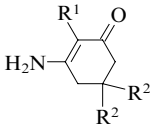


5

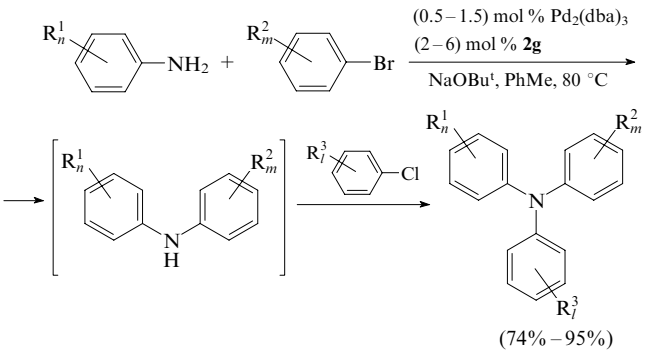
R = Me, Pr^i.

The amination of bromoarenes in the presence of ligand **2g** followed by the reaction of obtained diarylamines with chloroarenes is a convenient one-pot synthesis of non-symmetrical triarylamines.[67]

Table 2. The amination of chloroarenes (RC_6H_4Cl or $R_2C_6H_3Cl$) in the presence of palladium complexes and dialkylphosphinobiphenyls.

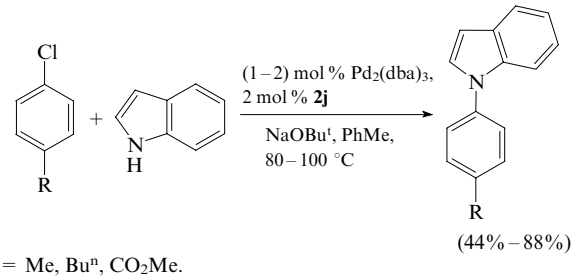
R or R_2	Amines [a]	Catalyst	Conditions	Yield (%)	Ref.
4-Me, 4-OMe, 4-CN, 2,5-Me_2	secondary and primary aliphatic and aromatic	0.5 mol % $Pd(dba)_2$, 1.5 mol % **2c**	$NaOBu^t$, toluene, 80 – 100 °C, 11 – 27 h	83 – 99	61
4-NO_2, 3-OMe, H, 2-Me, 4-CO_2Me	 R^1 = H, R^2 = Me; R^1 = Bn, R^2 = H	0.5 mol % $Pd(dba)_2$, 1 mol % **2c**	Cs_2CO_3, THF, 80 °C, 2.5 – 48 h	80 – 98	62
4-NO_2, 4-Ac, H, 3-CO_2Me	secondary aliphatic and aromatic, primary aromatic, benzophenone imine	the same	K_3PO_4, DME,[b] 100 °C, 16 – 22 h	81 – 83	63
3-OH, 3-$(CH_2)_2$OH, 3-NHAc	secondary and primary aliphatic and aromatic	(0.5 – 1.5) mol % $Pd(dba)_2$, (1.2 – 3.6) mol % **2c**	$LiN(SiMe_3)_2$, THF, 65 °C, 14 – 25 h	59 – 83	64
3-CN, 4-NO_2, 3-Ac, 3-CO_2Me, 2-NO_2	secondary aliphatic and aromatic, primary aromatic	(0.5 – 2.5) mol % $Pd(dba)_2$, (1 – 5) mol % **2a**	K_3PO_4, DME, 100 °C, 16 – 40 h	75 – 95	63
4-OMe, 2-OMe, 2-pyridyl	$LiN(SiMe_3)_2$	0.5 mol % $Pd(dba)_2$, 1.2 mol % **2a**	toluene – THF, 65 – 100 °C, 16 – 20 h	95 – 98	65
2-Me, 4-Bu^n, 3-$CONH_2$, 4-CO_2H, 4-NHAc, 4-$NHCO_2Bu^t$	secondary and primary aliphatic and aromatic	1 mol % $Pd(dba)_2$, (4 – 5) mol % **2d**	K_2CO_3, Bu^tOH; or $NaOBu^t$, toluene; or Cs_2CO_3, dioxane, 80 – 110 °C, 11 – 24 h	78 – 98	66
3-NO_2, 3-CF_3, 2,5-Me_2, 4-Bu^t, 4-Ph, 4-Bu^n, 3-pyridyl	the same	0.5 mol % $Pd(dba)_2$, 2 mol % **2d**	KOH, H_2O, 110 °C, 3 – 18 h	84 – 96	66
4-Me, 2,5-Me_2, 4-OMe, 4-CN, 2-OMe, 3-OMe, 3,5-MeO_2		(1 – 2) mol % $Pd(dba)_2$, (2 – 4) mol % **2g**	$NaOBu^t$, toluene, room temperature 14 – 21 h	71 – 99	63
4-Me, 2,5-Me_2, 4-OMe, 2-OMe, 3,5-$(OMe)_2$, 2,6-Me_2, 2,6-Pr^i_2	secondary and primary aliphatic and aromatic, benzophenone imine	(0.5 – 4) mol % $Pd(dba)_2$, (1 – 8) mol % **2g**	$NaOBu^t$, toluene, 80 °C, 2.5 – 24 h	73 – 100	63
4-Me, 2,3-Me_2	the same	0.025 mol % $Pd(dba)_2$, 0.1 mol % **2g**	$NaOBu^t$, toluene, 110 °C, 19 – 22 h	89 – 97	63
4-Me, 2-OMe, 2-Me, 2-pyridyl	$LiNH_2$	1 mol % $Pd(dba)_2$, 2.4 mol % **2g**	$NaOBu^t$, toluene – dioxane, 80 – 100 °C, 19 – 22 h	64 – 95 [b]	65

[a] And related compounds, for example benzophenone imine; [b] DME is 1,2-dimethoxyethane.



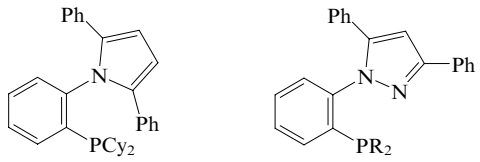
R^1_n	R^2_m	R^3_l
4-Me	3,5-Me_2	2,5-Me_2
	2,5-Me_2	3-OMe
	4-OMe	4-Bu^n
4-OMe	3-OMe	2-OMe
3-Me	4-NMe_2	4-OMe
2,4-Me_2	4-OMe	3-Me
3-NH_2	4-Bu^t	4-Me

The *N*-arylation of indole proceeds with a high yield in the presence of dialkylphosphinobiphenyl **2j**.[68]



R = Me, Bu^n, CO_2Me.

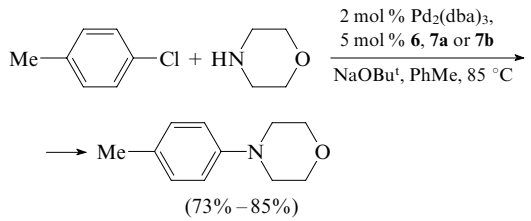
Dialkylphosphinobiaryls **6**, **7a**,**b** containing a heterocyclic (pyrrole or pyrazole) fragment in *ortho*-position with respect to the phosphine group efficiently catalyse the C–N-coupling reactions of substituted bromoarenes with primary and secondary aromatic and aliphatic amines.



6 **7a**,**b**

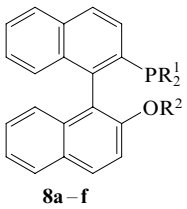
R = Pr^i (**a**), Bu^t (**b**).

The reaction of 4-chlorotoluene with morpholine in the presence of $Pd_2(dba)_3$ and one of the mentioned ligands also proceeds with a good yield.[69]



4. 2-Dialkylphosphino-1,1′-binaphthyls

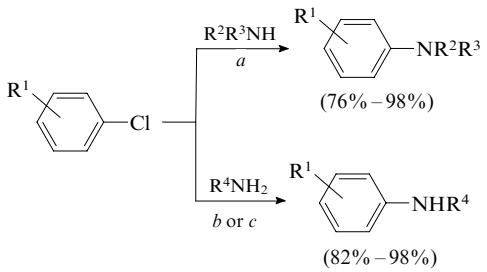
The formation of P,O-chelates is typical of 2-dialkylphosphino-1,1′-binaphthyls **8a**–**f** (similarly to ligands **1a**,**b**,**e**).



8a–**f**

R^1 = Cy: R^2 = Me (**a**), Pr^i (**b**), Bn (**c**);
R^1 = Bu^t: R^2 = Me (**d**), Pr^i (**e**), Bn (**f**).

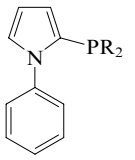
Binaphthyl **8e** containing a bulky alkyl group at the oxygen atom is more efficient in reactions with primary amines, while binaphthyl **8a**, in reactions with secondary amines.[70]



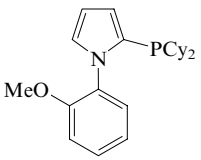
(*a*) R^1 = H, 4-CO_2Me; R^2, R^3 = Alk, Ar; (2–3) mol % $Pd(dba)_2$, (3–5) mol % **8a**; $NaOBu^t$, PhMe, 110 °C, 12–24 h;
(*b*) R^1 = H, 2-OMe, 4-OMe; R^4 = Alk, Ar; (1–2) mol % $Pd(dba)_2$, (2–4) mol % **8e**; $NaOBu^t$, PhMe, 110 °C, 12–24 h;
(*c*) R^1 = 4-CO_2Me; R^4 = Alk, Ar; 2 mol % $Pd(OAc)_2$; (2–4) mol % **8e**; Cs_2CO_3, DME, 110 °C, 12–24 h.

5. 2-Dialkylphosphinohetaryls

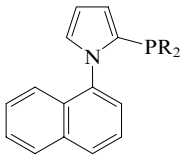
A new catalytic system based on palladium and N-substituted hetarylphosphines **9**–**12** (trademark cataCXium® P) was developed in 2004. Among these phosphines, 2-dialkylphosphino-*N*-phenylindoles **12a**,**b** (trademark cataCXium® PIn) are most widely used in the reactions of C–N bond formation.



9a–**d** (cataCXium® P)
R = Ph (**a**), Cy (**b**), Bu^t (**c**), Ad (**d**).

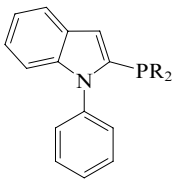


10



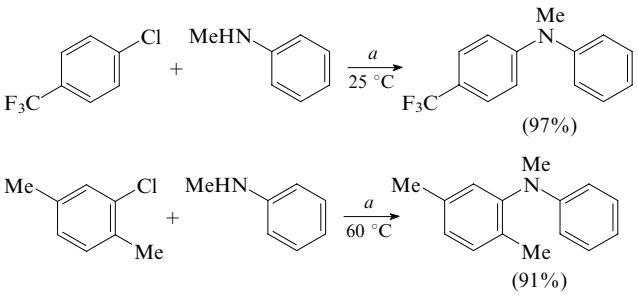
11a,**b**

R = Cy (**a**), Bu^t (**b**).



12a–**c** (cataCXium® PIn)
R = Cy (**a**), Bu^t (**b**), Ad (**c**).

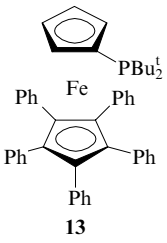
CataCXium® PIn-based catalysts make possible the amination of chloroarenes with low catalyst loading and under fairly mild conditions.[71]



(*a*) 0.5 mol % $Pd(OAc)_2$, 1 mol % **12a**,**b**, $NaOBu^t$, PhH, 20 h.

6. Monophosphines with ferrocenyl, fluorenyl, indenyl and cyclopentadienyl substituents

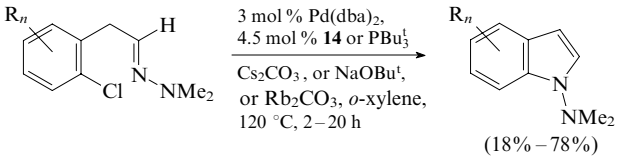
The palladium complex with the bulky Hartwig phosphine Q-Phos-Ph (**13**) catalyses the reactions of chloroarenes with primary and secondary aromatic and aliphatic amines (Table 3).[72]



13

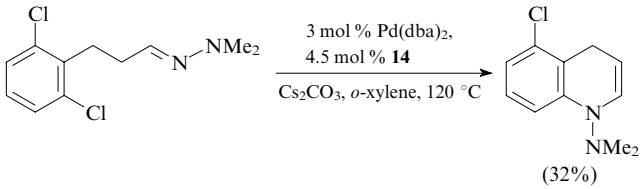
Ligand **13** is highly active and very convenient to use as it is stable against atmospheric oxygen in solutions and in solid state.

The intramolecular catalytic amination can be applied for the synthesis of heterocycles.[73] Such reactions are most typical of bromoarenes. However, there are examples of intramolecular amination of chloroarenes. For instance, the cyclisation of 2-chloroarylacetaldehyde *N*,*N*-dimethylhydrazones results in indoles.

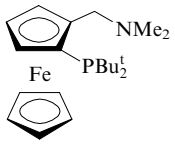


R = Cl, F; $R_2 = OCH_2O$.

Similar reaction of 3-(2,6-dichlorophenyl)propanal *N*,*N*-dimethylhydrazone yields 1-dimethylamino-4*H*-quinoline.[74]

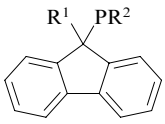


Phosphine **14** or PBu^t_3 may be used as ligands in these cases.



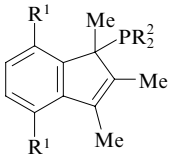
14

Alkylphosphines **15**–**17** with fluorenyl, indenyl and cyclopentadienyl substituents also possess characteristics required for highly efficient catalysts, *viz*., electron-donating properties and steric hindrance. The catalysts based on the corresponding phosphonium salts are efficient in the Suzuki, Sonogashira and Buchwald–Hartwig coupling reactions, catalysts in the form of salts make it possible to perform the reaction in aqueous media, which is of great ecological advantage.[75, 76]



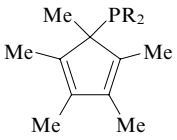
15

R^1 = Me, Et, Pr^i, Pr^n, $n\text{-}C_{18}H_{37}$;
R^2 = Pr^i, Cy, Bu^t.



16

R^1 = H, Me, OMe;
R^2 = Pr^i, Cy.



17

R = Pr^i, Cy.

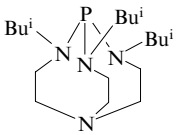
7. Bicyclic triaminophosphines

2,8,9-Trialkyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecanes, which possess increased nucleophilicity due to neighbourhood of the phosphorus atom to the nitrogen atoms, may also be used as ligands. The configuration of one of the nitrogen atoms of acyclic triaminophosphines is pyramidal. The direction of its lone pair is opposite to that of a lone pairs of the phosphorus atom and, as a whole, this nitrogen atom is an acceptor. Bicyclic triaminophosphines are devoid of this drawback. Triisobutyl derivative **18** is the most efficient among them.[77] Its palladium complexes catalyse coupling of reactions of chloroarenes with various amines,[78] arylboronic acids [79] and nitriles.[80]

Table 3. The amination of chloroarenes (RC_6H_4Cl and $R_2C_6H_3Cl$) in the presence of palladium complex with ligand **13** (Ref. 72).[a]

Amine	R or R_2	Amount of $Pd(dba)_2$ (mol %)	Temperature and reaction time	Yield (%)
Diphenylamine	H, 4-OMe, 2-Me, 4-CN, 2-OMe	0.5–1.0	45–100 °C, 5–21 h	95–99
N-Methylaniline	2-Me	0.5	100 °C, 28 h	89
Morpholine	4-OMe, 4-CN, 4-Me	1.0	45–70 °C, 27 h	82–98
Di-n-butylamine	H, 4-OMe	0.5–1.0	100 °C, 20 h	93–94
Aniline	H, 4-OMe, 2-Me, 4-CN [b]	0.5–1.0	70–100 °C, 15 h	86–97
Benzylamine	H, 4-OMe, 4-Me, 4-CN [b]	1.0	100 °C, 4–24 h	92–95
n-Hexylamine	4-OMe, 2-Me, 4-COPh, 2-OMe, 2,5-Me_2, 2,6-Me_2, 4-CN [b], 3-dox [c]	1.0–2.0	50–100 °C, 8–24 h	78–97

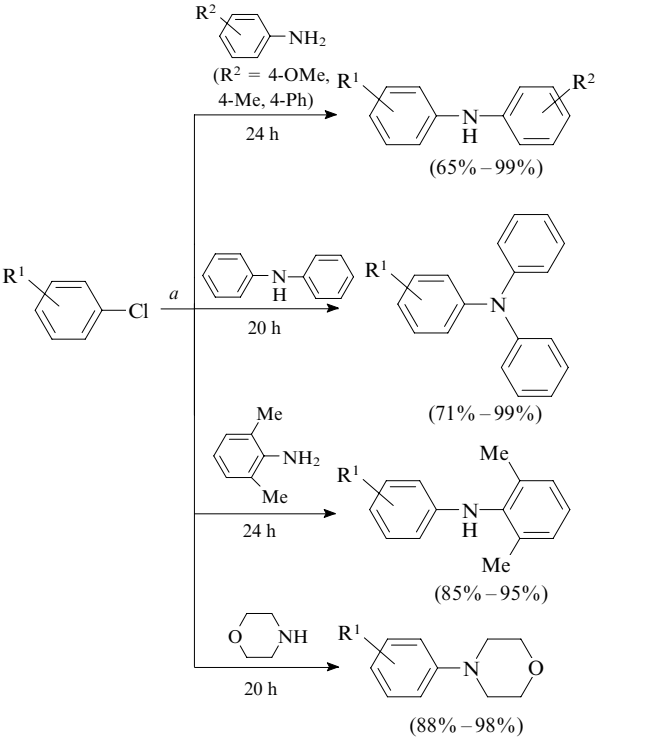
[a] The reaction conditions: Pd : ligand = 1 : 2, $NaOBu^t$, toluene; [b] in these cases, the reactions were performed in the presence of K_3PO_4 in DME; [c] dox is 1,3-dioxolan-2-yl.

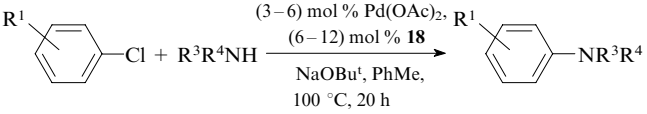


18

Sodium hydroxide without any phase-transfer catalyst may be used in the amination as a base, but in this case the reaction rate slightly decreases. This may be caused by insufficient solubility of NaOH in toluene (Scheme 6).[78]

Scheme 6



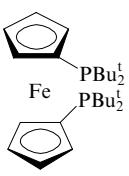


(*a*) 0.5 mol % $Pd_2(dba)_3$, (1–2) mol % **18**; $NaOBu^t$, PhMe, 100 °C;
R^1 = 4-CN, 4-Me, 2-Me, 2-OMe, 3-OMe;
R^3R^4NH = $CyNH_2$, $HexNH_2$, Bu^n_2NH.

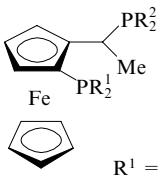
IV. Catalysis by palladium diphosphine complexes

1. Diphosphine derivatives of ferrocene

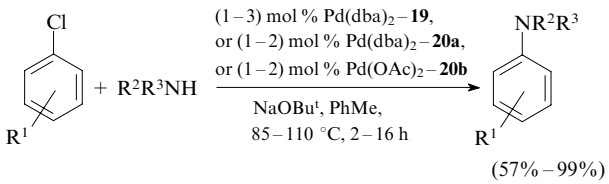
Bis(dialkylphosphino)ferrocenes are the most efficient among diphosphine derivatives of ferrocene since they combine the increased electron density on the phosphorus atom with high chelating properties. Thus in the presence of palladium complexes with diphosphines **19**, **20a**,**b** non-activated chloroarenes react with primary and secondary amines with high yields.[81]



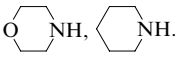
19



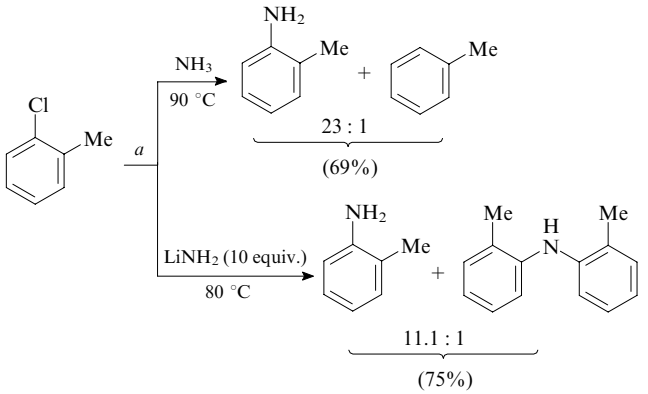
20a–c R^1 = Ph, R^2 = Bu^t (**a**);
R^1 = Cy: R^2 = Cy (**b**), Bu^t (**c**).



R^1 = 4-Me, 2-Me, 3-OMe;
R^2R^3NH = $PhNH_2$, Bu^nNH_2,

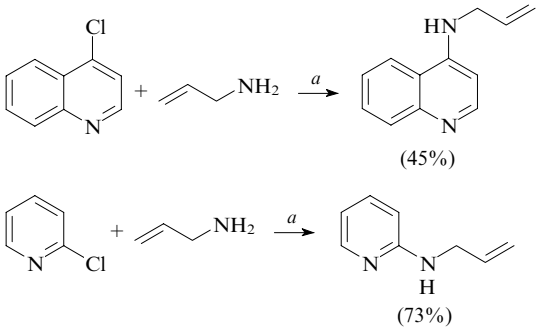


The reaction of haloarenes with ammonia and lithium amide catalysed by a palladium complex with ligand **20c** furnishes substituted anilines.[82] In this reaction, the formation of arenes or diarylamines as by-products was observed.



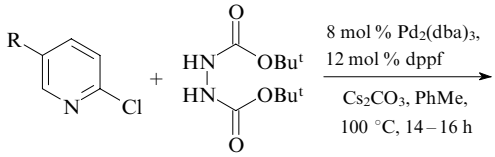
(*a*) 1 mol % $PdCl_2$, 1 mol % **20c**, $NaOBu^t$, 24 h.

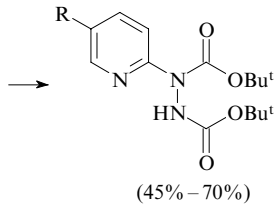
1,1′-Bis(diphenylphosphino)ferrocene is less efficient in coupling reactions than the analogous complex **19**. Palladium complexes with dppf catalyse only the amination of π-deficient hetaryl and aryl chlorides.[83,84] Thus the reaction of 2-chloropyridine and 4-chloropyridine with *N*-allyl- and *N*,*N*-diallylamines results in the formation of corresponding secondary or tertiary amines.[83] The latter are easily converted into primary hetarylamines by refluxing in ethanol with methanesulfonic acid in the presence of catalytic amounts of 10% Pd/C.



(*a*) 5 mol % $PdCl_2$, 15 mol % dppf, $NaOBu^t$, THF, 80 °C, 3 h.

Hydrazine derivatives can be used as amination agents.[84]





(45% – 70%)

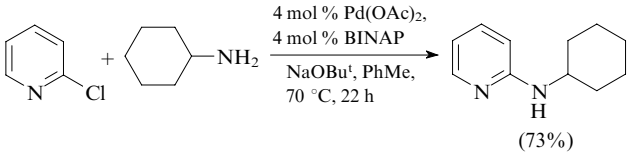
R = H, CO_2Ph.

The reaction of 2,3-dichloro-1,4-naphthoquinone with nitroarylamines in the presence of the system $Pd(dppf)Cl_2$ – dppf proceeds at 80 °C (the product yields are 40% – 90%).[85]

2. BINAP as a ligand

Similarly to the ligand dppf, other diphosphines with aromatic substituents are efficient in amination of iodo- and bromoarenes and aryl triflates. Being less nucleophilic than trialkylphosphines, these diphosphines allow amination of only chloro derivatives of some π-deficient heterocycles and arenes with electron-withdrawing groups.

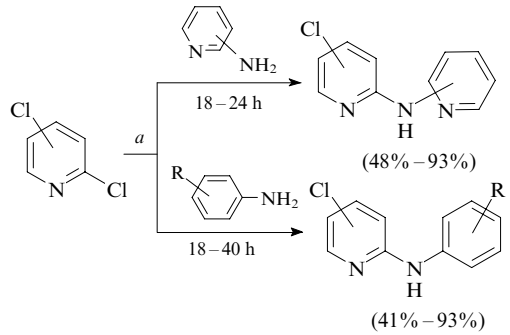
The first report on C – N-coupling by substitution of chlorine atom in the presence of palladium complex, namely, the amination of 2-chloropyridine in the presence of a catalytic system $Pd(OAc)_2$ – BINAP, was published in 1996.[86]



(73%)

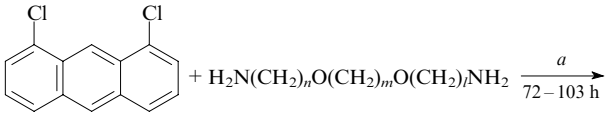
The abovementioned system, alongside with the system $Pd_2(dba)_3$ – BINAP, makes possible the amination of chloro derivatives of other heterocycles: quinoline, benzimidazole, benzothiazole, benzoxazole, purine, pyridazinone, *etc.* (Table 4).[87 – 92]

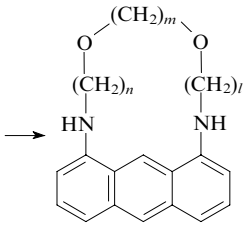
Due to different mobility of chlorine atoms in *ortho-, meta-* and *para*-positions of the pyridine ring, the substitution can proceed selectively. Thus only chloro-substituted 2-aminopyridines are formed in the reactions of 2,3-, 2,5- and 2,6-dichloropyridines in the presence of BINAP.[92 – 94] The substitution of chlorine atom in deactivated position 3 can be achieved in the presence of a more electron-donating Cyclohexyl JohnPhos ligand.[93]



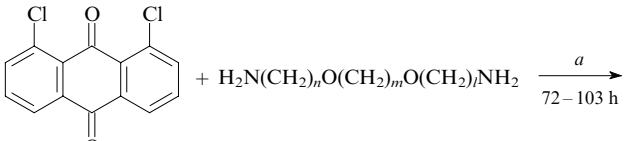
R = 2-CN, 4-OMe, 4-NO_2, 4-CO_2Et;
(*a*) 2 mol % $Pd(OAc)_2$, 2 mol % BINAP, 20 equiv. Cs_2CO_3, PhMe, refluxing.

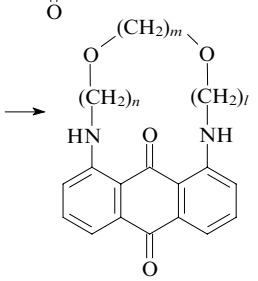
There are very few examples of amination reactions of chloroarenes involving BINAP as a ligand. For instance, the reaction of 1,8-dichloroanthracene and 1,8-dichloroanthraquinone with tetraamines, trioxadiamines and aza-crown ethers proceed with low yields, requires prolonged refluxing and large amounts of the catalyst.[95 – 97]





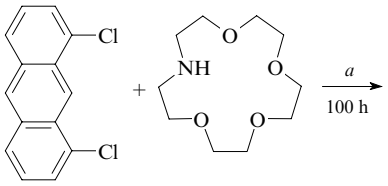
(10% – 28%)

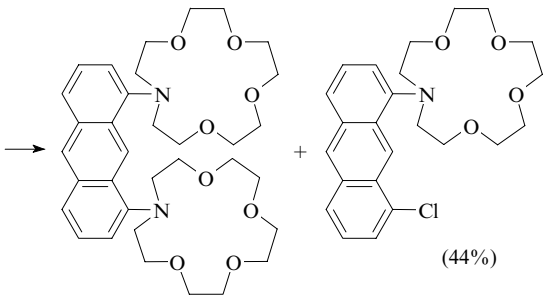




(29% – 35%)

n = 2, 3; m = 2, 4; l = 2, 3.





(11%) (44%)

(*a*) $Pd(dba)_2$, BINAP, $NaOBu^t$, dioxane, refluxing.

3. Xantphos as a ligand

Xantphos-based catalysts are mainly used for the amination of bromoarenes. However, in the presence of this diphosphine the π-deficient heterocycles and nitroarenes react with primary aromatic amines (Table 5).[92, 98]

A new approach to the synthesis of indolo[3,2-*c*]quinoline system is based on the sequence of the Buchwald – Hartwig

Table 4. The amination of chlorohetarenes in the presence of palladium complexes and BINAP as a ligand.

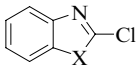
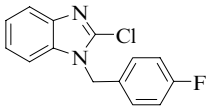
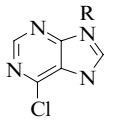
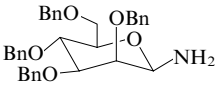
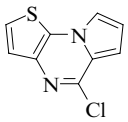
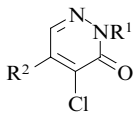
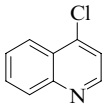
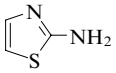
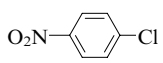
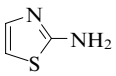
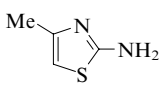
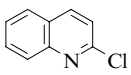
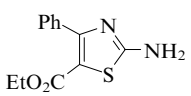
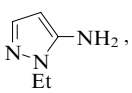
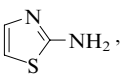
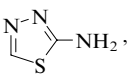
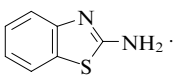
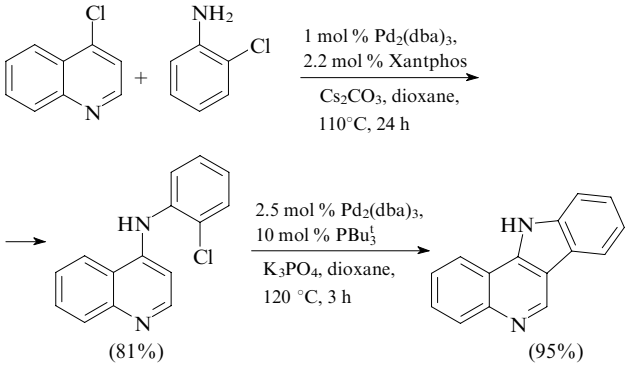
Chlorohetarenes	Amines	Catalyst	Conditions	Yield (%)	Ref.
 X = O, S, NR	secondary aliphatic (cyclic)	(0.5–4) mol % $Pd(OAc)_2$ or $Pd_2(dba)_3$, (0.75–6) mol % BINAP	$NaOBu^t$, toluene, 85 °C, 1–16 h	66–98	87
	primary aliphatic	(2–5) mol % $Pd_2(dba)_3$, (6–15) mol % BINAP	the same	67–81	88
 R = H, 4-$MeOC_6H_4CH_2$, $Me_3Si(CH_2)_2OCH_2$		10 mol % $Pd_2(dba)_3$, (12–20) mol % BINAP	$NaOBu^t$, toluene 140 °C, 1–14 h	61–79	89
	primary aliphatic and aromatic	2.5 mol % $Pd_2(dba)_3$, 7.5 mol % BINAP	$NaOBu^t$, toluene or xylene, 110–130 °C, 1–24 h	72–94	90
 R^1 = Me, Ph, Bn; R^2 = OMe, SEt, OPh	primary aromatic	2 mol % $Pd(OAc)_2$, 2 mol % BINAP	K_2CO_3 or Cs_2CO_3 (5-fold excess), toluene, 120 °C, 2–48 h	81–100	91
	the same	the same	K_2CO_3 (20-fold excess), dioxane 110 °C, 24 h	60	92

Table 5. The amination of aryl and hetaryl chlorides with primary hetarylamines in the presence of palladium complexes and Xantphos as a ligand.[98]

Aryl and hetaryl chlorides	Amines	Catalyst	Conditions	Yield (%)
	see [a]	(1–2.5) mol % $Pd_2(dba)_3$ (2–3) mol % Xantphos	Cs_2CO_3, or Na_2CO_3, dioxane, K_3PO_4, 100 °C, 15–16 h	64–91
		2 mol % $Pd_2(dba)_3$, 2.2 mol % Xantphos	K_3PO_4, dioxane, 100 °C, 15–16 h	96
		the same	Na_2CO_3, toluene, 100 °C, 15–16 h	91
		"	the same	87
		"	"	98

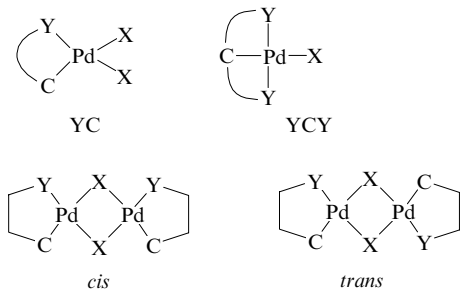
[a] The amines used: $PhNH_2$, , , , .

reaction in the presence of Xantphos ligand and the Heck coupling.[92]



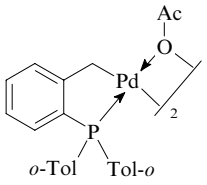
V. Catalysis by palladacycles and palladates

The role of palladacycles in homogeneous catalysis has increased in recent years.[99–101] Most of the palladacycles are 4e- or 6e-donating ligands of the CY and YCY types, respectively. The former usually exist as either *cis*- or *trans*-dimers with acetate or halide bridges.



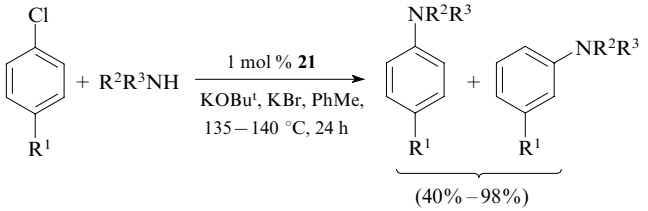
The electronic and steric parameters of palladacycles depend on several factors: on the size of the metallacycle (from 3 to 11 atoms), on the type of the metallated carbon atom (aliphatic, aromatic, vinylic); on the type of the donor atoms (N, P, S, O) and its substituents (Alk, Ar); on the character of the group X (Hal, OTf or a solvent). Depending on these factors, the palladacycles can be either monomeric or dimeric, anionic, cationic or neutral. Obviously, their properties can be modified changing the corresponding parameters. Alongside with thermal and air stability, these factors are responsible for the wide application of palladacycles in catalytic reactions.[100]

Thus, the first amination of activated chloroarenes in the presence of palladacycle **21** was performed in 1997.[102–104]



21

However alongside with the chlorine substitution products, this reaction yields substitution products of hydrogen atom in adjacent position, which suggests the possibility of the reaction mechanism *via* dehydrobenzene. The fact that similar transformation takes place in the presence of KOBu^t without a palladium catalyst and a ligand is in favour of this suggestion.[105]



R^1 = CF_3, C(O)Ph; R^2R^3NH = Bu^n_2NH, PhMeNH, NH.

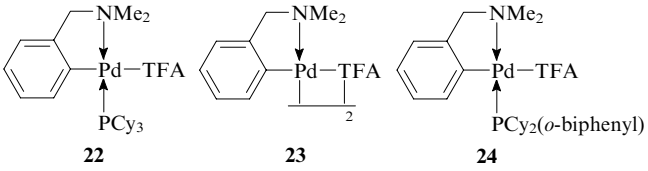
This side reaction was not observed when weaker bases were used. On the whole, palladacycles **4**, **22**–**28** efficiently catalyse amination of chloroarenes (Table 6), including ami-

Table 6. The amination of chloroarenes (RC_6H_4Cl and $R_2C_6H_3Cl$) in the presence of palladacycles.

R or R_2	Amines	Catalyst	Conditions	Yield (%)	Ref.
4-Me, 3-OMe, 2-OMe, 4-Bu^t, 3-CN, 3-NO_2, 3-CO_2Me, 2,5-Me_2	secondary and primary aliphatic and aromatic	(0.5–2) mol % **4** [a]	NaOBu^t, toluene, 80 °C; or KOH, toluene, 90 °C; or NaOMe, Et_3N, toluene, 120 °C, 1–20 h	75–98	106
4-OMe	morpholine	0.5 mol % **22**	NaOBu^t, toluene, 110 °C, 17 h	25	107
	"	0.1 mol % **23**,	the same		
	"	0.1 mol % PBu^t_3	"	92	107
		0.5 mol % **24**	"	63	107
H, 4-OMe, 4-CF_3, 4-Me, 2-Me, 2-OMe	secondary aliphatic and aromatic	1 mol % **25**, 2 mol % PBu^t_3	NaOBu^t, toluene, 100 °C, 17 h	71–96	108
H, 4-OMe, 4-Me, 2-OMe, 4-CN, 4-CF_3, 3-pyridyl, 2-pyridyl	secondary and primary aliphatic and aromatic	1 mol % **26**	NaOBu^t, dioxane, 70 °C, 0.5–4 h	87–100	109
4-Me, 4-OMe	secondary aliphatic and aromatic	(0.5–2) mol % **27**	NaOBu^t, toluene, 110 °C, 15 h	100	110
H, 4-Me, 2-Me, 4-OMe, 2-OMe, 2,6-Me_2, 4-Ac, 3-NO_2, 3-pyridyl	secondary and primary aliphatic and aromatic	(0.2–2) mol % **28**	KOH, Bu^{t}OH, H_2O, 95 °C, 24 h	39–98	111

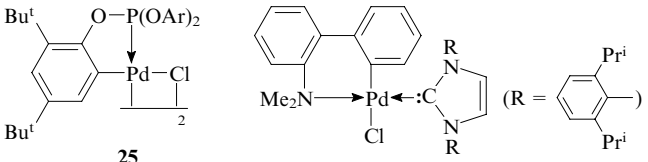
[a] In the case of the system KOH–toluene, 0.01 mol of ligand **2g** was also added.

nation in aqueous media.[111] Palladacycles with phosphine or carbene ligands are the most effective.

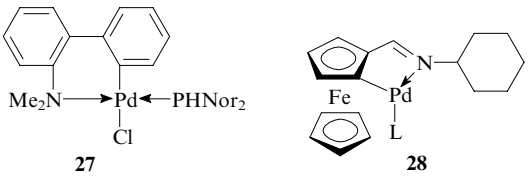


22 **23** **24**

TFA = $CF_3CO_2^-$.



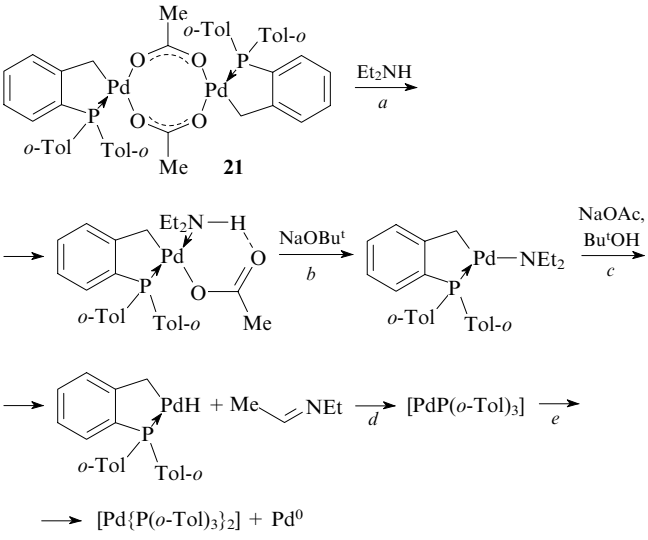
25 **26**



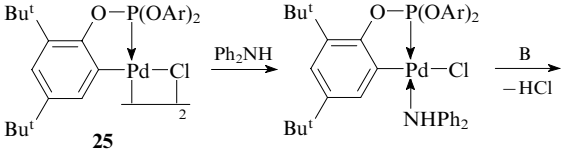
27 **28**

(Nor is 2-norbornyl) (L is ligand **2a**)

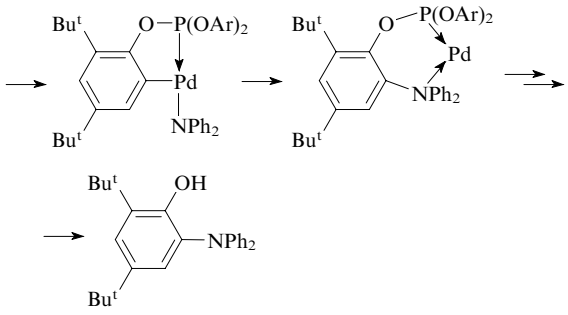
The plausible mechanism of the formation of active species of the Pd^0 catalyst depends on the structure of the palladacycle. Thus for palladacycle **21** it includes cleavage of the dimer (*a*), deprotonation (*b*), β-hydrogen elimination (*c*), reductive elimination (*d*) and disproportionation (*e*).[101, 104]



Ring opening resulting in the formation of *o*-aminophenol cannot be ruled out for compound **25**.[108]

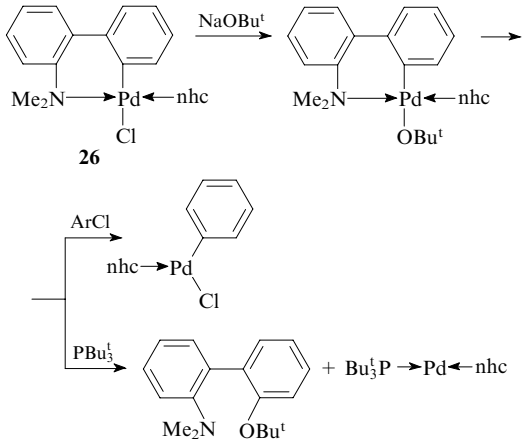


25

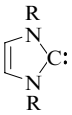


B is base

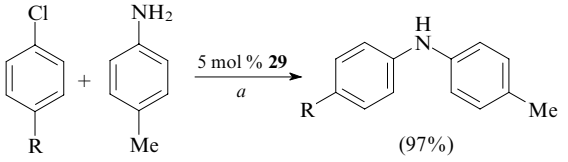
There are two possible ways of activation in the case of palladacycle **26**. One of them includes the formation of palladacycle with N-heterocyclic carbene (nhc) as a ligand.[109]



26

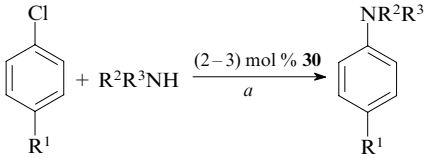
nhc =  (R = 2,6-$Pr^i_2C_6H_3$, Mes).

The reaction of chloroarenes with aromatic amines and morpholine proceeds with high yields in the presence of palladium complexes with phosphinous acid derivatives **29**, **30**.[112, 113]



(97%)

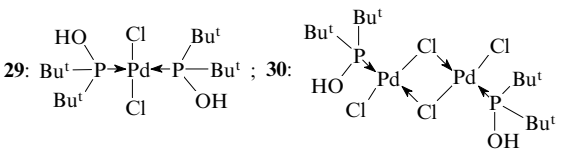
R = H, Me.



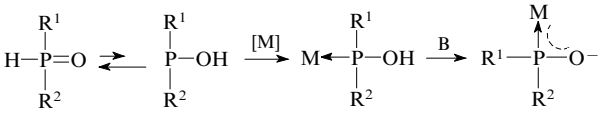
(43%–76%)

(*a*) $NaOBu^t$, PhMe or dioxane, 110 °C, 24 h;

R^1 = H, Me; R^2R^3NH = PhMeNH, .



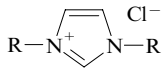
Complexes **29**, **30** are formed from phosphine oxides, which are transformed into acidic form in the presence of transition metals. The acids are coordinated to a metal site through phosphorus atoms. Deprotonation of the complex formed results in the anion, which favours oxidative addition.



VI. Catalysis by palladium carbene complexes

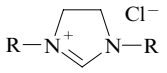
N-heterocyclic carbenes (nhc), which, like phosphines, donate two electrons, represent an alternative to phosphine ligands in the cross-coupling reactions.[101, 114, 115]

There are several reasons that explain the use of these ligands. Their spatial properties can be changed by variation of the substituents at the nitrogen atoms. The complexes of carbene ligands with a metal site do not dissociate easily and as a whole are quite stable. Therefore, the reactions do not require an excess of the ligand and inert atmosphere. The amination in the presence of nhc may proceed at room temperature and with small amounts of the catalyst. Of course, hydrochlorides **31**–**33** are not the only precursors of N-heterocyclic carbenes. The catalysts based on compounds **31a** and **32a** are the most efficient in the Buchwald–Hartwig reactions (Table 7).[114]



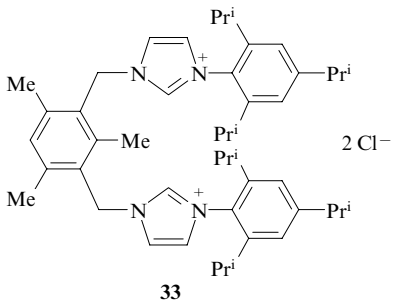
31a–**e**

R = 2,6-$Pr^i_2C_6H_3$ (**a**), Mes (**b**), *p*-Tol (**c**), Ad (**d**), Cy (**e**).



32a,**b**

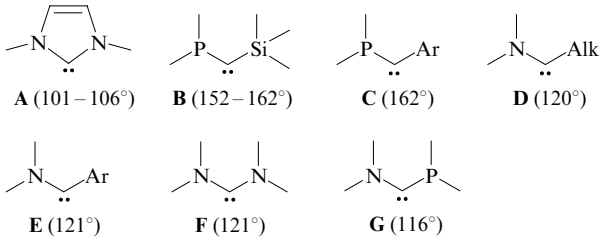
R = 2,6-$Pr^i_2C_6H_3$ (**a**), Mes (**b**).



33

The palladium complex with carbene **31a** is also active in the synthesis of arylamino derivatives of some π-deficient heterocycles.[121]

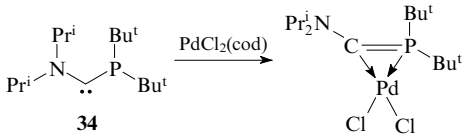
Among acyclic carbenes of the **B**–**G** types the spatial parameters of carbenes **G** are most similar to those of N-heterocyclic carbenes **A**.[122] The poor coordination ability of many acyclic carbenes is caused by the large value of the bond angle at the carbon atom (shown in the parentheses) (for the **B**–**F** types) and by sensitivity to atmospheric oxygen (for the types **C**–**E**).



A (101–106°) **B** (152–162°) **C** (162°) **D** (120°)

E (121°) **F** (121°) **G** (116°)

Amino(phosphino)carbene **34** in the presence of $PdCl_2$(cod) (cod is cycloocta-1,5-diene) forms a stable complex **35**, which effectively catalyses the amination of bromoarenes. Analogous reaction with 4-chlorotoluene proceeds with low yield.[122]

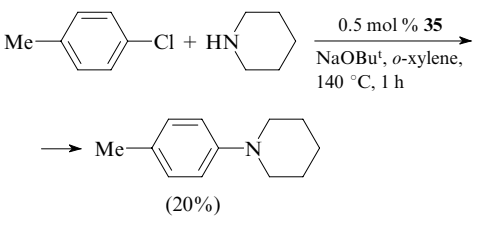


34 **35**

Table 7. The amination of chloroarenes (RC_6H_4Cl and $R_2C_6H_3Cl$) in the presence of palladium carbene complexes.

R or R_2	Amines [a]	Catalyst	Conditions	Yield (%)	Ref.
4-Me, 4-OMe, 2,5-Me_2	secondary cyclic, secondary and primary aliphatic and aromatic, benzophenone imine	1 mol % $Pd_2(dba)_3$, 4 mol % **31a**	$KOBu^t$, dioxane, 100 °C, 3–48 h	59–99	116, 117
4-N, 4-Me, 4-OMe, 2-Me, 2-pyridyl, 3-pyridyl	secondary cyclic, aliphatic and aromatic, primary aromatic, benzophenone imine	(0.02–2) mol % $Pd(dba)_2$, (0.08–2) mol % **32a**	$NaOBu^t$ or $KO(t\text{-}C_5H_{11})$, DME, room temperature or 100 °C (with small amount of a catalyst)	71–100	118, 119
4-Me	secondary cyclic	4 mol % $Pd_2(dba)_3$, 4 mol % **33**	$NaOBu^t$, dioxane, 100 °C, 30 h	66	120

[a] And related compounds, for example, benzophenone imine.



* * *

Over last years, palladium-catalysed amination has been significantly changed. The transformations that initially required inert atmosphere and prolong refluxing nowadays proceed at room temperature and under aerobic conditions, which makes the classical Buchwald – Hartwig reaction closer to 'green chemistry' methods. However, the development of new catalytic systems still continues because the Buchwald – Hartwig amination is a simple and effective method of synthesis of aromatic amines. The main efforts in this field are directed towards the search for ligands superior in catalytic activity to the known ones and which require less expensive and laborious synthesis.

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