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Palladium-catalysed reactions of aryl halides with soft, non-organometallic nucleophiles

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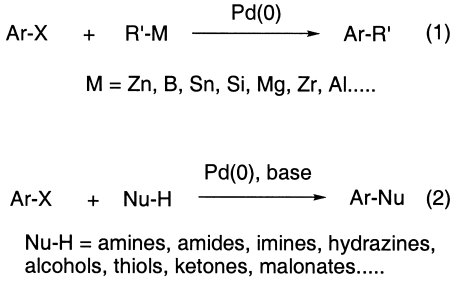
1. Introduction

Over the last three decades, palladium-catalysed reactions of aryl and vinyl halides (or pseudo halides) with 'hard' organometallic nucleophiles have proved to be a widely used class of C–C bond formations. Variants of these reactions have found widespread applications in modern organic chemistry including the Suzuki (boron-mediated),[1] Corriu–Kumada–Tamao (magnesium-mediated),[2] Stille (tin-mediated),[3,4] Negishi (zinc-mediated)[5] and Sonogashira (copper-mediated)[6] coupling reactions (Scheme 1, Eq. (1)).

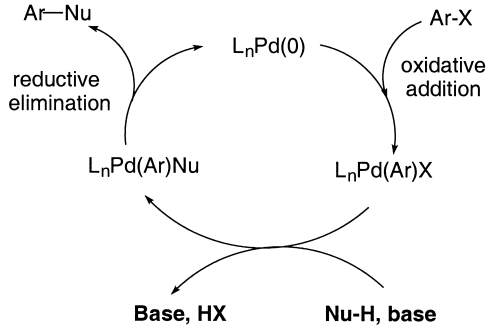
In contrast, the palladium-catalysed coupling reaction involving soft non-organometallic nucleophiles has long remained an underexplored synthetic transformation. Following the pioneering studies (1995) of Buchwald and Hartwig with amine nucleophiles, this new type of coupling reactions has rapidly proved to be successful in the field of synthetic organic chemistry has been applied to a wide range of soft non-organometallic nucleophiles including oxygen-, sulfur-, phosphorus-, boron-, silicon-, and carbon-based nucleophiles (Scheme 1, Eq. (2)).



Scheme 1.

The common key step of the catalytic transformations covered in this review implies a base-assisted generation of the nucleophile. According to the general mechanism depicted in Scheme 2, the reaction of Nu–H with the oxidative addition product $L_nPd(Ar)X$ in the presence of a base leads to a novel $L_nPd(Ar)Nu$ complex. When the latter complex undergoes a reductive elimination, the coupled product Ar–Nu is produced.

This review intends to describe the use of the different types of soft, non-organometallic nucleophiles (N, O, B, Si, P, S and C) in the palladium-catalysed coupling reactions, with



Scheme 2.

literature coverage through to mid-2001. Special emphasis will be placed upon applications of palladium coupling-type reactions in organic synthesis and materials chemistry.

2. Nitrogen-based nucleophiles

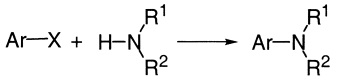
2.1. Introduction

Palladium-catalysed aminations of aryl halides (and pseudo halides) have already been reviewed several times.[7–13] In order not to be redundant, this section will mainly cover recent developments (1999–2001) in this powerful methodology and is divided into three parts: the first part deals with the current efforts devoted towards the development of 'universal conditions' (palladium source, ligand, base, etc.) that will allow the largest substrate combination with smooth conditions (temperature, base), high turnover numbers and fast reaction rates; the second part will briefly describe the various types of nitrogen nucleophiles (amines, amides, hydrazines) used in these reactions; and the third part will cover recent applications of this methodology.

2.2. Towards the development of a universal tool box

The original set of conditions, involving a palladium catalyst using P(*o*Tol)$_3$ as ligand, was concomitantly developed by Buchwald and Hartwig,[14,15] but these reactions suffer from a lack of generality. In particular: (1) electron-rich aryl bromides were prone to give large amounts of reduction products through a competitive β-elimination process, (2) aryl triflates could not be used, (3) primary or secondary acyclic amines gave only low yields and (4) base-sensitive substrates could not be used (Scheme 3, Table 1).

These problems were partially solved when Buchwald[16] and Hartwig[17] introduced a second generation catalyst based on chelating diphosphines (dppf or BINAP). This new set of conditions allowed a broader scope of reactions including the use of primary alkyl amines, anilines, hetero aromatic halides or triflates as leaving groups. In addition, amination reactions on solid support became possible,[18,19] and the introduction of weaker bases such as cesium carbonate[20] and potassium phosphate[20,21] allowed the use of base-sensitive substrates (ketones, esters, etc.), and electron-deficient aryl triflates in these reactions.



Scheme 3.

One of the last classes of amines which were reluctant to arylation appeared to be secondary acyclic amines. This problem was solved by the introduction of electron-rich bi- and then mono-dentate phosphines **1**–**13** (Scheme 4),[21–33] thus considerably expanding (third generation catalysts) the scope of the methodology, allowing the use of small amounts of palladium, of less reactive arylchlorides [nickel-catalysed aminations of aryl chlorides have also been reported[34,35]] and aryl tosylates[22] and the possibility of performing most of these reactions at room temperature. Interestingly, some of these phosphines (**1**, **2**, **5**, **10** and **11**) are commercially available. Noticeably, phosphines **10** and **11** are air-stable[36] compounds. With these new conditions being employed, a general solution to the palladium-catalysed aryl amination seems very close to achievement.

Mechanistically (for a general discussion about the mechanistic aspects of this reaction, see Refs. 9,41) (Scheme 5), the use of bulky monodentate electron-rich ligands is believed to: (1) accelerate the oxidative addition step, which has been shown to be rate-limiting in the second generation ligands (dppf, BINAP),[11] thus allowing amination of less reactive aryl chlorides[42] and (2) increase the reductive elimination rate[9] and probably facilitate the formation of the Pd–N bond via the formation of monophosphine–palladium complexes.[30–32]

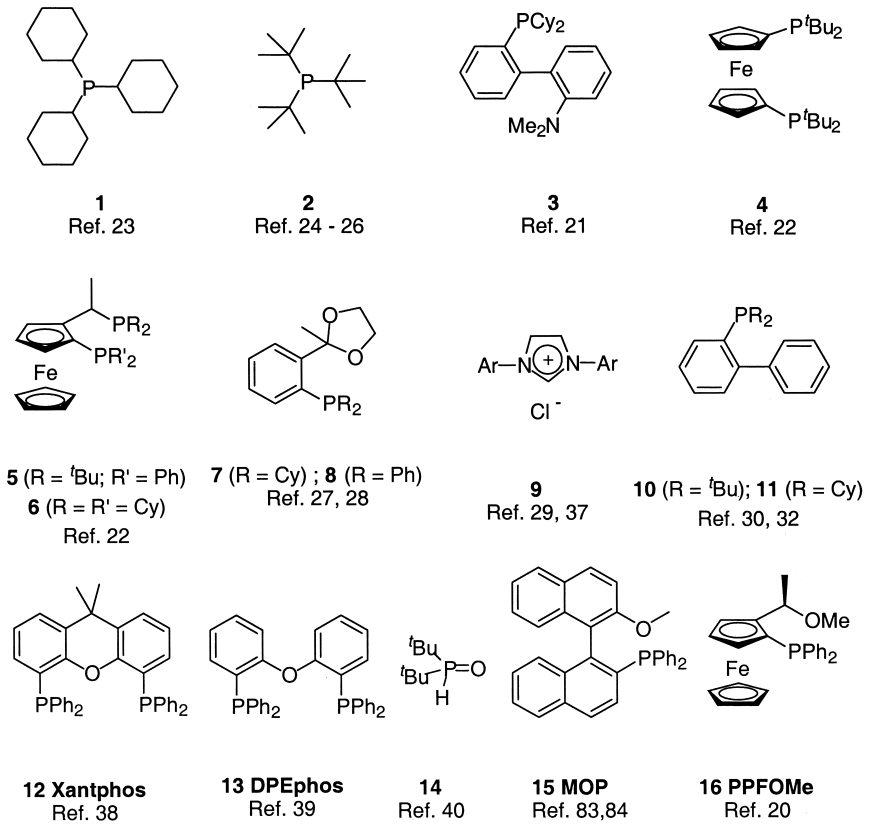
Among the recent developments reported in the literature during the last 2 years, the introduction of the third generation catalysts based on monodentate electron-rich phosphines **1**–**11** is undoubtedly (as shown in Tables 2–4) the most important. It has been shown that the amination rates are dependent on various factors: the intrinsic properties of the ligand, the class of the amine and the aryl substrates but also the Pd/ligand ratio and premixing (or not) the catalyst components are determining.[10,13,43]

2.3. Different classes of nitrogen-based nucleophiles

2.3.1. Amines and anilines. The aforementioned reviews,[7–13] particularly emphasised *N*-arylation of primary or secondary cyclic, acyclic, alkyl or aryl amines.[11] Therefore our first goal is to briefly review most of the available synthetic transformations and, subsequently, recent advances will be addressed (Scheme 6).

Table 1. Historical development of catalytic systems

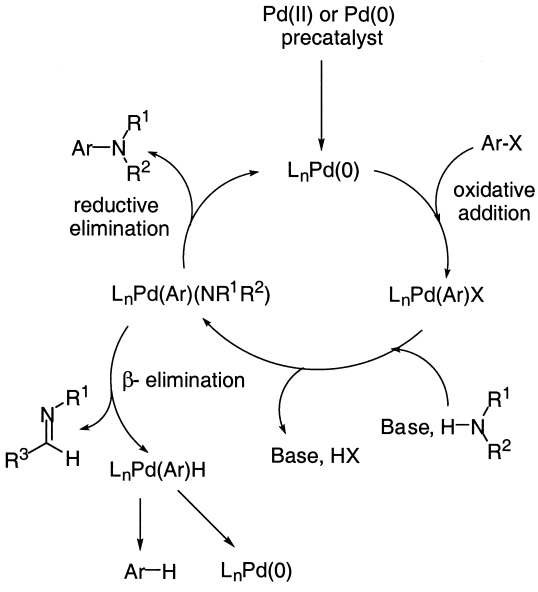
Generation of catalyst	Ligand	Nature of the electrophile	Nature of the amine	Experimental conditions
First	P(*o*Tol)$_3$	X=Br, I Ar=non-hindered, electron deficient or neutral	Secondary cyclic	Pd(0), P(*o*Tol)$_3$ NaO^{t}Bu or LiHMDS 80–100°C, toluene
Second	Chelating diphosphines	X=Br, I, OTf Ar=electron rich, poor, neutral, heteroaromatic	Secondary cyclic primary anilines	$PdCl_2$(dppf)+dppf or Pd_2dba_3+BINAP NaO^{t}Bu, Cs_2CO_3 or K_3PO_4 80–100°C, toluene
Third	Electron-rich monodendate phosphines	X=Br, I, OTf, Cl, OTs Ar=electron rich, poor, neutral, heteroaromatic	Secondary cyclic primary anilines secondary acyclic	$Pd(OAc)_2$ or Pd_2dba_3 electron rich monophosphine NaO^{t}Bu, Cs_2CO_3 or K_3PO_4 rt to 80–100°C toluene



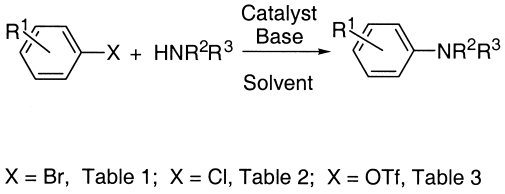
Scheme 4.

Couplings of aryl bromides with amines have been extensively studied in the last 5 years. It appears that BINAP is one of the most widely used ligand for this type of synthetic transformation (Table 2) and its efficiency has been stressed in several papers.[7–13]

In general, chelating bidendate ligands are often preferred as they provide less reduced arene side product. In the cases where BINAP leads to the reduced arene (acyclic alkylaryl amines or dialkylamines as well as electron-rich aryl halides), ferrocenyl-based ligands such as PPF–OMe or PPFA improved the results.[11]



Scheme 5.



Scheme 6.

NaO^{t}Bu proved to be efficient for most purposes. It did, however, exhibit a lower functional group tolerance compared to milder bases such as Cs_2CO_3 or K_3PO_4.[11,30–32]

The general reactivity of amines have been found to be secondary cyclic amines>primary amines>secondary acyclic amines. The last generation of electron-rich monophosphines **1**–**11** now allows the reaction of a large variety of amines under mild conditions and low palladium loading (see Tables 2–4).

Compared to aryl bromides, aryl iodides have not been extensively studied. The higher cost of the latter with respect to the former may be responsible for this lack of interest. Although their use under finely tuned conditions using ligands **3** and **10**–**12**, in the presence of NaO^{t}Bu or Cs_2CO_3 improved the results,[38] electron deficient

Table 2. Amination of aryl bromides: selected examples

Entry	R^1	Amine	Catalyst, base, solvent	Yield (%)	Ref.
1	4-^{t}Bu	H_2NPh	Pd_2dba_3, BINAP, NaO^{t}Bu, toluene	94	31
2	2,6-diMe	2,6-Diisopropylaniline	$Pd(OAc)_2$, DPEphos, Cs_2CO_3, toluene	90	39
3	4-NMe_2	4-Methoxyaniline	Pd_2dba_3, **10**, NaO^{t}Bu, toluene	90	32
4	3,5-diMe	H_2NBn	Pd_2dba_3, **10**, NaO^{t}Bu, toluene	86	32
5	3,5-diMe	3-Cyanoaniline	$Pd(OAc)_2$, **13**, Cs_2CO_3, toluene	87	39
6	4-Me	2-Methylaniline	$Pddba_2$, dppf, NaO^{t}Bu, toluene	89	14
7	4-^{t}Bu	$HNBu_2$	Pd_2dba_3, **16**, Cs_2CO_3, dioxane	73	20
8	4-^{t}Bu	$HNoct_2$	$Pddba_2$, **8**, NaO^{t}Bu, toluene	93	28
9	3-OMe	Piperazine	Pd_2dba_3, P^{t}Bu$_3$, NaO^{t}Bu, xylene	96	24
10	2,5-diMe	Pyrrolidine	Pd_2dba_3, BINAP, Cs_2CO_3, toluene	93	31
11	2-NMe_2	HNMePh	Pd_2dba_3, BINAP, NaO^{t}Bu, toluene	98	31
12	2-Cl	2,6-Diisopropylaniline	Pd_2dba_3, BINAP, Cs_2CO_3, toluene	80	31
13	4-CN	H_2NHex	Pd_2dba_3, BINAP, NaO^{t}Bu, toluene	88	16
14	4-Et_2NCO	H_2N^tBu	$dppfPdCl_2$, dppf, NaO^{t}Bu, THF	82	17
15	2-CO_2Me	2-Methylaniline	Pd_2dba_3, **10**, Cs_2CO_3, toluene	96	32
16	4-NO_2	Piperidine	Pd_2dba_3, BINAP, Cs_2CO_3, toluene	83	31
17	4-CO_2Et	Piperidine	Pd_2dba_3, PPFOMe, Cs_2CO_3, toluene	80	45
18	4-MeCO	Morpholine	$Pd(OAc)_2$, **3**, K_3PO_4, DME	82	21
19	2,4-diMe	*o*-Anisidine	$Pd(OAc)_2$, **12**, NaO^{t}Bu, toluene	97	45

Table 3. Amination of aryl chlorides: selected examples

Entry	R^1	Amine	Catalyst, base, solvent	Yield (%)	Ref.
1	2,5-diMe	H_2NBn	$Pd(OAc)_2$, **10**, NaO^{t}Bu, toluene	98	44
2	2-OMe	H_2NBn	$Pd(OAc)_2$, **10**, NaO^{t}Bu, toluene	94	44
3	4-Me	H_2NBu	Pd_2dba_3, **4**, NaO^{t}Bu, toluene	89	22
4	4-OMe	$HNPh_2$	Pd_2dba_3, P^{t}Bu$_3$, NaO^{t}Bu, toluene	97	26
5	4-Me	$HNBu_2$	Pd_2dba_3, P^{t}Bu$_3$, NaO^{t}Bu, toluene	88	26
6	3-OMe	Morpholine	$Pd(OAc)_2$, **4**, NaO^{t}Bu, Toluene	81	22
7	4-OMe	$HNBu_2$	Pd_2dba_3, **3**, NaO^{t}Bu, Toluene	90	21
8	H	HN(Tol)Ph	$Pd(OAc)_2$, P^{t}Bu$_3$, NaO^{t}Bu, xylene	94	25
9	4-OMe	Morpholine	$Pd(OAc)_2$, **10**, Cs_2CO_3, toluene	90	22
10	2,5-diMe	Pyrrolidine	$Pd(OAc)_2$, **10**, Cs_2CO_3, toluene	99	22
11	4-MeO	$HNBu_2$	Pd_2dba_3, **9**, NaO^{t}Bu, toluene	98	29
12	4-Me	Morpholine	$Pd(OAc)_2$, **10**, Cs_2CO_3, toluene	94	22
13	4-Me	HNMePh	$Pd(OAc)_2$, **10**, Cs_2CO_3, toluene	98	22
14	4-CF_3	$HNoct_2$	$Pddba_2$, **8**, NaO^{t}Bu, toluene	97	28
15	4-CN	HNMePh	$Pd(PCy)_3$, NaO^{t}Bu, toluene	82	23
16	4-CN	Morpholine	$Pd(OAc)_2$, **10**, Cs_2CO_3, toluene	86	30
17	4-CF_3	Piperidine	Palladacycle, KO^{t}Bu, LiBr, toluene	98	47
18	2-Me	HNMePh	$Pddba_2$, **3**, NaO^{t}Bu, DME	97	50

Table 4. Amination of aryl triflates

Entry	R^1	Amine	Catalyst, base, solvent	Yield (%)	Ref.
1	4-^{t}Bu	H_2NHex	$Pd(OAc)_2$, BINAP, NaO^{t}Bu, toluene	55	48
2	4-Me	H_2N^tBu	$Pddba_2$, dppf, NaO^{t}Bu, toluene	96	51
3	2,4-diMe	H_2NBn	$Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene	90	52
4	4-^{t}Bu	4-Anisidine	Pd_2dba_3, **10**, K_3PO_4, DME	85	32
5	4-OMe	4-Nitro aniline	Pd_2dba_3, **10**, K_3PO_4, DME	76	32
6	2-OMe	H_2NPh	$Pddba_2$, dppf, NaO^{t}Bu, toluene	96	51
7	4-Ph	H_2NPh	$Pddba_2$, dppf, NaO^{t}Bu, toluene	96	52
8	4-^{t}Bu	$HNBu_2$	Pd_2dba_3, **10**, K_3PO_4, DME	76	32
9	4-Me	H_2NPh	$Pd(OAc)_2$, DPEphos, Cs_2CO_3, Et_3N	90	53
10	4-^{t}Bu	*N*-Methyl piperazine	$Pd(OAc)_2$, BINAP, NaO^{t}Bu, toluene	53	39
11	4-CN	H_2N^nBu	$Pddba_2$, dppf, NaO^{t}Bu, toluene	51	51
12	4-MeCO	H_2Nhex	$Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene	87	52
13	4-CN	2-Anisidine	Pd_2dba_3, **10**, K_3PO_4, DME	85	32
14	4-NO_2	Piperidine	Pd_2dba_3, **10**, K_3PO_4, DME	76	32
15	3-CO_2Me	Morpholine	$Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene	91	52

aryliodides gave lower yields than the corresponding bromides. Remarkably, it is worth noting that amination of aryliodides can also be performed at room temperature using 18-crown-6.[22,30,46]

Aryl chlorides have only recently been considered as efficient partners in palladium amination reactions.[35,49] Although arylchlorides were found to be less reactive than the corresponding bromides, similar catalytic systems can

be used for their amination (Table 3). Their reactions, however, often require higher temperatures and concentrations of halide. Under these conditions, BINAP was found to be unreactive. In contrast, electron-rich monodendate ligands provided high yields of amination products, and in some cases, the reactions can even be performed at room temperature with high turnover numbers (entry 18). Recent application of saturated carbene (generated in situ from **9**)[29,37,50] or phosphine oxide **14**[40] ligands in amination reactions led to high turnover numbers at room temperature.

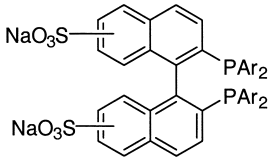
Due to their low cost, conversion of phenols (through an aryl triflate) to anilines is of great interest. Dppf and BINAP are the most widely used ligands, offering good yields of amination products for both electron-rich and deficient aryl halides (Table 4). Introduction of the third generation catalysts will, however, certainly improve the situation still further.

Under similar conditions aryl tosylates have been shown to react with primary amines.[22]

In general, electron-deficient aryl triflates give lower yields than the corresponding electron-rich triflates because NaO^{t}Bu promotes the cleavage of the triflate moiety. This problem can be overcome using weaker bases such as Cs_2CO_3.[22] In order to prevent hydrolysis, slow addition of triflate was also recommended by Hartwig and it was noted that added salts, useful in Stille-coupling chemistry (LiCl, LiBr) inhibited amination reactions.

2.3.2. Recent developments in amine and aniline preparations

2.3.2.1. Green amination. In order to propose a reusable catalyst, two different approaches were reported. The first involves a biphasic amination of aryl halides and the use of a water–alcohol mixture as well as a hexasulfonated ligand (Scheme 7).[54]

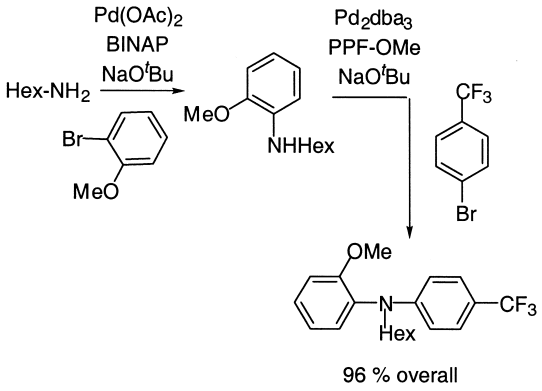


Scheme 7.

The second procedure involves a heterogeneous palladium-catalysed amination system.[55]

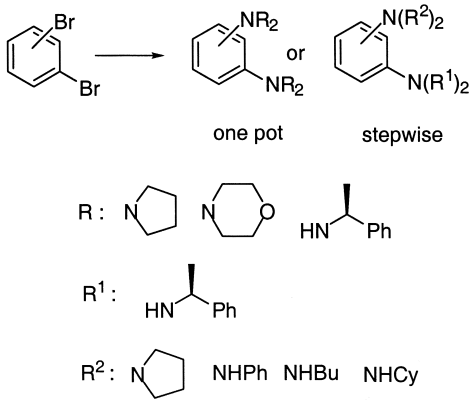
With a similar goal, Buchwald has recently reported the preparation and use of Merrifield resin-bound ligands for palladium-catalysed amination.[56]

2.3.2.2. Multiple amination. Buchwald[57] has described a sequential synthesis of unsymmetrical alkyl diarylamines starting from primary amine and two different aryl bromides. The choice of the ligands and the sequence of addition of aryl bromides are crucial with respect to the electronic properties of aryl bromide and arylamine intermediates (Scheme 8).



Scheme 8.

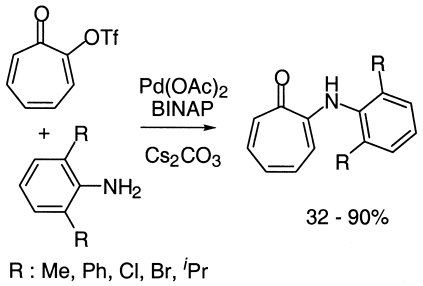
Symmetrical and unsymmetrical 1,2-, 1,3- and 1,4-diaminobenzenes were prepared in one pot or stepwise amination from the parent dibromobenzenes (Scheme 9).[58,59]



Scheme 9.

Several mono- and di-arylations of C2-symmetric diamines have also been reported and these reactions will be discussed in Section 2.4.4.

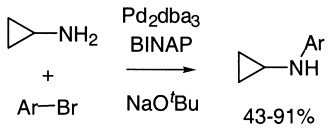
2.3.2.3. Access to anilinotropones. Palladium-catalysed amination has also been applied to triflatotropones.[60] Various substituted anilines (even 2,6-disubstituted) afforded anilinotropones in 32–90% yields (Scheme 10).



Scheme 10.

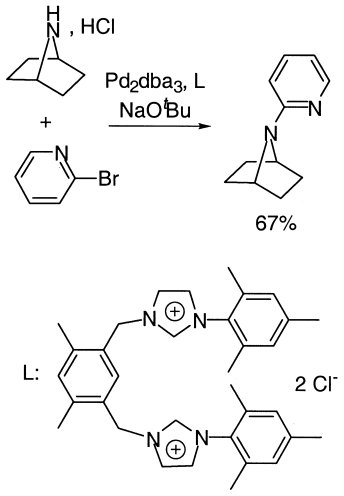
2.3.2.4. Access to cyclopropylamines and azabicyclo[2.2.1]heptanes. The use of palladium-catalysed

N-arylation of cyclopropylamines[61] and 7-azabicyclo[2.2.1]heptane hydrochloride[62] significantly improved (yields and shorter access) previously described procedures (Schemes 11 and 12).



Ar = phenyl, naphthyl, anthryl, phenanthryl, pyridyl

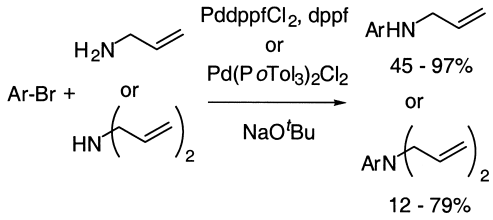
Scheme 11.



Scheme 12.

2.3.3. Ammonia equivalents. Conversion of aryl halides into the corresponding primary arylamines can be achieved using a palladium-catalysed reaction of ammonia equivalents and subsequent deprotection. Ammonia equivalents include (di)allylamines, *t*butylcarbamate, imines and sulfoximines.

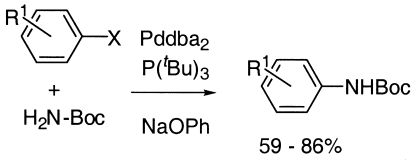
2.3.3.1. Allyl and diallylamine. As described by Putman[63] and Buchwald,[31] *N*-allyl and *N*,*N*-diallylamine readily coupled with aryl halides affording the desired secondary or tertiary amines, respectively (Scheme 13). This palladium-catalysed process formally leads to primary aryl amines. Indeed, deallylation of *N*-allyl or *N*,*N*-diallylamines can be conveniently accomplished with palladium on carbon and methanesulfonic acid yielding the corresponding free aniline.



Ar : 4-bromobenzophenone, 4- and 2-chloroquinoline, 2- and 3-bromoquinoline, 3-bromopyridine, 4-bromobiphenyle

Scheme 13.

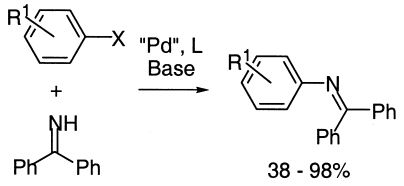
2.3.3.2. *t*Butylcarbamate (NH_2Boc). The catalytic system involving $P(^tBu)_3$ and $Pddba_2$ allows *t*butylcarbamate to react with aryl halides to form *N*-Boc-protected anilines. The use of sodium phenoxide rather than classical bases such as Cs_2CO_3 or NaO^tBu was found to be critical for this transformation (Scheme 14).[26]



X : Br, Cl
R^1 : 2-Me, 4-Me, 4-OMe, 4-CN

Scheme 14.

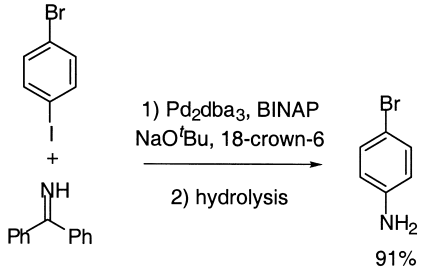
2.3.3.3. Imines. Benzophenone imine can also be considered as a substitute for ammonia in palladium-catalysed amination. Indeed, it efficiently couples with aryl halides (I, Br and Cl) and triflates to afford the corresponding *N*-aryl imine. The latter can be isolated or directly converted to anilines. Various conditions (palladium precatalyst, ligand and base) have been successfully tested including reactions on heteroaromatic compounds at room temperature (Scheme 15).[11,12,64–69]



X : Cl, Br, I, OTf
R^1 : 2-OMe, 4-OMe, 4-^{t}Bu, 2,5-diMe, 3,5-diOMe, 4-COMe, 4-CO_2Me, 4-CN, 4-NO_2

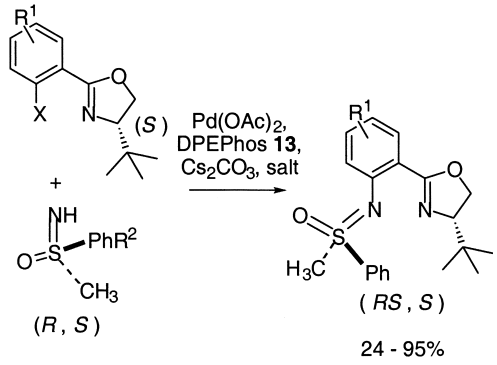
Scheme 15.

Interestingly, selective amination of *p*-bromo-iodobenzene can be achieved in high yield using benzophenone imine in the presence of Pd_2dba_3, BINAP, NaO^tBu, 18-crown-6 and subsequent cleavage of the ketimine with hydroxylamine hydrochloride (Scheme 16).[64]



Scheme 16.

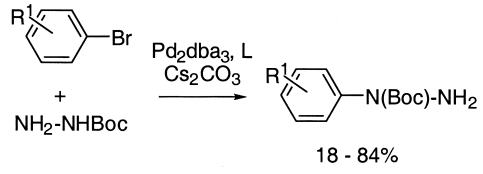
2.3.3.4. Sulfoximines. Despite the lower nucleophilic character of sulfoximines compared to amines or imines, Bolm and co-workers have developed an attractive preparation method for novel aryl sulfoximines. The palladium-catalysed direct arylation of sulfoximines was found to be general and high yielding. Additionally, this methodology has been extended to chiral sulfoximines leading to potential ligands for asymmetric catalysis. Noticeably, the coupling of aryl iodides requires lithium or silver salts (Scheme 17).[70,71]



X : Br, I
R^1 : H, 4-^{t}Bu, 3-OMe, 2-CN, 3-CN, 4-CN, 4-CF_3, 4-NO_2, 4-CO_2Me
R^2 : Me
salt : LiBr, LiCl, AgOTf

Scheme 17.

2.3.4. Hydrazines and hydrazones. Aryl hydrazides can also be obtained by palladium-catalysed coupling of ^{t}butylcarbazate with substituted arylbromides. Indeed, the use of Pd_2dba_3 and either dppf, BINAP or **5** in the presence of cesium carbonate allows the regioselective coupling of ^{t}butylcarbazate and aryl bromides leading to the amination products (Scheme 18).[72]



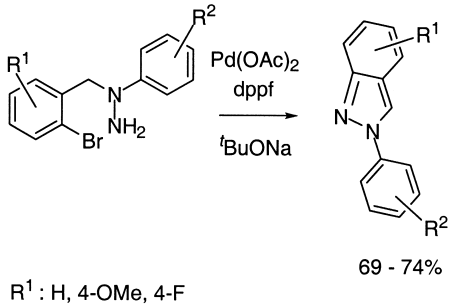
R^1 : H, 4-COMe, 4-CO_2Me, 4-CN, 4-NO_2, 4-COPh, 4-CF_3, 3-Cl,
L : dppf, BINAP, **5**

Scheme 18.

For aryl bromides bearing an additional substituent in the *o*-position, a reversed regioselectivity was observed leading to 1-aryl-2-Boc hydrazines in 69–74% yields.[72]

Similar results were described in the synthesis of pyridyl-(Boc)hydrazines.[73]

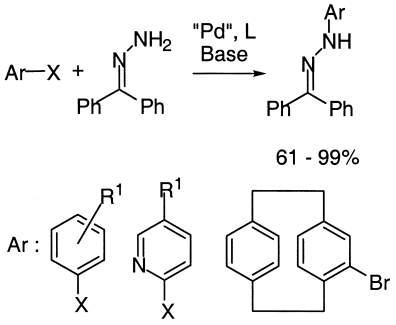
Song has recently published efficient intramolecular versions resulting in the synthesis of various indazoles (Scheme 19).[73,74]



R^1 : H, 4-OMe, 4-F
R^2 : H, 4-OMe, 4-Cl, 4-CN, 4-Me

Scheme 19.

Buchwald, Hartwig and other workers have reported a palladium-catalysed method for the synthesis of *N*-aryl-hydrazones.[75–78] Electron-poor, electron-rich or sterically hindered aryl bromides or iodides were reacted with benzophenone hydrazone under catalytic conditions (Scheme 20). The stronger acidity of the hydrazones compared to the corresponding amines allows the use of common ligands (dppf or BINAP). The *one-pot* two-steps synthesis of non-symmetrical diarylhydrazones, and its application to a Fischer indole synthesis, will be described in Section 2.4.2.



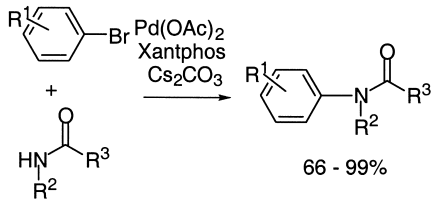
X : Br, I, OTf
R^1 : 2-Me, 4-Me, 3,5-diMe, 3-OMe, 4-OMe, 3,5-diOMe, 4-Cl, 4-Br, 4-CF_3, 4-COMe
Pd : $Pd(OAc)_2$, Pd_2dba_3
L : BINAP, Xantphos, dppf, P^tBu_3
Base : NaO^{t}Bu, Cs_2CO_3

Scheme 20.

2.3.5. Amides, carbamates, hydroxamates, ureas and related nucleophiles. Carbon–nitrogen bonds have been generated from aryl halides and acyclic amides[79] and ureas[80] using palladium catalysis with **12** as a ligand. For both substrates, similar conditions (base, solvent and temperature) led to the coupling products in 66–99 and 64–92% yield, respectively (Scheme 21).

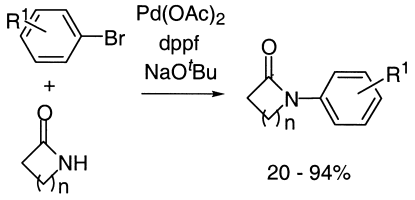
A similar efficient palladium-catalysed method for the preparation of *N*-aryl lactams has recently been reported. Four-, five-, six- and seven-membered ring lactams were coupled to aryl halides in the presence of $Pd(OAc)_2$, dppf and NaO^{t}Bu, affording modest to high yields of amidation (Scheme 22).[79,81,82]

In addition, intramolecular palladium-catalysed amidation



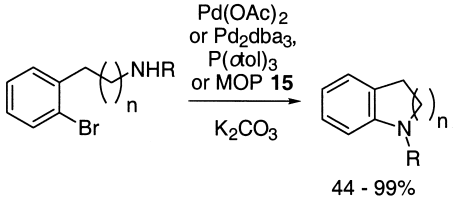
R^1 : 4-CN, 4-CHO, 4-CO_2Me, 4-NO_2, 3-CO_2Me,2-CO_2Me
X : I, Br, Cl, OTf
R^2 : Ph, Me, OEt, OBn
R^3 : H, Me, Et, NH_2, NHPhR^1

Scheme 21.

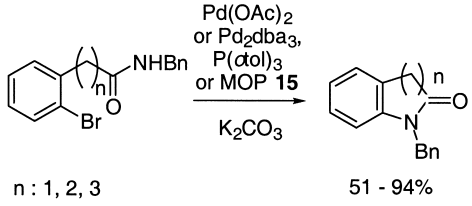


R^1 : H, 3-OMe, 4-CN, 4-COPh, 4-CF_3
n : 1, 2, 3, 4

Scheme 22.



R : MeCO, tBuCO, $TolSO_2$, tBuOCO
n : 1, 2, 3



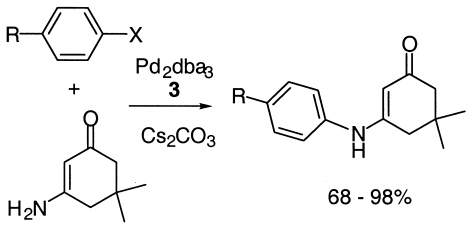
n : 1, 2, 3

Scheme 23.

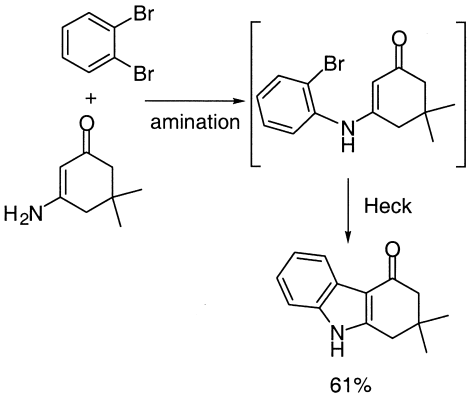
of aryl halides gave rise to the formation of fused heterocycles. As depicted in Scheme 23, amides as well as sulfonamides and carbamates afforded five-, six- and seven-membered rings in similar conditions.[83,84]

Reactions of vinylogous amides with aryl bromides and chlorides have recently been described.[85] A one pot synthesis of N-containing heterocycles by tandem amination–Heck reaction using the same procedure has additionally been reported as well (Scheme 24).

2.3.6. Heterocycles. Whereas the reductive elimination affording arylamines is sensitive to the nucleophilicity of

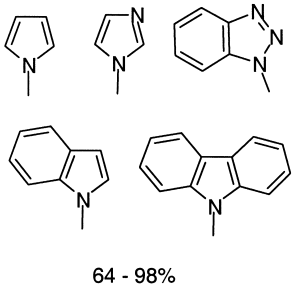


R : H, NO_2, CN, Me, MeO
X : Cl, Br



Scheme 24.

the nitrogen atom, the scope of aromatic C–N bond formation has recently been extended to the preparation of *N*-arylazole derivatives. Indeed the combination of $Pd(OAc)_2$ or $Pddba_2$ and dppf or P^{t}Bu$_3$ catalysed the formation of *N*-arylazoles in the presence of Cs_2CO_3 (better than NaO^{t}Bu) in refluxing toluene (Scheme 25).[26,66,69,86–88]

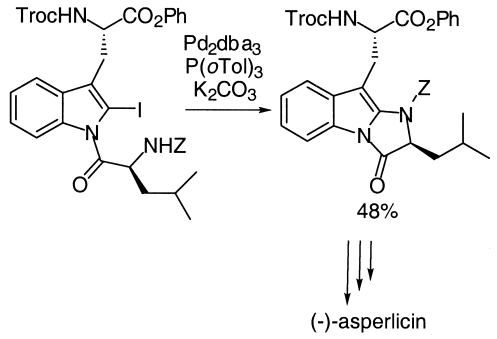


Scheme 25.

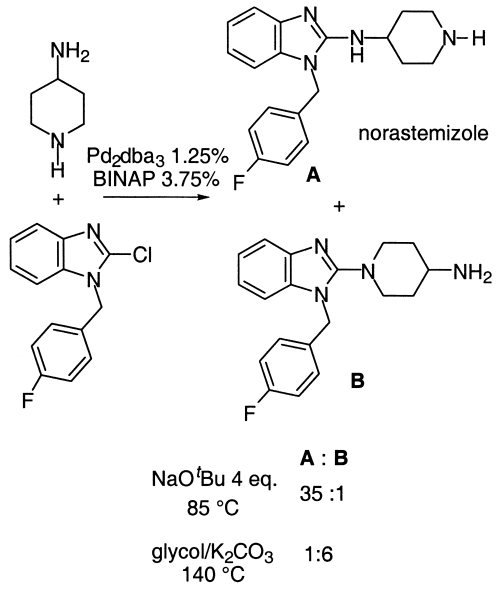
2.4. Applications

2.4.1. Total synthesis of natural and/or pharmacologically active products. In 1998, Snider et al. described the total synthesis of (−)-asperlicin using a palladium-catalysed intramolecular amination of a carbamate on an indole residue (Scheme 26).[89]

Senanayake et al. have reported the synthesis of the non-sedating antihistaminic, norastemizole, in 84% yield with a ratio of 35:1 for the arylation of the primary amine vs the cyclic secondary amine (the same reaction performed under



Scheme 26.



Scheme 27.

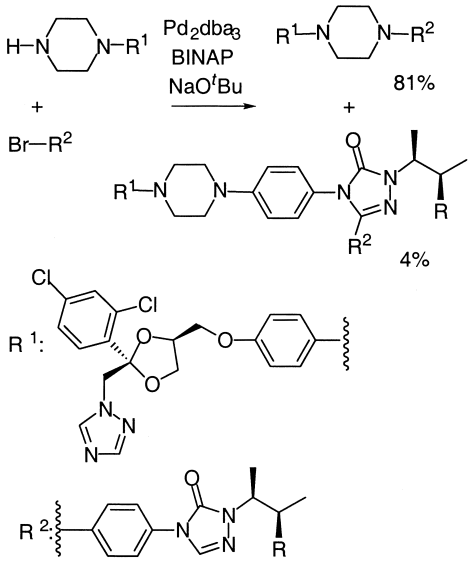
thermal conditions gave an opposite ratio of 1:6 in favour of the more nucleophilic secondary amine) (Scheme 27).[90]

The same group reported the synthesis of the hydroxy derivative (R=OH) of the potent antifungal and antiyeast itraconazole (R=H) using a palladium-catalysed amination between a highly functionalised piperidine and a *p*-substituted aryl bromide.[91] The coupling product was obtained in a spectacular 81% yield along with 4% of the product resulting from the Heck coupling of the aryl bromide on the tetrazolone residue (Scheme 28).

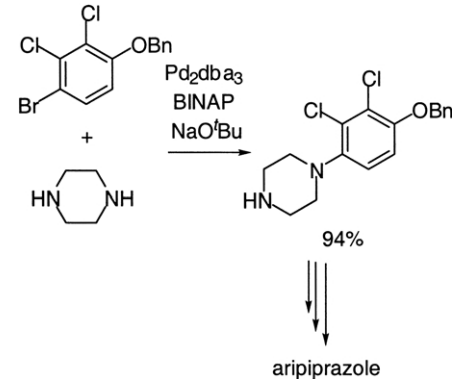
The same year, Morita described the synthesis of an active hydroxy metabolite of the antipsychotic agent aripiprazole using the intermolecular reaction of a trisubstituted aryl bromide with piperazine in 94% yield (Scheme 29).[92]

More recently, Lopez-Rodriguez reported a palladium-catalysed amination of halobenzimidazoles to new benzimidazolylpiperazines and related amines with high affinity for the serotonin 5-HT receptor (Scheme 30).[93]

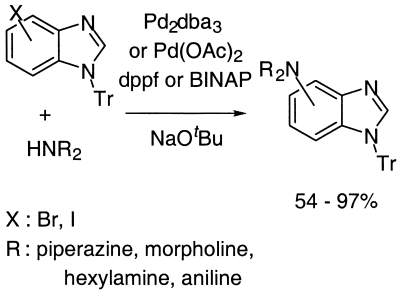
An intramolecular approach to the benthocyanin A skeleton has been proposed by Kamikawa.[94] The use of $Pd(OAc)_2$, BINAP and Cs_2CO_3 affords the tetracyclic phenazines (Scheme 31).



Scheme 28.

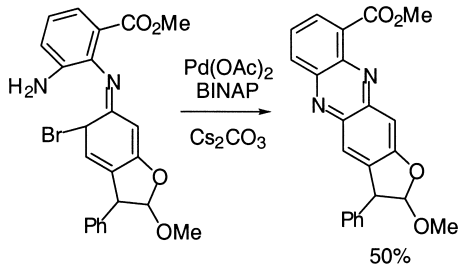


Scheme 29.

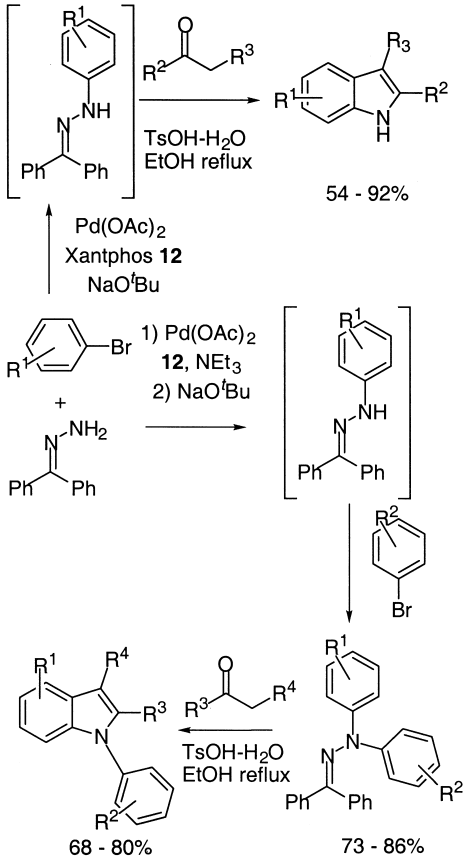


Scheme 30.

2.4.2. Heterocyclic chemistry. Buchwald has described an efficient and brilliant one-pot palladium-catalysed Fischer indole synthesis. The palladium-catalysed coupling reaction of benzophenone hydrazone with an aryl bromide led to the corresponding *N*-arylbenzophenone hydrazone intermediate. The latter compound was then directly submitted to the Fischer cyclisation conditions affording the corresponding indoles in 54–92% yields (Scheme 32).[75]



Scheme 31.

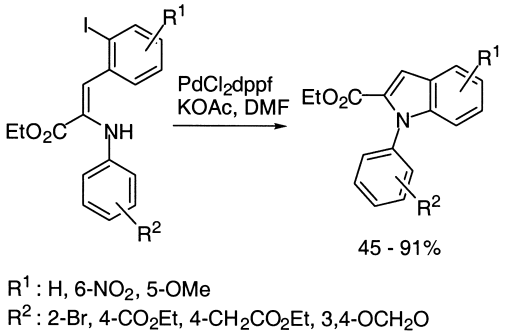


Scheme 32.

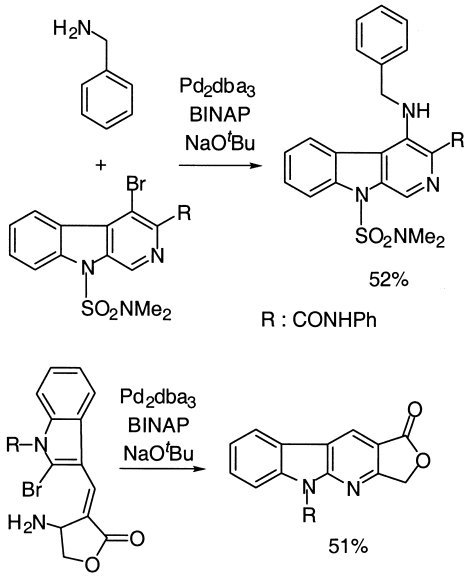
The two-step synthesis of *N*-arylindoles was also described in the same paper. The first step corresponds to a one-pot sequential bis-arylation of the benzophenone hydrazone. The less reactive (more electron-rich) aryl bromide is first reacted, and then at a higher temperature (120°C), the second (more reactive) arylbromide is introduced, affording the diarylated benzophenone hydrazone in 73–86% yield. In the second step, the Fischer cyclisation occurs in high yield and high regioselectivity on the more electron-rich arene as previously described (Scheme 32).[95]

N-Arylindoles have also been prepared via intramolecular palladium-catalysed amination of didehydrophenylalanine derivatives as shown in Scheme 33.[96]

The introduction of amino substituents on the 4-position of β-carbolines was described by Dodd in 1998.[97,98] In the same paper, an intramolecular access to the biologically active α-carboline family is also reported.[98] Palladium aminations have also been described in the synthesis of various carbolines and carbazoles[99] or quinoxalines (Scheme 34).[100]



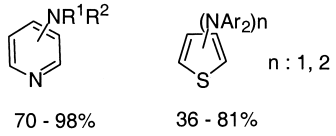
Scheme 33.



Scheme 34.

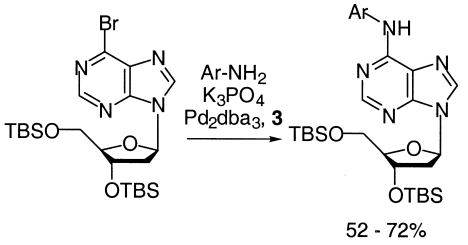
In addition, primary alkylamine as well as secondary cyclic or acyclic alkylamines react with bromo- or chloropyridines under palladium[11,53,101] or nickel[64] catalysis to afford various aminopyridines in high yield. In parallel, the preparation of mono- and bis-diarylaminothiophenes was performed under palladium catalysis using $P(^tBu)_3$ or BINAP as ligand in refluxing xylene in modest to good yields (Scheme 35).[101,102]

2.4.3. Nucleotide chemistry. Palladium-catalysed aminations have been used in the field of nucleotide



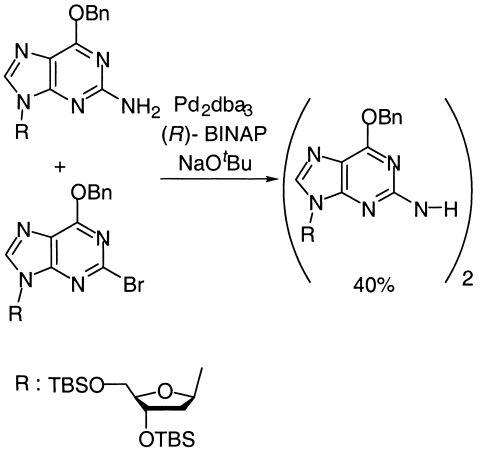
Scheme 35.

chemistry.[103,104] Lakshman described the formation of various carcinogenic arylamines on the C-6 position in nucleosides (Scheme 36).[104]



Scheme 36.

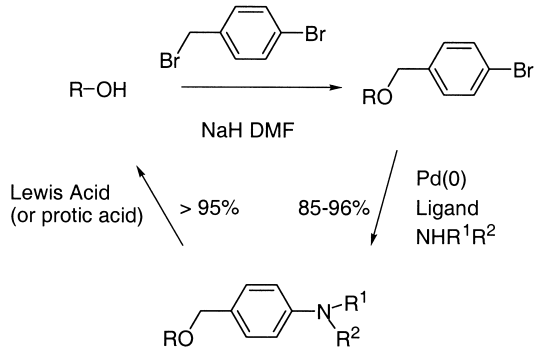
The same year, Sigurdsson and Hopkins applied a similar methodology to the synthesis of a cross-linked DNA (Scheme 37).[105]



Scheme 37.

The same strategy was independently developed by De Riccardis and Johnson[106] in the synthesis of symmetrical and non-symmetrical adducts.

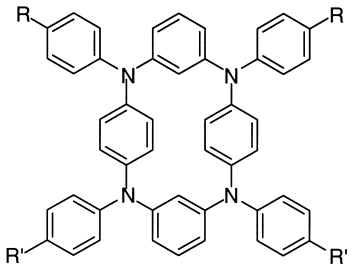
2.4.4. Protecting groups. Buchwald described an interesting application of palladium-catalysed aminations in the field of halobenzyl bromides as protecting groups for alcohols.[107] The protected halobenzyl ethers can be mildly deprotected in high yields using a two-step sequence in which the halobenzyl ether is first transformed, using a standard palladium-catalysed amination, into a tertiary aniline, which can then be easily cleaved by exposure to a Lewis acid (or a protic acid) (Scheme 38). This protection is orthogonal with a wide range of different protecting group such as Bn, PMB, TBDMS, TIPS, acetals and esters. The methodology has been further applied to the synthesis of a trisaccharide.[107]



Scheme 38.

2.4.5. Synthesis of ligands for organometallic chemistry. Palladium-catalysed mono-[108a] and di-arylation[51,108b] of chiral non-racemic diamine ligands without any racemisation have been reported. The diamidoamide ligand $[MesNHCH_2CH_2]_2NH$ used in the zirconium-catalysed polymerisation of alkenes has been synthesised in quantitative yield using the palladium-catalysed diarylation of the unprotected triamine.[109] The syntheses of diverse amino derivatives of optically pure binaphthyl ligands were also described by Buchwald.[110]

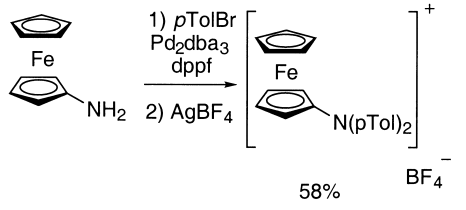
2.4.6. Organic materials. Since the discovery of their conductive and magnetic properties,[111] oligomeric and polymeric arylamines have found an increasing number of industrial applications.[102,112–114] This development was, however, hampered by a high temperature-demanding, non-regular quality, low-yielding Ullman coupling process. The development of efficient palladium-catalysed processes allowed the efficient synthesis of polyanilines,[114,115,117–120] triarylamine dendrimers[67,113–117] and C_{60}-bound triarylamines.[121] Hartwig also described the palladium-catalysed synthesis of symmetrical (one-step synthesis) and non-symmetrical (multistep synthesis) tetraazacyclophanes which led, after oxidation, to stable and geometrically defined dication diradicals (Scheme 39).[122]



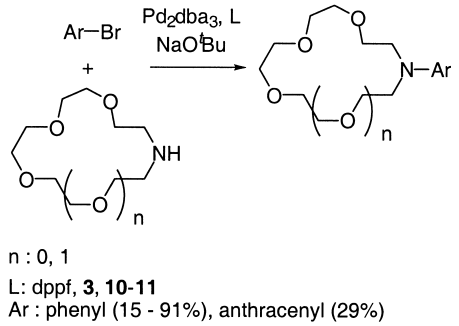
Scheme 39.

Palladium amination has also been used in the synthesis of electronically rich ferrocenes useful for magnetic materials, electrode surface modifiers, and for non-linear optical chromophores (Scheme 40).[123]

The palladium-catalysed synthesis[124,125] as well as a description of the physical and binding properties[124] of



Scheme 40.



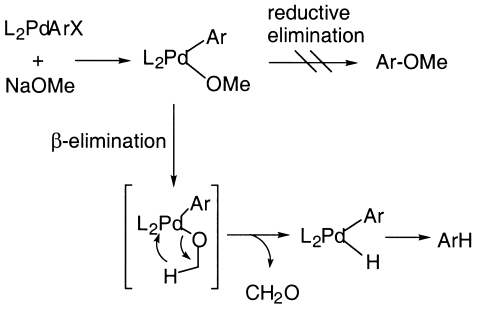
Scheme 41.

N-arylaza-crown ethers have also been reported (Scheme 41).

3. Oxygen-based nucleophiles

3.1. Introduction

Despite the importance of aryl ethers in pharmacologically active molecules,[126] palladium-catalysed formation of such compounds from their parent halides has remained almost unexplored for the last two decades. Indeed, palladium-catalysed reactions of aryl halides with sodium alkoxides were known to involve reduction of the carbon–halide bond through β-elimination rather than reductive elimination, as depicted in Scheme 42.[127]

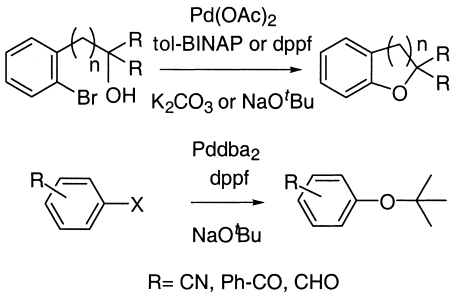


Scheme 42.

One of the few metal-catalysed ether formations from phenoxides (no β-hydrogen) and aryl halides was actually reported by Cramer and Coulson under harsh nickel catalysis.[128] These workers reacted sodium phenoxide with *p*-bromotoluene at 210°C in presence of $TPP_2Ni(COD)_2$ to afford the corresponding ether in low yield (39%).

Recent advances in transition metal, coordination and ligand chemistry, concomitantly developed by Buchwald and Hartwig, have led to novel outcomes in this research area. The first palladium-catalysed C–O bond formations from aryl halides has been reported by Buchwald[129] and Hartwig[130] in 1996. These two groups described intra- and intermolecular C–O bond formations from *o*-haloaryl-substituted alcohols and various aromatic bromides (Scheme 43).

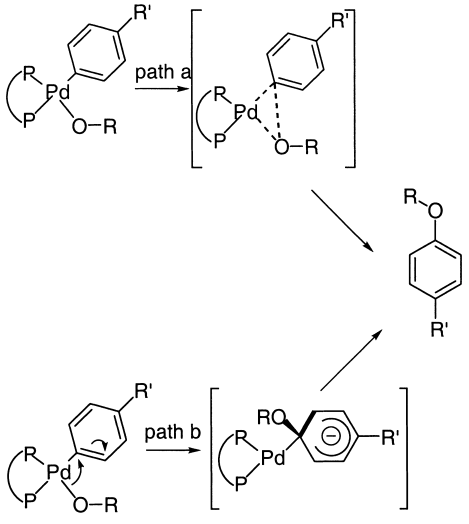
The mechanism most likely proceeds via a sequence similar to that suggested for the aryl amination process.[9,131,132,161]



Scheme 43.

As in amination chemistry, the conversion of aryl halides into the corresponding ethers requires a fast reductive elimination compared to the β-hydrogen elimination of the alkoxide. As (1) alkoxides are less nucleophilic than amines, (2) C–O bond formation from reductive elimination is significantly slower than the corresponding rate to form C–N bonds,[9] and (3) β-hydrogen elimination is rather fast for alkoxides, the formation of aryl ethers using this approach appears to be mainly limited to electrophilic aryl groups. Nevertheless, novel catalytic systems have recently been developed to partly overcome the alkoxide reactivity problems and to allow the use of electron-rich or neutral aryl halides.

While the exact mechanism for the key reductive elimination step remains unknown, some mechanistic insights have been reported.[133,134] Two plausible mechanisms have been proposed. The first (path a, Scheme 44) corresponds to a concerted process similar to that proposed for C–C reductive elimination and the second (path b, Scheme 44) deals with an inner sphere nucleophilic attack of the alkoxide ligand at the *ipso* carbon atom of the palladium-bound aryl group via a Meisenheimer type species (Scheme 44).



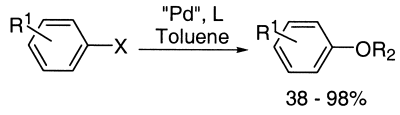
Scheme 44.

For electron-deficient aryl halides, capable of delocalising the negative charge, pathway b seems to be favoured.[134] On the other hand, for electronically neutral or electron-rich aryl halides a three-centered transition state has been suggested.[134]

Very recently, Hartwig reported the in situ transformations of poorly active transition metal complex intermediates into highly active species leading to unprecedented C–O bond formation at room temperature.[135] Alkylaryl, arylsilyl and diaryl as well as cyclic ethers were prepared with fast rates (i.e. 10 min) and high yields (93%).

3.2. Alkyl aryl ethers

Alkyl aryl ethers can be readily obtained using aryl bromides or chlorides and alkoxides under palladium catalysis as shown in Scheme 45.[130,136] A large variety of substituted arenes is tolerated. Indeed, electronically rich, neutral and deficient aromatic groups have been used. Alcohols ranging from acyclic, cyclic and benzylic to more elaborated derivatives were tested. Sodium or potassium alkoxides can be preformed or prepared in situ. In the latter case, various bases such as NaH, CsF, Cs_2CO_3, K_3PO_4 or NaO^{t}Bu have been reported. Toluene appears to be one of the most widely used solvents in C–O coupling reactions. $Pd(OAc)_2$ and $Pddba_2$ or Pd_2dba_3 exhibit similar efficiency as precatalysts in most cases. In addition to the palladium precatalyst, several ligands have been tested, depending on the substituent of the aryl group. Although fast reductive elimination rates were observed for electron-deficient aryl groups,[130] unactivated arylpalladium complexes were also shown to undergo reductive elimination, especially with hindered phosphines (**4** or P(^{t}Bu)$_3$).[137] Indeed the use of electron-rich, bulky, chelating ligands (diphosphine ligands) improved the reactions.[138]



X : Cl, Br; Y : Na, K

R^1 : 4-PhCO, 4-CN, 4-CF_3, 4-Et_2NCO, 4-CHO, 4-^{t}Bu

R^2 : ^{t}Bu, $CH(Me)_2$,$CH(Et)_2$, Bn, Cyclohexyl, Cyclopentyl

"Pd" : $Pddba_2$, Pd_2dba_3, $Pd(OAc)_2$, $PdTPP_4$

L: TolBINAP, dppf, **4**

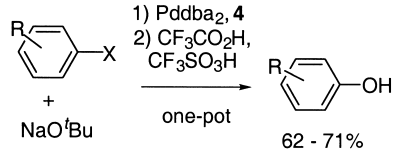
Scheme 45.

The direct formation of ethers by nucleophilic aromatic substitution has been ruled out by isolation of the palladium arylalkoxo complex intermediate and subsequent thermal reductive elimination.[13]

3.3. Access to phenols

On the other hand, aryl halides can be efficiently converted to aryl alcohols using NaO^{t}Bu under palladium catalysis. After completion of the etheration, subsequent treatment of the crude reaction mixture with triflic acid and 2,2,2-trifluoroethanol or trifluoroacetic acid allows a direct one-pot/two step access to phenols (Scheme 46).[129,130,139]

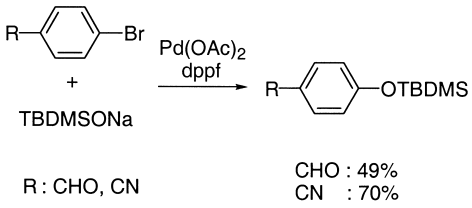
Access to silyloxy ethers has also been developed starting from aryl bromides and sodium silyloxides.[140] The use of $Pddba_2$ and dppf in toluene at 120°C afforded the corresponding silyl ether in good yields (Scheme 47).



X : Cl, Br, I

R : 2,5-diMe, 4-PhCO

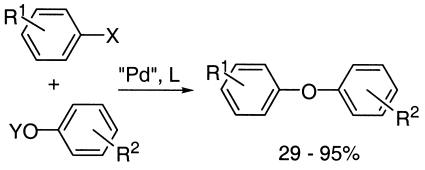
Scheme 46.



Scheme 47.

3.4. Diaryl ethers

The preparation of diaryl ethers can also be performed through reductive elimination of arylpalladium phenoxides. The latter can be obtained by the reaction of arylpalladium halides with sodium aryloxides (Scheme 48).[139,141] In most cases the use of preformed sodium phenolates can be obviated. A wide range of substrates and functional groups such as aryl halides and triflates, and electronically neutral, electron-rich or deficient arenes are compatible with this approach.



X : Cl, Br, I, OTf; Y : Na, K

R^1 : H, 2,5-diMe, 3,5-diMe, 4-PhCO, 4-CN, 4-CF_3, 4-Et_2NCO, 4-CHO, 4-^{t}Bu, 4-$COCF_3$, 4-COMe, 4-COOMe, 4-nBu, 4-MeO, 3-MeO, 2-Me

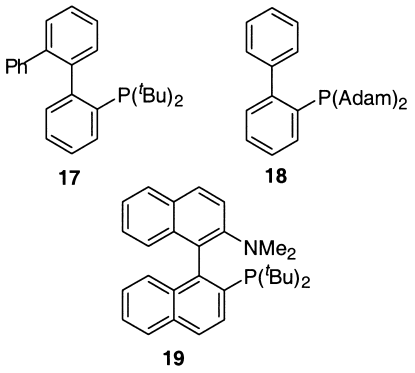
R^2 : 4-OMe, 4-Me, H, 2-Me, ^{t} Bu, 3-^{i}Pr, 2-^{i}Pr, 2,6-diMe, 3,4-diMe, 2-OMe-4-Me

"Pd" : $Pddba_2$, $Pd(OAc)_2$

L : **4, 3, 12-14**

Scheme 48.

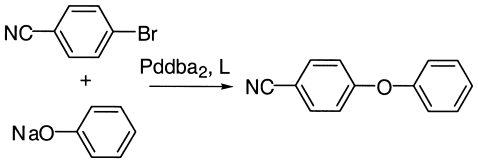
Because phenoxides are less nucleophilic than alkoxides, the formation of diaryl ethers often requires ligand modification. In both catalytic and stoichiometric studies, the ligand properties (size and electronic properties) seem to play a major role in the preparation of diaryl ethers. A considerable amount of effort has been dedicated towards the development of novel highly efficient ligands **17**–**19** (Scheme 49).[141] Particularly in the diaryl ether field, it has been shown that palladium complexes with sterically

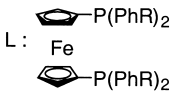


Scheme 49.

hindered ligands accelerate the reductive elimination step, thus facilitating the formation of diarylethers. In these cases, bulky ligands (Scheme 49) are necessary to destabilise the ground state of the aryl(phenoxy)palladium complex. Steric hindrance pushes the substituents toward each other in a conformation favouring the three-centered transition state.[132]

Additionally, it has been shown that the electronic properties of the ligand substantially affect the yields of formation of diaryl ethers.[142] For example, the reaction of sodium phenoxide, *p*-bromobenzonitrile and $Pddba_2$ in a mixture of toluene/THF at 100°C depends on the nature and properties of the ligand. As depicted in Scheme 50, when dppf is used, a 51% yield is obtained. This yield increases with electron-poor-substituted dppf ligands such as CF_3–dppf. In general, an electron-rich phosphine such as MeO–dppf leads to a low-yield reaction. Electron-poor ligands are expected to accelerate the reductive elimination process, leading to an improved yield.





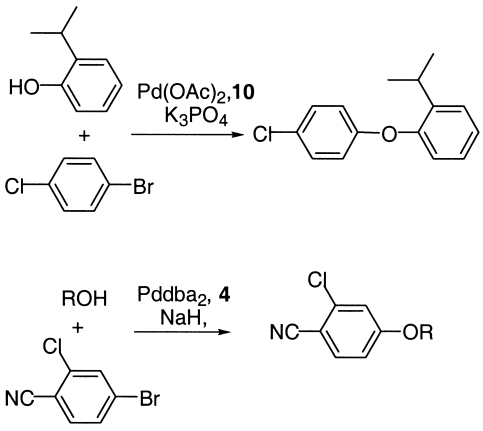
R	Yield (%)
H (dppf)	51
CF_3	74
MeO	8.5

Scheme 50.

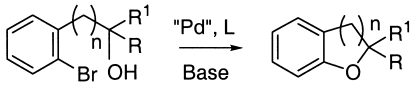
As expected, when both chlorine and bromine atoms are present on a substrate, the palladium-catalysed reaction affords the diaryl ether product resulting from exclusive bromine substitution (Scheme 51).[136,141]

3.5. Intramolecular C–O bond formation

Several authors have also reported intramolecular



Scheme 51.

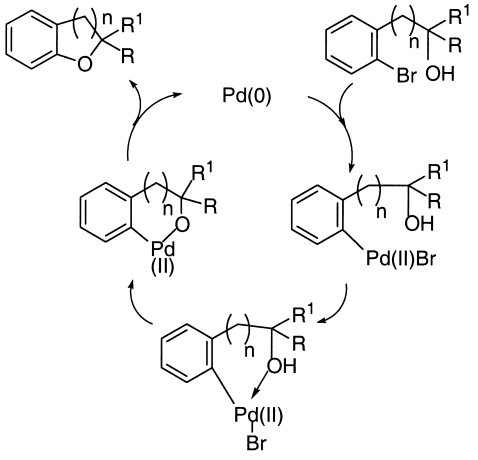


R, R^1 : alkyl, cycloalkyl, H
n : 1, 2, 3
"Pd" : $Pddba_2$, $Pd(OAc)_2$
Base : K_2CO_3, NaO^tBu
L : dppf, tolBINAP, **4**

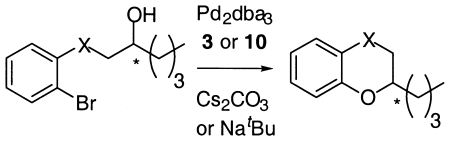
Scheme 52.

palladium-catalysed *ipso* substitution of aromatic halides, as depicted in Scheme 52.[129,133,134]

Thus, five-, six- and seven-membered heterocycles have been obtained. Commonly, the nucleophile is prepared in situ using potassium carbonate or sodium ^{t}butoxide. As already mentioned, the use of chelating ligands improves the chemical yields. These reactions not only proceed with tertiary alcohols, but also with secondary alcohols. It is believed that the reaction occurs through oxidative addition of the aryl halide, subsequent formation of the palladium oxametallacycle and C–O bond formation after reductive elimination (Scheme 53). The proposed oxametallacycle intermediate has never been observed or isolated.



Scheme 53.

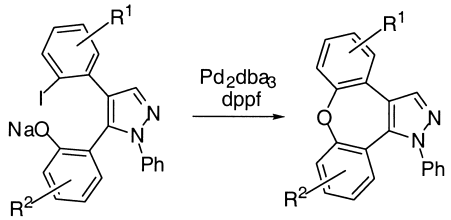


X : O; 93% yield; 90% ee
X : NMe; 95% yield; 99% ee

Scheme 54.

In a similar way, *N*- and *O*-heterocycles were prepared by cyclisation of optically active alcohols providing access to optically active cyclic ethers with up to 99% ee (Scheme 54).[143]

Using an intramolecular palladium-catalysed diaryl ether reaction, an efficient methodology has been used for the preparation of dibenzoxepine structures (Scheme 55).[144]



R1 : H, 3, 4-diOMe
R2 : H, 3-NEt2, 3, 5-diOMe, 2,3-diOMe

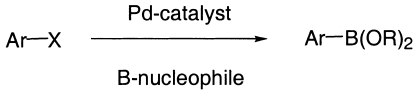
Scheme 55.

At the present time, the palladium-catalysed synthesis of aryl ethers from aryl halides does not seem to be as general as the formation of aryl amines from arylhalides. Some general comments can, however, be addressed: (1) in most cases a non-polar solvent proved to be useful for the catalytic process, (2) $Pd(OAc)_2$, $Pddba_2$ and Pd_2dba_3 exhibit a similar efficiency as the precatalyst, (3) classical combination of Pd precatalyst and dppf, Binap or tolBinap as ligand provides good to high yields of etheration products with electron-deficient aryl halides, and (4) bulkier chelating ligands have to be employed when electron-rich or neutral aryl halides are reacted.

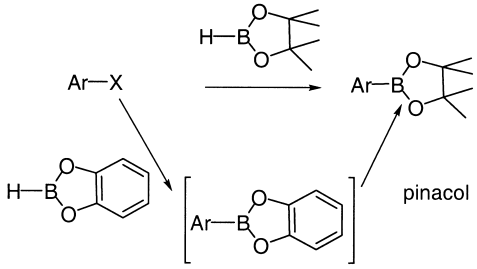
4. Boron-based nucleophiles

Palladium-catalysed reactions involving arylboronic acids or esters have found widespread applications in organic synthesis and constitute the popular Suzuki coupling procedure.[145]

Although arylboronic acid derivatives are available by several methods, a considerable amount of effort has been devoted to palladium-catalysed C–B bond formation. It has been shown that aryl halides undergo borylation reactions under palladium catalysis using two different boron nucleophiles: alkoxydiboron derivatives, $(RO)_2B–B(OR)_2$[146] or alkoxyboranes, $H–B(OR)_2$. The first route that involved a transmetallation step in the catalytic cycle will not be covered by the present review (Scheme 56).[147]



Scheme 56.

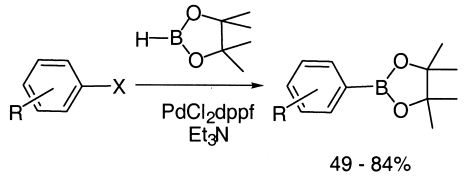


Scheme 57.

Arylboronic esters can either be prepared from pinacolborane[148] and arylhalides or triflates in the presence of $PdCl_2$dppf as catalyst or from catecholborane using similar conditions.[149]

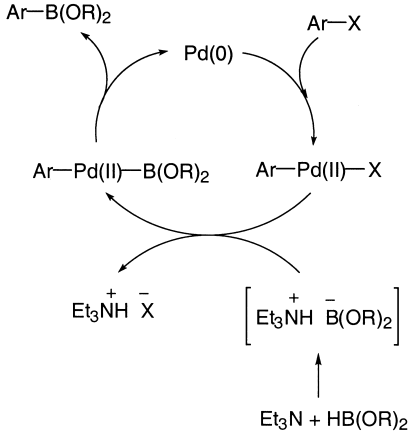
As catechol esters are moisture sensitive, they have to be converted into the more stable pinacol esters by transesterification (Scheme 57).

In this procedure, tertiary amines, especially Et_3N, which is known not to participate in the Suzuki type reaction, have been shown to be the most effective base. In the presence of Hünig's base, pyridine, DBU or KOAc, the reduced species Ar–H were observed predominantly (Scheme 58).



X : I, Br, OTf
R : H, 4-Cl, 4-Me, 2-Me, 4NMe2, 4-CH2CN, 4-NHAc, 4-CO2Me, 4-COMe, 4-MeO, 4-NO2, 4-CN

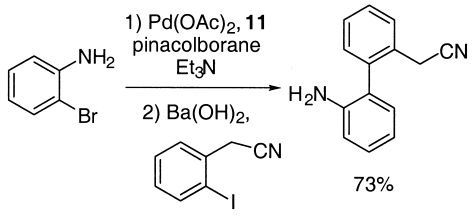
Scheme 58.



Scheme 59.

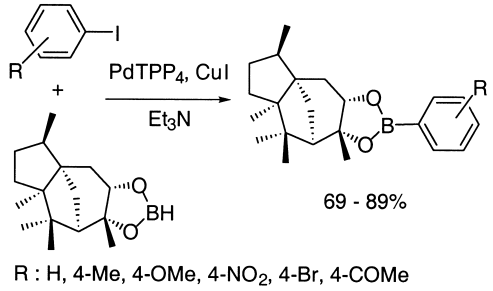
According to the general mechanism described for nitrogen- and oxygen-based nucleophiles, the proposed mechanism[149] involves the reaction of a boryl anion (generated by the reaction of triethylamine and dialkoxyborane) with the product resulting from the oxidative addition of the aryl halide on the palladium catalyst. The production of Ar–Pd(II)–$B(OR)_2$ and subsequent reductive elimination afford the arylboronate (Scheme 59).

Borylation of hindered *o*-substituted phenyl halides using $Pd(OAc)_2$, **11** and Et_3N in dioxane has recently been described.[150] This strategy has been applied to the one-pot preparation of *o*-substituted biphenyls by a Suzuki type reaction of the in situ-formed aryl boronate with an aryl iodide in the presence of barium hydroxide (Scheme 60).

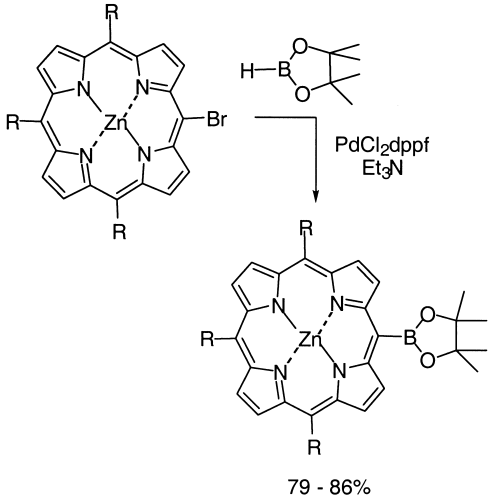


Scheme 60.

Morin has recently introduced a useful novel borylating agent,[151] cedranediolborane, which can be readily coupled to various aryl iodides to afford the corresponding boronates in high yields (Scheme 61).



Scheme 61.



Scheme 62.

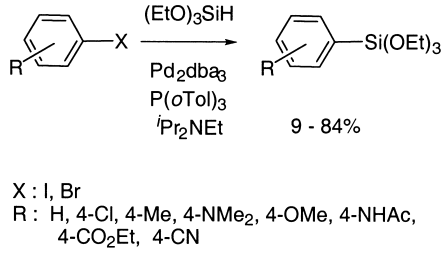
Therien et al.[152] have applied both Miyaura[146] and Masuda[149] procedures in order to obtain borylated porphyrins. According to their study, the best yields were obtained using the latter strategy (Scheme 62).

5. Silicon-based nucleophiles

Silylation of aryl halides under palladium catalysis can be achieved using disilanes ($R_3Si–SiR_3$), but will not be covered in this review.[153–158]

Until recently, the use of a combination of trialkylsilanes and a palladium catalyst was known to efficiently afford the reduction of aryl halides to a C–H bond.[159] Kunai was the first, however, to report a C–Si bond formation (as by-product of the major C–H bond) under similar reaction conditions.[160]

Although the mechanism is still unclear and no explanation for the exact role of the tertiary amine employed is given, a relevant example of palladium-catalysed silylation has been reported.[161] Indeed, Masuda found that triethoxysilane, $(EtO)_3SiH$, reacted with aryl halide in the presence of $^iPr_2NEt$, Pd_2dba_3 and $P(o\text{Tol})_3$ to afford arylsiloxanes (Scheme 63).

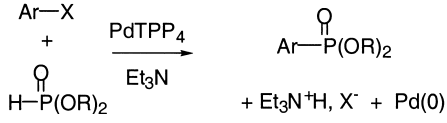


Scheme 63.

6. Phosphorus-based nucleophiles

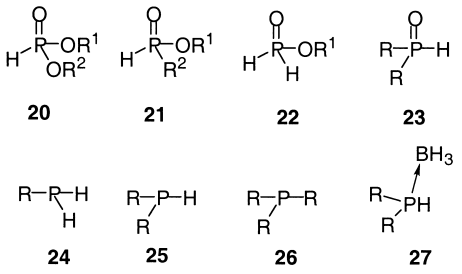
6.1. Introduction

Palladium-catalysed *ipso*substitution of aryl halides by phosphorus-based nucleophiles has been known since the early 1980s, when, Hirao[162,163] reported the reaction of dialkylphosphites with aryl halides in the presence of triethylamine and a catalytic amount of $PdTPP_4$ (Scheme 64).



Scheme 64.

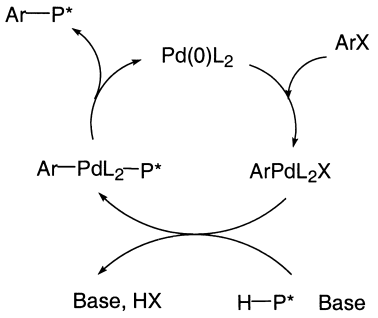
Based on these initial reports with dialkylphosphites **20**, the methodology has been extended to a wide variety of phosphorus nucleophiles, i.e. phosphonous esters **21**, hypophosphites **22**, dialkyl- or diaryl-phosphine oxides **23**, mono-, di- or tri-phosphines **24**–**26** and phosphine–borane complexes **27** (Scheme 65).



Scheme 65.

6.2. Mechanism

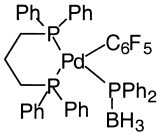
Although few detailed studies on the reaction mechanism have been published in the literature,[164] the general mechanism[165] proposed for these transformations involves the reaction of the oxidative addition product ArPdX with a phosphorus nucleophile. The resulting palladium(II) $ArPdL_2–P^*$ species then undergoes a reductive elimination affording the coupling product and regenerating the Pd(0) complex (Scheme 66).



Scheme 66.

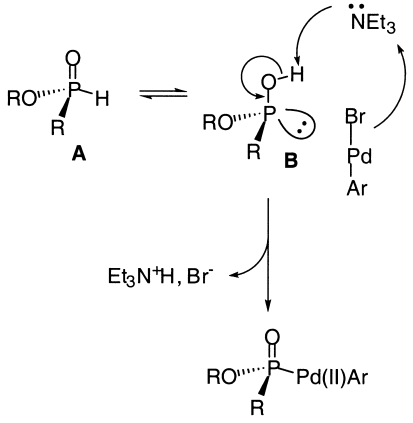
The major issue arising from the mechanism concerns the nature of the nucleophile. Is a phosphorus anion involved in these reactions, or does the base only act as an HX scavenger in the regeneration of the palladium(0) complex? This issue mainly depends on the nature of the phosphorus nucleophile.

When phosphine–borane is involved, a phosphorus anion actually takes part in the mechanism leading to the Ar–Pd(II)–P species. The latter has been be crystallised with a chelating diphosphine ligand (Scheme 67).[164]



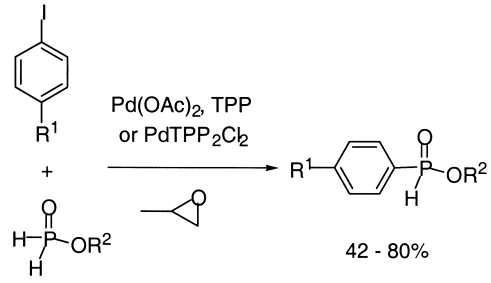
Scheme 67.

With oxophosphorus nucleophiles, the situation is more complex and, to the best of our knowledge, is not yet stated. In the case of the palladium-catalysed arylation of a chiral non-racemic hypophophorous ester in the presence of triethylamine, a complete retention of configuration of the phosphorus atom has been observed.[166] According to the authors, this observation could be attributed to the reaction of the tricoordinated tautomer **B** of the phosphorus nucleophile. The lone pair of the P(III) species reacts with the palladium complex and facilitates the base-assisted loss of a proton (Scheme 68).



Scheme 68.

On the other hand, it has been shown[167–170] that, in the reactions involving hypophosphite nucleophiles, tertiary amines can be substituted by simple HX scavengers such as propylene oxide (Scheme 69).

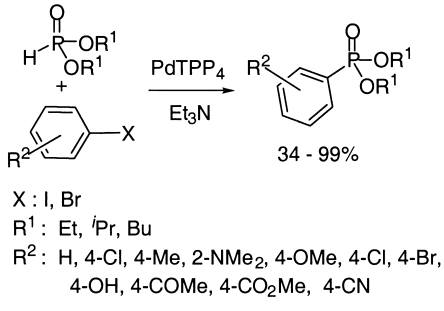


Scheme 69.

6.3. Different classes of phosphorus-based nucleophiles

6.3.1. Dialkylphosphites: access to arylphosphonates. Palladium-catalysed reactions of dialkylphosphites and aryl halides provide a useful access to arylphosphonates. Various aryl halides have been used in C–P bond formation.[164,165,171,172]

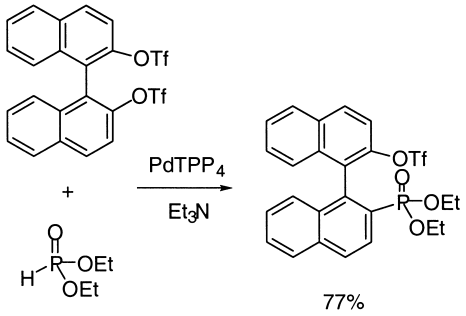
In most examples, $PdTPP_4$ and Et_3N were used as the



Scheme 70.

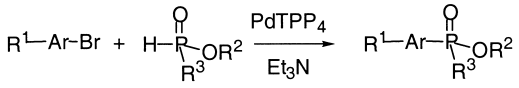
catalyst and base, respectively. Usually, the best results were obtained with a 2- to 4-fold excess of base and dialkylphosphite (Scheme 70).

It is of interest to note that, only monophosphorylation[173] occurs when treating binolbistriflate with diethylphosphite, even when a large excess of the phosphorylating agent is employed (for similar examples using other phosphorus-based nucleophiles, see Section 6.4.1) (Scheme 71).



Scheme 71.

6.3.2. Hypophosphonous esters: access to arylphosphinate esters. Arylphosphinates can also be obtained in high yields under palladium catalysis. As shown in Scheme 72, various aryl halides and phosphonous esters have been successfully used.[165,172,174]

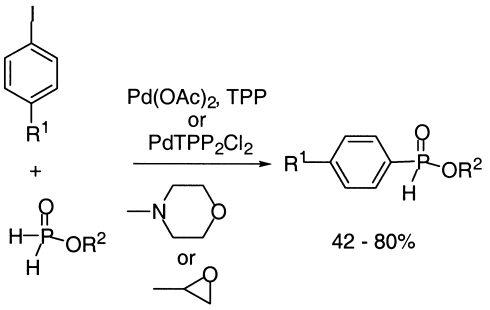


Ar : Ph, 1-naphthyl, 2-thienyl
R^1 (Ph): H, 4-Me, 2-Me, 4-Cl, 4-OMe, 4-NMe_2, 4-Ph, 4-NO_2, 3-NO_2, 4-COMe, 4-CN, 3-CN, 4-NHCOMe, 4-$NHCO_2Me$
R^2 : Et, ^{n}Bu
R^3: Ph, Me, ^{n}Bu, $CH(OEt)_2$

Scheme 72.

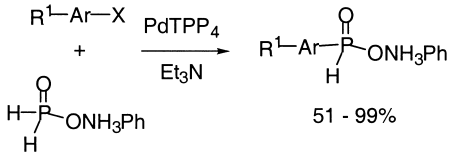
6.3.3. Hypophosphites: access to phosphonous esters and phosphinates. Selective mono- and di-arylation of hypophosphites have been described by Schwabacher[167–170] leading, respectively, to phosphonous esters and phosphinates. Hypophosphites readily couple with aryl iodides to afford mono-arylated products in 42–80% yield (Scheme 73).[167,170] In order to avoid the formation of diarylated products, a 3:1 or 2:1 ratio of methylphosphinate/arylhalide is recommended. In contrast, reducing the amount of methylphosphinate results in disubstitution.

More recently, Montchamp has reported the use of anilinium hypophosphite as a novel phosphorylating agent.[175] This conveniently prepared hypophosphite salt—which avoids the preparation and use of classical hazardous hypophosphorous derivatives—proved to be general and has allowed selective mono-arylation with aryl iodides, bromides and triflates in high yields (Scheme 74).



R^1 : H, 4-Me, 4-Ph, 4-OH, 4-NO_2, 4-CO_2Me, 4-$CH_2CH(NHBoc)CH_2NHBoc$
R^2 : Me, ^{t}Bu

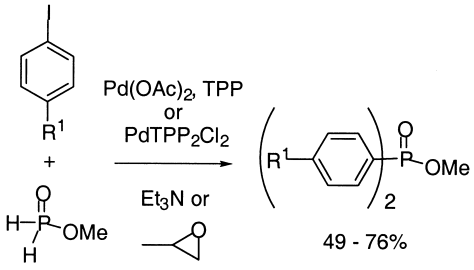
Scheme 73.



X : I, Br, OTf
Ar : Ph, 1-napthyl, 2-napthyl
R^1 (Ph) : H, 2-Me, 3-Me, 4-COMe, 4-NO_2, 4-OMe, 2-Br, 3-Cl, 4-Cl, 4-CO_2H, 4-CO_2Me

Scheme 74.

Symmetrical diarylphosphinates can be obtained in one step using 3 equiv. of aryl halides (Scheme 75).[168,170]



R^1 : H, 4-Me, 4-OH, 4-$CH_2CH(NHBoc)CH_2NHBoc$

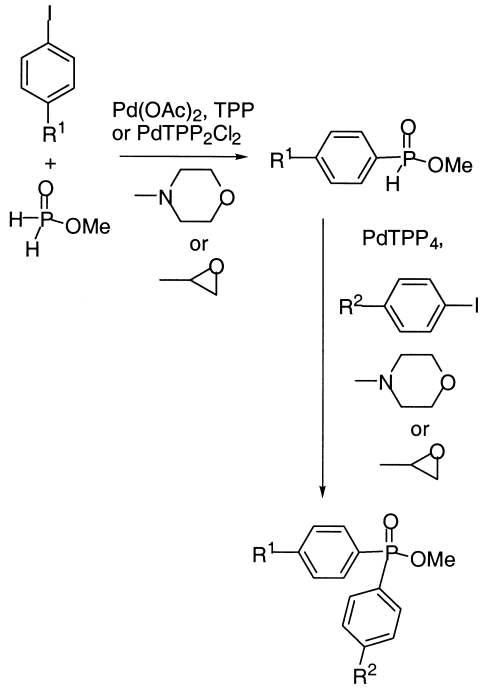
Scheme 75.

On the other hand, unsymmetrical diarylphosphinates have also been prepared by the stepwise introduction of the two different aryl fragments (Scheme 76).[169,170]

Xu has developed an intramolecular version of the phosphorylation described earlier, leading to benzoxaphosphacycloalkanes (Scheme 77).[176]

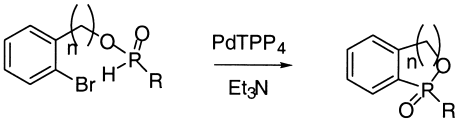
As mentioned in Section 6.2, when chiral phosphonous esters are used, the palladium-catalysed transformation has been shown to proceed with complete retention of configuration at the phosphorus atom (Scheme 78).[166,177,178]

6.3.4. Phosphine oxides: access to trialkyl(aryl)phosphine oxides and phosphines. Since triarylphosphine



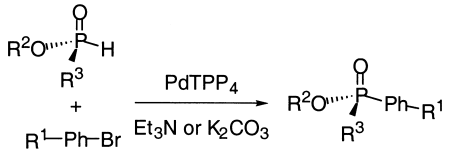
R^1: 4-Ph, 4-CO_2Et, 4-$CH_2CH(NHCbz)CH_2CO_2R$
R^2: 4-Me, 4-$CH_2CH(NHCbz)CH_2CO_2R$

Scheme 76.



R : Ph, Me, *n*Bu
n : 1, 2, 3

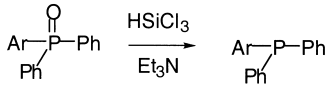
Scheme 77.



R^1: H, 4-Me, 2-Me, 4-OMe, 2-OMe, 4-Ph, 4-NO_2
R^2: *i*Pr, menthyl
R^3: Ph, Me

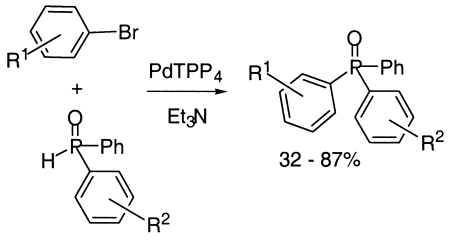
Scheme 78.

oxides were shown to be readily converted into valuable triarylphosphines (Scheme 79),[179] the palladium- (and nickel-[180]) catalysed arylations of phosphine oxides have been widely studied.



Scheme 79.

Tertiary alkylarylphosphine oxides have been prepared using alkylphenylphosphine oxides, aryl bromides and triethylamine under palladium catalysis (Scheme 80).[181,182]

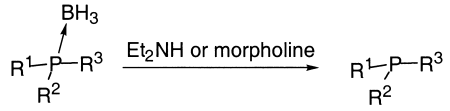


R^1: *n*Hex, *n*Bu, benzyl
R^2: H, 4-Me, 2-Me, 4-COMe, 4-Ph, 4-CN, 4-NHCOMe

Scheme 80.

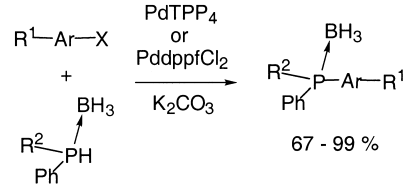
The reaction involving binaphthyl bistriflate in the preparation of Binap-type ligands will be detailed in Section 6.4.1.

6.3.5. Phosphine–borane complexes. The second class of phosphorus-based nucleophiles requiring deprotection step to afford a phosphine is the phosphine–boranes. It has been shown that the borane moiety can be easily removed using a large excess of diethylamine or morpholine (Scheme 81). This deprotection occurs with complete retention of configuration.[183]



Scheme 81.

The use of phosphine–borane complexes takes advantage of the stability of the phosphorus-adduct nucleophile. Moreover, it allows reactions at room temperature (or below). Several examples of C–P bond formation have been reported (Scheme 82).[164,182,183]

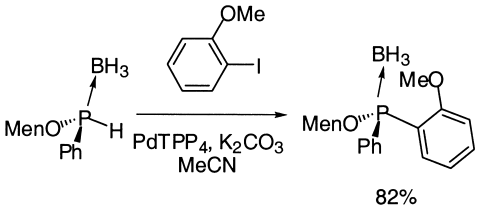


X : I, OTf, ONf
Ar : Ph, naphthyl, binaphthyl
R^1 (Ph): H, 4-MeO, 2-F, 3-Cl, 4-Br
R^2 : Me, Ph, 2-MeOPh

Scheme 82.

Significant acceleration of phosphorylation reactions has been observed when Pd/Cu catalytic systems were employed. Additionally, the use of CuI as a cocatalyst allows the reaction to proceed at 0°C. Livinghouse proposed a base-assisted P–Cu bond formation prior to the coupling reaction.[184]

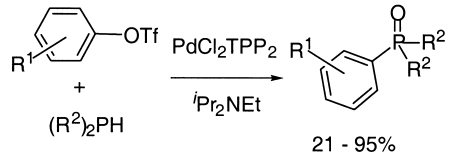
Stereospecific introduction of aryl groups has also been reported on chiral phosphine–borane complexes (Scheme 83).[178]



Scheme 83.

In classical reaction conditions ($PdTPP_4$, K_2CO_3, MeCN) a complete retention of configuration is observed. In contrast, Imamoto described a dramatic solvent effect with inversion of configuration in ethereal solvents.[178]

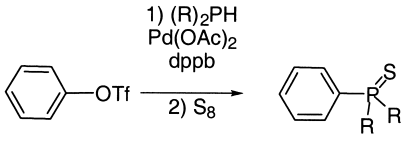
6.3.6. Phosphines. A direct access to secondary or tertiary phosphines from primary or secondary phosphines, avoiding a further deprotection step, is of considerable interest. In contrast to nickel chemistry,[185,186] however, palladium-catalysed processes have been much less studied. Indeed, palladium(0) and palladium(II) as well as residual oxygen (or their combination) are known to promote oxidation of R_2PH to $R_2P(O)H$ (Scheme 84).[187]



R^1: 4-OMe, 2-OMe-6-CO_2Me, 2-OMe-6-CH_2OMe, 4-CO_2Me, 3-CO_2Me, 3,5-diCO_2Me,
R^2: Et, Ph

Scheme 84.

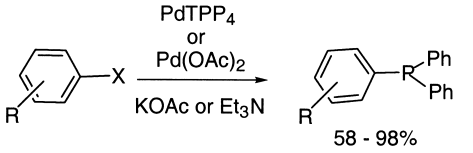
To avoid oxidation, potentially air-sensitive phosphines are usually converted into the more stable phosphine sulfide group in situ (Scheme 85).[188]



Scheme 85.

The preparation of variously substituted phosphines by palladium-catalysed cross-coupling has been reported by Stelzer.[189] Tertiary phosphines bearing one mono- or di-substituted phenyl ring were obtained without oxidation or protective groups in 58–98% yields (Scheme 86).

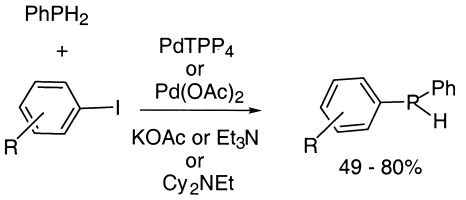
Selective arylation of phenylphosphine may also be obtained. Indeed, mono-arylation leading to diarylphosphines has been reported in modest to high yields,



X : I, Br
R : 4-Me, 4-NH_2, 2-NH_2, 4-OH, 3,5-diMe, 4-CO_2H, 3-CO_2H, 2-CO_2Me, 3,5-diCO_2H

Scheme 86.

affording a potential sequential access to unsymmetrical triarylphosphines (Scheme 87).[188]



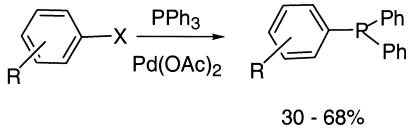
R : 4-NH_2, 2-NH_2, 3,5-diMe, 3-CO_2H, 4-SO_3Na

Scheme 87.

Similarly, when an excess of the phosphorus nucleophile is used, diarylation of phenylphosphine is obtained.

6.3.7. Triarylphosphines. Recently phosphorylation using a triarylphosphine as the phosphorylating agent emerged as a general and convenient route to unsymmetrical triarylphosphines. Additionally, this approach tolerates base-sensitive functional groups.[190–192] Although the methodology does not involve base-assisted formation of a phosphorus anion nucleophile, it was found to be of practical importance and completes the C–P bond formation methods.

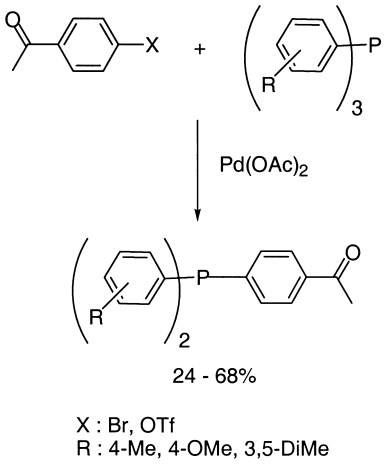
This methodology utilises a catalytic aryl–aryl exchange reaction on the triarylphosphine. The reaction proceeds using an excess of PPh_3 in DMF at 110°C (Scheme 88).



X : Br, OTf
R : 3-OMe, 4-OMe, 3,5-diMe, 4-Cl, 4-Me, 4-^{t}Bu, 4-CN, 4-CHO, 4-COMe, 4-CO_2Me

Scheme 88.

Naphthyl, pyridyl, pyridylphenyl or naphthylquinoline substrates have been subjected to C–P bond formation. As shown in Scheme 89, not only triphenylphosphine but also various phosphorylating agents have been used for this purpose.[190–192]



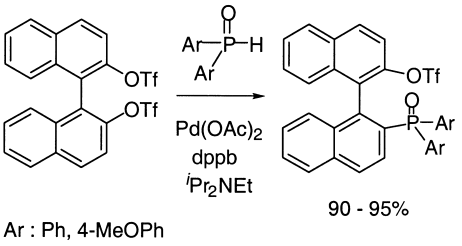
Scheme 89.

6.4. Applications

6.4.1. Ligands and materials chemistry. During the last two decades, continuous efforts have been devoted to the development of improved asymmetric catalytic systems involving phosphorus-based ligands.[193,194]

As a consequence, the search for convenient accesses to novel efficient phosphorus-based ligands has attracted much attention. Among transition metals, palladium (as well as nickel) proved to be highly efficient in the preparation of binap-type ligands.

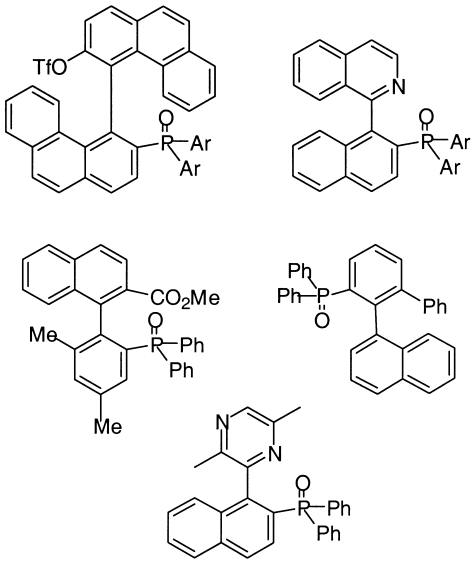
Monophosphorylation of binaphthyl bistriflate provides a facile route to MOP-type ligands.[195] Interestingly, no diarylated products[180] were observed, even when the phosphorylating agent was used in excess or when the isolated monophosphorylated adduct was subjected to a second cross-coupling reaction.[196] Steric hindrance of the newly formed phosphine oxide has been proposed to explain the failure of the second cross-coupling. Monophosphorylations with palladium complexes are in sharp contrast with the results obtained under nickel catalysis, where products of diphosphorylation are prepared in high yields (Scheme 90).[180]



Scheme 90.

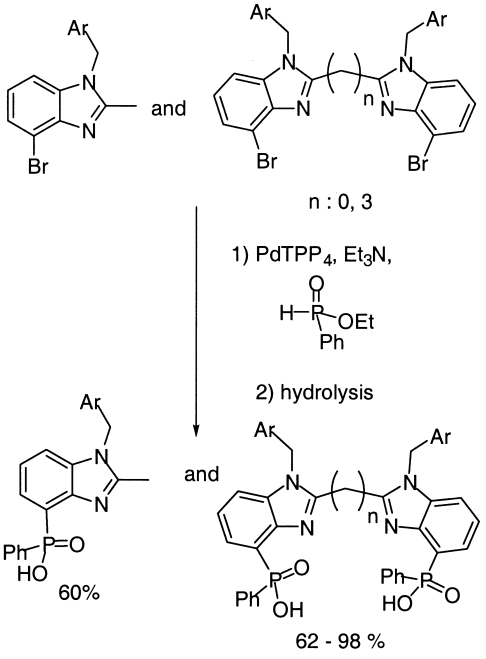
Variously substituted binaphthyl monophosphine oxides have also been obtained from the parent monotriflate in 52–95% yields.[197–200]

In order to obtain axially chiral ligands, the same strategy has been applied to bisphenanthryl,[201] isoquinolyl,[202] or arylnaphthalenyl[179,203,204] backbones (Scheme 91).



Scheme 91.

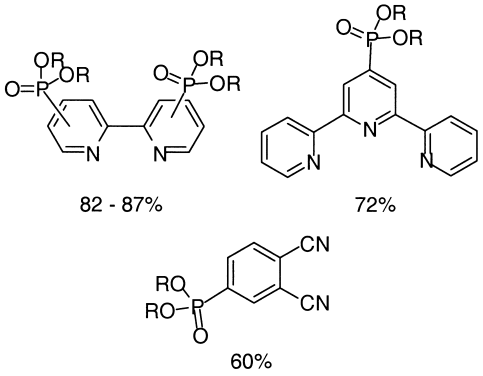
Phosphorylations of the benzimidazole skeleton and subsequent hydrolysis to mono- and bis-phosphinic acids have been used for the preparation of selective zinc binding azaphosphinic acid ligands (Scheme 92).[205]



Scheme 92.

A similar strategy has been employed for the functionalisation of bi- or ter-pyridines and phthalocyanine precursors, which are intermediates in the preparation of potential new organic devices (Scheme 93).[206–208]

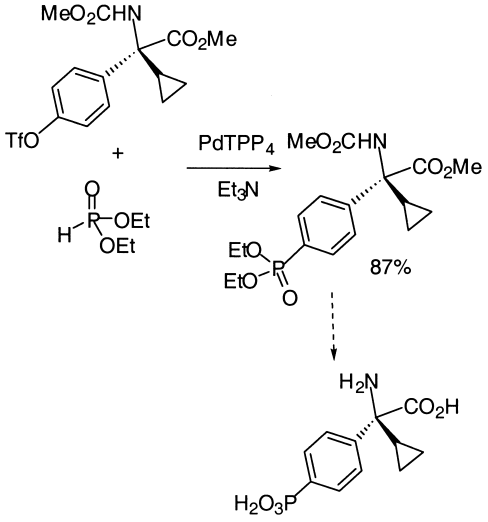
6.4.2. Phosphorylation in medicinal chemistry. Since phosphotyrosine is an important amino acid involved in many biological processes, the synthesis of non-hydrolysable mimics is of considerable interest in order to develop novel drugs. The palladium-catalysed phosphorylation has



Scheme 93.

therefore been applied to the synthesis of phosphorus pseudotyrosine.[169,182,209–211]

The same strategy has been applied to design phenylglycine mimics, such as *N*-methyl-D-aspartate receptor antagonists[212] and metabotropic glutamate receptors antagonists (Scheme 94).[213,214]



Scheme 94.

7. Sulfur-based nucleophiles

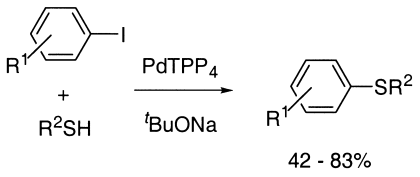
7.1. Introduction

Despite the early work of Migita,[215] that described the reaction of substituted iodobenzenes, with thiophenol or butanethiol in the presence of sodium *t*-butoxide and a catalytic amount of palladium, C–S bond-forming reactions under palladium catalysis have only recently received increased attention (Scheme 95).

Recent aspects of transition metal thioether synthesis have been partly reviewed elsewhere.[216]

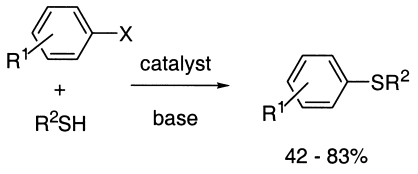
7.2. Access to thioethers

Palladium-catalysed reactions of aryl halides or triflates



R^1 : 4-Me, 4-OMe, 4-Cl
R^2 : Ph, Bu

Scheme 95.



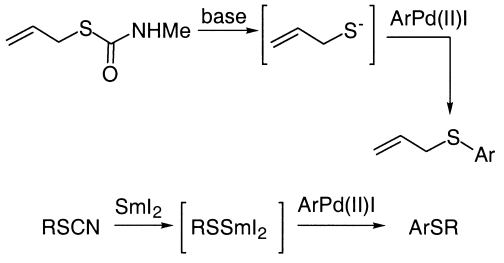
X :Cl, Br, I, OTf
R^1 : 4-Me, 3-Me, 4-OMe, 2-OMe, 2-Me, 4-^{t}Bu, 2,4,6-triMe, 4-NH_2, 3-NH_2, 4-Cl, 4-CN, 4-PhCO, 4-NO_2, 4-CF_3
R^2 : Ph, ^{t}Bu, 4-OMePh
base : NaO^{t}Bu, KO^{t}Bu, Et_3N
catalyst : $PdTPP_4$, $Pd(OAc)_2$-(tol-BINAP), Pd_2dba_3 - DPEPhos or $(^t Bu)_2P(O)H$

Scheme 96.

with thiols in the presence of a base provide a convenient access to diaryl or alkylaryl sulfides (Scheme 96).[8,40,217–220]

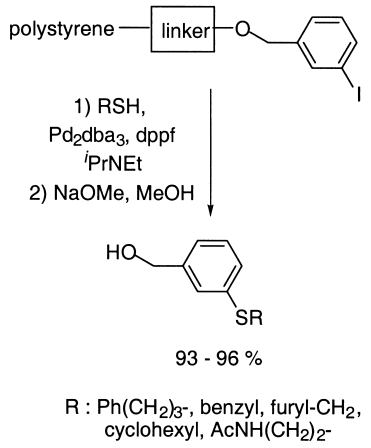
Although aryl sulfides have been mostly obtained under palladium catalytic homogeneous conditions, the application of phase transfer techniques has also proved to be successful.[221]

Aryl sulfides have also been prepared by palladium-catalysed reactions between aryl halides and in situ-generated thiolates, obtained either from allylic thiocarbamates in basic media[222] or from thiocyanates and SmI_2 (Scheme 97).[223]



Scheme 97.

Optimised couplings between thiols and resin-bound aromatic iodides have been successfully reported.[224,225] The subsequent release of the newly formed sulfides is also reported in high yields (Scheme 98).

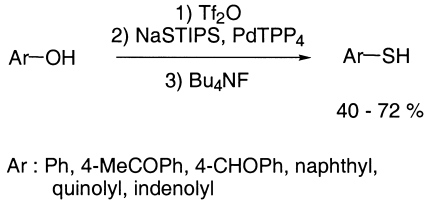


Scheme 98.

Despite relatively few mechanistic studies reported on this catalytic transformation,[8,216,217,220] Hartwig showed that the rate of the reductive elimination increases in the presence of PPh_3 and concluded that a reductive elimination from a palladium tetracoordinate complex occurs.[220]

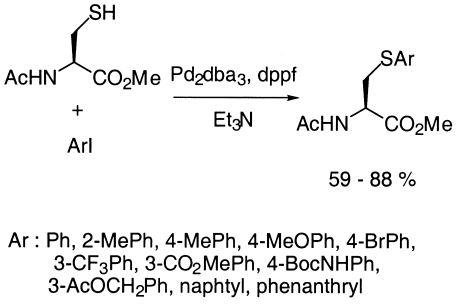
7.3. Applications

Sodium silathiolates have been used as sulfur-type nucleophiles, leading to a three-step access to aromatic thiols from phenols (Scheme 99).[226]



Scheme 99.

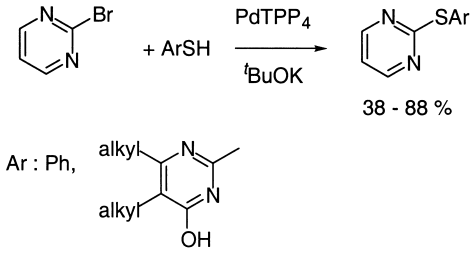
The preparation of mercapturic acid derivatives has been achieved by a palladium-catalysed reaction of *N*-acetylcysteine methyl ester with various aryl halides in the presence of triethylamine (Scheme 100).[227]



Scheme 100.

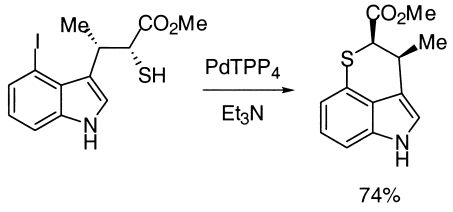
Similarly, cross-coupling of iodophenylalanine with ^{t}BuSH or ^{t}BuSNa in the presence of Pd_2dba_3, dppf and Et_3N proceeds efficiently.[228]

Pyrimidine-based sulfides with potent antibacterial activity have been obtained under palladium-catalysed conditions (Scheme 101).[229]



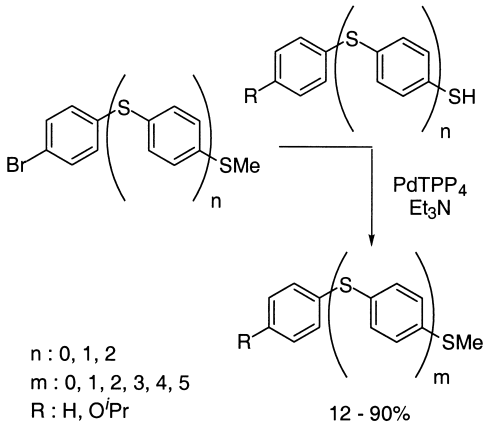
Scheme 101.

An intramolecular version of C–S bond formation was successfully applied to the preparation of chuangxinmycin derivatives (Scheme 102).[230]



Scheme 102.

The synthesis of polyphenylene sulfide-containing molecular wires of various lengths has also been achieved under palladium catalysis (Scheme 103).[231]

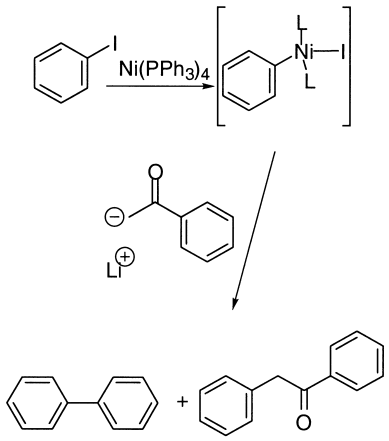


Scheme 103.

8. Carbon-based nucleophiles

8.1. Introduction

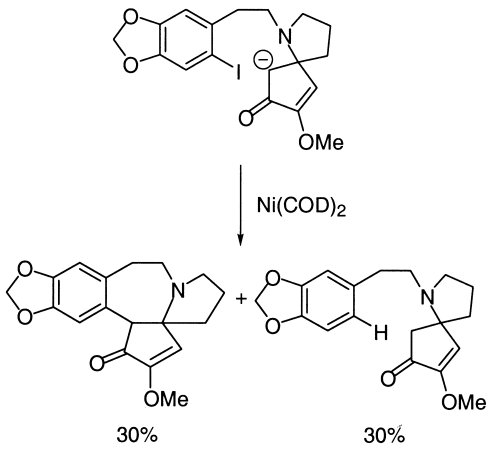
Historically, to the best of our knowledge, the first examples of transition metal- (Pd- or Ni-) catalysed reactions of soft non-organometallic, carbon nucleophiles were reported by Semmelhack in 1973.[232] The oxidative addition product of iobenzene on $Ni(PPh_3)_4$ was reacted with the lithium salt of acetophenone to give a 1:1 mixture



Scheme 104.

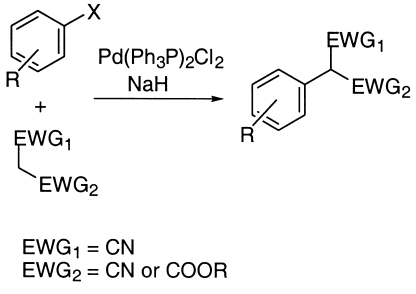
of the arylated ketone and the homocoupled biphenyl compound (Scheme 104).

The same authors described an intramolecular version of this new reaction in a total synthesis of cephalotaxinine. It is noteworthy, however, that the reaction required a stoichiometric amount of $Ni(COD)_2$. The desired cyclised product was obtained in only 30% yield, in addition to the reduced product (Scheme 105).[232]



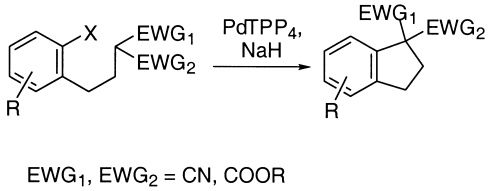
Scheme 105.

Later, the use of malonate-type nucleophiles in these reactions was reported by Takahashi[233] (Scheme 106).



Scheme 106.

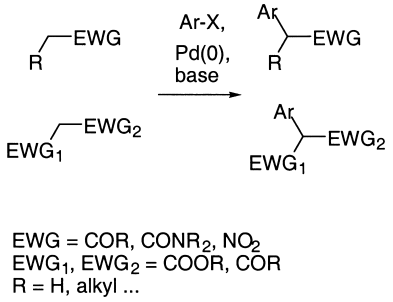
This reaction was applied by the same group[234,235] in the synthesis of dioxaborinanes. In addition, Ciufolini has described an intramolecular version in 1987 (Scheme 107).[236,237]



Scheme 107.

Despite these important earlier reports and the great synthetic potential of these reactions, this chemistry long remained unexplored (palladium (nickel) cyanation will be discussed in Section 8.2). Interestingly, it attracted further attention in 1997 when five papers dealing with inter- and intramolecular palladium-catalysed arylation of ketones were published.[238–242]

Starting from these seminal reports, the palladium-catalysed arylation was then extended to a wide range of soft carbon nucleophiles including ketones, amides, nitro- and malonate-type nucleophiles. This section will mainly cover the aforementioned nucleophiles (Scheme 108) including cyanation (see Section 8.2).



Scheme 108.

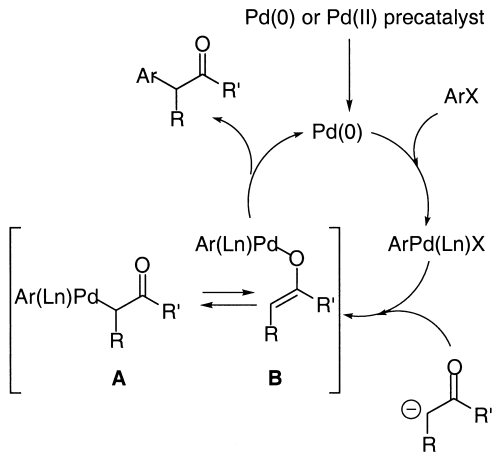
The related uses of stable preformed enolates,[243] aromatic C–H activation,[244] Sonogashira type reactions,[6,245] and hydropalladation of allenes,[246] will not be covered in this review.

8.2. Mechanism

The general mechanism presented in the amination reactions can account for the general process observed in these reactions (Scheme 109).

Some issues, however, remain to be solved:

- How many phosphine ligands are coordinated to the palladium? Very recently, Hartwig addressed this question.[247] Using ^{31}P NMR, he showed that a mono-chelated intermediate is involved in these reactions. This observation led to the use of electron-rich mono-dentate phosphines. It should also be emphasised that



Scheme 109.

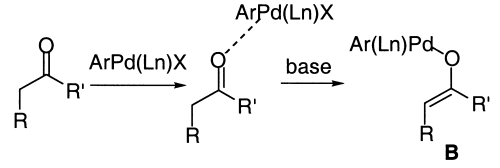
ligandless reactions are also possible in some non-demanding reactions.[248] The issue concerning the use of mono- or bi-dentate ligands is further discussed in Section 8.3.1.

- Another point concerns the nature of the anion involved in the reaction: is it a *C*- (**A**) or an *O*-anion (**B**) intermediate and are these two intermediates in equilibrium?

The two questions are not trivial and not yet solved. The reason why intermediate **A** is not prone to β-elimination (at least, when R possesses β-protons) was first explained using strongly chelating bidentate ligands.[249]

- Does coordination of the ketone to the palladium occur prior to the deprotonation?

Initial works reported a deprotonation of the nucleophile prior to coordination to the metal.[239,241,247] On the contrary, the possible coordination of the ketone to the palladium before the deprotonation step was recently disclosed by Buchwald and co-workers,[253] who found that potassium phosphate is an efficient base in these reactions. By simply comparing the pK_as, it may be concluded that potassium phosphate (pK_a(K_2HPO_4)=12) is not basic enough to α-deprotonate aliphatic ketones (pK_a=16). Prior coordination of the ketone to the palladium (with a resulting increase in the α-proton acidity) could account for the reported efficiency of potassium phosphate as a base in these reactions. The formation of intermediate **B** is probably therefore preferred (Scheme 110).

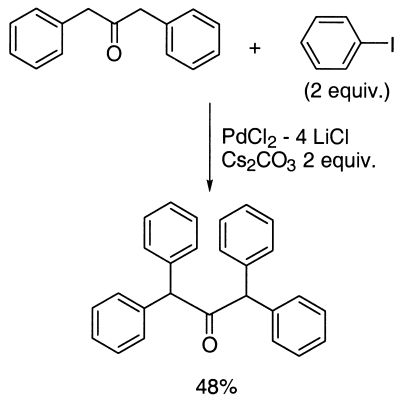


Scheme 110.

8.3. Ketones, amides, malonates and related nucleophiles

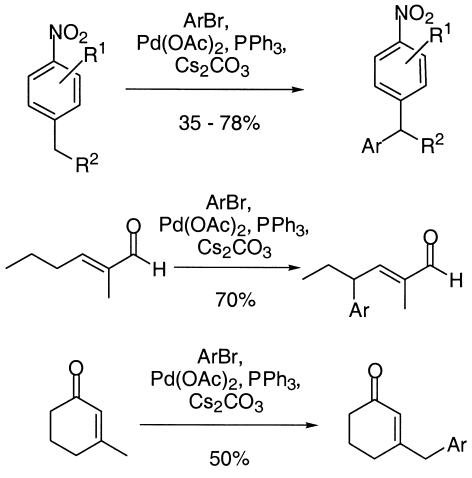
8.3.1. Intermolecular reactions. Miura,[238] Buchwald[239] and Hartwig[240] have essentially studied intermolecular reactions.

In their study of palladium-catalysed arylation of phenol-type substrates in 1997, Miura and coworkers reported one example of the diarylation of a ketone using $PdCl_2$–4LiCl as the palladium source (Scheme 111).[238]



Scheme 111.

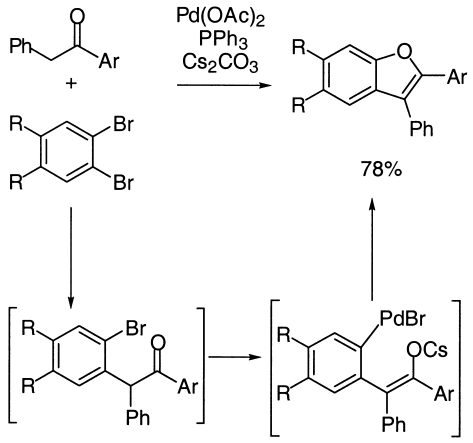
The same group reported palladium-catalysed arylations of *p*-nitrobenzyl compounds[250] and α,β-unsaturated carbonyl compounds.[251] Interestingly, when both α- and γ-positions are prone to arylation, only γ-arylation is observed. This reaction is an interesting case of vinylogy[252] since a palladium dienolate intermediate seems to be involved (the same reaction performed on 2-methyl-2-hexene does not lead to any reaction) (Scheme 112).



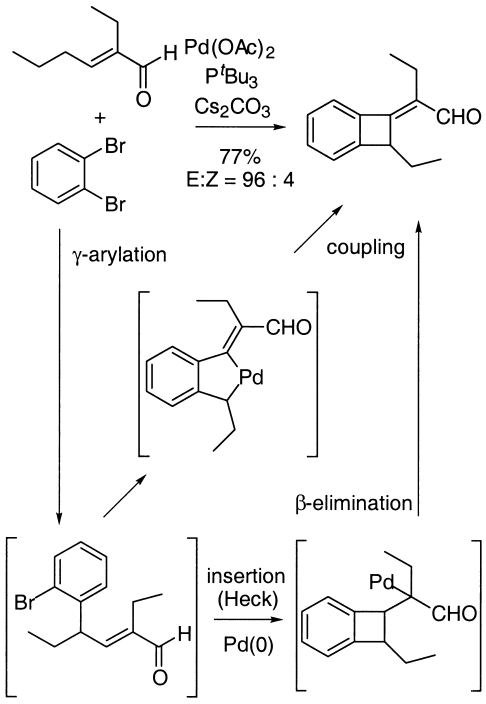
Scheme 112.

More recently, the same group introduced the use of 1,2-dibromo-aromatic compounds in this chemistry leading to some spectacular tandem reactions.[253] In the first example (Scheme 113), the benzofuran ring results from a tandem C-enolate arylation–O enolate arylation.

In the second example, the first γ-arylation is followed by a Heck-type insertion (path a) (although, according to the authors, the direct coupling (path b) cannot be ruled out) to afford the benzocyclobutane ring in a 77% yield (Scheme 114).



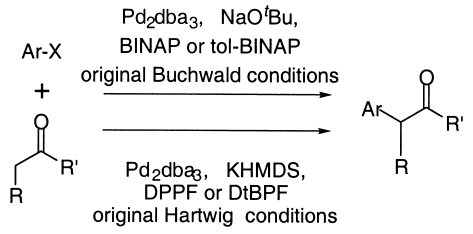
Scheme 113.



Scheme 114.

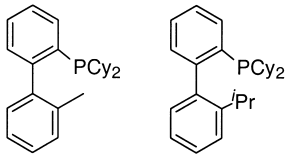
Following their success in palladium-catalysed aminations and etherifications, the groups of Buchwald[239] and Hartwig[240] independently proposed two efficient, general, and quite similar catalytic systems for the α-arylation of ketones in 1997 (Scheme 115).

Starting from these two seminal reports, both groups then refined their catalytic systems and reported improved procedures that were able to considerably expand the scope of substrates prone to be arylated under mild conditions. Ligands, bases, aromatic substrates, and nucleophiles currently used will now be surveyed.



Scheme 115.

Ligands. Catalytic systems using bidentate phosphorus ligands were originally designed by Buchwald (BINAP, tol-BINAP) and Hartwig (dppf) to form strongly chelated intermediates in order to prevent any β-elimination. During further synthetic and mechanistic (vide supra) studies, however, a monochelated intermediate was observed (^{31}P NMR) by Hartwig in a reaction using the DtBPF ligand **4**.[247] This observation led the authors to test different hindered mono-dentate phosphines in these reactions and they found that the more simple, commercial, hindered PPF–^{t}Bu$_2$ **5**, P(^{t}Bu)$_3$ **2** and P(Cy)$_3$ **1** phosphines are powerful ligands in these catalytic systems. Very recently, Buchwald[248] ended up with the same conclusion and described the use of several monodentate ligands **2**, **3**, **10**, **11**, **28** and **29**. Ligands **28** and **29** (Scheme 116) proved to be the most efficient in harder cases but the commercial and air stable ligands **10** and **11** are quite versatile and can be used in most reactions. When the reactions fail with these ligands, the use of a bidentate ligand (BINAP or Xantphos) usually solves the problem.[248]



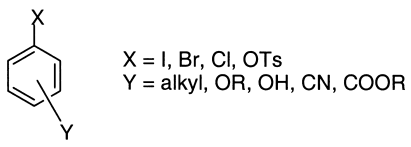
28 **29**

Scheme 116.

Additionally, Buchwald has shown that for some simple ketone arylation processes, ligandless reactions can also be performed.[248]

Bases. Strong non-nucleophilic bases such as NaO^{t}Bu or KHMDS were originally, and are still commonly used in these reactions. Recently, Buchwald disclosed the use of a weak base such as potassium phosphate (mechanistic implications of this discovery is dicussed earlier). The use of base-sensitive substrates can now be envisaged in these reactions.

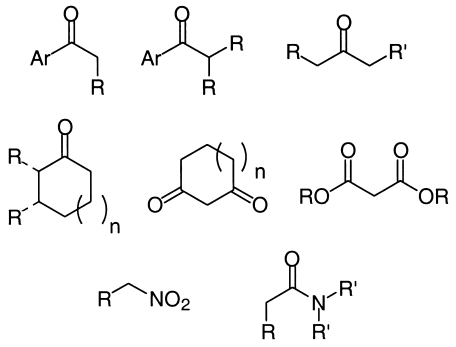
Aromatic substrates. Obviously, aryl bromides and iodides are the best substrates in these reactions. As previously stated for amination reactions, Hartwig and Buchwald have shown that, using electron-rich bulky ligands, chloroarenes (including electron-rich chloroarenes) and aryl tosylates act as efficient electrophiles in these reactions (Scheme 117).



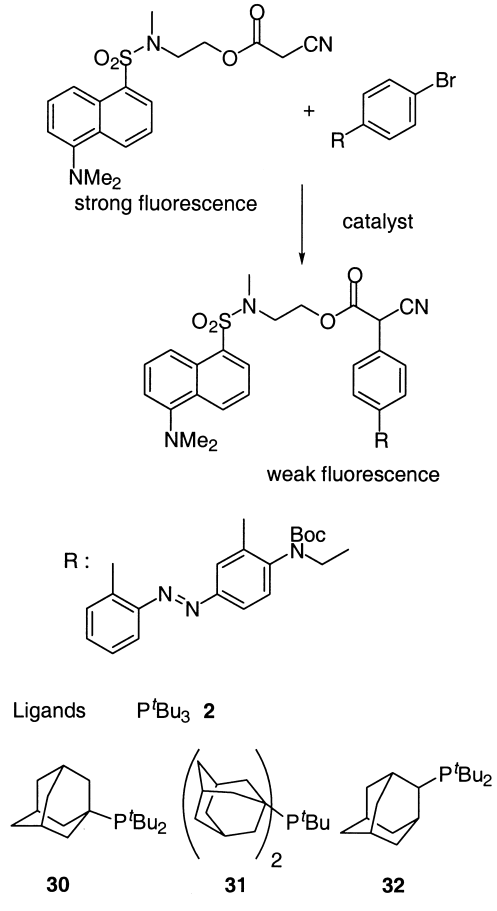
Scheme 117.

Nucleophiles. Due to recent developments in the field, the scope of nucleophiles has considerably expanded. A non-exhaustive list of these nucleophiles is reported in Scheme 118. Along with the traditional ketones, 1,3 diketones, malonates, amides and nitro-compounds can be α-arylated (Scheme 118).[236,248,254,255]

Very recently, Hartwig[256] and co-workers used a high throughput screening in order to optimise the arylation of ethyl cyanoacetate. Using fluorescence to assess the activity of the catalysts, they were first able to discriminate four candidates **2**, **30**, **31** and **32** in a 113-member ligand library (Scheme 119).

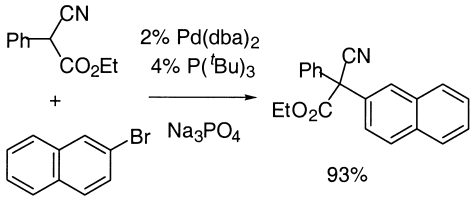


Scheme 118.



Scheme 119.

Further optimisation, using these four ligands, led to the development of a general and high-yielding arylation of ethyl cyanoacetate. This methodology was further applied to the synthesis of hindered quaternary cyanoacetates (Scheme 120).[256]



Scheme 120.

8.3.2. Intramolecular reactions. During synthetic studies towards the preparation of duocarmycin analogues, Muratake and coworkers described an efficient and simple intramolecular palladium-catalysed arylation of methyl aryl ketones in 1997 (Scheme 121).[241] Starting from ABC cores, the intermediates were further transformed into duocarmycin analogues according to a strategy previously developed by the same group.[257]

In a following paper,[242] the same group described the generalisation of their intramolecular arylations (Scheme 122).

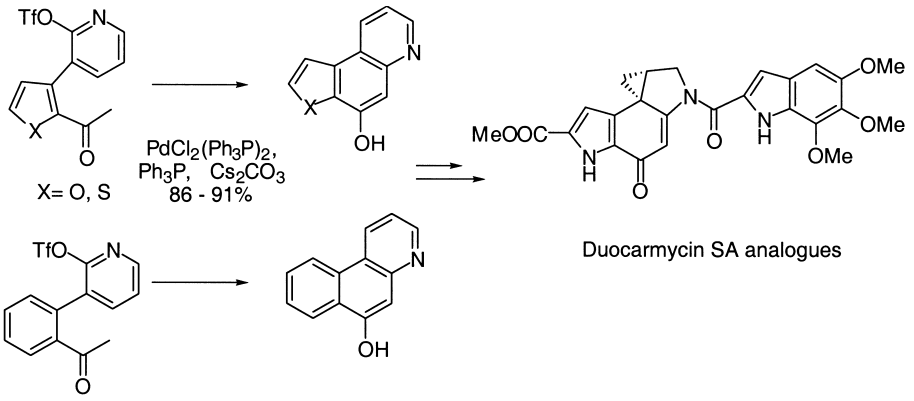
In 1998, Hartwig and co-workers described the formation of oxindoles using an intramolecular amide arylation (Scheme 123).[254,255]

More recently, the same group has disclosed improved conditions and an asymmetric version of this reaction (ees up to 71%).[256]

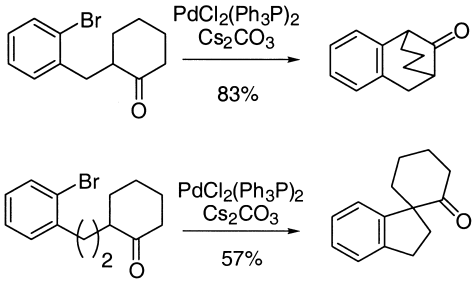
8.3.3. Asymmetric catalysis. Despite disappointing results obtained in asymmetric arylations of simple ketones using either enantiomerically pure tol-BINAP (BINAP) or PPF–^{t}Bu$_2$, Buchwald[258] reported some interesting enantioselectivities in the formation of quaternary centers using α′-blocked cyclic ketones (Scheme 124). These reactions, however, suffer from a lack of generalisation since, in the last example, the five-member ketone led to high enantioselectivities (>95% ee), when the six-member ketones gave only poor ees. Undoubtedly, these asymmetric reactions will undergo extensive development in the near future.

8.4. Palladium- (nickel-) catalysed cyanations

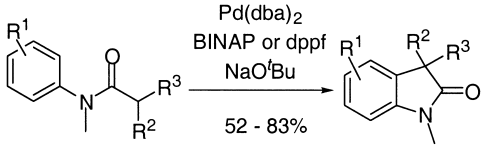
Palladium- (nickel-) catalysed cyanation is a long-known process originally and independently described in 1973 by Cassar[259] (Ni) and Sakakibara[260] (Pd). In this section, the reactions of organometallic cyano derivatives, i.e. $ZnCN_2$,[261,262] CuCN[263] will not be covered since the catalytic cycle is supposed to proceed through a transmetallation step. The use of lithium, sodium or potassium salts of cyanhydric acid (which are formally the products of the reaction of cyanhydric acid with an alkali base) is, however, within the scope of this review. Palladium- (nickel-) catalysed cyanations have been, partly reviewed in 1994.[153]



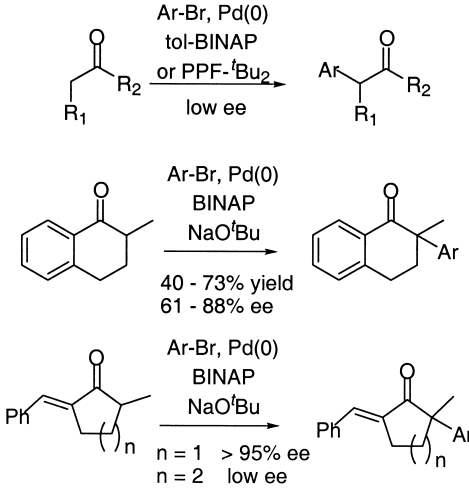
Scheme 121.



Scheme 122.



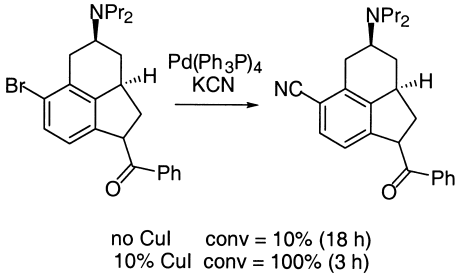
Scheme 123.



Scheme 124.

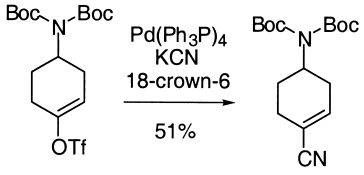
The mechanism usually proposed is the same as the general mechanism described for ketone type nucleophiles.[264] Starting from aryl halides, palladium-catalysed cyanation proved to be an efficient process used, for example, in the synthesis of ligands derived from Binol.[173,197] The uses of crown ethers or crowned phosphines were found to be beneficial for these reactions.[265] Palladium-catalysed solid phase cyanation of immobilised aryl halides was also reported.[266]

These reactions were found not to be general[267,268] and were recently re-investigated. It was found that the use of a catalytic amount[269] of CuI had a dramatic effect on both yield and conversion.[268] These new conditions were then successfully applied to a large variety of substrates (Scheme 125).



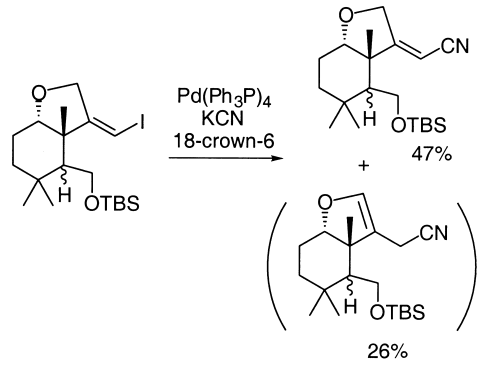
Scheme 125.

Starting from vinyl halides or pseudohalides, the palladium-catalysed cyanation can be used for the formation of α,β-unsaturated nitriles[264,270,271] as shown in Scheme 126.[270]



Scheme 126.

This approach was also used in a synthesis of forskolin.[272] Starting from a hindered trisubstituted vinyl iodide derivative, the corresponding α,β-unsaturated nitrile was obtained in 47% yield along with 26% of the product resulting from the migration of the double bond (Scheme 127).



Scheme 127.

9. Concluding remarks

This review summarises recent developments in palladium-catalysed reactions involving aryl halides and pseudohalides with soft non-organometallic nucleophiles, i.e. nitrogen, oxygen, boron, silicon, phosphorus, sulfur and carbon-based nucleophiles.

An important breakthrough, initiated by Buchwald and Hartwig, now allows reactions at room temperature, the use of base-sensitive substrates and asymmetric transformations. The authors have no doubt that many further applications and improvements will arise in the near future.

References

1. Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168.
2. Tamao, K. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 3, pp 435–480.
3. Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1–652.
4. Gallagher, W. P.; Terstiege, I.; Maleczka, Jr., R. E. *J. Am. Chem. Soc.* **2001**, *123*, 3194–3204.
5. Erdik, E. *Tetrahedron* **1992**, *48*, 9577–9648.
6. Kraft, P.; Bajgrowitcz, J. A.; Denis, C.; Frater, G. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2980–3010.
7. Hartwig, J. F. *Synlett* **1997**, 329–340.
8. Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852–860.
9. Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046–2067.
10. Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805–818.
11. Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125–146.
12. Frost, C. G.; Mendonça, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2615–2623.
13. Belfield, A. J.; Brown, G. R.; Foubister, A. J. *Tetrahedron* **1999**, *55*, 11399–11428.
14. Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348–1350.
15. Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 4708–4709.
16. Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215–7216.
17. Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217–7218.
18. Ward, Y. D.; Farina, V. *Tetrahedron Lett.* **1996**, *37*, 6993–6996.
19. Willoughby, C. A.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*, 7181–7184.
20. Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359–6362.
21. Old, D. W.; Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722–9723.
22. Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369–7370.
23. Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807–4810.
24. Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617–620.
25. Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367–2370.
26. Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575–5580.
27. Bei, X.; Guram, A. S.; Turner, H. W.; Weinberg, W. H. *Tetrahedron Lett.* **1999**, *40*, 1237–1240.
28. Bei, X.; Uno, T.; Norris, J.; Turner, H. W.; Weinberg, W. H.; Guram, A. S.; Petersen, J. L. *Organometallics* **1999**, *18*, 1840–1853.
29. Huang, J.; Grasa, G.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307–1309.
30. Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2413–2416.
31. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144–1157.
32. Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158–1174.
33. Uemura also developed new catalysts for amination of aryl-bromides and chlorides based on phosphinosubstituted arene tricarbonylchromium complexes. See Kamikawa, K.; Sugimoto, S.; Uemura, M. J. *J. Org. Chem.* **1998**, *63*, 8407–8410.
34. Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054–6058.
35. Brenner, E.; Fort, Y. *Tetrahedron Lett.* **1998**, *39*, 5359–5362.
36. $^{t}Bu_3P$ and $P(Cy)_3$ phosphines are air sensitive and require the use of a glove-box.
37. Caddick, S.; Cloke, F. G. N.; Clentsmith, G. K. B.; Hitchcock, P. B.; McKerrecher, D.; Titcomb, L. R.; Williams, M. R. V. *J. Organomet. Chem.* **2001**, *617–618*, 635–639.
38. Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560–2565.
39. Sadighi, J. P.; Harris, M. C.; Buchwald, S. L. *Tetrahedron Lett.* **1998**, *39*, 5327–5330.
40. Li, G. Y. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 1513–1516.
41. Alcazar-Roman, L. M.; Hartwig, J. F.; Rheingold, A. L.; Liable-Sands, L. M.; Guzei, I. A. *J. Am. Chem. Soc.* **2000**, *122*, 4618–4630.
42. Electronically rich ligands have also been used in other palladium-catalysed reactions involving arylchlorides: see Ref. 27,29,30.
43. 1:1 or 1:0.8 ratio have been successfully proposed. See Ref. 9,10.
44. Marcoux, J. F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1568–1569.
45. Guari, Y.; Van Es, D. S.; Reek, J. N. H.; Kamer, P. C. J.; Van

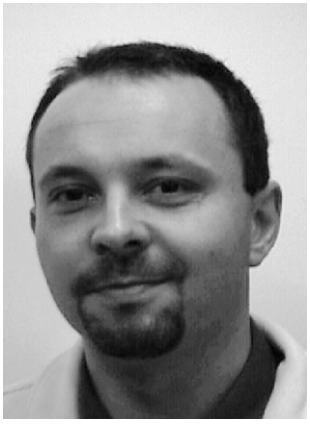
Leunwen, P. W. N. M. *Tetrahedron Lett.* **1999**, *40*, 3789–3790.
46. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066–6068.
47. Beller, M.; Riermeier, T. H.; Reisinger, C. P.; Herrmann, W. A. *Tetrahedron Lett.* **1997**, *38*, 2073–2074.
48. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264–1267.
49. For heterogeneous Ni/C catalysed amination see: Lipshutz, B. H.; Ueda, H. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 4492–4494.
50. Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423–1426.
51. Denmark, S. E.; Su, X.; Nishigaichi, Y.; Coe, D. M.; Wong, K. T.; Winter, S. B. D.; Choi, J. Y. *J. Org. Chem.* **1999**, *64*, 1958–1967.
52. Ahman, J.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6363–6365.
53. Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451–8458.
54. Wüllner, G.; Jänsch, H.; Kannenberg, S.; Schubert, F.; Boche, G. *Chem. Commun.* **1998**, 1509–1510.
55. Djakovitch, L.; Wagner, M.; Köhler, K. *J. Organomet. Chem.* **1999**, *592*, 225–234.
56. Parrish, C. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 3820–3827.
57. Harris, M. C.; Geis, O.; Buchwald, S. L. *J. Org. Chem.* **1999**, *64*, 6019–6022.
58. Rivas, F. M.; Riaz, U.; Diver, S. T. *Tetrahedron: Asymmetry* **2000**, *11*, 1703–1707.
59. Beletskaya, I. P.; Bessmertnykh, A. G.; Guilard, R. *Synlett* **1999**, 1459–1461.
60. Hicks, F. A.; Brookhart, M. *Org. Lett.* **2000**, *2*, 219–221.
61. Cui, W.; Loeppky, R. N. *Tetrahedron* **2001**, *57*, 2953–2956.
62. Cheng, J.; Trudell, M. L. *Org. Lett.* **2001**, *3*, 1371–1374.
63. Jaime-Figueroa, S.; Liu, Y.; Muchowski, J. M.; Putman, D. G. *Tetrahedron Lett.* **1998**, *39*, 1313–1316.
64. Wolfe, J. P.; Ahman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367–6370.
65. Tonks, L.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3637–3652.
66. Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernandez-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827–828.
67. Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 4960–4976.
68. Prashad, M.; Hu, B.; Lu, Y.; Draper, R.; Har, D.; Repic, O.; Blacklock, T. J. *J. Org. Chem.* **2000**, *65*, 2612–2614.
69. Beletsakya, I. P.; Davydov, D. V.; Moreno-Manas, M. *Tetrahedron Lett.* **1998**, *39*, 5617–5620.
70. Bolm, C.; Hildebrand, J. P. *Tetrahedron Lett.* **1998**, *39*, 5731–5734.
71. Bolm, C.; Hildebrand, J. P. *J. Org. Chem.* **2000**, *65*, 169–175.
72. Wang, Z.; Skerlj, R. T.; Bridger, G. J. *Tetrahedron Lett.* **1999**, *40*, 3543–3546.
73. Song, J. J.; Yee, N. K. *Org. Lett.* **2000**, *2*, 519–521.
74. Song, J. J.; Yee, N. K. *Tetrahedron Lett.* **2001**, *42*, 2937–2940.
75. Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251–10263.
76. Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2090–2093.
77. Arterburn, J. B.; Rao, K. V.; Ramdas, R.; Dible, B. R. *Org. Lett.* **2001**, *3*, 1351–1354.
78. Ortner, B.; Waibel, R.; Gmeiner, P. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 1283–1285.
79. Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101–1104.
80. Artamkina, G. A.; Sergeev, A. G.; Beletskaya, I. P. *Tetrahedron Lett.* **2001**, *42*, 4381–4384.
81. Shakespeare, W. C. *Tetrahedron Lett.* **1999**, *40*, 2035–2038.
82. Madar, D. J.; Kopecka, H.; Pireh, D.; Pease, J.; Pliushchev, M.; Sciotti, R. J.; Wiedeman, P. E.; Djuric, S. W. *Tetrahedron Lett.* **2001**, *42*, 3681–3684.
83. Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35–37.
84. Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525–7546.
85. Edmondson, S. C.; Mastracchio, A.; Parmee, E. R. *Org. Lett.* **2000**, *2*, 1109–1112.
86. Watanabe, M.; Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **2000**, *41*, 481–483.
87. Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657–2660.
88. Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403–1406.
89. He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417–6418.
90. Hong, Y.; Senanayake, C. H.; Xiang, T.; Vandenbossche, C. P.; Tanoury, G. J.; Bakale, R. P.; Wald, S. A. *Tetrahedron Lett.* **1998**, *39*, 3121–3124.
91. Tanoury, G. J.; Senanayake, C. H.; Hett, R.; Kuhn, A. M.; Kessler, D. W.; Wald, S. A. *Tetrahedron Lett.* **1998**, *39*, 6845–6848.
92. Morita, S.; Kitano, K.; Matsubara, J.; Ohtani, T.; Kawano, Y.; Otsubo, K.; Uchida, M. *Tetrahedron* **1998**, *54*, 4811–4818.
93. Lopez-Rodriguez, M. L.; Benhamu, B.; Ayala, D.; Rominguera, J. L.; Murcia, M.; Ramos, J. A.; Viso, A. *Tetrahedron* **2000**, *56*, 3245–3253.
94. Emoto, T.; Kubosaki, N.; Yamagiwa, Y.; Kamikawa, T. *Tetrahedron Lett.* **2000**, *41*, 355–358.
95. Ishii, H.; Takeda, H.; Hagiwara, T.; Sakamoto, M.; Kosgusuri, K.; Murakami, Y. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2407–2414.
96. Brown, J. A. *Tetrahedron Lett.* **2000**, *41*, 1623–1626.
97. Batch, A.; Dodd, R. H. *J. Org. Chem.* **1998**, *63*, 872–877.
98. Abouabdellah, A.; Dodd, R. H. *Tetrahedron Lett.* **1998**, *39*, 2119–2122.
99. Iwaki, T.; Yasuhara, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1505–1510.
100. Malapel-Andrieu, B.; Mérour, J.-Y. *Tetrahedron* **1998**, *54*, 11095–11110.
101. Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240–7241.
102. Watanabe, M.; Yamamoto, T.; Nishiyama, N. *Chem. Commun.* **2000**, 133–134.
103. Luker, T. J.; Beaton, H. G.; Whiting, M.; Mete, A.; Cheshire, D. R. *Tetrahedron Lett.* **2000**, *41*, 7731–7735.
104. Lakshman, M. K.; Keeler, J. C.; Hilmer, J. H.; Martin, J. Q. *J. Am. Chem. Soc.* **1999**, *121*, 6090–6091.
105. Harwood, E. A.; Sigurdsson, S. T.; Edfeldt, N. B.; Reid, B. R.; Hopkins, P. B. *J. Am. Chem. Soc.* **1999**, *121*, 5081–5082.
106. De Riccardis, F.; Johnson, F. *Org. Lett.* **2000**, *2*, 293–295.
107. Plante, O. J.; Buchwald, S. L.; Seeberger, P. H. *J. Am. Chem. Soc.* **2000**, *122*, 7148.

108. (a) Frost, C. G.; Mendonça, P. *Tetrahedron: Asymmetry* **1999**, *10*, 1831–1834. (b) Cabanal-Duvillard, I.; Mangeney, P. *Tetrahedron Lett.* **1999**, *40*, 3877–3880.
109. Liang, L.; Schrock, R. R.; Davis, W. M.; McConville, D. H. *J. Am. Chem. Soc.* **1999**, *121*, 5797–5798.
110. Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 1095–1098.
111. Tour, J. M. *Chem. Rev.* **1996**, *96*, 537–554.
112. Louie, J.; Hartwig, J. F.; Fry, A. J. *J. Am. Chem. Soc.* **1997**, *119*, 11695–11696.
113. Thayumanavan, S.; Barlow, S.; Marder, S. R. *Chem. Mater.* **1997**, *9*, 3231–3235.
114. Goodson, F. E.; Hauck, S. I.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 7527–7539.
115. Goodson, F. E.; Hartwig, J. F. *Macromolecules* **1998**, *31*, 1700–1703.
116. Louie, J.; Hartwig, J. F. *Macromolecules* **1998**, *31*, 6737–6739.
117. Singer, R. A.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 213–214.
118. Harris, M. C.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5327–5333.
119. Zhang, X.-X.; Sadighi, J. P.; Mackewitz, T. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 7606–7607.
120. Witulski, B.; Senft, S.; Thum, A. *Synlett* **1998**, 504–506.
121. Ohno, T.; Moriwaki, K.; Miyata, T. *J. Org. Chem.* **2001**, *66*, 3397–3401.
122. Hauck, S. I.; Lakshmi, K. V.; Hartwig, J. F. *Org. Lett.* **1999**, *1*, 2057–2060.
123. Mendiratta, A.; Barlow, S.; Day, M. D.; Marder, S. R. *Organometallics* **1999**, *18*, 454–456.
124. Witulski, B.; Zimmermann, Y.; Darcos, V.; Desvergne, J.-P.; Bassani, D. M.; Bouas-Laurent, H. *Tetrahedron Lett.* **1998**, *39*, 4807–4808.
125. Zhang, X.-X.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 8027–8031.
126. Theil, F. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2345–2347 and references cited therein.
127. Zask, A.; Helquist, P. *J. Org. Chem.* **1978**, *43*, 1619–1620.
128. Cramer, R.; Coulson, D. R. *J. Org. Chem.* **1975**, *40*, 2267–2273.
129. Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333–10334.
130. Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109–13110.
131. Louie, J.; Paul, F.; Hartwig, J. F. *Organometallics* **1996**, *15*, 2794–2805.
132. Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030–3039.
133. Widenhoefer, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6504–6511.
134. Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6787–6795.
135. Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 10718–10719.
136. Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395–3396.
137. Watanabe, M.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1999**, *40*, 8837–8840.
138. Parrish, C. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2498–2500.
139. Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224–3225.
140. Mann, G.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 5413–5418.
141. Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369–4378.
142. Mann, G.; Hartwig, J. F. *Tetrahedron Lett.* **1997**, *38*, 8005–8008.
143. Olivera, R.; SanMartin, R.; Dominguez, E. *Tetrahedron Lett.* **2000**, *41*, 4357–4360.
144. Torraca, K. E.; Kuwabe, S.-I.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12907–12908.
145. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
146. Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508–7510.
147. For related reactions involving the access to alkenylboronates see: Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *Synthesis* **2000**, 778–780.
148. Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458–6459.
149. Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164–168.
150. Baudoin, O.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2000**, *65*, 9268–9271.
151. Song, Y.-L.; Morin, C. *Synlett* **2001**, 266–268.
152. Hyslop, A. G.; Kellett, M. A.; Iovine, P. M.; Therien, M. J. *J. Am. Chem. Soc.* **1998**, *120*, 12676–12677.
153. Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047–1062.
154. Horn, K. A. *Chem. Rev.* **1995**, *95*, 1317–1350.
155. Matsumoto, H.; Yoshihiro, K.; Nagashima, S.; Watanabe, H.; Nagai, Y. *J. Organomet. Chem.* **1977**, *128*, 409–413.
156. Eaborn, C.; Griffiths, R. W.; Pidcock, A. *J. Organomet. Chem.* **1982**, *225*, 331–341.
157. Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1987**, *28*, 4715–4718.
158. Shirakawa, E.; Kurahashi, T.; Yoshida, H.; Hiyama, T. *Chem. Commun.* **2000**, 1895–1896.
159. Boukherroub, R.; Chatgilialoglu, C.; Manuel, G. *Organometallics* **1996**, *15*, 1508–1510.
160. Kunai, A.; Sakurai, T.; Toyoda, E.; Ishikawa, M.; Yamamoto, Y. *Organometallics* **1994**, *13*, 3233–3236.
161. Murata, M.; Suzuki, K.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 8569–8571.
162. Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. *Synthesis* **1981**, 56–57.
163. Hirao, T.; Masunaga, T.; Yamada, N.; Ohshiro, Y.; Agawa, T. *Bull. Chem. Soc. Jpn* **1982**, *55*, 909–913.
164. Gaumont, A.-C.; Hursthouse, M. B.; Coles, S. J.; Brown, J. M. *Chem. Commun.* **1999**, 63–64.
165. Xu, Y.; Li, Z.; Xia, J.; Guo, H.; Huang, Y. *Synthesis* **1983**, 377–378.
166. Xu, Y.; Zhang, J. *J. Chem. Soc., Chem. Commun.* **1986**, 1606.
167. Schwabacher, A. W.; Stefanescu, A. D. *Tetrahedron Lett.* **1996**, *37*, 425–428.
168. Schwabacher, A. W.; Zhang, S.; Davy, W. *J. Am. Chem. Soc.* **1993**, *115*, 6995–6996.
169. Lei, H.; Stoakes, M. S.; Herath, K. P. B.; Lee, J.; Schwabacher, A. W. *J. Org. Chem.* **1994**, *59*, 4206–4210.
170. Lei, H.; Stoakes, M. S.; Schwabacher, A. W. *Synthesis* **1992**, 1255–1260.
171. Casalnuovo, A. L.; Calabrese, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4324–4330.
172. Xu, Y.; Zhang, J. *Synthesis* **1984**, 778–780.
173. Kurz, L.; Lee, G.; Morgans, Jr., D.; Waldyke, M. J.; Ward, T. *Tetrahedron Lett.* **1990**, *31*, 6321–6324.

174. Bennett, S. N. L.; Hall, R. G. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1145–1151.
175. Montchamp, J.-L.; Dumond, Y. R. *J. Am. Chem. Soc.* **2001**, *123*, 510–511.
176. Xu, Y.; Zhang, J. *Tetrahedron Lett.* **1985**, *26*, 4771–4774.
177. Zhang, J.; Xu, Y.; Huang, G.; Guo, H. *Tetrahedron Lett.* **1988**, *29*, 1955–1958.
178. Oshiki, T.; Imamoto, T. *J. Am. Chem. Soc.* **1992**, *114*, 3975–3977.
179. Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354–362.
180. For diphosphination using nickel catalysis see: Gelpke, A. E. S.; Kooijman, H.; Spek, A. L.; Hiemstra, H. *Chem. Eur. J.* **1999**, *5*, 2472–2482 and references cited therein.
181. Xu, Y.; Li, Z.; Xia, J.; Guo, H.; Huang, Y. *Synthesis* **1984**, 781–782.
182. Lipshutz, B. H.; Buzard, D. J.; Yun, C. S. *Tetrahedron Lett.* **1999**, *40*, 201–204.
183. Imamoto, T. *Pure Appl. Chem.* **1993**, *65*, 655–660.
184. Al-Masum, M.; Livinghouse, T. *Tetrahedron Lett.* **1999**, *40*, 7731–7734.
185. Cai, D.; Payack, J. F.; Bender, D. R.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *Org. React.* **1999**, *76*, 6–11.
186. Evnev, V.; Ewers, C. L. J.; Harre, M.; Nickisch, K.; Mohr, J. T. *J. Org. Chem.* **1997**, *62*, 7092–7093.
187. Martorell, G.; Garcias, X.; Janura, M.; Saa, J. M. *J. Org. Chem.* **1998**, *63*, 3463–3467.
188. Gilbertson, S. R.; Starkey, G. W. *J. Org. Chem.* **1996**, *61*, 2922–2923.
189. Herd, O.; Hessler, A.; Hingst, M.; Tepper, M.; Stelzer, O. *J. Organomet. Chem.* **1996**, *522*, 69–76.
190. Kwong, F. Y.; Lai, C. W.; Tian, Y.; Chan, K. S. *Tetrahedron Lett.* **2000**, *41*, 10285–10289.
191. Kwong, F. Y.; Chan, K. S. *Chem. Commun.* **2000**, 1069–1070.
192. Kwong, F. Y.; Chan, K. S. *Organometallics* **2000**, *19*, 2058–2060.
193. Kumobayashi, H.; Miura, T.; Sayo, N.; Saito, T.; Zhang, X. *Synlett* **2001**, 1055–1064 and references cited therein.
194. McCarthy, M.; Guiry, P. J. *Tetrahedron* **2001**, *57*, 3809–3844.
195. Uozumi, Y.; Tanahashi, A.; Lee, S.-Y.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 1945–1948.
196. Cai, D.; Payack, J. F.; Bender, D. R.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1994**, *59*, 7180–7181.
197. Uozumi, Y.; Suzuki, N.; Ogiwara, A.; Hayashi, T. *Tetrahedron* **1994**, *50*, 4293–4302.
198. Vyskocil, S.; Smrcina, M.; Kocovsky, P. *Tetrahedron Lett.* **1998**, *39*, 9289–9292.
199. Ding, K.; Wang, Y.; Yun, H.; Liu, J.; Wu, Y.; Terada, M.; Okubo, Y.; Mikami, K. *Chem. Eur. J.* **1999**, *5*, 1734–1737.
200. Vyskocil, S.; Smrcina, M.; Hanus, V.; Polasek, M.; Kocovsky, P. *J. Org. Chem.* **1998**, *63*, 7738–7748.
201. Hayashi, T.; Iwamura, H.; Uozumi, Y.; Matsumoto, Y.; Ozawa, F. *Synthesis* **1994**, 526–532.
202. Doucet, H.; Brown, J. M. *Tetrahedron: Asymmetry* **1997**, *8*, 3775–3784.
203. Bringmann, G.; Wuzik, A.; Vedder, C.; Pfeiffer, M.; Stalke, D. *Chem. Commun.* **1998**, 1211–1212.
204. McCarthy, M.; Guiry, P. J. *Tetrahedron* **1999**, *55*, 3061–3070.
205. Edlin, C. D.; Parker, D. *Tetrahedron Lett.* **1998**, *39*, 2797–2800.
206. Sharman, W. M.; Kudrevich, S. V.; Van Lier, J. E. *Tetrahedron Lett.* **1996**, *37*, 5831–5834.
207. Zakeeruddin, S. M.; Nazeeruddin, M. K.; Pechy, P.; Rotzinger, F. P.; Humphry-Baker, R.; Kalyanasundaram, K.; Grätzel, M.; Shklover, V.; Haibach, T. *Inorg. Chem.* **1997**, *36*, 5937–5946.
208. Penicaud, V.; Odobel, F.; Bujoli, B. *Tetrahedron Lett.* **1998**, *39*, 3689–3692.
209. Petrakis, K. S.; Nagabhushan, T. L. *J. Am. Chem. Soc.* **1987**, *109*, 2831–2833.
210. Thurieau, C.; Simonet, S.; Paladino, J.; Prost, J.-F.; Verbeuren, T.; Fauchère, J.-L. *J. Med. Chem.* **1994**, *37*, 625–629.
211. Stankovic, C. J.; Surendran, N.; Lunney, E. A.; Plummer, M. S.; Para, K. S.; Shahripour, A.; Fergus, J. H.; Marks, J. S.; Henera, R.; Hubbell, S. E.; Humblet, C.; Saltiel, A. R.; Stewart, B. H.; Sawyer, T. K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1909–1914.
212. Bigge, C. F.; Johnson, G.; Ortwine, D. F.; Drummond, J. T.; Retz, D. M.; Brahce, L. J.; Coughenour, L. L.; Marcoux, F. W.; Probert, Jr., A. W. *J. Med. Chem.* **1992**, *35*, 1371–1384.
213. Ma, D.; Tian, H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3493–3496.
214. Ma, D.; Zhu, W. *J. Org. Chem.* **2001**, *66*, 348–350.
215. Migita, T.; Shimizu, T.; Asami, Y.; Shiobara, J.-I.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn* **1980**, *53*, 1385–1389.
216. Kondo, T.; Mitsudo, T.-A. *Chem. Rev.* **2000**, *100*, 3205–3220.
217. Baranano, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 2937–2938.
218. Zheng, N.; McWilliams, J. C.; Fleitz, F. J.; Armstrong, III, J. D.; Volante, R. P. *J. Org. Chem.* **1998**, *63*, 9606–9607.
219. Schopfer, U.; Schlapbach, A. *Tetrahedron* **2001**, *57*, 3069–3073.
220. Mann, G.; Baranano, D.; Hartwig, J. F.; Rheingold, A. L.; Guzei, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 9205–9219.
221. Foa, M.; Santi, R.; Garavaglia, F. *J. Organomet. Chem.* **1981**, *206*, C29–C32.
222. Harayama, H.; Nagahama, T.; Kozera, T.; Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *Bull. Chem. Soc. Jpn* **1997**, *70*, 445–456.
223. Still, I. W. J.; Toste, F. D. *J. Org. Chem.* **1996**, *61*, 7677–7680.
224. Wendeborn, S.; Berteina, S.; Brill, W. K.-D.; De Mesmaeker, A. *Synlett* **1998**, 671–675.
225. Wendeborn, S.; De Mesmaeker, A.; Brill, W. K.-D.; Berteina, S. *Acc. Chem. Res.* **2000**, *33*, 215–224.
226. Arnould, J.-C.; Didelot, M.; Cadilhac, C.; Pasquet, M.-J. *Tetrahedron Lett.* **1996**, *37*, 4523–4524.
227. Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1995**, *36*, 4133–4136.
228. Rajagopalan, S.; Radke, G.; Evans, M.; Tomich, J. M. *Synth. Commun.* **1996**, *26*, 1431–1440.
229. Harr, M. S.; Presley, A. L.; Thorarensen, A. *Synlett* **1999**, 1579–1581.
230. Kato, K.; Ono, M.; Akita, H. *Tetrahedron Lett.* **1997**, *38*, 1805–1808.
231. Pinchart, A.; Dallaire, C.; Gingras, M. *Tetrahedron Lett.* **1998**, *39*, 543–546.
232. Semmelhack, M. F.; Stauffer, R. D.; Rogerson, T. D. *Tetrahedron Lett.* **1973**, *14*, 4519–4522.

233. Uno, M.; Seto, K.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* **1984**, 932–933.
234. Uno, M.; Seto, K.; Ueda, W.; Masuda, M.; Takahashi, S. *Synthesis* **1985**, 506–508.
235. Matsubara, H.; Seto, K.; Tahara, T.; Takahashi, S. *Bull. Chem. Soc. Jpn* **1989**, *62*, 3896–3901.
236. Ciufolini, M. A.; Browne, M. E. *Tetrahedron Lett.* **1987**, *28*, 171–174.
237. Ciufolini, M. A.; Qi, H.-B.; Browne, M. E. *J. Org. Chem.* **1988**, *53*, 4149–4151.
238. Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740–1742.
239. Palucki, M.; Buchwald, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 11108–11109.
240. Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382–12383.
241. Muratake, H.; Hayakawa, A.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7577–7580.
242. Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581–7582.
243. Agnelli, F.; Sulikowski, G. A. *Tetrahedron Lett.* **1998**, *39*, 8807–8810.
244. Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1698–1712.
245. Sonogashira, K. *Comprehensive Organic Chemistry*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 3, pp 521–549.
246. Yamamoto, Y.; Radhakrishnan, U. *Chem. Soc. Rev.* **1999**, *28*, 199–207.
247. Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473–1478.
248. Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360–1370.
249. Whitesides, G. M.; Gaasch, J. F.; Stedronsky, E. R. *J. Am. Chem. Soc.* **1972**, *94*, 5258–5270.
250. Inoh, J.-I.; Satoh, T.; Pivsa-Art, S.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 4673–4676.
251. Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 6203–6206.
252. Bruneau, P.; Taylor, P. J.; Wilkinson, A. J. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2263–2269.
253. Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn* **1999**, *72*, 2345–2350.
254. Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546–6553.
255. Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402–3415.
256. Stauffer, S. R.; Beare, N. A.; Stambuli, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4641–4642.
257. Muratake, M.; Tonegawa, M.; Natsume, M. *Chem. Pharm. Bull.* **1996**, *44*, 1631–1633.
258. Ahman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918–1919.
259. Cassar, L. *J. Organomet. Chem.* **1973**, *54*, C57–C58.
260. Tagaki, K.; Okamoto, T.; Sakakibara, Y.; Oka, S. *Chem. Lett.* **1973**, 471–473.
261. Tschaen, D. M.; Desmond, R.; King, A. O.; Fortin, M. C.; Pipik, B.; King, S.; Verhoeven, T. R. *Synth. Commun.* **1994**, *24*, 887–890.
262. Maligres, P. E.; Waters, M. S.; Fleitz, F.; Askin, D. *Tetrahedron Lett.* **1999**, *40*, 8193–8195.
263. Sakamoto, T.; Ohsawa, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2323–2326.
264. Piers, E.; Fleming, F. F. *Can. J. Chem.* **1993**, *71*, 1867–1872.
265. Okano, T.; Iwahara, M.; Kiji, J. *Synlett* **1998**, 243–244.
266. Berteina, S.; Wendeborn, S.; Brill, W. K. D.; De Mesmaeker, A. *Synlett* **1998**, 676–678.
267. Tagaki, K.; Sakakibara, Y. *Chem. Lett.* **1989**, 1957–1958.
268. Anderson, B. A.; Bell, E. C.; Ginah, F. O.; Harn, N. K.; Pagh, L. M.; Wepsiec, J. P. *J. Org. Chem.* **1998**, *63*, 8224–8228.
269. For stoichiometric use of copper salts, see: Ellis, G. P.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779–794 and references cited therein.
270. Yamamura, K.; Murahashi, S.-I. *Tetrahedron Lett.* **1977**, 4429–4430.
271. Quirante, J.; Escolano, C.; Massot, M.; Bonjoch, J. *Tetrahedron* **1997**, *53*, 1391–1402.
272. Anies, C.; Pancrazi, A.; Lallemand, J.-Y. *Bull. Chem. Soc. Fr.* **1997**, *134*, 183–202.

Biographical sketch



Damien Prim received his PhD at the University of Metz in 1994. After a postdoctoral period at the Université Catholique de Louvain with Professor L. Ghosez, he returned to the University of Metz as Assistant Professor (1995–1999). Then, he moved to the University Pierre et Marie Curie in Paris as CNRS research associate for 2 years and joined the University of Versailles as Assistant Professor in 2001. His current research interests include organic chemistry in aqueous media, heterocyclic chemistry and transition metal (Cr, Mn, Pd) assisted organic and organometallic chemistry.

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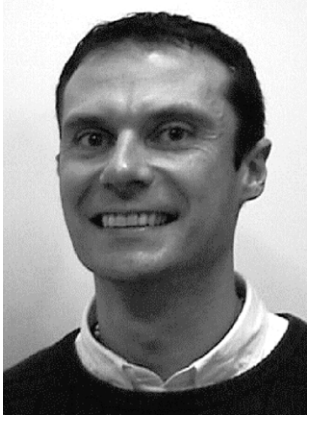

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