The Synthesis of Important Pharmaceutical Building Blocks by Palladium-Catalyzed Coupling Reaction: Access to Various Arylhydrazines

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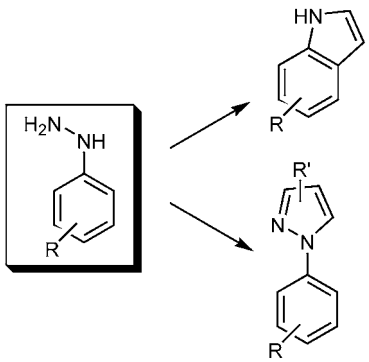
Abstract: Various arylhydrazones have been successfully synthesized *via* a highly efficient palladium-catalyzed cross-coupling reaction between aryl halides and benzophenone hydrazone. All the reaction parameters have been studied and coupling products were obtained with excellent yields from the corresponding bromides or chlorides.

Keywords: Buchwald phosphines; cross-coupling; heterogeneous catalysis; hydrazines; hydrazones; palladium

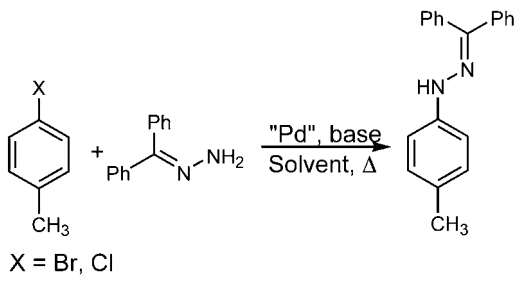
Introduction

Arylhydrazines are an important class of aromatic compounds which are extensively used as synthetic building blocks and appear as a subunit in many natural products and substances of relevance for industry.[1] Thus, they are important to a diverse array of fields, such as agrochemicals, pharmaceuticals or photography.[2] They constitute intermediates to various azaheterocycles or indoles *via* the Fischer reaction (Scheme 1).[3]

Arylhydrazines are easily accessible *via* the reduction of diazonium salts with tin(II) salts or sulfite ions,[4] but this classical method is not very productive (low concentration in aqueous media) and generates large amounts of wastes (tin wastes). Therefore, the carbon-nitrogen coupling reaction constitutes a great alternative.[5] In the last decade palladium-catalyzed amination, independently discovered by Buchwald[6] and Hartwig,[7] has established itself as a powerful method for the synthesis of arylamines. Historically, these aminations have been developed first for aryl bromide substrates. Unfortunately, because of the strength of the carbon-chlorine bond, aryl chlorides were generally less reactive towards an oxidative addition to palladium catalysts. Nevertheless, aryl chlorides are more interesting substrates than bromides because of their lower cost and wider availability. Our research group was particularly interested in applying this C–N coupling methodology on a large scale for the synthesis of hydrazones from aryl chlorides thus leading after hydrolysis to the corresponding arylhydrazines. We focused our work on having a better knowledge of this reaction to be able to scale it up. Herein, we describe our results in developing an improved protocol for a robust, economically viable and safe industrial process. We have studied a model reaction: the C–N coupling reaction between *p*-bromotoluene or *p*-chlorotoluene and benzophenone hydrazone and all the reaction parameters have been examined and optimized (Scheme 2).



Scheme 1.



Scheme 2.

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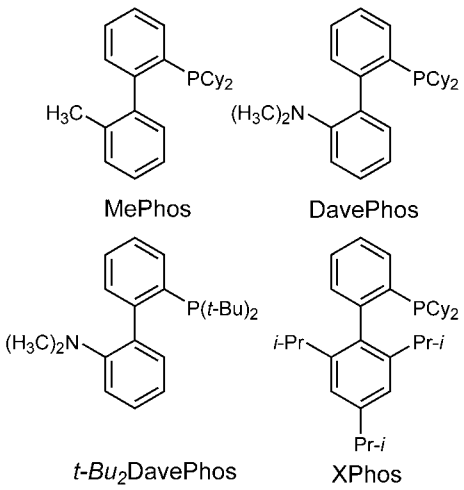
Results and Discussion

Initially, we followed the standard conditions developed by Buchwald [toluene, *t*-BuONa, 1 mol % $Pd(OAc)_2$, 3 mol % Binap, 110 °C, 24 h].[8] In our first attempts we did not observe any good conversion of *p*-tolyl bromide into the corresponding arylhydrazone. We had to undertake extensive investigations on the C–N coupling to achieve an efficient C–N bond formation.

We first conducted a methodical screening using catalytic amounts (0.5 mol %) of different palladium salts [$Pd(OAc)_2$, PdI_2, $Pd(NO_3)_2$] in combination with MePhos[9] (Scheme 3) as the ligand (Pd/phosphine = 1/2) and an excess of sodium *tert*-butoxide in toluene at 110 °C. The conversions of *p*-bromotoluene were measured by GC analysis. We learned that the nature of the palladium counterion was not really crucial for the success of the transformation. Indeed, in each case, reactions reached completion in less than 5 hours with no formation of by-products but in terms of kinetics, palladium nitrate and acetate appeared to be the most efficient salts with a nearly linear conversion profile. Heterogeneous catalysts such as Pd/C, Pd/zeolite (1% Pd–0.9% Na/Z–Si/Al = 87/13) or Pd/alumina did not display any good activity towards this coupling reaction and many side reactions (reduction of aryl bromide, hydrolysis of benzophenone hydrazone into benzophenone) occurred (Table 1).

We have chosen to continue our experiments with palladium acetate because of its industrial availability. Several reactions were carried out with five samples of palladium acetate obtained from different suppliers. We were surprised to discover the importance of the palladium acetate quality. With four of the samples (samples 1, 3, 4, 5), conversions of *p*-bromotoluene were 100% in about 4 hours at 110 °C in toluene (or xylene), the last one (sample 2) displayed the worst catalytic activity and the reaction did not reach completion. However, their performances were exactly identical at 145 °C in xylene. The amounts of palladium and of chlorine and nitrate impurities, measured in each sample, being totally different (Table 2), the elementary composition could not explain the differences in catalytic behavior observed in the coupling reaction. We then turned out our attention to the crystallographic data of samples 1 and 2. As shown in the X-ray analysis (Figure 1) and confirmed by microscopic characterizations (MEB and EDX), sample 2 is much more crystalline than sample 1, it contains more large regular particles than the latter. Therefore the difference in reactivity can be explained by these morphologies which generate different solubil-



Scheme 3.

Table 1. Coupling between *p*-bromotoluene and benzophenone hydrazone catalyzed by supported palladium in toluene under reflux

Palladium source	Conversion [%]	*N*-Arylhydrazone [%]
1% Pd-0.9% Na/zeolite (Si/Al = 87/13)	8	6
2% Pd/Al_2O_3-SiO_2	13	11
3% Pd/C acetylene	14	9
3% Pd/C with 50% H_2O	67	50
0.5% Pd/alumina powder	13	7

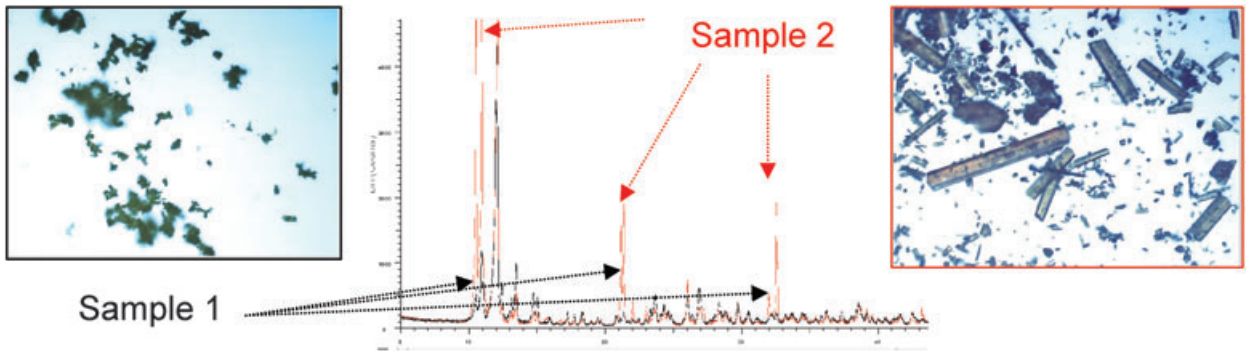


Figure 1.

Table 2. Analytical composition of various palladium acetate samples.

Sample	% Pd (w/w)	% Cl^-	% NO_3^-	mp [Lit 205 °C (DC)]
1	47.39			204 °C (DC)
2	47.92	0.1	0.02	180–183 °C (DC)
3	48.12	0.2	2	208–215 °C (DC)
4	47.97			218–220 °C (DC)
5	48.12	0.042	0.52	208–210 °C (DC)

ities at 110 °C, while at a higher temperature (145 °C), no main difference remains. To avoid problems of reproducibility from one batch to another, we continued our experiments with sample 1.

The experimental set-up also allowed us to screen a variety of phosphine ligands. It turned out that the reaction was really sensitive to the nature of the ligand. Classical ligands of the Heck reaction[10] such as *rac*-2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl (BINAP, Table 3), dppf, triphenylphosphine failed to promote the desired coupling reaction while the biphenylphosphines described by Buchwald[11] gave excellent results.

We have then proceeded to examine the choice of the best base using $Pd(OAc)_2$ and various ligands (MePhos, DavePhos, *tBu*$_2$-DavePhos, *rac*-Binap) as catalyst in toluene under reflux (Scheme 3). Experiments were carried out in the presence of 0.5 mol % of catalyst (Pd/phosphine = 1/2) and 1.4 equivs. of base. As can be seen in Table 3, the ligands showed different reaction behaviors depending on the nature of the base. It was found that the base had a deep impact on both kinetics and conversion. Indeed, potassium or cesium carbonate and potassium phosphate led to almost no product or low conversions (< 30%, entries 1–10) while the use of sodium *tert*-butoxide could afford the coupling in excellent yields in short reaction times depending on the nature of the ligand (entries 13 and 14). The best catalytic activity was displayed by MePhos and DavePhos. The former was chosen to screen other inorganic and organic bases. Bulk quality phosphates and polyphosphates from in-house sources were not efficient for the C–N coupling, probably due to an inappropriate pK_a (entries 15–21). With bases like potassium *tert*-butoxide, cesium carbonate or sodium hydroxide low conversions (< 40%) have been obtained in contrast to sodium *tert*-butoxide. This alkoxide is usually reported in the literature as a common base for C–N coupling reactions. Nevertheless, its main disadvantage is to promote the formation of diphenylmethane *via* a Wolf–Kishner[12] type reaction as described by Buchwald.[13] Another alcoholate, sodium *tert*-amylate, a common industrial base with high solubility in organic solvents, gave a high conversion of starting material (entry 26) but induced the formation of the same side-product.

These first experiments have clearly demonstrated that tertiary sodium alcoholates were the most efficient to perform this coupling reaction in aromatic solvents. Since one equivalent of alcohol is formed during the reaction process, the use of *tert*-butyl alcohol as solvent was investigated in our following studies. Reactions were carried out in test tubes with *tert*-butyl alcohol under reflux using 0.5 mol % of palladium catalyst (Pd/MePhos = 1/2). Sodium *tert*-butoxide gave a higher conversion of aryl bromide than its potassium derivative (entries 27 and 28) but showed no improvement in terms of reaction selectivity. Indeed 20% of diphenylmethane was formed in the alcohol while toluene allowed the generation of only about 10%. Surprisingly with an inorganic base such as ground sodium hydroxide (entry 29), the reaction was complete in less than 3 hours without any by-product formation. Encouraged by these results, we have proceeded to examine the effect of other metallic hydroxides in this coupling reaction. No reaction could occur with lithium and calcium hydroxide (entries 31 and 32). The conversion was complete with potassium and cesium hydroxide (entries 30 and 33), but while the former generated only 20% of diphenylmethane as by-product, the latter only induced the Wolff–Kishner type reaction, no coupling compound could be detected. The use of such bases seems to accelerate the kinetics of the side reaction at the cost of the palladium-catalyzed cross-coupling. KOH and CsOH display pK_a values[14] compatible with the Wolff–Kishner reaction which requires bases strong enough to deprotonate the benzophenone hydrazone.

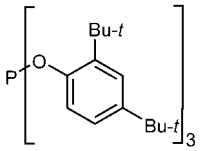
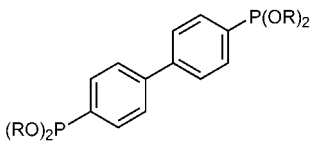
These studies have shown the importance of the nature of the base to avoid the formation of side-products. We tried to explain this key role through the reaction mechanism. Several studies have been published since the discovery of palladium-catalyzed cross-coupling between aryl halides and amines,[15] but the mechanism of the catalytic cycle is still a matter of scientific debate. For our reaction, like in many other cases,[16] we followed the classical four-step catalytic cycle. First, we assumed that palladium acetate, as a source for palladium(II), was reduced *in situ* by the excess of phosphine ligand to give the catalytically active palladium(0) species. This concept has been reported by Amatore and co-workers[17] who proved that the formation of palladium(0) from palladium acetate and triarylphosphine was faster when the aryl group was substituted by an electron-withdrawing group. To corroborate this point, we have conducted a series of experiments, replacing one Buchwald phosphine by another ligand. The results, summarized in

Table 3. Coupling between *p*-bromotoluene and benzophenone hydrazone with 1.4 equivs of base under reflux in the presence of 0.5 mol % $Pd(OAc)_2$ and 1 mol % phosphine.

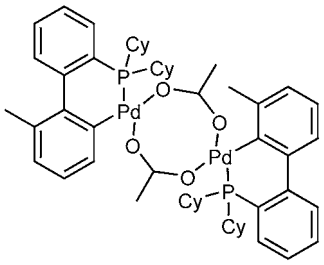
Entry	Base	Solvent	Ligand	Time [h]	Conversion [%][a]	*N*-Arylhydrazone [%][a]
1	K_2CO_3	Toluene	DavePhos	18	3	2
2	K_2CO_3	Toluene	MePhos	18	4	3
3	K_2CO_3	Toluene	*tBu*$_2$-DavePhos	18	3	2
4	K_2CO_3	Toluene	*rac*-Binap	18	19	2
5	K_3PO_4	Toluene	MePhos	18	31	29
6	K_3PO_4	Toluene	*tBu*$_2$-DavePhos	18	2	0.5
7	K_3PO_4	Toluene	*rac*-Binap	18	8	1
8	Cs_2CO_3	Toluene	MePhos	18	26	22
9	Cs_2CO_3	Toluene	*tBu*$_2$-DavePhos	18	21	15
10	Cs_2CO_3	Toluene	*rac*-Binap	18	90	12
11	*t*-BuONa	Toluene	*tBu*$_2$-DavePhos	2	22	18
12	*t*-BuONa	Toluene	*rac*-Binap	2	19	7
13	*t*-BuONa	Toluene	MePhos	2	90	87
14	*t*-BuONa	Toluene	DavePhos	2	86	81
15	$Na_4P_2O_7$	Toluene	MePhos	20	0	0
16	Na_2HPO_4	Toluene	MePhos	20	0	0
17	Na_3PO_4, 10.5 H_2O	Toluene	MePhos	20	0	0
18	Na_3PO_4	Toluene	MePhos	20	0	0
19	Na_2HPO_4, 2 H_2O	Toluene	MePhos	20	0	0
20	$(CaO)_{10}(P_2O_5)$, H_2O	Toluene	MePhos	20	0	0
21	$K_4P_2O_7$	Toluene	MePhos	20	0	0
22	Ground NaOH	Toluene	MePhos	20	0	0
23	Cs_2CO_3	Toluene	MePhos	20	40	32
24	*t*-BuOK	Toluene	MePhos	20	<10	6
25	*t*-BuONa	Toluene	MePhos	6	>98	76
26	Na *tert*-amylate	Toluene	MePhos	6	>98	89
27	*t*-BuONa	*t*-BuOH	MePhos	6	>98	77
28	*t*-BuOK	*t*-BuOH	MePhos	6	20	15
29	NaOH	*t*-BuOH	MePhos	<3	>98	>98
30	KOH	*t*-BuOH	MePhos	<3	>98	79
31	$Ca(OH)_2$	*t*-BuOH	MePhos	24	0	0
32	LiOH	*t*-BuOH	MePhos	24	0	0
33	CsOH	*t*-BuOH	MePhos	8	>98	0

[a] Determined by gas chromatography.

Table 4. Couplings with 0.05 mol % $Pd(OAc)_2$, 0.05 mol % MePhos and 0.05 mol % ligand, with 1.4 equivs. *t*-BuONa.

Entry	Phosphorus ligands	Solvent	*T* [°C]	Time [h]	*N*-Arylhydrazone [%][a]
1	MePhos	Toluene	115	3	>98
2	$P(Cy)_3$	Toluene	115	3	11
3	$P(t\text{-Bu})_3$	Toluene	115	3	91
4		Toluene	115	3	50
5	 R = (2,4-di-*tert*-butylphenyl)	Toluene	115	3	86

[a] Determined by gas chromatography.



Scheme 4.

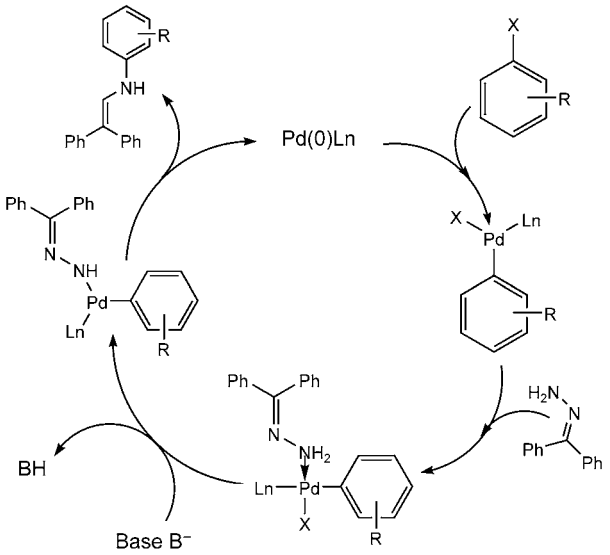
Table 4, show that even if the kinetics is sometimes much slower it is possible to substitute one Buchwald ligand by a less expensive phosphine or phosphite ligand. It must be noted that the reaction could not proceed with total replacement of MePhos, this tends to prove again the essential role of the biphenyl ligand in the reaction and of the second equivalent of ligand as reducing agent.

Besides these observations, we carried out this coupling reaction using a preformed catalyst: a palladacycle isolated from one equivalent of palladium acetate and MePhos (Scheme 4). Surprisingly, nothing occurred after 20 hours heating in toluene, but the addition of one more equivalents of MePhos allowed the reaction to proceed. Thus the palladacycle is a palladium(II) dimer catalyst precursor which is totally inactive towards the C–N cross-coupling. This is proof that the excess of MePhos is necessary to generate the active palladium(0) species.

We even tried to replace one phosphine by zinc powder as a reducing agent since it is a non-flammable and cheap reagent. The experiment was performed in a 500-mL reactor with *tert*-amyl alcohol at reflux with 0.1 mol % Pd, 0.1 mol % of MePhos and 0.2 mol % zinc. The reaction was complete overnight, no by-product was formed and the arylhydrazone was obtained in a good yield (about 90%). As decreasing of the catalyst amount is still a challenging problem to have an economically viable industrial process, some more studies are still underway in this field in our laboratories.

The palladium(0) thus generated then becomes a part of the catalytic cycle (Scheme 5). The first step of this cycle is an oxidative addition of aryl halide to the usually supposed 14-electron complex $Pd(0)L_n$ to afford a σ-arylpalladium(II) complex. The second step is the coordination of the nucleophile (benzophenone hydrazone) to the palladium complex *via* the nitrogen free electrons. At that point, the base must be strong enough to catch the hydrazone proton and thus to allow the formation of a σ-N–Pd bond in the intermediate complex. However, the benzophenone hydrazone must not be deprotonated before complexation to avoid the Wolff–Kishner reaction. Finally, the desired product is generated by a reductive elimination (cross-coupling).

In order to understand the role of the nature of the ligand in this mechanism, we have decided to screen a variety of biaryl- and arylphosphines prepared in our laboratories.[18] Reactions were carried out in test tubes in the presence of 0.1 mol % of $Pd(OAc)_2$ and 0.2 mol % of ligand using two base/solvent systems (namely NaOH/*tert*-amyl alcohol and *tert*-BuONa/xylene). In all cases, conversions are worse than those obtained with XPhos and MePhos. A biphenyl group is crucial to allow the reaction to proceed (entries 7 and 8). Moreover comparing the position of the substituents, it seemed that a catalyst should bear some substituents at the *ortho* or *para* position of the second aromatic to be efficient. This is well related in the literature[19] as electron-donor groups can stabilize the cationic charge generated in the palladium complex by the σ-C–Pd bond formation.



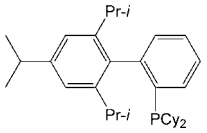
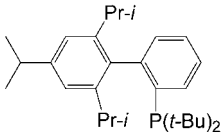
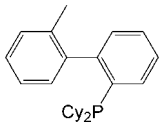
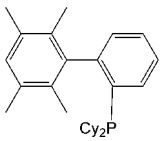
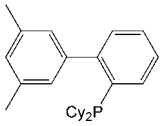
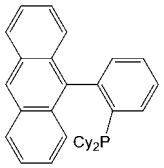
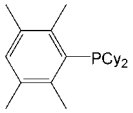
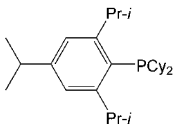
Scheme 5.

In light of the high reactivity of ground sodium hydroxide, we explored the possibility to carry out the reaction even in other solvents using only 0.1 mol % of palladium catalyst (Table 6). The kinetics could be improved by replacing *tert*-butyl alcohol with *tert*-amyl alcohol, a solvent which has a higher boiling point (103 °C instead of 90 °C). Indeed, to our delight, the reaction performed in *tert*-amyl alcohol at 103 °C reached completion in less than four hours. The reaction was totally selective, no side-product formation was observed.

Ground NaOH in refluxing toluene or xylene resulted in no transformation even in the presence of a phase transfer catalyst such as TDA-1 [$N(CH_2CH_2OCH_2CH_2OMe)_3$].

Using methoxyethanol, the hydrazonation of 4-bromotoluene could be achieved with better kinetics than with *tert*-butyl alcohol. However, for safety reasons due to its high toxicity, methoxyethanol is totally unsuitable in an industrial process. Other polar solvents like glycol, diethylene glycol, *N*,*N*-dimethylethanolamine

Table 5. Screening using 0.1 mol % $Pd(OAc)_2$ and 0.2 mol % ligands in two base/solvent systems.

Entry	Ligand	*N*-Arylhydrazone [%][a]	
		in *t*-BuONa/ xylene	in NaOH/*tert*-amyl alcohol
1		>98	>98
2		3	4
3		>98	>98
4		69	52
5		0	5
6		12	18
7		5	2
8		2	3

[a] Determined by gas chromatography.

and *n*-butanol resulted in low conversions (<30%), gaiacol (2-methoxyphenol) gave even worse results.

Aromatic solvents with different donor/acceptor substituents were also examined. Thus, anisole, veratrole (1,2-dimethoxybenzene), 2-chloroanisole, 1,3-benzodioxole, 1,3,5-trimethoxybenzene or 1,3-diethoxybenzene are suitable for this kind of chemistry. The kinetics cannot be compared for these solvents because no systematic sampling has been performed during these experiments. However, these studies have clearly shown the pertinence of the couple alcohol/hydroxide for the palladium-catalyzed carbon-nitrogen coupling reaction.

In order to control an eventual exotherm, it is generally advised for industrial processes to add one of the reagents dropwise over a long time period. An experiment was carried out by adding the aryl bromide dropwise to the reaction mixture in standard conditions (0.1 mol % catalyst, xylene, *t*-BuONa and benzophenone hydrazone). After 24 hours of stirring, conversion was not more than 20%. This experiment was reproduced twice and displayed the same result. In contrast, when the benzophenone hydrazone is added dropwise, the reaction reached completion in less than two hours. These experiments have shown that the introduction order of the reagents can be crucial for the outcome of the reaction. As described by Amatore,[17,20] the nucleophile can often form a complex with the palladium, a new complex which can totally inhibit the catalytic activity. This can occur in our process as hydrazones have already been reported to be good ligands for palladium(II).[21] Moreover, mixing one equivalent of palladium acetate with one of benzophenone hydrazone allowed us to isolate a palladacycle[22] which was totally inactive towards the coupling reaction between *p*-tolyl bromide and benzophenone hydrazone. Even the addition of MePhos did not allow the reaction to proceed.

To have an economically viable process compared to the classical diazonium synthesis, we have conducted a set of experiments to reduce the palladium loading. Finally, optimized reaction conditions allowed the benzophenone hydrazone to react with *p*-tolyl chloride or bromide in *tert*-amyl alcohol under reflux using only 0.05 mol % of palladium acetate, 0.1 mol % of MePhos with 1.4 equivs. of sodium hydroxide as a base. On work-up, the crude solution was directly hydrolyzed with water to remove the salts. Layers were separated and the arylhydrazone crystallized from the organic layer at a lower temperature. This protocol affords the *p*-tolylphenylhydrazone as a white powder with an excellent yield (92%).

This protocol was transferred to a range of various aryl halides in a 500-mL jacketed glass vessel (Table 7). The reaction was performed in the presence of 0.1 mol % of catalyst in *tert*-amyl alcohol with 1.4 equivs. of ground sodium hydroxide. Upon conversion and treatment, the target arylhydrazones were directly crystallized in *tert*-amyl alcohol and isolated as solids in excellent yields (entries 1–7, 85–97%). In each case, the kinetics were fast (completion in about 4 hours). The reaction is totally selective towards bromides. Indeed, in the case of *o*-bromochlorobenzene (entry 3), no coupling occurred at the chloro position. Moreover, aryl triflates are totally unreactive towards this chemistry. With 4-methylphenyl triflate, the experiment resulted in a low conversion (<5%) within 20 hours. Surprisingly, no coupling reac-

Table 6. Screening of solvents using 1.4 equivs. of ground NaOH and 0.1 mol % catalyst (Pd/MePhos = 1/2).

Entry	Solvent	Time [h]	T [°C]	*N*-Arylhydrazone [%][a]
1	Toluene	6	110	0
2	Xylene	6	110	0
3	*t*-BuOH	5	90	>98
4	*tert*-amyl alcohol	4	103	>98
5	$MeOCH_2CH_2OH$	4	100	>98
6	Glycol	20	100	~30
7	Diethylene glycol	20	100	~30
8	*N,N*-Dimethylethanolamine	20	100	~30
9	Gaiacol	20	100	0
10	*n*-BuOH	20	100	15
11	Anisole	18	100	100
12	Veratrole	18	100	100
13	2-Chloroanisole	18	100	100
14	1,3-Benzodioxole	18	100	100
15	1,3,5-Trimethoxybenzene	18	100	100
16	1,3-Diethoxybenzene	18	100	100

[a] Determined by gas chromatography.

Table 7. Screening of aryl halides using 0.1 mol % $Pd(OAc)_2$ and 0.2 mol % MePhos in *tert*-amyl alcohol.

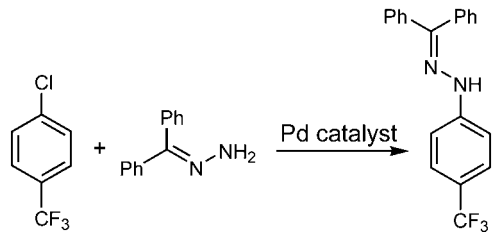
Entry	Substrate	Base	T [°C]	Time [h]	Conversion [%][a]	Yield [%][b]
1	4-Bromotoluene	NaOH	103	3	100	92
2	4-Bromobenzene	NaOH	103	4	100	95
3	4-Bromochlorobenzene	NaOH	103	<5	100	97
4	4-Bromoanisole	NaOH	103	4	100	87
5	2-Bromotoluene	NaOH	103	<4	100	85
6	4-Bromofluorobenzene	NaOH	103	4	100	91
7	4-Chlorotoluene	NaOH	103	<3	100	93
8	4-Methylphenyl triflate	NaOH	103	20	0	0
9	4-Chloro-trifluoromethylbenzene	NaOH	103	24	0	0

[a] Determined by GC analysis.
[b] Isolated yield after crystallization in *tert*-amyl alcohol.

Table 8. Screening of conditions using 1.4 equivs. of base and Pd/MePhos = 1/2.

Entry	Pd [%]	Ligand [%][a]	Base	Solvent	T [°C]	Conversion (yield [%])
1	0.1	MePhos	NaOH	*tert*-Amyl alcohol	103	0
2	0.5	MePhos	*t*-BuONa	Xylene	145	<10
3	0.5	MePhos	NaOH	Anisole	110	<5
4	0.5	XPhos	K_3PO_4	Anisole	110	100 (88)
5	0.1	XPhos	K_3PO_4	Anisole	110	97 (85)
6	0.5	XPhos	*t*-BuONa	Anisole	110	47
7	0.5	XPhos	*t*-BuOK	Anisole	110	51
8	0.5	XPhos	Sodium *tert*-amylate	Anisole	110	93
9	0.5	XPhos	K_2CO_3	Anisole	110	78
10	0.5	XPhos	Cs_2CO_3	Anisole	110	70
11	0.5	XPhos	KOH	Anisole	110	>98
12	0.5	XPhos	NaOH	Anisole	110	>98

[a] Pre-catalyst formation in xylene at room temperature.



Scheme 6.

tion occurred between *p*-chlorotrifluoromethylbenzene (*p*-Cl-TFMB) and benzophenone hydrazone (entry 9).

p-Cl-TFMB was subjected to other coupling conditions (base, solvent in the presence of MePhos, Table 8, entries 1–3). Nevertheless, all attempts to realize a cross-coupling reaction resulted in the decomposition of the starting hydrazone. We then turned our attention to another biphenylphosphine (XPhos, Scheme 6) reported to be more efficient than MePhos.[23] Using 0.5 mol % $Pd(OAc)_2$, 1 mol % XPhos in anisole at 110 °C, benzophenone hydrazone (1.0 equiv.) and *p*-chlorotrifluoromethylbenzene (1 equiv.) are converted to *p*-trifluoromethylphenylbenzophenone hydrazone with good to excellent conversions depending on the nature of the base and no side reaction was observed. We successfully decreased the palladium loading to 0.1 mol % with potassium phosphate. The target molecule was afforded with a good yield (85%, entry 5) after crystallization. Thus, the choice of ligand is crucial to the successful Pd-catalyzed preparation of *N*-arylbenzophenone hydrazones. The Pd/Xphos combination is the only catalyst system that allows a complete conversion of benzophenone hydrazone and *p*-Cl-TFMB.

As *N*-arylhydrazones were not stable enough to be kept for a month, it is more advantageous to isolate and store the corresponding hydrazine hydrochlorides. These salts can be prepared by reacting a hydrazone in an acidic medium. We have studied the synthesis of *p*-tolylhydrazine chloride. In our procedure, the *N*-*p*-tolylbenzophenone hydrazone is directly stirred in a mixture of concentrated aqueous hydrochloric acid and ethanol (9/1) at room temperature. The hydrazine salts are insoluble in the reaction mixture, so a simple filtration and several washes with dichloromethane afforded the hydrazine salt as a white powder with an excellent yield (91%). We reproduced this reaction several times in a 500-mL reactor before transferring successfully the protocol to the pilot plant.[18b]

Conclusions

In conclusion, we have studied the palladium-catalyzed C–N coupling reaction to develop a simple, efficient and general methodology for the synthesis of a variety of structurally diverse hydrazones thus leading to the corresponding hydrazines salts. The significant advantages offered by this method are : (a) general applicability to all types of aryl chlorides and bromides, (b) high yields, (c) considerably lower catalyst loading, (d) reaction conditions mild enough to be compatible with sensitive functional groups, (e) no by-product formation. We believe that this procedure provides a practical and better alternative to the existing process for arylhydrazines synthesis.

Experimental Section

General Procedure

All reagents were obtained commercially and used without further purification. ^1H and ^{13}C NMR spectra were determined on a 200 MHz spectrometer. Melting points were determined on a Büchi B-545 capillary melting point apparatus and are uncorrected.. Each compound prepared herein was characterized by GC, GC-MS and ^1H NMR spectroscopy. All reported yields are based on the weight of the isolated product.

Gas Chromatography

Gas chromatography was carried out using a Varian CP-3800 gas chromatograph equipped with an FID detector and a fused silica capillary column DB-17 (30 m × 0.32 mm × 0.25 μm). All samples were examined under the following temperature gradient: temp 1, 100 °C (0 min); temp 2, 300 °C (5 min); rate 30 °C/min, total run time 11.67 min. Conversions were determined by direct integration of the peak areas of the gas chromatograph rather than by constructing calibration curves using standard solutions of each component. GC-MS data were acquired using an HP 5890 series II gas chromatograph using the same temperature gradient as described for GC analysis.

General Procedure for the Palladium-Catalyzed Coupling Reactions

In a 500-mL glass reactor equipped with a condenser and a mechanical stirrer, were charged under a nitrogen atmosphere the aryl halide (0.2 mol), benzophenone hydrazone (39.25 g; 0.2 mol) and ground sodium hydroxide (11.2 g; 0.28 mol) in freshly degassed *tert*-amyl alcohol (120 mL). The mixture was heated at reflux. The complex catalyst was preformed under argon by mixing $Pd(OAc)_2$ (44.8 mg; 0.2 mmol) and MePhos (145.6 mg; 0.4 mmol) in degassed *tert*-amyl alcohol (15 mL) for 20 minutes at room temperature and then added into the glass vessel. The reaction was followed by GC analysis. When completion was reached, the reaction mixture was cooled to room temperature and unsoluble salts were quenched with water. Layers were separated and the arylhydrazone crystallized at about 5 °C in the organic layer. The solid was filtered, washed twice with *tert*-amyl alcohol and dried at 40 °C (10 mbar). The arylhydrazone was isolated as a solid in a good yield (see Table 7).

N-*p*-Tolyl Benzophenone Hydrazone[18b]

In a 16-L glass reactor equipped with a condenser, a mechanical stirrer and linked by an optic fiber to a Raman spectrometer, were charged under a nitrogen atmosphere 4-chlorotoluene (1.605 kg, 12.675 mol) and ground sodium hydroxide (709.8 g, 17.745 mol) in 8 L of freshly degassed *tert*-amyl alcohol. The mixture was heated at reflux. The complex catalyst was pre-formed under argon by mixing $Pd(OAc)_2$ (1.42 g, 6.3 mmol) and MePhos (4.61 g, 12.7 mmol) for 20 minutes at room temperature in 100 mL of *tert*-amyl alcohol and then added into the glass vessel. Benzophenone hydrazone (2.487 kg, 12.675 mol) was added in 13 portions every 10 minutes. The reaction was followed by Raman spectroscopy. When the reaction had reached completion, the mixture was cooled to room temperature and insoluble salts were quenched with water (2 L). Layers were separated and the arylhydrazone crystallized at about 5 °C in the organic phase. The solid was filtered, washed with 2.5 L of *tert*-amyl alcohol and dried at 40 °C (10 mbar). The arylhydrazone was obtained as a pale yellow solid (93%). ^1H and ^{13}C NMR are in accordance with the literature data.[24]

N-*p*-Trifluoromethylphenyl Benzophenone Hydrazone

In a 500-mL glass reactor equipped with a condenser and a mechanical stirrer, were charged under a nitrogen atmosphere 4-chlorotrifluoromethylbenzene(0.2 mol), benzophenone hydrazone (39.25 g, 0.2 mol) and ground potassium phosphate (59.4 g, 0.28 mol) in freshly degassed anisole (120 mL). The mixture was heated at 145 °C. The complex catalyst was preformed under argon by mixing $Pd(OAc)_2$ (44.8 mg; 0.2 mmol) and XPhos (47.7 mg; 0.4 mmol) in degassed xylene (15 mL) for 20 minutes at room temperature and then added into the glass vessel. The reaction was followed by GC analysis. When completion was reached, the reaction mixture was cooled to room temperature and unsoluble salts were quenched with water. Layers were separated and the organic layer was concentrated under vacuum. *tert*-Amyl alcohol (100 mL) was added to the solid residue and the arylhydrazone crystallized at about 5 °C. Upon filtration, two washes with *tert*-amyl alcohol, and drying at 40 °C (10 mbar), the *N*-*p*-trifluoromethylphenyl benzophenone hydrazone was isolated as a pale yellow solid in a good yield (85%).

N-*p*-Tolylhydrazine Salt

In a 16-L Büchi glass reactor equipped with a condensor, a mechanical stirrer and under argon was placed *N*-*p*-tolyl benzophenone hydrazone (2.477 kg, 8.65 mol) in 9.9 L of hydrochloric acid (aqueous solution at 37% wt). 990 mL of ethanol were then added. The mixture was allowed to stirr for 24 hours at room temperature. Conversion was followed by GC analysis. On conversion, the solid formed was filtered, washed three times with 4 L of dichloromethane and dried at 40 °C (10mbar). The hydrazine salt was obtained as a white solid; yield: 1.477 kg (> 95%).

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