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An Efficient and Safe Procedure for the Large-Scale Pd-Catalyzed Hydrazonation of Aromatic Chlorides Using Buchwald Technology

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Abstract:

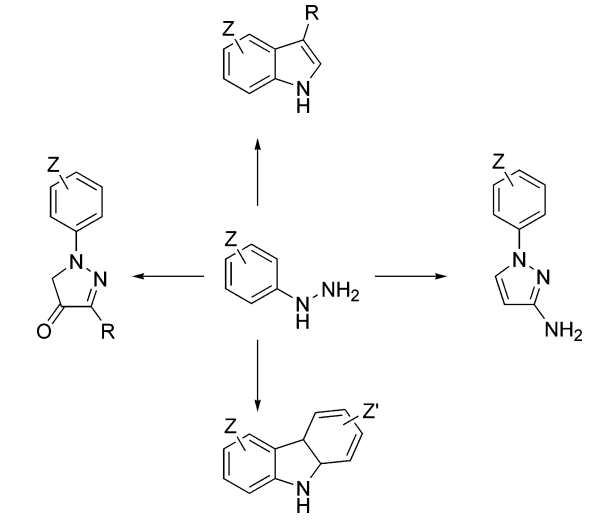
A convenient, optimized and safe synthesis of *N*-arylhydrazines, useful as intermediates for active ingredients in agricultural and pharmaceutical applications, is reported. Starting from aryl halides (chlorides and bromides), a palladium-catalyzed carbon−nitrogen coupling reaction followed by an acidic treatment afforded the target molecules in good to excellent yields using low catalyst loadings. This technology has then been successfully applied on a large scale in a pilot plant. This contribution also describes the major improvements in ligand synthesis and the thermal data required to develop a process on a pilot scale.

Introduction

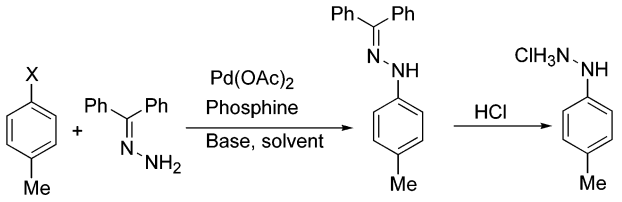
The formation of a carbon−nitrogen bond is an important process in synthetic organic chemistry. In this area, the metal-catalyzed C−N bond formation is an extremely powerful tool for the synthesis of aniline and hydrazine derivatives which are important to a diverse array of fields, such as agrochemicals, pharmaceuticals, or photography. The Buchwald and Hartwig groups have first reported a general method for C−N coupling catalyzed by a palladium complex.[1] Rhodia was particularly interested in applying this methodology for the synthesis of hydrazones. Indeed, those compounds constitute intermediates to arylhydrazines, leading to various azaheterocycles or indoles via the Fischer reaction[2] (Scheme 1). Those heterocycles can be afforded via diazonium salts, but in the case of sensitive functions, the carbon−nitrogen coupling constitutes a great alternative.

This methodology has only been described on a lab scale; therefore, we focused our work on developing an improved protocol to have a robust, viable, and safe industrial process. Herein, we describe our results on a model reaction: the C−N coupling reaction between *p*-bromotoluene or *p*-chlorotoluene and benzophenone hydrazone,[3] thus leading to the synthesis of the *N*-*p*-tolyl benzophenone hydrazone on an industrial scale (Scheme 2).

Scheme 1



Scheme 2



Results and Discussion

Synthesis of *N*-*p*-Tolyl Benzophenone Hydrazone 1. Initially, we followed the standard conditions developed by Buchwald (toluene, tBuONa, 1% mol palladium catalyst, 3% mol BINAP, 110 °C, 24 h).[1] Much to our surprise, those first attempts were unsuccessful. No good conversion of *p*-tolylbromide into the corresponding arylhydrazone could be observed in our laboratories, and we encountered several problems in reproducing this reaction on a large scale. We had to undertake extensive investigations on the C−N coupling. Thus, we conducted a methodical screening using catalytic amounts of different palladium salts ($Pd(OAc)_2$, $Pd(Acac)_2$, $PdCl_2$, $PdBr_2$) in combination with an excess of base (tBuONa, K_3PO_4, Cs_2CO_3, K_2CO_3, KOH, NaOH) and different solvent systems (xylene, toluene, anisole, dioxane, tBuOH, *tert*-amyl alcohol) at a range of temperatures (80−150 °C).[4] A majority of these conditions failed in our hands to afford satisfying conversion of the *p*-chlorotoluene into the target hydrazone molecule. The experimental setup also

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(1) (a) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6621. (b) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 1251. (c) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2090.

(2) (a) Robinson, B. *The Fischer Indole Synthesis*; John Wiley and Sons: Chichester, 1982. (b) Sundberg, R. *Best Synthetic Methods*; Academic Press: London, 1996, Vol.16. (c) Hughes D. L. *Org. Prep. Proced. Int.* **1993**, *25*, 609.

(3) Benzophenone hydrazone was commercially available at an industrial scale from Atofina.

(4) *Adv. Synth.Catal*. Paper to be submitted.

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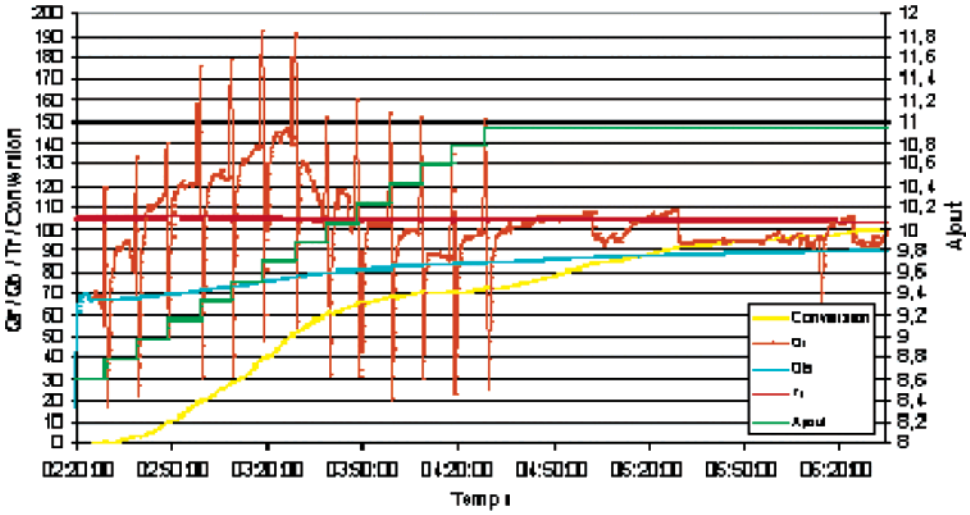
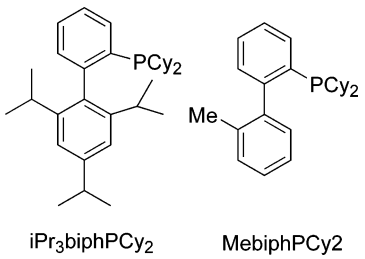


Figure 1. **Energy profile for standard reaction with benzophenone hydrazone addition. (Orange) Heat flow (*y*-axis in W). (Blue) T_j jacket temperature (*y*-axis in °C). (Yellow) GC conversion to product (*y*-axis in %). (Green) Starting benzophenone hydrazone addition (*y*-axis in kg). (*x*-axis is time for experiment in hours).**

allowed us to screen a variety of phosphine ligands. We learned that the nature of the palladium source was not crucial for the success of the transformation. We assumed that palladium acetate as a source for palladium (II) was reduced in situ by the excess of phosphine ligand to give the catalytic active palladium (0) species. In contrast, it turned out that the reaction was really sensitive to the nature of the ligand. Ligands such as rac-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), dppf, triphenylphosphine failed to promote the desired coupling reaction, while Buchwald biphenyl phosphines gave excellent results. Finally, optimized reaction conditions allowed the benzophenone hydrazone to react with *p*-tolylchloride or bromide in *tert*-amyl alcohol under reflux using only 0.05% mol of palladium acetate, 0.1% mol of MePhos (see Scheme 3) with 1.4 equiv

Scheme 3



$iPr_3biphPCy_2$ MebiphPCy2

of sodium hydroxide as base. On conversion, the crude solution was directly hydrolyzed with water to remove the salts. Layers were separated, and the arylhydrazone was allowed to crystallize in the organic layer at a lower temperature (4 °C). This protocol afforded the *p*-tolylphenylhydrazone as a pale-yellow powder with an excellent yield (93%). This product was slightly contaminated by palladium (500 ppm); however, it did not interfere in the following transformations, and it could conveniently be removed in the next step by the acidic treatment. Moreover, recovery protocols usually focus on adsorption with charcoal, the best material to use for conducting a test. This subject is still a matter of ongoing studies in our laboratories.

Before applying this technology on a large scale, we turned our attention to the thermodynamic data for safety reasons. In this course, we undertook some calorimetric and thermal studies in a Mettler RC-1 calorimeter on the model reaction with *p*-chlorotoluene. The instrument is equipped with a 2-L vessel, temperature sensor, calibration heater, and propeller stirrer. The resulting heat flow curve showed that the reaction is very exothermic (Figure 1, $\Delta H = -97.5$ kcal/mol). The RC-1 program calculated a very large temperature rise potential that suggested that, if loss of reactor control (cooling or stirring) and full accidental mischarge of all the hydrazone occurred, this would result in vigorous solvent reflux and vaporisation of 78% of the initial charge of alcohol. Moreover, the reaction is not instantaneous. Indeed, at the end of the benzophenone hydrazone addition, the thermal conversion is only 43.3% (210 kJ, GC conversion $\approx$ 70%). All those thermal data confirm the necessity to introduce slowly the benzophenone hydrazone over at least 2 h. Moreover, according to differential scanning calorimeter (DSC) analysis, both arylhydrazone and its xylene solution are stable up to an onset temperature of 250 °C.

Since the protocol works reliably on a 500-mL scale, we considered a scale-up and a transfer of this sequence to the pilot plant. The standard procedure is applied to an 18-L glass reactor linked to a Raman RXN1 spectrometer (Kaiser Optical Systems, Inc.), particularly adapted for processes studies. Indeed, this process monitoring enables us to determine the reaction completion with optimization of the cycle time, avoidance of unnecessary stirring periods, and no sampling for traditional analysis.[5] When the reaction is complete, a crystallization in *tert*-amyl alcohol affords the arylhydrazone in an excellent yield (93%) as a pale-yellow solid (see Figures 2 and 3).

(5) (a) Wiss, J.; Zilian, A. *Org. Process Res. Dev.* **2003**, *7*, 1059. (b) Lee, M.; Kim, H.; Rhee, H.; Choo, J. *Bull. Korean Chem. Soc.* **2003**, 24, *2*, 205. (c) Jeon, S.; Woo J.; Kyong, J.; Choo, J. *Bull. Korean Chem. Soc.* **2001**, 22, *11*, 1264. (d) McCaffery, T. R.; Durant, Y. G. *J. Appl. Polym. Sci.* **2002**, *86*, 1507. (e) Bruneel, J. L.; Lassegues, J. C.; Sourisseau, C. *J. Raman Spectrosc.* **2002**, *33*, 815. (f) Jeon, S.; Choo, J.; Kim, S.; Kwon, Y.; Kim, J.; Lee, Y.; Chung, H. *J. Mol. Struct.* **2002**, *609*, 159.

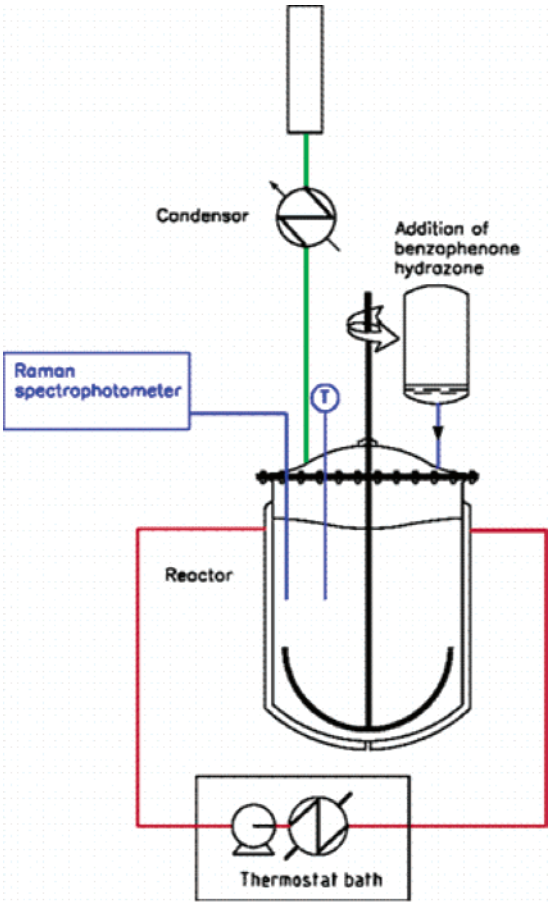


Figure 2. **Apparatus used in the C−N coupling reaction.**

The Raman apparatus can be easily used in heterogeneous media. A fiber-optic connection is installed between the probe and the spectrometer which is totally appropriate for industrial applications. With this technology, the spectrometer can be used in the pilot plant without any modification of the available equipment. The formation of the final arylhydrazone was followed in line by Raman spectroscopy according to the characteristic bands of all the materials. Indeed, the intensity is directly proportional to the species concentration; therefore, kinetics is followed by the variation of the intensity of the bands. As shown in Figure 4, benzophenone hydrazone, *p*-bromotoluene, and final arylhydrazone present characteristic bands respectively at 180, 290, and 1620 cm^{-1}. A spectrum is automatically recorded every 5 min and clearly shows the kinetic profile in three dimensions.

Reaction profiles are constructed from normalized spectra which are less noisy. Normalizations for the Raman spectra are carried out taking two regions 150−320 and 1500−1600 cm^{-1} (see Figures 5, 6, 7, and 8). The most important changes in the Raman spectra can be summarized as follows:

(i) decrease of peaks at around 290 and 1580 cm^{-1}: conversion of *p*-bromotoluene,

(ii) decrease of peak at around 180 cm^{-1}: conversion of benzophenone hydrazone,

(iii) appearance and increase of peaks at around 1540 and 1620 cm^{-1}: formation of *N*-*p*-tolyl benzophenone hydrazone.

The Raman spectroscopy allows the detection and monitoring of byproducts (such as benzophenone in our case) during the completion of the reaction. This is very important for the assessment of the procedure safety. Therefore, this analysis method is appropriate and useful to ensure a safe completion of the chemical process.

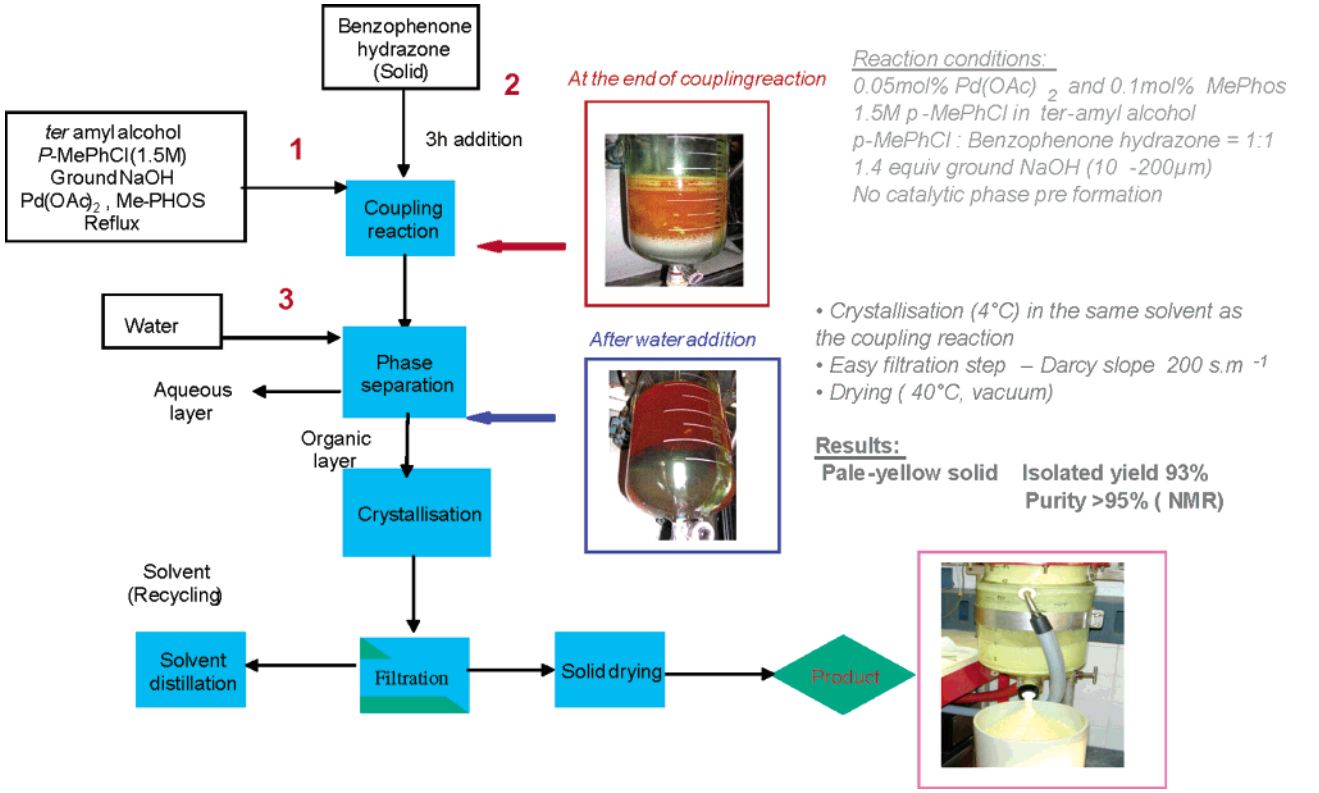


Figure 3. **Schematic diagram of the hydrazonation process.**

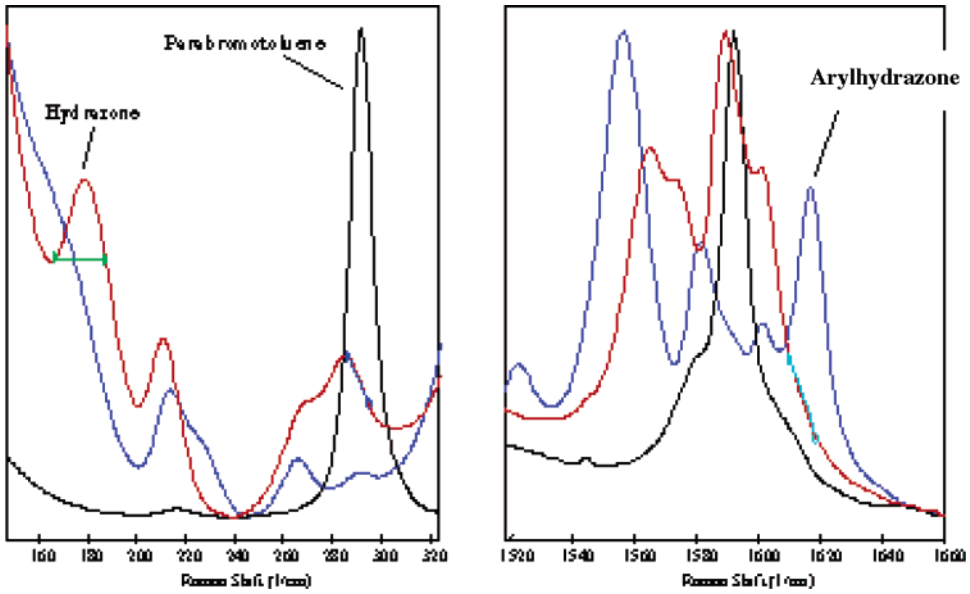


Figure 4. **Raman spectra of coupling product and starting materials.**

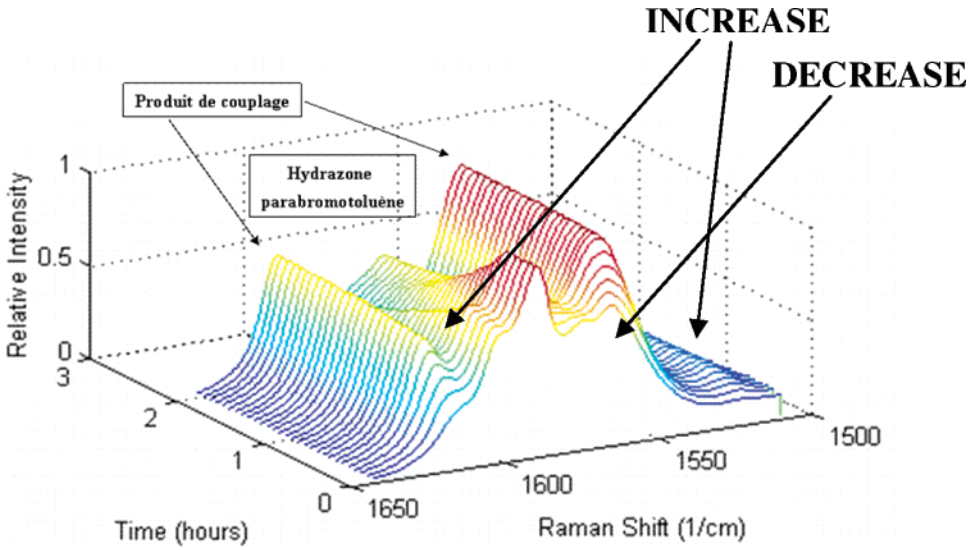


Figure 5. **Raman spectra of the hydrazonation (1500−1650 cm^{-1}).**

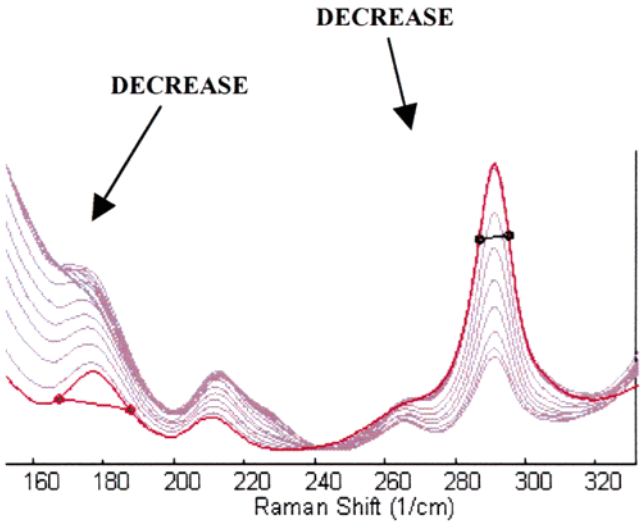


Figure 6. **Raman spectra at intervals of 1 h; normalized data; spectral range: 160−320 cm^{-1}.**

Synthesis of *N*-*p*-Tolylhydrazine Salt. Hydrazine salts are particularly interesting for pharmaceutical companies as they constitute intermediates to azaheterocycles such as indoles and pyrazoles.[1b,6] As *N*-aryl-hydrazones are not stable enough to be kept for month, it is more advantageous to isolate and store the corresponding hydrazine hydrochloride. These salts can be prepared by reacting a hydrazone in an acidic medium. We have studied the synthesis of the *p*-tolylhydrazine chloride. In our procedure, the *N*-*p*-tolyl benzophenone hydrazone is directly stirred in a mixture of concentrated aqueous hydrochloric acid and ethanol (90/10) at room temperature. The hydrazine salts are insoluble in the reaction mixture; consequently, a simple filtration and several washes with methylene chloride afforded the hydrazine salt as a white powder with a quantitative yield. We reproduced this reaction several times on a 500-mL reactor before transferring the protocol to the pilot plant (Figure 9).

(6) Bush M.; Schaffner, S. *Chem. Ber*. **1923**, *56*, 1612

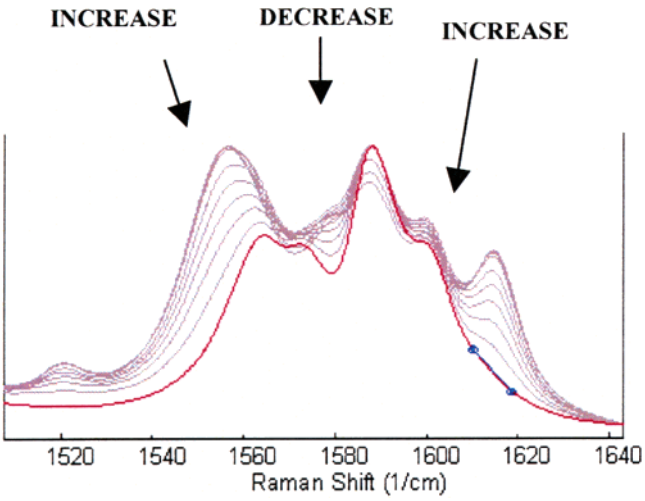


Figure 7. **Raman spectra at intervals of 1 h; normalized data; spectral range: 1520−1640 cm^{-1}.**

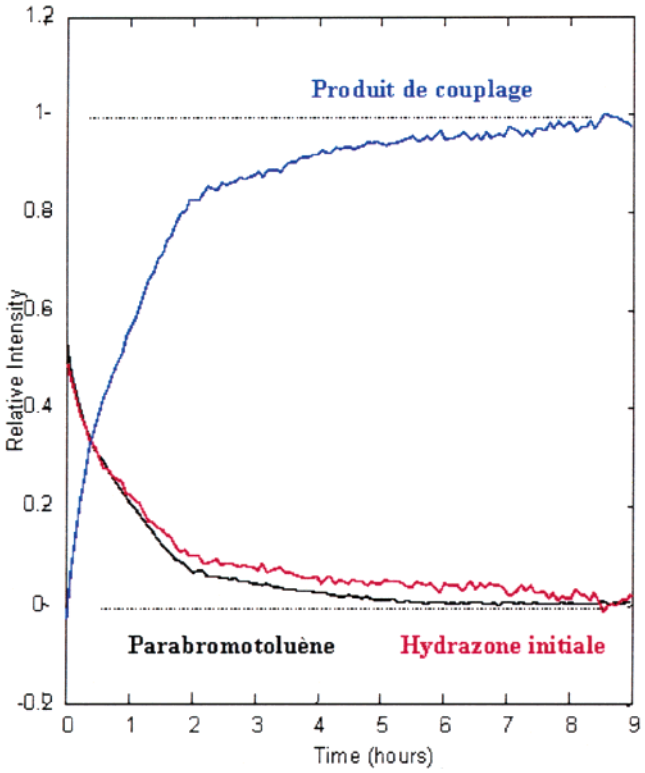


Figure 8. **Normalized reaction profiles (maximum change in peak area set to 100%).**

The reaction was then performed in a 16-L Buchi glass reactor with 2.5 kg of *N*-*p*-tolyl benzophenone hydrazone using 10 L of concentrated HCl and 100 mL of EtOH. The hydrazine salt was isolated from the crude solution with a quasi-quantitative yield. With the use of NMR we observed only traces of benzophenone (0.2% mol).

Indeed, a fluorescence X-ray analysis determined that the palladium rate in the sample was less than 5 ppm; this result is appropriate to the current European legislation on the pharmaceutical compounds.[7]

Moreover, in the course of our studies on the process safety, a differential scanning calorimeter (DSC) analysis was carried out on the hydrazine salt. The thermogram showed endothermic phenomena at about 100 °C corresponding to the melting point. Then it displayed an exothermal from 110 °C (highest temperature reaches 192 °C) representing the salt degradation. Therefore, the salt is considered thermally stable at room temperature and can be stored and easily handled for months. The calorimetric energy displayed during the reaction has also been measured in an RC-1 Mettler calorimeter. It is only 12.2 kcal mol^{-1} of starting arylhydrazone, and the corresponding adiabatic temperature is +13.5 °C. Thus, this reaction is slightly exothermic but relatively safe.

Synthesis of MePhos and XPhos. As demonstrated by Buchwald and co-workers, bulky and electron-rich dialkylphosphane ligands, more particularly the MebiphPCy$_2$ (or MePhos[8]) and the ^{i}Pr$_3$biphPCy$_2$ (or XPhos,[9] Scheme 3), are efficient for this coupling reaction.

Their synthesis has been reported on a lab scale using a Grignard strategy (Scheme 4).

For our industrial purposes, we had to develop those phosphines on a large scale (up to 25 kg). The entire experimental procedure is identical for both of the phosphines except the crystallisation process at the final stage.

For an industrial process and for safety reasons, magnesium powder should be avoided, and we chose to replace it by turnings which are easier to handle. We used a technical grade tetrahydrofuran (THF) which was provided by SDS and contains 0.1% of water. The chlorodicyclohexylphosphine was provided in-house.

In the course of our studies on the protocol improvement, we found that the addition of magnesium turnings in two crops provides a higher yield in biarylphosphine, as opposed to the one-crop addition of magnesium powder as reported in Buchwald's original investigation. The formation of the intermediates and of the final C−P coupling can be easily followed by GC analysis. The kinetics are fast for each step which reached completion within approximately an hour, straight on the end of the product addition, respectively arylbromide, bromochlorobenzene and chlorodicyclohexylphosphine. This brought to the fore that the reaction was nearly instantaneous.

The improvement of the workup has also been investigated. In the new standard procedure, the addition of aqueous sodium sulfite (37%) hydrolyses the nonreacted Grignards and magnesium salts, thus avoiding the phosphine oxidation. Layers are separated, and in the case of the XPhos, the THF is replaced by *n*-butanol via a distillation. A crystallisation affords the phosphine as a white powder in a reasonable yield (65%) (^{31}P NMR purity > 98%). The procedure is slightly different for the MePhos. Ethyl acetate is added to the organic layer, and several washes with hot water allow the removal of THF. The MePhos crystallises directly in ethyl acetate at low temperature. On filtration it is obtained as a white powder (^{31}P NMR purity 98%) with a moderate yield (50%).

Thermodynamic Data. The development of a safe industrial procedure requires the knowledge and determina-

(7) The European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, London, 2002.

(8) (a) Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334. (b) Buchwald, S. L. *Adv. Synth. Catal.* **2001**, *343*, 789.

(9) Private communication by S. L. Buchwald.

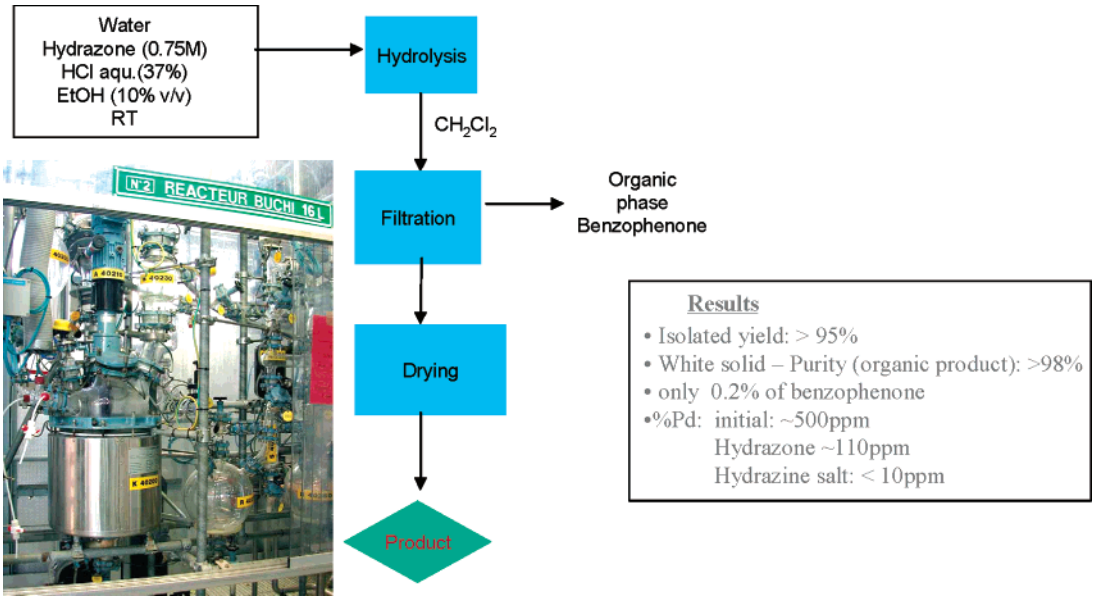
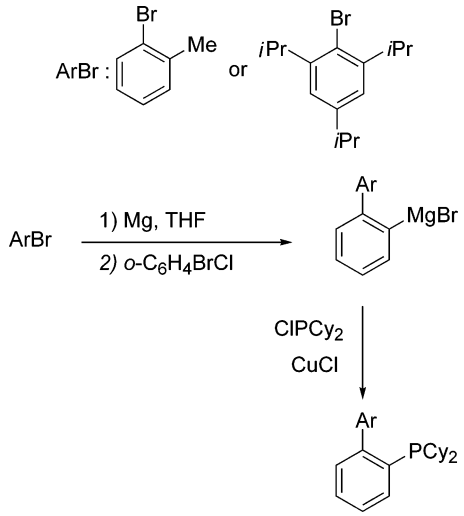


Figure 9. **Schematic diagram of the hydrolysis process.**

Scheme 4



tion of all the thermal phenomena which occur or could occur during the experiment. In this course, and to confirm the GC kinetics, we undertook some calorimetric and thermodynamic studies in a Mettler RC-1 calorimeter. The instrument is equipped with a 2-L vessel, temperature sensor, calibration heater, and propeller stirrer. We first investigated the MePhos synthesis. The resulting heat flow curve showed that the formation of the methyl-2-phenylmagnesium bromide was exothermic ($\Delta H = -68.0$ kcal/mol). The RC-1 program calculated a very large temperature rise potential (244.8 °C) that suggested that, if loss of reactor control (cooling or stirring) occurred, this would result in vigorous solvent reflux and vaporisation of 93% of the initial charge of THF. Nevertheless, the reaction is instantaneous. The conversion, measured at the end of the addition, is 95.9% into the Grignard reagent. A slow introduction of the arylbromide is required to control the exotherm. The second step, formation of the *o*-tolyl-2-phenylmagnesium bromide, is also very exothermic ($\Delta H = -208.1$ kcal/mol, $\Delta T_{adiabatic} = 96.6$ °C), and this heat is able to vaporise the whole initial charge of THF. Nevertheless, this exotherm can be easily controlled by a slow addition of the bromochlorobenzene. The copper-catalysed C−P coupling is also quite exothermic ($\Delta H = -56.3$ kcal/mol) and instantaneous (about 98% of the chlorodicyclohexylphosphine has reacted at the end of the addition). All those thermodynamic data confirm the necessity to introduce the reagents slowly over at least an hour. The workup protocol has also been studied. The calorimetric energy of the medium neutralization using diluted $NaHSO_3$ is 51.1 kcal/mol mol^{-1} of *o*-bromotoluene. This reaction is exothermic, but the thermal flux decreases straight after this addition. We have then investigated the XPhos synthesis. According to the thermal data, the same safety procedure can be recommended and all the reagents must be slowly introduced to the reactor. Indeed, the formation of the tris-isopropylphenylmagnesium bromide, of the 2,4,6-triisopropyl-1-phenylmagnesium bromide and the C−P coupling are also very exothermic (respectively $\Delta H = -77.1$ kcal/mol, $\Delta H = -137.7$ kcal/mol and $\Delta H = -50.0$ kcal/mol).

Both of the phosphines synthesis have then successfully been manufactured in a 250 L reactor with good isolated yields, 55% for the MePhos and 56% for the XPhos.

Conclusions

In summary, we have developed a very general and efficient process to prepare arylhydrazones and Buchwald ligands on a large scale. We succeeded in optimising the work up procedure, and we determined the thermodynamic and kinetic profiles to have a safe and reproducible industrial process. The palladium cross-coupling reaction was successfully achieved with a low catalyst loading and was reproduced several times on a large scale. Reaction calorimetry and Raman spectroscopy proved to be invaluable tools in the development of an improved and safe procedure. Therefore, many important aspects such as safety and kinetic or thermal data have been investigated to be able to develop a safe, reproducible, and easy procedure to form carbon−nitrogen bonds on a large scale.

Experimental Section

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

Gas Chromatography. Gas chromatography is carried out using a Varian CP-3800 gas chromatograph equipped with a FID detector and a fused silica capillary column DB-17 (30 m × 0.32 mm × 0.25 μm). All samples are 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 are 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 are acquired using a HP 5890 series II gas chromatograph using the same temperature gradient as described for GC analysis.

***N*-*p*-Toyl Benzophenone Hydrazone.** In a 16-L glass reactor, equipped with a condenser and a mechanical stirrer and linked by an optic fiber to a Raman spectrometer, are charged, under 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 is heated at reflux. The complex catalyst is preformed under argon by mixing $Pd(OAc)_2$ (1.42 g, 6.3 mmol) and MePhos (4.61 g, 12.7 mmol) for 20 min at room temperature and then adding into the glass vessel. Benzophenone hydrazone (2.487 kg, 12.675 mol) is added by 13 portions every 10 min. Reaction is followed by Raman spectroscopy. When the reaction has reached completion, the reaction mixture is cooled to room temperature, and the insoluble salts are quenched with water (2 L). The layers are separated, and the arylhydrazone is crystallized at about 5 °C in the organic phase. The solid is filtered, washed with 2.5 L of *tert*-amyl alcohol, and dried at 40 °C (10 mbar). The arylhydrazone is afforded as a pale yellow solid (93%). ^{1}H and ^{13}C NMR spectra are in accordance with the literature data.[1b]

***N*-*p*-Tolylhydrazine Salt.** In a 16-L Buchi glass reactor equipped with a condenser and a mechanical stirrer is placed, under argon, *N*-*p*-tolyl benzophenone hydrazone (2.477 kg, 8.65 mol) in 9.9 L of hydrochloric acid (aqueous solution at 37% w). Ethanol (990 mL) is then added. The reaction is allowed to stirr for 24 h at room temperature. Conversion is followed by GC analysis. On conversion, the solid formed is filtered, washed three times with 4 L of dichloromethane, and dried at 40 °C (10 mbar). The hydrazine salt is afforded as a white solid (1.477 kg, yield 95%).

MePhos. In a 316-L steel reactor equipped with a mechanical stirrer and a condenser is charged, under nitrogen, magnesium (3.2 kg) in 25.3 kg of anhydrous THF. The reaction mixture is heated under reflux, and 0.3 kg of 1,2-dibromoethane is then added to the reactor. 2-Bromotoluene (19.03 kg) and THF (51.6 kg) are slowly and simultaneously added over an hour. The Grignard formation is followed by GC, the reaction is complete after an hour of stirring.

The second crop of magnesium (3.2 kg) is added to the reactor. The *o*-bromochlorobenzene (23.3) and THF (50.2 kg) are then simultaneously introduced dropwise over an hour. Stirring is maintained an hour under THF reflux until the formation of the diarylGrignard reaches completion (reaction followed by GC).

The mixture is cooled to room temperature. Copper chloride (1.1 kg) is added. The dicyclohexylphosphine chloride (29.6 kg) is added dropwise over an hour, and the reaction mixture is stirred overnight at room temperature.

The mixture is quenched with 71 kg of aqueous sodium bisulfite and 72 L of water. Thirty-eight kilograms of ethyl acetate is added. The layers are separated. THF is distilled from the organic layer, and the phosphine is allowed to crystallise in ethyl acetate at 0 °C for an hour. The solid is filtered and rinsed with 2 × 13 kg of ethyl acetate. The phosphine is afforded as white crystals.

Isolated yield: 55% (22.3 kg; mp: 107.4 °C; potentiometric titre: 94%).

XPhos. In a 316-L reactor equipped with a mechanical stirrer and a condenser is charged, under nitrogen, magnesium (1.3 kg) in 13.6 kg of anhydrous THF. The reaction mixture is heated under reflux, and 0.12 kg of 1,2-dibromoethane is then added to the reactor. 1-Bromo-2,4,6-triisopropylbenzene (14.5 kg) and THF (20 kg) are simultaneously added slowly over an hour. The Grignard formation is followed by GC, and the reaction is complete after an hour of stirring.

The second crop of magnesium (1.3 kg) is added to the reactor. The *o*-bromochlorobenzene (9.8 kg) is then introduced dropwise over 3 h. Stirring is maintained an hour under THF reflux until the formation of the diarylGrignard reaches completion (reaction followed by GC).

The mixture is cooled to room temperature. Copper chloride (0.485 kg) is added. The dicyclohexylphosphine chloride (11.8 kg) is added dropwise over an hour to control the exothermal, and the reaction mixture is stirred overnight at room temperature.

The mixture is quenched with 37 kg of aqueous sodium bisulfite and 30 L of water. The layers are separated. Thirty-three kilograms of *n*-butanol are added in the organic layer. THF is distilled, and the phosphine allows crystallising in ethyl acetate at 0 °C for an hour. The solid is filtered and rinsed with 2 × 20 kg of *n*-butanol. The phosphine is afforded as white crystals.

Isolated yield: 56% (13.7 kg; mp: 185.9 °C; potentiometric titre: 96.7%).

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