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Industrial-Scale Palladium-Catalyzed Coupling of Aryl Halides and Amines – A Personal Account

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Abstract: The palladium-catalyzed coupling of amines and aryl halides or aryl alcohol derivatives has matured from an exotic small-scale transformation into a very general, efficient and robust reaction during the last ten years. This article reports several applications of this method from an industrial vantage point, including ligand synthesis, synthesis of arylpiperazines, arylhydrazines and diarylamines. Much emphasis in placed on issues of scale-up and safety to underline the potential of C–N couplings as solutions for industrial-scale synthetic problems.

Keywords: amination; anilines; C–N cross-coupling; homogeneous catalysis; palladium; phosphane ligands

1 Introduction

The development of a new, general methodology for the formation of aromatic carbon-nitrogen bonds is of great significance in many areas of organic synthesis. As the Heck, Suzuki–Miyaura, Stille, Kumada and Negishi procedures have revolutionized the way we construct sp^2C–sp^2C bonds,[1] the palladium-catalyzed aromatic amination has the potential to modify analogously our approach to the synthesis of aniline derivatives. Aromatic carbon-nitrogen bonds are structural constituents for the preparation of compounds of interest to those in the pharmaceutical and agrochemical industries. In addition, compounds with this motif are important for the preparation of new ligands, electronic materials, polymers, liquid crystals and xerographic materials.[2]

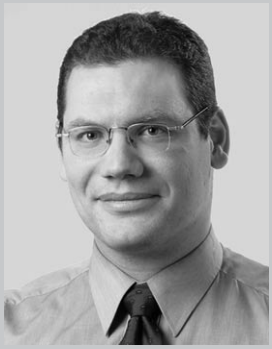
Over the first ten years since its development, small-scale applications of the palladium-catalyzed aromatic amination have appeared in publications from academic, medicinal and process chemistry laboratories. This method is able to connect highly functionalized components and is compatible with a wide variety of functional groups. This generality makes it well-suited for the construction of a body of amine analogues from a common intermediate. The versatility and applicability of the method has been thoroughly documented in two recent reviews.[3]

Stephen L. Buchwald was born (1955), raised and received his precollege education in Bloomington, Indiana. He received his Sc. B. degree, Magna Cum Laude, in chemistry, from Brown University in 1977. During his undergraduate years he worked in the laboratories of Professors Kathlyn A. Parker and David E. Cane at Brown University and Professor Gilbert Stork at Columbia University. He entered Harvard University as a National Science Foundation Predoctoral Fellow in 1977 and received his Ph. D. in 1982. His thesis work, under the supervision of Professor Jeremy R. Knowles, concerned the mechanism of phosphoryl transfer reactions in chemistry and biochemistry. In early 1982 he took up a position as a Myron A. Bantrell postdoctoral fellow at the California Institute of Technology where he worked in the laboratory of Professor Robert H. Grubbs. His work at Caltech concerned the study of titanocene methylenes as reagents in organic synthesis. During this time he was also involved in work on the mechanism of the Ziegler–Natta polymerization. In 1984 he began as an assistant professor of chemistry at the Massachusetts Institute of Technology. He was promoted to the rank of associate professor in 1989 and to Professor in 1993. He was named the Camille Dreyfus Professor of Chemistry in January of 1997. During his time at MIT he has received numerous honors including the Harold Edgerton Faculty Achievement Award of MIT, an Arthur C. Cope Scholar Award, the 2000 Award in Organometallic Chemistry from the American Chemical Society, a MERIT award from the National Institutes of Health, the Bristol-Myers Squibb Distinguished Achievement Award in Organic Synthesis (2005), the CAS Spotlight Award (2005) and the American Chemical Society Award for Creative Work in Synthetic Organic Chemistry (2006). In 2000, he was elected as a member in the American Academy of Arts and Sciences. He has been a named lecturer at numerous universities. He is the coauthor of 245 published or accepted papers and 30 issued patents. He serves as a consultant to Amgen, Merck, Infinity Pharmaeuticals, Rhodia Pharmaceutical Solutions, Lanxess, Englehard and Collegium Pharmaceuticals. He and Eric Jacobsen have co-taught a short course on Organometallic Chemistry in Organic Synthesis at over 35 companies in the U. S. A. and in Europe.

Christelle C. Mauger was born in Saint-Lô in Normandy (France) in 1974. She completed her undergraduate degree at the University of Caen and obtained her Ph. D. degree in organic chemistry in 2000 under the guidance of Dr Serge Masson (Laboratoire de Chimie Moléculaire et Thioorganique, Caen, France). She then moved to Huddersfield (England) to join Avecia Pharmaceuticals for an industrial postdoctoral position. She worked on the rapid development of new routes to pharmaceutical intermediates and on the "CaTHy" catalytic transfer hydrogenation reaction. In 2001 she accepted a postdoctoral position granted by Rhodia Organic at the University of Poitiers (Laboratoire de Catalyse en Chimie Organique, France) where she worked in the fields of fluorine chemistry. In 2002, she joined Rhodia Recherches (Lyon Research Centre) as a research engineer in the Process Research Group. Her main area of activities was the development of pharmaceutical intermediates using organometallic catalysis and aromatic bond forming reactions (ABF). In January 2006, she moved to the Reckitt Benckiser scientific services department in Kingston-upon-Hull (UK).

Gérard Mignani studied chemistry in Orsay and Rennes Universities where he received his Ph. D. (Docteur Ingénieur) in 1980 and his "Thèse d'Etat" in 1982 in the field of organometallic chemistry and homogeneous catalysis especially in steroid chemistry (Rhône-Poulenc Grant) in Professor Dabard's group. He joined the Rhône-Poulenc Research group in Lyon in 1980 where he developed new processes in organic and terpene chemistry and in homogeneous and heterogeneous catalysis. Thereafter he performed postdoctoral research with Professor D. Seyferth at the Massachusetts Institute of Technology (Cambridge, U. S. A.) on ceramic precursors and organosilicon chemistry. He came back to Rhône-Poulenc research where he developed new ceramic precursors, new non-linear optic derivatives, polymers, and homogeneous catalysis processes. He spent ten years as a Group Leader in Silicon Chemistry. His research interests were the poly-functionalization of

polysiloxanes, new organometallic catalysis for organosilicon applications and the functionalization of mineral charges. Now, his research interests are the new processes and scale-up in organic chemistry, organometallic catalysis (homogeneous and heterogeneous) and new methodology in chemistry synthesis. He received the "Prix de la Recherche" in 1995, in 2001 "Prix RHODIA Group" and in 2004 "Prix Centre de Recherches-RHODIA".



Ulrich Scholz started his studies in chemistry in 1990 at the University of Hannover, Germany. In 1993, he joined Professor Paul A. Wender's research group at Stanford University, California, USA on a DAAD scholarship. After returning to his home town of Hannover, he finished his basic studies in chemistry and received his diploma degree in Professor E. Winterfeldt's research group in 1996 on the synthesis of unsymmetrical pyrazines. He stayed in Professor Winterfeldt's group and spent the subsequent three years on the elaboration of bile acids as potential building blocks for the synthesis of cephalostatin analogues. After graduation he continued as a teaching assistant at Hannover University to finally join the Central Research Department for homogeneous catalysis of Bayer AG at the end of 1999. In 2002, he moved to the process development department of the Bayer Chemicals Company, now Lanxess – Fine Chemicals as a project manager of the Speciality Chemicals Department. Since 2001, he also headed the Bayer part of an industrial collaboration between Bayer Chemicals, Professor Steve L. Buchwald from MIT and Rhodia Pharma Solutions (formerly Rhodia Chirex) on palladium-catalyzed aromatic aminations. In 2005, he moved to Boehringer-Ingelheim's Process Development Department.

2 Motivation: Technology gives an Edge

With the increasing competition between custom manufacturers of chemicals, one way for a company to differentiate itself is by quick reduction to practice of a new and powerful technology. To focus on a process as new as the palladium-catalyzed aromatic amination, the level of risk is high for one company to bear on its own. Therefore a joint venture between two companies, Bayer Chemicals, now Lanxess, and Rhodia Pharma Solutions, was undertaken. We decided to join efforts with complete exchange of knowledge gained by both sides. Since confidentiality plays a major role in custom manufacturing, it was decided to set up specific goals inside the collaboration, while all customer inquiries and projects remained outside of the collaboration and therefore confidential. To further this endeavor, one of us (SLB) was brought in as a consultant for this venture (Figure 1).

We first identified three key success factors: 1) Establishment of a quick method for the optimization of the technology. 2) The scale-up of several model targets. 3) A safe and reliable supply route to the dialkylphosphinobiaryl ligands that are used for these reactions (Scheme 1).

This model, in our opinion, has the potential to speed the transfer of promising new technology from academic

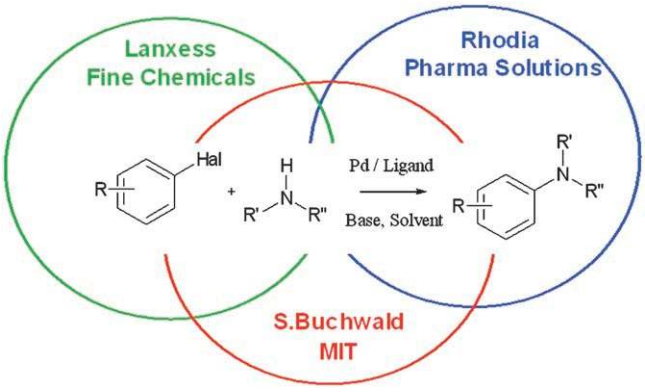
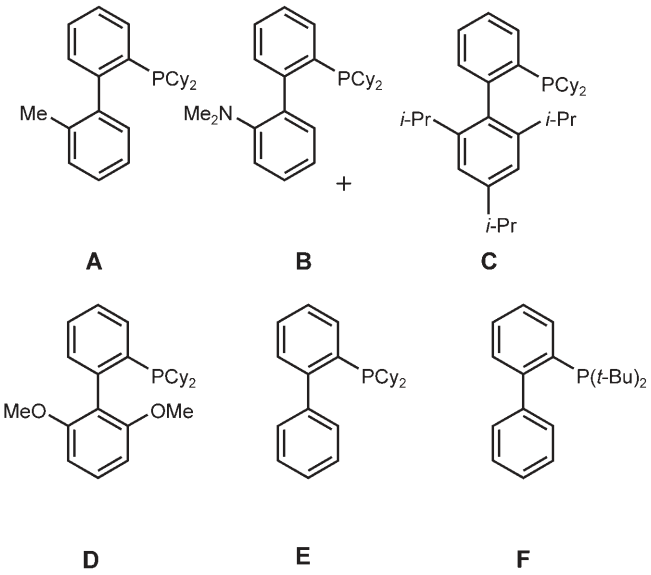


Figure 1. Collaboration model: two companies, one university.



Scheme 1. Important members of the dialkylphosphinobiaryl ligand family.

discovery into industrial application. Over the course of two years, the participants have had a good chance to scrutinize the chemistry and decide whether it is adaptable to industrial requirements. For the palladium-catalyzed aromatic amination reaction, this strategy has worked well. All three of the goals mentioned above have been realized. In addition, several customer projects, not a part of the information exchange or collaboration, have been carried out on a pilot scale.

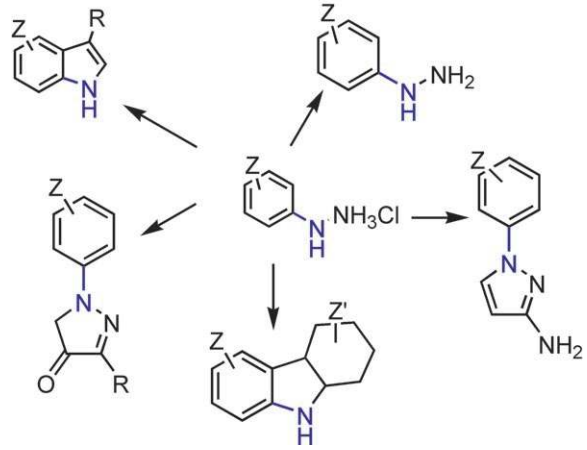
3 The Synthesis of Arylhydrazones and their use as Synthetic Intermediates

As an initial example of a class of compounds to be investigated during this collaboration, we studied the application of this methodology to the synthesis of arylhydrazones. These are precursors to arylhydrazines and, thus, to various heterocycles, including indoles *via* the Fischer indole synthesis (Scheme 2).

Hydrazines are normally accessed *via* the intermediacy of diazonium salts. For compounds that contain sensitive functional groups, the palladium-catalyzed route can be an important alternative.

Literally thousands of indoles have been prepared and evaluated as potential pharmaceuticals.[4] A few clinically important examples are shown in Table 1.

The development of a viable, robust and safe industrial process is a challenging problem and a prerequisite for large-scale applications of this reaction. We have studied, as a model reaction, the coupling of *p*-bromotoluene or *p*-chlorotoluene with benzophenone hydrazone in order to examine the important parameters for the preparation of an *N*-arylbenzophenone hydrazone on an industrial scale. We first examined a modification of the previously reported conditions[5] (Scheme 4).

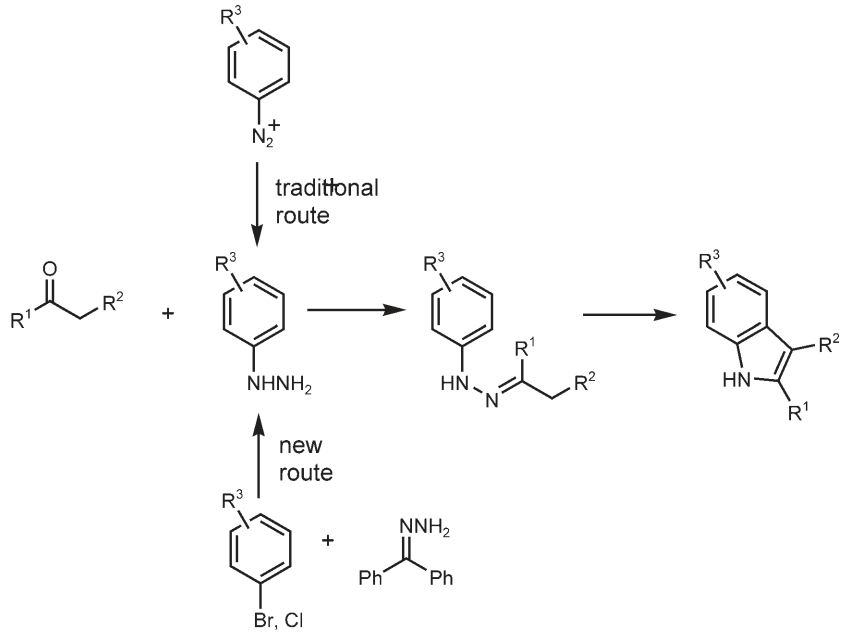


Scheme 3. Potential applications of arylhydrazines.

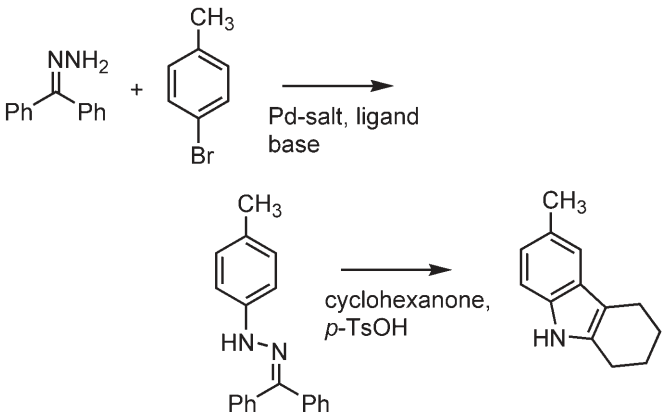
Table 1. Selection of pharmaceutically important indoles.

Entry	Name	Company	Use
1	Sumtriptan	GSK	Anti-Migraine
2	Odensetron	GSK	Anti-Emetic
3	Fluvastatin	Novartis	Anti-Cholesterol
4	Zafirlukast	AstraZeneca	Asthma
5	Indomethacin	Merck	Anti-Inflammatory

Screening experiments showed that catalysts based on dialkylphosphinobiaryl ligands gave the best performance. With **A** or **B**, the coupling reaction was achieved in 94% and 93% yield, respectively, using 1 mol %



Scheme 2. Fischer indole synthesis.



Scheme 4. Indole synthesis by palladium-catalyzed C–N coupling.

Table 2. Variation of base and solvent in arylhydrazone formation.

Entry[a]	Base	Solvent	Time [h]	GC Yield [%][b]
1	NaOH	Toluene	20	0
2	Cs_2CO_3	Toluene	20	40
3	KO-*t*-Bu	Toluene	20	<10
4	NaO-*t*-Am	Toluene	6	100
5	NaO-*t*-Bu	Toluene	6	100
6	NaO-*t*-Bu	*t*-BuOH	6	100
7	KO-*t*-Bu	*t*-BuOH	6	20
8	NaOH	*t*-BuOH	5	100

[a] 0.5 mol % $Pd(OAc)_2$, 1 mol % **A**, 1.4 equivs. base, 1.0 equiv. benzophenone hydrazone, solvent, reflux.
[b] GC Yields determined with dodecane as internal standard.

$Pd(OAc)_2$ in refluxing toluene with NaO-*t*-Bu as the base.

We next examined the effect of changing the base, using $Pd(OAc)_2$/2 **A** in toluene or xylene at reflux.[6] With potassium *tert*-butoxide, cesium carbonate or sodium hydroxide in toluene, low conversion of starting material (<10%) was observed. In contrast, the use of NaO-*t*-Bu or NaO-*t*-Am provided complete conversion of starting material to product. Given these results, the use of *tert*-butanol as the reaction solvent was investigated. With this solvent, either NaO-*t*-Bu or NaOH as base both led to quantitative yield of product.

In view of our results using NaOH in *tert*-butanol, we examined the use of a variety of solvents (Table 3). Using refluxing *tert*-amyl alcohol, which has a higher boiling point than *tert*-butanol, the standard reaction took place even more rapidly than before. The use of other solvents such as ethylene glycol, diethylene glycol, *N,N*-dimethylethanolamine, *n*-butanol and 1,2-dimethoxybenzene resulted in low conversions (<30%) of starting material.

To have an economically viable process it was necessary to reduce the level of catalyst that was necessary. With **C**/$Pd(OAc)_2$ in xylene and NaO-*t*-Bu as base, the reaction reached completion within one hour using 0.1 mol % catalyst. In order to further improve the efficiency of the coupling process, we next examined the use of NaOH as the base. Unfortunately, when using finely ground NaOH in refluxing toluene with or without a phase-transfer catalyst, no reaction was observed. When the reaction solvent was changed to *tert*-amyl alcohol, however, with **A** as supporting ligand, excellent results were obtained with solid sodium hydroxide pellets as the base. In xylene, the use of NaO-*t*-Bu as base provided the most active system (Table 4). In both cases the reaction was rapid and no by-products such as benzophenone, benzophenone azine or compounds resulting from Wolff–Kishner reduction were detected. In these procedures only 0.05 mol % of $Pd(OAc)_2$ was needed for full conversion of chloro- or bromotoluene to the desired product. Also of note is that the process was complete after twelve minutes with 0.25 mol % Pd.

Thus, both the combinations **C**/NaO-*t*-Bu/xylene and **A**/NaOH/*tert*-amyl alcohol represent very good conditions for the coupling reaction between aryl halides and benzophenone hydrazone.

In fact, the coupling of benzophenone hydrazone with *p*-tolyl chloride or bromide in refluxing *tert*-amyl alcohol using 0.05 mol % of $Pd(OAc)_2$, 0.1 mol % of **A**

Table 3. Solvent screening for arylhydrazone formation.

Entry[a]	Solvent	Time [h]	*T* [°C]	GC Yield [%][b]
1	Toluene	6	110	0
2	Xylene	6	110	0
3	*t*-BuOH	5	90	100
4	*t*-AmOH	4	103	100
5	$MeOCH_2CH_2OH$	4	100	100
6	Glycol	20	100	~30
7	Diethylene glycol	20	100	~30
8	*N,N*-Dimethylethanolamine	20	100	~30
9	Dimethoxybenzene	20	100	0
10	*n*-BuOH	20	100	15

[a] 0.5 mol % $Pd(OAc)_2$, 1 mol % **A**, 1.4 equivs. NaOH, 1 equiv. benzophenone hydrazone, solvent, reflux.
[b] GC Yields determined with dodecane as internal standard.

Table 4. Time to reach completion of reaction of aryl halide with benzopheone hydrazone under varying conditions.

Entry	Conditions[a]	Pd [mol %]	Time[b] [h]
1	a	0.05	30
2	a	0.1	1
3	a	0.25	0.2
4	b	0.05	4
5	b	0.1	2
6	b	0.25	1

[a] Conditions a: $Pd(OAc)_2$, ligand **C**, refluxing xylene, NaO-*t*-Bu.
[b] $Pd(OAc)_2$, ligand **A**, refluxing *tert*-amyl alcohol, NaOH.

Table 5. Yields of arylhydrazones from different starting materials.

Entry[a]	Substrate	GC Yield [%][b]
1	4-Bromotoluene	92
2	4-Bromobenzene	95
3	4-Bromochlorobenzene	97
4	4-Bromoanisole	87
5	2-Bromotoluene	85
6	4-Bromofluorobenzene	91
7	4-Chlorotoluene	93
8	4-Methylphenyl triflate	0

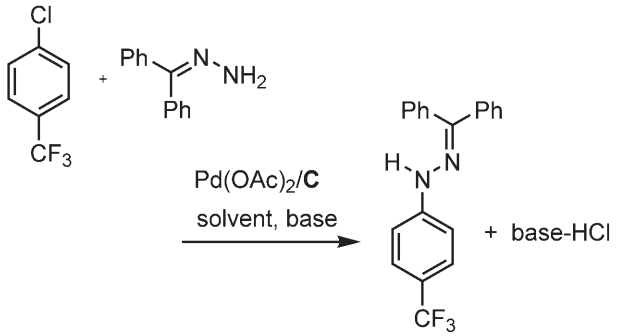
[a] 0.5 mol % $Pd(OAc)_2$, 1 mol % **A**, aryl halide:benzophenone hydrazone = 1:1, 1.4 equivs. NaOH, *p*-MePhBr: 1.5 M in *tert*-amyl alcohol reflux.
[b] GC Yields determined with dodecane as internal standard.

with 1.4 equivs. of sodium hydroxide as base was complete in less than two hours.

Upon work-up, the crude solution was directly treated with water to remove inorganic salts. The layers were separated and the aryl hydrazone crystallized from the organic layer which had been cooled to 3 °C. This afforded the *p*-tolylphenylhydrazone as a pale yellow powder in 92% yield.

This protocol was applied to the coupling of other halogenated aromatics in a 500-mL glass-jacketed vessel; results are shown in Table 5. The yields reported correspond to material isolated by crystallization. In each case, the reaction proceeded in less than four hours. Although 4-chlorotoluene is an excellent substrate, the reaction is completely selective for substitution of the bromine when using bromochlorobenzene as substrate (Table 5, Entry 3). Using this procedure, unfortunately, aryl triflates were not converted to product. In fact, using 4-methylphenyl triflate, less than 5% product was observed. In all likelihood, competitive cleavage to the phenol occurs at a rapid rate.

Trifluoromethylphenylhydrazines are important intermediates for the preparation of pharmaceuticals.[7] Thus, we queried whether we could apply our coupling method to the preparation of these compounds.



Scheme 5. Arylhydrazone formation by palladium-catalyzed C–N coupling.

Scheme 5 shows the results using *p*-CF_3PhCl as starting material.

Good results were obtained when the reaction was performed in the presence of 0.5 mol % of $Pd(OAc)_2$, 1 mol % of **C** in anisole at 110 °C using one equivalent of benzophenone hydrazone and *p*-CF_3PhCl; use of K_3PO_4 (1.4 equivs.) as base gave the best results. After 24 hours of stirring, we observed a quantitative conversion of aryl chloride to product. Upon crystallization from ethanol, the *N*-(4-trifluoromethylphenyl)-benzophenone hydrazone was isolated in 88% yield. With a yield of 93%, similar results were obtained using KOH or sodium *tert*-amylate.[8]

Before applying this protocol on scale, calorimetric data were collected using a Mettler RC1 apparatus in order to assess safety issues. The coupling of 4-chlorotoluene with benzophenone hydrazine was used as the model reaction. The reaction is very exothermic ($\Delta H = 409$ kJ/mol), an amount that could potentially evaporate 78% of the solvent if the reaction occurred spontaneously. However, we found that the reaction is not instantaneous, with only 43% of the reaction heat generated by the end of the addition of the benzophenone hydrazone. This observation indicates that it is necessary to introduce the benzophenone hydrazone slowly to prevent build-up of thermal potential.

The reaction protocol was then studied in an 18-liter glass reactor and its progress was monitored by Raman spectrometry.[9]

This apparatus can be used in the heterogeneous media and the probe is stable to water. As shown below, benzophenone hydrazone, 4-bromotoluene and the final arylhydrazone each have characteristic bands appearing at 180 cm^{-1}, 290 cm^{-1} and 1620 cm^{-1}, respectively.

When the reaction was complete, water was added to dissolve the salts that had formed. The layers were separated at a temperature of about 40 °C. Further cooling of the *tert*-amyl alcohol solution afforded crystals of the arylhydrazone that could be isolated in quantitative yield as a pale yellow solid (Figure 3).

Since *N*-arylhydrazones cannot be stored indefinitely, it is more advantageous to isolate and store the corre-

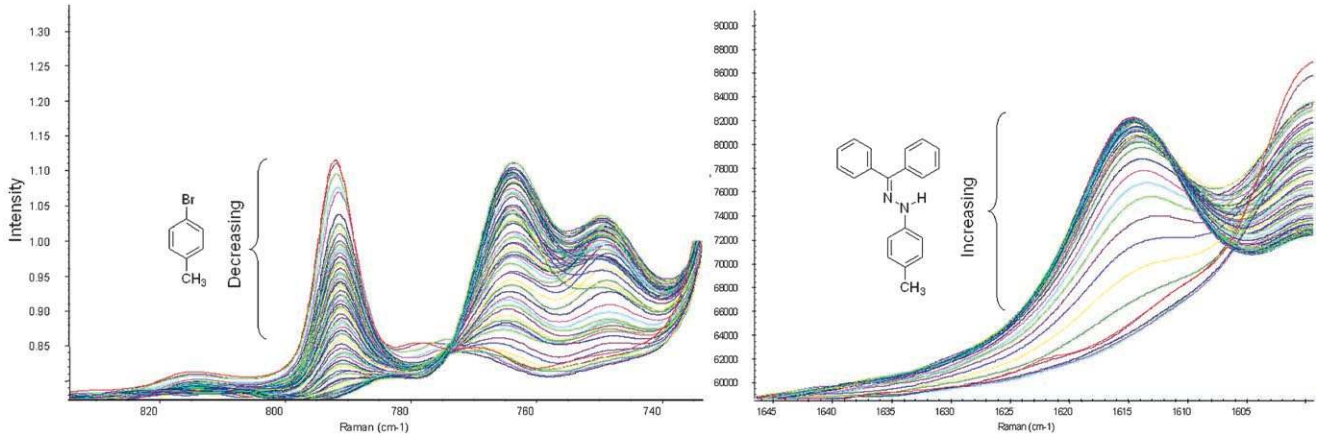


Figure 2. *In situ* continuous Raman analysis of final hydrazone formation.

Figure 3. Glass reactor (18 liters) for synthesis of arylhydrazones.

sponding hydrochloride of the arylhydrazine. The preparation of *p*-tolylhydrazine·HCl can be affected by treatment of the arylhydrazone with acid. Different sets of conditions were screened and the results are summarized in Table 6. For reactions performed at 80 °C, several by-products were generated.

Treatment of *N*-*p*-tolylbenzophenone hydrazone in a mixture of concentrated aqueous hydrochloric acid and ethanol (90:10) at room temperature led to the precipitation of the hydrazine salt, so that simple filtration and washing of the solid several times afforded the product as a white powder in 92% yield. The reaction was then examined in a 16-liter Büchi steel reactor with 2.5 kg of *N*-*p*-tolylbenzophenone hydrazone in 10 liters of concentrated hydrochloric acid (Figure 4). The hydrazine salt could be isolated from the crude solution in quantitative yield. The palladium contamination of the sample was determined to be less than 10 ppm.[10]

Table 6. Screening of acids for the conversion of the arylhydrazone to the arylhydrazine hydrochloride.

Acid	*T* [°C]	Time [h]	Conversion [%]
HCl (10%)	80	2	20
HCl (37%)	80	2	100
HCl (37%)	r.t.	20	100
Acetic acid	80	2	75
PTSA	80	2	100

Safety data were also obtained on the hydrazine salt by differential thermal analysis (DTA), which showed an endothermic behavior at 100 °C. This corresponds to the melting point of the salt. Exothermic behavior was again observed at 110 °C[11] which represents the thermal decomposition of the salt. From these data we can discern that the salt is stable at room temperature and can be easily stored and handled for months. The precipitation reaction itself is not very exothermic and can also be regarded as safe.[12]

4 The Preparation of Arylpiperazines as a Model Process for the Scale-Up of Palladium-Catalyzed Aromatic Amination

A second process selected to examine at scale was the synthesis of arylpiperazines. The advantages of using the palladium-catalyzed methodology in lieu of the clas-

Figure 4. Inox 16-liter Büchi reactor used for hydrolysis of the arylhydrazone.

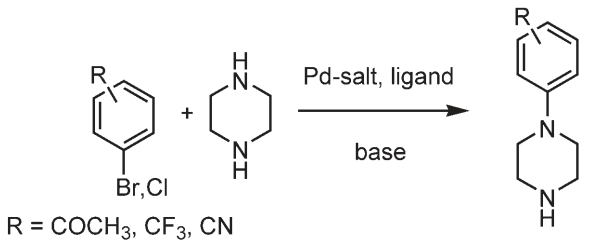
sical reaction of anilines with activated diethanolamines include: 1) No toxic intermediates are required. 2) A wide range of aryl halide starting materials, which are available in bulk, can be used. 3) No side reactions other than diarylation are observed. Compared to alternative processes such as the nucleophilic aromatic substitution of, for example, fluoroaromatics, copper- or nickel-catalyzed processes, the palladium-catalyzed coupling allows the use of milder reaction conditions, has a broader substrate scope and generally results in higher chemical yields.

As indicated in Table 7, the arylpiperazine structural motif is common among pharmaceutical substances. The list of pharmaceuticals already launched in the market containing an arylpiperazine subunit, while not demonstrating the applicability of palladium-catalyzed aromatic amination, indicates the importance of molecules with this substructure. Additionally, 39 substances are currently in clinical or preclinical trials.[13] Thus, future syntheses of these or structurally related molecules might well be undertaken using a palladium-catalyzed aromatic amination reaction.

Three arylpiperazine-containing molecules were initially selected as targets. These were chosen such that the corresponding aniline derivatives either were not available on scale or could only be purchased at a significantly higher cost than the corresponding aryl chloride. The aromatic amination in these cases not only offers a new set of starting materials in the making of arylpiperazines, it is also an approach with economic advantages over traditional methodology.

Table 7. Arylpiperazines launched in the pharmaceutical market.

Entry	Name	Company	Use
1	Aripiprazole	Otsuka	Neuroleptic
2	Ciprofloxacin	Bayer	Antibacterial
3	Dapiprazole	Angelini	Antiglaucoma
4	Etoperidone	Angelini	Antidepressant
5	Fleroxacin	Kyorin	Antibacterial
6	Iomefloxacin	Abbott	Antibacterial
7	Itraconazole	J&J	Antifungal
8	Ketoconazole	J&J	Antifungal
9	Levodropropizin	Dompe	Antitussive
10	Levofloxacin	Daiichi	Antibacterial
11	Naftopidil	Roche	Antihypertensive
12	Nefazodone	Bristol-Myers Squibb	Antidepressant
13	Niaprazine	Sanofi-Synthelabo	Insomnia
14	Norfloxacin	Kyorin	Antibacterial
15	Ofloxacin	Daiichi	Antibacterial
16	Pefloxacin	Aventis	Antibacterial
17	Prulifloxacin	Nippon Shinyaku	Antibacterial
18	Rufloxacin	Mediolanum	Antibacterial
19	Terconazole	J&J	Antifungal
20	Trazodone	Angelini	Antidepressant
21	Urapidil	Altana	Antihypertensive
22	Vesnarinone	Otsuka	HIV



Scheme 6. Synthesis of arylpiperazines by palladium-catalyzed aromatic amination.

As a representative example for arylpiperazine synthesis, formation of *p*-trifluoromethylarylpiperazine by the selective coupling of *p*-bromobenzotrifluoride with piperazine was investigated (Scheme 6). Using 1 mol % of $Pd(OAc)_2$ in combination with a variety of ligands and bases, good conversion of the starting materials to product was observed. The results differed mainly in the amount of bisarylated piperazine by-product that was formed. The most promising ligand/base combinations were then investigated on a larger scale and the results are summarized in Table 8.

As a general trend, it is necessary to use strong bases like NaO-*t*-Bu to achieve high catalytic activity. The use of $P(t\text{-Bu})_3$ and several of the dialkylphosphinobiphenyl ligands, especially **C**, gave good results. If weaker bases such as cesium carbonate were used, similar results were seen, however, it was necessary to employ higher amounts of catalyst. With $P(t\text{-Bu})_3$ and a large excess of piperazine and NaO-*t*-Bu as base, no detectable product of double arylation was observed and a 97% yield of the desired product was realized (Entry 1). Decreasing the excess of piperazine to 2.5 equivs. caused a slight diminution of the yield, largely due to double arylation (Entry 2). With sterically encumbered ligand **C**, a yield of 97% could be achieved even with this smaller excess of piperazine (Entry 3). In *tert*-butanol, a 93% yield of desired product was obtained (Entry 4). Attempts to reduce the catalyst loading in toluene resulted in incomplete conversion of the starting material using $P(t\text{-Bu})_3$ as ligand (Entry 5).

Since the aryl chloride, in this case, is available in bulk quantities, and is therefore far better suited for use in an industrial process, the coupling of chlorobenzotrifluoride with piperazine was also investigated (Table 9).

Using the same conditions that worked well for the reaction of the aryl bromide, only moderate yields of the arylpiperazine were observed with $P(t\text{-Bu})_3$ as ligand (entry 1). On changing to **D** in a mixture of toluene and THF and NaO-*t*-Bu as base, a 93% yield was obtained even when using only a slight excess of piperazine (Entry 2). It is interesting to note that with half of the quantity of catalyst approximately the same yield of product was found (Entry 3). Use of **D** in amine solvents like tributylamine also provided excellent results (Entry 4). The nature of the base is very important both for the substrate scope of a reaction and also for economic reasons. Using ligand **C** in a mixture of toluene/methanol gave good results with solid sodium hydroxide (Entry 5).

Summarizing this work, the dialkylphosphinobiaryl ligands **C** and **D** proved to be especially valuable for the coupling of 4-chlorobenzotrifluoride with piperazine using a strong base and this avoids the need to use a large excess of piperazine to minimize the formation of double arylated product.

Different stages of the coupling of chlorobenzotrifluoride with piperazine in a jacketed glass vessel are shown in Figure 5.

It is important to note, from an industrial point of view, that addition of the catalyst in four equal portions yields

Table 8. Synthesis of 4-trifluoromethylarylpiperazine from bromobenzotrifluoride.

Entry	Piperazine (equivs.)	Solvent	T [°C]	Catalyst	Pd [mol %]	L:Pd	Base	GC Yield [%][a]
1	6	Xylene/DMF	120	$Pd(OAc)_2/P(t\text{-Bu})_3$	0.1	4	NaO-*t*-Bu	97
2	2.5	Toluene/DMF	110	$Pd(OAc)_2/P(t\text{-Bu})_3$	0.1	4	NaO-*t*-Bu	92
3	2.5	Toluene	110	$Pd(OAc)_2$/**C**	0.1	3	NaO-*t*-Bu	97
4	2.5	*tert*-Butanol	90	$Pd(OAc)_2$/**C**	0.1	3	NaO-*t*-Bu	93
5	2.5	Toluene	110	$Pd(OAc)_2/P(t\text{-Bu})_3$	0.05	4	NaO-*t*-Bu	85[b]

[a] GC yields determined with dodecane as internal standard.
[b] Reaction did not go to completion.

Table 9. Synthesis of 4-trifluoromethylarylpiperazine from chlorobenzotrifluoride.

Entry	Piperazine (equivs.)	Solvent	T [°C]	Catalyst	Pd [mol %]	L:Pd	Base	GC Yield [%][a]
1	6	Xylene/DMF	120	$Pd(OAc)_2/P(t\text{-Bu})_3$	0.1	4	NaO-*t*-Bu	54
2	1.5	Toluene/THF	90	Pd_2dba_3/**D**	0.1	2	NaO-*t*-Bu	93
3	1.5	Toluene/THF	90	Pd_2dba_3/**D**	0.05	2	NaO-*t*-Bu	92
4	1.5	Tributylamine	110	Pd_2dba_3/**D**	0.1	2	NaO-*t*-Bu	97
5	1.5	Toluene/MeOH	78	Pd_2dba_3/**C**	0.1	2	NaOH	93

[a] GC yields determined with dodecane as internal standard.

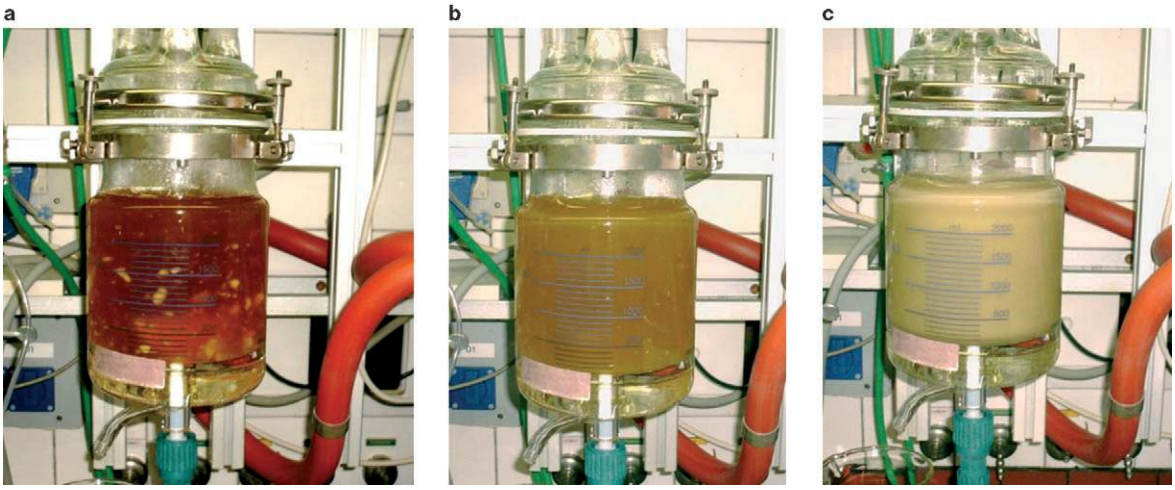
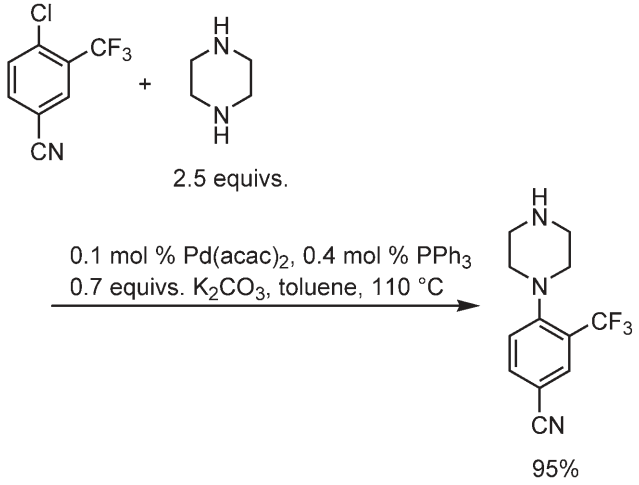


Figure 5. Arylpiperazine formation conducted in jacketed reaction vessels, from left to right: (**a**) at room temperature before reaction; (**b**) after heating at reflux for one hour; (**c**) after completion of the reaction (2 h).

very similar results to those obtained when all the catalyst is added at one time. Each portion of added catalyst converts about one quarter of the starting material to product. Therefore, if during a manufacturing run, in-process analytical data indicate that significant catalyst deactivation has occurred, more catalyst can be added to complete the reaction. This is a situation that is not always the case when using homogeneous catalysts.

To obtain a clean, palladium-free product, after the reaction, a pH-controlled work-up was utilized that also allowed for the selective removal of any excess piperazine. After complete consumption of the starting material, the reaction medium was allowed to cool to room temperature and the inorganic salts were removed by filtration. The organic phase was then mixed with water and the pH was adjusted to 3. At this pH, product and the excess piperazine were selectively extracted into the aqueous layer. Phase separation and adjustment of the pH to 10 caused the selective precipitation of the final product in high yield and in a purity of about 99%.[14] ICP analysis indicated that there was no detectable contamination of the product by residual palladium. An additional attribute of this method of work-up is that it yielded very clean product even if the conversion was incomplete (Table 8, Entry 5), since residual aryl halide starting material stayed in the organic phase during the acid extraction and excess piperazine does not precipitate from the water layer at a pH of 10.

For the amination of very activated aryl chlorides, even simpler catalyst combinations can be applied. In the example shown in Scheme 7, use of a mixture of palladium acetylacetonate and triphenylphosphine with K_2CO_3 as base led to formation of the desired product in high yield. Since triphenylphosphine is one of the cheapest of all phosphines, it may be, in certain cases, the ligand of choice.



Scheme 7. Alternative ligands for the formation of arylpiperazines.

5 Synthesis of Industrially Important Diarylamines by C–N Coupling

Diarylamines are not only used as pharmaceutical intermediates, but also in applications such as electronic materials and as antioxidants. Their usual mode of manufacture includes high temperature Ullmann coupling[15] or, for example, by various nucleophilic aromatic substitution methods.[16]

The palladium-catalyzed aromatic amination reaction adds to these known methods and significantly extends the scope of readily available substrates.

We again began our work in this area by screening the important reaction parameters for the transformation shown in Scheme 8. We chose a simple reaction set-up and used one mmol of starting material per reaction to investigate the effect of eight bases and eight ligands

with toluene as the solvent. A set of these 64 reactions can be run in a laboratory in one day, giving rapid information on changes brought upon by the different reaction parameters. Once the best combination of base and catalyst has been identified, other parameters such as solvent, additives or the ratio of the different reaction components can be investigated, either in a similar screening manner or using a serial optimization approach.

As an example, for *N*-2,6-dichlorodiphenylamine, the retrosynthetic disconnection can be made on either side of the nitrogen (Scheme 8).

This yields two catalyst/base combinations as shown, one for approach 1, and one for approach 2[17]. For approach 1, starting with 2,6-dichloroaniline, **F** as ligand and NaO-*t*-Bu as base resulted in almost complete formation of the desired product. For approach 2, with K_3PO_4 as base, **B** was the most efficient ligand. Only a very moderate yield, however, was realized. Thus, we chose to pursue approach 1 for further studies.

We next carried out the reaction on a 0.5-mol scale with a concentration of 10% w/w of starting material to solvent, 0.25 mol % of Pd_2dba_3 and a ratio of Pd:L of 1:2. We found it advantageous to first charge the reaction flask with Pd_2dba_3 and the ligand dissolved in toluene at room temperature, this was stirred for 10 minutes. Next bromobenzene was added, followed sequentially by 2,6-dichloroaniline and the base. The addition of base caused the solution to warm noticeably. The reaction mixture was then quickly heated to reflux. After one hour, analysis indicated that full conversion of the starting material to product had occurred. Water was added to the reaction mixture at 50 °C, the phases were separated and the organic layer was washed once with brine. The crude solution was then distilled under vacuum to give the final product in 94% yield.

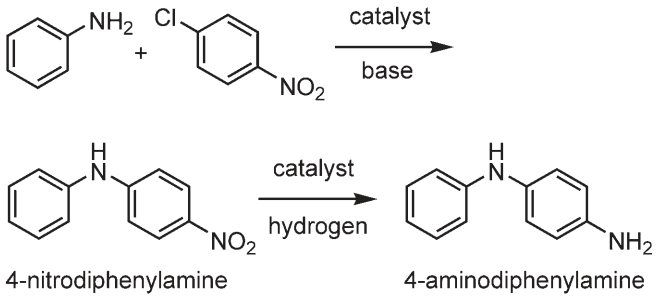
When the reaction was repeated on the same scale but with 0.1 mol % of catalyst, a level typical for an economically viable application of such catalytic processes, full conversion of the starting material was not observed. Additional portions of catalyst (0.05 mol % Pd_2dba_3, 0.2 mol % **F**) were added to the reaction mixture, to a total of 0.15 mol % Pd_2dba_3, 0.6 mol % **F** and full conversion of the starting material to product was observed.

In this case purification of the product can be achieved by distillation and no palladium was detected in the final product.[18]

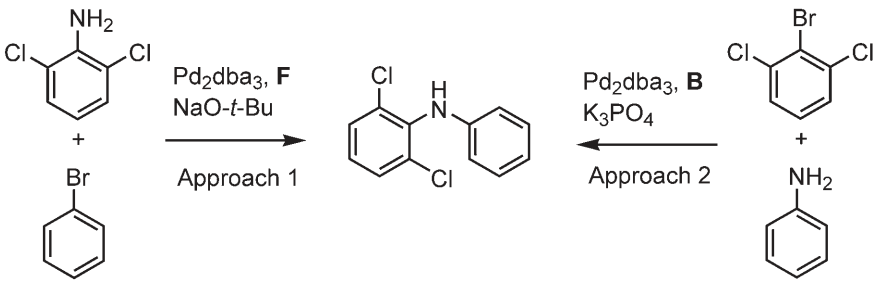
Another application in the synthesis of diarylamines was a Lanxess in-house product, 4-nitrodiphenylamine[19] (Scheme 9), a precursor of the antioxidant component 4-aminodiphenylamine. These diarylamines and their derivatives are of widespread use in car tyres today.

The current process at Lanxess uses a copper-catalyzed Ullmann coupling. The palladium-catalyzed method offered the chance to avoid the formation of unwanted triarylamine by-product, which considerably reduces the overall yield of the current process (Table 10). Obviously, the economic constraints for the manufacture of such commodity products are quite severe.

In this case quantitative formation of 4-nitrodiphenylamine could be observed even using 0.005 mol % of the combination of (+/−)-BINAP and $PdCl_2$. Moreover, the subsequent reduction of the nitro group could be accomplished by the addition of palladium on charcoal to the crude reaction solution under hydrogen pressure. This makes for a more efficient use of the palladium as well as facilitating its recycling. Following the procedure described in Entry 2, analysis of the aqueous phase after work-up of the palladium coupling process showed no detectable amount of palladium.[18] The organic phase, however, showed a concentration that summed to over 95% of the palladium originally added as catalyst. After hydrogenation with palladium on charcoal, the metal cleanly precipitated on the support and a total of 85%



Scheme 9. Lanxess process for the synthesis of antioxidant component 4-aminodiphenylamine.



Scheme 8. Synthesis of 2,6-dichlorodiphenylamine.

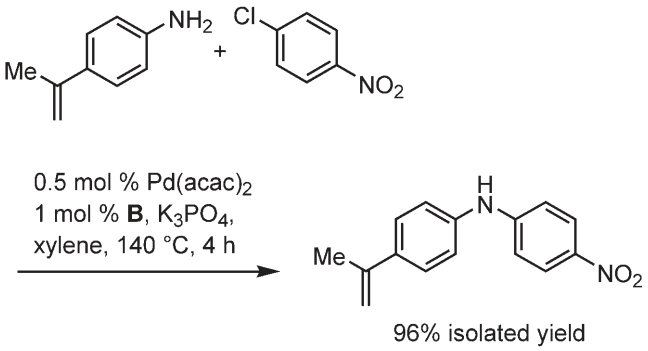
Table 10. Formation of 4-nitrodiphenylamine.

Entry	Conditions	Yield [%][a]
1	5 mol % CuO, K_2CO_3, $CsHCO_3$, refluxing aniline (184 °C)	60–70
2	0.1 mol % $Pd(acac)_2$, 0.4 mol % PPh_3, K_2CO_3, refluxing aniline	99
3	0.03 mol % $PdCl_2$, 0.13 mol % PPh_3, 5 mol % AcOH, K_2CO_3, refluxing aniline	99
4	0.005 mol % $PdCl_2$, 0.005 mol % (+/−)-BINAP, K_2CO_3, refluxing aniline	99

[a] Yields were determined by calibrated HPLC after work-up.

of the palladium used in the coupling reaction could be recovered.[20]

To summarize this work, an alternative to the copper-catalyzed method for the large-scale production of a low value-added substance was identified. Even with the strict economic restrictions for the preparation of a commodity intermediate like 4-aminodiphenylamine, the palladium-catalyzed technology was competitive with the established route that uses a copper catalyst.



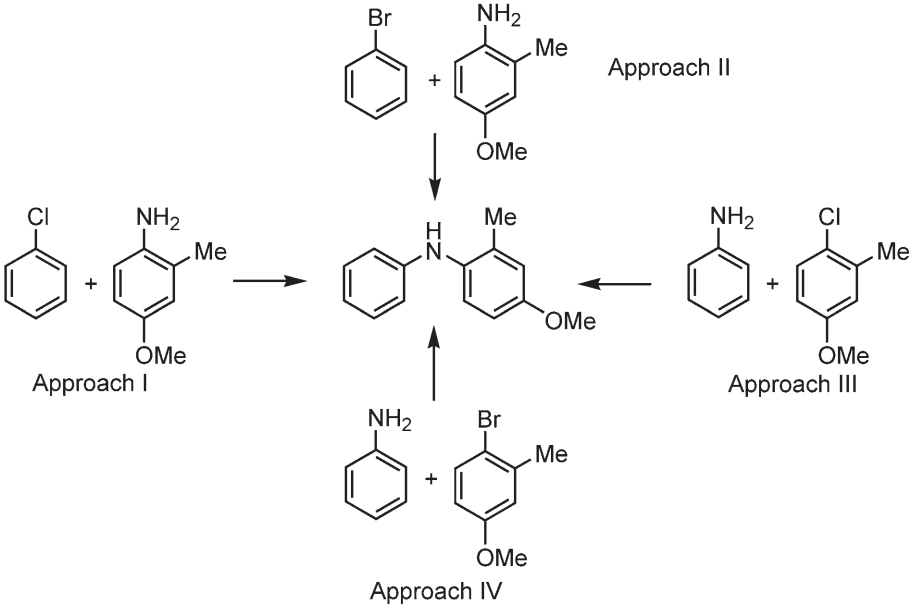
Scheme 10. Synthesis of alkenyl-diarylamines.

With these results in hand we saw the possibility of preparing a new class of antioxidant additives with a substituent on the diarylamine that could be vulcanized into a rubber for tyres, therefore rendering longer protection from oxidation. 4-Isopropyleneaniline, which is readily available by ammonolysis of bisphenol A,[21] a common polymer building block, could be cleanly coupled with 4-chloronitrobenzene (Scheme 10); no competitive by-product of Heck arylation could be detected.[22] In this instance, use of ligand **B** provided a 96% yield of the desired product.

The versatility of the palladium-catalyzed aromatic amination can further be demonstrated by the synthesis of *N*-2-methyl-4-methoxyphenylaniline, another important intermediate in the fine chemical industry (Scheme 11).

Classically, this molecule can be prepared by a transfer hydrogenation between phenol and 2-methyl-4-methoxyaniline using catalytic amounts of cyclohexanone.[23] While the aromatic amination approach is probably not economically competitive, it offers the chance to choose from a wider pool of starting materials.

As 2-methyl-4-methoxyaniline is available inexpensively on scale, approach I is a realistic alternative to



Scheme 11. Synthesis of 2-methyl-4-methoxy-diarylamine by palladium catalysis.

Table 11. Approaches to 2-methyl-4-methoxy-diarylamine.

Entry	Approach	Conditions	Yield [%][a]
1	I	2 mol % **B**, 0.5 mol % Pd_2dba_3, K_3PO_4, refluxing toluene	95
2	II	1 mol % BINAP, 0.5 mol % Pd_2dba_3, Cs_2CO_3, refluxing toluene	95
3	III	2 mol % **B**, 0.5 mol % Pd_2dba_3, K_3PO_4, refluxing aniline (184 °C)	96
4	IV	4 mol % PPh_3, 0.5 mol % Pd_2dba_3, Cs_2CO_3, refluxing aniline (184 °C)	93
5	II	5 mol % PPh_3, 5 mol % Pd/C, Cs_2CO_3, refluxing toluene	12

[a] Isolated yield after distillation.

the current synthesis. Our usual screening method directly yielded a protocol that could be scaled to the multigram level. Product purification could be achieved by distillation with no detectable amount of palladium remaining in the final product (Entry 1). However the amount of catalyst necessary would have to be significantly decreased to render this an economically competitive process.

Approach II, which is slightly less attractive due to the use of bromo- rather than chlorobenzene, provides a nearly quantitative yield of the product (Entry 2).

When looking at other alternatives, approach III, in refluxing toluene as solvent, gave only a moderate yield of the product. However, on changing the solvent to aniline and raising the reaction temperature to 184 °C (reflux), the desired product is obtained in nearly quantitative yield (Entry 3).

The last possible combination of starting materials is represented by approach IV. On first inspection, an economically attractive catalyst could be identified to perform this reaction, consisting of a palladium precatalyst with triphenylphosphine as the ligand. Unfortunately, it is necessary to employ Cs_2CO_3 as base, which is quite expensive. Last, the use of aryl-4-bromo-3-methylanisole as starting material in approach IV, a compound that for the time being is available in laboratory quantities only, compromises this route (Entry 4).

Unfortunately our attempts to use Pd/C with triphenylphosphine as ligand gave a poor yield of 2-methyl-4-methoxy-diarylamine (Entry 5).

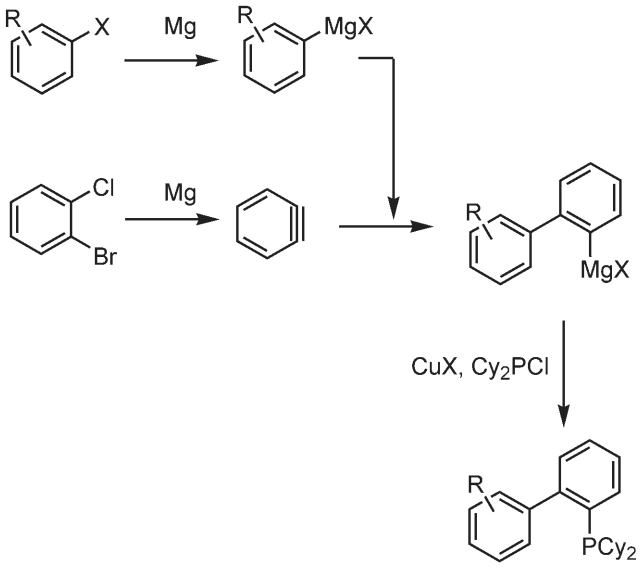
To summarize the results for the synthesis of 2-methyl-4-methoxy-diarylamine, the palladium-catalyzed aromatic amination probably will not supersede the classical synthesis, *via* transfer hydrogenation, from an economic point of view. All four approaches (I–IV) showed almost complete formation of the desired product. This is an indication of the flexibility of this technology and bodes well for future synthetic endeavors. Of special interest to the custom manufacturer is that the choice of the synthetic disconnection can be determined by the availability of the starting material, enhancing the versatility of this method even further.

6 Synthesis of the Dialkylphosphinobiaryl Ligands

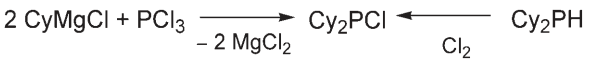
Dialkylphosphinobiaryls are, in our view, the most general ligands for palladium-catalyzed C–N bond-forming processes. Six members of this ligand family whose use usually provided excellent results are shown in Scheme 1. Studies at MIT have indicated that substitution on the bottom (non-phosphorus-containing) ring is important.[24] It is believed that this lessens the tendency for the formation of palladacycles, while favoring the formation of monoligated palladium. While it is not yet possible to identify one ligand for all amination processes, this small set of ligands available from a single process covers a range of possibilities for a custom manufacturer to flexibly scale-up today's demanding targets from pharmaceutical companies.

Despite the apparent complexity of these ligands, **A** through **C** are available in a one-pot procedure as depicted in Scheme 12,[24a] while **D** can be synthesized by an equally attractive, but slightly different route.[25]

With two metallation steps, one C–C bond formation, one C–P bond formation and a potentially complex work-up, their scale-up is challenging.



Scheme 12. Synthesis of dialkylphosphinobiaryl ligands.



Scheme 13. Two possible routes for the synthesis of chlorodicyclohexylphosphine.

7 Synthesis of Chlorodicyclohexylphosphine

One of the key issues for the synthesis of the dialkylphosphinobiaryl class of ligands is the availability of chlorodicyclohexylphosphine. With a very limited number of manufacturers of chlorodicyclohexylphosphine, usually producing only on a kilogram scale, we considered its in-house synthesis by the controlled addition of a Grignard reagent to phosphorus trichloride in solvents such as THF (Scheme 13).

Companies specialized in the handling of pyrophoric and highly toxic phosphorus intermediates might prefer a route involving the chlorination of dicyclohexylphosphine. The Grignard approach, however, is a way to handle this chemistry without specialized expertise.

For the synthesis, the reaction temperature needs to be kept at 0 °C in order to avoid the formation of tricyclohexylphosphine. It was even more important that a strict stoichiometry of 2:1 of cyclohexylmagnesium chloride to PCl_3 be ensured. Strict exclusion of moisture and oxygen was necessary to prevent formation of impurities that poisoned the subsequent C–P bond-forming step. During the reaction, several equivalents of magnesium chloride are formed. Since these magnesium salts show considerable solubility in THF, it was necessary to change the reaction solvent from THF to toluene. Running the reaction in toluene provides a reaction solution that, after filtration, can be used directly. However, more reliable results in terms of product quality were realized if the crude solution of chlorodicyclohexylphosphine was concentrated and distilled under a high vacuum. Interestingly, if the mixture contained more than 3% w/w of tricyclohexylphosphine, the distillation was unsuccessful. Dicylohexylphosphinous oxide, a white solid, deposited throughout the distillation apparatus when the heating reached a temperature of 170 °C. This is probably due to a phosphine-catalyzed disproportionation reaction. Even distillation techniques used for the purification of sensitive materials such as short-path distillation or thin-film distillation did not solve this problem.

8 Synthesis of Ligands A and C

A reliable protocol for the lab-scale synthesis of **A** has been published by the MIT group[24a] and was subsequently used to prepare **C**, as well, on a 20-gram scale. For industrial purposes, the scale of the synthesis needed to be increased to the multi-kilogram level.

Rhodia's work resulted in two procedures that, interestingly, only differ from the MIT protocol in the way the work-up was performed.

In the original procedure, the reaction was carried out in anhydrous THF using two equivalents of magnesium powder and an aryl bromide (2-bromotoluene or 1-bromo-2,4,6-triisopropylbenzene). The intermediate Grignard reagent is then coupled with benzyne, generated *in situ* from 1,2-chlorobromobenzene and magnesium. The carbon-phosphorus bond is formed by the CuCl-catalyzed reaction between the newly formed Grignard reagent and chlorodicyclohexylphosphine.

For safety reasons, magnesium powder had to be avoided and we chose to replace it by magnesium turnings, which are easier to handle and manipulate. We used technical grade THF as the solvent.[26] The chlorodicyclohexylphosphine was provided by Rhodia PPD and was at least 92% pure.[27]

In the course of our studies, we found that the addition of magnesium turnings in two batches provides a higher yield of product. In this way, formation of Wurtz-type by-products was avoided. Generation of the first Grignard species, the following C–C coupling and C–P coupling are fast reactions and occurred to a large extent during the addition of the reactants; one hour after their introduction the reactions are complete. A new procedure for product isolation was developed. This involved the addition of aqueous sodium sulfite (37%) to the reaction mixture to hydrolyze any excess Grignard reagents and to dissolve the magnesium salts that had formed. Through the use of this reducing solution, phosphine oxidation was also avoided. At this point the layers were separated and, in case of **C**, THF was replaced by *n*-butanol *via* solvent exchange. Crystallization afforded **C** as a white powder in 65% yield.[28] The procedure was slightly different for the preparation of **A**. In that case, at the end of the reaction procedure, after cooling the reaction mixture to room temperature, ethyl acetate was added. The resulting organic layer was washed several times with hot water to remove the THF. Ligand **A** then crystallizes directly from the ethyl acetate solution upon cooling and is obtained, after filtration, as a white powder in a 50% yield.[29]

The development of a safe industrial procedure requires the determination of all the thermal characteristics of the process that occur or could occur during the reaction protocol.[30] We first investigated the synthesis of **A**. We found that the formation of 2-methylphenylmagnesium bromide is exothermic ($\Delta H = 285$ kJ/mol) which translates into an adiabatic temperature rise of 245 °C. This heat is potentially sufficient to evaporate 93% of the initial THF charge. The reaction is quite fast and the conversion, measured at the end of the addition, to the Grignard reagent is 96%. Thus, the slow introduction of the aryl bromide to the magnesium turnings was required to control any exotherm and to ensure a safe process. The second step, the formation of 2-(2′-

Figure 6. Vessel (250 liters) for the pilot-scale production of **A** and **C**.

methylphenyl)-phenylmagnesium bromide, is also exothermic ($\Delta H = 872$ kJ/mol, $\Delta T_{adiabatic} = 97\,^{\circ}C$) and this quantity of heat is able to potentially evaporate the entire initial charge of THF. Nevertheless, this exotherm can again be easily controlled by the slow addition of the 1,2-bromochlorobenzene. Finally, the copper-catalyzed C–P coupling is also quite exothermic ($\Delta H =$ 236 kJ/mol) and rapid (about 98% of the chlorodicyclohexylphosphine has been consumed at the end of its addition). All these data confirm the necessity to slowly introduce the reagents over the course of at least one hour. Finally the work-up protocol has also been studied. The energy of the neutralization of the reaction solution using dilute $NaHSO_3$ is 214 kJ/mol, which is dissipated by dilution. No corrosion effect of copper or bromide onto the steel surface of the reaction vessel was observed.[31]

In summary, a safe reaction protocol was devised for the preparation of **A** and **C** in which potential exotherms were controlled by the rate of addition of the reagents. It was also necessary to change the nature of the work-up to adapt this protocol from an academic realm to an industrial one. The procedure for ligands **A** and **C** could be carried out in a 250-L apparatus (Figure 6) on a scale of 10 kg of product isolated per batch.

9 Synthesis of Ligand B

For the synthesis of the last of the three ligands prepared on a larger scale, *o*-chloroaniline (produced on a multiton scale at Lanxess) was employed as starting material. Methylation of *o*-chloroaniline could be achieved by several methods. The reaction of the aniline with formaldehyde under reductive amination conditions with formic acid provided a good yield of product on a small scale. On a larger scale, however, we observed the formation of polymeric by-products. Methylation with dimethyl sulfate in alkaline solution worked well on both small and large scales. However, even if only small amounts of overmethylated products were formed, aqueous work-up proved to be very difficult, since the trimethylammonium by-products formed strongly inhibited phase separation. To solve this problem, we added an excess of *o*-chloroaniline to the reaction mixture (up to 3% of monomethylated aniline was seen in the crude material) and the problems observed during work-up disappeared. However, the monomethylated product could not be removed by simple distillation, since the boiling point differs only by one degree from that of the *N,N*-dimethyl-2-chloroaniline. The solution, in this case, was the addition of acetic anhydride to the distillation vessel, thereby transforming the monomethylated aniline to the acetanilide, which allowed *N,N*-dimethyl-2-chloroaniline to be separated by distillation. This procedure was successfully applied to produce ~100 kg of *N,N*-dimethyl-2-chloroaniline as starting material for the synthesis of **B** in an overall yield of 44–48%.

The conversion of *N,N*-dimethyl-2-chloroaniline into the corresponding Grignard reagent is challenging. To safely conduct this transformation on a moderate scale requires its simultaneous addition, along with dibromoethane (10 mol %), to a suspension of activated magnesium turnings in a minimal quantity of refluxing THF. With an adiabatic temperature rise of 170 °C this first reaction demanded special care. To avoid build-up of heat potential, the addition of the aryl halide had to be done in small portions with analytical checks made to determine if the reaction had started. Compared with the preparation of other dialkylbiphenylphosphines starting from aryl bromides rather than aryl chlorides, this first step took considerably longer, usually eight to twelve hours, to reach completion.

The addition of 1,2-bromochlorobenzene behaved as for the preparation of the other two ligands and was easily controlled by adjusting the rate of its addition. Extending the reaction time of this step, however, leads to the formation of several Wurtz-type coupling products, which could be avoided by keeping the reaction time as short as possible. If an excess of bromochlorobenzene was used in this step, the incorporation of a second and third phenyl ring into the system was observed and work-up became more difficult.

The catalyst for the C–P coupling in this case was a mixture of CuI and LiBr instead of CuCl.[32] In this way the reaction solution was more homogeneous and the work-up was easier; the rate of the C–P coupling was similar in both cases.

Analysis of the work-up method described in the original procedure indicated that the addition of water to the reaction mixture would involve tripling of its volume. To achieve better volumetric productivity, the addition of a small amount of methanol was used not only to quench any excess Grignard reagent, but also to destroy magne-

Figure 7. Vessel (150 liters) for the pilot-scale production of **B**.

sium complexes still in solution. To achieve complete precipitation of the magnesium salts, a solvent change from THF to toluene was again necessary, giving rise to an easily filtered suspension and with a filter cake which contained no product.

The toluene solution containing the product was concentrated, mixed with methanol, and, upon cooling, white crystals formed that were isolated by filtration and showed a purity of $>98\%$.[33] Analysis of this material showed that it contained up to 400 ppm of magnesium-containing impurities, while the copper content was about 20 ppm. Further purification of the material was possible by recrystallization from acetone, where copper and magnesium impurities dropped below 10 ppm, and the overall yield of the process ranged between 55 and 63%. The reaction was performed in the 150-L vessel depicted in Figure 7.

10 Removal/Recycling of Palladium after the Reaction

According to economic estimates, recovery of the palladium might become an important factor to reduce the overall material cost of palladium-catalyzed C–N bond-forming processes. Several methods can be investigated to remove the palladium from either the organic or aqueous layer. To our knowledge, for this kind of chemistry the oxidation state of the palladium is unknown. However, we determined that in our process the majority of the metal is in the Pd(0) oxidation state and is therefore soluble in the organic layer. Thus, we concentrated our efforts on recovery from this phase. A screening of different charcoals and resins as adsorbents was carried out by the chemists at Rhodia. The best results were obtained with three types of charcoal: CECA Acticarbon BGX, CECA Acticarbon CXV and NORIT C Grand removed all but 5 ppm of palladium from the organic layer when it was stirred with the adsorbent at 80 °C. The ability to remove palladium decreased slightly at room temperature; 10–14 ppm of palladium remained.

Table 12. Results of adsorption studies, shown is the contamination level of palladium in the organic layer

Adsorbent	Trade name	Pd (ppm)
Charcoal	NORIT GAC	62–67
Charcoal	NORIT SX	75
Charcoal	NORIT CNI	34
Charcoal	NORIT C GRAND	<5
Charcoal	CECA Acticarbon CXV	<5
Charcoal	CECA Acticarbon BGX	<5
Charcoal	IRC 50 (CO2H)	114
Charcoal	IRC 48 (aminodiacetate)	116
Resin	Lewatit SP 112	105
Resin	Amberlyst A21	104
Resin	Amberlyst 36 DRY	32

ESCA studies of the charcoal from the reaction mixture indicated the presence of carbon, oxygen, palladium, sodium and traces of bromides. The palladium was found to only be in the zero oxidative state.

11 Conclusions and Prospects for Future Work

In this paper we have described how the implementation of a unique three-way collaboration between two companies and one academic institution has led to the scale-up and commercial utilization (several hundreds of kg/product so far) of a new technology. While the original chemistry emanated from MIT, the technical skills available from those in Rhodia and Lanxess were essential for overcoming issues of safety and scale. Moreover, the latter were responsible for bringing to fruition the production of over 100 kg of ligands, ostensibly, *via* the original academic route. Of importance to the success of this project was that all participants realized that they had much to gain by listening to the points of view of the others. In this way not only was the project more successful, but valuable information and lessons

were learned by all involved that will be instrumental in future endeavors.

The palladium-catalyzed formation of aromatic carbon-heteroatom bonds is increasingly becoming a daily tool for those in the discovery laboratories of pharmaceutical companies. More recently, a number of projects have made it to process groups and scale-ups of the transformations have occurred. Clearly, much work is still necessary to overcome a variety of practical limitations. As the chemistry is more widely practiced and the methodology matures, we are optimistic that it will be practiced on increasingly large scale.

References and Notes

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[5] C. Mauger, G. Mignani, *Org. Proc. Devel.* **2004**, *8*, 1065.

[6] The use of commercial bulk phosphates including $Na_4P_2O_7$, Na_2HPO_4, $Na_3PO_4 \cdot 10.5\,H_2O$, Na_3PO_4, $Na_2HPO_4 \cdot 2\,H_2O$, $(CaO)_{10}(P_2O_5)H_2O$, and $K_4P_2O_7$, proved to be ineffective.

[7] Trifluoromethylphenyl hydrazines are important compounds for the preparation of azaheterocycle intermediates in pharmaceutical and agrochemical domains, for examples, see a) WO 2003076409 (Syngenta Participations AG, Switzerland); b) WO 2003068223 (Bayer Corporation, USA); c) FR 2815346 (Les Laboratoires Servier, France); d) WO 2001089457 (SmithKline Beecham Corporation, USA; Glaxo Group Limited); e) WO 2000069849 (Ortho-McNeil Pharmaceutical, Inc., USA); f) Y. Nalavde, V. Joshi, Ind. *J. Chem. Sect. B* **2000**, *39*, 634–637; g) EP 1044970 (Adir et Compagnie, France).

[8] The use of the following bases resulted in lower conversions: NaO-*t*-Bu (47%), KO-*t*-Bu (51%), K_2CO_3 (78%), Cs_2CO_3 (70%). No reaction occurred using **A** as the ligand.

[9] Description of Raman spectrometer: *in situ* Raman Rxn1 Analyzer from Kaiser Optical Systems Inc., immersion probe with TE-cooled CCD detector technology using laser 785 nm.

[10] Quantitative palladium analysis was performed by FX analysis.

[11] The highest temperature reached in this exotherm was 192 °C.

[12] The calorimetric energy displayed during the reaction was measured in a RC1 Mettler calorimeter to be 62.4 kJ/mol of starting arylhydrazone. This heat corresponds to an adiabatic temperature rise of +13.5 °C, therefore due to the long reaction time of about 20 h the reaction can be regarded as safe.

[13] CASIS Search 01/2004.

[14] Determined by quantitative ^{1}H-NMR.

[15] a) F. Ullmann, *Ber. dtsch. Chem. Ges.* **1901**, *34*, 2174; b) F. Ullmann, *Ber. dtsch chem. Ges.* **1903**, *36*, 2382–2384; c) F. Ullmann, P. Sponagel, *Ber. dtsch. chem. Ges.* **1905**, *36*, 2211–2212; d) I. Goldberg, *Ber. dtsch. chem. Ges.* **1906**, *39*, 1691–1692; e) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558–5607; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449; f) K. Kunz, U. Scholz, D. Ganzer, *Synlett* **2003**, 2428–2439.

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[17] The ligands investigated were: (+/−)BINAP, $P(t\text{-Bu})_3$, PPh_3, **B**, dppf, $P(o\text{-Tol})_3$, **E** and **F**. Bases examined included K_2CO_3, NaO-*t*-Bu, KO-*t*-Bu, CsF, K_3PO_4, Na_2CO_3, NaOH and Cs_2CO_3.The palladium precatalyst was 0.5 mol % of Pd_2dba_3.

[18] Determined by ICP-MS.

[19] German Patent DE 19942394.

[20] 75% of the original charcoal precipitated of the Pd/C and could be isolated by filtration. The remaining 10% of palladium could be recovered by addition of CECA 4S activated charcoal and 1 h stirring at 50 °C.

[21] 2,2-Bis-(4-hydroxybiphenyl)-propane.

[22] Lanxess, *German Patent* DE 10235834.

[23] Mitsui, *Japanese Patent* JP61218560, JP 05003867.

[24] a) S. Kaye, J. M. Fox, F. A. Hicks, S. L. Buchwald, *Adv. Synth. Catal.* **2001**, *344*, 789; b) X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653.

[25] Due to the fact that 2,6-dimethoxybromobenzene is not available as a starting material, a separate route for the synthesis of ligand was developed: T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.

[26] THF was provided by SDS and contained 0.1% of water.

[27] Determined by ^{31}P NMR.

[28] Purity by ^{31}P NMR was > 98%.

[29] Purity by ^{31}P NMR was 98%, a second crop yielded an additional 10% yield of **A**.

[30] The calorimetric and thermodynamic studies were performed in a 2-liter RC1 Mettler calorimeter.

[31] Similar results were obtained for the synthesis of ligand **C**.

[32] F. Rampf, H. C.Militzer, (Lanxess), *European Patent* EP 1354886, **2003**.

[33] Determined by calibrated HPLC.

