Industrial R&D on Catalytic C–C and C–N Coupling Reactions: A Personal Account on Goals, Approaches and Results

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Abstract: R&D issues for the application of Pd- and Ni-catalyzed C–C and C–N coupling reactions in the fine chemicals industry are discussed. In a first part, some background is given on industrial R&D and the role of C–C and C–N coupling for preparative applications is described. The following principal approaches to industrial research are illustrated with relevant examples from the literature and from our own laboratories: i) development of catalysts and catalytic methodologies with industrial potential; ii) finding shorter routes to target molecules using catalytic methods; iii) development of industrial catalytic processes in multi-step syntheses.

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Keywords: C–C coupling reactions; C–N coupling reactions; industrial research; Ni catalysis; Pd catalysis

1 Introduction

Traditionally, fine and specialty chemicals have been produced using predominantly non-catalytic organic synthesis but there are many indications that catalytic methods are being used more often in recent years. One reason for this positive trend is the significant research effort in the last decades, especially in academia but also in industrial laboratories. Among the many different feasible catalytic transformations, C–C and C–N bond forming reactions and selective hydrogenation have received special attention and consequently had a particularly high impact on organic synthesis.[1] This is due to the versatility of these methodologies for the construction of important structural motifs and the transformation of functional groups, respectively. In the following discussions we will focus on C–C and C–N coupling reactions which have become an effective tool for the organic chemist to prepare a variety of commercially important target molecules.[2–4]

While both industrial catalysis R&D and academic research aim at high scientific quality as well as originality they do differ in some important aspects. Whereas academia strives for fundamental new catalysts and reactions and for mechanistic understanding, in industrial research priority is given to the application of catalytic methods in a time- and cost-effective manner with the goal to gain a competitive advantage. Catalysis opens up various business opportunities and specific R&D goals differ accordingly. For product-oriented companies such as integrated agrochemical or pharmaceutical companies, important opportunities are the discovery of new product classes *via* catalytic routes and more efficient syntheses by applying catalytic steps. For technology-oriented companies such as custom manufacturers (CMO) or custom research (CRO) organizations, developing proprietary catalysts or

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From left to right: Hans-Ulrich Blaser, Anita Schynder, Adriano Indolese, Frédéric Naud, and Ulrike Nettekoven.

Hans-Ulrich Blaser received a Diploma in Natural Sciences from the Federal Institute of Technology (ETH) Zürich in 1966. His doctoral research was carried out with A. Eschenmoser at the same institution, from which he received his Ph. D. in 1971. Between 1971 and 1975 he held postdoctoral positions at the University of Chicago (J. Halpern), Harvard University (J. A. Osborn), and Monsanto (Zürich). During 20 years at Ciba-Geigy (1976–1996) he gained practical experience at R&D in the fine chemicals and pharmaceutical industry, which continued at Novartis (1996–1999) and Solvias where he is presently chief technology officer. During his industrial carrier, he has developed and implemented numerous catalytic routes for agrochemicals, pharmaceuticals and fine chemicals (both as project leader and section head).

Anita Schnyder graduated in chemistry from the Federal Institute of Technology (ETH) Zurich in 1993. Her doctoral research in the field of metal-organic chemistry and homogeneous catalysis was carried out with Prof. Antonio Togni at the same institution, where she received her PhD degree in 1996. After a postdoctoral stay at the University of British Columbia with Prof. Mike Fryzuk, she started her industrial career in 1997 in the catalysis development group of Novartis. This continued at Solvias where she is presently a project leader specialized in C–C coupling catalysis as well heterogeneous hydrogenation projects. During her industrial career, she has developed and implemented numerous catalytic routes for agrochemical, pharmaceuticals and fine chemicals.

Adriano F. Indolese received his diploma in chemistry in 1987 from the University of Basel and his Ph. D. from the ETH Zürich for his work on enantioselective transition metal catalysis under the supervision of Prof. G. Consiglio. After postdoctoral studies with Prof. B. Trost at Stanford University he joined the Catalysis Research Group of Ciba-Geigy AG in 1993. He worked for eight years as research scientist in the field of metal-catalyzed coupling reactions using palladium and nickel catalysts. In 2002, Adriano Indolese moved to Rohner AG, Pratteln where he currently is a development chemist. His interests are the search for more efficient and ecologically more benign production processes by applying transition metal-catalyzed reaction.

Frédéric Naud performed his university studies in chemistry at Université Poitiers, France followed by graduate research at the University of British Columbia under Prof. M. D. Fryzuk. He received a Ph. D. in 1999 from the Université Louis Pasteur, Strasbourg working for Prof. P. Braunstein. Following a postdoctoral fellowship at the University of Basel with Prof. A. Pfaltz, he joined Solvias AG where he works in Organic and Organometallic Synthesis, with an emphasis on homogeneous catalysis and ligand design.

Ulrike Nettekoven graduated in chemistry from the University of Vienna in 1996. She continued her studies at the University of Amsterdam, where she worked in the group of Prof. Piet W. N. M. van Leeuwen in the field of organometallic chemistry (ligand synthesis and asymmetric catalysis). After obtaining her Ph. D. in 2000, she spent two years as a postdoctoral researcher in the group of Prof. John F. Hartwig at Yale University. She joined the catalysis research group of Solvias in 2002 and has been regularly involved in customer projects. Her research interests are in the fields of catalytic C–C and C–N coupling chemistry as well as in asymmetric homogeneous and heterogeneous hydrogenation.

catalytic technologies will be an important asset and for catalysis manufacturers, proprietary catalysts and efficient catalyst preparation methods will be important.

In order to understand the goals and priorities of industrial R&D, the characteristics of manufacturing fine chemicals and consequences for the application of catalytic processes in this context are briefly characterized in Table 1.

Our catalysis team has been active in R&D since the early 1970s, first in the central research department of Ciba-Geigy/Novartis, both integrated companies with a broad product spectrum, and since 1999 in Solvias,

Table 1. Characteristics of fine chemicals and consequences for catalysis

Characteristics of fine chemicals manufacture	Consequences for catalysis
Rather complex molecules (isomers, stereochemistry, several functional groups) with limited thermal stability produced *via* multi-step syntheses with short product lives (often <20 years).	Catalysts should have good functional group tolerance; catalytic step must be fitted to over-all synthesis. Only catalysts with well known scope and limitation will be considered.
Products and sometimes intermediates usually patent-protected.	Especially for new chemical entities processes need to be competitive but not the best; patent-protected processes for major intermediates and very large volume products.
Relatively small-scale products usually manufactured in solution, at ambient pressure and low to medium temperature in small to medium-sized multi-purpose batch equipment.	Catalytic reaction should not require harsh reaction conditions and/or special apparatus.
Often short development times, especially for new chemical entities. Relatively high fail rate, therefore often relatively low development budget for individual products.	No time for the development of new catalysts/catalytic reaction. Only established methods and commercially available catalysts will be considered. High throughput experimentation methods are of increasing importance.
Medium to very high value-added products, i.e., production costs are only a medium to very low part of the selling price of the end product.	Catalyst costs can be relatively high but must be competitive with other (non-catalytic) methods.
High purity requirements with narrow specifications (usually $>99\%$ and <10 ppm metal residue in pharmaceuticals).	Separation methods for homogeneous catalysts and removal of trace metals should be known.
Development usually carried out by organic chemists with little catalytic know how.	Outsourcing to internal or external catalyst specialists.

Table 2. Important topics in catalysis R&D at Ciba-Geigy/Novartis/Solvias in the area of C–C and C–N coupling reactions

Start	Topic/Milestone	Ref.
1970	Ni-catalyzed reactions of butadiene with C=N bond systems; synthesis of novel C_{10} diamines and amino alcohols, and C_9 amines.	[6]
1978	Investigations of the Heck reaction: acid chlorides as starting materials; high performance catalysts; Heck–Matsuda reaction for product discovery;	[7, 8, 9]
ca. 1985	Development of first industrial processes (selected milestones see below)	[7, 10]
1995	Ni catalysts for Suzuki coupling developed	[11]
1998	Catalysts for the activation of aryl chlorides for Heck, Suzuki, Buchwald–Hartwig amination etc.; secondary phosphines; palladacycles – secondary phosphines	[13, 14]
1998	Systematic investigation of the carbonylation of aryl halides; carbonylation of (hetero) aryl chlorides	[10, 15]
2001	Synthesis of small libraries *via* parallel carbonylation	[12]

an independent technology company[5] providing R&D services as well as producing selected homogeneous catalysts and ligands. Some milestones of this research are listed in Table 2.

In the following sections we will discuss three specific approaches to catalysis R&D in more detail:

- Adaptation of existing or development of new catalysts and catalytic methodologies with industrial application potential.
- Shorter routes to target molecules by applying catalytic steps.
- Process development of catalytic steps for the synthesis of specific target molecules.

We will illustrate the general discussion with case studies from our work at Ciba-Geigy/Novartis/Solvias and also with examples from the catalysis research groups of the former Hoechst[3] and of DSM.[4]

2 Development of Catalysts and Catalytic Methodologies with Industrial Potential

Several factors determine whether the industrial application of a catalyst is technically as well as economically feasible. The first criterion for judging a catalyst is usually selectivity (chemo-, regio-, stereoselectivity) and selectivity is often the only focus of academic research. However, since noble metal catalysts are quite expensive, an economically viable catalytic process must also have reasonable *catalyst productivity* (turnover number, TON, mol product per mol of catalyst) and, to achieve an economical space-time yield, good *catalytic activity* (expressed as turnover frequency, TOF, TON/h). The catalyst costs for noble metal catalysts consist of the following cost elements: *preparation* of the metal precursor (salt, complex) or the heterogeneous catalyst, including costs for the support; *metal losses* (process and handling losses in the range of 1 to 10% are considered normal; recovery losses for Pd vary between 1–2%); *metal recovery* fees of the catalyst manufacturer; *interest costs* for the noble metal inventory (usually treated as investment). Besides catalysts costs, expensive starting materials can also be a hurdle for applying catalytic reactions; for a discussion see Zapf and Beller.[3]

When discussing absolute figures, one should always keep in mind that these can vary broadly depending on the situation for a specific process development. Inspection of the results summarized in Section 3.2 for industrial processes shows that for pharma applications TONs > 100 and TOFs > 10 h^{-1} are often sufficient, at least for initial production. Later on and also for higher volume products with less added value, TONs > 1000 and TOFs > 100 h^{-1} are required. Similarly, rather expensive substituted aryl bromides or even iodides are feasible for pharma applications but not for cheaper commodities. In addition to these quantitative aspects, other concerns such as functional group tolerance and the possibility to integrate the catalytic step into the over-all synthesis also become important considerations when deciding on synthetic routes. In this phase, the decision will be influenced by the familiarity of the development chemist with scope and limitations of a catalyst, and whether the catalyst is available commercially in the required quantities. Later on, issues like catalyst separation and metal recycling or the problem of trace metal impurities will be important issues to be solved.

Because of the often narrow time-frame available for process development, industrial research should create generic solutions for all these problems. Since this is rarely possible, the strategy chosen most often is the investigation of (hopefully) relevant model reactions where the effects of catalyst and ligand type, of solvent, and of the reaction conditions are studied. These results serve as basis for the development of processes for "real-world" problems and must of course be adapted to each specific problem. Furthermore, methodologies should be amenable to high throughput experimentation in order to accelerate the development of catalytic processes both in the screening as well as in the optimization phase. The following subsections describe case studies showing how some of these issues have been addressed and the results which have been obtained.

2.1 Development of Catalytic Systems with Very High Turnover Numbers

2.1.1 Amide Solvents and Inorganic Bases[8]

At the Central Research Laboratories of the former Ciba-Geigy we started to investigate Pd-catalyzed coupling reactions in the late 1970s. This was triggered by the fascinating reaction of olefins with aryl iodides and bromides published almost simultaneously by Mizoroki and Heck with the potential to prepare substituted styrene and stilbene derivatives, interesting structures for brighteners. Heck studied the reaction in detail and tried to improve the relatively low catalyst activity but had only limited success. In order to get good yields 1–2% catalyst had to be applied, prohibitive for many of the potential applications.

We systematically studied the effect of the reaction parameters, particularly of the ligand, the base and the solvent for the Heck reaction of several *para*-substituted aryl bromides. It was found that the combination of amide solvents with carboxylates as base allowed the realization of > 100,000 turnovers, for many years the most effective Heck reaction known (see Figure 1).[8a] Indeed, similar solvent-base combinations are now routinely used to carry out Heck reactions. For *p*-nitrobromobenzene, a record TON of 134,000 was obtained, albeit at only 67% conversion. The report by Heck that $P(o\text{-Tol})_3$ was slightly more effective than PPh_3 was confirmed but it was also shown that up to 7800 turnovers

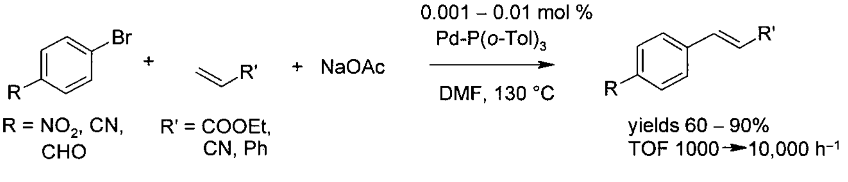


Figure 1. The first high performance catalytic system for the Heck reaction of activated aryl bromides.

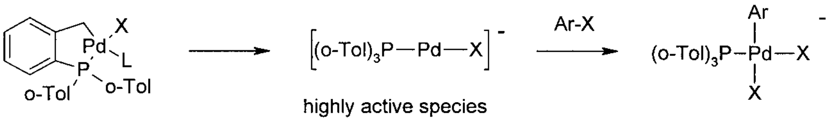


Figure 2. Palladacycle as catalyst precursor and proposed structure of catalytically active species.[3]

could be obtained without phosphine ligand. This was surprising at the time because it was thought that ligand-less catalysts worked only for aryl iodides (se also Section 2.1.2).

It was also tried to extend the reaction to aryl chlorides but with only limited success.[8b] Due to the low reactivity of even the most activated aryl chlorides, temperatures of 160 °C were necessary and under these conditions, the catalyst was not stable and inactive Pd metal precipitated. Nevertheless, methyl *p*-chlorobenzoate reacted with methyl acrylate in about 50% yield to the corresponding aryl acrylate (for further studies with ArCl, see Section 2.3).

2.1.2 *Palladacycles and "Homeopathic" Catalysts*

The quest for more active catalyst systems was later taken up by the Hoechst[3] and the DSM[4] catalysis groups. In 1995, Herrmann and Beller et al.[16] described palladacycles (see Figure 2) giving TONs > 100,000 for the Heck and Suzuki reactions using deactivated aryl bromides as well as activated aryl chlorides, again a major breakthrough for Pd-catalyzed coupling reactions. Interestingly, there is strong evidence that the palladacycle is not involved in the catalytic cycle but is rather a stable precursor for Pd-monophosphine complexes which are highly reactive but relatively unstable. Palladacycles with high catalytic activity for non- and deactivated aryl chlorides were later developed by Solvias and others (see Section 4.3.)

De Vries[4] has described several approaches to solve the problem of catalyst productivity. For the very reactive aromatic iodides, catalysts formed *in situ* from $Pd(dba)_2$ (dba = dibenzylidene acetone) and a bulky phosphoramidite achieved TONs up to 500,000 and TOFs up to 8,000 h^{-1} (MeCN, Et_3N, 80 °C).[4a] Iodide can be recovered *via* oxidation to $NaIO_4$ which can be sold as such, making the method industrially interesting. The DSM group has also described the application of $Pd(OAc)_2$ without phosphine ligands which gave good yields at Pd loadings of 0.01–0.1% for reactions with a variety of aryl bromides. Since S/C ratios of > 80,000 are possible, they called this a "homeopathic Heck reaction".[17] It is well known that under these conditions Pd precipitates at the end of the reaction in the form of Pd black and it was found that Pd can be almost completely separated and recovered by filtration over celite (< 6 ppb Pd in the filtrate). The catalyst activity is fully restored by re-oxidation with 2 equivalents of iodine.[4a]

2.2 New Substrates for Heck-Type Arylation Reactions

2.2.1 *Aroyl Chlorides*[9]

The original Heck reaction worked well for aryl iodides and bromides.[18] Since these starting materials are sometimes quite expensive and/or a particular substrate not easily accessible, we started to look for alternative substrates. At about the same time, Matsuda and coworkers[19] described an effective olefin arylation reaction with aryldiazonium salts, easily accessible by diazotation of the corresponding anilines, i.e., ubiquitous and cheap starting materials. In 1982 we reported that aroyl chlorides were also suitable coupling components with a reactivity similar to aryl bromides (see Figure 3).[9] This was of industrial interest since a wide range of aromatic carboxylic acids are available and usually cheaper than aryl bromides.

A systematic optimization of the reaction conditions showed the following combination to be optimal for a variety of aroyl chlorides and activated alkenes: catalyst $Pd(OAc)_2$, solvent *p*-xylene, base *N*-benzyldimethylamine at 100–130 °C. Most reactions were carried out with 1% catalysts in 2–4 hours. It was possible to work with catalyst loadings as low as 0.001%, albeit at incomplete conversion. Very good yields were obtained with electron-rich aroyl chlorides, whereas electron-deficient ones gave slightly lower yields, just the reverse trend as observed for aryl halides. Other activated alkenes (R′ =

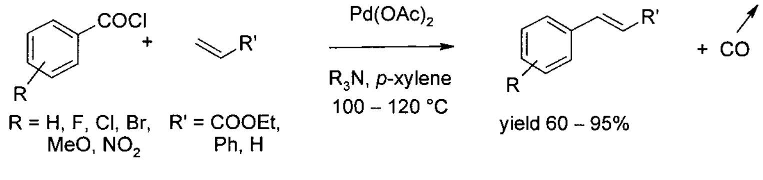


Figure 3. Blaser–Spencer variation of the Heck reaction.

Ph, $CONEt_2$, CN, COMe) were also suitable coupling partners whereas disubstituted alkenes often led to isomeric mixtures.[9c] Since the reaction involves a decarbonylation, it is best performed in an open vessel to allow the CO to escape, which is a drawback of this method. Nevertheless, reactions with ethylene were possible under pressure with yields of up to 60%. Tertiary amines were the bases of choice, but especially the more basic ones reacted with the aroyl chlorides. Phosphine ligands were shown to be detrimental and the presence of 2 moles completely blocked the reaction. This fact was exploited to selectively prepare non-symmetrically substituted divinylbenzenes starting from bromobenzoic acid derivatives.[9d]

2.2.2 Aromatic Anhydrides and Activated Esters

In the late 1990s, de Vries[4] and Goossen[20a] developed the idea further and found that also anhydrides and activated phenolic esters served as substrates for the Pd-catalyzed arylation of olefins in moderate to very good yields (see Figure 4). A major advantage claimed for this variant is the fact that no extra base is needed and no inorganic salt is produced, thereby eliminating a waste disposal problem. On the other hand, the remaining carboxylic acid or phenol, respectively, has to be recycled in order to make the process acceptable. De Vries had to apply high temperatures (160 °C in NMP) with 0.1 mol % catalyst and 0.4% of a bromide salt to get good yields (TOFs *ca.* 300 h^{-1}); Goossen achieved TONs of 30–150 but much lower TOFs in the presence of chloride ions and isoquinoline as necessary additives. Goossen has reported two further methods which do not need substrate recycling. In the first variant,[20b] mixed anhydrides were prepared *in situ* by treating ArCOOH with di-*tert*-butyl dicarbonate and coupled directly with the olefin under conditions similar to those of de Vries. In the second it was shown that enol esters can also be used as substrate, albeit requiring 3 mol % Pd catalyst and temperatures of 160 °C.[20c] As by-products only CO and CO_2/*t*-BuOH or acetone, respectively, are formed, making work-up very easy. However, compared to other coupling methods, the atom economy of the reaction is diminished.

2.3 Catalysts for C–C and C–N Coupling Reactions with Aryl Chlorides

As described above and elaborated by Beller,[3] the use of the cheaper aryl chlorides instead of aryl bromides or even iodides would be highly desirable from an industrial point of view. After Spencer's[8b] limited success with ArCl for the Heck reaction, the results of Milstein[21] with Pd-bis(diisopropylphosphino)butane complexes and especially of Herrmann and Beller et al.[16] for palladacycles initiated a remarkable revival of research in this area. In the last few years, numerous highly active catalyst systems for the use of even deactivated aryl chlorides have appeared for various transformations.[22–25] Here, we will not discuss the very remarkable results obtained by various academic research groups but will briefly describe three case studies carried out at Solvias, on the one hand to illustrate different approaches and on the other hand to describe successful catalysts which are commercially available on technical scale.

2.3.1 Secondary Phosphines as Efficient Ligands[13]

In search of such new catalyst systems, we screened a wide variety of supporting ligands for the Heck reaction of 4-chloroanisole (known to be a substrate which is difficult to activate) and 4-chlorobenzotrifluoride with butyl acrylate using a Chemspeed parallel synthesizer. Besides many different tertiary phosphines, also secondary phosphines, used in a chiral ligand project as intermediates, were included. Quite surprisingly, some palladium complexes with bulky secondary dialkylphosphines (see Figure 5) gave highly active catalytic systems. They showed equal or even better performance than tri-*t*-butylphosphine or tricyclohexylphosphine, often the best ligands for activating aryl chlorides. Since secondary phosphines are easily synthesized from PH_3 and the corresponding olefins and are available in bulk quantities at a relatively low price, we investigated the scope of this ligand class in some detail using $HPAd_2$ for these tests. At a catalyst loading of 1–2 mol %, 80–100% conversion was observed with a wide variety of electron-poor and even electron-rich aryl chlorides. Also less activated

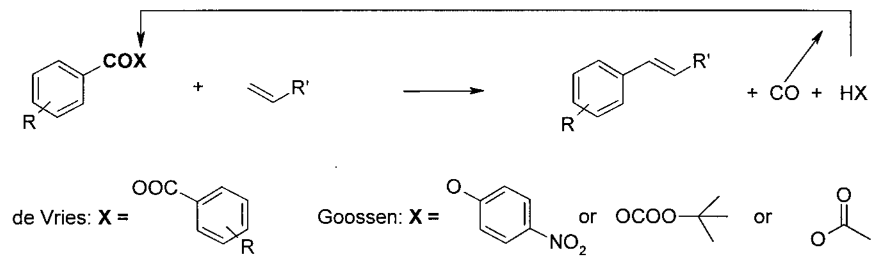


Figure 4. Anhydrides and activated esters for Heck reactions.

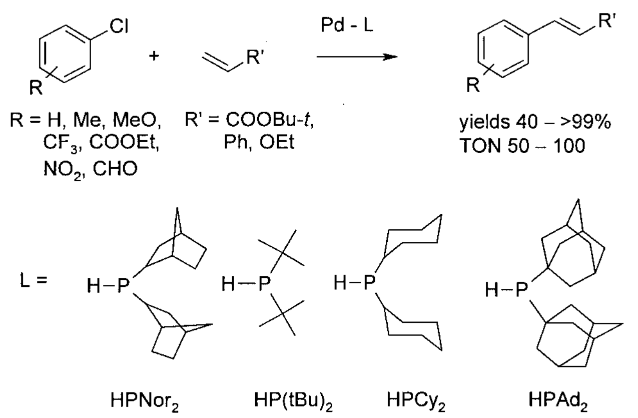


Figure 5. Secondary phosphines as catalyst for the Heck reaction with aryl chlorides.

alkenes such as enol ethers were coupled successfully with *p*-tolyl chloride.

2.3.2 The Combination of Palladacycles and Secondary Phosphines[14]

These results encouraged us to investigate this system further, also in the hope to find catalysts with better handling properties than the rather sensitive secondary phosphines. As already mentioned, palladacycles are versatile catalyst precursors for a number of coupling reactions and they are stable, easily accessible palladium species. We therefore tested combinations of various palladacycles and secondary phosphines and found that both the *in situ* prepared as well as the isolated complexes gave high yields for several Pd-catalyzed reactions using aryl chlorides.

In a first phase,[14a] we screened *in situ* prepared combinations of 5 different palladacycles with 6 secondary phosphines using the Suzuki coupling as test reaction (see Figure 6). In order to carry out this screening effectively, a standard procedure was developed to run the test reactions in parallel on a Chemspeed robot. We identified a number of very active catalysts and the most effective complexes were isolated and shown to be stable and easy to handle. Selected results for the Suzuki and Heck coupling, for the Buchwald–Hartwig amination and for the ketone arylation are listed in Table 3. The complex SK-CC01-A, incorporating a bis(2-norbornyl)phosphine moiety, proved to be the most versatile catalyst for C–C coupling reactions with aryl chlorides and as a result it was commercialized.[5]

Even though the new catalysts were well suited for many Buchwald–Hartwig aminations, the results with

Table 3. Selected results for various isolated palladacycles (structures, see Figure 6; GLC yields after 15–20 h).

Phosphine (catalyst conc.)	Suzuki (1%)	Heck (1%)	Heck (0.25%)	Amination[a] (0.5%)	Amination[b] (2%)	Arylation (0. 5%)
$HPNor_2$	95	100	48	100	100	100
$HP(t\text{-}Bu)_2$	45	100	46	94	100	60
$HPCy_2$	91	100	89	98	82	69
PCy_3	99	95	42	66	38	99

[a] Substrate *N*-methylaniline.
[b] Substrate morpholine.

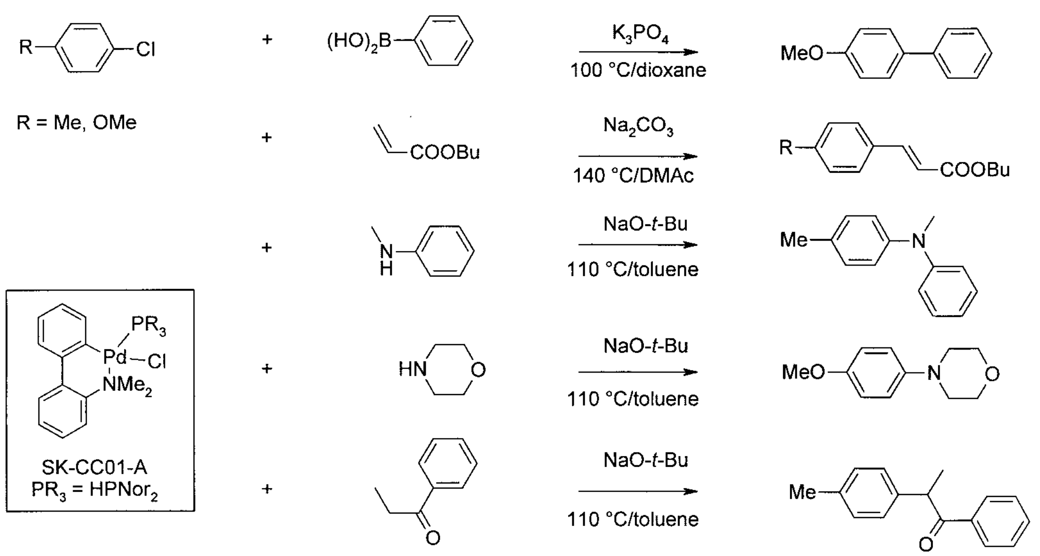


Figure 6. Structures of substrates and best palladacycle, and reaction conditions used for catalyst testing.

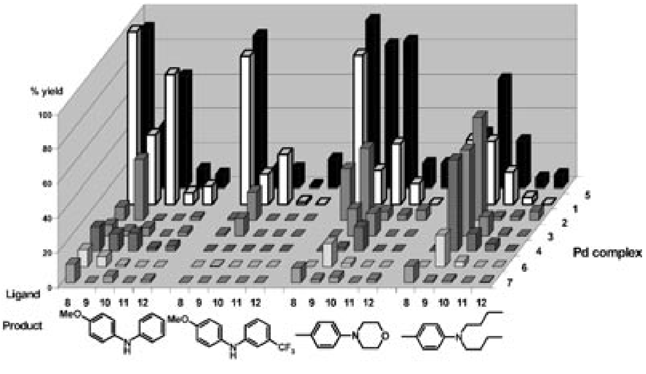


Figure 7. Parallel screening results for the Buchwald–Hartwig amination using combinations of 7 different palladacycles and 5 phosphines (for details see Ref.[14b]).

some more difficult C–N couplings were not always satisfactory. Especially alkylamines and bulky substrate combinations gave some problems. In a second phase of this project,[14b] we searched for a more active catalyst for this important class of transformations. We chose the same strategy as described above and screened further palladacycles and also some additional secondary phosphines. The results of this high throughput screening are depicted in Figure 7. We found that several ferrocene-based palladacycle again combined with bulky secondary phosphines gave very active catalysts. Finally, we chose dimethylaminomethylferrocene in combination with bis(2-norbornyl)phosphine (SK-CC02A) for commercialization.[5] SK-CC02A gives very good yields for a variety amination reactions as depicted in Figure 8.

2.4 Carbonylation of Aryl and Heteroaryl Halides

While carbonylation reactions are used for the production of a variety of large scale chemicals, applications of gaseous carbon monoxide, not only a detonable gas but also highly toxic, are less common in the fine chemicals industry. Consequently, such transformations are usually developed by specialized groups, either inside a company or by a CRO such as Solvias.

2.4.1 Synthesis of Primary Aromatic Amides[26]

The Pd-catalyzed aminocarbonylation is an important method for the selective and direct synthesis of aromatic amides starting from aryl halides. While reactions of primary and secondary amines to the corresponding amides work well, no convenient catalytic method for

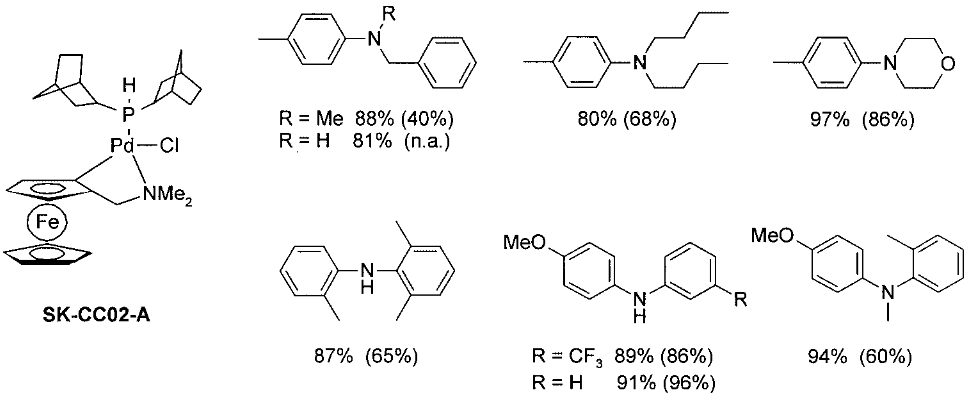


Figure 8. Structure of SK-CC02A and yields for a variety of substituted anilines using 0.5 mol % catalyst at 110 °C, 2 h (in parenthesis yields for SK-CC01A).[14b]

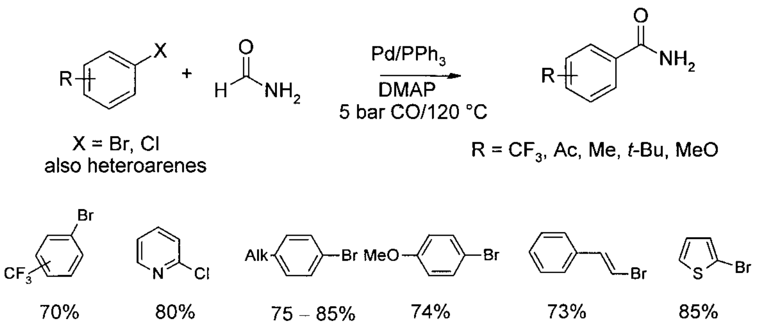


Figure 9. Aminocarbonylation using formamide as amine source; yields with selected substrates.

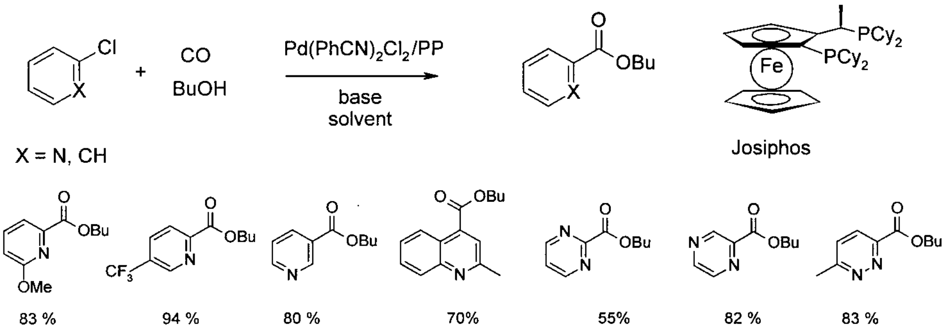


Figure 10. Alkoxycarbonylation of 2-chloropyridine and chlorobenzene; yields of selected products.

the synthesis of primary amides existed. Starting from a chance observation that amide solvents can react with arylpalladium species, an efficient procedure for the preparation of primary aromatic amides using formamide as the amine source was developed (see Figure 9).

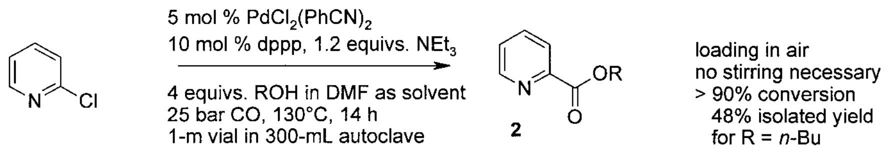
The reactions require a palladium catalyst in combination with a nucleophilic Lewis base which acts as an acylating catalyst such as imidazole or 4-dimethylaminopyridine (DMAP). Aryl, heteroaryl and vinyl bromides and chlorides were converted to the primary amides under mild conditions (5 bar, 120 °C) using 1 mol % of a palladium phosphine complex. Best results were obtained in dioxane using triphenylphosphine as the ligand and DMAP as the base. For activated aryl bromides, a phosphine to palladium ratio of 2 was sufficient, but less reactive aryl bromides or aryl chlorides required ligand to palladium ratios up to 8 in order to stabilize the catalyst and achieve full conversion. The new protocol also allows the efficient preparation of methylamides and dimethylamides with the corresponding amides as amine sources.

2.4.2 Alkoxycarbonylation of (Hetero) Aryl Chlorides[15]

In a joint project with the Beller group at Rostock, we also investigated the alkoxycarbonylation of aryl chloride. For these studies 2-chloropyridine and chlorobenzene were chosen as model substrates (see Figure 10) and the effect of solvent, base, ligand and reaction conditions was studied systematically. In both reactions, the use of chelating diphosphines turned out to be crucial, probably because the strongly coordinating CO replaces monodentate ligands. For the more activated 2-chloropyridines[15a] the optimal ligand turned out to be dppb (bis-diphenylphosphinobutane) which gives good results for a variety of pyridines and analogues thereof. By optimizing CO pressure and ligand concentration, TONs up to 13,000 and TOFs > 900 h^{-1} were achieved. For chlorobenzene which is more difficult to activate the more basic and bulky Josiphos-type ligands had to be used at pressures < 3 bar CO resulting in TONs up to 1360 and TOFs > 100 h^{-1}.[15b] An interesting temperature effect was observed: At 130 °C a strong influence of CO pressure was observed, whereas at 145 °C the phosphine/Pd ratio was dominant. Somewhat unexpectedly, the catalysts did not work well when alcohols other than *n*-butanol were used.[15c]

2.4.3 Synthesis of Small Libraries via Parallel Carbonylation[12]

Due to the versatility and high functional group tolerance of most Pd catalysts, there is growing interest to apply such reactions in parallel synthesis for combinatorial chemistry and to synthesize compound libraries. Carbonylation with CO in the presence of various nucleophiles is of appeal due to the usefulness of the products and the high atom economy of the method. A drawback is that stirred autoclaves have to be used to work with CO at elevated pressure, thereby rendering parallel synthesis cumbersome and expensive. We have developed a simple reaction set-up allowing the parallel carbonylation of aryl halides with 6–25 bar CO in 1-mL vials in a standard autoclave. 4-Bromoacetophenone and 2-chloropyridine (see Figure 11) were used as model substrates with 102 different O nucleophiles (primary and secondary alcohols, phenols). No inertization during



loading in air
no stirring necessary
> 90% conversion
48% isolated yield
for R = *n*-Bu

Figure 11. Parallel carbonylation of 2-chloropyridine.

Table 4. Analysis of the results obtained in the parallel carbonylation of 2-chloropyridine.

Nucleophile	Primary alcohols	Secondary alcohols	Phenols	Total
No. of experiments	59	31	12	102
Products isolated	30	12	7	49
Purity ($>98/>90>70\%$)	17/5/8	7/1/4	7/0/0	31/6/13
Average yield (%)	30	12	14	23

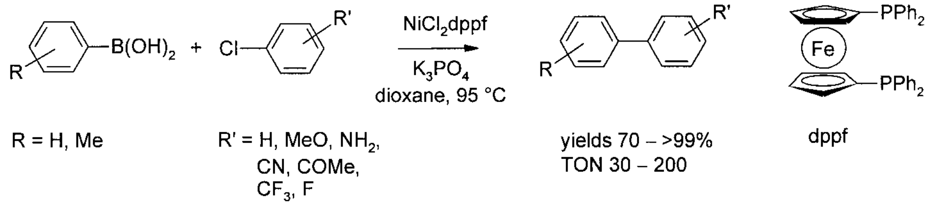


Figure 12. Ni-catalyzed Suzuki reaction: Reaction conditions and ligand structure.

the loading was necessary. 50 Esters were isolated and characterized; for a statistical summary see Table 4. Ether, ester, ketone and sometimes even olefin functions were usually tolerated. The protocol is suitable for screening and small scale products synthesis.

2.5 Replacing Pd by Ni Catalysts

There are two reasons for trying to replace palladium by nickel (or other metals). From an industrial perspective the first is of course the lower cost of Ni complexes, the second is the different reactivity profile of Ni compared to Pd. Unfortunately, the latter point usually does not work in favor of Ni since Pd is the much more versatile catalytic metal. However, there are instances where Ni catalysts activate aryl–chloro bonds better than Pd.[27] Before describing two cases in a bit more detail, we would like to mention two significant contributions in this area. The group of Fort[28] developed Ni-carbene complexes for the amination of aryl chlorides and Buchwald[29] successfully applied Cu complexes as catalysts for the amination and amidation of aryl chlorides under relatively mild conditions.

2.5.1 Suzuki Reaction[11]

After a systematic screening of mono- and diphosphine ligands, solvents and various bases, a NiCl$_2$dppf complex was found to be the best catalyst giving good to very high yields for a variety of substituted coupling partners (see Figure 12). Catalyst loadings as low as 0.5% were possible for activated aryl chlorides, for less reactive coupling partners 3–10% were necessary at a reaction time of 16 hours. In contrast to other Ni catalysts, the presence of a reducing agent was not required to achieve good results.

2.5.2 Negishi Reaction and Grignard Coupling[4a,30]

A similar approach was chosen by the DSM team for the coupling of ArZnCl (Negishi) and ArMgCl (Grignard) reagents. In analogy to our results, several ArZnCl species could be coupled with aryl chlorides carrying a wide variety of functional groups (CN, COOR, NH$_2$) in good to excellent yields with NiCl$_2$(PPh$_3$)$_2$ as preferred catalyst.[30a] The industrial usefulness is somewhat limited since relatively low TONs (20–50) and TOFs (1–5 h^{-1}) are observed and up to 20 mol % PPh$_3$ must be added to the reaction mixture. A variant with only sub-stoichiometric amounts of Zn was also developed[30b] and actually applied to produce up to 70 tons of sartan intermediates.[31] Similar yields of biaryls were obtained by coupling ArMgCl species directly with aryl chlorides, albeit with a relatively complex mixture of catalysts and promoters. Best results are achieved with 4–6% Ni(acac)$_2$, 8–13% P(O-*i*-Pr)$_3$, 4–6% water and 8–10% of a reducing agent such as MeMgCl or vitride.

2.6 Optimized Protocol for the Pd-Catalyzed Synthesis of Aryl Malononitriles[32]

Whereas alkylmalononitriles are easily accessible by alkylation with alkyl halides, arylation requires catalysts and, up to now, no generally applicable protocol existed for this transformation.[33] In the course of the process development for a new herbicide, we became interested in this reaction and investigated the effect of reaction parameters such as ligand type, solvent, base as well as reaction conditions. In the course of this work, a protocol was developed which is applicable for the synthesis of a large variety of arylmalononitriles (see Figure 13). It was also shown that the process is scalable (>100 kg per batch) and can be carried out in multi purpose equipment.

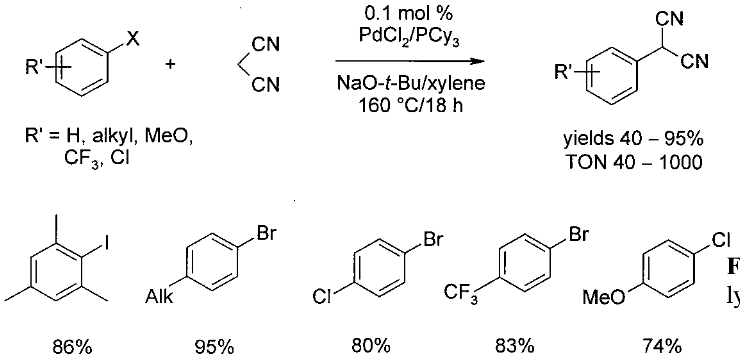


Figure 13. Pd-catalyzed synthesis of arylmalononitriles and yields for selected substrates.

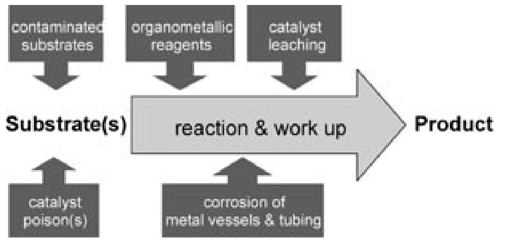


Figure 14. Typical contamination problems: metals and catalyst poisons.

2.7 Catalyst Separation and Removal of Trace Metals

In homogeneous catalysis, separation of the catalyst from the product solution is always a major issue and there is no easy general solution. Especially for Pd and Ni complexes with predominantly monodentate ligands the problem is often complicated by ligand dissociation making ligand immobilization strategies unpractical. Nevertheless, we have made the experience that catalyst separation is very seldom the reason for not implementing a catalytic process. Adsorption of Pd on active carbon or celite is often the method of choice, especially for the removal of un-ligated Pd, sometimes used in combination with distillation or crystallization. Another successful method is complexation of the Pd with cyanide or S-containing ligands in a two-phase mixture and extraction of the product.[34]

However, metal from catalysts is not the only source of contamination as depicted in Figure 14. In pharma, the tolerated metal content is quite low; for the sum of heavy metals it varies between <10 and 20 ppm and for some specific metals such as Cr (<1 ppm) or Ni (<2 ppm) it is extremely low. In order to solve the problem of trace metals, Solvias has developed a two-pronged approach. For early phases of development when relatively low quantities of material are involved (kg to hundreds of kg), adsorption is a quick and viable solution. For this purpose we have developed a number of custom-designed high surface materials. With this adsorber collection, Solvias has been able to solve the problem of trace metal contamination with a success rate of $>90\%$ and some examples are listed in Table 5. However, for the application in (larger scale) manufacturing, the catalytic process should be redesigned to either find a catalyst which does not leach metal (for heterogeneous catalysts) or where the catalyst separation is solved by a better scalable method.

3 Design and Implementation of Catalytic Processes

3.1 Strategies

Obviously, the ultimate goal of all industrial R&D either internally in product-oriented companies or as an external service in a CMO or CRO is the implementation of catalytic processes for the manufacture of products. At the start of a process development, a strategy must be chosen that promises the best answer in the shortest time. This strategy will depend on a number of considerations: The goal of the development, the know-how of the investigators, the time-frame, the available manpower and equipment, and so on. In process development, there is usually a hierarchy of goals (or criteria) to be met. It is not possible to reach all the prerequisites for a technically useful process in one step. For the catalytic step, the catalyst selectivity (combined of course with an acceptable activity) is the first criterion – just as in academic research. But when a reasonable selectivity has been obtained, other criteria will become important: catalyst activity, productivity and stability, availability of catalyst and ligand, catalyst separation (and maybe recycling). Then, questions like, e.g., the effect of sub-

Table 5. Selected results for removal of metals from reaction solutions.

Metal	g Adsorber/kg product	ppm Metal before and after treatment		Solvent
Pd	25	32	4	ethyl acetate
Pt	500	80	<5	xylene
Ni	125	115	0.8	alcohol
Rh	100	144	<5	alcohol
Cr	500	11	<1	alcohol

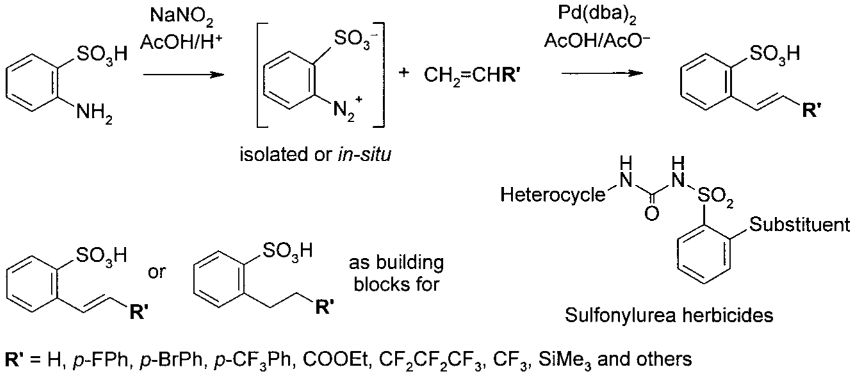


Figure 15. Building blocks for sulfonylurea herbicides *via* the Matsuda–Heck reaction.

strate quality and last but not least the cost of the catalyst and other materials have to be addressed. The final process is a compromise since usually not all of these requirements can be fulfilled maximally. It is not possible to proceed in a linear fashion, i.e., very often one has to go back to an earlier phase and sometimes additional questions turn up that have to be answered before it is possible to go on.

It is useful to divide the development of a manufacturing process into different phases:

Phase 1: Outlining and assessing possible synthetic routes on paper. Here the decision is made whether to use a catalytic step.

Phase 2: Demonstrating the chemical feasibility of the key step, usually the catalytic reaction. The result is often a bench-scale process.

Phase 3: Optimizing and scale-up of the process. The result is either a pilot process or directly the manufacturing process.

Even though catalysis can open up new and often shorter syntheses, synthetic routes incorporating catalytic steps are usually not the first to be considered since their development is undeniably more complex. As a rule, more efficient processes (so-called second generation processes) are often developed when the production volumes increase strongly and/or when the product patents expire and the cost for the generic pharmaceutical or agrochemical becomes more important. Besides the cases described below, we have worked on many further projects where catalytic methods have allowed significant improvement of both economy and ecology of existing processes. Unfortunately much of this information is proprietary and cannot be published (at least yet).

3.1.1 *Building Block for a New Herbicide via the Matsuda–Heck Reaction*[7]

This case history is somewhat special since catalysis was not only used for production purposes but already as a tool during product discovery. At the same time as the just published Pd-catalyzed reaction of olefins with aryldiazonium salts[19] (a variant of the Heck[18] reaction) was investigated at the Central Research Laboratories of Ciba-Geigy, its Agro Research Department was interested in new sulfonylurea herbicides (see Figure 15). When the involved chemists realized that a variety of *o*-substituted benzenesulfonic acids would be accessible *via* this methodology, about 30 different derivatives were prepared. These as well as the corresponding hydrogenated analogues were then used to synthesize a series of candidates. It turned out that many of the new derivatives were very active herbicides and that the trifluoropropyl derivative shown in Figure 16 had the best properties. The new compound was finally commercialized under the name Prosulfurone (Fig. 16).

As usual when developing a production process for important products, several other synthetic routes were considered and evaluated. However, despite some sizeable efforts to find alternative syntheses for the trifluoropropanesulfonic acid, none could be found with reasonable yields – a rare case in fine chemicals production. Process development started with a three-step laboratory process with isolated intermediates as depicted in Figure 15. After a considerable effort, we succeeded to develop a one-pot procedure as the final production process (see Figure 16). An important issue was the choice of a suitable solvent which had to meet three prerequisites: i) to be compatible with three different chemical reactions, ii) to have good solvating properties for the olefin to avoid the olefin from being stripped of the reaction medium by the evolving nitrogen and iii) to be non-toxic and easy to regenerate. Pentan-1-ol showed the above properties to a high degree despite the fact that Matsuda stated alcohols to be unsuitable solvents. The Matsuda–Heck reaction is carried out with Pd(dba)$_2$ (dba = dibenzylidene acetone) as the optimal catalyst precursor and the subsequent hydrogenation is accomplished in the same reactor with a Pd/C catalyst prepared *in situ* by adding active carbon to the reaction mixture. After filtration, the Pd is recovered by traditional work-up and the Pd(dba)$_2$ complex is pre-

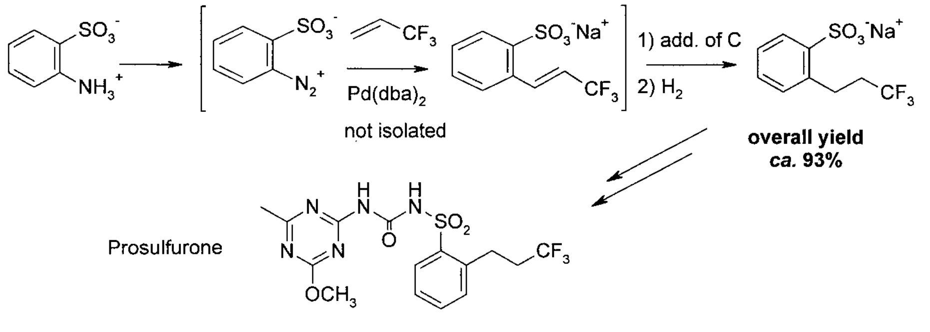


Figure 16. Industrial synthesis of a Prosulfurone intermediate.

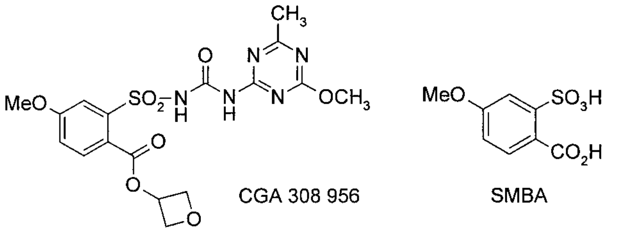


Figure 17. Structures and abbreviations of target compounds.

pared again; Pd losses over the whole cycle are *ca.* 5%. The overall yield of the trifluoropropanesulfonic acid intermediate is around 93% and due to the dual use of the Pd metal the process is competitive, even though the catalyst activity and productivity for the coupling step are relatively low.

3.1.2 2-Sulfo-4-methoxybenzoic Acid via Carbonylation of a Diazonium Compound[10]

2-Sulfo-4-methoxybenzoic acid (SMBA) is a key intermediate in the synthesis of CGA 308 956, a development herbicide of the former Ciba-Geigy AG (see Figure 17). Since the compound was not available commercially and this specific substitution pattern is not easily accessible by classical synthetic methods, a new and efficient synthesis had to be developed. The first kilograms for field trials and toxicological tests were prepared from 2,2′-disulfo-4,4′-dinitrostilbene, a dyestuff intermediate readily available within Ciba-Geigy. SMBA was obtained in the four-step synthesis depicted in Figure 18 *via* oxidation of the C=C bond and substitution of the nitro group in a non-optimized overall yield of *ca.* 25%. However, it was obvious from the start that with an atom efficiency of 4.8% this could not be a large-scale technical synthesis.

A laboratory process was developed for the preparation of 2-sulfo-4-methoxybenzoic acid (SMBA) *via* diazotization of 2-amino-4-methoxybenzenesulfonic acid followed by Pd-catalyzed carbonylation in presence of water. The most important process parameters were catalyst precursor and water content. Both a two-step procedure using isolated diazonium compound as well as a one-pot reaction proved to be feasible. A yield of > 95% SMBA was obtained after 3–4 h, using 1 mol % $PdCl_2$ at 8 bar and 60 °C. The catalyst was removed *via* adsorption on carbon in the presence of hydrogen followed by filtration. At the time, this was the first technically feasible catalytic carbonylation of an arenediazonium compound, a reaction originally developed by Matsuda and coworkers[35].

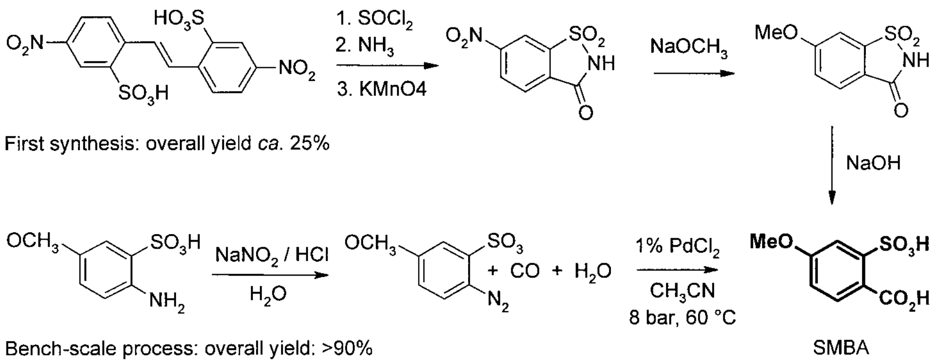


Figure 18. Kilogram-scale synthesis starting from dyestuff intermediate (upper part) and bench-scale process for the production of SMBA (lower part).

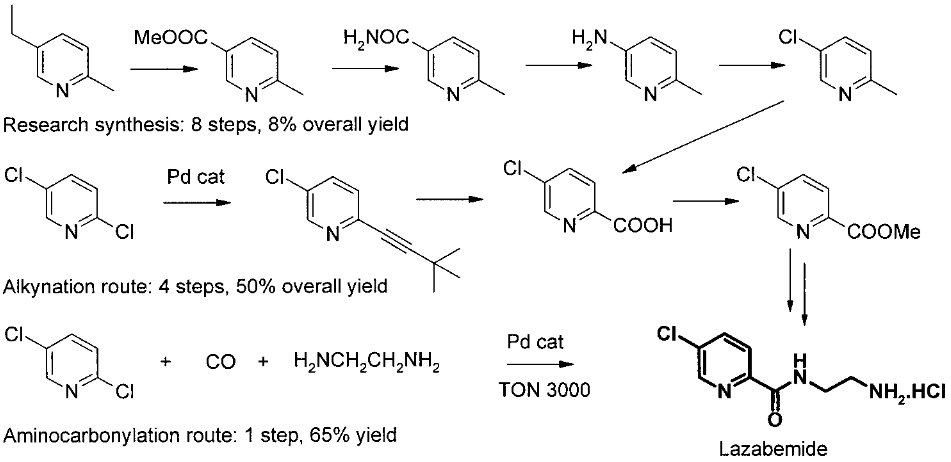


Figure 19. Synthetic routes to Lazabemide.

3.1.3 *Lazabemide Intermediate via Aminocarbonylation*[36]

Another striking example for the power of Pd catalysis to prepare aromatic compounds with specific substitution patterns is Lazabemide, a 5-chloropyridine-2-carboxamide derivative, first prepared *via* a rather complicated 8-step synthesis (see Figure 19). A first improvement was a Pd-catalyzed Sonogashira alkynation, but the final production process is a direct one-step aminocarbonylation starting from 2,5-dichloropyridine. The reaction is carried out under 10 bar of CO at 130 °C in the presence of a Pd-phosphine complex,[36b] and the Pd is removed by treatment with an aqueous NaCN solution.

3.2 Industrial Applications of C–C and C–N Coupling Reactions

For usually good reasons, industry is very reluctant to publish and it is quite difficult to get reliable information concerning manufacturing processes. Most useful are case studies which often allow some insight into the motivation of the work, the chosen strategy as well as of the major problems encountered. In this context it is useful to distinguish three stages of development:

- *Production processes*, which are operated on a more or less continuous basis, i.e., all relevant problems concerning catalyst performance and separation, supply of materials, product isolation and purification, noble metal recovery etc. have been solved.
- *Pilot processes*, where the catalyst performance has been optimized for commercial production and most technical and logistics problems have been solved; depending on the field of application, pilot batches range from 10 to >100 kg.
- *Bench-scale processes*, where the catalyst performance has been optimized to various degrees and the first kilograms of product have been produced, e.g., for toxicological studies or field tests.

In the Supporting Information we have collected information on 18 C–C and C–N coupling processes where we give (if available) information on the following aspects: catalyst (metal precursor, ligand), nature of solvent and base, reaction temperature, TON and TOF. Additional short texts describe the name of the company, the nature of the developed process and give some indication how the catalyst was separated from the reaction mixture.

From this (undoubtedly incomplete) list of industrial processes we can draw a few conclusions which also serve to sum up our own experience:

- Most established production processes have been developed for relatively simple molecules with few additional functional groups present. Here, TONs in the range of 2,000–10,000 are usually required to make the process commercially viable due to the relatively low added value of the intermediates.
- Many of the recently published pilot and bench-scale processes are for more complex molecules, leading to more expensive products. In these cases, higher catalyst costs are acceptable (0.5–1 mol % Pd is standard) but the catalysts should tolerate other functional groups and should work under milder conditions.
- There are now several catalyst types available which activate aryl chlorides under relatively mild conditions but especially for the more complex pharma intermediates bromide is still the leaving group of choice.
- While the production processes are predominantly carbonylation (3) and Heck reactions (4), the more recently developed pilot and bench-scale processes involve above all Suzuki (3) and Heck (3) reactions

but only 1 carbonylation. To our knowledge, there is detailed information on only one C–N coupling reaction but there is every indication that this versatile reaction will be applied more frequently soon. Indeed, Bayer Chemicals AG has recently developed the Buchwald technology to technical maturity but little detailed information is available yet.[37] Besides these reaction types, Grignard (1) and Sonogashira (1) couplings were also applied.

- Catalyst separation is an important issue for most Pd-catalyzed reactions. Adsorption of Pd on active carbon or celite is the method applied most often, sometimes in combination with distillation or crystallization. Another successful method is complexation of the Pd with cyanide or S-containing ligands in a two-phase mixture and extraction of the product.
- As a general conclusion one can state that the considerable R&D carried out both in industrial and academic laboratories has paid off quite nicely and that Pd (and also Ni and Cu) catalyzed C–C and C–N coupling reactions are well behaved and scalable methodologies for the manufacture of complex molecules.

Acknowledgements

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References and Notes

[1] For a broad overview, see: a) B. Cornils, W. A. Herrmann (Eds.), *Applied Homogeneous Catalysis by Organometallic Complexes*, 2nd edn., Wiley-VCH, Weinheim, **2002**; b) J. G. de Vries, *Homogeneous catalysis for fine chemicals.* In: *Encyclopedia of Catalysis*, (Ed.: I. T. Horvath), Wiley, New York, **2003**, Vol. 3, p. 295.

[2] a) J. Tsuji, *Palladium Reagents and Catalysts*, John Wiley and Sons Ltd., Chichester, **1995**; b) A. de Meijere, F. Diederich, (Eds.), *Metal-Catalyzed Cross-Coupling Reactions,* Wiley-VCH, Weinheim, **2004**; c) G. Stark, T. H. Riermeier, M. Beller, in: *Transition Metals for Organic Synthesis*, (Eds.: M. Beller, C. Bolm), Vol. 1, Wiley-VCH, Weinheim, **1998**, p. 208; d) B. H. Young, S. L. Buchwald, *J. Organomet. Chem.* **1999**, *576*, 125.

[3] A. Zapf, M. Beller, *Topics in Catalysis* **2002**, *19*, 101.

[4] a) C. E. Tucker, J. G. de Vries, *Topics in Catalysis* **2002**, *19*, 111; b) J. G. de Vries, *Can. J. Chem.* **2001**, *79*, 1086.

[5] www.solvias.com.

[6] D. Reinehr, *Pure Appl. Chem.* **1980**, *52*, 3417.

[7] a) P. Baumeister, W. Meyer, K. Oertle, G. Seifert, U. Siegrist, H. Steiner, *Chimia* **1997**, *51*, 144; b) P. Baumeister, W. Meyer, K. Oertle, G. Seifert, U. Siegrist, H. Steiner, *Stud. Surf. Sci. Catal.* **1997**, *108*, 37.

[8] a) A. Spencer, *J. Organomet. Chem.* **1983**, *258*, 101; b) A. Spencer, *J. Organomet. Chem.* **1983**, *258*, 101.

[9] a) H.-U. Blaser, A. Spencer, *J. Organomet. Chem.* **1982**, *233*, 267; b) A. Spencer, *J. Organomet. Chem.* **1983**, *247*, 117; c) A. Spencer, *J. Organomet. Chem.* **1982**, *240*, 209; d) A. Spencer, *J. Organomet. Chem.* **1984**, *265*, 323.

[10] U. Siegrist, T. Rapold, H.-U. Blaser, *Org. Process Res. Dev.* **2003**, *7*, 429.

[11] A. F. Indolese, *Tetrahedron Lett.* **1997**, *38*, 3513.

[12] H.-U. Blaser, M. Diggelmann, F. Naud, E. Scheppach, A. Schnyder, M. Studer, *J. Org. Chem.* **2003**, *68*, 3725.

[13] A. Schnyder, T. Aemmer, A. F. Indolese, U. Pittelkow, M. Studer, *Adv. Synth. Catal.* **2002**, *344*, 495.

[14] a) A. Schnyder, A. F. Indolese, M. Studer, H.-U. Blaser, *Angew. Chem. Int. Ed.* **2002**, *41*, 3668; b) U. Nettekoven, F. Naud, A. Schnyder, H.-U. Blaser, *Synlett* accepted for publication.

[15] a) M. Beller, W. Mägerlein, A. F. Indolese, C. Fischer, *Synthesis* **2001**, 1098; b) W. Mägerlein, A. Indolese, M. Beller, *Angew. Chem. Int. Ed.* **2001**, *40*, 2856; W. Mägerlein, A. F. Indolese, M. Beller, *J. Organomet. Chem.* **2002**, *641*, 30; c) A. Schnyder, Solvias AG, unpublished results.

[16] W. A. Herrmann, C. Brossmer, K. Öfele, C.-P. Reisinger, T. Priermeier, M. Beller, H. Fischer, *Angew. Chem. Int. Ed.* **1995**, *34*, 1844.

[17] A. H. M. de Vries, J. M. C. A. Mulders, J. H. M. Mommers, H. J. W. Henderickx, J. G. de Vries, *Org. Lett.* **2003**, *5*, 3285.

[18] For a historical overview see R. F. Heck, *Palladium Reagents in Organic Synthesis*, Academic Press, New York, **1985**.

[19] K. Kikukawa, T. Matsuda, *Chem. Lett.* **1977**, 159; K. Kikukawa, K. Nagira, F. Wada, T. Matsuda, *Tetrahedron* **1981**, *37,* 31.

[20] a) L. J. Gooßen, J. Paetzold, *Angew. Chem. Int. Ed.* **2002**, *41*, 1237; b) L. J. Gooßen, J. Paetzold, L. Winkel, *Synlett* **2002**, *10*, 1721; c) a) L. J. Gooßen, J. Paetzold, *Angew. Chem. Int. Ed.* **2004**, *43*, 1095.

[21] Y. Ben-David, M. Portnoy, M. Gozin, D. Milstein, *Organometallics* **1992**, *11*, 1995.

[22] General review: A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4176.

[23] Suzuki coupling: N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2475; G. Y. Li, G. Zheng, A. F. Noonan, *J. Org. Chem.* **2001**, *66*, 8677 and references cited therein; N. Miyaura, in: *Advances in Metal-Organic Chemistry*, (Ed.: L. S. Liebeskind), JAI Press, London, **1998**, Vol. 6, p. 187.

[24] Buchwald–Hartwig amination: J. P. Wolfe, H. Tomori, J. P. Sadighi, J. Yin, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 1158; J. P. Stambuli, R. Kuwano, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2002**, *41*, 4746.

[25] Heck reaction: N. J. Whitcombe, K. K. Hii, S. E. Gibson, *Tetrahedron* **2001**, *57*, 7449; I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009; R. Stürmer, *Angew. Chem. Int. Ed.* **1999**, *38*, 3307.

[26] A Schnyder, M. Beller, G. Mehltretter, T. Nsenda, M. Studer, A. F. Indolese, *J. Org. Chem.* **2001**, *66*, 4311.

[27] E. Negishi, F. Liu, in: *Metal-Catalyzed Cross-Coupling Reactions,* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH Verlag, Weinheim, **1998**, p. 1.

[28] B. Gradel, E. Brenner, R. Schneider, Y. Fort, *Tetrahedron Lett.* **2001**, *42*, 5689; C. Desmarets, R. Schneider, Y. Fort, *J. Org. Chem*. **2002**, *67*, 3029.

[29] F. Y. Kwong, S. L. Buchwald, *Org. Lett.* **2003**, *5*, 793; A. Klapars, X. Huang; S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 7421.

[30] a) J. A. Miller, R. P Farrell, *Tetrahedron Lett.* **1998**, *39*, 6441; b) J. A. Miller, R. P. Farrell, *Tetrahedron Lett.* **1998**, *39*, 7275.

[31] J. G. de Vries, DSM, personal communication.

[32] A. Schnyder, A. F. Indolese, Solvias AG, unpublished results.

[33] For leading references, see: M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, *121*, 1473; J. M. Foc, X. Huang, A. Chieffi, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 1360 and references cited therein.

[34] V. W. Rosso, D. A. Lust, P. J. Bernot, J. A. Grosso, S. P. Modi, A. Rusowicz, T. C. Sedergran, J. H. Simpson, S. K. Srivasta, M. J. Humora, N. G. Anderson, *Org. Proc. Res. Devel.* **1997**, *1*, 311.

[35] K. Kikukawa, K. Kono, K. Nagira, F. Wada, T. Matsuda, *Tetrahedron Lett.* **1980**, *21*, 2877; K. Kikukawa, K. Nagira, F. Wada, T. Matsuda *J. Org. Chem*. **1980**, *45*, 2365; K. Kikukawa, K. Kono, K. Nagira, F. Wada, T. Matsuda, *J. Org. Chem*. **1981**, *46*, 4413.

[36] a) R. Schmid, Roche, *Chimia* **1996**, *50*, 110; b) M. Scalone, P. Vogt, *European Patent* 385,210, **1990** (to F. Hoffmann-La Roche).

[37] W. Mägerlein, U. Scholz, *Book of Abstracts, ISHC-14*, Munich, **2004**, p. 55.