Supported palladium catalysts for fine chemicals synthesis

Hans-Ulrich Blaser*, Adriano Indolese, Anita Schnyder, Heinz Steiner, Martin Studer

Solvias AG, P.O. Box, CH-4002 Basel, Switzerland

Abstract

The contribution reviews the application of heterogeneous Pd catalysts for the manufacture of fine chemicals with special emphasis of their organic synthetic potential. In a first part, some background is given on the scope and limitations of homogeneous and heterogeneous catalysis and on significant parameters and the various types of supported Pd catalysts. Then, the application of supported Pd catalysts for important classes of transformations are reviewed organized according to reaction type. The general statements are illustrated with relevant examples from the literature and from our own laboratories. Hydrogenation, hydrogenolysis, and dehydrogenation reactions are considered to be mature technologies with an extremely broad scope both for small-scale laboratory applications and large to very large-scale manufacturing processes. Oxidation reactions and C–C coupling reactions usually have a rather narrow scope and only relatively few have been developed to the technical stage. Especially for C–C coupling reactions, the nature of the active Pd species is under debate because it is not clear whether the reaction takes place on the metallic surface or whether leached soluble Pd complexes are the active catalysts. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Supported palladium catalysts; Fine chemicals manufacture; Hydrogenation; C–C coupling

1. Introduction

Without any doubt, there is an increasing tendency to apply catalytic methods for the synthesis and production of multifunctional, complex fine, and specialty chemicals such as agrochemicals and pharmaceuticals. On the one hand, the catalysts used are homogeneous metal complexes with organic ligands ([1] emphasis on industrial applications; [2] up-to-date monograph) and on the other hand heterogeneous catalysts, either in the metallic state or as oxides [3]. From an industrial point of view, catalysts not soluble in the same phase as the organic reactant have the inherent advantage of easy separation and very often also of better handling properties, but homogeneous catalysts are

better defined and understood (for a short comparison see Table 1).

In the field of fine chemicals, palladium is arguably the most versatile and the most widely applied catalytic metal. However, with the exception of hydrogenation/dehydrogenation where many commercial processes with Pd catalysts are in operation, most reactions described in the open as well the patent literature are carried out with homogeneous Pd catalysts, either with or without organic ligands. This is best illustrated by the fact that several books have been devoted exclusively to the application of homogeneous Pd catalysts to organic synthesis, the most recent one by Tsuji in 1996 [4]. [1] Homogeneous Pd catalysts have several important advantages: (i) many different metal precursors are known and available;

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* Corresponding author. Tel.: +41-61-686-6155.
E-mail address: hans-ulrich.blaser@solvias.com (H.-U. Blaser).

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[1] With references to earlier books.

Table 1
Strong and weak points of homogeneous and heterogeneous catalysts

	Homogeneous	Heterogeneous
Strong points	Defined on molecular level (close to organic chemistry)	Separation, recovery, recycling
	Scope, variability (design?)	Stability, handling
	Preparation	Many (hydrogenation) catalysts commercially available
Weak points	Sensitivity (handling, stability)	Characterization (understanding on molecular level)
	Activity, productivity (of many literature procedures)	Preparation (needs special know-how), reproducibility
	Separation	Diffusion to and within catalyst

(ii) Pd forms complexes with a wide variety of organic ligands with P, N, and O atoms; (iii) many of these complexes are relatively easy to prepare and to handle; (iv) many Pd-catalyzed reactions give reliable results and are easy to run in ordinary equipment; (v) the functional group tolerance is often very good. The list of synthetically useful transformations is now truly impressive and explains why Pd catalysis has found its place into the repertoire of so many organic chemists.

The literature for the application of heterogeneous Pd catalysts in fine chemical synthesis is much less broad, and until a decade ago was restricted to hydrogenation and dehydrogenation reactions [5–7]. This situation is changing slowly and in the last few years the application of supported metallic palladium for C–C bond-forming transformations has increased significantly. However, it must be pointed out that the heterogeneous examples listed in Table 2 in many cases have only been carried out with model substrates and under non-optimized conditions.

2. Catalysts

2.1. Catalyst types

As a rule, heterogeneous catalysts are still chosen on an empirical basis by trial and error, and it is rarely understood why a given catalyst is superior to another one. Many factors influence the catalytic properties of such catalysts, and it is important to realize that even today it is not possible to adequately characterize a heterogeneous catalyst on a molecular level (also see the contributions by M.V. Twigg and B. Coq).

Of the many parameters affecting the catalytic performance of a heterogeneous Pd catalyst, the following

Table 2
Useful transformations for fine chemical synthesis catalyzed by homogeneous and heterogeneous Pd catalysts[a]

Transformation	Homogeneous	Heterogeneous
Carbonylation of alkenes	3	4
Carbonylation of Ar–X	2	4
Carbonylation of dienes	2	–
Chemoselective hydrogenation of various functions	4	1
Cyanation of Ar–X	3	–
Debenzylation	–	1
Dimerization of dienes	2	–
Heck reaction (and variants thereof)	1	3
Hydrogenolysis of C–Hal bonds	–	1
Oxidation of alkenes (Wacker)	1	–
Oxidation of dienes	2	–
Reductions of various functions using hydrogen donors	4	2
Suzuki coupling reaction	1	3
Telomerization of dienes	2	–
Various C–C coupling reactions with R–X (R = allyl, aryl, benzyl, vinyl)	1	3

[a] 1: broad synthetic and/or industrial application; 2: broad synthetic application; 3: narrow synthetic application; 4: single examples.

are the most important ones [8]. *Type of catalyst*: Pd is usually supported on a carrier, sometimes Pd black is used as fine powder. *Metal loading*: the concentration of the metal is usually given in the description of the catalyst, e.g. 5 wt.% of palladium metal on an active carbon support is designated as 5% Pd/C (for the calculation, the dry weight of the catalysts is used). For most Pd catalysts, a 5% content is standard, however for special purposes higher loadings are used (e.g. the Pearlman catalyst often used for debenzylation reactions has a Pd content of 20%). *Type of support*: charcoal (also called active carbon) is most common. Charcoals can adsorb large amounts of water, and for safety reasons many Pd/C catalysts are sold with a water content of 50%. Aluminas and silicas as well as $CaCO_3$, $BaSO_4$ are also used for special applications.

Two commercial catalysts with the same designation (e.g. 5% Pd/C) can still differ significantly because of different carbon types or different preparation methods, leading to different catalyst parameters that sometimes correlate with the catalyst performance. Parameters for the active metal are the surface area, the dispersion (typically only 10–60% of the metal atoms are exposed), the size of the crystallites (typically in the range from 2 to >20 nm), the location in the pores of the support, and oxidation state (reduced or unreduced). Important support parameters are the particle size (for slurry catalysts typically 1–100 µm), the surface area (typically in the range of 100–1500 m^2/g), the pore structure (pore volume, pore size distribution), and acid–base properties.

2.2. Catalyst suppliers

The following manufacturers supply a full range of noble metal catalysts for technical applications (only European suppliers are listed): Degussa [9], Engelhard [10], Heraeus [11], and Johnson Matthey [12]. These catalyst suppliers also have a large know-how which catalyst type is most suitable for a given problem and our experience has shown that it is of advantage to find or optimize a heterogeneous catalysts in close collaboration with them. This is especially true for the development of technical processes, when catalyst users have little catalytic experience or when a difficult problem should be solved. Screening and development should always be carried out with specified

catalysts that can be supplied in technical quantities when needed. For laboratory use, Fluka and Aldrich Inorganics offer a wide variety of hydrogenation catalysts that are well suited for preparative purposes. With some exceptions, the catalyst manufacturer and the exact catalyst type are not specified.

The catalogue of Aldrich [13] lists the following Pd catalysts: 14 Pd/C, six Pd/Al$_2$O$_3$, two Pd/BaSO$_4$, Pd/CaCO$_3$, Pd/BaCO$_3$, Pd/SrCO$_3$, Pd/BaCO$_3$, two Pd black, Pd sponge, and Pd-Pb/CaCO$_3$ (Lindlar); the catalogue of Fluka [14] lists four Pd/C, two Pd/Al$_2$O$_3$, two Pd/BaSO$_4$, two Pd/CaCO$_3$, Pd/SrCO$_3$, and Pd black.

2.3. Modified palladium catalysts

Modified palladium catalysts are known since almost a century, but recently new modification procedures were developed. The following list is not exhaustive but illustrates the diversity of modification strategies.

- The earliest modification of a hydrogenation catalyst was carried out by Rosenmund who used sulfur compounds ("quinoline-S") as modifiers for the Pd-catalyzed conversion of acid chlorides to aldehydes [15]. The sulfur modifier prevents further reduction to the corresponding alcohol. The original Rosenmund reduction is carried out under reflux in order to remove the HCl which would poison the catalyst. A modified version using non-nucleophilic bases like 2,6-lutidine or ethyl-diisopropylamine was first described in the 1970s [16]. It was proposed that the base acts both as HCl scavenger as well as modifier for the palladium catalyst [17].
- Lindlar developed a Pb-modified Pd/CaCO$_3$ catalyst for the hydrogenation of C≡C bonds to double bonds [18]. The Lindlar catalyst is also the catalyst of choice for the selective hydrogenation of azide functions in presence of C=C bonds [19].
- Pd catalysts modified with ethylenediamine or other nitrogen bases were developed by Sajiki and coworkers [20,21] for selective debenzylation reactions.
- Pd catalyst modified with alkaloids for the enantioselective hydrogenation of the C=C bond of α,β-unsaturated acid derivatives and ketones [22] (see also the contribution by Tungler).

Table 3
Functional group tolerance of Pd catalysts for the hydrogenation of Ar–NO$_2$, Ar–C=O, and C=C groups[a]

Function to be reduced	Function to be retained													
	Ar–Hal[b]		C≡C		C=C[c]		C=O		C≡N		Y[d]–benzyl		Ar–NO$_2$[e]	
	Tolerance	Reference	Tolerance	Reference	Tolerance	Reference	Tolerance	Reference	Tolerance	Reference	Tolerance	Reference	Tolerance	Reference
Ar–NO$_2$	+[f,g]	[23]	+[f,g]	[23]	+[f,g]	[23]	+[f,g]	[23]	+[f,g]	[23]	+[f,g]	[23]		
	+	[6] (p. 520)	–	[5] (p. 109)	±	[6] (p. 519)	+	[6] (p. 528)	+	[6] (p. 531)	±	[7] (p. 200)		
	–	[6] (p. 520)				[7] (p. 193)		[7] (p. 194)		[7] (p. 198)				
Ar–C=O	±	[6] (p. 210)	NF[e]		±[f]	[6] (p. 224)			±	[7] (p. 305)	±	[7] (p. 306)	NF[e]	
	±[g]	[7] (p. 307)	NF[e]										NF[e]	
C=C	+[g]	[24]	NF[e]				+[g]	[5] (p. 40)	+	[6] (p. 168)	+	[25]	NF[e]	
	±	[7] (p. 160)	NF[e]				+	[6] (p. 161)	+	[7] (p. 157)	+	[26]	NF[e]	

[a] +, selective; ±, partially selective; –, unselective.
[b] Rate of dehalogenation: I > Br > Cl > F.
[c] Rate of double-bond hydrogenation: mono > di > tri > tetra substituted.
[d] Y = N, O.
[e] NF: no examples found.
[f] Modified with second metal.
[g] Nonmetallic modifier.

3. Hydrogenation and hydrogenolysis reactions

3.1. Some general comments

Palladium on carbon (Pd/C) are the most widely used hydrogenation catalysts both in research laboratories of academia and the chemical industry. There are probably hundreds of Pd-catalyzed processes in operation for the production of fine chemicals and of biologically active ingredients. The catalytic profile of Pd catalysts differs significantly from hydrogenation catalysts based on Pt, Rh, Ru, Ni, or Cu in the following properties:

- Pd is the most active metal for hydrogenolysis reactions, i.e. the reductive cleavage of C–X bonds;
- Pd is the most active metal for the saturation of double bonds in conjugation with an aromatic ring, such as Ar–C=C, Ar–C=O, or Ar–C=NR;
- the catalytic behavior of Pd catalysts can be tuned by adding organic or inorganic modifiers;
- at low temperatures, Pd is inactive for the hydrogenation of most aromatic rings;
- Pd shows low activity for the hydrogenation of aliphatic ketones and aldehydes.

These characteristics allow a wide range of chemoselective hydrogenations in the presence of other reducible functional groups as illustrated in Table 3 and described in this section.

3.2. Selective catalytic debenzylation (deprotection)

N– and O– benzyl groups are among the most useful protective groups in synthetic organic chemistry (see Fig. 1), and the method of choice for the removal of benzylic protecting groups is catalytic hydrogenolysis, usually with heterogeneous palladium catalysts. Details for conventional debenzylation reactions are described in a number of textbooks and reviews about catalytic hydrogenation and transfer hydrogenation ([5] p. 158, [6] p. 379, [7] p. 398, [27–31]). Here, we will give a short summary of important aspects and discuss new developments in this area.

3.2.1. Catalysts and reaction parameters

Usually, hydrogenolysis reactions are carried out under mild conditions and are unproblematic. In multifunctional molecules, selectivity and activity problems can occur. Rate and selectivity of a debenzylation reaction depend on the nature of the benzyl group, the character of the protected group R, the basicity of substrate or product, steric and electronic effects, the type and amount of catalyst, solvents, modifiers and reducing agent. Even though, there are many reports of selective debenzylations, generalization is not easy, but the following rules of thumb can be given [30,31].

3.2.1.1. Catalysts.
In most cases, the catalysts of choice are 5–20% Pd/C catalysts combining high activity for hydrogenolysis with a low tendency for the
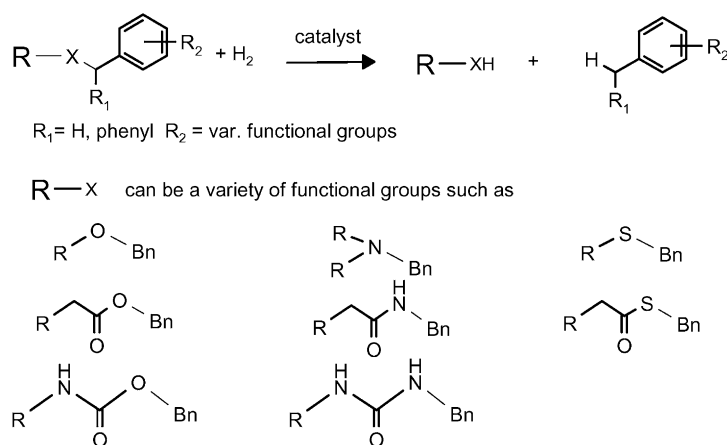

Fig. 1. Debenzylation reaction, structural variability of substrate and protecting group.

reduction of aromatic rings. Unreduced or oxidic metal and high Pd concentrations as, e.g. the Pearlman catalysts (20% Pd(OH)$_2$/C) are often advantageous.

3.2.1.2. Reducing agent. Molecular hydrogen at low pressure is the favorite hydrogen source for catalytic debenzylation, but there also are numerous reports describing hydrogen transfer reactions with donors like cyclohexene, cyclohexadiene, ammonium formate or 2-propanol, often with good selectivity [29].

3.2.1.3. Solvents, modifiers, and promoters. Debenzylation reactions very often are carried out in alcoholic solvents or in acetic acid. Other solvents are also suitable, but the catalyst activity is usually low. Acids promote debenzylation; amines can both promote and hinder hydrogenolysis (see also below). The water content can also significantly affect the activity of the catalyst.

3.2.2. New developments

As described in [30], it is often possible to remove one benzyl group selectively in the presence of another, but generalizations are not trivial. One strategy is to use protecting groups that are easier or more difficult to remove than benzyl. Spencer and coworkers [32–36] developed the application of 2-naphtylmethyl (NAP) and of 4-trifluoromethyl benzyl for the protection of dicarboxylic acids and amines as carbamates. While the NAP is removed very easily, 4-trifluoromethyl benzyl is more stable under hydrogenolysis conditions leading to high yields of the mono-protected derivative. Another approach for accelerating debenzylation is the use of a Ti-loaded mesoporous silica which acts as a solid acid, thereby allowing the selective debenzylation of Bn-ethers in the presence of acid labile silyl protecting groups [35]. Inhibition of hydrogenolysis of certain benzyl groups was investigated in some detail by Sajiki and coworkers [20,21]. They found that by modifying Pd/C catalysts with ethylene diamine or other nitrogen bases, the deprotection of Bn–O–Ar and sometimes

Bn–O–alkyl groups was suppressed, while N–Cbz, Bn–esters or nitro groups reacted selectively. Two recent publications described high selectivity with NH$_2$NH$_2$ and NaH$_2$PO$_2$ as donors for Pd-catalyzed debenzylation [36,37], indicating a growing interest in the use of transfer hydrogenation systems [29].

3.3. Hydrodehalogenation reactions

Palladium is by far the most active metal for the hydrogenolysis of aromatic halogen atoms and a vast literature exists on this topic [38] (also see the contribution by F.J. Urbano). Under basic conditions, halogen atoms can be removed selectively even in presence of functional groups that are easy to reduce [39]. Thus, 2-, 3-, and 4-bromonitrobenzene can be hydrogenolized to nitrobenzene with selectivities > 95% (at 98% conversion) using relatively apolar solvents such as THF in presence of an HBr-scavenger like triethylamine [40]. On the other hand, under non-basic conditions, some hydrogenation reactions can be carried out using similar Pd catalysts without affecting aromatic halogen atoms! Examples are the selective debenzylation of arylbenzylethers or the selective hydrogenation of activated C=C with preservation of aromatic chlorine (see Fig. 2) [40].

Pd/C is also the catalyst of choice for the hydrodehalogenation of most aliphatic halogen atoms with many examples described in hydrogenation handbooks ([7] p. 449). Remarkable exceptions are vinylic fluorine atoms: whereas Pt catalysts hydrogenate the C=C as well as the C–F bond, Pd catalysts hydrogenate the C=C bond only (see Fig. 3) [41].

3.4. Hydrogenation of Ar–C=X bonds

It has been known for a long time that conjugation of a C=X bond with an aromatic system leads to an enormous increase in activity not observed to such an extent for other metals ([6] p. 200). This very often makes Pd the metal of choice for the selective hydrogenation of Ar–C=C bonds as in styrene and stilbene
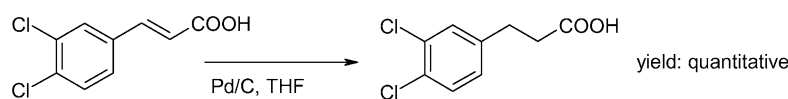

Fig. 2. Selective hydrogenation of a C=C in the presence of aromatic chlorine.
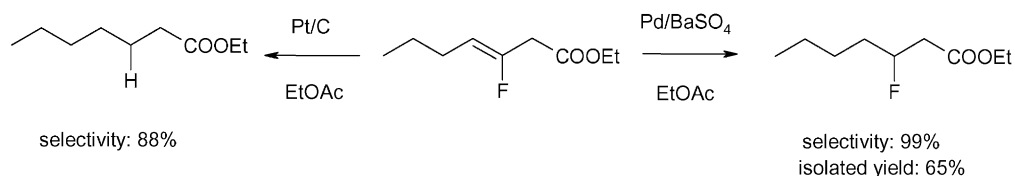
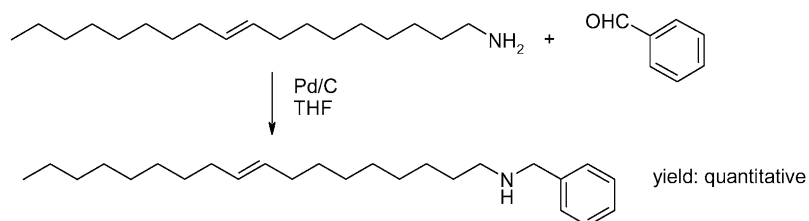Fig. 3. Selective hydrogenation of a vinyl fluoride.

Fig. 4. Selective hydrogenation of an in situ formed aromatic imine.

derivatives. Similarly, palladium catalysts are often superior to Pt for aromatic aldimines or ketimines, in contrast to aliphatic imines ([7] p. 314). An example is depicted in Fig. 4, where the imine derived from benzaldehyde can even be hydrogenated in the presence of a C=C double bond [40]. A striking example of the preferential hydrogenation of an Ar–C=O group in presence of a non-conjugated one is depicted in Fig. 5 [42]. The hydrogenation of nitroarenes is discussed in the contribution of F. Figueras.

3.5. Hydrogenation of aromatic ring systems

In the series of Pt, Pd, Rh, and Ru, palladium is the least active metal for aromatic ring hydrogenation. This opens opportunities for selective hydrogenations, e.g. of condensed aromatic systems, such as depicted in Fig. 6 [43]. Similarly, under acidic conditions, Pd is able to hydrogenate nitrogen-containing heterocycles in preference to phenyl rings (see Fig. 7) [40].
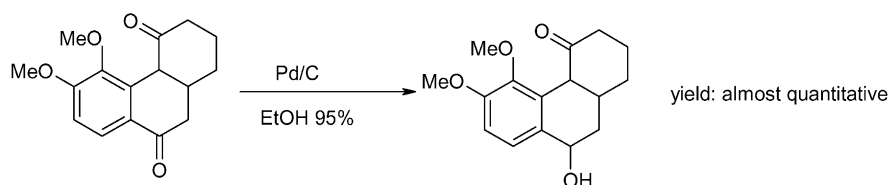
Fig. 5. Selective hydrogenation of a conjugated C=O group.
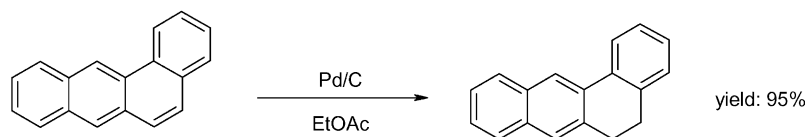

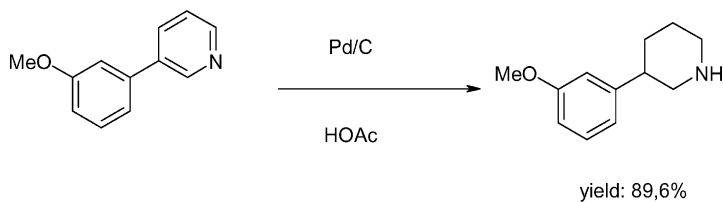Fig. 6. Selective hydrogenation of benz[a]anthracene.

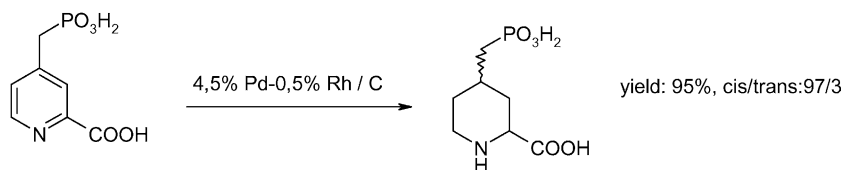Fig. 7. Selective hydrogenation of a pyridine ring in the presence of a phenyl ring.

Fig. 8. Stereoselective hydrogenation of a substituted pyridine.

A remarkable example for the synergism of bimetallic catalysts is the hydrogenation of pyridine-2-carboxylic acid derivatives, as shown in Fig. 8. Surprisingly, a 4.5% Pd-0.5% Rh/C catalyst is twice as active as a 5% Rh/C and, in addition, shows better *cis*-selectivity [44].

The hydrogenation of phenol is an industrial method for the production of cyclohexanone ([6] p. 182). Pd is the metal of choice for this conversion due to its low activity for the hydrogenation of aliphatic or cycloaliphatic ketones.

3.6. Selective hydrogenations of various functions in the presence of C=O groups

Aliphatic and cycloaliphatic C=O bonds are hydrogenated only very slowly by Pd catalysts. This opens the opportunity for a variety of selective hydrogenation reactions. Two examples:

- Selective hydrogenolysis of the most activated chlorine atom occurs with retention of the formyl group, as shown in Fig. 9. When two equivalents 2,6-lutidine are used, the second α-chlorine can be hydrogenolyzed as well [45].
- Selective hydrogenation of an α,β-unsaturated ketone (see Fig. 10) [46].

3.7. Stereoselective hydrogenation of C≡C and C=C bonds

Pd catalysts are used in many types of diastereoselective hydrogenation reactions. This topic is beyond the scope of this article but will be discussed in the
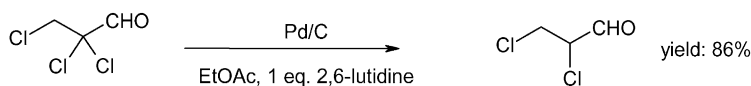

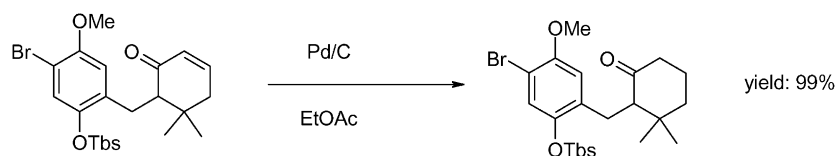Fig. 9. Selective hydrogenolysis of an activated C–Cl bond.

Fig. 10. Chemoselective hydrogenation of a C=C bond in the presence of a C=O and an Ar–Br group.
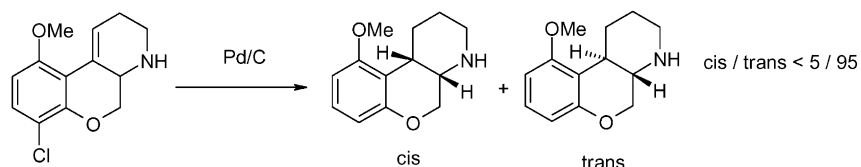
Fig. 11. *Trans*-selective hydrogenation of a C=C bond in a tricyclic system.

contributions of Molnar and Tungler. Nevertheless, we will give a short overview on a few areas that are of relevance to the synthetic organic chemist in the fine chemicals industry.

3.7.1. Stereo- and chemoselective hydrogenation of alkynes and alkenes

Pd catalysts, especially Pd-Pb/CaCO$_3$ originally developed by Lindlar for vitamins syntheses and catalysts modified by bases are very useful for this purpose ([5], [47] p. 220). The *cis*-olefins can often be obtained with chemo- and diastereoselectivities of >95% under very mild conditions, because the reaction essentially stops after uptake of 1 mol of hydrogen.

In the absence of hydrogen, Pd catalysts have the unique ability to isomerize C=C bonds. Therefore, depending on the reaction conditions either the thermodynamically or the kinetically preferred products will be observed ([43] p. 96). An example from our own work is shown in Fig. 11, where pressures < 1 bar and a high catalyst loading were required in order to get the desired *trans*-isomer of the tricyclic product in >95 selectivity. At higher pressures and/or lower catalyst loadings, much more of the undesired *cis*-isomer was observed [48].

3.7.2. Various diastereoselective hydrogenation reactions

The stereoselective synthesis of amino acids has been a topic of intense interest for many years. Several approaches have been devised based on the diastereoselective hydrogenation of dehydro-precursors attached to a chiral auxiliary with heterogeneous Pd, Pt, and Ni catalysts [49,50]. In all cases, the chiral auxiliary can easily be removed from the product molecule and sometimes can be recycled as well. It has been found that the stereoselectivity (here expressed as diastereomeric excess, de) is strongly dependent on the type of the metal and that Pd is very often the metal of choice. Using Pd/C catalysts, very high de's were obtained for cyclic amino acid precursors (see Fig. 12) which can easily be explained by assuming preferential adsorption via the unhindered side of the molecule. Non-cyclic precursors, aryl ketimines [49–51] and also an α-hydroxy acid derivative [52] usually give lower but still respectable de's (Fig. 13).

3.7.3. Enantioselective hydrogenation of α,β-unsaturated acid derivatives and ketones [22]

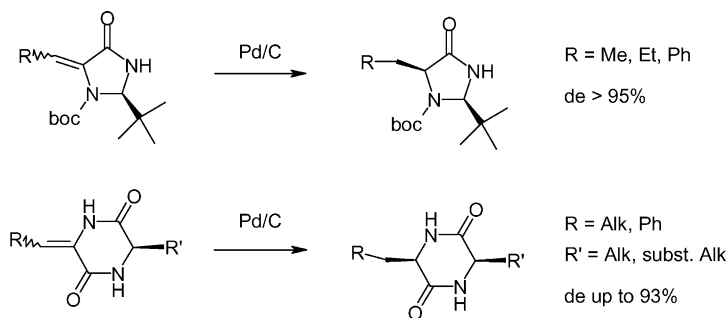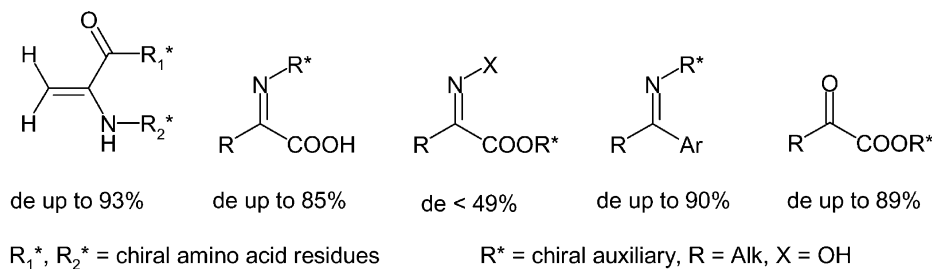Cinchona-modified Pd systems have been used for the enantioselective hydrogenation of C=C double

Fig. 12. Diastereoselective hydrogenation of α,β-dehydroamino acid derivatives and dehydroketopiperazines.

de up to 93%   de up to 85%   de < 49%   de up to 90%   de up to 89%

R_1*, R_2* = chiral amino acid residues   R* = chiral auxiliary, R = Alk, X = OH

Fig. 13. Diastereoselectivities for the hydrogenation of dehydrotripeptides, various C=N systems and α-keto acid derivatives.
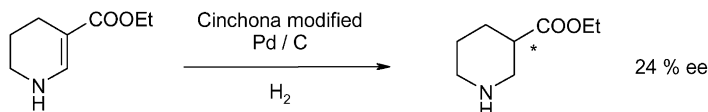
Fig. 14. Enantioselective hydrogenation of an α,β-unsaturated ester.

bonds in alpha-phenyl-cinnamic acid with up to 72% ee [53] and in 2-ethyl-2-pentenoic acid with up to 66% ee [54,55]. The only example of an enantioselective hydrogenation of an α,β-unsaturated ester was reported in [56] with modest 24% ee (see Fig. 14). Tungler et al. have developed a Pd catalyst modified with vinca alkaloids for the hydrogenation of isophorone with ee's up to 55% [57]. In all cases, the modified systems were significantly slower than the unmodified systems, and none has yet reached synthetic utility.

4. Dehydrogenation reactions

Due to its high affinity to hydrogen atoms and low activity for the saturation of aromatic rings, palladium is the metal of choice for aromatization of unsaturated or partially unsaturated rings via dehydrogenation [58,59]. Examples of partially saturated starting materials which lead to aromatic products are shown in Fig. 15 [60–62]. If a hydrogen acceptor like nitrobenzene or α-methylstyrene is used, dehydrogenation usually occurs at temperatures of 200°C and below, as can be seen in Fig. 16 [63].

5. Oxidation reactions

Relatively few reports exist on the use of heterogeneous Pd catalysts for oxidation reactions using either oxygen or similar oxidants. An important exception is the selective oxidation of alcohols to aldehydes or ketones and of aldehydes to carboxylic acids in

Pd/C, neat, 270 °C
yield 75 % [60]

Pd/C, 250°C,
triisopropylbenzene
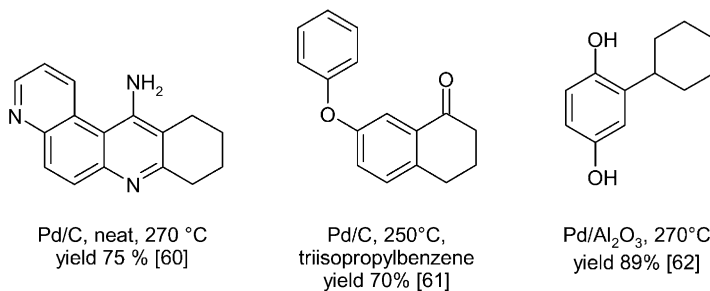yield 70% [61]

Pd/Al$_2$O$_3$, 270°C
yield 89% [62]

Fig. 15. Dehydrogenation with Pd catalysts: starting materials, catalysts, reaction conditions, and yields.
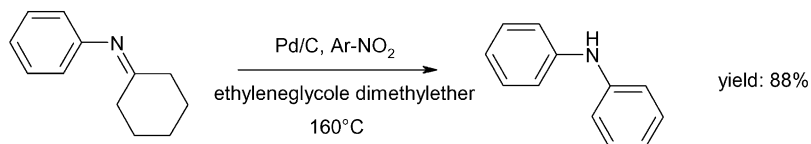
Fig. 16. Dehydrogenation in presence of nitrotoluene as acceptor.
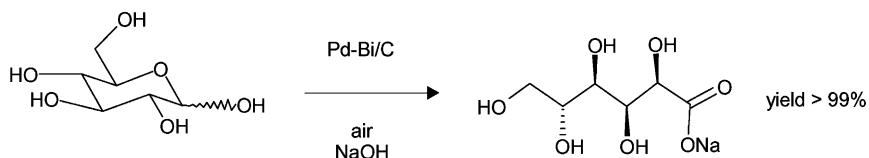

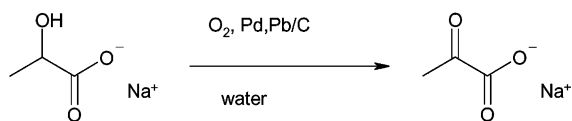Fig. 17. Air oxidation of glucose to gluconic acid.

Fig. 18. Oxidation of sodium lactate.

presence of metallic Pd and other platinum group metals on carbon supports [64,65]. Especially useful is the highly selective oxidation of carbohydrates with oxygen or H_2O_2-catalyzed by Pd-Bi/C [66]. An example is shown in Fig. 17, where glucose is converted to gluconate with a conversion of 99.6% and a selectivity of 99.8% [65] and in Fig. 18 where Na lactate is oxidized to pyruvic acid [67]. These reactions occur at relatively low pressure and under mild conditions, and therefore have both environmental and economical benefits. To increase the longterm stability (reusability) as well as activity and selectivity, the catalysts must be promoted with a second metal such as Bi or Pb [64,65]. The mode of action of these metal additives is not well understood.

6. C–C coupling and carbonylation reactions

For the organic chemist, palladium-catalyzed C–C-forming reactions have become very important synthetic tools and many of these reactions were used both in academia and in industry so extensively that they became name reactions [4,68]. In general,

soluble palladium complexes with ligands like phosphines, amines, or carbenes are used as the catalysts where the choice of the ligand allows tuning of the catalytic activity and selectivity. Despite the potential benefits of using heterogeneous catalysts, there exist only a limited number of examples for these reactions, maybe because homogeneous systems were simply superior in respect of selectivity, versatility, and activity [69] (see also contribution by M. Basato et al.).

6.1. Heck reaction and analogous transformations

The most extensive efforts to find heterogeneous versions for Pd-catalyzed C–C coupling reactions have been made for the Heck reaction, i.e. the coupling of aryl halides with olefins and several reviews have already summarized these results [69–71]. Heterogeneous catalysts have also been successfully applied for the Matsuda Heck reaction using aryl diazonium salts [72,73] and the Blaser Heck reaction with aryl chlorides [74,75] (see Fig. 19). In general, commercially available supported palladium catalysts on supports like charcoal, SiO_2, Al_2O_3, MgO, $BaSO_4$, $CaCO_3$, or TiO_2 have been used. Besides these classical catalysts, colloidal Pd [76], Pd clusters [77], Pd nanoparticles [78], Pd-modified zeolites [79,80] and clays [81,82], palladium on porous glass [83], and palladium grafted onto molecular sieves [84] were also shown to be suitable.

Heterogeneous catalysts generally gave good yields for aryl iodides and aryl bromides, but exhibited low
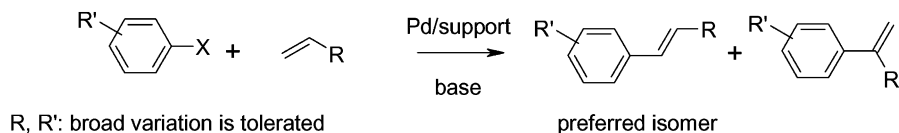
Fig. 19. Heck reaction (X = Cl, Br, I, OTf), Matsuda Heck reaction (X = N_2^+), Blaser Heck reaction (X = COCl).

activity with the commercially more attractive but less reactive aryl chlorides [78,84,85]. In general, supported palladium catalysts require more drastic conditions than homogeneous catalysts. However, since the supported palladium catalysts are thermally more stable, this is usually not problematic. As a result, the lower activities are somewhat compensated by using higher temperatures and catalyst loadings and the productivity of the heterogeneous catalysts can often be improved by reusing them several times.

Some technical applications using heterogeneous strategies have already been developed. Eisenstadt and coworkers [69,71] mention a multi-ton scale process for octyl *p*-methoxy cinnamate, the most common UV-B sunscreen, starting from 4-bromoanisol and using a Pd/C catalyst. Because of the high cost of bromoanisole, this synthesis is only commercially competitive if the recycling of the bromine and the bromination of anisol are part of this overall process (Fig. 20).

An interesting combination of a homogeneous and heterogeneous approach is the production process developed for an intermediate of the Prosulfuron® sulfonylurea herbicide of Novartis/Syngenta, as shown in Fig. 21 [86]. While the Matsuda Heck reaction is catalyzed by a homogeneous Pd catalyst, the subsequent hydrogenation is carried out in the same reactor with Pd/C catalysts prepared in situ by adding active carbon to the reaction mixture. The overall yield is around 93%, but the catalyst activity and productivity are relatively low.

6.2. C–C and C–N coupling reactions (Suzuki, Sonogashira, Buchwald–Hartwig)

The Suzuki coupling of aryl halides with arylboronic acids is the most versatile method for the synthesis of biaryls [4]. However, despite its importance, there are only a handful of publications describing the application of heterogeneous catalysts [87–89].
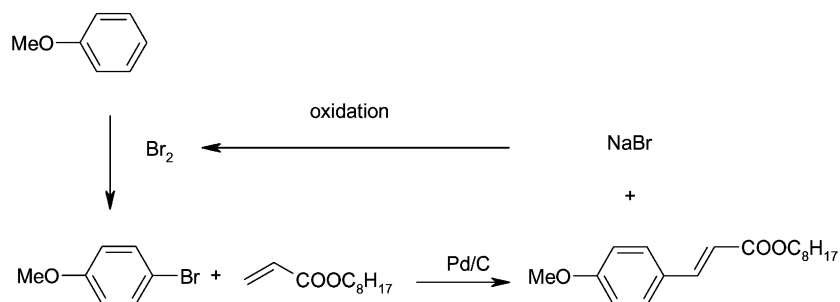

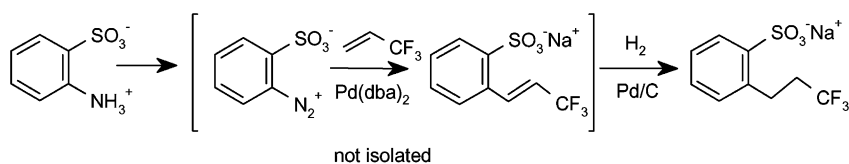Fig. 20. Production process for octyl methoxy cinnamate.

Fig. 21. Production process for an intermediate of the Prosulfuron® herbicide.
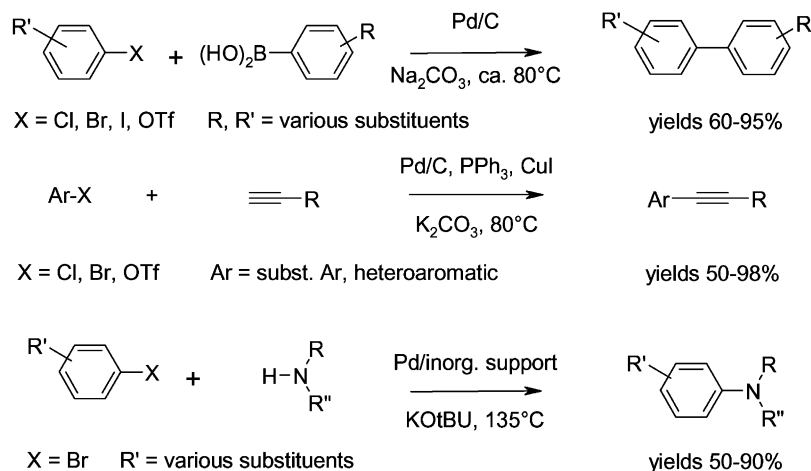
Fig. 22. Typical catalysts, additives, and reaction conditions for the Suzuki and the Sonogashira coupling and the Buchwald–Hartwig amination.

The same is true for other palladium-catalyzed reactions like the Sonogashira coupling (coupling of aryl halides with terminal acetylenes) [83,90], the Buchwald–Hartwig amination (coupling of aryl halides with amines) [91], or the Trost allylation [92] (examples for some of these reactions are depicted in Fig. 22). The conditions for these reactions are quite similar to the homogenous versions, and often phosphine ligands are used in these reactions as well.

Somewhat special is the homocoupling reaction of aryl halides to symmetrical biphenyl depicted in Fig. 23 [93,94]. In this case, aryl chlorides can be coupled under very mild condition, whereas in other reaction types higher reaction temperatures are needed for its activation.

6.3. Carbonylation reactions

Only few heterogeneous examples have been described for the potentially interesting carbonylation re-

actions. Suitable substrates are aryl halides [95] (see Fig. 24), olefins [96], and allylic and benzylic alcohols [97,98] (see Fig. 25). Yields are generally satisfactory to very good but except for aryl halide carbonylations CO pressures are sometimes rather high.

6.4. General comments for C–C coupling reactions

From the very first experiments with heterogeneous Pd catalysts, the question was discussed whether the active species is on the Pd surface or a leached soluble Pd complex (for a more detailed discussion see the contribution of M. Basato et al.). For the Heck reaction, where this issue has been investigated quite extensively, the answer is ambiguous. Wali et al. [99,100] and Augustine and O'Leary [74] concluded that the reaction was indeed catalyzed by the metallic palladium, because catalyst selectivity as well as activity were influenced by the type of support. Other studies came to the opposite conclusion because the reaction
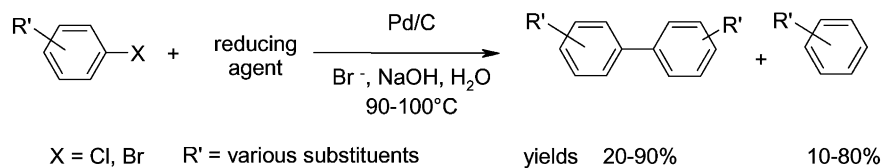

Fig. 23. Typical catalysts, additives, and reaction conditions for the reductive homocoupling reaction.
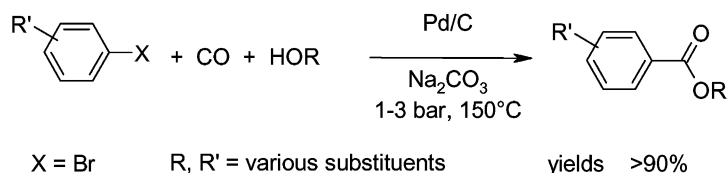
Fig. 24. Typical catalysts, additives, and reaction conditions for the carbonylation of aryl halides.
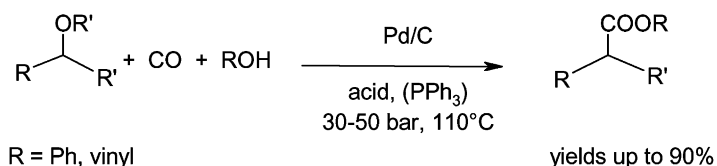

Fig. 25. Carbonylation of allylic and benzylic substrates.

proceeded even after the catalyst had been filtered off, whereas the removed heterogeneous catalyst showed only a low catalytic activity [101–103]. In addition, it was also found that the amount of palladium staying in solution depended very much on the reaction conditions and catalyst type and that most of the Pd was redeposited on the support when the reaction was complete [104]. Finally, Reetz and Westermann [105] proposed Pd nanoparticles to be the active form as long as no phosphine ligands were present. For the reductive homocoupling, the heterogeneous reaction was considered to be more likely [93,94].

Despite these disputes, heterogeneous catalysts can be an interesting alternative to soluble complexes when it comes to technical applications. Under favorable conditions, the supported palladium shows the same catalytic performance as the homogeneous analog, but is easier to separate from the reaction mixture and can be recycled.

7. Conclusions

The most important conclusions of this contribution can be summarized as follows.

- Palladium is the most versatile and the most widely applied metal for catalytic organic synthesis and the manufacture of fine chemicals.
- Two types of catalysts are used: heterogeneous catalysts where metallic Pd is supported on a carrier and homogeneous catalysts consisting of mononuclear Pd (ligand) complexes.
- The most important applications for heterogeneous catalysts both in preparative chemistry and on a technical scale are hydrogenolysis, hydrogenation, and dehydrogenation reactions. Important transformations are the debenzylations of protected O- and N-compounds, hydrodehalogenation of Ar–Hal and R–Hal, hydrogenation of nitroarenes and other C=C, C=O, and C=N bonds conjugated with an aromatic group and various stereoselective hydrogenation reactions.
- The chemo- and sometimes also the stereoselectivity of heterogeneous Pd catalysts can often be tuned by using catalyst modifiers, thereby increasing the usefulness for the synthetic chemist.
- The application of heterogeneous Pd catalysts for oxidation and C–C coupling reactions is far less developed and in many cases homogeneous Pd catalysts are more effective and more versatile. In many cases, leached Pd has been detected in solution, and generally the nature of the catalytic species (surface or dissolved) is under discussion for transformations in absence of hydrogen.

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