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All authors contributed to this issue in honour of the 2010 Nobel Prize in Chemistry winners, Professors Richard F. Heck, Ei-ichi Negishi and Akira Suzuki

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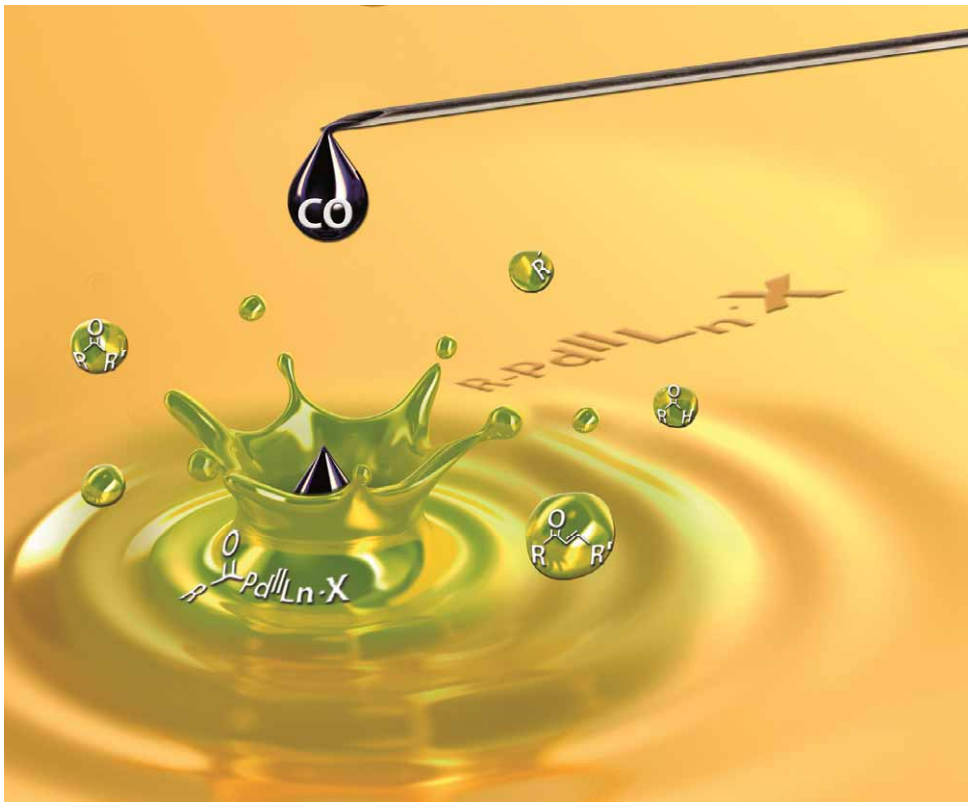

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TUTORIAL REVIEW

Palladium-catalysed hydroxylation and alkoxylation†

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The formation of oxygen–carbon bonds is one of the fundamental transformations in organic synthesis. In this regard the application of palladium-based catalysts has been extensively studied during recent years. Nowadays it is an established methodology and the success has been proven in manifold synthetic procedures. This *tutorial review* summarizes the advances on palladium-catalysed C–O bond formation, means hydroxylation and alkoxylation reactions.

1. Introduction

An immense number of hydroxy and ether containing chemicals are produced by pharmaceutical, bulk and fine chemical industries and applied for the synthesis of pharmaceuticals, agrochemicals, polymers *etc.* (Fig. 1).[1] Aside from nitrogen oxygen is the most abundant heteroatom in man-made organic products. In addition a plethora of naturally occurring

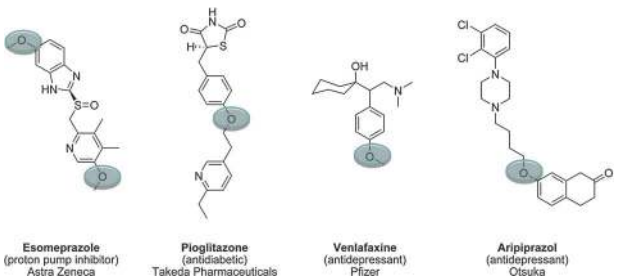

Fig. 1 Selected pharmaceuticals that contain alkoxy functionalities potentially accessible by Pd-catalysed reactions.

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† Part of a themed issue on the topic of palladium-catalysed cross couplings in organic synthesis in honour of the 2010 Nobel Prize winners Professors Richard F. Heck, Ei-ichi Negishi and Akira Suzuki.

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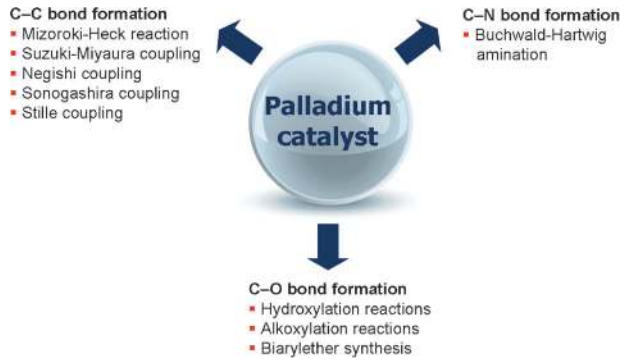


Fig. 2 Selection of palladium-catalysed bond formations.

chemicals containing hydroxy and ether functionalities, for example carbohydrates, lignin, alkaloids, amino acids, and nucleotides, have a fundamental role in biological processes. Over the years a huge number of purposes for the access of hydroxy and ether based chemicals has been established. Nevertheless, due to an increasing demand and changes of regulations (sustainability and environmental considerations) novel methodologies for C–O bond formations are still of interest and a challenging task for industrial and academical research. In this regard, transition-metal catalysed reactions offer a versatile strategy and represent one of the key technologies for the progress of green and sustainable chemistry.[2]

Specifically, organometallic compounds turned out to be an outstanding synthetic toolbox for organic chemistry. In this regard special attention was directed to palladium, because of its superior catalytic performance and its distinct abilities.[3] Based on the milestones in coupling reactions of the groups of Heck, Suzuki and Negishi in the 60s and 70s of the last century, during recent decades palladium catalysis has become a powerful methodology in organic synthesis.[3,4] Impressively, palladium-catalysts perform a multitude of transformations, *e.g.*, coupling reactions, oxidations, reductions, isomerizations, additions, substitutions, hydrogenations, cycloadditions, rearrangements, and polymerizations. In Fig. 2 a selection of the scope of palladium-based coupling reactions is presented including the formation of C–C bonds (*e.g.*, Mizoroki–Heck reaction, Suzuki–Miyaura coupling, Negishi coupling, Sonogashira coupling, Stille coupling), C–N bonds (*e.g.*, Buchwald–Hartwig amination) and C–O bonds.

Herein, we wish to emphasize the potential of homogeneous palladium catalysts in hydroxylation and alkoxylation reactions.

2. Hydroxylation of arenes

The importance of phenols and hydroxylated arenes is nicely underlined by their application in various fields of chemistry, *e.g.*, pharmaceuticals, agrochemicals, and polymers.[3b,5] For instance phenol is a central commodity chemical in industry, which is produced in a three step synthesis (cumene-process) starting from benzene and propylene.[6] However, this protocol has limitations related to its high reaction temperature and low functional group tolerance. An alternative has been presented recently by applying homogeneous palladium catalysts for the direct oxidation of aromatic C–H bonds and transformation of aromatic C–X bonds (X = halides).[7]

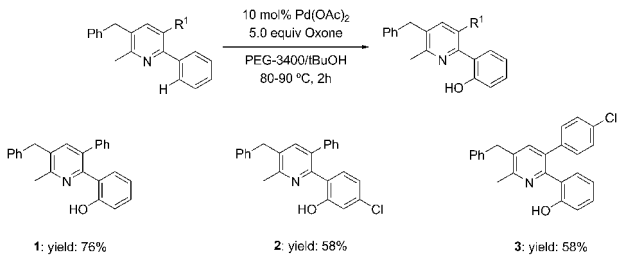
2.1 Hydroxylation of aromatic C–H bonds

In the early 90s Jintoku, Fujiwara and co-workers reported on the transformation of benzene and molecular oxygen to phenol in the presence of catalytic amounts of $Pd(OAc)_2$ (OAc = acetate).[8] The palladium precursor was modified by addition of 1,10-phenanthroline and dissolved in a mixture of benzene and acetic acid. After pressurising with oxygen (15 atm), carbon monoxide (15 atm) and heating to 180 °C a TON (turnover number) of 1200 was observed. As a major side product the acetylated phenol was monitored.

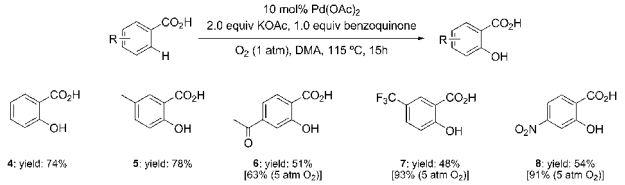
More recently, the regioselective *ortho*-hydroxylation of 2-arylpyridines with a palladium catalyst was described by Kim and co-workers.[9] Catalytic amounts of palladium acetate (10 mol%) in combination with Oxone® (potassium peroxymonosulfate, 5.0 equiv.) afforded the desired hydroxylated product with reasonable yields in a mixture of PEG-3400/*tert*-butanol (PEG = polyethylene glycol) as solvent at 80–90 °C (Scheme 1).

The combination of palladium and Oxone® is highly efficient for a wide range of pyridines and arenes with different substitutions, except for those substrates with an *ortho*-methyl group in the aryl moiety which completely inhibited the described reactivity. Most probably, this phenomenon is related to the steric effect of the *ortho*-substituent, which obstructs the formation of the putative palladacycle intermediate.

Recently the group of Yu described a palladium(II)-based catalytic system that performed the regioselective *ortho*-hydroxylation of potassium benzoates which are *in situ* generated by reaction of benzoic acid derivatives with potassium acetate (2 equiv.).[10] The palladium source was $Pd(OAc)_2$ with a catalyst loading of 10 mol% and as an oxidant the environmentally-friendly molecular oxygen was applied (Scheme 2). In more detail, at 1 atm O_2-pressure the catalyst hydroxylated 3-methylbenzoic acid selectively in the 2-position to obtain 2-hydroxy-5-methylbenzoic acid in 20% yield at 115 °C with DMA (dimethylacetamide) as the solvent. Although under these conditions the catalyst only effected two turnover



Scheme 1 Synthesis of 2-pyridyl substituted phenols catalysed by palladium and Oxone® as oxidant.



Scheme 2 Palladium-catalysed *ortho*-hydroxylation of benzoates with molecular oxygen.

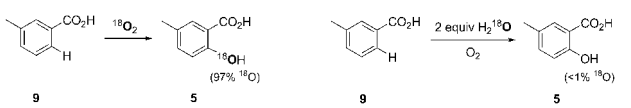
numbers, the yield of the reaction was significantly improved (up to 55%) using 5 atm O_2-pressure. Finally, the presence of benzoquinone (BQ) was found to significantly increase the reaction rates and in the presence of 1.0 equiv. BQ, the substrate could be converted into the desired *ortho*-hydroxylated product in 78% yield (1 atm O_2).

Under these optimized conditions, the system is compatible with a wide range of functional groups, means either electron-rich arenes (methoxy, amide or alkyl functionalities) or electron-deficient arenes (halides, trifluoromethyl, acetyl, cyanide or nitro functionalities) are reasonably *ortho*-hydroxylated (Scheme 2).

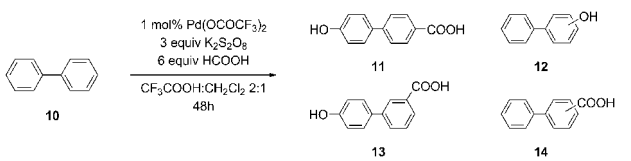
Labeling experiments with $^{18}O_2$ as an oxidant unambiguously established that the source of the oxygen-atom incorporated into the hydroxylated product is originated from molecular oxygen (Scheme 3). On the other hand, no incorporation of oxygen from water was observed in experiments performed in the presence of 18-oxygen-labelled H_2O. Finally, in the absence of molecular oxygen no reaction took place even if other oxidants, such as H_2O_2, were present. These experiments support a direct oxygenation of the arylpalladium intermediates instead of an acetoxylation/hydrolysis sequence.

In 2004 Nozaki and co-workers reported the palladium-catalysed consecutive hydroxylation–carboxylation of arenes (Scheme 4).[11] For example, biphenyl (**10**) was treated with formic acid and potassium persulfate ($K_2S_2O_8$) in a mixture of trifluoroacetic acid and dichloromethane (2 : 1) at 50 °C for 48 h in the presence of $Pd(OCOCF_3)_2$ as the pre-catalyst (1 mol%) to obtain 4′-hydroxy-4-biphenylcarboxylic acid (**11**), a polyester monomer and its *meta*-isomer **13** in a combined yield of 45%. Other substrates such as benzene or naphthalene also gave the hydroxylated–carboxylated products, but in lower yields (4% and 12% yield, respectively).

The reaction outcome was found to be highly sensitive to the reaction temperature. In more detail, when the temperature was decreased to 40 °C, 4-hydroxybiphenyl (**12**) was the major product accompanied by a small amount of the simple carboxylation products **14**, while at 80 °C exclusively products **14** were obtained. The authors suggested that both the hydroxylation and the carboxylation reactions proceeded through a common aryl-Pd σ-complex formed by the well-known electrophilic-substitution of an aromatic hydrogen-atom by palladium(II) species. However, at 40 °C this intermediate



Scheme 3 Isotopic labelling experiments in the *ortho*-hydroxylation of benzoates by palladium catalyst with O_2 as oxidant.



Scheme 4 Hydroxylation–carboxylation protocol by Nozaki and co-workers.

undergoes preferentially hydroxylation, while at 80 °C the carboxylation process is preferred. Instead, at 50 °C, both hydroxylation of biphenyl and carboxylation of the same molecule take place to provide the hydroxyl-biphenylcarboxylic acids **11** and **13** as products. It is important to note that the hydroxylation–carboxylation reaction is a stepwise process that starts by the introduction of the hydroxy-functionality as deduced by two important experimental evidences: no hydroxylation of 4-biphenylcarboxylic acid (**14**, *para*-isomer) took place under the given reaction conditions, while carboxylation of biphenyl-4-ol (**12**, *para*-isomer) (or the corresponding ester) could be performed in good yields.

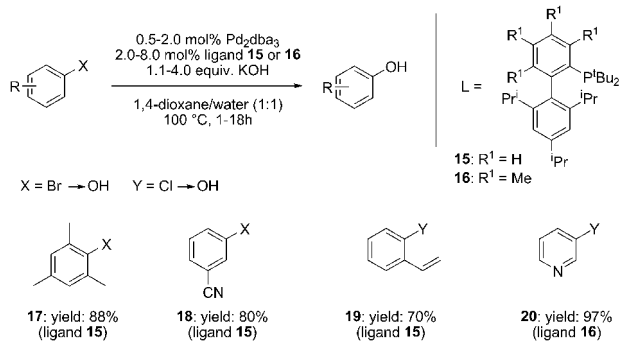
More recently Ishii *et al.* introduced an alternative system for the hydroxylation–carboxylation of biphenyl.[12] The catalyst consisted of a mixture of $Pd(OAc)_2$ (2.5 mol%) and $H_4PMo_{10}V_2O_{40}{\cdot}nH_2O$ (2 mol%) and the reaction took place under an atmosphere of CO/O_2 (0.5 atm/0.5 atm) using acetic acid as a solvent. The major product of the reaction was **14** (54%), but also significant amounts of the hydroxyl-biphenylcarboxylic acids **11**, **13** (34%) and **12** (3%) were detected. In contrast to the protocol reported by Nozaki and co-workers, in this case it seems that the carboxylation of biphenyl is the first step followed by the hydroxylation reaction to yield the final product. The mechanism operating in this transformation is, however, unknown and the exact role played by palladium within the system still needs to be unraveled.

Besides homogeneous catalysts based systems, various heterogeneous systems for the synthesis of phenols have been introduced, but they require high reaction temperature.[6,13]

2.2 Transformation of aryl halides to hydroxylated arenes

Within the synthetic procedures one key approach to phenols can be the direct coupling of aryl halides with suitable hydroxides to form the corresponding hydroxylated product.[14] On the one hand the use of aryl halides allows a broad range of potential products, because of their great abundance and variety. On the other hand the use of hydroxides offers the possibility for the direct synthesis of the hydroxylated product without additional deprotection steps. Noteworthily, a better control of selectivity is feasible compared to direct oxidation of aromatic C–H bonds.

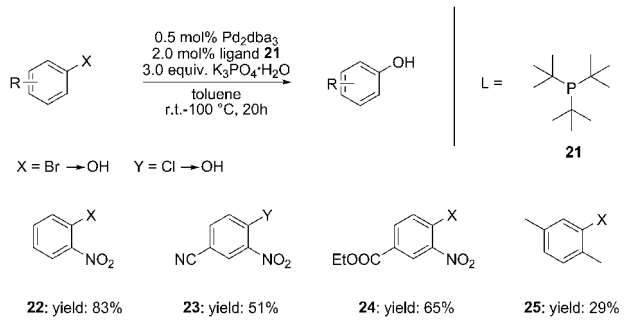
Initial attempts have been reported by Buchwald and co-workers applying an *in situ* formed complex as catalyst precursor composed of $Pd_2(dba)_3$ (dba = dibenzylideneacetone) and the bulky phosphanes **15** or **16** in a metal to ligand ratio of 1 : 4 (Scheme 5).[15] After studying and optimisation of the reaction parameters for the hydroxylation of 3-bromoanisole excellent yields and selectivities of 3-methoxyphenol were demonstrated by the system. As a nucleophile KOH was applied. The reaction was performed in a mixture of dioxane/water (1 : 1) or in pure water as solvent at 80 °C, while for aryl chlorides 100 °C were necessary to obtain reasonable amounts of product. The abilities of the system were extended to the hydroxylation of various aryl bromides and chlorides. Noteworthily, excellent selectivities towards the hydroxylation were observed, since various functional groups were accepted by the system, including nitrile, carboxylic acid, ester, aldehyde,



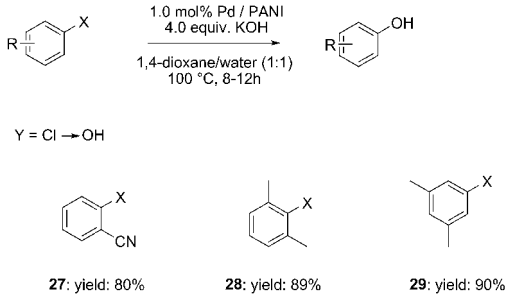
Scheme 5 Pd-catalysed hydroxylation of arene halides according to Buchwald and co-workers.

halides, vinyl, hydroxyl, and heteroaromatic compounds. Difficulties arose with the combination $Pd_2(dba)_3$/ligand **16** since bulky substrates such as 2-bromomesitylene were not efficiently transformed. For those substrates $Pd_2(dba)_3$/ligand **15** has been favoured, but for aryl chlorides and heteroaryl halides better performance was observed for $Pd_2(dba)_3$/ligand **16**. Remarkably, the application of ligand **16** resulted in more stable complexes than with ligand **15**. The authors assume a faster C–O reductive elimination step of the LPdAr(OH) intermediate for ligand **16**. Moreover, the protocol was embedded in the synthesis of substituted benzofurans applying 2-chloroaryl alkynes as starting material and $Pd_2(dba)_3$/**15** or **16** was applied as a tandem catalyst.

At the same time the group of Kwong reported on the direct synthesis of phenols based on the hydroxylation of aryl halides (Scheme 6).[16] The application of an *in situ* catalyst composed of easily accessible $Pd_2(dba)_3$ and tri-*tert*-butyl phosphane (**21**) allows the efficient synthesis of phenols. It was observed that arylphosphanes resulted in lower yields compared to alkyl phosphanes. After optimisation of the reaction conditions K_3PO_4 hydrate in toluene was proved as the best base, while anhydrous K_3PO_4 gave reasonable lower yields. Next, the scope and limitation of the straightforward *in situ* catalyst were investigated. A series of halonitroarenes was successfully converted to the corresponding phenol derivatives. Noteworthily, the reaction temperature was in the range of 25 °C to 50 °C, while for unactivated aryl halides higher temperatures (100 °C) were necessary to observe product formation. In some cases (sterically non-hindered aryl halides) the authors observed the formation of diaryl ethers as side products.



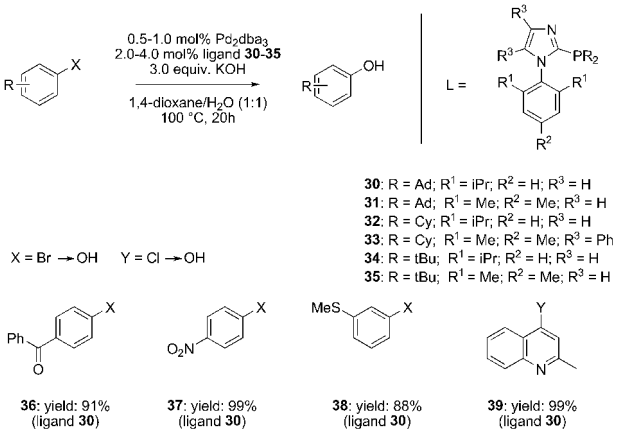
Scheme 6 Pd-catalysed hydroxylation of arene halides reported by Kwong and co-workers.



Scheme 7 Palladium nanoparticles supported on polyanilines as hydroxylation catalyst.

Aside the application of homogeneous catalysts the group of Diaconescu reported on the use of palladium-nanoparticles supported on polyaniline (PANI) nanofibers as semi-heterogeneous catalyst for the conversion of aryl halides to phenols (Scheme 7).[17] The catalyst is easily obtained by stirring palladium(II) salts in an aqueous suspension of polyaniline nanofibers with a high surface area. In analogy to the reaction parameters shown by Buchwald and co-workers, the supported palladium was reacted with aryl chlorides/bromides and potassium hydroxide in dioxane/water at 100 °C. Yields up to 90% were achieved after 8–12 hours. Noteworthily, no differences in reactivity between chloride and bromide leaving groups were noticed. In addition, the material was applied as a tandem catalyst: first a Suzuki coupling was performed with dihalogenated arenes subsequently followed by the phenol formation to obtain the product in good yields (70%). Unfortunately no information is given on recycling of the catalytic material.

More recently the group of Beller demonstrated the excellent abilities of palladium complexes containing monodentate phosphanes based on an imidazole unit (Scheme 8).[18] A series of ligands was synthesized and tested in the hydroxylation of aryl halides to explore the influence of the ligand scaffold on the reaction outcome. Two factors were found to be crucial for obtaining reasonable amounts of the product. First the substituent connected to the nitrogen should be sterically demanding, and the same fact is true for the substituent bonded to the phosphorous, since best results were

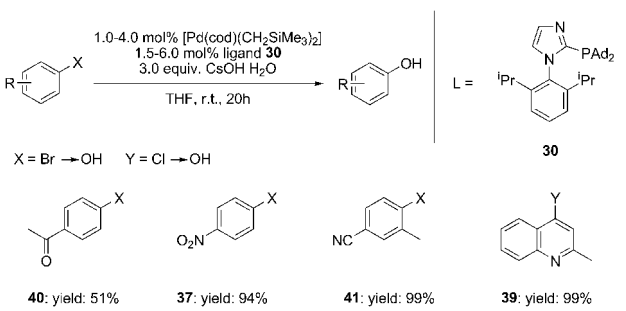


Scheme 8 Hydroxylation of aryl halides according to Beller and co-workers.

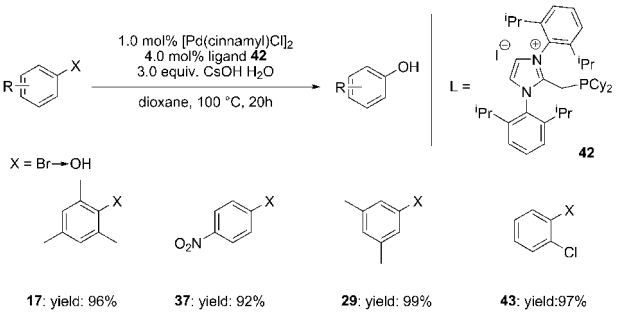
achieved with the ligand containing *N*-2,6-diisopropylphenyl and PAd_2 units (Scheme 8, ligand **30**). Along with monodentate phosphane ligands bidentate systems were evaluated. However, no product formation was monitored. With the *in situ* formed complex of $Pd_2(dba)_3$ and ligand **30** a variety of reaction parameters were studied in detail. First different bases and solvents were applied showing best performance for potassium hydroxide in 1,4-dioxane as reported by Buchwald and co-workers (*vide supra*). Moreover the influence of the palladium source was examined showing still best performance for $Pd_2(dba)_3$ with selectivities >95%. To further demonstrate the selectivity of the *in situ* catalyst, the hydroxylation reaction was performed in the presence of competing nucleophiles (olefins, alkynes, amines). Noteworthily, excellent selectivity for the phenol formation was detected in the presence of amines (>50 : 1), while lower values were noticed for olefins (>15 : 1) and alkynes (2.5 : 1.1). Finally, the catalyst abilities were examined in the hydroxylation of 15 different aryl halides. The catalyst showed an excellent performance and group-tolerance for the hydroxylation of substrates containing functional groups *e.g.*, ketone, nitro, sulfide, nitrile, and additional halide groups. Note that also hetero aromatic substrates resulted in the quantitative formation of the hydroxylated product.

Following this work, recently an improvement of the catalyst system has been reported by Beller and co-workers (Scheme 9).[19] Changing the palladium precursor from $Pd_2(dba)_3$ to $Pd(cod)(CH_2SiMe_3)_2$ (cod = 1,5-cyclooctadiene) an extraordinary active catalyst is formed with ligand **30** since the reaction is now feasible at ambient temperature accompanied by excellent yields and selectivities. The catalyst allows the reaction of activated and non-activated aryl chlorides and halides containing various functional groups (*e.g.*, nitro, nitrile, trifluoromethyl, keto and hetero aromatics). However, carboxyl groups and hydroxy groups are not tolerated. Along with that, different experiments were carried out to understand the role of the ligand and the reaction mechanism.

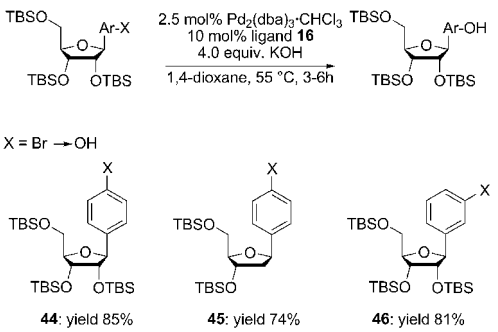
To overcome the problem of recycling the homogeneous catalysts, Beller and co-workers introduced a novel type of phosphane ligands which contain an imidazolium salt unit **42** (Scheme 10).[20] These ligands were mixed with $[Pd(cinnamyl)Cl]_2$ resulting in a highly active pre-catalyst for the transformation of aryl bromides to the corresponding phenol derivatives. Thanks to the solubility abilities of the ligand **42** in 1,4-dioxane (insoluble at rt, soluble at higher temperature)



Scheme 9 Hydroxylation at ambient conditions reported by Beller *et al.*



Scheme 10 Hydroxylation with a recyclable catalyst.



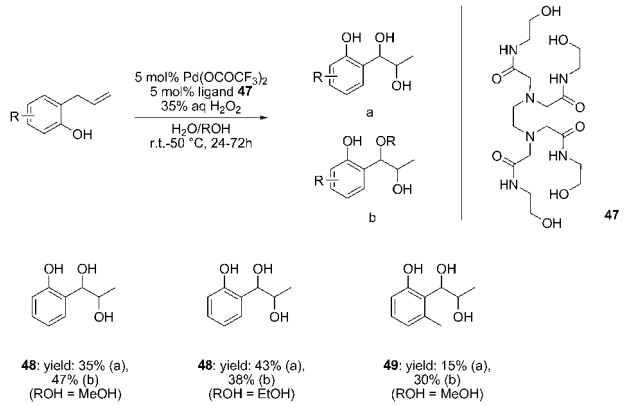
Scheme 11 Application of palladium-catalysed hydroxylation of aryl halides in carbohydrate chemistry (TBS = *tert*-butyldimethylsilyl).

the catalyst was recycled several times (up to 8 times) with only small depletion of reactivity. Furthermore, the presented catalyst was highly selective for bromoarenes, while chloro functionalities were unaffected.

Finally, the applicability of the palladium-catalysed hydroxylation protocols has been demonstrated by the group of Hocek for the synthesis of carbohydrate (ribofuranose) based phenols using the corresponding haloarenes as starting material (Scheme 11).[21] Extraordinary selectivity towards the hydroxylation reaction was noticed in the presence of various functional groups for a palladium catalyst based on ligand **16** introduced by Buchwald *et al.* (*vide supra*). Furthermore, the reaction conditions were crucial and a careful adjustment was necessary to avoid deprotection of other functional groups present in the substrate.

3. Hydroxylation of alkenes

1,2-Diols are valuable intermediates for the preparation of pharmaceuticals, agrochemicals and fine chemicals.[22] Alkene *cis*-dihydroxylation constitutes an interesting synthetic method for their preparation and, indeed, this transformation has been traditionally performed stoichiometrically by osmium oxide.[23] However, the toxicity of the resulting by-products and the low-atom economy of this process requested for the development of environmentally-friendly alternatives. In this line, extensive efforts have been devoted to the design of catalytic systems for the efficient conversion of olefins into *cis*-1,2-diols. Besides several *cis*-dihydroxylation catalysts based on ruthenium, iron or manganese also palladium has been successfully applied for such transformations.[24]



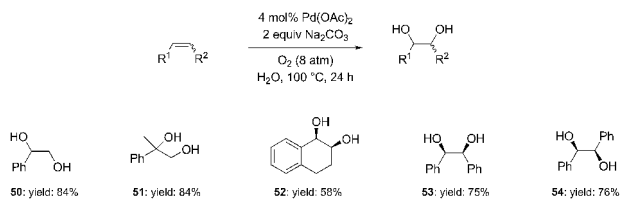
Scheme 12 Dihydroxylation of styrene derivatives in the presence of palladium catalysts.

In 2005 the group of Le Bras reported on the palladium-catalysed dihydroxylation of olefins applying hydrogen peroxide as an oxidant (Scheme 12).[25] In order to increase the solubility of the palladium source the hydrophilic ligand **47** was added which allowed the reaction to proceed in a mixture of water and alcohols as solvent.

However, due to the addition of alcohols, the replacement of the α-hydroxy functionality by the corresponding alcohol (alkoxylation reaction) was observed. Based on these results and additional mechanistic studies by Muzart and co-workers the authors assumed as an initial step a palladium-catalysed rearrangement of the C=C bond to form an internal olefin, which is epoxidised in a second step catalysed by palladium.[26] Finally, epoxide opening occurred by nucleophilic attack of water or the corresponding alcohol. Noteworthily, the group of Muzart reported also the catalyst recycling and good performance was still observed after 4 cycles.

The use of palladium to perform dihydroxylations has very recently been introduced by Wang and Jiang (Scheme 13).[26] This palladium-system is especially interesting as it relies on the use of molecular oxygen as the sole oxidant, which poses evident advantages (*vide supra*). In more detail, a wide range of olefins was selectively oxidized to the corresponding *cis*-1,2-diols in water at 8 atm of O_2-pressure and in the presence of 4 mol% $Pd(OAc)_2$ and 2 equiv. of base.

Mono- and disubstituted terminal alkenes as well as 1,2-disubstituted *cis*- or *trans*-olefins were transformed in good yields. The reaction could even be performed on a synthetically useful scale, here, 10 mmol of styrene were converted into the corresponding diol in 81% isolated yield. It is important to note that the presence of a base in the reaction mixture was essential to achieve selective dihydroxylation, while in its absence the system favoured the cleavage of the



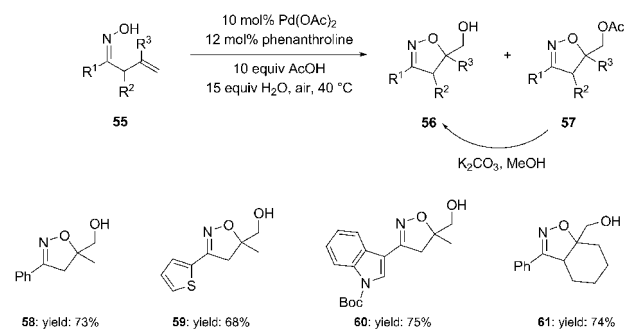
Scheme 13 Palladium-catalysed *cis*-dihydroxylation of olefins with molecular oxygen.

alkene to generate aldehydes. Furthermore, the presence of acid (*p*-toluenesulfonic acid) afforded a practical methodology for the oxidative cleavage of a wide range of olefins.

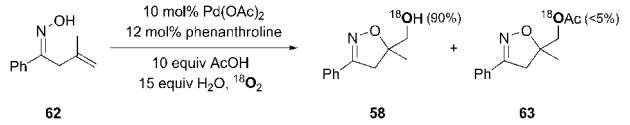
Although the aforementioned system developed by the group of Jiang for the dihydroxylation of alkenes employed molecular oxygen as the sole oxidant, an important drawback is related to the high pressure required for the reaction (8 atm). In this sense, it is especially interesting to mention the recent work reported by Loh and co-workers in which they demonstrated the efficiency of palladium complexes to perform the hydroxylation of alkenes with molecular oxygen as the oxidant under very mild conditions, *i.e.* low temperatures and atmospheric pressure.[27] The substrates of choice were synthetic molecules with a very particular design, so that it was *a priori* possible to combine intramolecular nucleopalladation and reductive elimination, while retarding the undesired β-hydride elimination. The substrates (Scheme 14) possessed a (*Z*)-oxime containing a strategically positioned disubstituted terminal alkene **55**. Treatment of those compounds in acetic acid with catalytic amounts of $Pd(OAc)_2$ in the presence of phenanthroline resulted in the oxygenation of the olefin to attain the hydroxylated **56** and the acetoxylated **57** products (~1 : 1 ratio). Several ligands and oxidants were examined, but so far the best results were obtained with phenanthroline as a ligand and air as an oxidant, which entails important advantages as far as practical and economical factors are concerned. As part of the work-up procedure, the initial mixture of **56** and **57** was treated with K_2CO_3 in methanol, to give exclusively alcohol **56**. The highest yields of products (45–75%) were obtained by combination of 1 atm of air, 10 mol% $Pd(OAc)_2$, 12 mol% phenanthroline, 10 equiv. AcOH and 15 equiv. H_2O, at 40 °C for several hours.

The substituents on the oxime moiety (R^1, Scheme 14) did not have any significant impact on the efficiency of the reaction and aliphatic, aromatic and heterocyclic groups were well tolerated.

Molecular oxygen was crucial for the reaction. Indeed, isotopic labeling experiments with $^{18}O_2$ (Scheme 15) showed that the oxygen atom incorporated into the hydroxylated product originated directly from O_2. The complementary experiment with $H_2{}^{18}O$ confirmed this result and almost no ^{18}O-incorporation into the hydroxyl group was detected in this case. It was postulated that the oxygenation or acetoxylation of a palladium-alkyl intermediate, formed by intramolecular nucleopalladation, led to the formation of the observed



Scheme 14 Palladium-catalysed oxime assisted intramolecular oxidation of alkenes with air as oxidant (Boc = *tert*-butoxycarbonyl).

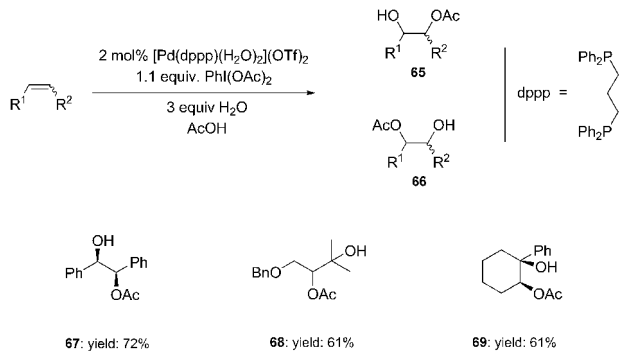


Scheme 15 Isotopic labelling experiments in the oxime-assisted intramolecular oxygenation of alkenes by palladium.

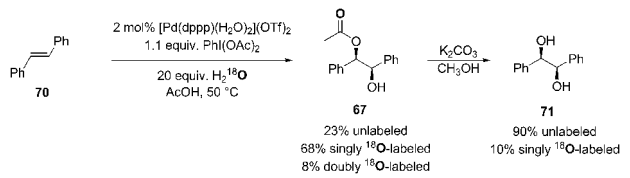
hydroxylated **58** and acetoxylated **63** products. The authors suggest the involvement of a Pd(II)/(IV) catalytic system as the formation of a C–O bond from a palladium-alkyl complex is usually observed in these systems.[28,29]

The palladium-catalysed oxidation of alkenes can also be applied to selectively hydroxyacetoxylate the C–C double bond, leading to a product bearing an alcohol with a vicinal acetate group.[30] It has been reported that $[Pd(dppp)(H_2O)_2](OTf)_2$ (2 mol%) (dppp = 1,3-bis(diphenylphosphino)propane) can be used to perform the hydroxyacetoxylation of *trans*-stilbene in wet acetic acid using $PhI(OAc)_2$ (1.1 equiv.) as an oxidant to obtain the *syn*-vicinal oxygenated product in 72% yield (Scheme 16). The selective formation of the hydroxyacetate product, in preference to the corresponding acetate, is especially surprising considering that acetic acid is used as a solvent. Apart from stilbene, other asymmetric 1,2-substituted olefins or monosubstituted terminal alkenes could be efficiently oxidized but, in such cases, a regioisomeric mixture of hydroxyacetate products (**65**:**66** = 1:1, Scheme 16) was observed. In sharp contrast, for trisubstituted olefins the hydroxyacetate regioisomer bearing a tertiary alcohol was exclusively formed.

In order to get insight into the reaction mechanism operative in this unprecedented transformation, isotopic labeling studies were performed by running the hydroxyacetoxylation of *trans*-stilbene in the presence of ^{18}O-labeled water (20 equiv.) in dry acetic acid (Scheme 17). MS-analysis of



Scheme 16 Palladium-catalysed hydroxyacetoxylation of olefins with $PhI(OAc)_2$ as oxidant.



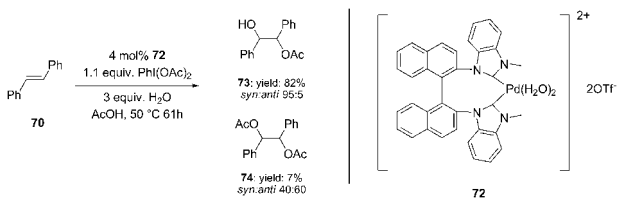
Scheme 17 Isotopic labeling experiments in the palladium-catalysed hydroxyacetoxylation of olefins with $PhI(OAc)_2$.

the final reaction mixture indicated the major presence of singly ^{18}O-labeled product (68%). Hydrolysis of the hydroxyacetate product with K_2CO_3 in methanol afforded the corresponding *cis*-diol, which was essentially unlabeled (90%). This result clearly indicates that the reaction product incorporates one oxygen-atom from water into the carbonyl group of the acetate moiety. The results of the isotope-labeling experiments together with the observed *syn*-selectivity allowed the authors to draw a mechanistic proposal. The key step in the proposed catalytic cycle corresponds to the acetoxypalladation of the palladium olefin complex. Oxidation of the acetoxypalladated species with $PhI(OAc)_2$ gives a Pd^{IV} species that after intramolecular cyclisation regenerates the catalyst and affords an acetoxonium ion, which gives after hydrolysis the *syn*-hydroxyacetate products with the carbonyl oxygen-atom originating from water (Scheme 17, **67**).

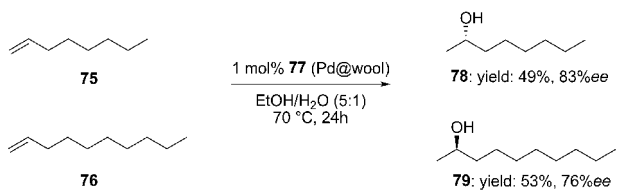
A quite similar reaction has been recently reported by the group of Shi applying palladium catalysts modified by *N*-heterocyclic carbene ligands **72** (Scheme 18).[31] However, longer reaction times are required to obtain reasonable amounts of product.

Besides the incorporation of two oxygen functionalities Jia and co-workers demonstrated the addition of water to C–C double bonds to form secondary alcohols (Scheme 19).[32] As a catalyst palladium(II) chloride supported on the chiral biopolymer wool was applied, which gave a heterogeneous catalyst. Due to the structure of wool, a chiral sphere around the palladium was created. Indeed, chirality was transferred to terminal aliphatic olefins such as 1-octene and 1-dodecene with enantioselectivities up to 83% ee. Surprisingly, the chain length of the olefin is crucial for the configuration of the product, so that in the case of 1-octene the *S*-enantiomer was detected, while for 1-dodecene the corresponding *R*-enantiomer has been found. Furthermore, the heterogenisation led to the recycling of the catalyst without any loss in activity after 4 cycles.

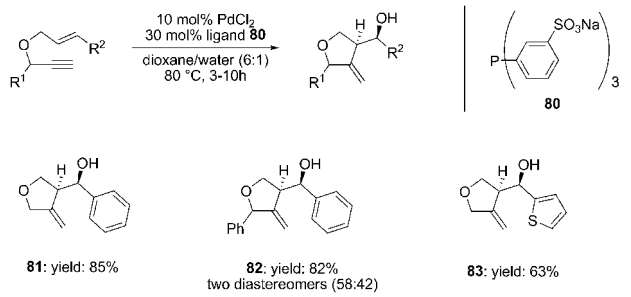
The group of Genêt reported a cyclisation and hydroxyfunctionalisation protocol of 1,6-enynes to obtain tetrahydrofuran derivatives (Scheme 20).[33] Applying a straightforward catalyst composed of $PdCl_2$ and the water-soluble phosphane



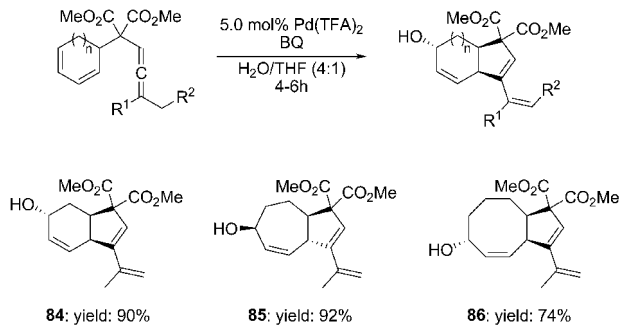
Scheme 18 Palladium catalyst modified by NHC-ligand (NHC = *N*-heterocyclic carbene).



Scheme 19 Palladium-catalysed hydration of aliphatic olefins.



Scheme 20 Carbohydroxypalladation of 1,6-enynes.



Scheme 21 Carbohydroxylation of allene-substituted conjugated dienes.

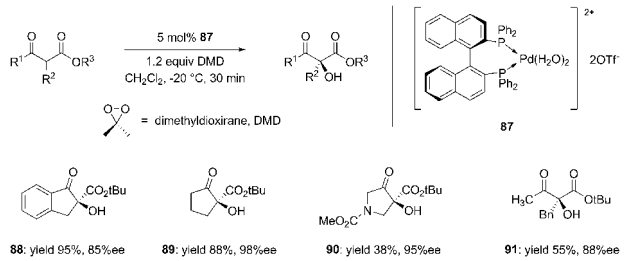
ligand **80** good yields of the corresponding tetrahydrofurans were obtained in a mixture of dioxane/water as solvent. The addition of the phosphane ligand was also important for selectivity reasons, since in its absence side products were detected.[34] Unfortunately, the stereochemistry was not completely investigated in some cases, while for **81** and **83** single diastereomers were found.

Additional experiments suggested a reaction mechanism *via* the coordination/activation of the triple bond by palladium, resulting in the reaction with the double bond to attain a cyclopropyl derivative, which undergoes ring-opening in the presence of water.[35]

More recently Bäckvall and co-workers reported the palladium-catalysed oxidative carbohydroxylation of allene-substituted conjugated dienes (Scheme 21).[36] The starting material was reacted with *p*-benzoquinone in the presence of catalytic amounts of palladium trifluoroacetate in a mixture of water/THF as solvent. Excellent stereocontrol was noticed with respect to the stereocenter in the starting material. Different ring sizes were feasible embedding the diene.

4. Hydroxylation of alkyl C–H bonds

α-Hydroxy-β-dicarbonyl compounds constitute valuable intermediates for the synthesis of attractive organic molecules including natural products and pharmaceuticals. The arguably most convenient and direct route to these compounds is the direct α-hydroxylation of readily accessible 1,3-dicarbonyls and for this reason, great efforts have been devoted to such useful transformation.[37] As an example, the use of stoichiometric amounts of base and a chiral oxaziridine (Davis reagent) has been employed in the asymmetric hydroxylation of β-ketoesters and enolates for the synthesis of natural products. Nevertheless, the catalytic version of these asymmetric hydroxylations has only

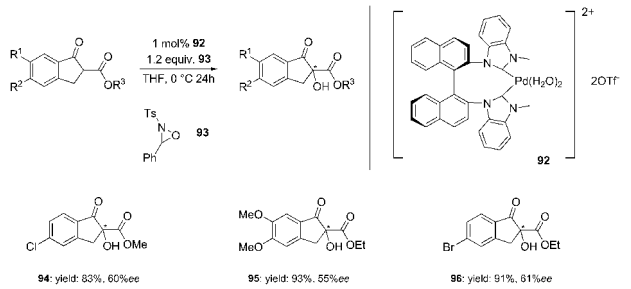


Scheme 22 Palladium-catalysed α-hydroxylation of β-ketoesters with DMD as oxidant.

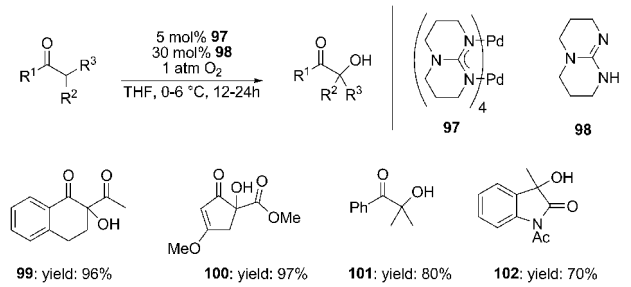
been recently developed. Some successful results include the use of chiral titanium, zinc or nickel-based catalysts.[38] Although high enantioselectivities can be obtained with these systems, in most cases they are limited to the hydroxylation of cyclic 1,3-ketoesters, as acyclic ones usually provide much lower yields.

Very recently Hii *et al.* developed a palladium-based system that could perform the same transformation in good yields with excellent enantioselectivity under mild conditions (Scheme 22).[39] The catalyst of choice was $[(R–BINAP)Pd(OH_2)_2](OTf)_2$, which had been already successfully used in asymmetric α-fluorination and α-amination of 1,3-ketoesters.[40] With a loading of 5 mol% of the palladium precursor the hydroxylation of a wide range of cyclic substrates was feasible using dimethyldioxirane (DMD, 1.2 equiv.) as an oxidant at low temperature (−20 °C) and in very short reaction time (30 min). The bulkiness of the ester substituent did not significantly affect the yield of the reaction but it was directly related to the enantioselectivity, so that the presence of a bulky *tert*-butyl group afforded higher enantioselectivity than ethyl or methyl groups. Remarkably, the hydroxylation reaction of acyclic 1,3-ketoesters was also achieved in reasonable yields and good enantioselectivity, although in this case higher catalyst loading, longer reaction times and slightly higher temperatures were required.

Improvements of the catalytic system were attempted by testing other oxidants and ligands for palladium(II) without much success.[41] The use of other simple oxidants (H_2O_2, tBuOOH, *m*-CPBA or Oxone®) only afforded decreased yields, lower enantioselectivities or both. Only the use of a *N*-sulfonyloxaziridine derivative as an oxidant gave comparable results to those obtained with dimethyldioxirane (DMD) but it failed to oxidize acyclic 1,3-ketoesters. However, the use of DMD was preferred as it presents an important advantage, *i.e.* both the oxidant and the side-product (acetone) are volatile and they can be easily removed from the reaction mixture at the end of the reaction. On the other hand, a ligand screening with different chiral diphosphines and *P*,*N*-ligands indicated that some systems could give even higher selectivities than R–BINAP but the low-availability and cost of these compounds rendered them as non-suitable metal-scaffolds for synthetic applications. Thus, the combination of palladium(II)/R–BINAP and DMD was established as the system of choice for the hydroxylation of 1,3-ketoesters. This transformation is proposed to occur through the initial formation of a palladium–enolate complex generated by the easy deprotonation of the acidic α-hydrogen of the 1,3-ketoester substrate. Electrophilic addition



Scheme 23 Asymmetric α-hydroxylation of β-ketoesters.



Scheme 24 Application of a dimeric complex in α-hydroxylation.

of DMD into the carbon–carbon double bond affords an epoxide intermediate that rearranges to a putative alkoxide complex. Final protonolysis (facilitated by the presence of triflic acid) regenerates the initial catalyst and liberates the hydroxylated product.

Later on the research group of Shi modified the pre-catalyst structure by embedding NHC-ligands in the chiral binaphthyl unit (Scheme 23).[42] Under mild reaction conditions cyclic β-ketoesters were converted to the corresponding α-hydroxy-β-dicarbonyl compounds with moderate enantioselectivity, while acyclic substrates were not transformed at all.

More recently the group of Ritter reported on the application of a high valent dimeric palladium-catalyst which is capable to perform the α-hydroxylation of β-ketoesters, β-ketones, β-ketoamides, esters, diesters, and ketones applying molecular oxygen as an oxidant (Scheme 24).[43] The paddle-wheel complex **97** demonstrated, in combination with an extra portion of the pure ligand **98**, excellent selectivities towards the α-hydroxylation, since functional groups were well tolerated, *e.g.* additional carbon–carbon double bonds were stable under the reaction conditions and no epoxidations or hydroxylations were observed. Furthermore, highly functionalised compounds such as the biotin residue or indoles were converted. In addition, mechanistic investigations revealed that the oxygen of the hydroxy group originated from molecular oxygen.

5. Palladium-catalysed alkoxylation

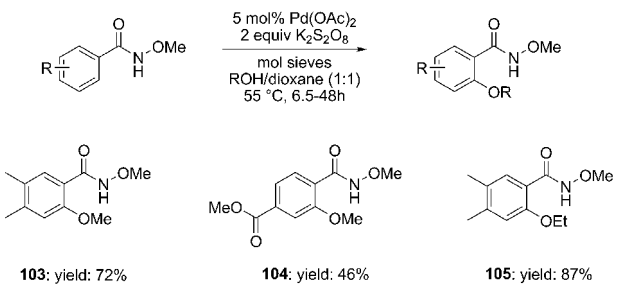
An immense number of ether-containing chemicals are produced for pharmaceutical, bulk and fine chemical industries (see for instance Fig. 1).[44–46] One possibility to form ether bonds can be the reaction of alcohols with appropriate electrophiles. Despite the fact that various protocols are already established, novel methodologies for C–O bond formations are still of interest and a challenging task. Here the ability of palladium to activate electrophiles can be useful. Indeed, manifold catalytic reactions based on palladium have been reported so far. Since excellent overviews have been collected recently by Muzart and Beccalli, we will focus on the transformation of aromatic C–H and C–X (X = halides) bonds.[47,48]

5.1 Formation of aryl alkyl ethers—transformation of aromatic C–H bonds

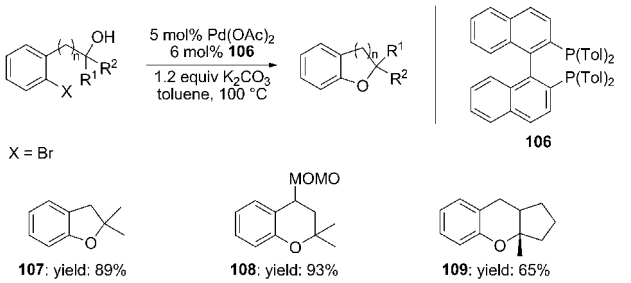
The formation of aryl alkyl ethers by activation of aromatic C–H bonds has been scarcely presented. The group of Wang reported on the alkoxylation of aromatic C–H bonds using *N*-methoxyamides as directing group (Scheme 25).[49] After exploration of the reaction conditions (*e.g.*, solvents, oxidants), the best system was found to be a combination of catalytic amounts of $Pd(OAc)_2$ (5 mol%) and $K_2S_2O_8$ in a mixture of dioxane and an alcohol, which was applied as an alkoxylation reagent. After having set up suitable reaction conditions, more than 20 different aromatic substrates containing the *N*-methoxyamide functionality were converted to the corresponding ethers. Noteworthily, for all substrates an excellent selectivity was observed, so that the C–O bond was formed at the *ortho*-position with respect to the directing group. The potential of this method and especially the impact of the *N*-methoxyamide was demonstrated for substrates containing additional directing groups, such as ester functionalities, since only the *ortho*-substitution was observed. Wang and co-workers proposed a mechanism based on a C–Pd species, which is stabilised by the *N*-methoxyamide group.

5.2 Formation of aryl alkyl ethers—transformation of aryl halides

In contrast to the transformation of aromatic C–H bonds to ethers, the conversion of aromatic C–X bonds has been studied more frequently.[50] At an early stage the group of Buchwald demonstrated the abilities of palladium-catalysts modified by bidentate phosphane ligands in the intramolecular C–O bond formation (Scheme 26).[51] Applying a pre-catalyst composed of $Pd(OAc)_2$ and ligand **106** or dppf[1,1′-bis(diphenylphosphino)ferrocene] various heterocycles could be synthesised at 100 °C in toluene. The addition of base was crucial to allow the cyclisation reaction. The authors assumed an oxidative addition of the bromoarene to the palladium, which eliminates after basification the desired heterocycle and a Pd(0) species which can undergo the transformation of the next substrate molecule. Several kinetic measurements and isolation of intermediates have been carried out to support this assumption.[52,53] The protocol was also applicable in the



Scheme 25 Palladium-catalysed alkoxylation of aromatic C–H bonds.



Scheme 26 Synthesis of oxygen containing heterocycles (MOM = methoxymethyl).

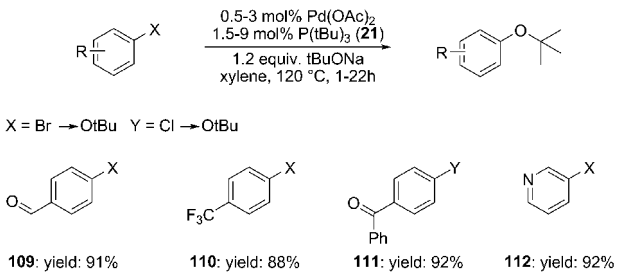
presence of protecting groups. The procedure has been later on transferred to the transformation of secondary and primary alcohols but using milder reaction conditions.[54]

In the same year Hartwig and co-workers studied the reductive elimination of aryl alkyl ethers from a palladium alkoxide complex modified by the dppf ligand.[55–58] This investigation resulted in the catalytic transformation of substituted bromoarenes and sodium *tert*-butoxide to the corresponding ethers.

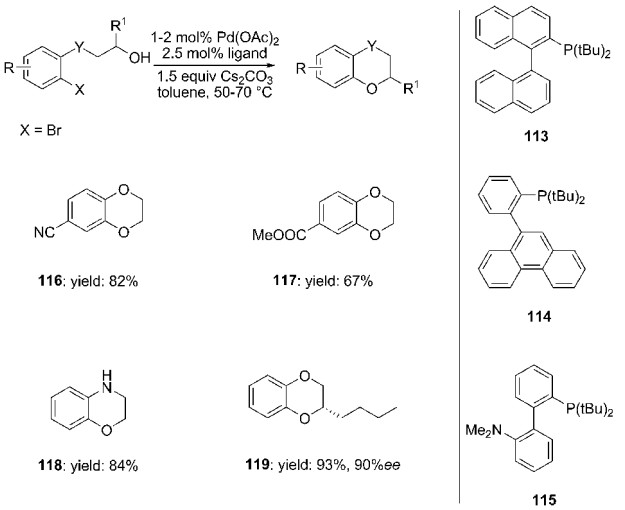
The system was later on adapted by the group of Watanabe (Scheme 27).[59] Applying a straightforward system composed of $Pd(OAc)_2$ and ligand **21** with very low catalyst loadings in the range of 0.5–3 mol% various aryl bromides and even chlorides were converted with potassium *tert*-butoxide to the corresponding aryl alkyl ethers. A careful investigation of the reaction mixture showed the formation of the dehalogenated arene or biaryls. The protocol was furthermore applied in the synthesis of benzofurans.

In 2000 the group of Buchwald continued their earlier work on the synthesis of oxygen containing heterocycles (Scheme 28).[60] They enlarged the applicability of the palladium-catalysed reaction towards the production of 5–7 membered rings. A special attention was directed to the utilisation of monodentate phosphane ligands (**113–115**), which showed excellent performance with low loadings. Further on the protocol was directed to products, which contain different heteroatoms, such as oxygen or nitrogen. Excellent results were obtained in the presence of functional groups at low temperature (50–70 °C).[61,62] Additional experiments showed the stability of chiral groups under the described reaction conditions (Scheme 28, **119**).

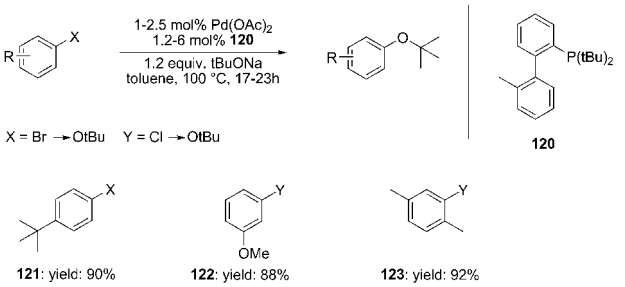
The concept of monodentate phosphane ligands (*e.g.*, **115** and **120**) was furthermore applied in the case of unactivated aryl halides demonstrating the advantages of this ligand class (Scheme 29).[63] With those ligands, especially biphenyl-based



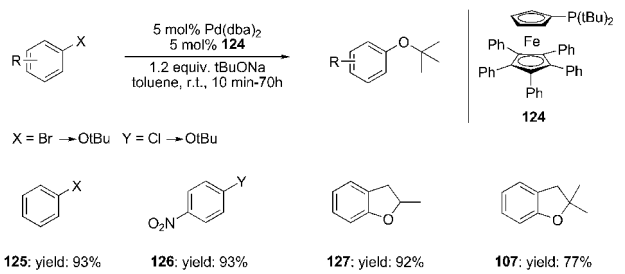
Scheme 27 Alkoxylation protocol established by Watanabe *et al.*



Scheme 28 Palladium-catalysed synthesis of oxygen containing heterocycles.



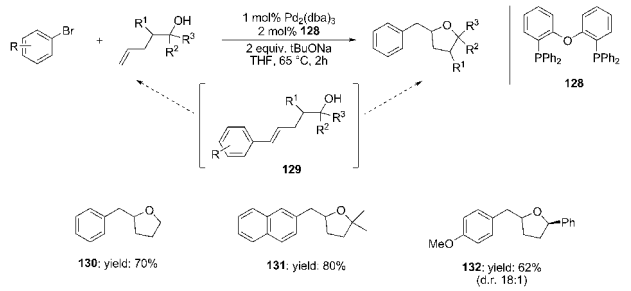
Scheme 29 Palladium-catalysed formation of ethers from unactivated aryl halides.



Scheme 30 Palladium-catalysed formation of ethers.

ligands, low catalyst loadings and lower reaction temperature were feasible to convert various halides in good to excellent yields.

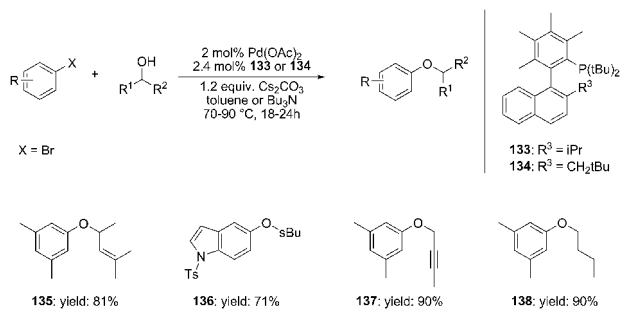
In 2000 the group of Hartwig demonstrated an extraordinary catalyst for palladium-catalysed alkoxylation reactions (Scheme 30).[64,65] An *in situ* formed pre-catalyst composed of $Pd(dba)_2$ and the ferrocene based phosphane ligand Q-Phos (**124**) was highly active at room temperature and it alkoxylated various substrates within 30 min. Furthermore an excellent group tolerance was noticed. Also the synthesis of heterocycles in analogy to Buchwald *et al.* (*vide supra*) was feasible at room temperature within short reaction times. Noteworthily, no significant difference was observed for bromo and the less activated chloro substrates.



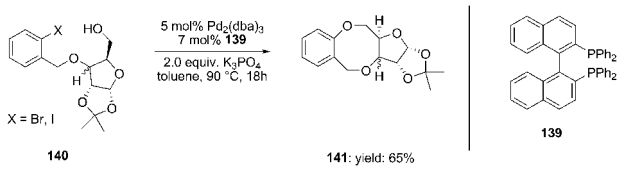
Scheme 31 Palladium-catalysed cascade reaction.

The research group of Wolfe embedded the alkoxylation protocol in the synthesis of substituted furan derivatives (Scheme 31).[66] A palladium catalyst based on $Pd_2(dba)_3$ and the bidentate phosphane ligand DPE-Phos (bis(2-diphenylphosphinophenyl)ether, **128**) was capable, on the one hand, to perform a Heck reaction to create a C–C bond between the aromatic system and the γ-hydroxy alkenes. On the other hand the double bond of the intermediate is activated by the palladium-catalyst to allow the nucleophilic attack of the hydroxyl group *via* an intramolecular cyclisation. The impact of this methodology was demonstrated for more than 50 different substrates, including various functional groups, various substitution patterns with excellent diastereoselectivity. Noteworthily, the reaction was complete within 2 hours at 65 °C.

In their early works Buchwald and co-workers have demonstrated the need of sterically hindered basic phosphanes. In 2005 the group reported their proceedings in the development of easy to access monodentate ligands (Scheme 32). After initial screening of various ligands in the alkoxylation of aromatic substrates with secondary alcohols, the ligands with the 1-phenyl naphthyl backbone were found to be superior (Scheme 32, **133** and **134**). With this system in hand various substrates, including functional groups such as trifluoromethyl, methoxy, C–C double bonds, alkyne, ester, indole, and tosylate, were converted in good to excellent yields in combination with secondary or primary alcohols to the corresponding aryl alkyl ethers. Noteworthily, the described catalyst system was able to distinguish between primary and secondary alcohols, since the primary alcohol was transformed to the ether, while the secondary remained untouched. In addition, the group drew some conclusion concerning the relationship between the ligand structure and the preferred transformation (*e.g.*, primary or secondary alcohols).



Scheme 32 Application of monodentate phosphanes in palladium-catalysed alkoxylation.

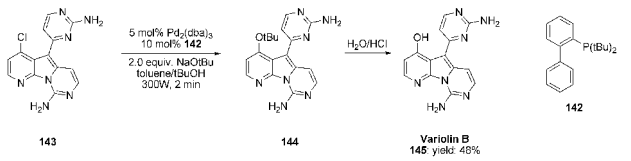


Scheme 33 Synthesis of 8-membered rings *via* palladium-catalysed alkoxylation.

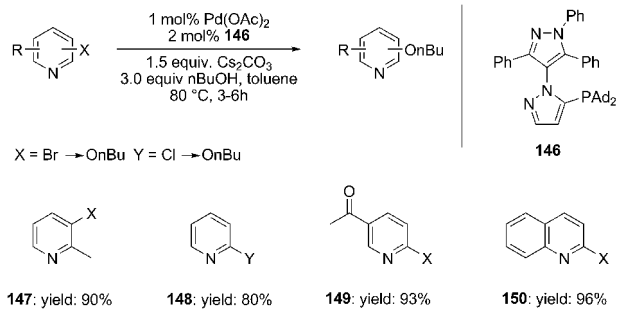
Chattopadhyay and co-workers embedded a palladium-catalysed alkoxylation protocol in the synthesis of benzodioxocines, which are interesting compounds in nature as well as for pharmaceutical applications (Scheme 33).[67] This was the first report on the synthesis of 8-membered rings, because so far only 5 to 7 membered rings had been reported (*vide supra*). The applied pre-catalytic system $Pd_2(dba)_3$ and racemic BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, **139**) was able to perform the ether formation at 90 °C in toluene with good yields. Noteworthily, the backbone of the substrate containing a furanose derivative was quite stable, as no deprotection or racemisation was reported. Furthermore, the system was applicable for pyranose derivatives with similar results.

Moreover, in the same year Burgos, Vaquero and co-workers invented a palladium-catalysed alkoxylation procedure for the synthesis of Variolin B (**145**), which is a marine alkaloid with antitumoral activity (Scheme 34).[68] After the search for suitable reaction conditions with a model substrate, they found a suitable protocol based on $Pd_2(dba)_3$ and monodentate ligand **142**. The reaction was accomplished within minutes using microwave techniques. A transfer of the conditions to the synthesis of Variolin B was successful. Alkoxylation of the chloro compound **143** led to the aryl alkyl ether **144**, which was further on cleaved to yield a hydroxy functionality and **145**.

More recently the group of Beller reported the synthesis and application of a novel type of monodentate phosphane ligand



Scheme 34 Application of monodentate phosphanes in palladium-catalysed alkoxylation in natural product synthesis.



Scheme 35 Application of monodentate phosphanes in palladium-catalysed alkoxylation of heteroaromatic compounds.

146 in palladium-catalysed alkoxylation reactions (Scheme 35).[69] This bulky phosphane ligand in combination with palladium(II) acetate revealed an excellent catalyst for the reaction of aryl bromides and chlorides with the primary alcohol. In the presence of caesium carbonate as base and toluene as solvent more than 20 different substituted arenes were transformed to the corresponding ether. In comparison, applying bromides as starting material a better performance of the catalyst was observed, while the chloride substrate gave to some extent lower yields. The presented system tolerates various functional groups, *e.g.*, nitriles, aldehydes, esters or ketones. After having found a suitable catalyst, Beller and co-workers tried to react more challenging nitrogen-based heteroaromatic substrates with butanol. Indeed, the system led to excellent conversions of various substituted pyridines, quinolines and isoquinolines.

6. Conclusions

The formation of C–O bonds, *e.g.* hydroxylations and alkoxylations, is one of the fundamental transformations in organic synthesis. In this regard the application of homogeneous palladium-based catalysts has been extensively studied during recent years. Nowadays it is an established methodology and the success has been proven in manifold synthetic procedures and applications in natural product synthesis.

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