Catalysis by Palladium Pincer Complexes

ARTICLE *in* CHEMICAL REVIEWS · NOVEMBER 2010

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Catalysis by Palladium Pincer Complexes

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1. INTRODUCTION

1.1. General Considerations

Palladium catalysis is one of the most important synthetic tools in modern organic synthesis. A particularly attractive synthetic feature of palladium catalysis is its broad synthetic scope and the possibility to control the selectivity of the transformations.[1−3] An ideal catalyst has to be stable and highly selective, but also highly active to ensure high turnover numbers and permit low catalyst loadings. Moreover, it needs to be amenable to rational design, giving the possibility for fine-tuning the catalytic properties of the metal center. These issues can usually be solved by an appropriate choice of ligands. One of the successful strategies is to use tridentate ligands, such as pincer ligands, to accomplish a well-defined metal−ligand bonding. Since the first reports from Shaw,[4] van Koten,[5] and Noltes[5] in the 1970s, a plethora of different pincer complexes has been synthesized and studied in multifarious catalytic applications. Although several excellent reviews[6−16] on palladium pincer complexes have been published so far, a large number of recent studies have been reported on the catalytic application of these complexes in the last five years. The aim of this review is to summarize the key achievements for catalytic application of pincer complexes in organic synthesis from 2005 to early 2010. Accordingly, the main focus is directed to the properties, synthesis, and reactivity of those pincer complexes that are successfully employed or could be important for catalytic applications. Thus, this review is, of course, not comprehensive for description of all the properties and structural details of palladium pincer complexes. We briefly discuss the nomenclature, basic properties, and synthesis of pincer complexes important for catalytic applications, followed by a survey of the most important types of catalytic transformations, in which these complexes are involved.

1.2. Nomenclature

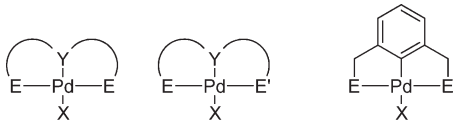
Cyclic palladium complexes incorporating at least one carbon−palladium bond are called palladacycles.[15,17−21] Pincer complexes are a subclass of these species incorporating two fused palladacycles (Scheme 1). The basic type of the complexes has a typical ECE architecture (**1a**, Y = carbon) in which E are a versatile class of usually neutral species, such as NR_2, PR_2, SR,

Special Issue: 2011 Frontiers in Transition Metal Catalyzed Reactions

Received: July 7, 2010
Published: November 18, 2010

dx.doi.org/10.1021/cr1002112 | *Chem. Rev.* 2011, 111, 2048–2076

Scheme 1. Schematic Representation of the Pincer Complex Architecture



and SeR. These neutral species (E) with their spacer are usually referred to as the side arms.

A practical way of classifying the various pincer ligands is based on the three atoms coordinating to the metal center, abbreviated to ECE. For example, complex **1b** with amino ligands (E = NR_2) in the side arms would be called an NCN complex and with phosphines (E = PR_2) a PCP complex. The side arms stabilize the pincer complexes and strongly affect the electronic properties of the palladium center. There are some recent catalytic applications in which interesting new catalytic properties arise from the replacement of the carbon−palladium bond with other isoelectronic structure elements,[22−24] such as silicon−palladium, phosphorus−palladium bonds (Y = Si and P, respectively). In some cases, the palladium atom is coordinated to a neutral aromatic nitrogen atom (Y = N)[25−28] instead of an anionic carbon. Since replacement of carbon in the C−Pd bond with heteroatoms (such as Si, P, and N) sometimes leads to important improvements of the catalytic activity, we also discuss the reactivity of these complexes. Another important strategy to improve the catalytic activity is application of two different donors in the side arms (EYE′, **1a′**),[14] creating unsymmetrical palladium pincer complexes. However, the most commonly employed pincer complexes are based on an aryl group and symmetrical side arms (**1b**). One obvious reason for using symmetrical pincer complexes in catalysis is the relatively easy synthesis of these species (section 2). Considering the fact that the most widespread applications of pincer complexes in organic synthesis involve ECE type pincer complexes, this review is largely focused on recent studies on these complexes. As the main goal of this review is to demonstrate the efficiency of using pincer complexes in organic synthesis, we refer the reader to previously published reviews[6,7,10−15] for a more comprehensive treatment of the synthesis, properties, and other application areas of pincer complexes.

1.3. Basic Properties

The unique pincer architecture accounts for many desirable properties of palladium pincer complexes in catalytic transformations. As a consequence of the firm tridentate coordination mode, the palladium pincer complexes show a high thermal stability. In addition, most of the complexes are stable toward moisture and air, resulting in easy handling and storage. These important aspects ensure high durability of the catalyst and a broad reaction scope. The pincer ligand is also crucial for the selectivity of the catalysis. Under ambient conditions, the oxidation state of palladium is largely restricted to +II. Thus, in the d^8 square planar Pd(II) pincer complexes, only one free coordination site is available for catalysis. This implies that formation of undesirable side products arising from ligand exchange processes can be avoided. Reduction of the palladium atom of pincer complexes to Pd(0) leads to a usually irreversible cleavage of the palladium−carbon (or Pd−Y) bond,[29,30] which eventually leads to decomposition of the complex. Under such reaction conditions, the pincer complexes are not direct catalysts of the transformations but serve as dispensers of often highly active Pd(0) species, such as Pd(0) clusters or nanoparticles. However, it is important to note that Milstein and co-workers[31] provided convincing evidence that under mild reaction conditions the palladium atom of PCP pincer complexes may undergo reversible Pd(II) to Pd(0) transformations. Unlike reduction of the Pd(II) central atom to Pd(0), its oxidation to Pd(IV) does not lead to a cleavage of the palladium−carbon bond of the complex.[32−35] The electron-donating character of the formally anionic carbon attached to palladium renders oxidation of pincer complexes easier than that for most of the common inorganic palladium salts, such as $PdCl_2$ and $Pd(OAc)_2$, often used as catalyst precursors in synthesis. Thus, several examples of Pd(IV) pincer complexes have also been reported and suggested as catalytic intermediates,[34,36−38] expanding both the coordination sphere of palladium and, thus, the synthetic scope of catalysis.

Perhaps the most attractive feature of palladium pincer complexes is the unique possibility for fine-tuning the catalytic activity of the palladium atom. Since the meridional oriented pincer ligand is coplanar with the coordination site available for catalysis, steric and electronic properties of the pincer ligand can efficiently be transferred to the palladium center. Varying the side arms (E) of the pincer ligand, using different donor groups, has a direct impact on the reactivity of the pincer complex. Furthermore, the accessibility of the active site of palladium can be altered by steric factors, and many different asymmetric applications have been developed using chiral groups on the side arms. Pincer complexes with aromatic backbones give the possibility to induce remote electronic effects with para substitution[39] of the aryl moiety. Additionally, dendrimers[39] and polymer supported[40] pincer complexes have been synthesized, representing valuable contributions to environmentally benign and sustainable catalysis.

2. SYNTHESIS OF PALLADIUM PINCER COMPLEXES

The synthesis of pincer complexes is sometimes considered as a limiting factor for their application in catalysis. Some synthetic precursors of pincer complexes are commercially available; however, development and conscious use of pincer complex catalysis often require synthesis of both the pincer proligands and the complexes. Moreover, the efficient tunability of the complexes is a great advantage, but it requires that a set of pincer complexes with widely different substituents (E) in the side arms are to be tested in the studied catalytic transformations. This section concentrates on the most basic techniques applied for the synthesis of pincer complex catalysts, starting with the simplest modular methods for preparation of aryl based symmetrical pincer complexes (such as **1b**). It is important to emphasize that the most common type of NCN, PCP, and SCS complexes are as easy to prepare as some of the commonly used palladium sources, such as $Pd(PPh_3)_4$ or $Pd_2(dba)_3$.

2.1. Oxidative Addition

Probably the simplest and most efficient way to synthesize pincer complexes is based on an oxidative addition of Pd(0) species, such as $Pd_2(dba)_3$, to the carbon−halogen bond of the pincer proligand. For example, this synthetic route can be employed to obtain NCN complex **1c** (Scheme 2).[41] The process starts from tribromide **2**, which is reacted with dimethyl amine to afford **3**. In our experience, the yield of **1c** is higher when **3** is purified by silica chromatography prior to the palladation step. It is important to keep in mind that **3** is relatively

dx.doi.org/10.1021/cr1002112 |*Chem. Rev.* 2011, 111, 2048–2076

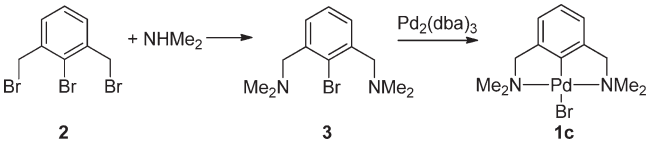
unstable under ambient conditions (reacts with CO_2 from air); therefore, it is advisable to use it directly after purification. Reaction of **3** with $Pd_2(dba)_3$ in benzene or toluene affords **1c** in high yield (88%). Complex **1c** is air and moisture stable (interestingly, much more stable than its precursor **3**), and it can be purified without any loss using silica-gel chromatography.

Phosphine containing PCP complexes are also easily available by the above-described C−X bond oxidative addition sequence. Synthesis of the versatile phosphinite based PCP complex **1d** can easily be achieved starting from resorcinol derivative **4** and chlorophosphine **5** (Scheme 3).[42] The first step is very sensitive to any traces of moisture, and therefore, it has to be carried out under inert conditions. Compound **6** is also unstable under ambient conditions, and it cannot be purified by chromatography without extensive degradation. Therefore, it is used directly in the palladation process.

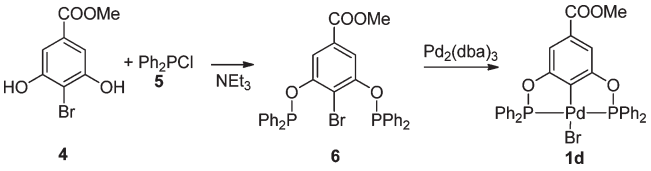
This strategy can be used for the synthesis of a broad variety of PCP complexes (see, for example, Scheme 4). Very often, iodoresorcinol (**7**) is used for synthesis of the proligand (Scheme 5). In this way, the palladation involves oxidative addition of Pd(0) species to a reactive C−I bond, which is beneficial for two major reasons: (i) the palladation occurs easily even in the presence of bulky substituents in the side arms, such as in chiral pincer complexes (**1e**−**j**), and (ii) the halophosphonate proligands (such as **6** or **9**) are usually air-sensitive compounds with low thermostability. Therefore, a high yield for the complex requires mild conditions and a relatively fast oxidative addition of Pd(0).

A highly modular synthesis of various chiral pincer complexes was reported starting from TADDOL (**1e**),[43] BINOL (**1f**−**i**),[43−45] and bisphenanthrol[44] (**1j**) derivatives (Scheme 4). The synthesis of these complexes (Scheme 5) was based on conversion of the corresponding chiral diol (such as **8**) to halophosphinate (such as **9**), which was reacted with iodoresorcinol **7**, affording proligand **10**. These types of proligands are relatively easily palladated to give C_2-symmetrical chiral complexes, such as bisphenanthrol complex **1j**. The procedure is efficient even in the presence of γ-substituents (Cl, S-alkyl groups) on the chiral diol and can be used even for relatively bulky side arms. It is important to emphasize that **9** and **10** and their analogues are water sensitive, and therefore, these compounds have to be handled under inert atmosphere and normally used without purification. On the other hand, the final products, complexes **1e**−**j**, are highly stable to air, to moisture, and at elevated temperatures. In some catalytic applications (see section 5), the iodide counterion has to be replaced by a less coordinating anion, such as trifluoroacetate. This usually can be carried out by using the corresponding silver salts (such as silver trifluoroacetate), with the exception of **1i**, which decomposes by treatment with silver salts.

Scheme 2. Synthesis of NCN Complex 1c by Oxidative Addition of Pd(0) to a C−X Bond[41]



Scheme 3. Synthesis of PCP Complex by Oxidative Addition[42]

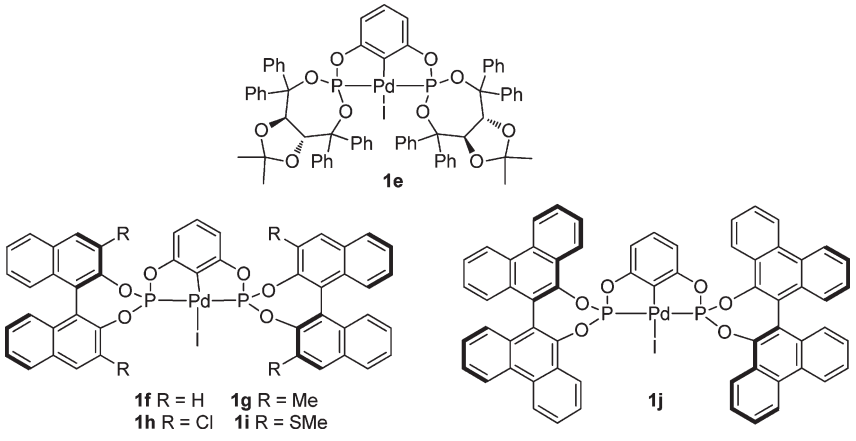


2.2. C−H Activation

The C−H activation/cyclometalation is also a major strategy for the preparation of palladium pincer complexes.[46,47] These methods involving C−H activation require simpler precursors than the above-described procedures based on C−X bond activation (section 2.1). However, the success of these procedures is more dependent on the electronic character and bulkiness of the side arm ligands (E in **1b**). Therefore, the C−H activation based synthesis of pincer complexes usually requires more experience in organometallic synthesis than the alternative methods involving oxidative addition of C−X bonds (Schemes 2 and 5).

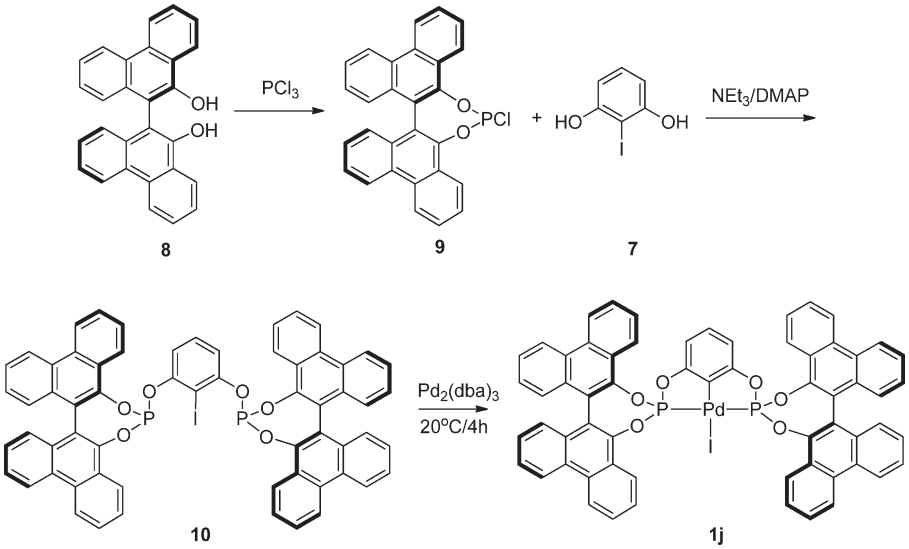
An important difference between the C−X and C−H activation strategies is the different oxidation states of the employed palladium precursor. The oxidative addition to the C−X bond is performed using Pd(0) species (often $Pd_2(dba)_3$), while the C−H activation is done with Pd(II) species. The C−H activation is usually dependent on the ancillary ligands on the Pd(II)

Scheme 4. Examples of Chiral Pincer Complexes Easily Accessible by C−I Bond Metallation[43−45]



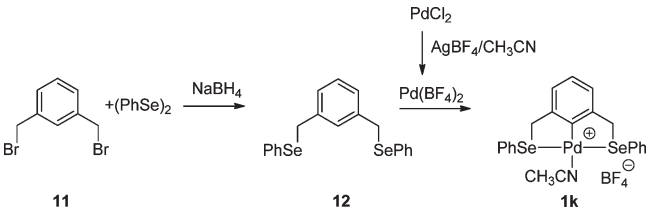
dx.doi.org/10.1021/cr1002112 |Chem. Rev. 2011, 111, 2048–2076

Scheme 5. Examples of Synthesis of Chiral Palladium Pincer Complexes[44]



8 9 7 10 1j

Scheme 6. Synthesis of Pincer Complexes via C−H Activation by in Situ Generated $Pd(BF_4)_2(CH_3CN)_4$[50]



11 12 1k

precursor. Very efficient C−H activation can be achieved using palladium(II) salts with weakly coordinating ligands, such $Pd(OCOCF_3)_2$[48] or $Pd(BF_4)_2(CH_3CN)_4$.[30,42,49,50] Although these reagents are commercially available, they are rather expensive. However, it was found that, for example, $Pd(BF_4)_2(CH_3CN)_4$ can be easily generated in situ prior to the C−H activation process. Accordingly, selenium-based complex **1k** was synthesized from pincer-proligand **12** obtained by selenylation[51] of **11** using diphenyl diselenide under reductive conditions. Proligand **12** is now also commercially available from Aldrich. The key step is the C−H activation by $Pd(BF_4)_2(CH_3CN)_4$ generated in situ from relatively inexpensive $PdCl_2$ and $AgBF_4$ in acetonitrile (Scheme 6).[50] A great advantage of complex **1k** is that the ligand on palladium can be easily varied by adding lithium halides, pyridines, phosphines, or other relatively tightly bonding ligands, in order to fine-tune the activity of the pincer complex. The first synthesis of SeCSe-Pd complexes from **11** was reported by Yao and co-workers[51] using a different C−H activation technique.

An alternative way of obtaining pincer complexes by C−H functionalization is via so-called "transcyclometallation" reactions.[52] This strategy (Scheme 7) can be used for the synthesis of PCP type complexes (such as **1d**).[53] An excellent palladium source for transcyclometalation is complex **13**,[54] which is commercially available. Thus, PCP complex **1l** can be prepared by a simple two step sequence starting with the phosphorylation of resorcinol **14**, followed by transcyclometalation of **13** with phosphinite proligand **15**. An alternative method for the synthesis of **1l** is by reaction of **15** with $Pd(OCOCF_3)_2$ reported by Bedford and co-workers.[48]

Synthesis of chiral pincer complexes such as **1m** can also be achieved by the C−H activation methodology (Scheme 8).[47] Thus, *tert*-butyl resorcinol derivative **16** was reacted with chlorophosphinate **17** to obtain proligand **18**, which was metalated by $PdCl_2(CH_3CN)_2$, affording complex **1m**. Interestingly, the aromatic ^{t}Bu groups have an accelerating effect on the C−H activation process, probably for steric reasons.[47]

2.3. Ligand Introduction Route

The above presented methods (sections 2.1 and 2.2) are based on the synthesis of pincer proligands (such as **3**, **6**, **10**, **12**, **15**, and **18**) followed by metalation of the C−X and C−H bonds with Pd(0) and Pd(II) species, respectively. As in these methodologies, the last step of the synthesis is the introduction of palladium, these techniques are also called "metal introduction routes". As mentioned above, these methods usually provide easy access to pincer complexes, but they are sometimes sensitive to the steric bulk of the substituents in the side arms. Uozumi and co-workers[55−58] described an interesting alternative to the metal introduction route, which circumvents the problems caused by bulky substituents in the side arms. The basic element of their strategy is introduction of the palladium atom in an early stage of the synthesis of the complex, and therefore, this method is called a "ligand introduction route". A representative example of this methodology is the synthesis of chiral NCN complex **1n** (Scheme 9). The key step is synthesis of complex **20** by oxidative addition of $Pd_2(dba)_3$ to the C−OTf bond of **19** in the presence of PPh_3 and subsequent addition of LiCl. The next step is addition of prolinol derivative **21** to furnish complex **1n**. The bulky chiral auxiliaries are important to obtain high selectivity in asymmetric Michael addition reactions (section 4.2).[56] Uozumi and co-workers[57,58] have demonstrated that a large variety of NCN and PCP complexes can be prepared using the "ligand introduction" strategy.

Another innovative ligand introduction approach for the synthesis of aminophosphine-based palladium pincer complexes was reported recently by Frech and co-workers.[59] This strategy was based on synthesis of a palladium tri(piperidinyl)phosphine

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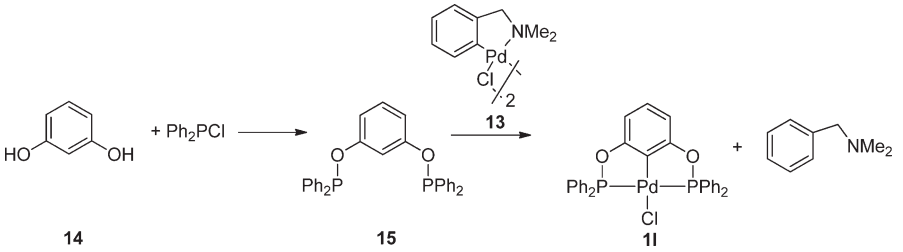
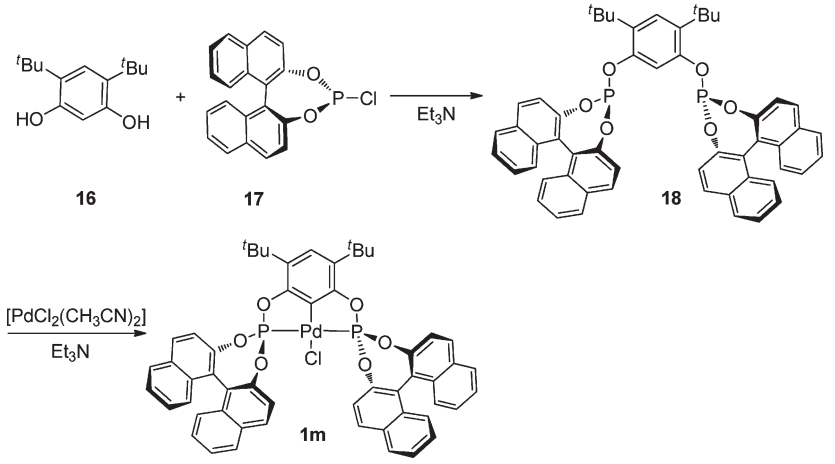
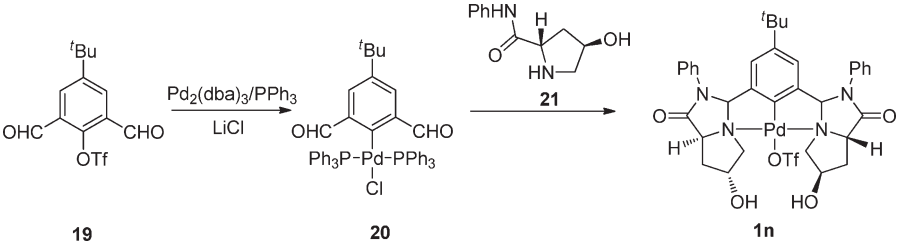
Scheme 7. Pincer Complexes Obtained by Transcyclometallation[48]



Scheme 8. Synthesis of Chiral Pincer Complexes by C−H Activation[47]



Scheme 9. Synthesis of Pincer Complexes by the "Ligand Introduction Route"[55−58]



complex that subsequently was reacted with 1,3-diaminobenzene or resorcinol to construct the pincer architecture.

3. CROSS-COUPLING REACTIONS

Cross-coupling reactions represent one of the most important types of catalytic carbon−carbon bond forming reactions.[1−3] Accordingly, pincer complex catalysts have been extensively used in these processes. The first Heck reaction with palladium-pincer complex catalysts was published by Milstein and co-workers,[36] and since then a large number of publications has appeared on cross-coupling reactions. The largest areas are the Heck-coupling/Heck-type reactions[25,38,51,60−86] and Suzuki−Miyaura coupling and related processes.[28,59,62,68,72,73,87−108] In addition, there are several recent publications on Sonogashira,[72,95,107,109,110] Stille,[74,111] Negishi,[26,27] and Hiyama[95] coupling reactions as well. The most important synthetic results are characterized by high turnover numbers (TON),[19,93,112] as well as interesting asymmetric applications.[76,92] The mechanistic aspects of the palladium pincer complex-catalyzed processes are particularly well-studied. An important reason for this is an ongoing debate on the actual role of pincer complexes in these reactions. Several studies[20,29,30,60,69,78,82,86,113] concluded that pincer complexes decompose under the applied, often harsh conditions, and the catalytic activity arises from the Pd(0) decomposition products, such as colloidal palladium in the form of palladium clusters or nanoparticles. In these processes, the pincer complexes are not direct catalysts of the coupling reactions but dispensers of reactive palladium species, which are released from their pincer ligands. Formation of palladium nanoparticles or homogeneous Pd(0) catalysts can be detected using various methods, which are very often employed in these studies. However, precipitation of palladium-black (amorphous metallic Pd(0)) is a clear indication for decomposition of the applied pincer complex catalysts. On the other hand, a great number of studies present convincing evidence that palladium pincer complexes are, in fact, the direct

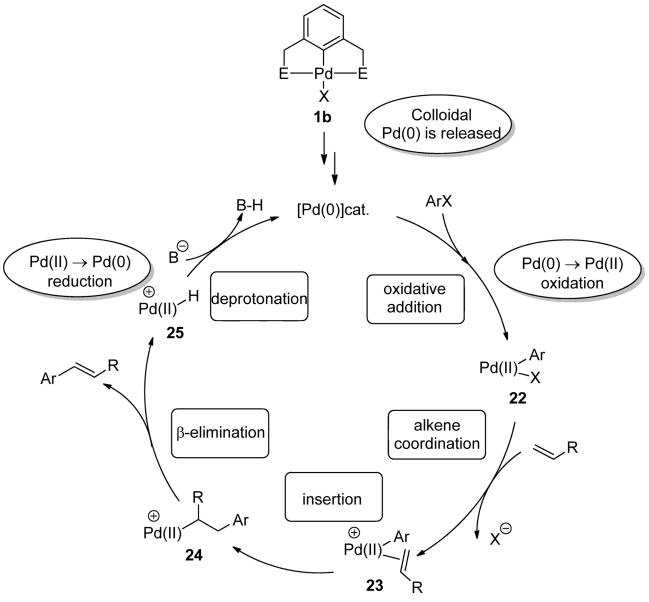
dx.doi.org/10.1021/cr1002112 |*Chem. Rev.* 2011, 111, 2048–2076

catalysts in coupling reactions. In these studies, the most important questions are arising from the understanding of the mechanism of the redox processes of the palladium atom. As mentioned above, reduction of the palladium atom to Pd(0) leads to cleavage of the palladium−carbon bond and usually irreversible decomposition of the complex. On the other hand, oxidation of the palladium atom to Pd(IV) is a thermodynamically disfavored process requiring strong oxidants. A further possibility is that the coupling reaction takes place without a redox reaction of the palladium atom, and thus, the pincer complex-catalyzed process does not follow the classical coupling mechanisms.[87−89,92] Because of the important mechanistic implications of the pincer complex-catalyzed coupling reactions, several DFT modeling studies have also been published on this topic.[38,77,80,89,114]

3.1. Heck Reaction—Catalyst or Catalyst Precursor?

One of the synthetically most important coupling reactions is the Heck reaction (Mizoroki−Heck reaction), which is a palladium-catalyzed cross-coupling of olefins with aryl or vinyl halides in the presence of a base. The high stability of pincer complexes under the harsh conditions of the Heck coupling was very promising for achievement of high turnover numbers (TON's), which strongly stimulated the development of pincer complex-catalyzed reactions.[25,38,51,60−86]

Scheme 10. Heck Coupling via the Pd(0) → Pd(II) Based Catalytic Cycle



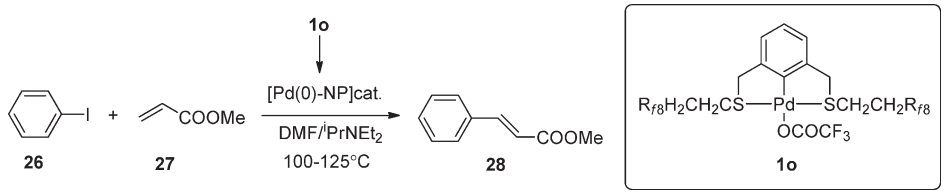
The classical Pd(0)/Pd(II) catalytic cycle of the Heck coupling is based on the oxidative addition of the aryl (or vinyl) halide to the Pd(0) catalyst. The catalytic cycle (Scheme 10) starts with oxidative addition of the aryl halide component to the palladium(0) catalyst to give palladium(II) complex **22**. Ligand exchange with the alkene gives olefin complex **23**, which subsequently undergoes insertion of the olefin to the aryl palladium bond, affording η^1-alkyl palladium complex **24**. This complex undergoes β-hydride elimination, providing the coupling product and hydridopalladium complex **25**, which is deprotonated by the employed base and regenerates the catalyst.

3.1.1. Evidence Indicating that Pd(0) Species Released from Pincer Complexes are the Active Catalysts. As mentioned above, palladium pincer complexes usually decompose, when the palladium atom is reduced to Pd(0) because of the cleavage of the Pd−C bond. Therefore, Pd(0) species do not have the usual pincer complex architecture, such as **1a**,**b**. Experimental data indicate[29,30,60,69,78,82,86,113] that under basic conditions and elevated temperatures pincer complexes decompose, releasing colloidal Pd(0) in the form of clusters or nanoparticles. Accordingly, under catalytic conditions, palladium pincer complexes may release Pd(0) nanoparticles, which then become the direct catalysts in the reactions.[19,21,115] In these cases, the pincer ligand is separated from the palladium atom, and thus fine-tuning of the reactivity/selectivity of the palladium catalyst by ligand effects is not possible any more. Thus, efficient design of new catalytic properties of pincer complexes is usually encumbered, when Pd(0) nanoparticles (arising from pincer complexes) are the active catalysts of the studied organic transformations.

Gladysz and co-workers[60] have shown (Scheme 11) that the cross-coupling reaction of phenyl iodide (**26**) and methyl acrylate (**27**) results in **28** on addition of fluorous pincer complexes, such as **1o**. A careful analysis of the reaction mixture has shown that **1o** is not a direct catalyst but dispenser of palladium(0) nanoparticles. The colloidal palladium(0) particles exhibit a reddish color of the reaction mixture. The presence of nanoparticles could be verified by transmission electron microscopy (TEM). Thus, the nanoparticles catalyzed the coupling reaction according to the classical mechanism shown in Scheme 10.

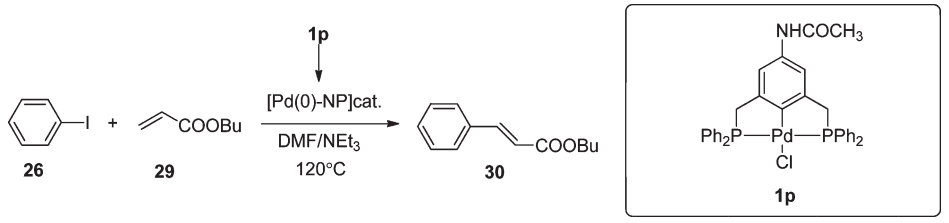
Weck, Jones and co-workers[30,78,82,113] conducted several studies to explore the possible mechanism of the formation of Pd(0) particles arising from pincer complex precatalysts. Complex **1p** was used as precatalyst for presumably Pd(0) species in the coupling of **26** and **29** to styrene derivative **30** (Scheme 12). It is interesting to point out that the substrates and the reaction conditions are very similar to the process performed by Gladysz and co-workers[60] (Scheme 11). This indicates that application of trialkyl-amine base and relatively high temperatures are favorable for generation for Pd(0) nanoparticles from pincer-complex precatalysts.

Scheme 11. Heck Reaction with Pincer Complex 1o as a Dispenser of Pd(0) Nanoparticles (R_{f8} Indicates a Polyfluorinated Side Chain)[60]

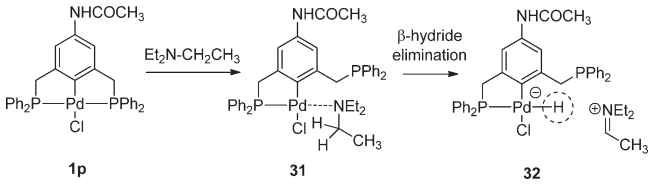


dx.doi.org/10.1021/cr1002112 |Chem. Rev. 2011, 111, 2048–2076

Scheme 12. Heck Reaction via Decomposition of PCP Complex 1p (see Scheme 13 as Well)[30,78,82,113]



Scheme 13. Proposed Decomposition Pathway of Pincer Complexes in the Presence of Alkyl-Amine Base[30]



It was hypothesized[30] (Scheme 13) that the decomposition of **1p** under the applied reaction conditions (Scheme 11) starts with the coordination of triethyl amine to palladium by opening one of the side arms (**31**). The next step is a β-hydride elimination, resulting in anionic complex **32**, which is supposed to decompose to Pd(0) species by reductive deprotonation. This hypothesis was backed up by NMR, MS, and DFT modeling studies. The high temperature is probably an important factor for the irreversible decomposition of the complex, as Milstein and co-workers[31] have shown that, under mild reaction conditions, PCP complexes may undergo reversible Pd(II)/Pd(0) redox reactions.

It was also pointed[30] out that PCP complexes (such as **1p**) are more stable to reductive decomposition than SCS complexes (such as **1o**), probably because of the easier opening of the side arms in SCS than in PCP complexes.[30] In several other[29,60,78,82,112,113] studies, qualitative tests were also performed to verify that colloidal Pd(0) species (and not pincer complexes) are the direct catalysts for the coupling reactions. A typical qualitative method for observation of catalytic activity by colloidal palladium is the so-called "mercury drop" test.[116] Colloidal Pd(0) reacts with Hg(0) by forming an amalgamate, thus quenching the palladium nanoparticles released from pincer complexes. A positive mercury drop test (also called mercury poisoning) implies that the catalytic reaction is stopped or slowed down by several orders of magnitude on addition of 100−300 equiv of Hg(0) per palladium to the reaction mixture. This indicates that Pd(0) arising from decomposition of the pincer complex is the direct catalyst in the reaction. Another qualitative test is the application of cross-linked poly(vinylpyridine) (PVPy), which traps soluble palladium species by coordinating to the metal center. This test is employed to study the catalytic activity of supported pincer complexes, as PVPy coordinates only to homogeneous palladium species, leaving support tethered palladium species untouched. There are several reports on positive PVPy tests, indicating that palladium leached out from supported pincer complexes on application as catalysts in Heck reactions.[60,78,82,113]

The above-described studies suggest that the pincer ligand has practically no effect in the Heck reaction, when the complex decomposes under the employed conditions, releasing ligandless Pd(0) species. On the contrary, van Koten, Klein Gebbink, and co-workers[69] have shown (Scheme 14) that pincer−porphyrin complexes **1r** have different catalytic activities depending on the metal atom (M) coordinated to the porphyrin ligand. Based on kinetic and spectroscopy studies, it was concluded that the reaction is catalyzed by Pd(0) species arising from decomposition of **1r**. However, the decomposition rate and, thus, the amount of catalytically active Pd(0) species were controlled by the electronic effects of the metal atom in the porphyrin ligand. The catalytic activity of **1r** was increased in the order M = MnCl < 2H < Ni < Mg, which coincides with the increasing electron density in the porphyrin ring.

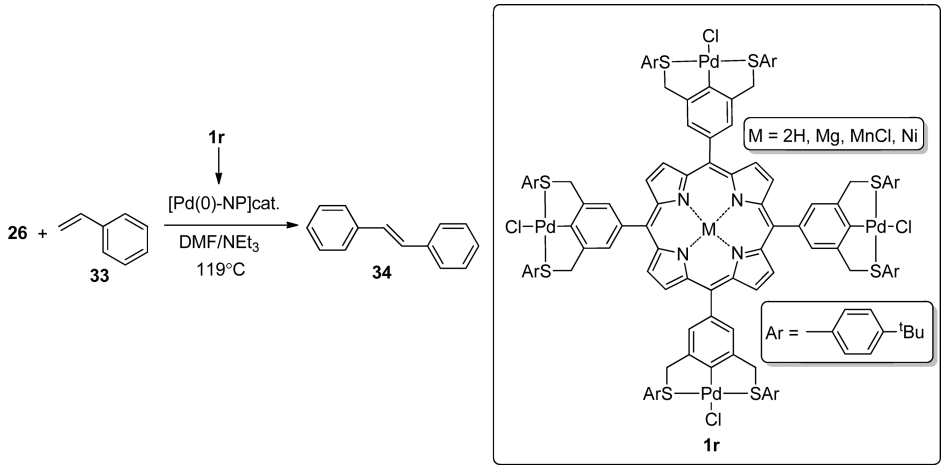
3.1.2. Heck Reactions via Proposed Pd(II)/Pd(IV) Cycles.

As shown in Scheme 10, one of the crucial steps in the Heck coupling reaction is the oxidative addition of the aryl halide to the Pd(0) catalyst to form Pd(II) adduct **22**. In principle, the same reaction would be possible by an oxidative addition of the aryl halide to a Pd(II) species, such as a pincer complex to generate a Pd(IV) species.[36,37,65,68,117] At this specific point, the research community tends to agree that the oxidation potential of aryl iodides or other halides is too low to efficiently oxidize Pd(II) to Pd(IV), unless some unusual structure elements in the complex or some kind of special additives are employed. To this date no convincing evidence has been presented to prove that conventional pincer complexes of type **1a,b** are direct catalysts in Pd(II)/Pd(IV) based catalytic cycles using simple aryl halides as oxidants. DFT modeling studies (see below) also indicate that the oxidation of the palladium atom of pincer complexes to Pd(IV) with aryl halides is unlikely under the reaction conditions of Heck coupling.[77,80,114]

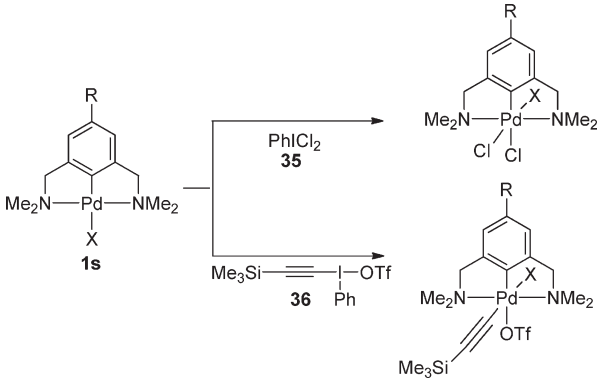
Although aryl iodide is not able to efficiently oxidize Pd(II) complexes, stronger oxidants, such as hypervalent iodine salts can be used. Canty[118] and van Koten[33] have shown that hypervalent iodine salts **35** and **36** easily oxidize Pd(II) NCN pincer complexes **1s** to the corresponding Pd(IV) complexes (Scheme 15). These studies inspired Szabó and co-workers[38] to develop pincer complex-catalyzed Heck type coupling of hypervalent iodine salts and allyl acetates (Scheme 16). Allyl acetates easily undergo oxidative addition to Pd(0) species to form Pd(II) allyl palladium complexes.[1−3] However, under the applied reaction conditions, Pd(0) species are not expected to occur using oxidant **37** (close analogue to **35** and **36**), which is supposed to generate a Pd(II)/Pd(IV) redox cycle. Therefore, the allylic acetate functionality remains intact during the catalytic reaction. In contrast to the pincer complex-catalyzed coupling of aryl iodide (**26**) and alkenes (Schemes 11 and 12), the pincer complex catalyst could be fully recovered after the reactions and the mercury drop test was negative. This is probably due to the high oxidation potential of **37** (vs **26**), the weak base ($NaHCO_3$), and the mild conditions (50 °C) employed in the process.

dx.doi.org/10.1021/cr1002112 |*Chem. Rev.* 2011, 111, 2048–2076

Scheme 14. Metalated Pincer−Porphyrin Hybrid Complexes as Precatalysts for Heck Reactions (M = 2H Indicates That No Metal Atom Is Coordinated to the Porphyrin)[69]



Scheme 15. Stoichiometric Oxidation of Pd(II) Pincer Complex 1s to Pd(IV) Complexes Using Hypervalent Iodines 35 and 36[33,118]



DFT modeling studies have been performed to study the mechanism of the oxidative addition of iodonium salts (**41**) to NCN pincer complex **1u**.[114] This complex is also an active catalyst in the above Heck type coupling (Scheme 16)[38] and a close analogue of complex **1s** used for stoichiometric generation of Pd(IV) complexes (Scheme 15). These studies clearly indicate that hypervalent iodine reagents (e.g., **37** or **41**) outperform aryl iodide (**26**) in the Pd(II) to Pd(IV) oxidation in the pincer complexes. It was shown that the oxidative addition of iodonium salt **41** (Scheme 17) requires an activation barrier of 28.1 kcal mol^{-1} (via **42**) to generate Pd(IV) complex **43** in an exothermic reaction (−6.2 kcal mol^{-1}). Although the oxidative addition of phenyl iodide **26** (Scheme 18) requires only a 5 kcal mol^{-1} higher barrier (c.f. **42** and **44**), this process is strongly endothermic (+24.9 kcal mol^{-1}). As a consequence, the reverse reaction, reductive elimination of **45**, requires a very low barrier of about 9 kcal mol^{-1} (vs 34 kcal mol^{-1} with the iodonium salt, Scheme 18). Under catalytic conditions, such a low barrier for the reverse reaction probably encumbers the coupling process, as it leads to rapid decomposition of **45** to **1u** and **26** instead of proceeding in the catalytic cycle (see Scheme 10).

Frech and co-workers[80] performed comprehensive DFT-studies on the involvement of palladium pincer complexes as direct catalysts in Heck coupling reactions. These authors studied the possibilities of the oxidative addition of phenyl bromide to the Pd(II) center of various pincer complexes and came to the conclusion that the Pd(II) → Pd(IV) redox cycle using aryl bromides or iodides as oxidant at high temperatures (140 °C) can be a viable mechanistic alternative to a palladium nanoparticle-catalyzed reaction.

3.1.3. Complexes Surviving Pd(0)/Pd(II) Redox Reactions. Although traditional types of pincer complexes, such as **1a,b**, usually decompose when the palladium atom is reduced to Pd(0) under the harsh conditions of the Heck-coupling, palladium−carbene complexes are expected to maintain the Pd−C bonding intact even in a low oxidation state. Accordingly, several important attempts were reported to employ carbene based pincer type complexes to catalyze Heck coupling reactions.[73,76,93,119] A particularly interesting application was published by Jung and co-workers[76] on an oxidative (boron) Heck type reaction (Scheme 19) catalyzed by **1v**, which is an **1a′** type of pincer complex (Scheme 1). It was shown that aryl boronic acid **46** and alkene **47** undergo selective oxidative Heck-coupling in the presence of **1v** as catalyst. Since the reaction proceeds with high enatioselectivity, the integrity of the pincer type catalyst is certainly preserved under the reaction. The authors postulated a plausible mechanism involving the Pd(0)/Pd(II) cycle, in which the Pd−C bond to the carbene ligand is preserved. These results show that pincer complexes have a high potential in asymmetric catalysis based on the Pd(0)/Pd(II) catalytic cycle if the chiral complex incorporates a palladium−carbene linkage.

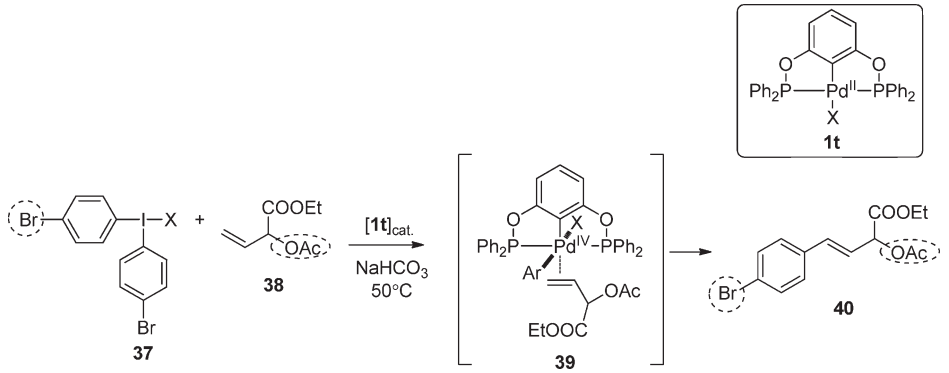
3.2. Suzuki−Miyaura Coupling and Related Reactions

The Suzuki−Miyaura coupling[1,3,120−123] is one of the most important selective carbon−carbon bond formation reactions, based on coupling organoboronates with aryl halogenides under basic conditions, often in the presence of water. Achievement of high TONs and finding mechanistically new Suzuki−Miyaura type processes stimulated the application of pincer complex catalysts in these reactions.[28,59,62,68,72,73,87−108]

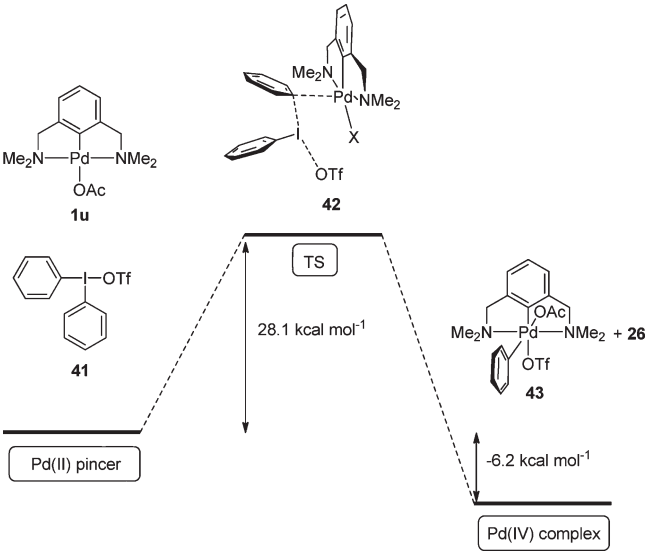
An important difference between the Heck-coupling and Suzuki-coupling is that in the latter case one of the crucial steps

dx.doi.org/10.1021/cr1002112 |Chem. Rev. 2011, 111, 2048–2076

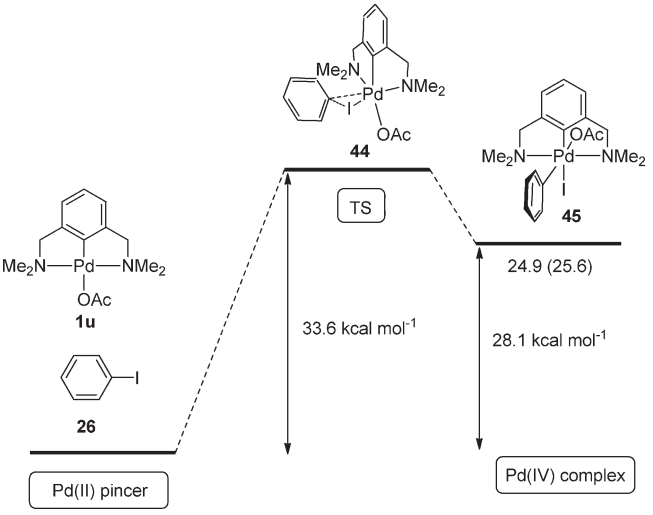
Scheme 16. Heck Type Coupling of Allylacetates and Iodonium Salts[38]



Scheme 17. DFT Reaction Profile of Oxidative Addition of Iodonium Salt 41 to NCN Complex 1u[114]



Scheme 18. DFT Reaction Profile of Oxidative Addition of Aryl Iodide (26) to NCN Complex 1u[114]



is transmetalation[1,3,120,121] of the organoboronate with a Pd(II) species, which does not involve redox reactions. This is important for application of pincer complexes, as this catalytic step does not change the oxidation state of the Pd(II) central atom of the complex.

3.2.1. Opening of Vinyl Epoxides and Vinyl Aziridines. The Szabó group,[87] and subsequently the van Koten−Klein Gebbink group,[88,89] have studied the cross-coupling reactions of aryl (**49**) and vinyl (**52**) boronates with vinyl aziridines, **48**, (Scheme 20) and epoxides, **51**, (Scheme 21) to obtain allylic amines (**50**) and allylic alcohols (**53**). The reactions could be performed under mild conditions and usually with high regioselectivity, providing linear allylic products (such as **50** and **53a**). The pincer complex-catalyzed reactions are supposed to proceed without redox processes, preserving the Pd(II) oxidation state.[87,89] As a consequence, the aromatic iodide functionality (**49**) survives the transformation. Although the reaction is also catalyzed by $Pd_2(dba)_3$, the mechanism of the pincer complex and Pd(0)-catalyzed reactions shows different features.[87] The reactivity and regioselectivity of the process was found to be highly dependent on the electronic properties of the pincer ligands.[87−89,124]

For example, the van Koten group has shown that bimetallic complex **1x** has a much higher catalytic activity than its monometallic counterpart **1y**.[88,89] It was reasoned that the higher reactivity of **1x** is a consequence of the electron-deficient palladium atom. The electron deficiency is generated by the ruthenium atom, which is η^6-coordinated to the aromatic ring of the pincer complex. Based on the above results, the mechanism[88,89,124] of the cross-coupling was suggested to consist of two major steps (Scheme 22): transmetalation of the organoboronate with the pincer complex catalyst and a subsequent nucleophilic attack by the activated organic ligand (**54**) on the vinyl epoxide. The reactivity differences between **1x** and **1y**, and the results of DFT modeling studies, suggested that the transmetalation is probably the rate determining step.[88,89]

3.2.2. Suzuki−Miyaura Type Aryl-Aryl Cross-coupling Reactions. Recently, the Wendt group[91] and the Nishiyama group[92] reported Suzuki−Miyaura reactions for cross-coupling of aryl boronates with aryl halogenides, which probably does not proceed via the usual Pd(0)/Pd(II) redox cycle. This involves the palladium atom of the complex maintaining its oxidation state, and the complex does not undergo irreversible dissociation of the pincer ligand.

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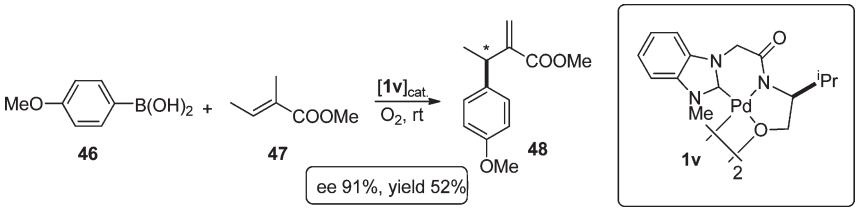
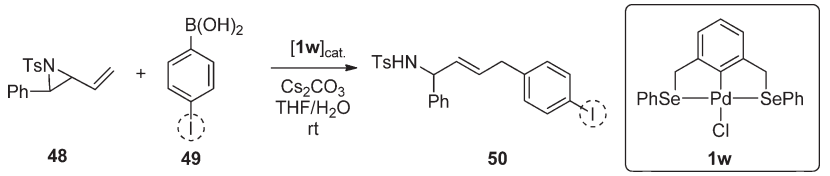
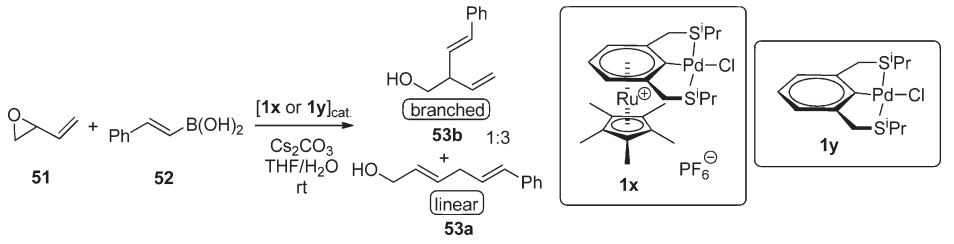
Scheme 19. Asymmetric Heck Coupling with Pincer Type Complex 1v[76]



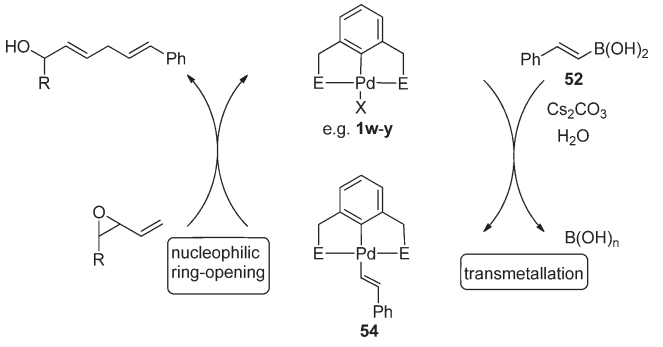
Scheme 20. Cross-coupling of Vinyl Aziridine with Organoboronates[87]



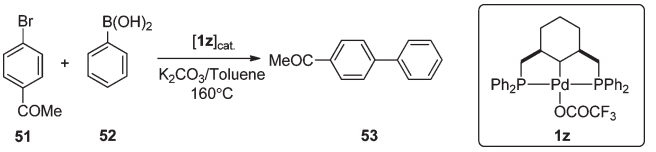
Scheme 21. Epoxide Opening with Vinyl Boronate Using Bimetallic Pincer Complex 1x[88,89]



Scheme 22. Suggested Mechanism of the Cross-coupling of Organoboronates with Epoxides/Aziridines[88,89,124]



Scheme 23. Cross-coupling Reaction with PC(sp^3)P Complex 1z[91]



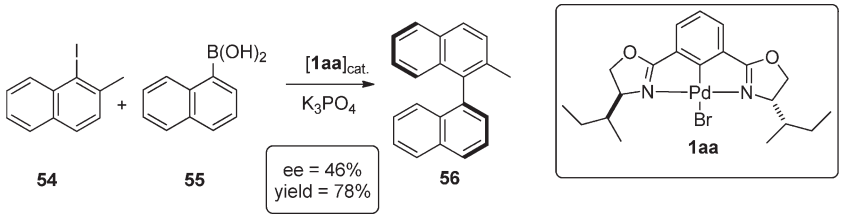
Wendt and Olsson[91] performed cross-coupling reactions of aryl bromides (such as **51**) and aryl boronic acid **52** using PCP complex **1z** (Scheme 23). An interesting feature of catalyst **1z** is that the palladium atom is attached to an sp^3 hybridized carbon and not to an aromatic one, as in the commonly employed pincer complexes. A negative mercury drop test indicated that Pd(0) nanoparticles are not involved in the catalytic process. When the trifluoroacetate counterion in **1z** was replaced with a phenyl group (which is supposed to take place under catalytic conditions as well), a highly reactive palladium species was obtained, which reacted directly with aryl bromides (such as **51**) without a redox process. This suggests that the catalytic procedure may follow a redox-free reaction pathway, similar to the mechanism of the cross-coupling of organoboronates with vinyl epoxides (Scheme 22). In a recent study, Frech and co-workers[125] obtained similar results employing an aliphatic phosphine-based pincer complex catalyst.

Nishiyama and co-workers[92] performed a spectacular asymmetric Suzuki−Miyaura coupling of **54** and **55** with chiral pincer complex **1aa** (Scheme 24). The fact that the product, **56**, was formed with 46% ee suggests that the bisoxazolidine ligand is kept on palladium under the entire catalytic reaction; thus, formation of Pd(0) species is unlikely. The catalyst was also very efficient in nonchiral Suzuki−Miyaura coupling, with TON's up to 900 000.

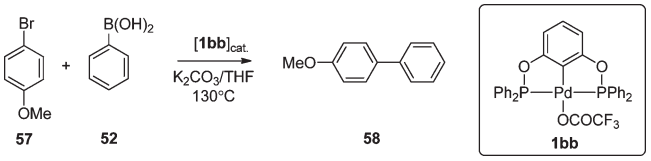
The first aryl−aryl cross-coupling reaction using PCP complex **1bb** was reported by Bedford and co-workers (Scheme 25).[48] The reactions could be carried out using very low catalyst loadings, and the processes are characterized by very high TON's. For example, the coupling of bromoanisole and phenylboronic acid

dx.doi.org/10.1021/cr1002112 |*Chem. Rev.* 2011, 111, 2048–2076

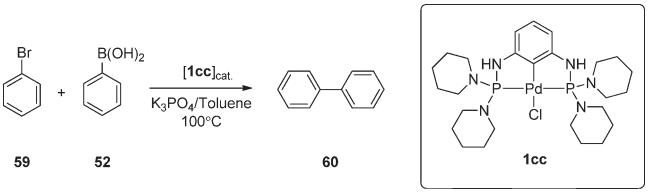
Scheme 24. Asymmetric Suzuki−Miyaura Cross-coupling with Phebox−Palladium Complex 1aa[92]



Scheme 25. Suzuki Coupling with High TON and Low Catalyst Loading[48]



Scheme 26. Aminophosphine Based Pincer Complex Catalyst for Suzuki−Miyaura Coupling[59,106]



(**52**) can be carried out with only 0.0001 mol % of **1bb**, producing **58** with a TON of 190 000. Complex **1bb** can be prepared by the procedure reported in this paper by Bedford and co-workers[48] or by ligand exchange from **1l** (Scheme 7). It is interesting to note that **1bb** (**1l**) is one of the most versatile pincer complex catalysts. This complex also catalyzes the coupling of allyl stannanes and allyl borates with aldehydes and imines (section 5.2), and it is also an excellent catalyst for condensation of imines with isocyanoacetates (section 4.1). Therefore, catalyst **1bb** (**1l**) can probably be designated as a "privileged" pincer complex catalyst.

Frech and co-workers[59,106] have employed easily accessible aminophosphinate complexes (such as **1cc**) as catalyst (Scheme 26). Complex **1cc** proved to be a particularly efficient catalyst for cross-coupling of **59** and **52** to obtain biphenyl **60** with a TON of 1 000 000. The reaction was characterized by a negative mercury drop test (see section 3.1.1), and the employed complexes (such as **1cc**) could be completely recovered after the reaction. According to the authors, these findings indicate that Pd(0) species/nanoparticles cannot be the active catalysts, which led to the conclusion that a cross-coupling reaction proceeds via a Pd(II)/Pd(IV) catalytic cycle.[59] Kirchner and co-workers[102] employed similar types of pincer complexes with a diaminobenzene backbone for efficient Suzuki−Miyaura coupling reactions.

In many cases, the qualitative analysis (Hg drop test) and complete decomposition of the added pincer complex catalyst indicates that the cross-coupling reaction takes place via reduction of the palladium atom to Pd(0) followed by formation of catalytically active nanoparticles.[14,28,90] In this case the integrity of the pincer catalyst is lost and the ligand does not affect the activity and selectivity of the palladium catalyst (see the discussion in section 3.1.1). For example, Protasiewicz and co-workers[90] carried out efficient cross-coupling reactions with PCP complexes (some of them closely related analogues of **1bb**,**cc**) and found that the pincer complex catalyst decomposes and, thus, these complexes are only dispensers of active nanoparticles. SanMartin, Domínguez, and co-workers[14,28] studied the mechanism and synthetic application of carbene-based water-soluble pincer type complexes, such as **1dd** (Scheme 27), for cross-coupling of **51** and **52** to obtain biphenyl derivative **53**. The results of the mercury drop test, kinetic measurements, and TEM images clearly showed that the reaction was catalyzed by Pd(0) nanoparticles arising from complete decomposition of **1dd**. Interestingly, Wendt and co-workers[91] (see Scheme 23) studied the reaction of the same substrates (**51** and **52**) under slightly different conditions but using complex **1z** instead of **1dd**, and these authors found that pincer complex **1z** was the direct catalyst of the cross-coupling reaction.

3.3. Sonogashira Coupling

The Sonogashira coupling is a widely used palladium-catalyzed process for cross-coupling of alkynes with aryl halides.[1,3] Due to its synthetic importance, several studies are reported on the improvement of this process by using pincer complex catalysts.[72,95,107,109,110] Frech and co-workers[109] employed aminophosphine based complexes (Scheme 28), such as **1cc**, as very efficient catalysts in Sonogashira cross-coupling. These types of catalysts have also performed well in Suzuki−Miyaura coupling reactions (see Scheme 26). The reaction takes place without using copper cocatalyst, with an impressive TON of 2×10^6 and in quantative yield. The reaction shows an induction period; however, the mercury drop test of the coupling process is negative, and therefore, it is unclear whether **1cc** is the direct catalyst of the transformation. Gu and Chen[110] have reported that carbene based pincer type catalysts are also suitable to perform copper-free Sonogashira coupling reactions with high isolated yields.

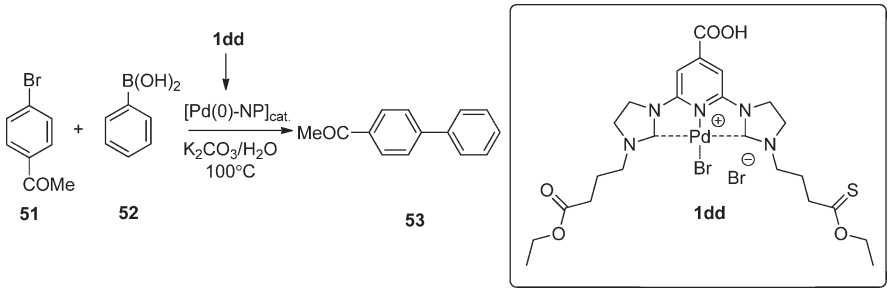
3.4. Hiyama, Stille, and Negishi Coupling

In addition to Heck, Suzuki, and Sonogashira coupling reactions, various other pincer complex-catalyzed cross-coupling processes have also been reported in the literature. Similarly to the above cross-coupling procedures, one of the main issues in these reactions is to determine whether the pincer complex is the direct catalyst of the reaction or it serves as dispenser for Pd(0) species. The main reason for this consideration is the fact that the classical Stille, Hiyama, and Negishi coupling reactions are based on a Pd(0)/Pd(II) redox cycle.[1,3]

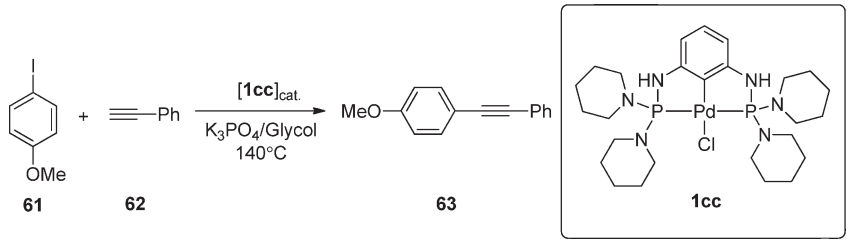
SanMartin and Domínguez reported[95] the first Hiyama coupling reaction in the presence of nonsymmetrical pincer complex

dx.doi.org/10.1021/cr1002112 |Chem. Rev. 2011, 111, 2048–2076

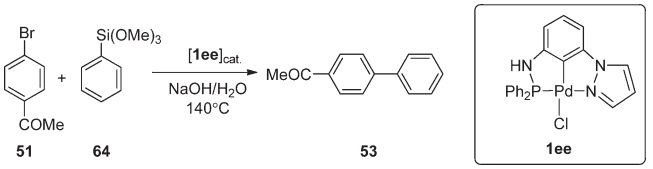
Scheme 27. Carbene Based Complexes as Dispensers of Pd(0) Nanoparticles[14,28]



Scheme 28. Sonogashira Cross-coupling of Aryl Halides with Terminal Acetylenes[109]



Scheme 29. Hiyama Coupling in the Presence of Pincer Complex Catalyst[95]



Scheme 30. Stille Coupling with 1ff as Dispenser of Pd(0) Particles[111]

1ee (Scheme 29). The coupling reaction of silane **64** and aryl bromide **51** was performed in water in the presence of NaOH as activator. Under similar conditions, Suzuki and copper-free Sonogashira coupling reactions could also be performed using catalyst **1ee**. Although the authors did not study whether **1ee** is the direct catalyst of the reactions, the results obtained for the corresponding Suzuki−Miyaura coupling suggest that **1ee** is probably a dispenser of colloidal Pd(0) particles.

Wendt and co-workers[111] studied the Stille coupling reaction using **1ff** as catalyst source (Scheme 30). The process proved to be very efficient, as low catalyst loadings (from 0.0001 mol %) could be employed and the reaction showed very high TON's (up to 690 000). However, a careful kinetic study and qualitative test indicated that **1ff** probably decomposed under the applied conditions and colloidal Pd(0) species was the active catalyst of the process.

The synthetic and mechanistic aspects of the Negishi coupling of aryl iodides (**66**) with alkyl zinc derivatives (**67**) using pincer type catalyst **1gg** were studied by Lei and co-workers (Scheme 31).[26,27] Under mild conditions the reaction affords the coupling product **68** with a high selectivity together with dehalogenated product **69**. The reactions required very low catalyst loadings (such as 0.00001 mol %) and proved to be easily scalable without a decrease of the excellent yields. The reaction mechanism was carefully investigated,[26] and it could be established that catalyst **1gg** survived the reaction without decomposition. According to the authors, Pd(0) species are probably not involved in the catalytic cycle; instead, a Pd(II)/Pd(IV) based catalytic cycle is suggested. It was proposed that complex **1gg** may undergo transmetalation with the alkyl zinc reagent (**67**) to give an electron rich complex, which subsequently undergoes oxidative addition with the applied aryl iodide component (**66**). In the final step, the Pd(IV) complex undergoes reductive elimination of the aryl and alkyl moieties to give the final product **68**.

4. ALDOL AND MICHAEL REACTIONS

Palladium pincer complexes have successfully been used as Lewis-acid catalysts in aldol[42,49,126−138] and Michael[39,40,55,56,126,139−141] types of reactions, first shown by Richards and co-workers.[126,139] Both the aldol and Michael type reactions are synthetically important, since they involve the formation of C−C bonds and novel stereocenters with the potential for chiral induction. The main focus has been directed toward the development of enantioselective applications using pincer catalysts incorporating chiral groups[55,56,126,127,129−131,134,135,137−139] and immobilization of the catalyst on solid support[40,130,133,136] or on dendritic[128,132] systems.

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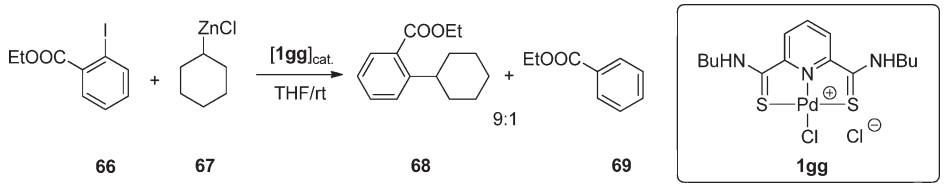
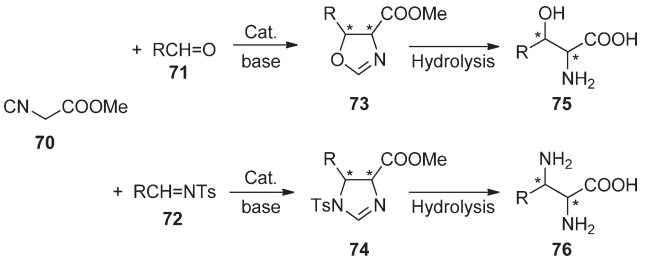
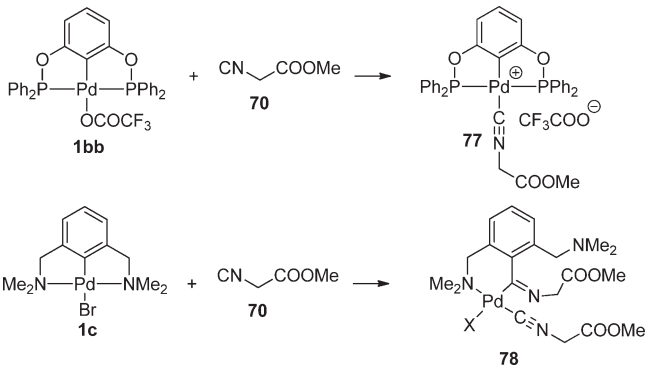
Scheme 31. Pincer Type Complex 1gg as Direct Catalyst for the Negishi Coupling[26,27]



Scheme 32. Generic Aldol Type of Reactions between Isonitriles and Electrophiles



Scheme 33. Different Modes of Activation of the Isocyanoacetates in Aldol Reactions[42,131,138,147]



4.1. Catalytic Aldol Type of Reactions

The catalytic reactions between isonitriles, such as **70** and aldehydes **71** or imines **72**, give easy access to oxazolines **73** and imidazolines **74** in the presence of a base. Since the products can be hydrolyzed to β-hydroxyamino acids **75**[142] and α,β-diamino acids **76**,[137,143−145] respectively, asymmetric versions of these transformations received particular attention (Scheme 32).

Hayashi and co-workers[142] were the first to develop an enantioselective coupling between aldehydes and isocyanoacetates using gold catalysis. The analogous gold-catalyzed coupling with imines, leading to enantioenriched imidazolines, was first reported by Lin and co-workers.[145,146] Since then, the potential for synthesis of optically active amino acid derivatives has inspired many groups to develop novel synthetic routes to chiral pincer complexes. There are two major strategies for the activation of isocyanoacetates with palladium pincer complexes (Scheme 33). In the case of tightly coordinating side arms, such as in PCP complexes, isocyanoacetate (**70**) coordinates to the palladium atom with its carbon terminus,[42,131,138] such as in complex **77**. In this complex, C−H deprotonation occurs very easily and the formed enolate readily reacts with electrophiles.[42] In such activations, pincer complexes are direct catalysts in the cyclization reactions (Scheme 32). For complexes with relatively weakly coordinating side arms, such as in NCN complexes, the isocyanoacetate undergoes insertion into the Pd−C bond, affording Pd(II) complex **78** (Scheme 33).[147] In this case, the pincer architecture of the complex is lost and insertion complex **78** is the direct catalyst of the aldol reaction.

Zhang and co-workers[127] reported (Scheme 34) a straightforward synthesis of chiral PCP−complex **1hh**, which was used as catalyst in the aldol reaction between methyl isocyanoacetate (**70**) and various aldehydes (such as **79**). The oxazoline product **80** was obtained in a *cis*/*trans* mixture with a preference for the *trans* isomer. Good enantioselectivity was obtained for the *cis* isomer, up to 77% ee, while the *trans* oxazolines were obtained with lower enantioselectivity, up to 31% ee. Interestingly, the enantioselectivity in Zhang's reaction was complementary to the gold-catalyzed[142] and platinum pincer complex-catalyzed[148] processes, which afforded the *trans* oxazolines in higher ee than that for the *cis* products.

The catalytic activity of chiral pincer complexes was studied by Nishiyama and co-workers[131] employing bis(oxazolinyl)phenyl palladium complex **1ii** (Phebox) for the synthesis of enantioenriched oxazoline derivatives (such as **82**). In these studies (Scheme 35), sulfonyl isocyanate derivative **81** was used in place of **70**. The cyclization reaction of **81** with benzaldehyde (**79**) proceeded with excellent stereochemistry, as exclusive formation of the *trans* isomer was reported. The reaction also proceeds with promising levels of enantioselectivity up to 57% ee. Interestingly, similar Phebox complexes were successfully applied to asymmetric Suzuki−Miyaura coupling reactions (section 3.2.2, Scheme 24) by the same group.

Recently, van Koten, Klein Gebbink, and co-workers[138] reported the synthesis and applications of chiral pincer complex **1jj** (Scheme 36). In this complex, the coordination sphere of palladium is different from that of the generic pincer complexes (such as **1a**,**b**). This type of coordination changes the flat character of the pincer complexes, which is expected to increase the efficiency of the chiral induction. In the applied aldol type cyclization, catalyst **1jj** was found to give a fairly high diastereoselectivity and enantioselectivity. For example, the reaction of methyl isocyanoacetate **70** and aldehyde **83** afforded **84** as the major stereoisomer with 42% ee (*cis*/*trans* ratio 70:30).

Other types of chiral PCP complexes,[129] chiral dinuclear SCS complexes,[130] and proline-[134] and pyridine-based[135] NCN−pincer complexes with chiral auxiliaries were also reported for enantioselective cyclization of isocyanoacetates with aldehydes. However, the reported enantioselectivities were relatively low. Several palladium pincer complexes attached on dendritic[128,132] or solid support[130,133,136] have been developed and found to catalyze the aldol reactions between aldehydes and isocyanoacetates. These

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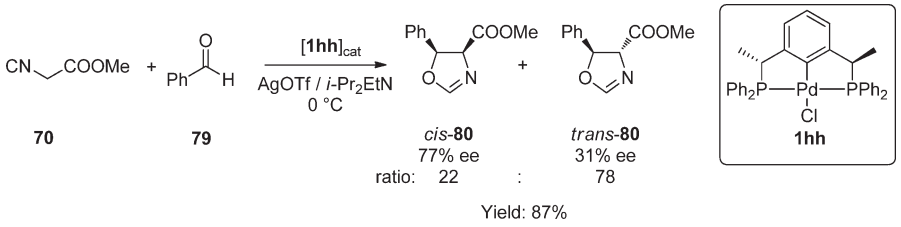
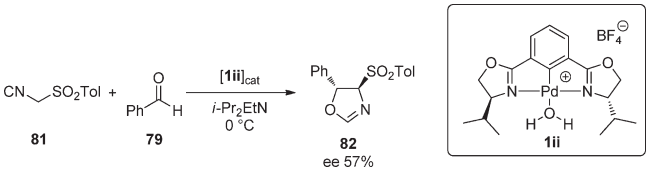
Scheme 34. Enantioselective Synthesis of Oxazolines Using Chiral Catalyst 1hh[127]



Scheme 35. Asymmetric Aldol Coupling Catalyzed by Chiral Phebox Catalyst[131]



supported catalysts were highly recyclable, as their catalytic activity was fully maintained after several catalytic runs.[136]

The Szabó group[42,137] has demonstrated that aldol type of reaction between isocyanoacetates and imines can also be efficiently catalyzed by palladium pincer complexes (Scheme 37). It was found that the heteroatoms in the side arm of the pincer ligand had a large influence on the diastereoselectivity of the reaction. Thus, the *cis*-derivatives of imidazoline **86** were obtained as major products with PCP−palladium pincer complex **1bb** (10:1 *cis* to *trans* ratio), while SeCSe−complex **1kk** gave a 1:4 ratio between the *cis* and *trans* isomers (Scheme 37).[42] The different diastereoselectivity is probably due to the different mechanisms of the aldol type of reactions. As mentioned above (Scheme 33), isocyanoacetate **70** has different modes of coordination to palladium depending on the heteroatoms in the side arms.[42,131,138,147] In the case of **1bb**, the reaction proceeds via pincer complex **77**,[42] while the reaction with SeCSe complex **1kk** with σ-donor ligands in the side arms probably proceeds via an insertion complex, such as **78**.

Subsequently, Szabó and co-workers[137] have shown that chiral bisphenanthrol-based PCP-complex **1j** (see also Scheme 5 for its synthesis) is an efficient catalyst for the enantioselective aldol type of reaction of **70** with imines (Scheme 38). The reaction between imine **85** and methyl isocyanoacetate **70** gave the enantioenriched imidazoline derivative **86** in 98% yield, which subsequently was hydrolyzed to α,β-diamino acids, affording **87a** with 86% ee and **87b** with 28% ee. Interestingly, the diastereoselectivity of the cyclization was dependent on the applied solvent. Compared to the gold-catalyzed enantioselective aldol reaction reported by Lin and co-workers,[145,146] the palladium pincer complex-catalyzed reaction gave lower ee but showed a higher preference for the formation of *trans*-substituted imidazolines.

4.2. Michael Reactions

Similarly to the aldol process described above, palladium pincer complexes have been used as Lewis-acid catalysts in the reaction between activated nitriles and Michael acceptors. Richards and co-workers[126,139] found that moderate levels of enantioselectivity could be induced by employment of chiral bisoxazolinyl-based pincer catalysts. Subsequent studies by Uozumi and co-workers showed that high levels of enantioselectivities, up to 83% ee, can be obtained in Michael reactions (Scheme 39)[55,56] using the pyrroloimidazolone-based NCN-complex **1n** (for the synthesis, see Scheme 9). For example, Michael adduct **90** was obtained with 81% ee from α-cyanoester **88** and Michael acceptor **89** in 89% yield. The high enantioselectivity of the reaction was attributed to the hydroxyl substituent in catalyst **1n**, as the corresponding catalysts bearing hydrogen or methoxy substituents at the same position gave less than 10% ee.

Similar Michael reactions were also studied by the van Koten group,[39,40,140] applying various para-functionalized pincer complexes[39] and multimetallic compounds[140] as Lewis-acid catalysts. A highly selective Michael type reaction was reported by Duan and co-workers,[149] employing chiral pincer complex **1ll** as catalyst. It was found that the addition of diphenylphospine **91** to Michael acceptor **92** proceeded with an excellent enantioselectivity, affording phosphine oxide **93** in 99% ee after oxidation (Scheme 40). It is interesting to note that **1ll** is closely related to complex **1hh**, previously used by Zhang and co-workers[127] for enantioselective synthesis of oxazolines (Scheme 34).

5. ALLYLATION OF ALDEHYDES AND IMINES

In addition to cross-coupling (section 3), aldol, and Michael reactions (section 4), allylation of imines and aldehydes are important carbon−carbon bond forming reactions. A wide range of allylation reactions catalyzed by palladium pincer complexes has been developed for the synthesis of homoallylic alcohols and amines.[150−153] The electrophilic allylation of aldehydes and imines was pioneered by Yamamoto and co-workers[154−159] using bis-allyl palladium complexes (**96**) generated from monoallyl palladium complexes (**95**) by transmetalation with allylic stannane **94** (Scheme 41a). DFT modeling studies have shown[160−162] that the η^1-coordinated allyl moiety in **96b** has a nucleophilic character, and therefore, it can readily react with electrophiles, such as aldehydes, imines, Michael acceptors, and related reagents. The Szabó group[43,44,163−166] and others[47,167−169] have demonstrated that pincer complexes may efficiently replace monoallyl palladium intermediates to provide nucleophilic allyl species under catalytic conditions (Scheme 41b). Accordingly, palladium pincer complexes readily catalyze the electrophilic allylation of aldehydes and imines using allylic stannanes[22,43,44,47,49,53,163,164,166,167,169−172] or potassium trifluoro(allyl)borates.[44,165,166] The application of palladium pincer catalysts in the allylation reactions has a number of benefits compared to bis-allyl palladium chemistry.[173] For example, the tridentate coordination of the pincer ligand forces the allyl fragment into an η^1-coordination mode (**98**),[164−167] which obviates the regiochemical issues that may occur with bis-allyl palladium complexes (**96b**) bearing two different allylic moieties.[174] Moreover, reductive allyl−allyl coupling[158,175] reactions

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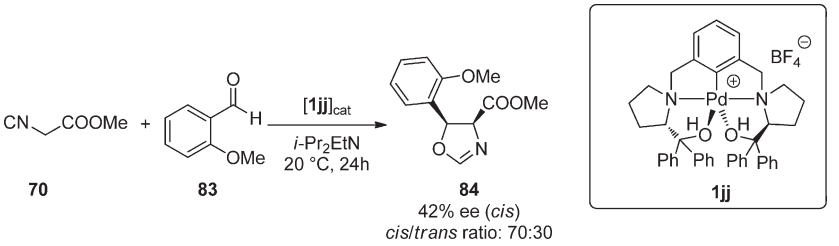
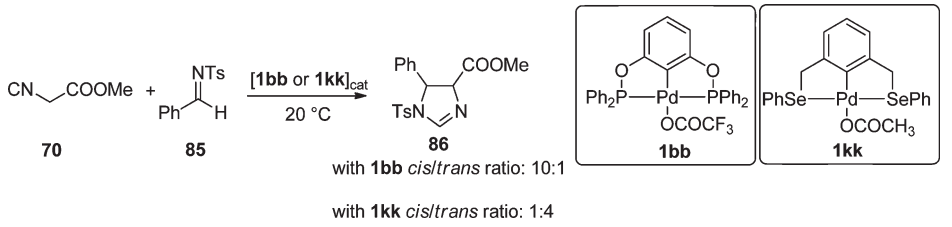
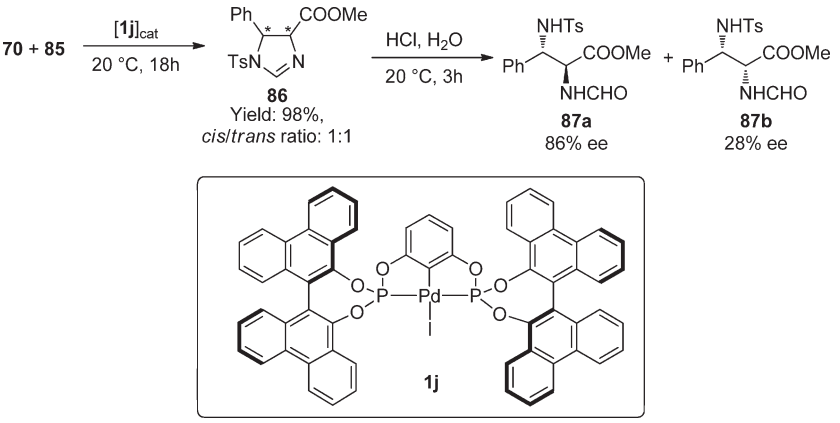
Scheme 36. Aldol Reaction of Substituted Aldehydes[138]



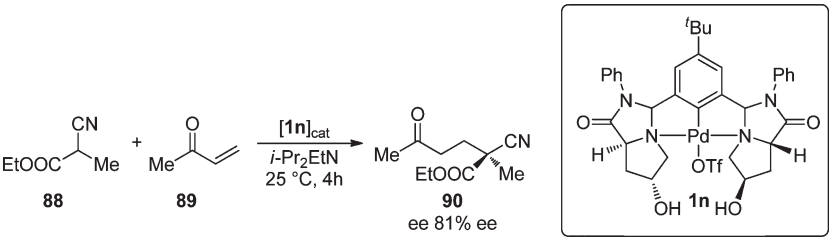
Scheme 37. Catalyst-Controlled Diastereoselectivity in the Aldol Condensation of Imines[42]



Scheme 38. Enantioselective Synthesis of α,β-Diamino Acids[137]



Scheme 39. Pincer-Catalyzed Asymmetric Michael Addition of α-Cyanoester to Methyl Vinyl Ketone[55,56]



from bis-allyl palladium complexes (such as **96**) can be avoided using pincer complex catalysts.

5.1. Allylation of Aldehydes and Carbon Dioxide

The first palladium pincer complex-catalyzed electrophilic allylation of aldehydes was reported by Szabó and co-workers in 2003.[163] In particular, the PCP type of pincer complexes (such as **1bb** and **1mm**) proved to be successful for coupling of allylic stannanes with aldehydes.[163,164] These complexes catalyzed the coupling reaction of cinnamyl stannane **99** and aldehyde **100** (R = H, F, NO_2), obtaining the homoallylic alcohol **101** in high yield and selectivity (Scheme 42). The pincer complex-catalyzed process provided exclusively the branched allylic product and the anti diastereomer with high stereoselectivity. Comparison of the catalytic activity of various pincer complexes revealed that pincer complexes with relatively electron poor palladium atom

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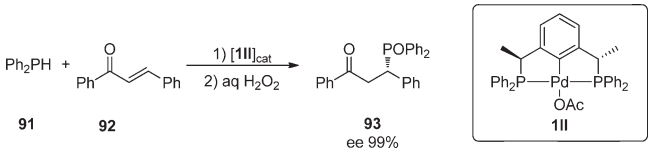
Scheme 40. Pincer-Catalyzed Asymmetric Addition of Diphenylphosphine to Chalcone[149]



performed well. Thus, PCP complexes (such as **1bb** and **1mm**) performed better than, for example, NCN complexes (such as **1c**). Furthermore, complexes with weakly coordinating trifluoroacetate counterion (such as **1bb**) displayed a higher catalytic activity than its counterpart **1l** with tightly coordinating chloride counterion.

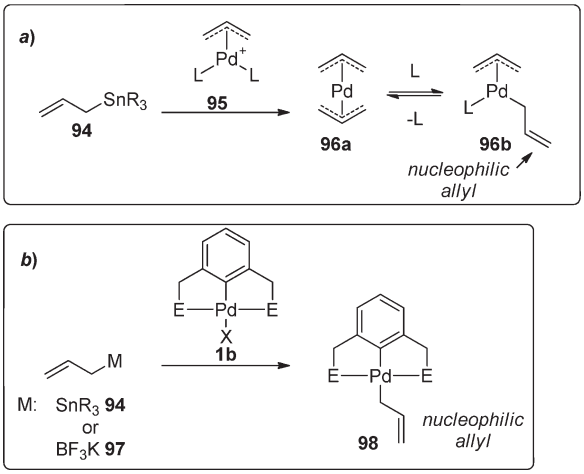
As pincer complexes with σ-donor heteroatoms in the side arms (such as **1c**) are excellent catalysts for synthesis of allylstannanes (see section 6.1), the catalytic protocol was also extended to a one-pot reaction. In these one-pot applications, the allylic stannane **99** was generated in situ from allylic chloride **102** and hexamethylditin **103** followed by allylation of the aldehyde **100** using the two catalysts **1c** and **1l** (Scheme 43).[53] Complex **1c** catalyzed the stannylation reaction (section 6.1), in which **1l** was inactive. Subsequently, the in situ formed allyl stannane **99** reacted with the aldehyde component **100**. This process was only very slowly catalyzed by **1c**, and therefore, PCP complex **1l** was employed to furnish this step. Although catalyst **1bb** is much more efficient in the allylation step than **1l** (see the discussion above), the high chloride concentration (arising from C−Cl bond cleavage of **102**) converts complex **1bb** to **1l** during catalysis. Thus, the benefits of the weakly coordinating counterion in **1bb** cannot be exploited under the one-pot conditions. A collaborative study of the van Koten and Szabó groups has shown that **1c** and **1l** can be replaced by a single pincer complex catalyst such as **1nn** or unsymmetrical SCP complexes.[49] In these reactions, **1nn** shows a tandem catalytic activity catalyzing both the stannylation and the allylation process, and thus, allyl chloride **102** and aldehyde **100** can be coupled by a single catalyst in the presence of **103**.

Yao and co-workers[167] employed selenium-based pincer complex (**1kk**) and found that the allylation of benzaldehyde **79** can be carried out using allyltributyltin **104** with very low catalyst loadings (0.02 mol %) (Scheme 44). The homoallylic alcohol **105** was obtained in excellent yield (96%) under mild reaction conditions (40 °C). The same catalyst (**1kk**) was employed in the aldol type of cyclization of isocyanoacetates and sulfonylimines (see Scheme 37), and related selenium-based pincer complexes are excellent catalysts for stannylation and borylation reactions as well (sections 6.1 and 6.3), rendering also SeCSe complexes as privileged pincer complexes.

An interesting phosphido palladium pincer complex **1oo** was prepared and applied by Mazzeo and co-workers[22] (Scheme 45). This complex was found to be an efficient catalyst for the allylation of various aldehydes using allylic stannane **104**, demonstrating that nonaryl based pincer complexes are also efficient catalysts in allylation reactions. Allylation of nitrobenzaldehyde was performed at room temperature, affording **106** in quantitative yield.

An enantioselective version of the allylation of aldehydes was presented by Bedford and co-workers (Scheme 46)[47] using BINOL-based bis(phosphite) complex **1m** (for the synthesis of this complex, see section 2.2). It was reasoned that the *tert*-butyl groups biased the BINOL moieties toward the active site of the complex. This is supported by the observation that the enantiomeric excess for product **105** was 62% using catalyst **1m**, while poor enantioselectivity (6%) was observed in the absence of the ^{t}Bu groups in the complex.

Scheme 41. Catalytic Generation of Nucleophilic Allyl Moieties by Formation of (a) η^1-η^3-Bis-allyl Palladium Species or (b) η^1-Allyl Palladium Pincer Complexes



Carbon dioxide undergoes palladium-catalyzed allylation of the carbonyl group similarly to aldehydes. Nicholas and Frank demonstrated[176,177] that allylstannanes readily reacted with carbon dioxide, probably via a bis-allyl palladium mechanism[177] (cf. Scheme 41a) using $Pd(PPh_3)_4$. Wendt and co-workers[168] reported a pincer complex-catalyzed version of this reaction. It was shown that PCP−palladium complex **1pp** catalyzed the carboxylation of allylstannane **104** using carbon dioxide (**107**) to give butenoate stannane **108** (Scheme 47) in 80% yield.

Pincer complex-catalyzed allylation of carbonyl compounds is not restricted to allyl stannanes as allyl sources. Iwasawa and co-workers[23,24] presented a useful carboxylation reaction of allenes (Scheme 48) using PSiP complex **1qq**, which comprises an electron rich palladium center. The reactions proceed under mild conditions, with high yields tolerating many functional groups. The process has an impressive regioselectivity, providing preferentially the branched allylic product (such as **111**). In the reaction, $AlEt_3$ (**110**) was used as hydride source for substitution of the sp carbon of the allene substrate (**109**). The subsequent formation of the η^1-allyl palladium pincer complex[23] (see also Scheme 41b) brings this process to a close mechanistic relationship with the above presented allylation reactions of aldehydes. The preferential formation of the sterically congested branched product is also similar to the related reactions of aldehydes (cf. with Schemes 42 and 43) and very typical of the regiochemical features of the reactions of η^1-allylmetal reagents.[3]

Szabó and co-workers carried out experimental studies and DFT-modeling to explore the mechanism of the pincer complex-catalyzed allylation of electrophiles, such as aldehydes and imines.[164,166] The mechanism reported for the allylation of aldehydes with allyl stannanes is shown in Scheme 49a. In the mechanistic studies, the catalytic activities of PCP complexes **112** were studied (X = Cl, **1l**; X = $OCOCF_3$, **1bb**), as the architecture of this and related complexes proved to be the most successful

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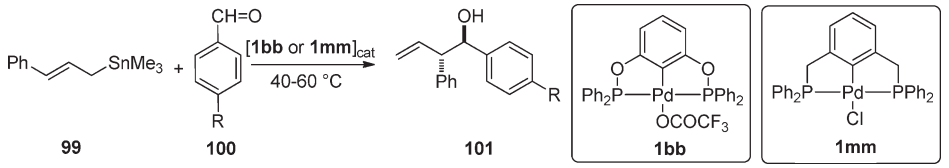
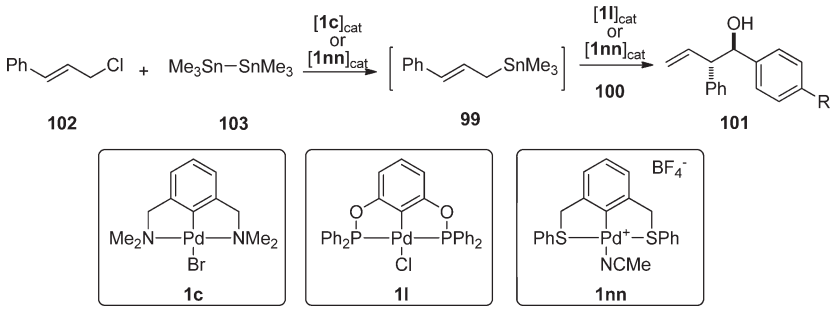
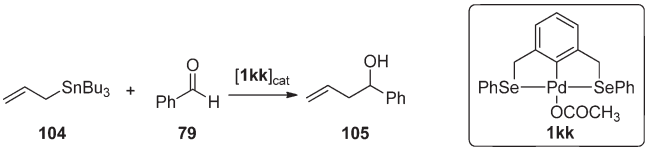
Scheme 42. Diastereoselective Allylation of Aldehydes with Allylic Stannanes[163,164]



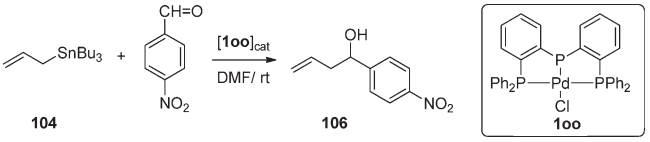
Scheme 43. Palladium Pincer Complex-Catalyzed One-Pot Stannylation−Allylation[49,53]



Scheme 44. Allylation of Aldehydes Using Selenium-Based Complex 1kk[167]



Scheme 45. PPP-Pd Catalyst in the Allylation of Aldehydes[22]



one for allylation of electrophiles.[44,163−166] In addition, the synthesis (see Scheme 3−5, 7, and 8) and handling of these complexes are very simple. ^{1}H NMR studies have shown that allylstannanes (and also potassium allyl trifluoroborates) undergo facile transmetalation at −10 °C, affording η^1-allyl palladium complex **113**. The characteristic ^{1}H NMR shift for the η^1-allyl moiety was assigned, and formation of **113** was also confirmed by the reaction of **112** and allyl magnesium bromide. The tridentate pincer structure of **113** hinders the formation of the thermodynamically more stable[178] η^3-allyl palladium complex. This feature is very important for the expected reactivity, as the allyl moiety in η^3-allyl palladium complexes is electrophilic, whereas for reactions with aldehydes, imines, and related compounds a nucleophilic η^1-allyl moiety is required. The transmetalation step (**112** → **113**) is probably rate determining (as in many palladium-catalyzed processes) and requires a relatively electron poor palladium center. This electron deficiency can be achieved by application of π-accepting side arms, such phosphines, and reinforced by ortho-oxygen substituents, such as in **112**. Weakly bound counterions, such as trifluoroacetate ion in **1bb**, may further increase the catalytic activity. Accordingly, a very useful combination of the electronic effects of the side arms, aromatic substituents, and the counterion is realized in **1bb**.

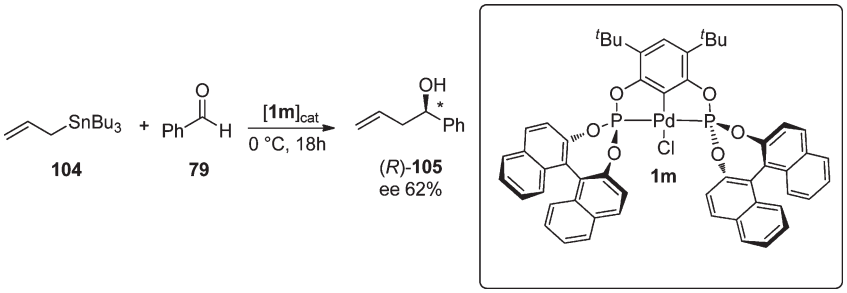
The feasibility of the reaction of **113** with aromatic aldehydes **114** (such as benzaldehyde **79**) was studied by DFT modeling.[164] The mechanistic features of the electrophilic attack of pincer complex **113** and those for bis-allyl palladium complex **96b** proved to be identical.[160,164,166] In both cases, the electrophilic attack takes place at the γ-position of the allyl moiety to give the branched allylic isomer (cf. Schemes 42−43 and 48). This regioselectivity is driven by electronic (rather than steric) factors. The main electronic effect is the hyperconjugative interaction between the low lying σ(Pd−C) and the empty π^*(C═C) orbitals, similarly to the activation of allyl silanes or stannanes.[179] This also involves that the electron demand in the electrophilic attack is the opposite of the transmetalation step. A high electron density on palladium allows an efficient electron transfer to the double bond, which increases the nucleophilicity of the allyl moiety. Considering that the transmetalation usually is the rate determining step, a relatively electron poor Pd atom is beneficial for the entire process. However, if the electron density on palladium is too low, the electrophilic attack can become rate determining or, in extreme cases, hinders the catalytic process. Therefore, dicationic (such as PNP or NNN) pincer type complexes are supposed to be inefficient as catalysts for these types of allylation reactions.

The final step of the catalytic cycle is the dissociation of the product (**116**) and regeneration of the catalyst **112**. It is important to point out that this transmetalation−electrophilic attack−dissociation sequence does not involve change of the oxidation state of palladium.

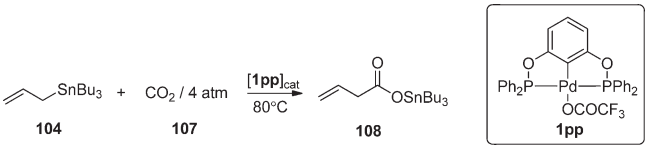
Probably a similar mechanism (Scheme 49a) operates in the allylation of other electrophiles, such as carbon dioxide and sulfonyl imines (section 5.2). Wendt and co-workers[111] isolated a closely related analogue of **113**, complex **113′**, and showed that this complex reacts immediately with CO_2 (**107**) to give a

dx.doi.org/10.1021/cr1002112 |*Chem. Rev.* 2011, 111, 2048–2076

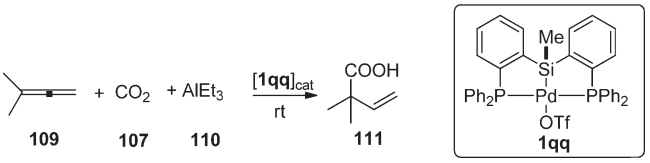
Scheme 46. Enantioselective Allylation of Aldehydes Using Chiral BINOL-Based Pincer Complex[47]



Scheme 47. Palladium Pincer Complex-Catalyzed Carboxylation of Allylstannane[168]



Scheme 48. Carboxylation of Allenes by PSiP Complex 1qq[23,24]



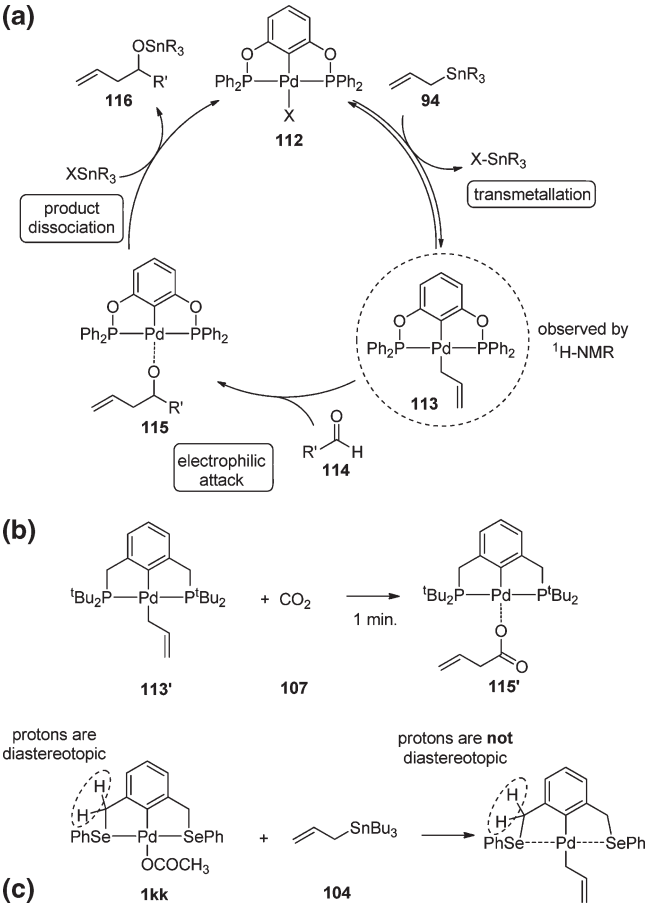
butenoate complex **115′**, which is a close analogue of **115** (Scheme 49b). The fast nucleophilic attack of the η^1-allyl moiety of **113′** is a crucial step in the related catalytic process (Scheme 47) based on allylation of CO_2 with allyl stannane **104**.

Yao and co-workers[167] suggested that the transmetalation of **1kk** with allylstannane is the key step of the pincer complex (**1kk**) catalyzed allylation of benzaldehyde (Scheme 44). Formation of the corresponding (η^1-allyl)pincer complex was observed by ^{1}H NMR spectroscopy (Scheme 49c). It was found that the benzylic protons (denoted in Scheme 49c) of the η^1-allyl complex are not diastereotopic, suggesting that the phenylselenide groups are either free or only loosely bound to palladium. In contrast, the benzylic protons in **1kk** are diastereotopic (resonate at different shift values), indicating a relatively strong Pd−Se bonding.

Le Floch and co-workers[169] studied the allylation of various aldehydes, such as **79**, using tributyl stannane **104** in the presence of pincer complex catalysts **1rr** and **1ss** (Scheme 50). Based on these experimental results, the authors performed DFT modeling studies to explore the mechanistic details of the allylation process.

In the DFT modeling studies by Le Floch and co-workers, two mechanistic alternatives were considered using slightly simplified substrates (Scheme 51): (i) Lewis-acid type activation by the palladium atom of cationic complexes **117a** (model for the intermediate formed from **1rr**) and **117b** (model corresponding to **1ss**), and (ii) allylation via η^1-allyl palladium complexes (**122a** and **122b**).

Scheme 49. (a) Proposed Mechanism for the Allylation of Aldehydes with Allylstannanes via an η^1-Allyl Palladium Intermediate;[164,166] **(b) Rapid Electrophilic Attack of the η^1-Allyl Moiety of Pincer Complex 113′ on the Carbon Atom of CO_2;**[111] **(c) Transmetallation of SeCSe Complex 1kk with 104 Monitored by ^{1}H-NMR**[167]



The first alternative (i) is based on the activation of formaldehyde **120** (used as model for benzaldehyde derivatives) by an electron deficient palladium atom. This mechanism does not require a transmetalation of the allyl stannane to palladium. The second alternative is similar to the mechanism presented by the Szabó group[164] and others[111,167] except that pincer complex models **117a,b** were applied instead of PCP complex **112**. Based on DFT calculations on these model reactions, Le Floch and

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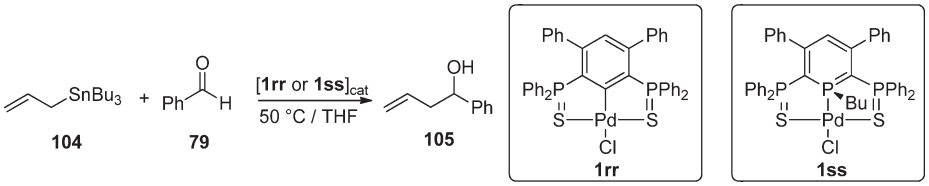
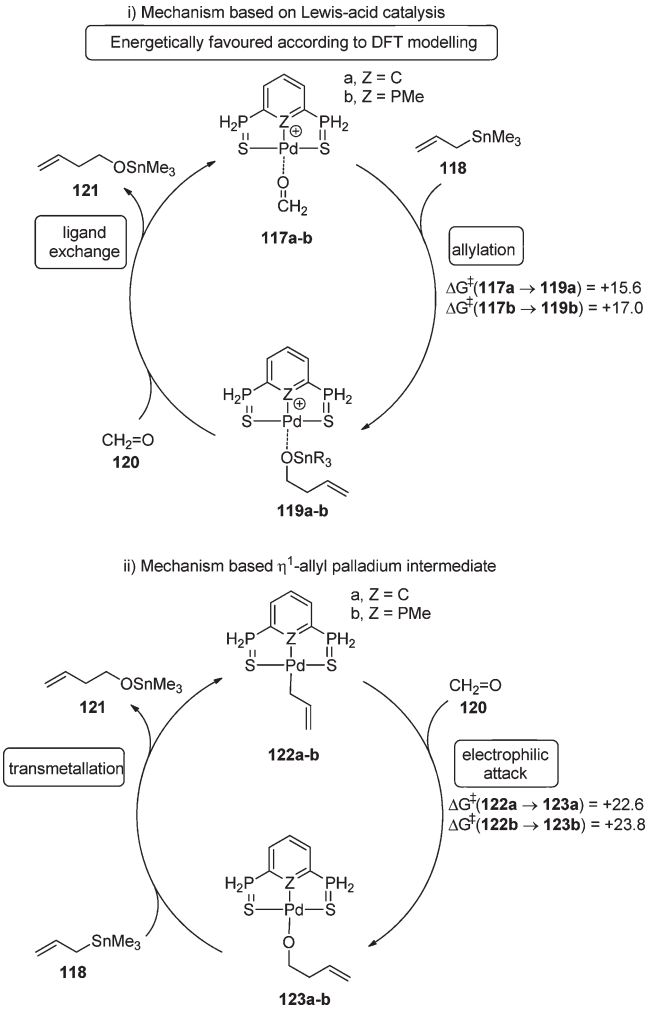
Scheme 50. Catalytic Allylation Reactions Studied by Le Floch and Co-workers[169]



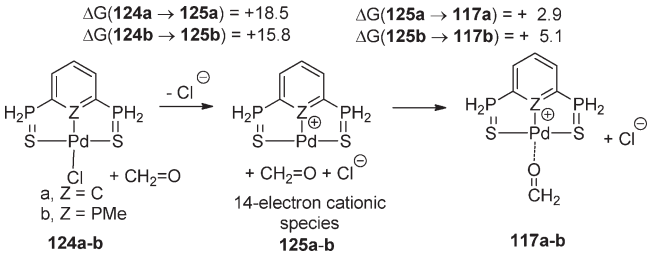
Scheme 51. Mechanistic Alternatives Studied by DFT Modeling (Energies Are Given in kcal mol^{-1})[169]



co-workers[169] found the Lewis-acid catalysis to be the most probable mechanism of the experimentally performed catalytic reactions (Scheme 50).

It is always important to consider a possible Lewis-acid activation mechanism in the case of allylation of carbonyl compounds with allylmetal species. However, comparison of the DFT activation energies for reactions involving cationic complexes (such as **117a,b** and **119a,b**) with neutral species (such as **122a,b** and **123a,b**) is usually problematic because of the huge energy differences generated by solvent participation effects in the different processes. The so-called "continuum models", such as the PCM model applied in this study,[169] do not account for the

Scheme 52. Highly Endoenergetic Formation of the Key Intermediates of the Lewis-Acid Catalyzed Process (Scheme 50i) (Energies Are Given in kcal mol^{-1})[169]



explicit electronic effects of the individual solvent molecules. Consequently, the dissociation and ionization reactions may require different activation energies than under gas-phase or PCM corrected gas-phase conditions. According to the DFT results of the Le Floch study,[169] formation of the cationic key intermediates of the Lewis-acid catalyzed process **117a,b** from **124a,b** (models for catalysts **1rr** and **1ss**) is highly endothermic[169] (Scheme 52). Under real catalytic conditions, a high activation energy, required for the chloride dissociation generating the highly electron deficient (cationic) complexes (**117a,b**), is prohibitive for a Lewis-acid catalyzed process (i). In addition, the formation of **117a,b** suggested by the authors would proceed via 14 electron cationic complexes **125a,b**, which cannot exist in solution, under real catalytic conditions, but most probably coordinates a solvent molecule.

Experimental evidence for an energetically favorable formation of **117a,b** versus **122a,b** would back up the Lewis-acid based mechanism (i) against the η^1-allyl palladium mechanism (ii). However, so far, no such experimental evidence was provided. On the contrary, for PCP complexes (Scheme 49), a facile formation (couple of minutes at −10 °C) of η^1-allyl complex **113** was observed, while the formation of aldehyde complexes, such as **117a,b** was not observed.[164]

5.2. Allylation of Imines with Allyl Metal Reagents

Allylation of aldehydes and other carbonyl compounds can be efficiently accomplished with a wide range of Lewis-acid catalysts.[152] However, allylation of imines leading to homoallylic amines is still a major challenge. This is because the imino functionality is much more difficult to activate by simple electron acceptors than the carbonyl functionality. Yamamoto and co-workers[156,159,162] pointed out that imines were more reactive than aldehydes in palladium-catalyzed allylation reactions via bis-allyl palladium intermediates. This reactivity difference is closely related to the key-role of the nucleophilic allyl moiety in η^1-allyl palladium complexes, which is also favorably stabilized in pincer complexes (e.g., Schemes 41 and 49). Therefore, pincer complex

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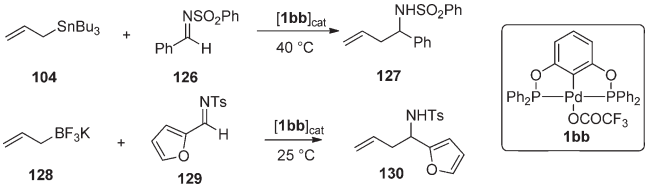
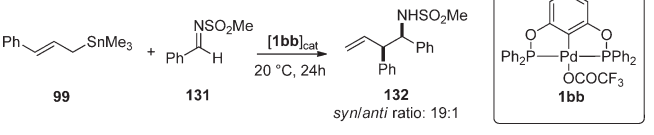
catalysts have been utilized in a broad range of coupling reactions between allyl metal species and imines to obtain homoallylic amines.[43,44,49,163−166,170−172] Similarly to the corresponding reactions with aldehydes (Scheme 42), PCP−palladium complex **1bb** was found to be an efficient catalyst in the allylation of sulfonylimines, such as **126**, using allyltributyltin **104** as allyl source (Scheme 53).[164] Szabó and co-workers[165,166] have shown that potassium trifluoro(allyl)borate (**128**) is also an excellent reagent for the allylation of tosylimines. Allylic borates, such as **128**, are less toxic than the corresponding tin reagents, and these reagents are easily accessible via pincer complex-catalyzed borylation of allylic alcohols and acetates (section 6.3). A variety of imines were allylated, affording homoallylic amines in high yields.[165,166] For example, tosyl protected homoallylic amine **130** was obtained in 95% yield (Scheme 53). It is important to point out that the coupling reaction of allyl trifluoroborates (such as **128**) and sulfonylimines (**129**) can be carried out without the addition of water and base, which is required in the related Suzuki−Miyaura type of coupling between aryl trifluoro borates and aryl halides.[180,181] In fact, it is beneficial that allyl trifluoroborates do not require activation for the coupling reaction, as sulfonyl imines quickly hydrolyze in the presence of water. Stoichiometric studies[166] with pincer complex **1bb** and allyl trifluoroborate **128** have shown that these reagents also form η^1-allyl palladium complexes, such as **113**, similarly to the corresponding reaction of **1bb** and allyl stannanes (Scheme 49a).

Scheme 53. Allylation of Imines Using Allylic Tin and Boron Reagents[164−166]



Scheme 54. Diastereoselective Allylation of Imines Using Substituted Allylic Tin Reagents[166]



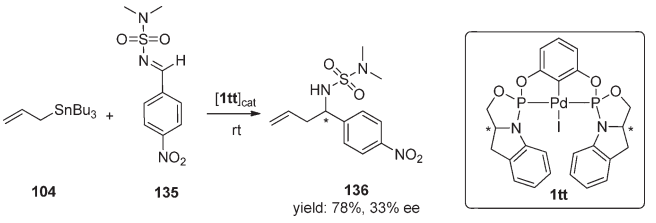
Similarly to aldehydes (see Schemes 42 and 43), imines also react with high diastereoselectivity using functionalized allyl stannanes and boronates. However, the stereoselectivity of the reactions is different. In contrast to the allylation of aldehydes reacting with *anti* stereoselectivity, the reaction between substituted allylic reagents and imines gave the *syn*-isomer of the homoallylic product (**132**) as the major diastereomer (Scheme 54). Up to 19:1 *syn*/*anti* ratio was obtained in the allylation of sulfonyl imine **131** with cinnamyl stannane **99** using **1bb** as catalyst (Scheme 54). According to DFT modeling studies,[166] the switch of the diastereoselectivity was attributed to the different transition state geometries for allylation of aldehydes and imines.

Szabó and co-workers[43,44] have developed an enantioselective procedure for the allylation of imines with allyl metal reagents using a series of BINOL- and TADDOL-based palladium pincer catalysts.[43,44] In these reactions, both allyl stannanes (such as **104**) and allyl borates (**128**) could be employed as allyl sources. The key for the successful development of the asymmetric allylation reactions was the development of a highly modular synthesis of a small library of BINOL- and bisphenanthrol-based chiral pincer complexes (see Scheme 5). The highest enantioselectivity was obtained with catalyst **1j** with the bulky bisphenanthrol substituents.[44] In the allylation of imine **133** with **104**, the homoallylic amine product **134** was isolated in 71% yield with 85% ee (Scheme 55).

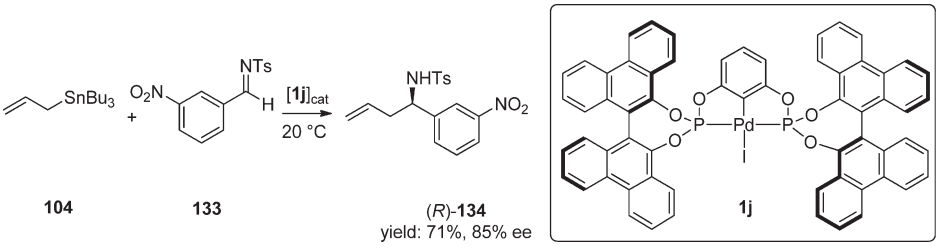
The allylation of dimethyl amine-substituted sulfonyl imines (**135**) was performed by the van Koten−Klein Gebbink group (Scheme 56).[170,171] An advantage of these types of imines is that the deprotection of the nitrogen to the homoallylic amine can be performed more easily than that of tosyl-protected amines. Moderate levels of enantioselectivity,[171] up to 33% ee, were obtained using *P*-chiral pincer complex **1tt** in the allylation of imine **135** with allylic tin reagent **104**.

Recently, Gong, Song, and co-workers[172] published an elegant method for the preparation of other *P*-chiral palladium pincer complexes. Up to 69% ee was obtained in the allylation of

Scheme 56. *P*-Chiral Pincer Complex in the Allylation of Dimethylsulfamoyl Imine[171]



Scheme 55. Enantioselective Allylation of Imines Using Chiral Complex 1j[44]



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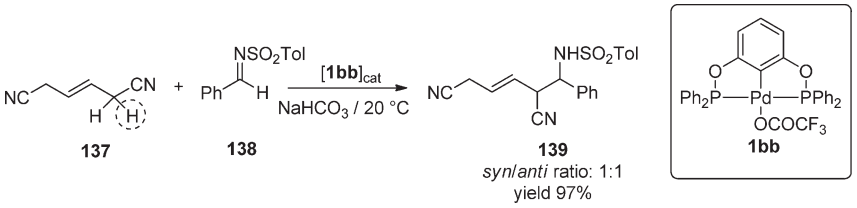
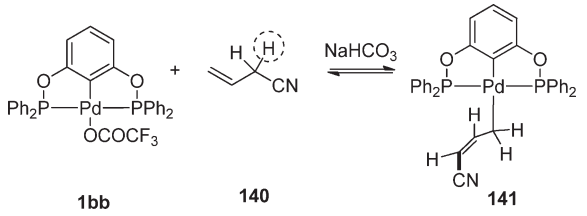
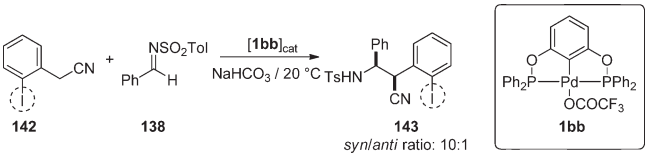
Scheme 57. Allylation of Sulfonyl Imines via C−H Activation of Allyl Cyanides[50]



Scheme 58. Suggested Reaction Mechanism via Base Mediated Formation of η^1-Allyl Palladium Complex[50]



Scheme 59. Coupling of Benzyl Cyanides and Sulfonyl Imines under Mild Conditions[45]

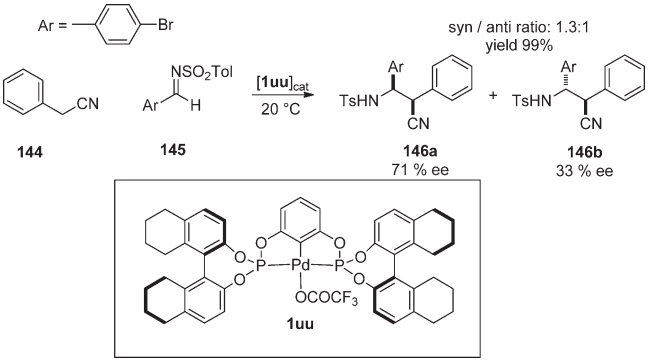


sulfonylimines, while the allylation of aldehydes proceeded with lower enantioselectivity (up to 23% ee).

5.3. Allylation of Imines via C−H Activation of Allyl and Benzyl Cyanides

The above presented reactions are based on the application of allyl metal reagents, such as allyl stannanes (**99** and **104**) or allyl borates (**128**). The Szabó group[50] has demonstrated that this reaction can also be carried out by C−H activation of allyl cyanides instead of C−Sn or C−B bond functionalization (Scheme 57). The reactions can be carried out under very mild conditions using a weak base ($NaHCO_3$). The reaction works well for allyl cyanides with both terminal and internal double bonds, and it provides the branched allylic products, with quantitative yields. However, the stereoselectivity of the reactions is usually poor. In the case of bifunctional nitriles, such as **137**, the reaction can be stopped after monosubstitution, and thus, desymmetrization of **137** to **139** could be carried out. Application of a very weak base ($NaHCO_3$) is highly beneficial for synthesis of functionalized allyl cyanides, as application of stronger bases (Cs_2CO_3) leads to rearrangement of the allyl cyanides to the corresponding vinyl cyanides. Interestingly, the reaction requires use of pincer complex catalyst **1bb**, as commonly employed palladium sources, such as $Pd(OCOCF_3)_2$ or $Pd_2(dba)_3$, are ineffective as catalysts.

Scheme 60. Asymmetric Catalysis for C−H Functionalization Based Coupling of Benzyl Cyanide and Sulfonyl Imine[45]



The reaction is suggested to proceed via a palladium-mediated deprotonation of the allyl cyanide component **140** (Scheme 58). It is very probable that this reaction takes place via a concerted metalation deprotonation (CMD) process of **140**. A similar mechanism was previously suggested for palladium-catalyzed C−H activation of aromatic compounds.[182−185] The η^1-allyl complex **141** formed in the deprotonation reaction may react with the imine electrophile **138** according to the mechanism given for aldehyde electrophiles in Scheme 49. The indicated stereochemistry of the olefin in complex **141** was proposed on the basis of DFT studies.[50]

Subsequent studies have shown that the reaction can be extended to benzyl cyanide substrates as well.[45] This reaction also proceeds under mild conditions. Benzyl cyanides have a relatively high pK_a value (21.9), and therefore, its direct deprotonation requires strong bases, such as LDA[186] or proazaphosphatranes.[187,188] However, the palladium assisted CMD mechanism allows the application of weak bases such as $NaHCO_3$. The reaction of ortho-substituted benzyl cyanide **142** with imine **138** afforded the product **143** with excellent diastereoselectivity (Scheme 59). The mild reaction conditions and application of pincer complex catalyst **1bb** led to a high level of functional group tolerance. For example, the aromatic iodo substituent of **142** survived the reaction unchanged, as Pd(0) species do not occur in the transformation.

The reaction was also extended to synthesis of chiral benzyl cyanide derivatives (such as **146**) using catalyst **1uu**. The coupling reaction of **144** and **145** could be achieved under base-free conditions with promising levels of enantioselectivity (Scheme 60). Catalyst **1uu** proved to be more reactive and selective than its BINOL analogue **1f**; however, the stereoselectivity of the process was rather poor, even with this pincer complex catalyst.[45]

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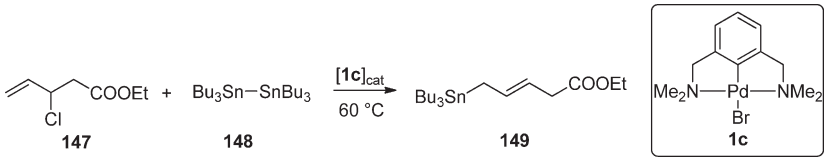
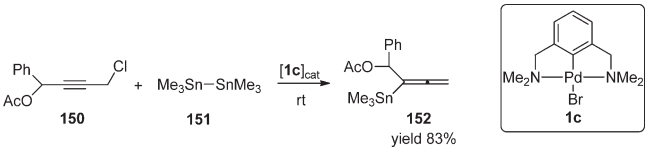
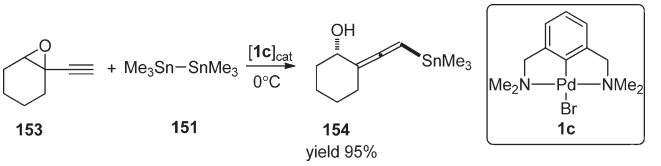
Scheme 61. Synthesis of Allyl Stannanes Using Pincer Complex Catalyst[53]



Scheme 62. Synthesis of Allenyl Stannanes from Propargyl Chlorides[192,193]



Scheme 63. Stereoselective Synthesis of Allenyl Stannanes from Epoxides[193]



6. SYNTHESIS OF ORGANOMETALLIC REAGENTS

In the above sections (sections 3 and 5), several examples are given for pincer complex-catalyzed transformations involving functionalization of carbon−metal bonds, such as allylation of aldehydes/imines with allyl stannanes and borates as well as cross-coupling reactions using aryl boronates, aryl stannanes, and aryl zinc compounds. A particularly attractive feature of the pincer complex chemistry is that by the right choice of the electronic properties of the pincer complexes both cleavage and formation of carbon−metal bonds can be performed. The above examples (section 5) demonstrate that allylic C−Sn and C−B bond functionalization can be efficiently achieved using PCP pincer complexes (such as **1l**−**j**, **1bb**, etc). On the other hand, pincer complexes with σ-donor heteroatoms in the side arms (such as in **1c**, **1k**, and their analogues) can be used for the synthesis of allenyl stannanes and silanes as well as the selective preparation of allyl stannanes and boronates. The pincer complex catalyst in most of these reactions is characterized by a unique reactivity and selectivity, and in many cases, they cannot be replaced with simple palladium sources, such as $Pd(OAc)_2$, $Pd_2(dba)_3$, and $Pd(PPh_3)_4$.

6.1. Formation of Allyl Stannanes using Dimetallic Reagents

The Szabó group has shown[53] that allyl chlorides (such as **147**) or phosphonates undergo pincer complex (**1c**) catalyzed stannylation using hexabutyl distannane[189,190] (**148**) as metal source (Scheme 61). The reactions proceeded very cleanly without formation of byproduct. However, the instability of the functionalized allyl stannane products (**149**) caused considerable purification losses; compound **149** could be isolated only in 62% yield. Some of the products bearing electron-withdrawing substituents on the double bond could not be isolated at all because of rapid decomposition. This gave the idea[49,53] to develop one-pot reactions, in which the allylstannane product is not isolated but reacted directly in pincer complex-catalyzed reactions with aldehydes or imines (section 5.1, Scheme 42). It should be noted that stannylation of allyl chlorides can also be carried out using common palladium sources,[191] such as $Pd(PPh_3)_4$. This reaction gives sizable amounts of allyl−allyl coupling product, indicating the formation of bis-allyl palladium intermediates (cf. Scheme 41a). Formation of bis-allyl palladium intermediates can be avoided by the use of pincer complex catalysis, and thus, formation of allyl−allyl coupling side product can also be avoided.

The van Koten−Klein Gebbink group[40] has reported a catalytic procedure for stannylation of cinnamyl chloride to cinnamyl stannane. In this procedure, the NCN complex (analogue to **1c**) was immobilized to a solid support using a "click chemistry" approach. The immobilized catalyst could be recycled several times without loss of the catalytic activity, indicating that the pincer catalyst complex remained intact under the catalytic conditions.

6.2. Allenyl Stannanes and Allenyl Silanes from Propargyl Chlorides

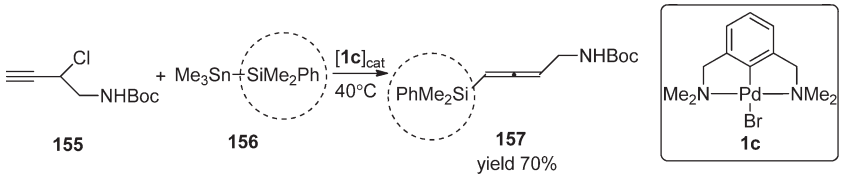
The above stannylation reaction of allylic chlorides could be extended to propargylic substrates.[192,193] Thus, allenyl stannane **152** could be prepared from propargyl chloride **150** and hexamethyl distannane **151** under mild conditions (at room temperature) with excellent yield using NCN catalyst **1c** (Scheme 62). The synthetic scope of this process is very broad, as the reaction proceeds under mild, neutral conditions without additives. The reaction usually proceeds with high allenyl selectivity, but for a couple of substrates, mainly with electron donating substituents on the triple bond, the propargyl product was obtained. Although **1c** is an excellent catalyst for stannylation of propargyl chlorides, SeCSe complexes (analogues of **1k** and **1kk**) are also highly efficient catalysts in these types of transformations.[193]

The stanylation process can also be carried out using propargyl epoxides instead of propargyl chlorides. For example, the synthesis of cyclic allenyl stannane **154** could be achieved from epoxides **153** and **151** using **1c** as catalyst (Scheme 63). The reaction proceeds under mild reaction conditions with excellent *anti* selectivity and in high isolated yield. The high yields obtained in these reactions are due to the fact that the allenyl stannanes (e.g., **152** and **154**) are more stable compounds than the corresponding allyl stannanes and, therefore, they can be purified without considerable losses by silica gel chromatography.

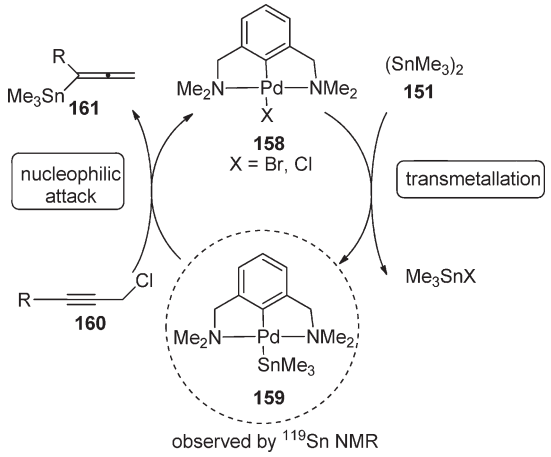
When the symmetrical dimetallic reagent distannane **151** was replaced by the unsymmetrical silyl stannane **156**, two different products could be expected: allenyl stannane or silyl stannane.[189,190] It was found that the silyl group of **156** was transferred exclusively to the organic substrate (Scheme 64). Thus,

dx.doi.org/10.1021/cr1002112 |*Chem. Rev.* 2011, 111, 2048–2076

Scheme 64. Synthesis of Allenyl Silanes Using Unsymmetrical Reagent 156[193]



Scheme 65. Proposed Mechanism for the Stanylation Process[164,193]



the procedure could be employed for synthesis of allenyl silanes, such as **157**, from propargyl chlorides (such as **155**).[193] Both allenyl silanes and allenyl stannanes are useful building blocks for introduction of allenyl and propargyl functionalities in modern organic synthesis and in natural product synthesis.[194−196]

The mechanism of the pincer complex-catalyzed stannylation reaction (Scheme 65) was studied by the Szabó group using NMR experiments and DFT modeling.[164,193] In a stoichiometric reaction, **158** (X = OAc) was reacted with distannane **151**. Monitoring the process with ^{119}Sn NMR spectroscopy revealed the formation of tin complex **159**, suggesting that the first step of the catalytic reaction is a transmetalation of the distannane reagent **151** with the palladium atom of **158**. The possible fate of complex **159** was studied by DFT modeling. The DFT studies showed that the transfer of the trimethyl group to the organic substrate **160** may occur with a relatively low activation barrier of 21 kcal mol^{-1}. These studies also indicated that the S_N2' type of attack leading to the allenyl product **161** proceeds with a lower activation barrier than the direct, S_N2 displacement of the chloride.

It is interesting to add that the above-described substitution of propargyl chlorides is probably a unique reactivity of pincer complex catalysts, as dimetallic reagents such as **148**, **151**, and **156** undergo addition to triple bonds (affording divinyl stannanes or vinyl silyl stannanes) using nonpincer reagents, such as $Pd(PPh_3)_4$.[189,190,197]

6.3. Borylation Reactions Catalyzed by Palladium Pincer Complexes

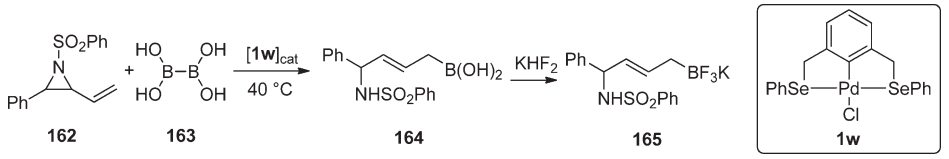
The above pincer complex-catalyzed stannylation and silylation processes could further be extended to include carbon−boron bond forming reactions. The extension of the synthetic scope of these reactions is strongly motivated by the fact that organoboronates are very important reagents in selective organic synthesis.[120] For example, allylic boronates serve as nontoxic and stable carbanion equivalents for the allylation of various electrophiles.[120,150,152,198,199] Several methods for the preparation of allylic boronates are reported; however, many of them require harsh conditions, resulting in a low functional group tolerance. Miyaura and co-workers[200] have shown that allylic boronic esters can be synthesized via a Pd(0)-catalyzed substitution of allylic acetates. The reaction was proposed to occur via η^3-allyl palladium intermediates, which gave some allyl−allyl dimerization byproduct. The allyl−allyl coupling product probably forms via bis-allyl palladium complexes, such as **96** (see Scheme 41a). In fact, this is the same type of undesired side reaction which occurs in stannylation with distannanes using nonpincer catalysts (see discussion in section 6.1).[191] In order to avoid the reductive allyl−allyl coupling via bis-allyl palladium complexes (such as **96**), the Szabó group[201] has developed a borylation procedure for allylic substrates catalyzed by palladium pincer complexes. Various functionalized allylic boronic acids were obtained from allylic acetates, but also vinyl cyclopropanes and aziridines, such as **162**, using selenium-based catalyst **1w** and diboronic acid **163** (Scheme 66).[201] The initial allylboronic acid product **164** is unstable under solvent-free conditions. Therefore, it was treated with aqueous KHF_2,[202] affording the corresponding air and moisture stable potassium trifluoroborate **165**. Potassium trifluoroborates (such as **165**) are useful reagents in organic synthesis for allylation of electrophiles;[165,166,203,204] for example, they can be coupled with sulfonyl imines in the presence of pincer complex catalysts (section 5.2, Scheme 53).[165,166]

Surprisingly, even allylic alcohols could be used as direct precursors for the synthesis of functionalized allylic boronates using palladium pincer catalyst **1w** (Scheme 67).[205] Using this methodology, a broad variety of allylic alcohols have been borylated in good to excellent yields. Interestingly, the borylation reaction of allylic alcohols was found to be even faster than that of the corresponding allylic acetates. The reactions proceeded under mild conditions with excellent levels of regio- and stereoselectivity. For example, the borylation of allylic diol **166** gave the 1,2-substituted borate **167** as a single diastereomer in high yield using catalyst **1w** (Scheme 67).[205]

The mechanism of the borylation reaction was proposed to be similar to that of the stannylation reaction[192,193] described in section 6.1 (Scheme 65). The activation of the hydroxy group of the allylic alcohol **168** (Scheme 68) was proposed to occur by formation of boronic acid ester **169**. Subsequently, ester **169** undergoes transmetalation of the boryl group with **171** (X = Cl is **1w**), affording intermediate pincer boronate **172** and activated allylic alcohol **170**. This step is supposed to be analogous with the corresponding transmetalation in the stannylation reaction (**158** → **159** in Scheme 64). Thereafter, the activated alcohol

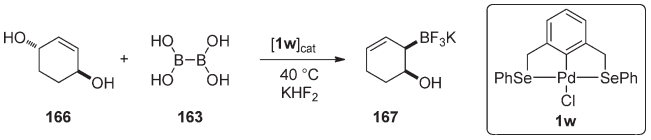
dx.doi.org/10.1021/cr1002112 |*Chem. Rev.* 2011, 111, 2048–2076

Scheme 66. Pincer Complex-Catalyzed Borylation of Vinyl Aziridine[201]



162 163 164 165 1w

Scheme 67. Diastereoselective Borylation of Allylic Alcohols Catalyzed by Palladium Pincer Complex[205]



166 163 167 1w

functionality of **170** is substituted by the boryl group in a S_N2/S_N2' type of mechanism to furnish the allylic boronate product **173**.[205]

The mild conditions and high functional group tolerance in the borylation reaction founded the basis for development of several one-pot reactions, where the allylic boronates were generated in situ followed by a Suzuki−Miyaura reaction[207] or allylation of various electrophiles.[206,208−211] For example, the allylboronic acid **175** generated from the borylation of allylic alcohol **174** was coupled with aryl iodides under Suzuki−Miyaura conditions in a sequential one-pot reaction without isolation of **175** (Scheme 69). Interestingly, the branched isomer of **176** was exclusively formed in this reaction.[207] This regioselectivity is rather unique,[212−214] since usual allylic substitution reactions via monoallyl palladium complexes (substituted analogues of **95**) give the linear allylic product selectively.[1]

A wide array of electrophiles, such as aldehydes, ketones, imines, and acetals were allylated using functionalized allylboronic acids generated in situ by palladium pincer catalysis.[206,208−211] The selectivity of these one-pot reactions was excellent, providing the homoallylic products as single diastereomers. For example, the borylation−allylation reaction of allylic alcohol **177** with diboronate **179**, catalyst **1vv**, and aldehyde **178** gave the homoallylic alcohol **180** in high yield as a single diastereomer (Scheme 70).[206]

The synthetic scope was further extended to include acetals as in situ generated sources of the aldehyde substrates. Using acetal **182**, amino alcohol **183** was obtained via the one-pot borylation of **181** (Scheme 71).[209]

Petasis[215−217] and Kobayashi[218] developed a versatile method for synthesis of amino acid derivatives based on addition of organoboronates to in situ generated imines. This reaction sequence was extended by Szabó and co-workers[206] to include one-pot generation of the allylboronate component. Stereodefined amino acid derivative **187** was obtained from the palladium pincer complex-catalyzed borylation of **184** followed by allylation of an imine formed from amine **185** and aldehyde **186** (Scheme 72).

Catalytic C−H borylation of easily accessible starting materials is a valuable method for the synthesis of various organoboronates.[120,219] Szabó and co-workers[220] found that the C−H borylation of unactivated olefins is a viable route to vinylic and allylic boronates, using complex **1c** (Scheme 73). An essential component of this reaction is the hypervalent iodine reagent **189**, which was proposed to oxidize the pincer complex to a palladium(IV) intermediate. Using **179** as boronate source and **189** as oxidant, allylsilane **188** could be efficiently borylated with **1c** as catalyst, affording silyl boronate **190** (Scheme 73). The oxidative conditions applied in this reaction obviate the formation of borohydrides that undergo hydroboration of the alkene substrates, giving an inseparable mixture of saturated and unsaturated organoboronate products.[221] Notably, pincer complex **1c** gave much higher yields in these C−H activation reactions than $Pd(OAc)_2$.

Szabó and co-workers[220] found that the palladium atom of **1c** can be readily oxidized by **189** to generate Pd(IV) complex **191** in a stoichiometric reaction. Such type of oxidation of **1c** and related NCN complexes is known from the literature[33,118] (see section 3.1.2, Scheme 15). Therefore, the suggested initial step in the mechanism of the C−H borylation reaction is the oxidation of **1c** to **191**, followed by transmetalation of **179** to give boronate complex **192**. After coordination of the alkene substrate, complex **193** undergoes an insertion−elimination sequence via **194**, affording the borylated product and regenerating catalyst **1c** (Scheme 74).[220]

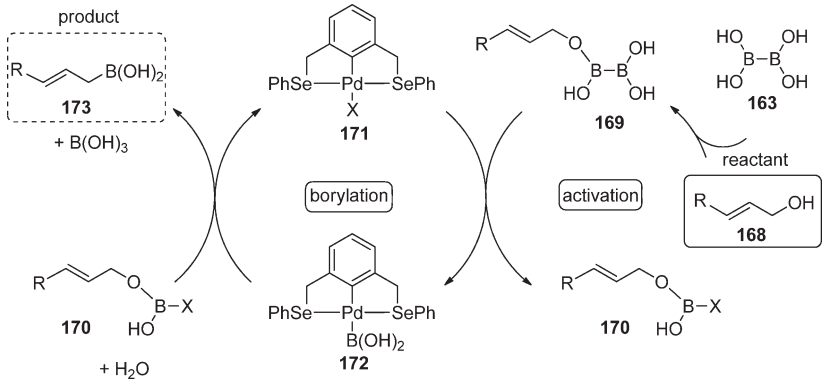
7. CONCLUSIONS AND OUTLOOK

Pincer complex catalysis offers a valuable toolbox complementing existing palladium-catalyzed synthetic methodologies. Pincer complexes have a well-defined stoichiometry, which facilitates conscious design of new catalysts. As the complexes are usually very stable because of the tight tridentate coordination, the metal and ligand are kept together under each catalytic step, and therefore, the ligand effects are efficiently transmitted to the metal atom. This is a very useful feature for the fine-tuning of the steric and electronic properties of the catalyst to achieve a high catalytic activity or selectivity. In addition, the well-defined stoichiometry is of high importance for the design of new pincer catalysts for asymmetric syntesis. The same properties can be used for construction of efficient recyclable catalysts by immobilization of pincer complexes.

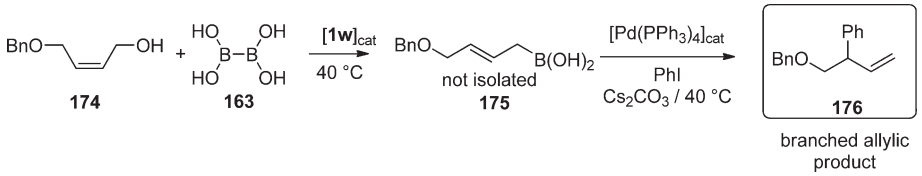
Although the stable tridentate coordination is advantageous in certain transformations, it can also be a limiting factor in pincer complex catalysis. Reduction of the palladium atom to Pd(0) usually leads to decomposition of the catalysts, in particular under harsh conditions, in the presence of strong bases and at elevated temperatures. This property imposes a limitation in use of pincer complexes as direct catalysts, in particular in Pd(0)/Pd(II) based redox cross-coupling reactions. These limitations can be avoided by application of cross-coupling conditions involving redox reaction free conditions on palladium or diverting the redox reaction to a Pd(II)/Pd(IV) catalytic cycle instead of a Pd(II)/Pd(0) one. This also means that development of new reactions is important to be coupled with mechanistic studies to confirm that pincer complexes are direct catalysts of the reactions

dx.doi.org/10.1021/cr1002112 |*Chem. Rev.* 2011, 111, 2048–2076

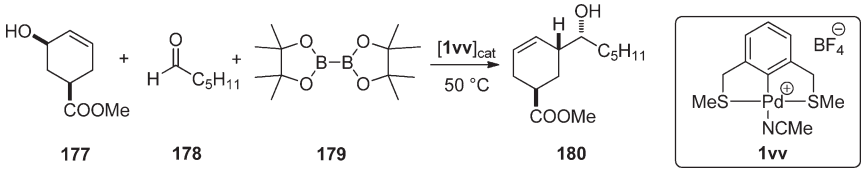
Scheme 68. Proposed Mechanism for the Borylation of Allylic Alcohols[205,206]



Scheme 69. Unusual Regiochemistry, Formation of the Branched Allylic Product 176, in Palladium-Catalyzed Coupling of Allyl Boronate 175 and Phenyl Iodide[207]



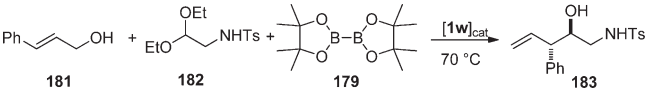
Scheme 70. One-Pot Borylation−Allylation of Aldehydes via in Situ Generated Allylboronates[206]



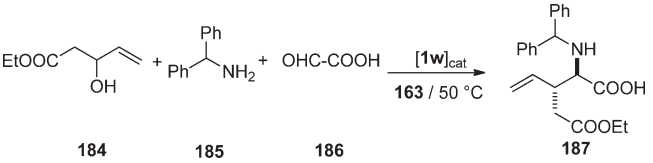
and not only dispensers of active, colloidal Pd(0). In this latter case, the advantageous effects of the pincer ligands cannot be employed in the catalytic reactions.

In the future one may expect development of novel asymmetric catalytic reactions based on chiral pincer complexes. There are already several examples of chiral C−C bond formation processes using chiral pincer catalysts. A particularly interesting area is the design of new catalysts for asymmetric C−H bond activation based C−C bond formation reactions. A further challenge is to widen the synthetic scope of the Pd(II)/Pd(IV) based reactions. In this field, pincer complexes with σ-donor ligands in the side arms, such as NCN or SeCSe complexes, are expected to perform particularly well, as these types of ligands efficiently stabilize the (otherwise thermodynamically instable) Pd(IV) oxidation state. Pincer complex catalysts proved to be very successful for synthesis of organometallic compounds based on catalytic formation of C−B and C−Sn bonds of allyl and allenyl substrates. Future development will probably involve an extension of the synthetic scope of pincer-complex catalysis to formation of other types of unusual carbon heteroatom bonds, such as C−Si bonds, and novel applications for synthesis of aryl and vinyl boronates and silanes.

Scheme 71. Synthesis of Amino Alcohols via Catalytic Borylation of Allylic Alcohols and in Situ Hydrolysis of Acetal 182[209]



Scheme 72. Selective Allylation of in Situ Generated Imines, Obtaining Amino Acid Derivatives[206]



Our intention was to demonstrate that synthesis of most of the complexes is straightforward and palladium pincer catalysts can be exploited for selective organic transformations including

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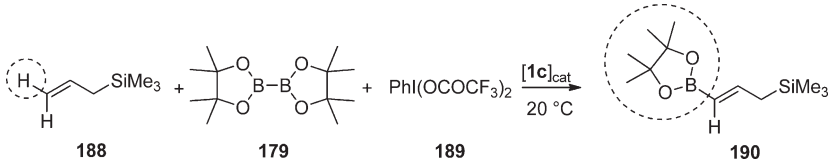
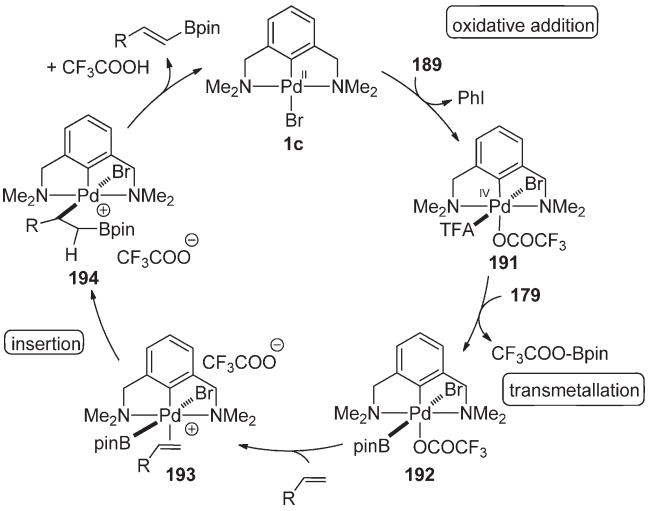
Scheme 73. Catalytic C−H Borylation of Alkenes under Oxidative Conditions Using Pincer Catalysis[220]



Scheme 74. Proposed Mechanism for the Palladium Pincer Complex-Catalyzed C−H Borylation[220]



asymmetric catalysis. The present review will hopefully inspire organic chemists to use pincer complex based methods as a complement to existing catalytic methodologies.

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BIOGRAPHIES

Nicklas Selander completed his Masters studies in 2006 at the Department of Organic Chemistry, Stockholm University, Sweden. Thereafter, he joined the group of Prof. Kálmán Szabó, and in 2010 he obtained his Ph.D. degree in organic chemistry, which was focused on the synthesis and catalytic applications of organometallic reagents. Dr. Selander made major contributions to the work of the Szabó group in the field of carbon−boron formation reactions and synthetic applications of allylic boronates.

Kálmán J. Szabó is professor at the Department of Organic Chemistry at the Arrhenius Laboratory, Stockholm University. He obtained his Ph.D. at Lund University, Sweden, with Professor Salo Gronowitz, in 1993, and did his postdoctoral research with Professor Dieter Cremer. Szabó did his habilitation at the Uppsala University in 1997, and in 1998 he joined the Department of Organic Chemistry at Stockholm University, where he was appointed Professor in 2003. His major research interests involves theoretical (DFT) and experimental aspects of organic synthesis, organometallic chemistry, and homogeneous catalysis. Prof. Szabó performed extensive research into the chemistry of allyl metal complexes, in particular the structure and reactivity of functionalized η^1- and η^3-allylpalladium complexes. In the past 15 years, he has developed synthetically useful transition metal catalyzed transformations based on palladium, iridium, ruthenium, and titan complexes. His group extensively studied the application of palladium pincer complexes in selective organic transformations including asymmetric catalysis, with a particular attention to carbon−carbon, carbon−boron, and carbontin formation reactions. In the last few years, his research interest has turned in the direction of C−H activation reactions and possibilities to employ higher oxidation states of transition metals, such as Pd(IV), for selective transformation of alkenes.

ACKNOWLEDGMENT

This work was mainly supported by the Swedish Natural Science Research Council (V.R.). Additional support to the IDECAT Network of Excellence of the European Community under Contract NMP3-CT-2005-011730 is greatly acknowledged.

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