1 INTRODUCTION

1.1 Domino Reactions

During the last decades, organic chemistry underwent continuous and rapid developments. Instead of preparing molecules in many sequential steps, chemists are able to perform complex transformations with only little synthetic effort. More complex reactions set the stage for more efficient procedures. Special emphasis is put on economic and ecological aspects of modern synthesis. That means, on the one hand, to sustain existing environmental resources and to avoid unnecessarily toxic chemicals. The main issue of an efficient synthesis can be regarded as the increase of complexity per transformation. In particular, this is characterized by high selectivities (chemo-, regio- and stereoselectivity) and efficiency of a transformation. Good selectivities can be obtained by using suitable reactions conditions or by differentiation of the reaction pathway. The efficiency can simply be attributed to the yield of the reaction and to the number of newly formed bonds in the product framework. In past and even today, target molecules were synthesised by stepwise formation of individual bonds or by the installation of appropriate functional groups. Every reaction step requires own work-up procedures and sometimes extensive purification effort. The costs and the expenditure of time can be dramatically reduced by utilizing more efficient pathways. Domino, tandem and multicomponent reactions satisfy these requirements.[1–3]

1.1.1 CLASSIFICATION

Domino reactions – sometimes also specified as cascade reactions – can be regarded as an elegant and highly efficient approach for the synthesis of complex molecular scaffolds. One key

player in the investigation of such reactions is the group of TIETZE, who defined a domino reaction as:

> *"Such a process would be the transformation of two or more bond-forming reactions under identical reaction conditions, in which the latter transformations take place at the functionalities obtained in the former bond-forming reactions."*[1]

A well established metaphor displays that as a row of domino stones, where after successful initiation one stone tips the next, and so on… until the process finds a defined end with the last stone. In contrast to polymerization reactions, where chemists obtain a broad polydisperse distribution of polymers – a domino reaction generally provides only one single product. Multicomponent reactions are special classes of reactions, in which more than two starting materials were utilized for the formation of the target molecule. These compounds were synthesized in a time-resolved manner, meaning that the components react step by step. The generation of side products plays an important role in this regard. The tendency of side product formation can be overcome by sequential addition of the starting materials or by running temperature programs (one pot reaction). Such a procedure disagrees with TIETZE's prior definition of a domino process, not to change the reaction conditions. However, the term "tandem process" describes a reaction, in which locally independent reaction steps are performed without any interaction.

***Table 1-1*:** Classification of domino processes according to Tietze.[1]

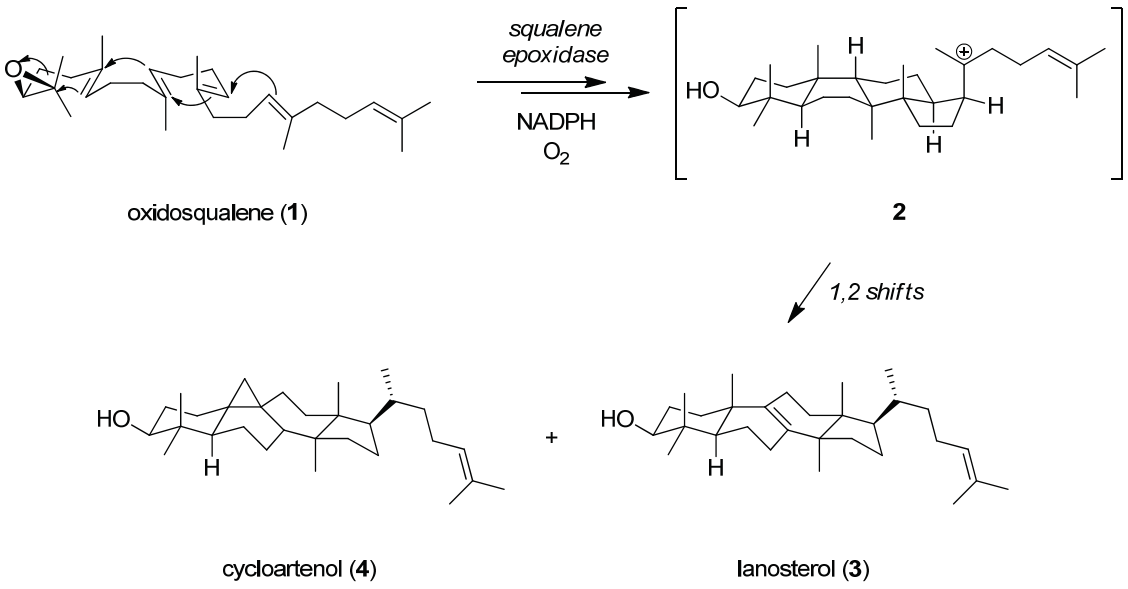
I. Transformation	II. Transformation	III. Transformation
1. Cationic	1. Cationic	1. Cationic
2. Anionic	2. Anionic	2. Anionic
3. Radical	3. Radical	3. Radical
4. Pericyclic	4. Pericyclic	4. Pericyclic
5. Photochemical	5. Photochemical	5. Photochemical
6. Transition metal cat.	6. Transition metal cat.	6. Transition metal cat.
7. Oxidative or reductive	7. Oxidative or reductive	7. Oxidative or reductive
8. Enzymatic	8. Enzymatic	8. Enzymatic

Furthermore, domino reactions are divided into different classes to distinguish various processes (Table 1-1). The important characteristic is the denotation of the bond forming step. Reactive intermediates and their propagation products serve as basis for this classification. Domino reactions are categorized in cationic, anionic, radical, pericyclic, photochemical, transition metal-catalyzed, oxidative or reductive and enzymatic reactions. Moreover, these transformations have to be divided into processes where all steps are from the same category (homo domino process) and to mixed domino processes.

1.1.2 Examples of Domino Reactions in Organic Synthesis

As so often – scientists have taken Nature as paradigm for the development of new strategies and technologies. Domino reactions did not find their origins in synthetic chemistry, since Nature utilizes this approach for billions of years. Although most of the naturally occurring domino processes can be attributed to multi-enzyme complexes, there are also several examples, in which only one enzyme catalyzes the whole transformation. The biosynthesis of fatty acids is known to be facilitated by the fatty acid synthase, which is a large multifunctional protein with up to seven discrete functional domains.[4]

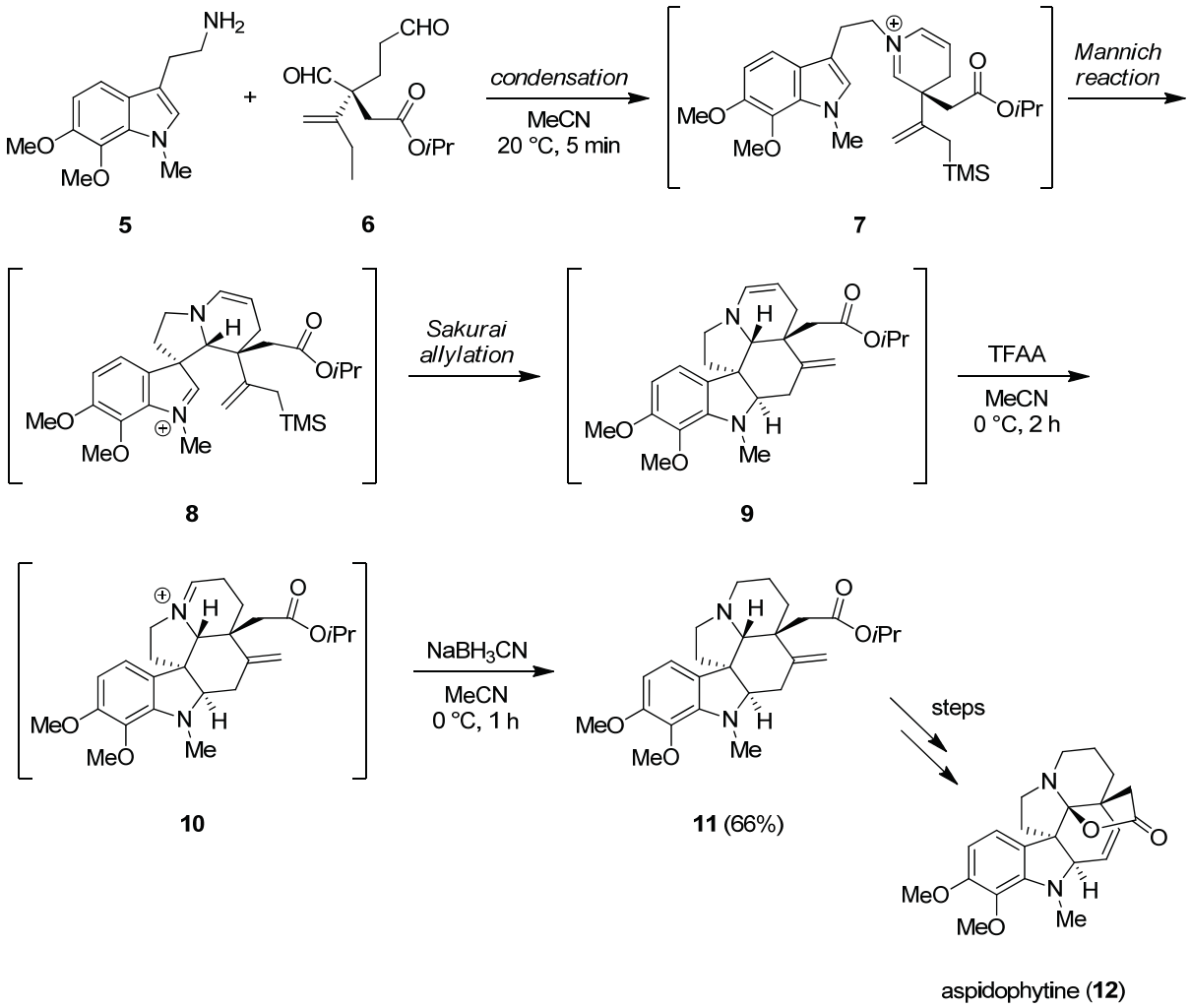
A very prominent example where a domino reaction is performed by only one enzyme is the enzymatic cyclization of oxidosqualene (**1**) to lanosterol (**3**) (*Scheme 1-1*). The cascade is initiated by protonation of epoxide **1** to form carbocation **2**. If **1** is suitably folded on the enzyme surface, the positive charge of the aliphatic triterpene migrates *via* four electrophilic attacks of neighbouring double bonds and a WAGNER-MEERWEIN rearrangement to form four cycles and four bonds. In animals and fungi, compound **2** undergoes several 1,2-shifts of hydrides and methyl groups until the loss of a proton leads to the final double bond of lanosterol (**3**). In comparison, plant-derived cyclic triterpenoids contain a cyclopropane ring, generated by formation of a three-membered ring at C-10. This reaction also causes subsequent 1,2-shifts of hydrides and methyl groups providing cycloartenol (**4**) as product. These natural products are versatile building blocks for steroid synthesis in both animals, fungi as well as in plants. [5–7]



***Scheme 1-1*:** Enzymatic cyclization of oxidosqualene (**1**) to lanosterol (**3**) and cycloartenol (**4**).

Enzyme-catalyzed reactions still display scarce examples in organic synthesis, since their use is often limited to certain molecular frameworks. Nevertheless, this type of reaction is gaining increasing significance, due to astonishing high selectivities and product yields. This led to the hypothesis that enzyme-mediated reactions will represent a key issue of synthetic chemistry in

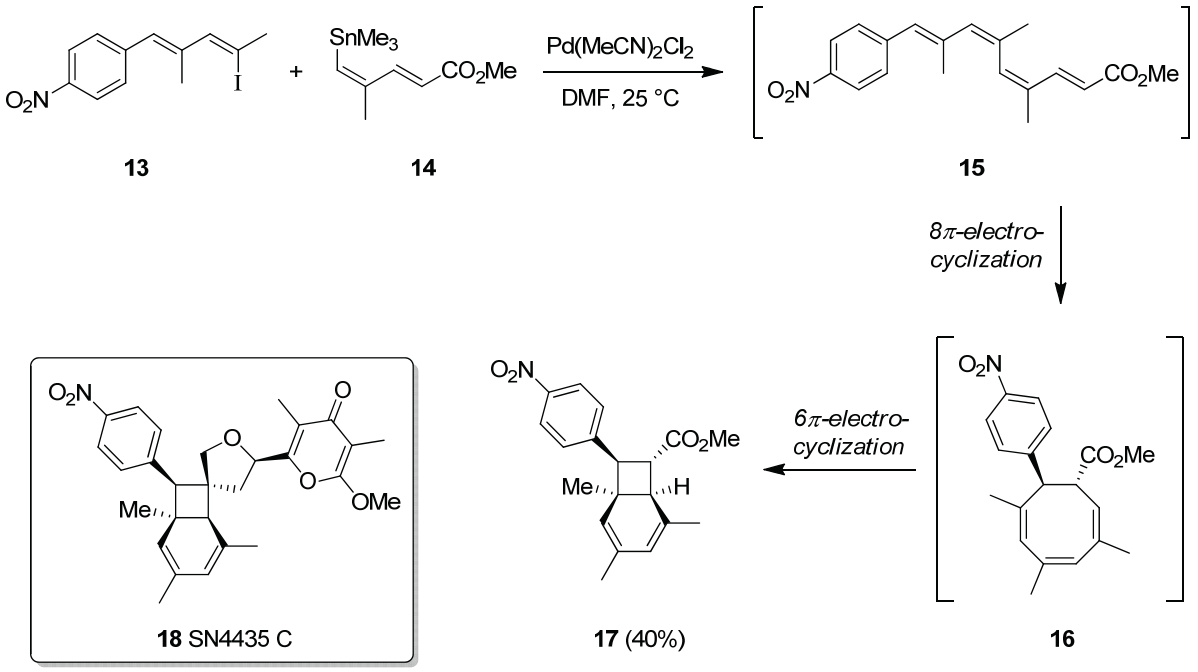
future. Therefore, it is necessary to find synthetic pathways which are accessible under laboratory conditions. Many different groups have taken up this mission and have discovered elaborated preparations to domino precursors.



***Scheme 1-2*:** Total synthesis of aspidophytine **12** according to COREY.

The group of COREY published in 1999 a remarkable total synthesis of the aspidospermine alkaloid (**12**) (Scheme 1-2).[8] The construction of **11** comprised the assembling of two building blocks, the substituted tryptamin derivative **5** and the enantiopure branched compound **6**. The domino reaction is initiated by condensation of the amine group and the aldehyde functionalities to form the quarternary iminium ion **7**. The indole unit reacts in a MANNICH-type[9–10] reaction with the prior formed iminium moiety. This transformation sets the stage for *spiro* substituted compound **8** and finally facilitates an intramolecular SAKURAI allylation[11–12] of the allyltrimethylsilane unit to afford pentacyclic compound **9**. A special feature of this procedure is that the domino approach is connected with a one-pot-synthesis. After 5 min aqueous trifluoroacetic anhydride is added to the reaction mixture to protonate the double bond within two additional hours. Sodium cyanoborohydride is able to reduce the newly formed double bond of **10** providing final compound **11** of the one-pot domino approach. Lactonization of the

*iso*propyl ester and derivatization of the *exo*-cyclic double bond generates aspidophytine (**12**) in six further steps. The asymmetric formation of all stereogenic centers can be traced back to compound **6** by diastereoselective induction in the MANNICH reaction and SAKURAI allylation.



***Scheme 1-3*:** Synthesis of immunosuppressant derivative **17** via an STILLE/electrocyclizytion domino approach by TRAUNER.

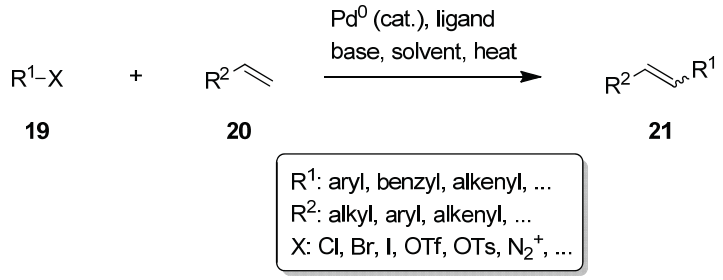
The second interesting example for a domino process is the asymmetric approach towards the immunosuppressant derivative SNF4435 (**18**) by TRAUNER *et al*. (Scheme 1-3).[13] The key step for the construction of this structural motif is a domino STILLE coupling/electrocyclization reaction. The starting materials of the cascade reaction are easily available from propargylic alcohol and a cinnamic aldehyde derivative, respectively. The reaction conditions for the STILLE cross-coupling were not optimized and yielded the desired product in 40% overall yield. The domino reaction proceeds through a STILLE type coupling followed by a 8π-electrocyclization of tetraene **15**. The initially formed triene **16** further reacts in a 6π-electrocyclization forming cyclobutane **17** in 40% overall yield. The perfect stereoselectivities can be attributed to the nature of the 8π-electrocyclizations and the repulsion of the sterically encumbered nitrophenyl unit and the ester group. The 6π-electrocyclization displays a disrotatory process in which the substituents rotate in opposite directions. This derivative sets the stage for the synthesis of many SNF4435 C (**18**) derivatives and their biological applications.

1.2 The HECK Reaction

Palladium-catalyzed cross-couplings became an indispensable tool in organic synthesis. Among different types of palladium catalysis, HECK-type reactions represent a special feature. Apart from the SONOGASHIRA cross-coupling and direct arylations, the HECK reaction is the only Pd-

catalyzed reaction in which no other prefunctionalized electrophile is needed. Due to this fact, HECK reactions allow complex transformations in an atom economic fashion and give rise to the fundament for state-of-the-art synthesis.[14–15]

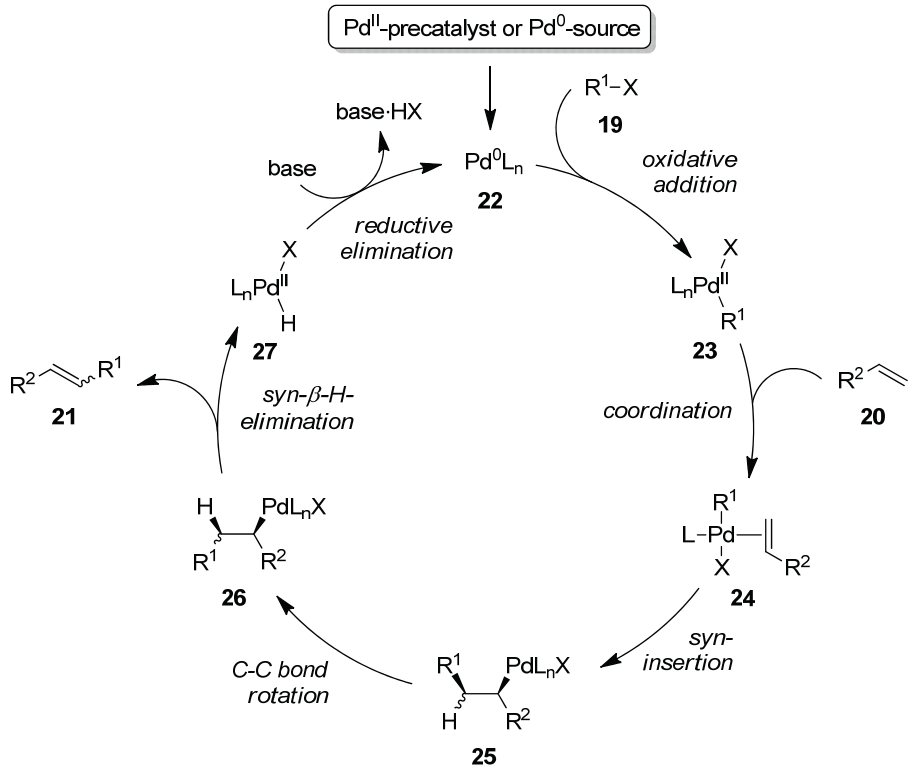
In the early 70's, MIZOROKI and HECK independently investigated the use of aryl, benzyl and alkenyl halides **19** and substituted olefins **20** in presence of a palladium catalyst and an amine base to provide aryl-, benzyl- or alkenyl-substituted olefins **21**, respectively.[16–19] In these years the reaction was limited to olefinic compounds with aryl mercury species (ArHgX) and stoichiometric amounts of the palladium source (e.g. $PdCl_2$ or $Pd(OAc)_2$). In this case, the transmetalation to an arylated *pallada*-species afforded the reactive species for the *C-C* coupling. Further investigations revealed that the reaction can be performed with only catalytic amounts of the palladium source in combination with hindered amine bases and phosphine ligands.



***Scheme 1-4*:** General palladium-catalyzed HECK reaction.

1.2.1 THE REACTION MECHANISM

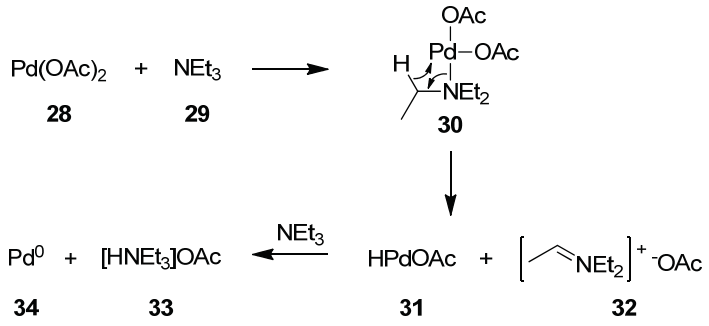
The mechanism of the HECK reaction is not fully elucidated to date.[20] A slight change of the reaction conditions might shift the reaction to another possible pathway. Nevertheless, many different aspects were already clarified to provide a better general understanding of this highly interesting reaction. Scheme 1-5 shows a simplified sequence for the HECK reaction, starting with the generation of an activated Pd^0-catalyst **22** from a Pd^{II}-precatalyst or from another Pd^0-source. The oxidative addition of **22** into the carbon-halide bond initiates the catalytic cycle forming the *pallada*-species **23**, which coordinates side on to the double bond of the olefin **20**. The migratory *syn*-insertion to the double bond provides **25** and after internal *C-C* bond rotation a *syn*-β-hydride elimination occurs to form **21** selectively. The palladium (0) catalyst **22** is regenerated by base-mediated reductive elimination of *pallada*-hydride species **27**.



***Scheme 1-5*:** General Reaction Mechanism of the HECK reaction.

1.2.1.1 The Catalyst Generation (Preactivation Step)

As mentioned above, the starting point for the catalytic cycle is the formation of a catalytically active Pd^0-catalyst. Depending on the reaction conditions, the activation can be achieved in several modes. At first, the generation of the catalytic precursor in absence of a phosphine ligand is presented.[21] Amines which are used as bases in HECK-type transformations have been proposed as reducing agents for the activation step (JEFFERY'S process). The amine first coordinates to the palladium(0) source and undergoes a β-hydride elimination leading to a *pallada*-hydride species **31** (Scheme 1-6). This intermediate collapses to the corresponding Pd^0-catalyst **34** and the respective ammonium acetate **33**.

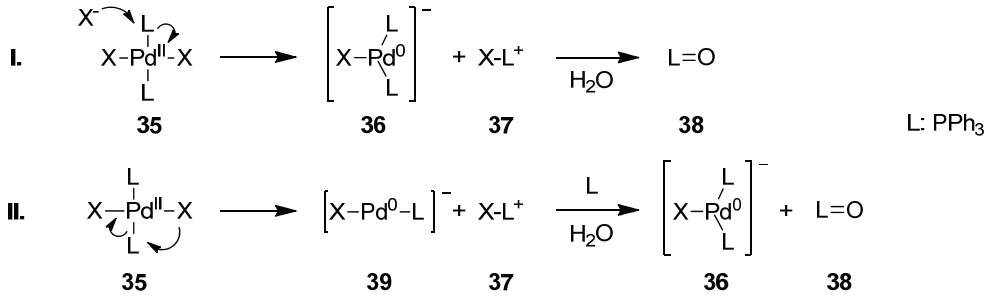


***Scheme 1-6*:** Catalyst formation in absence of ligands.

Some additives, such as quarternary ammonia salts (Bu_4NCl and Bu_4NBr) show a beneficial effect with respect to the JEFFERY process. It was found that thermolytic decomposition already

occurs at 100 °C in the presence of ammonium salts. The palladium(0) particles are stabilized by surrounding ammonium halide molecules. Due to this effect the palladium clusters stay in solution and are available for catalysis.[22–23]

The palladium(0) formation in presence of a monophosphine ligand represents a more common pathway.[24–25] The reduction is normally assisted by hard oxygen nuclephiles, such as alkoxides, hydroxide or water, in which the nucleophile attacks the phosphorus atom of the coordinated phosphine (Scheme 1-7, I.). A second pathway (II.) involves an inner-shell reductive elimination of the phosphonium species. In this case, the nucleophile attacks the palladium atom, before liberating phosphonium intermediate **37**, which is converted into respective phosphine oxide **38** in both cases. Contrary to usual oxidation behaviour of phosphines, electron poor compounds accelerate the reaction rate, due to the more electrophilic phosphorus atom. The role of water in phosphine-mediated reductions is not fully understood. There are evidences of a beneficial effect, but other studies revealed that the reaction prefers an absence of water.[26]



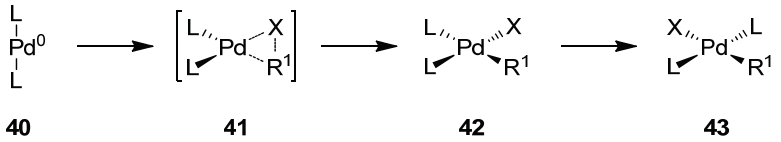
***Scheme 1-7*:** Catalyst formation in presence of phosphine ligands.

Today's demands on modern and efficient catalyst systems can only be fulfilled in a synthesis by a broad choice of ligands and palladium sources, which rely on practicability, selectivity and efficiency. Of course, there are numerous different palladium sources, which find application in organic synthesis. However the most common representatives are $Pd(OAc)_2$, $PdCl_2$, $Pd_2(dba)_3$, $Pd(PPh_3)_2Cl_2$ and $Pd(PPh_3)_4$. The opportunities to design ligands are endless. Monodentate phosphine ligands belong to the classical palladium ligands, whereupon they still find broad applications in manifold modern methods. Further ligands are based on other heteroatoms; nitrogen, sulfur, arsenic and carben ligands are utilized. Polydentate ligands offer some additional opportunities beside the normal catalytic activity, as well especially ligands bearing a phosphorus and/or a nitrogen donor atom are used for asymmetric transformations (PHOX-ligands). A frequently occurring drawback is the thermal stability of various ligands. Phosphine ligands are prone to thermal decomposition at high temperatures starting from ~120 °C. Therefore, many research groups shifted their focus to the development of new ligands with advanced features in thermal stability. Nevertheless, the quest for the "perfect" catalytic system does not only comprise the selection of appropriate catalyst sources and ligands. In addition to

these factors, an efficient synthesis requires elaborate composition of all reactions conditions. The choice of suitable additives, bases, temperatures, solvents and even the substrate dependence may have an impact on the catalytic process.[14,19]

1.2.1.2 Oxidative Addition

The oxidative addition of low valent transition metal species to an organic electrophile, represents an elementary step in organometallic chemistry.[27] For this purpose usually a palladium(0) species is converted to a *pallada* (II) compound. The oxidative addition is a concerted reaction, in which the *C-X* bond of the electrophile is broken to establish a connection between the central atom and the aryl group as well as the nucleofuge. This process displays the rate-limitating step in many HECK reactions. The reactivity correlates with the quality of the leaving group and a higher C(sp^2)-X bond energy to I > OTf > Br ≫ Cl.[28] The oxidative addition of electron-defiient aryl compounds is faster in comparison to electron-rich aromatics. Since electron-rich palladium (0) species are highly nucleophile, an insertion of the catalyst into electron-deficient *C-X* bonds is favored.



40 **41** **42** **43**

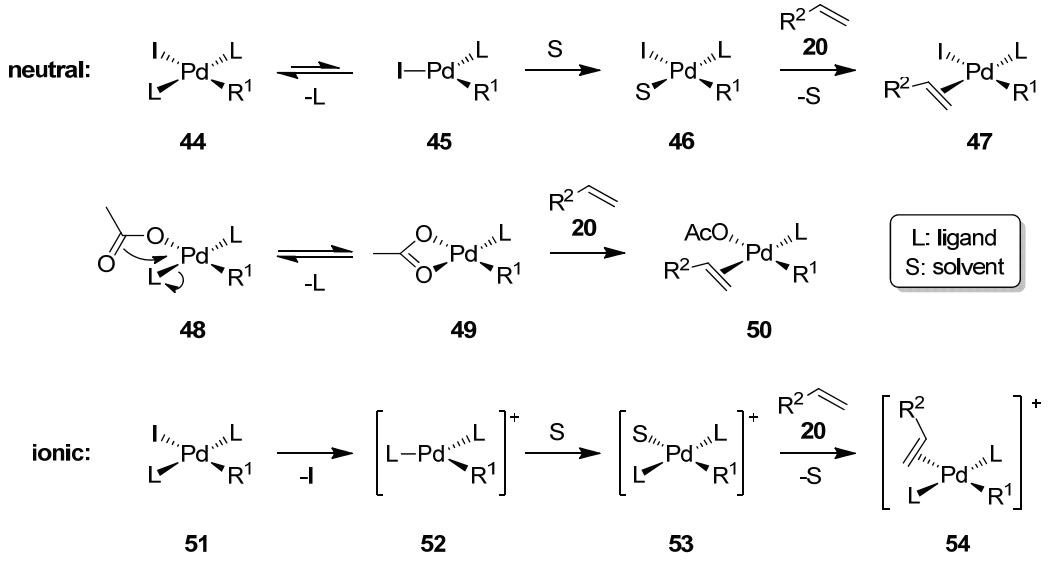
***Scheme 1-8*:** Oxidative addition of an aryl halide *via* a concerted *syn*-mechanism.

First, the starting material forms a three-center two-electron bond. A *syn*-addition of the aromatic halide affords compound **42** under retention of the configuration. By utilization of monodentate phosphine ligands a rapid *cis/trans*-isomerization occurs to the more stable *trans*-complex **43**.[24,26] Chelating ligands block this isomerization to force the more reactive *cis*-configuration. Apart from the quality of leaving group and electronic properties of the nucleofuge, the rate of the oxidative addition is subjected to additional factors. Excess of ligands decelerates the oxidative addition by forming the unreactive $Pd^0(L)_3(OAc)^-$ complex in an equilibrium with the reactive $Pd^0(L)_2(OAc)^-$ species. Triethylamine also decreases the reaction rate by stabilizing $Pd^0(L)_2(OAc)^-$ and repressing the formation of the most active species ($Pd^0(L)_2$).[29] The oxidative addition is also slower in presence of additional olefin.[30] At first, this may sound counterintuitive, but the alkene occupies free valences of the palladium catalyst and blocks the *syn*-addition of the substrate.

1.2.1.3 Complexation and Insertion of the Alkene

The next step of the catalytic cycle is a η^2-coordination of the alkene to the palladium complex. This process consists of a ligand or counterion exchange. Scheme 1-9 depicts both the neutral and the ionic mechanism for the coordination of the olefin. Whereas the neutral pathway applies for aryl chlorides, bromides and iodides, the reaction proceeds *via* a cationic sequence in

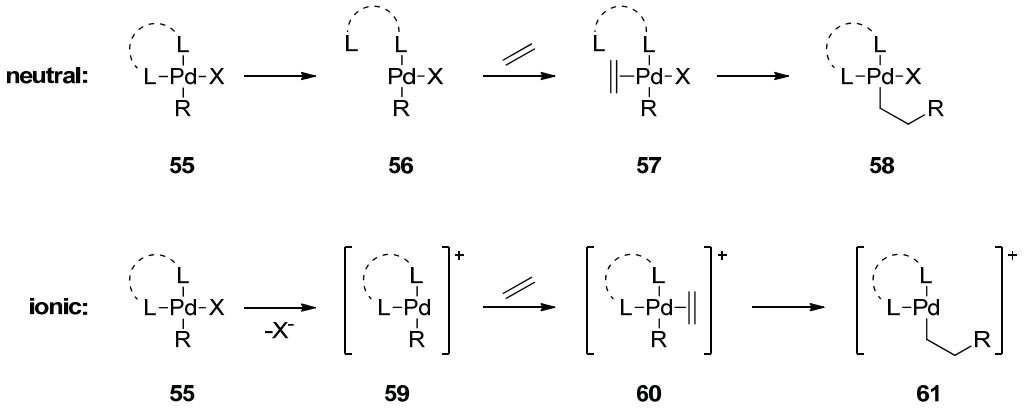
presence of Ag^+ or Tl^+ salts or by utilizing aryl triflates. In both cases a vacant coordination side is provided. The neutral pathway proceeds *via* a dissociative mechanism under the loss of one ligand. The vacant position can be occupied by a solvent molecule or directly by the olefin. The dissociation of one ligand is favored for acetate complexes **48**. The ester group is able to support the intramolecular disconnection of the respective ligand to form a four-membered ring species **49**. For the ionic mechanism, it is essential that the anion is substituted by a solvent molecule. Next, the olefin enters the complex in a bimolecular mechanism and releases the previously introduced solvent molecule. The stability of the newly formed complex depends on both the electronic effect of the ligands and the electronic structure of the olefin. Thus, electron-rich alkenes tend to form complexes with electron-deficient alkenes, due to strong σ-acceptor tendencies of the metal center. Fine-tuning by utilizing electron-donating or electron withdrawing ligands can change the electronic structure of the metal and its properties.[31]



***Scheme 1-9*:** Coordination of olefin **20** *via* neutral and ionic pathway.

The migratory insertion (carbopalladation) is the coupling step of the HECK reaction, in which a new *C-C* bond is formed. This process is attributed to be the stereo- and regiodiscriminating step in the reaction. The mechanism of the *syn*-insertion is not fully understood. Various studies take three different possibilities as a basis. The arylpalladium complex behaves as a carbanion and reacts in a nucleophilic addition, comparable to vinylic nucleophilic substitutions.[27] The second pathway comprises, that the central atom is attacked by an electrophlic addition of the double bond. The third possibility is a concerted mechanism in which a four-membered transition state is assumed. This mechanism is supported by many data and justified by several experiments. Therefore, in the following, a concerted sequence is assumed with respect to the migratory insertion step.

In accordance to theoretical investigations, the alkene shifts from an *out-of-plane* configuration to an *in-plane* conformation before the *syn*-insertion takes place.[32] Especially, bidentate ligands cause an interesting scenario (Scheme 1-10), in which the neutral pathway can almost be excluded. One side of the ligand would have to dissociate from the metal to free a vacant coordination side for the olefin. This would cause a loss of stereochemical information, which is mostly embedded in the ligand scaffold. Indeed, this process cannot be completely excluded for ligands with large bite angles of over 90°.[33]



***Scheme 1-10*:** Migratory insertion of olefins into arylpalladium complexes.

Special attention should be paid to the regioselectivity of the HECK reaction, since alkenes always provide two possible reactive postions for the *C-C* coupling.[34] Thus, styrene is a well understood substrate in HECK reactions, it represents a suitable model substrate for mechanistic investigations. The regiochemistry for styrene is highly dependent on the electronic nature of the central atom. The higher the contribution of the ionic species, the more 1,1-connected products can be obtained. Of course, steric reasons have a major effect on the regioselectivity of the HECK reaction as well.

The intramolecular variant of the HECK reaction can be considered as special, since an *endo* or *exo* cyclization can occur (Scheme 1-11). According to BALDWIN's rules, the majority of examples are showing an *exo-trig* process due to less steric demand of the carbopalladation step. The *endo-trig* mode requires much more space to reach proximity to the *pallada* species. The alkene part would have to arrange into the loop of the intermediate π-complex **65**. This conformation is only possible for compounds with flexible tethering units.[35–37]