

Computational Insights into Palladium-Mediated Allylic Substitution Reactions

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Abstract Allyl palladium complexes have a rich chemistry. Many aspects of their structure and reactivity have been studied computationally. This chapter gives an overview of the history in this field, from structural studies and the effect of ligands and substituents, to the rich reactivity of the title complexes. The latter includes complex formation, reactions with nucleophiles and electrophiles, and dynamic equilibria. An important focus area has been the Tsuji–Trost reaction, in particular asymmetric versions thereof. A brief overview of computational methods, aimed at modeling novices, can be found in the introduction.

Keywords Density functional theory · Molecular mechanics · Palladium-mediated allylation · Quantum mechanics · Reaction mechanisms

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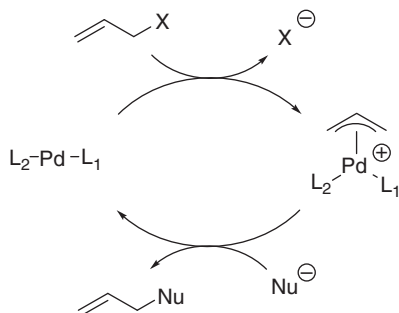
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1 Introduction

Historically, allyl metal complexes (e.g., allyl Grignard reagents) have been considered strong nucleophiles, but already in the early 70s Tsuji demonstrated that (η^3 -allyl)palladium complexes reacted as allylic electrophiles with stabilized carbanions such as malonates [1, 2]. This could be considered an umpolung, since allyl palladium complexes can be obtained from reaction of nucleophilic allyls, such as Grignards, with Pd^{II} salts. The nucleophilic attack on the (η^3 -allyl)palladium moiety produces Pd^0 , and by introduction of electrophilic allylic substrates capable of reacting with Pd^0 , such as acetates, a catalytic process can be realized. Palladium will bind to two auxiliary ligands throughout the process (Scheme 1), allowing for efficient reactivity control by ligand design. The allylation process allows formation of a wide range of bonds (e.g., C–C, C–N, and C–O), but the reaction is subject to regio- and stereo-chemical selectivity issues. Therefore, there has been a great interest in subjecting the reaction to detailed theoretical studies to elucidate the underlying factors controlling the selectivity.

2 Quantum Mechanics

Computational studies have mostly focused on the Pd-allyl complexes, the species that reacts with the incoming nucleophiles (Scheme 1). The earliest studies utilized the Extended Hückel Molecular Orbital (EHMO) method. This qualitative quantum mechanical (QM) method does not allow accurate energy calculations, and therefore cannot reliably be used to determine geometries by energy minimization.



Scheme 1 Palladium-catalyzed allylation

However, when based on accurate structures, for example from neutron diffraction or, if hydrogen positions are corrected, from X-ray crystallography, the EHMO method can be used to determine shapes and relative energy levels of frontier orbitals, allowing for a correlation with chemical reactivity. Other semiempirical approaches were developed where strongly simplified QM schemes were augmented with empirical parameters, but in general the reliability for transition metal complexes was too low to allow anything except qualitative studies.

2.1 *Hartree–Fock Calculations*

The Hartree–Fock (HF) method enabled a breakthrough in organic chemistry. Using the HF method, the Schrödinger equation can be solved iteratively, with the approximation that each electron only interacts with the average density of all other electrons. In simple terms, the HF method ignores the fairly important fact that as an electron moves to any specific point in space, all other electrons must move away from that point, so-called *electron correlation*. Despite this strong approximation, HF recovers a large part of the total energy of the molecule, and the remaining error is fairly constant, so that the relative energy of different atom configurations is reasonably accurate. In chemical terms, this means that molecular geometries and reaction barriers can frequently be reasonably well described by the HF method. However, many cases are known where the variation in electron correlation is large enough to give significant errors when the HF results are compared to experiments. Specifically, the high density of electrons in heavier elements such as transition metals tends to make the HF method too unreliable. For closed shell species (such as most Pd complexes), it is still possible to obtain qualitative results, but quantitative predictions of molecular geometries or relative reactivities generally require more accurate methods.

2.2 *Correlated Calculations*

Even though the HF method gives an approximate wavefunction, it is still possible to evaluate it using the Schrödinger equation. More specifically, it is possible to introduce small perturbations of the wavefunction to obtain an improved solution. One way to introduce well-controlled perturbations is to mix the HF ground state with other low-energy states. The most easily implemented way of doing this uses the HF excited states. Compared to HF calculations, such correlated calculations are costly, but can lead to significantly improved results. These methods are generally termed Many-Body Perturbation Theory (MBPT), or Møller–Plesset (MP) theory. In the simplest implementation, the HF ground state is mixed with all single and double electron excitations, MP2. Even better results, but at vastly increased cost, are obtained if 3, 4, or 5 electrons are excited simultaneously,

the MP3, MP4, and MP5 methods. Many studies of metal complexes have been performed at the MP2 level, frequently with validation of selected results at the MP4 level, or truncated versions thereof. It is possible to extrapolate perturbation theory, or to optimize the excited states variationally to arrive at even better wavefunctions, but such methods invariably carry a very high cost, and are in practice limited to very small model systems. Several such methods, such as CCSD(T) and MCPDF, have been applied to Pd complexes [3], but detailing such methods goes beyond the scope of this text. The interested reader is referred to several illuminating texts on this subject [4, 5].

2.3 *Density Functional Theory*

An alternative to wavefunction theory that has gained in popularity in later years is based on Density Functional Theory (DFT). In short, DFT does not solve the Schrödinger equation for a wavefunction, but rather an equivalent equation for the electron density. For a purist, DFT is deficient in that we do not know the exact form of the underlying equation, even though we know many of the properties it must have, and we cannot systematically improve it in the same way we can with wavefunction theory. However, several breakthroughs in the understanding of DFT have now led to a method that is as fast as HF, but with an accuracy on a par with MP2.¹ Introduction of nonlocal terms (i.e., making the energy dependent also on the gradient of the density) produced a method that could at least equal HF in accuracy. In the 90s, Becke solved some of the known deficiencies in DFT by combining it with HF theory, producing a hybrid method that has been the standard ever since. Currently, a majority of all published computational studies of palladium complexes are based on Becke's hybridization scheme, in many combinations, of which B3LYP [6–8] seems to be the most popular. More recent improvements include accounting for van der Waals dispersion forces [9–12], a weakly attractive interaction that was unimportant for the small models used in early studies, but with a strong impact on relative energies in medium to large systems [13].

¹This point can be discussed, the methods certainly are not equal. In some cases, MP2 will give better energies, in some cases a hybrid method such as B3LYP is more accurate, and simpler pure DFT methods such as BP86 generally give good geometries. All the methods can give large and very different errors in pathological cases. However, it is probably safe to say that if three different methods such as MP2, a GGA functional such as BP86, and a hybrid method such as B3LYP all agree, the result will be reliable.

2.4 *Basis Sets*

All quantum chemical approaches require mathematical descriptions of the spatial distribution of electrons, that is, orbitals. The most common approach is to construct the molecular orbitals from idealized atomic orbitals, the Linear Combination of Atomic Orbitals (LCAO) approach. Other methods have been used, such as plane wave and finite element approaches, but only LCAO will be discussed here. In the simplest cases (e.g., EHMO), rigid atomic orbitals are used directly as the basis set. However, accurate calculations require that the orbitals can change size and shape to accommodate shifts of electrons in a molecular environment. The most important modification is to include atomic orbitals of different sizes, allowing the self-consistent field (SCF) procedure to optimize the contribution of each. As a simple example, a calculation might include two different sizes of 1s-orbital on hydrogen. When the hydrogen is directly bound to Pd, it becomes more hydridic, and the program will accommodate the added electron density by including more of the large 1s-orbital, whereas a hydrogen bound to oxygen would use more of the smaller orbital (and correspondingly larger orbitals on oxygen). It is quite common to use one fixed orbital of each type for core electrons, and two different sizes for each orbital in the valence shell, a so-called split valence basis set. If each orbital exists in two differently sized versions, the basis set is termed double- ζ (acronym: DZ), if three copies are employed, it is triple- ζ (TZ), and so on. Sometimes a very large orbital, a so-called diffuse orbital, is added to accommodate anions. This is usually indicated by adding a “+” in the basis set name, or preceding the name by “aug-.”

The shape of orbitals can be modified by mixing in a small amount of an orbital with a higher quantum number, similar to forming sp-hybrids. For example, adding a few percent of an appropriately sized p-orbital to an s-orbital will produce a new, s-like orbital that has been shifted away from the atomic nucleus, and therefore is better at forming bonds. Similarly, adding a small amount of d-orbital character to a p-orbital produces a slightly bent, p-like orbital with better ability to form π -bonds. This is called polarization, and is a requirement for good descriptions of chemical bonds. Almost all calculations today add at least a set of d-orbitals to all elements heavier than helium, and if hydrogen bonding is important, p-orbital polarization on hydrogen is required.

The many core electrons on transition metals cause a huge increase in computational time without adding much to the accuracy since they are fairly constant under most chemical changes. It is therefore common practice to replace the core electrons by a so-called Effective Core Potential (ECP).

Calculations at the HF or DFT level generally require at least a split valence basis set with polarization. Frequently, larger basis sets are tested without further geometry optimization (so-called single point calculations), to check whether the conclusions are stable with respect to improvements in the method. Correlated methods such as MP2 require better basis sets. Since this is very expensive (MP2 scales with N^5 , where N is the number of orbitals employed), correlated

calculations have sometimes been reported with smaller basis sets, but a healthy dose of skepticism is recommended when evaluating such results.

2.5 *Solvent*

The QM methods described so far are basically valid only for molecules or complexes isolated from the surrounding, in vacuo or, more popular, in “gas phase”. However, homogeneous catalysis occurs in solvent. Most early studies ignored the solvent, or introduced one or a few solvent molecules in specific orientations. For a few metal complexes with a low and constant polarity, this treatment can be valid, but for ionic reactions, errors can be huge when the solvent is ignored. Structures, even of ionic intermediates, are usually good as long as they have no more than a single charge, but barriers for combination of two ionic species with opposite charge simply cannot be calculated in the gas phase; the combination is usually barrierless in the absence of solvent. Inclusion of several explicit solvent molecules rapidly makes the calculation intractable, in particular since all possible orientations of the solvent molecules must be sampled. An approximation that has gained in popularity is to employ continuum solvation models. Many brands of these models are available, but one of the most popular, the polarizable continuum model (PCM) [14, 15] encloses the entire molecule by a cavity dotted by point charges that have been parameterized to give a fair representation of the *average* influence of the solvent, alleviating the need for extensive sampling. Application of these models can be tricky, in particular for reactions where cavities are at the point of merging, and they certainly do not capture all aspects of solvation, but in general they improve results and allow location of structures that would undergo electrostatic collapse in the absence of solvent. In palladium allyl chemistry, solvation models were not employed until about a decade ago [16], but are now an essential component in describing these reactions.

2.6 *Molecular Mechanics*

Quantum mechanics is a great aid in understanding chemistry at the molecular level, but it has one serious drawback: the computational cost. Even today, accurate methods cannot be reliably applied to systems with more than a couple of hundred atoms, and in the 80s when QM was first applied to allyl-Pd complexes, the limit was more like 10 atoms. An alternative, introduced already in the 50s, is to ignore the movement of the electrons, assume that they are locked in chemical bonds with known properties, and look just at the movement of the atoms in the force field provided by the bonds. This method, molecular mechanics (MM), has been a standard tool in organic chemistry and biochemistry since the 70s. Today, MM allows studies of systems with several thousand atoms, and location of millions of

conformers, but application in organometallic and inorganic chemistry has been more limited [17]. MM is strongly reliant on availability of accurate parameters describing the chemical bonds making up the structure. Bonds in organic structures are fairly consistent, meaning that parameters (e.g., the ideal length of a bond between two sp^3 -hybridized carbons) can be transferred between different structures with reasonable reliability. Bonds to metals are much more varied, and usually parameters have to be derived for each system of interest, severely limiting the applicability of MM. However, (η^3 -allyl)palladium complexes are consistent enough to allow derivation of widely applicable parameters, *vide infra*.

3 Structure

Computationally, structures are obtained by changing the geometry until the energy is minimized. To do this efficiently, the program must be able to calculate the derivatives of the energy with respect to atomic coordinates. Today, modeling programs do this automatically for all but the most complex correlation methods. Structure prediction only depends on being able to calculate relative energies of very similar structures, and therefore can be reliable already at fairly low levels of theory, with the caveat that strong charge separation requires the use of accurate solvation models. The best performance/cost ratio for this purpose today is obtained from DFT methods, but for closed shell palladium complexes, even the HF structures used in some earlier studies were qualitatively correct. Before these methods became generally available, computational studies generally employed crystal structures, focusing only on the shape and energy of frontier orbitals and charge distribution (*vide infra*).

3.1 η^3 -Allyl Complexes

An early effort to use computational aid to gain insight into structures of palladium complexes was made in beginning of the 90s, when Norrby et al. developed an MM force field for the (η^3 -allyl)palladium moiety (Fig. 1). The parameterization of the force field was based on X-ray structures, MCPF calculations for small model systems, and equilibrium data from NMR [18]. The resulting force field was able to reproduce the structures of known (η^3 -allyl)palladium complexes, and used to predict *syn-anti* equilibria for substituted (η^3 -crotyl)palladium complexes with

Fig. 1 The (η^3 -allyl) palladium moiety



2,9-disubstituted phenantrolines as ligands. The results were in agreement with experimental results. The methodology has also been applied to the related (η^3 -cyclohexenyl)palladium system, and proved to be able to solve the intricate equilibrium between the different boat- and chair-like conformations [19]. The force field has been further developed and several publications dealing with different ligands have followed [20, 21].

Using semiempirical methods, Pregosin et al. calculated the structure of a simplified (η^3 -allyl)palladium, where the palladium atom was represented with a positive point charge. This rather crude method could reproduce the effect of substituents on the bonds in the allyl moiety. The effect was described as an electronic effect [22].

With the development of computational methods and resources, new methods could be employed. Szabó used MP2 and MP4 to calculate the structure of (η^3 -allyl)palladium without any ligands on Pd [23]. This structure was compared with results from the more advanced MCPF level [18]. The bond distances and angles from the two methods agreed well. For example, the Pd-C(allyl) distances differ by no more than 0.014 Å.

Several different studies have been carried out where DFT calculations has been used to examine (η^3 -allyl)palladium systems. Many diverse ligand combinations have been employed, such as P,P [24, 25], P,N [26, 27] and P,S [28]. In most DFT studies, the focus has been more on reactivity than on structure, and they will therefore be discussed in more detail later.

Through the work of Sakaki and Kurosawa, the nature of the dinuclear palladium (I) π -allyl (Fig. 2) has been investigated. When comparing to the monometallic species, the biggest difference is the much shorter Pd-C(allyl) bonds. Using MP2 calculations, this structural characteristic, along with other structural properties could be reproduced [29, 30].

Some effort has been put into sorting out one special case of the (η^3 -allyl) palladium family, the (η^3 -allyl)₂Pd structure (Fig. 3). The *cis:trans* ratio was the focus of a study by Casarin et al. The DFT calculations gave only a small energy difference of 0.8 kJ/mol between the geometries, with the *trans* orientation as the most favored [31]. Similar complexes with Pt, favoring *trans*, and Ni, favoring *cis*, were also investigated in the same study. The result for (η^3 -allyl)₂Pd has been

Fig. 2 A dinuclear palladium complex

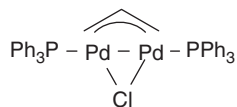
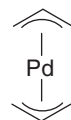


Fig. 3 (η^3 -allyl)₂Pd



confirmed in a study by Szabó, although a slightly larger energy difference of 3 kJ/mol was reported [32]. For further studies on the bisallyl-palladium complexes, see Sect. 5.2 of this chapter concerning *Nucleophilic allylic substitution*.

3.2 η^1 -Allyl Complexes

The allylic moiety can coordinate to palladium in two different ways, in a η^3 -fashion, where the coordination is a combination of a σ -bond (alkyl-like) and a π -bond (alkene-like), or through a single σ -bond, giving a η^1 -complex. Interestingly enough, even though η^3 -allyl complexes are electrophilic, η^1 -allyl seem to react as nucleophiles (*vide infra*).

Szabó has investigated the structure of the nucleophilic allylpalladium complexes computationally [32]. The bisallyl-palladium complex was scrutinized and, as mentioned earlier, an energy difference of ca 3 kJ/mol is found between the *cis* and *trans* forms. The nucleophilic reactivity of these complexes is observed in the presence of phosphines, modeled by Szabó as the PH_3 ligand. Addition of the ligand forces the bisallyl-palladium complex to go from the (η^3, η^3) -form to the (η^3, η^1) -form (Scheme 2). This process is found to be an exothermic process.

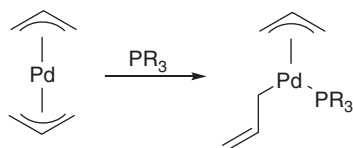
When expanding the calculations to the (η^3, η^1) -octadienylpalladium complex, the same process is also exothermic. The η^1 bond is found to be between the terminal carbon and the Pd, favored by 27 kJ/mol compared to the internal carbon.

The ligand effect is studied by exchanging the PH_3 (π -acceptor) for a NH_3 (σ -donor). The complexation energy for the σ -donor ligand is approximately 50 kJ/mol lower, indicating that the (η^3, η^1) -complexes are more easily formed using π -acceptor ligands. No significant structural differences could be found between the complexes with different ligands.

3.3 Calculated Structures vs. X-Ray and NMR

To verify the accuracy of the calculated structures, comparisons with X-ray structures and NMR results are useful tools. NMR is helpful when trying to elucidate unknown structures. It has the advantage over X-ray that it gives information about the solution structure, which in most cases is more relevant to reactivity than the solid structure. The downside is that the information is more difficult to analyze, is

Scheme 2 The exothermic $(\eta^3, \eta^3) - (\eta^3, \eta^1)$ transformation



less accurate than X-ray analysis, and never shows the entire picture. Nonetheless, several studies have been carried out within the field.

Pregosin and co-workers used NOE results together with MOLCAD to derive a solution structure of a $[(\eta^3\text{-pinene})\text{palladium BINAP}]$ complex [33]. In a further study, good structural agreement between the experimental and calculated (MM) results could be shown for a similar structure. This time, the predictions from the calculations could be verified from NOE studies [34].

X-ray crystallography yields structures that are easy to compare to computational models. Distances, angles, and torsions can be evaluated, even if one has to pay attention to the potential pitfalls of solid state properties, such as packing effects.

In a study by Pregosin et al., a β -pinene allyl coordinated to a Pd-(BINAP) complex was studied. MM2 calculations were employed, and the results were compared with the existing X-ray structure. The calculated structure differs only slightly from the experimental structure, the main difference being the rotations of the phenyls in the BINAP-part. These results were further extended in an attempt to calculate the solvent structure of a similar complex carrying a (S,S)-Chiraphos ligand instead of the BINAP ligand (Fig. 4). The chiral array of the Chiraphos ligand proved to be different from the BINAP, as expected from experimental results [22].

Jonasson et al. employed DFT calculations when studying *cis*- and *trans*-4-acetoxy- $[\eta^3\text{-(1,2,3-cyclohexenyl)}]\text{palladium chloride}$ dimers. The results were compared with X-ray structures and showed very small deviations from the measured distances in the crystal. Except for the Pd-Cl bond in the *cis*-structure, the deviation for all calculated parameters is within 0.03 Å. Several important features, such as the asymmetric allyl-palladium bonding were reproduced in the calculations [35].

In another example, Helmchen and co-workers investigated different allyl-phosphanyloxazoline)palladium complexes with both ab initio and DFT calculations and weighted these findings against the experimental results from NMR investigations and X-ray structures. Ab initio calculations were used when optimizing the different isomers, and the structural agreement was good, even if some bonds were slightly too long. To analyze the order of the energies of the different complexes, single point calculations using DFT were used. The ratios between the different isomers, obtained from NMR studies, were well reproduced [26, 27].

At the MP2 level of calculation, Sakaki et al. performed a study where they compared calculated structures of $\text{PdCl}(\eta^3\text{-C}_3\text{H}_4\text{R})(\text{PH}_3)$ ($\text{R}=\text{H, Me, CN}$) and $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)(\text{PH}_3)_2]^+$ with X-ray structures. Good agreement was achieved, but it was important to include d-polarization to reach this result [30].

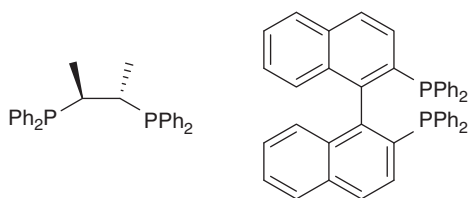


Fig. 4 Chiraphos and BINAP

3.4 Ligand Effects on Structure

Ligands can effect the (η^3 -allyl)palladium complex in different ways, mainly by electronic *trans* influence and through steric effects. The *trans* influence of different ligands affects the bond length of the *trans* carbon-palladium bond in the (η^3 -allyl)palladium complex. For example, in complexes of ligands with one phosphine and one other heteroatom (e.g., PN-ligands), the Pd–C bond *trans* to phosphorus is generally longer than the other terminal Pd–C bond. This effect is reproduced by calculations, for example in a study employing MP2/MP4 by Szabó, where a simple (η^3 -allyl)palladium is modeled with a series of small ligands: Cl, F, NH₃, H₂C=CH₂, PH₃. The pure σ -donors, F[−], Cl[−] and NH₃ induces a shortening of the *trans* Pd–C bond, with a difference of at least 0.07 Å between the strongest donor, F[−], and NH₃. The π -acceptor ligands H₂C=CH₂ and PH₃, on the other hand, elongates the *trans* Pd–C bonds compared to the unligated complex [23].

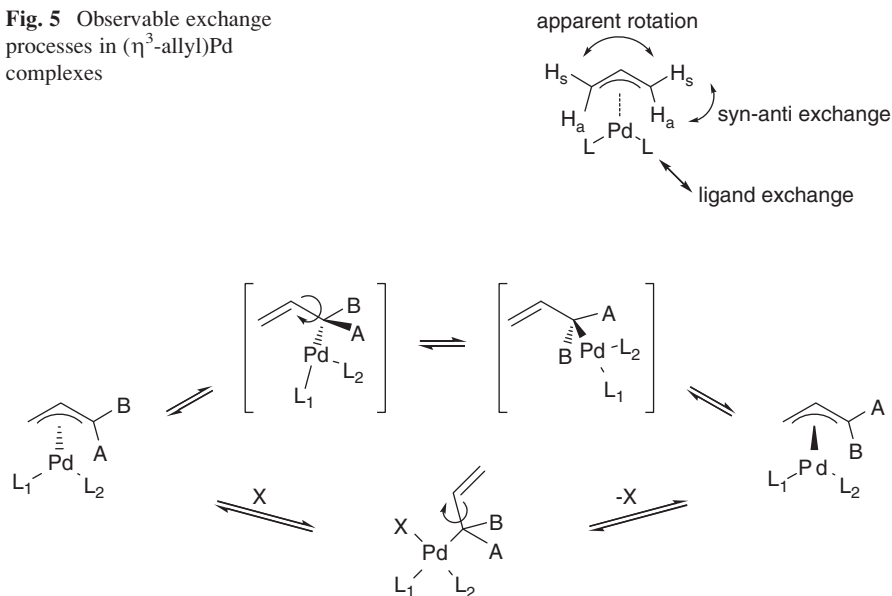
In another study, Blöchl et al. investigated a (η^3 -allyl)palladium with two different ligands, PH₃ and a *N*-coordinated pyrazole. The asymmetry in the palladium carbon bond lengths was reproduced using the projector augmented wave method [36].

Ligands coordinated to the (η^3 -allyl)palladium complex give rise to steric effects, which can affect the *syn-anti* configuration of a substituted allyl. The *syn* configuration is normally the most stable [37], but the ratio between the configurations differs when a bulky ligand is used. In a study by Norrby et al., the effect of substituted 1,10-phenanthroline ligands was investigated. Employing a modified MM2 force field with a special parameter set for the (η^3 -allyl)palladium moiety [18], it was found that substituents which provided bulk *in* the coordination plane would enhance the *anti* preference. This effect was also verified experimentally, yielding as much as 81% *anti* configuration with a simple 1-butenyl group. On the other hand, bulk outside the coordination plane gave a much lower preference for *anti* complexes [37]. Further studies by the same group revealed that a careful parameterization is needed to achieve good predications of different (η^3 -allyl)palladium complexes. On the other hand, when a well-parameterized force field is in hand, the accuracy and versatility is very good [21].

4 Dynamics

Dynamics in (η^3 -allyl)palladium complexes have mainly been studied by NMR techniques. The timescale of the relevant dynamic processes is suitable for investigation by coalescence or saturation transfer techniques. Some slower processes can also be seen by purification of one isomer followed by direct monitoring of the equilibration over minutes or hours. These were in fact some of the earliest exchange processes to be studied by NMR, and were reviewed already in 1975 by Vrieze [38]. The fast dynamic processes of (η^3 -allyl)Pd complexes can roughly be

Fig. 5 Observable exchange processes in (η^3 -allyl)Pd complexes



Scheme 3 η^3 - η^1 - η^3 isomerization, with and without assistance by added ligand X

divided into three classes: *syn-anti* exchange, apparent rotation, and ligand exchange (Fig. 5). There is also a slow exchange of allyl groups between Pd centers (*vide infra*).

4.1 Syn-anti exchange

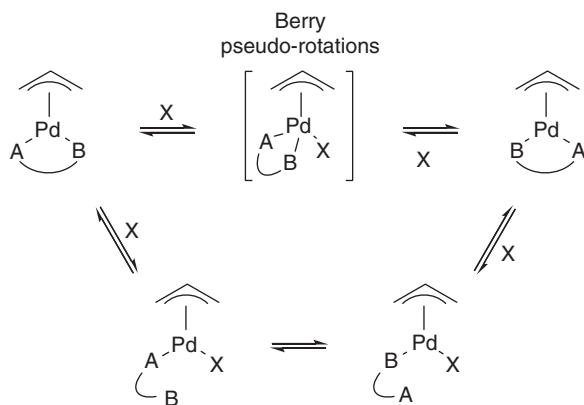
As opposed to most other unsaturated systems, the terminal substituents on the (η^3 -allyl)Pd moiety readily exchange on the NMR timescale. The process occurs through a bond rotation in a (η^1 -allyl)Pd complex, and is therefore also known as η^3 - η^1 - η^3 or, in older nomenclature, π - σ - π isomerization, Scheme 3. The rate of the reaction is dramatically increased by added ligand, such as halide ions, since these coordinate to Pd and stabilize the η^1 complex [38]. As already discussed, when the ligands are strong enough to out-compete η^3 coordination, the square planar η^1 complexes can be observed [39–41]. It is important to point out that the η^3 - η^1 - η^3 isomerization does not exchange the positions of the ligands in relation to the allyl termini, even in the absence of added ligand. The Pd center stays square planar throughout the process, even in the unobservable η^1 complexes without added ligands where the geometry is more properly described as T shaped [42]. This is illustrated in Scheme 3, where it can be seen that ligand L_1 stays *trans* to the exchanging terminus. We also note that the chirality of the exchanging terminus stays constant, whereas the two remaining allyl carbons are inverted; the process

can also be described as an exchange of coordinating π -faces of the alkene moiety in the (η^1 -allyl)Pd complex.

Several computational studies have included an evaluation of the η^3 - η^1 equilibration, mostly for cases where an added ligand coordinates to the empty coordination site in the (η^1 -allyl)Pd complex [39–41]. When no additional ligand was present in the calculations, the (η^1 -allyl)Pd complex was found to be a transition state for bond rotation, not a stable energy minimum [42], and thus cannot partake in additional processes, such as site rearrangements of the ligands. In the complexes studied, the rotation from η^3 to η^1 coordination mode will occur in the direction that will let the central hydrogen on the allyl interact agostically with the empty coordination site on Pd.

4.2 Apparent Rotation

The apparent rotation was first studied by ^1H NMR, and was initially termed “*syn-syn*, *anti-anti* exchange,” from the observable behavior of the protons [38]. However, the overall process can also be seen as an exchange between the two auxiliary ligands on the (η^3 -allyl)Pd complex. The process is distinct from the *syn-anti* exchange, and can easily be faster, in particular for cationic (η^3 -allyl)Pd complexes in the presence of halide anions [43]. The exchange in complexes with chiral ligands clearly shows that the apparent rotation does not involve breaking of any palladium–carbon bonds [43, 44]. In some cases, an apparent rotation can be obtained by rapid ligand exchange (*vide infra*), but it has been shown that bidentate ligands stay coordinated throughout the process [45]. The mechanism has been suggested to be Berry pseudo-rotation in a penta-coordinated complex obtained by addition of a halide anion to Pd (the allyl is considered a bidentate ligand here, Scheme 4) [38]. This mechanism has been supported by X-ray of a postulated intermediate for chloride-assisted apparent rotation in an (η^3 -allyl)Pd complex with



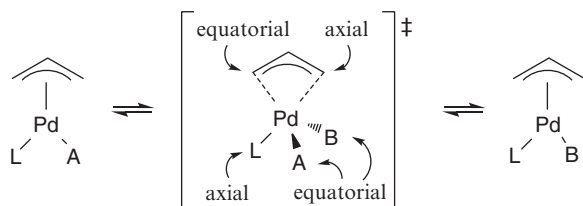
Scheme 4 Proposed mechanisms for apparent rotation

a rigid, bidentate ligand [43]. An alternative suggestion from Pregosin and co-workers involve breaking the bond to one arm of the bidentate ligand, followed by ligand rearrangement and reformation of the bond to Pd [44]. The bond breaking to one ligand arm was conclusively shown by NMR exchange (Scheme 4) [46]. A recent computational study of the dynamics in $(\eta^3\text{-allyl})\text{Pd}$ complexes at the B3LYP level identified transition states that seemed to correspond to Berry pseudo-rotation processes, but QRC calculations [47] clearly showed breaking of palladium–ligand bonds [42], indicating that the apparent rotation is indeed composed of three successive ligand substitution processes. Reevaluation of the X-ray structure from Hansson et al. [43], indicates that one bond to a dmphen nitrogen has indeed been broken, but is kept close to the palladium by the rigid framework of the dmphen ligand.

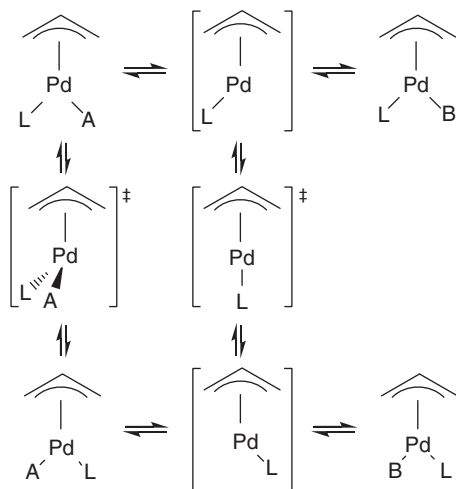
4.3 Ligand Exchange

In the presence of excess ligands, most $(\eta^3\text{-allyl})\text{Pd}$ complexes will undergo relatively rapid ligand exchange. This also includes reversible breaking of halide- or carboxylate-bridged dimers by added ligand. Ligand exchange can be associative (Scheme 5) or dissociative (Scheme 6). Both types of processes have recently been studied by DFT methods [42]. Associative processes were found to be favored, at least for reaction of cationic $(\eta^3\text{-allyl})\text{Pd}$ complexes with halide or neutral complexes with a neutral ligand. Successive ligand displacements can give the appearance of allyl rotation, even in the case of bidentate ligands (Scheme 4). There is a common misconception in the literature that associative ligand exchange at square planar complexes is initiated by ligand donation into an empty orbital (d_{z^2} or p_z), which is perpendicular to the coordination plane, an erroneous corollary of the 18-electron “rule.” Electronic structure calculations clearly show that this picture is incorrect; there are *no* low-lying empty orbitals in d^8 complexes, they are coordinatively saturated with two ω -bonds [48]. Associative processes in square planar complexes go through a trigonal bipyramidal transition state, without any pre-complexation of the approaching ligand. For trigonal bipyramidal $(\eta^3\text{-allyl})\text{Pd}$ transition states, the allyl spans one axial and one equatorial position, the spectator ligand occupies the remaining axial position, and the incoming and leaving ligands each lie in an equatorial position [42].

Scheme 5 Associative ligand exchange in $(\eta^3\text{-allyl})\text{Pd}$ complexes



Scheme 6 Dissociative ligand exchange in (η^3 -allyl) Pd complexes, also showing plausible but slow mechanisms for apparent rotation



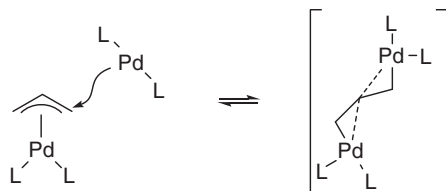
Dissociative processes were found to have a higher barrier [42], despite the known tendency of the DFT method to favor dissociation of dative ligands. The dissociation barrier was not insurmountable, only high compared to associative processes. In the complete absence of competing ligands, exchange would still be possible through dissociative processes. However, in such a situation, apparent rotation would still not occur through site exchange of the remaining ligand (Scheme 6, middle); the direct rotation without ligand dissociation has a slightly lower barrier (Scheme 6, left). We also note that the strong favoring of associative paths, by >80 kJ/mol, makes it likely that an associative exchange with a weak ligand such as a solvent molecule would be preferred compared to the purely dissociative path.

4.4 Allyl Exchange

None of the dynamic processes discussed so far allows for loss of stereochemical information in η^3 -cycloalkenyl complexes. Still, such complexes have been seen to lose stereochemical integrity over time [49–52]. The process is presumably slow under catalytic conditions, but it has been invoked to rationalize loss of stereospecificity [50, 51]. The postulated mechanism is nucleophilic attack of a Pd^0 complex on an (η^3 -allyl)Pd (Scheme 7). To our knowledge, there are no published computational studies of this process, but preliminary calculations using a small model system² indicates that the binuclear complex is a favored and symmetric ground

²B3LYP/LACVP* using PH_3 as a ligand model, gas phase calculations on the system depicted in Scheme 7.

Scheme 7 Allyl exchange through nucleophilic attack by Pd^0



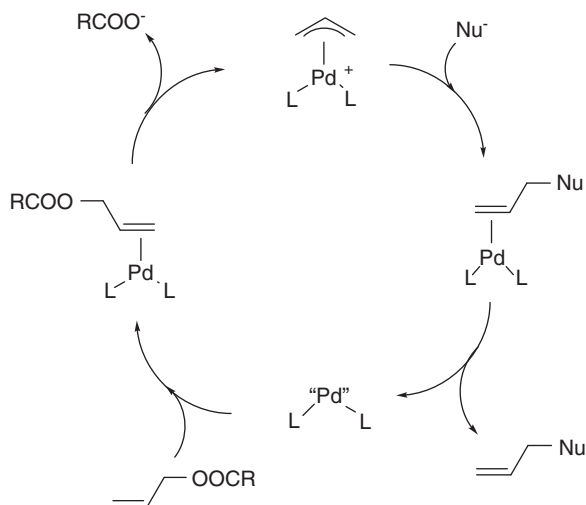
state, formed virtually without a barrier. We note that the binuclear complex in Scheme 7 could be seen as a *trans* analog of the known complex depicted in Fig. 2. The surprisingly facile allyl exchange process raises the question why this effect is not seen in more Pd-catalyzed allylic alkylations, where it should lower stereospecificity drastically. We can speculate that the low concentration of Pd^0 under catalytic conditions lowers the rate of this stereochemical scrambling, but since the concentration is still high enough to drive the regular catalytic process, we must further postulate that Pd^0 has a strong preference for reaction with the allylic substrate, a reaction which is obviously fast enough to out-compete the scrambling depicted in Scheme 7. A further clue to the mechanism comes from the observation that the scrambling that *has* been observed can be suppressed by addition of chloride anions in the form of lithium chloride [50, 51].

5 Reactivity

Allylation reactions can be both electrophilic and nucleophilic. Both types have been studied computationally. Here, we will first review palladium-assisted electrophilic allylation (e.g., the Tsuji–Trost reaction), which has been the subject of numerous studies since the 80s. We will then go through studies of nucleophilic allyl-palladium complexes.

5.1 Electrophilic Allyl

In general, Pd-assisted allylations are ionic. In a “standard” Tsuji–Trost reaction (Scheme 8), a neutral Pd^0 complex coordinates a neutral allyl carboxylate. $\text{S}_{\text{N}}2$ -like ionization produces a cationic $(\eta^3\text{-allyl})\text{Pd}$ complex and a carboxylate anion. The incoming nucleophile is frequently an anionic malonate. Reaction of the nucleophile with the cationic $(\eta^3\text{-allyl})\text{Pd}$ complex produces a neutral alkene complex that dissociates the product and enters a new catalytic cycle. A proper description of this seemingly simple reaction requires accounting for the surrounding solvent [16], since the combination of the two oppositely charged species occurs without a barrier in the gas phase. Only in more recent studies have the necessary solvation

Scheme 8 Catalytic cycle of palladium-assisted allylic substitution

models been available, and their utilization is not without problems. Earlier studies have circumvented these problems by limiting the investigation to the $(\eta^3\text{-allyl})\text{Pd}$ complex itself, attempting to correlate reactivity with frontier orbitals, charge distribution, or ligand-imposed structural distortions. Another approach has been to ensure minimal charge change by utilizing neutral model nucleophiles (e.g., ammonia). A study by Hagelin et al. showed that transition states could be found even for anionic nucleophiles, and also indicated that the transition state in solvent is significantly different from the gas phase transition state even for neutral nucleophiles [16].

5.1.1 Regioselectivity

Nucleophilic attack on $(\eta^3\text{-allyl})\text{metal}$ species can occur at any of the three carbons. Attack at the central carbon is generally followed by reductive elimination, forming cyclopropanes. However, with $(\eta^3\text{-allyl})\text{palladium}$ complexes, reaction with nucleophiles generally occur at the terminal positions. Already in the beginning of the 1980s, Eisenstein and Curtis could explain this observation using EHMO calculations. The study concluded that the observed regioselectivity was under frontier orbital control, and not charge control [53].

When using certain σ -donor ligands with less stabilized carbon nucleophiles, cyclopropanes can be produced by nucleophilic attack at the central carbon followed by reductive elimination [54]. The reason for this selectivity is examined by Bäckvall and co-workers and was found to be under frontier orbital control. MP2 calculations show that π -allyl complexes with σ -donor ligands, primarily N-ligands, have a low-lying empty symmetrical orbital with a large coefficient on the central carbon [55, 56].

An orbital description of the (η^3 -allyl)palladium moiety was given by Szabó, explaining the preference for the terminal attack. The activating effect of ligands was also rationalized, showing how reactivity increased when exchanging a σ -donor with a π -acceptor ligand [23].

One of the most studied problems in (η^3 -allyl)palladium concerns *which* allyl terminus is attacked in unsymmetric complexes. EHMO calculations have also been applied to this problem, showing increased reactivity of the carbon with the longest Pd–C bond [57].

The regioselectivity is sensitive to a variety of steric effects. Norrby and co-workers correlated MM-calculated structural features with experimental selectivities in the first application of QSAR methods to asymmetric catalysis [58]. The most important effects were found to be the previously mentioned Pd–C bond length, enforced rotation of the allyl toward a product-like geometry, and direct interactions with the incoming nucleophile.

5.1.2 Different Nucleophiles

Experimentally, many different nucleophiles have been employed in the allylic substitution reaction. The most common are carbon nucleophiles, usually malonates, but amines, phosphines, sulfinates, alcohols, and other heteroatom nucleophiles have been used to yield new carbon–heteroatom bonds.

Computationally, only a few types of nucleophiles have been studied. The most common is the carbon nucleophile, mostly represented by a malonate [28, 59–65]. In addition to this, not only amine nucleophiles have been the focus of some investigations [36, 63, 66], but also fluoride [16], cyanide [16], and acetate [42] have been investigated. We note that when the “nucleophile” is also a leaving group, this step is in fact the reverse of the ionization step (Scheme 8), and the calculated barriers can be directly applied to selectivities in the ionization.

Intramolecular allylation has been used successfully to create new rings, but only a few such cases have been studied computationally. Madec et al. studied reactions with tethered carbanion nucleophiles in systems where both 5- and 7-membered ring products had been observed experimentally. The high selectivity for 5-membered rings observed with an amide linker compared to the low selectivity with a methylene linker could be fully rationalized by rigidity observed in the computational model [67]. The modeling also predicted a strong counterion effect, and allowed design of a much more reactive system by removal of the chelating sodium counterion, either by crown ether or a two-phase reaction where sodium stayed in the water phase [67].

5.1.3 Substituent Effects

Substituted allyls are synthetically important in palladium-catalyzed allylic substitution reactions. The substitution pattern of the allyls gives implications for both the steric and electronic interactions. When the substituents on the two termini differ,

both regio- and stereoselectivity is influenced by the substituent itself, and by the interaction between the substituent and ligands on palladium. Substituents can occupy *syn* and *anti* positions (Fig. 5), with important differences in selectivity [37, 43, 65], but in many cases only *syn* complexes have been considered in computational studies.

The β -substituted (η^3 -allyl)palladium has been extensively studied by Szabó and co-workers. A new type of electronic interaction, occurring between the allylic β -substituents and palladium is described and characterized. The structure and stability, as well as the regiochemistry of a nucleophilic attack are influenced by this interaction [68–72].

5.1.4 Ligand Effects

The ligand effect on reactivity was discussed already in the beginning of the 1980s after the emergence of the synthetic use of the allylic substitution reaction. Sakaki et al. studied the nucleophilic attack on a (η^3 -allyl) palladium complex. The increased reactivity of the π -acceptor ligands was examined using semiempirical calculations, and explained with their ability to stabilize the important reacting orbitals and influencing the Pd–C bond strength [73].

Ligands with several heteroatoms, such as the bisthiazoline depicted in Fig. 6, can give different chelation options. In this situation, where a competition between the chelations was present, calculations have been helpful in sorting out the mechanistic possibilities. For the ligand in Fig. 6, DFT was used to deduce that the *N,N*-chelation was the lowest in energy, in agreement with experimental observations [60].

Each ligand will mostly affect structure and reactivity of the allyl terminus *trans* to itself. Thus, when employing two different ligands, or one heterodentate ligand, the relative reactivity of the two termini of the (η^3 -allyl)palladium moiety will be affected. The effect can also be observed in the Pd^0 complex, where Goldfuss and Kazmaier showed that the leaving group prefers a position *trans* to the phosphine in a complex with both Cl^- and PH_3 ligands [74]. In a more detailed study, Svensen et al. investigated the equilibria in systems with halides and monodentate phosphines, and found strong *trans* effects leading to significant memory effects [75].

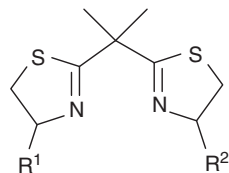


Fig. 6 A bisthiazoline ligand

Fig. 8 The “unconstrained” (η^3 -allyl)palladium complex used to investigate the electronic effect difference in PN-ligands

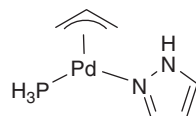
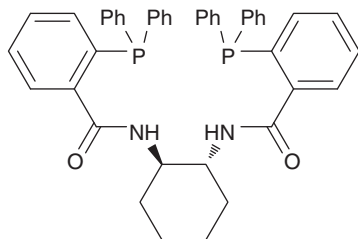


Fig. 9 A Trost modular ligand



Moberg et al. showed that the enantioselectivity could be dependent on the conformation of the ligand in a study of chiral pyridinoxazolines. Two different conformational minima could be found computationally and they gave rise to different steric environments leading to a stereoselective allylic alkylation [64].

Betz et al. have studied dithiazoline ligands in asymmetric allylic substitution (Fig. 6). The structure of the (η^3 -allyl)palladium complex was calculated, and the enantioselectivity as well as (N,N) vs. (N,S) competition is rationalized [60].

In a DFT study by Blöchl concerning bidentate phosphine-pyrazole ligands, the steric effects proved to be the reason for the high stereoselectivity. The bulky ligands force the allyl out of the “square planar” plane opening up for attack on one of the terminal carbons [36]. The authors also studied the importance of the *trans* effects in a small model system, and concluded that nucleophilic attack *trans* to phosphorus is favored by 8 kJ/mol, corresponding to a 20:1 preference for this attack at room temperature (Fig. 8).

The Trost modular ligand (Fig. 9) is one of the most frequently used ligands in asymmetric allylic alkylation. The origin of the powerful stereoselective ability of this ligand has been the focus of a study by Butts et al. The identification of a hydrogen-bond interaction, which influences both the ionization and nucleophilic attack, proves to be the source of the observed selectivity. This conclusion opens up the possibility for further development of this reaction including design of new ligands [61].

In their quest for new P,N-ligands, Andersson and co-workers performed DFT calculations to verify the observed enantiomeric excess. The resulting enthalpies were in agreement with the experimental observations, and the calculated structure was verified with NOE contacts [63].

The previously mentioned dinuclear palladium catalysts have been used in enantioselective palladium-catalyzed allylic substitution reactions, giving a moderate ee of 57%. The stereoselectivity is due to steric reasons, the strained arrangement assumed by the catalytic complex giving different environment for the terminal allylic carbons [62].

5.1.6 Reductive Elimination

In the allylic substitution, the nucleophilic attack takes place on the allyl and the role for the metal catalyst is to provide coordination sites for the allyl to form the (η^3 -allyl)palladium complex. For very basic nucleophiles, the reaction is believed to follow another pathway. Both the allyl and nucleophile coordinate to the metal catalyst, and a reductive elimination yields the final product.

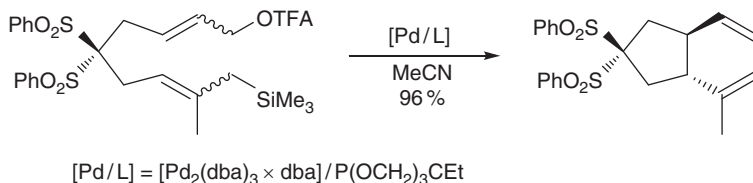
Some effort has been put in to calculations regarding the feasibility of this reaction. Sakaki et al. performed MP2/MP4 calculations on a $MH(\eta^1-C_3H_5)(PH_3)$ system ($M=Pd, Pt$). The η^1 -complex was found to be less stable, by at least 9 kcal/mol, than the corresponding η^3 -complex, but the reductive elimination from the η^1 -Pd complex had a small barrier of 5.4 kcal/mol, and was exothermic by almost 30 kcal/mol, making it a feasible reaction. The Pt complex, on the other hand, had a barrier for the reductive elimination of more than 20 kcal/mol [78].

In a further study, $Pd(XH_3)(\eta^3-C_3H_5)(PH_3)$ complexes ($X=C, Si, Ge, Sn$) were studied by the same group. The ability to do a reductive elimination was calculated at MP2/MP4 or CCSD(T) level. It was found that carbon gave the highest E_A with 23.3 kcal/mol; the other three had smaller E_A , 11–13 kcal/mol. The high E_A for C is explained with a large distortion energy required to increase the Pd–C bond length. The other three groups (Si, Ge, Sn) has much smaller energy costs when distorting the Pd–X bond, probably due to the hypervalency of these elements [79].

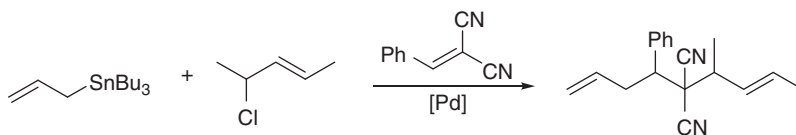
Mendez et al. studied an intramolecular diallyl reaction for the formation of five-membered rings through an improved variant of the Oppolzer cyclization (Scheme 9). A computational study was carried out to investigate the nature of the reductive elimination between the two allylic pieces. DFT calculations suggest that, in the presence of excess PH_3 , two η^1 -allyls react through the terminal carbons, in a somewhat unorthodox reductive elimination. These findings were supported by experimental evidence [80].

5.2 Nucleophilic Allyl

The umpolung of the allylpalladium reactivity, where the allyl shows nucleophilic abilities, has been known for several decades [81]. In the middle of the 90s, Yamamoto and co-workers could identify bisallyl-Pd structures through NMR



Scheme 9 Modified Oppolzer cyclization investigated by Mendez et al.



Scheme 10 Substituent effects on allylation

studies, and these reacted with aldehydes in a nucleophilic fashion [82]. This opened the field for a whole new type of reactivity. Further studies showed that the bisallyl-palladium complexes could undergo an initial *electrophilic* attack on one of the allyl moieties, followed by a *nucleophilic* attack on the other one. In other words, bisallyl-palladium complexes can be described as *amphiphilic* reagents, that is both nucleophilic and electrophilic species [32].

5.2.1 Substituent Effects

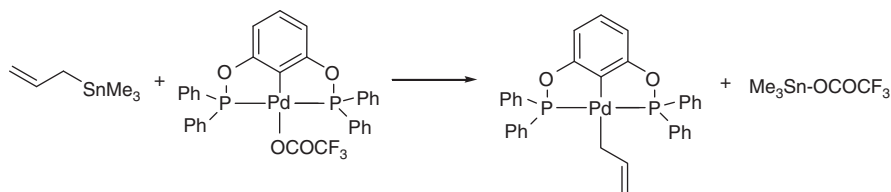
In a study by Solin et al., the effects of substitution on the allyls are examined. The reaction studied was between the above-mentioned bisallylpalladium complex, which reacts with benzylidenemalonitrile, yielding substituted 1,7-octadienes with very high regioselectivity (Scheme 10) [83].

With the aid of DFT calculations, the nature of the (η^3, η^1)-bisallyl complex was revealed. It was found that the unsubstituted allyl is the one forming the η^1 -bond. This form is favored by at least 12 kJ/mol over the competing coordination pattern. The energy barrier for the electrophilic attack was also found to be 12 kJ/mol lower for the former complex. The high regioselectivity was ascribed to the electronic effects of the alkyl substituents, the terminal alkyls have two important effects: destabilization of the η^3, η^1 -bis-allylpalladium intermediate when the η^1 -moiety is substituted and an increase in the activation barrier of the electrophilic attack caused by the alkyl substitution.

It has been speculated that a (η^1 -allyl)palladium complex could also be attacked by nucleophiles, and that this could help explain some observed memory effects [39, 40]. However, two separate computational studies have shown that approaching a nucleophile to an η^1 -allyl forces it into η^3 -allyl form, if necessary expelling another ligand on palladium. In experimental terms, this indicates the η^1 -allyl group cannot undergo reaction with nucleophiles, but must equilibrate to the η^3 -allyl form before reaction can take place [84, 85].

5.2.2 Different Electrophiles

Experimentally, several different electrophiles have been employed in the electrophilic allylic substitution [86]. The examples involving calculations are, on the



Scheme 11 Synthesis of a (η^1 -allyl)palladium with a pincer ligand

other hand, rather few. Szabó has studied acetic acid and formaldehyde as electrophiles. Both species were found to have small energy barriers for the electrophilic attack [32]. Low activation energy was also found for the attack of an NCO-electrophile in a study by Solin et al. [87].

5.2.3 Palladium Pincer Complexes

In development of electrophilic allylic substitution, Szabó searched for complexes where a mono-allyl palladium species would be forced into the η^1 binding mode. This can be achieved using ligands that require three of the available coordination sites on the Pd (Scheme 11), the so-called “pincer” ligands. This leaves one site open for coordination, which causes the allyl to coordinate in a η^1 -fashion. The allyl-pincer complex is synthesized *via* a transmetalation from an allylstannane (Scheme 11), and can sequentially be reacted with an electrophile to achieve an allylation. Both imines and aldehydes can be used as electrophiles.

Calculations on these systems have identified the η^1 allyl-pincer complex as the active catalyst and concluded that the electrophilic attack proceeds with a low activation barrier on the γ -position of the η^1 -allyl [88].

6 Summary

Molecular modeling has been shown to be a strong support in understanding all aspects of palladium-assisted allylation reactions. Structures of intermediates can be calculated with good accuracy at moderate levels of theory. Substantially more problematic is quantitative calculation of reaction selectivities, in particular when the reagents are ionic and oppositely charged. However, advances in DFT and use of continuum solvation now allow also these types of reactions to be understood on a molecular level. Among the most recent additions to the computational arsenal is the correction for dispersive van der Waals interactions, allowing a more accurate treatment of large complexes and bimolecular reactions.

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