

IV.2 The Heck Reaction (Alkene Substitution via Carbopalladation–Dehydropalladation) and Related Carbopalladation Reactions

IV.2.1 Intermolecular Heck Reaction

IV.2.1.1 Scope, Mechanism, and Other Fundamental Aspects of the Intermolecular Heck Reaction

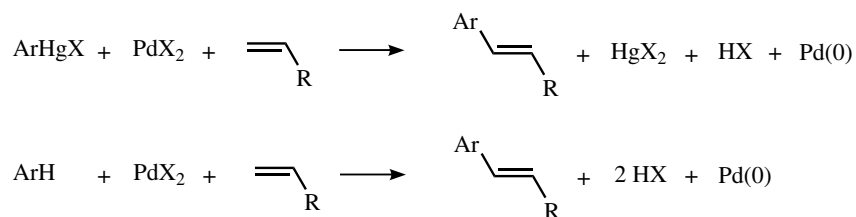
MATS LARHED and ANDERS HALLBERG

A. INTRODUCTION

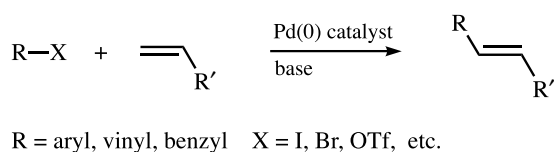
It was demonstrated by Heck in the late 1960s that arylpalladium salts, prepared by transmetallation of organomercury compounds, constitute useful reactants in various vinylic substitution reactions.^{[1]–[7]} Independently, Moritani, Fujiwara, and colleagues conducted similar vinylic substitutions, but generated the organopalladium intermediates by direct electrophilic palladation of arenes.^{[8]–[10]} In these reactions the palladium(II) salt employed is reduced to palladium(0) (**Scheme 1**).*

A major improvement from a preparative point of view was demonstrated by Mizoroki, Heck, and colleagues, who independently found that organic halides were suitable organopalladium precursors, and that the vinylic substitution reaction could be accomplished with a catalytic amount of palladium and a base, in the absence of a reoxidant.^{[11]–[13]} This reaction was developed further by Heck and co-workers and was later referred to as the Heck reaction or Heck olefination.^{[14]–[29]} The Heck reaction is defined as a vinylic substitution reaction where a vinylic hydrogen is substituted by an aryl, vinyl, or benzyl group (**Scheme 2**).

*A catalytic process was also developed by addition of Pd(0) reoxidants, such as cupric halides in combination with oxygen,^{[1], [9]} which enables a transmetallation or direct palladation to occur.

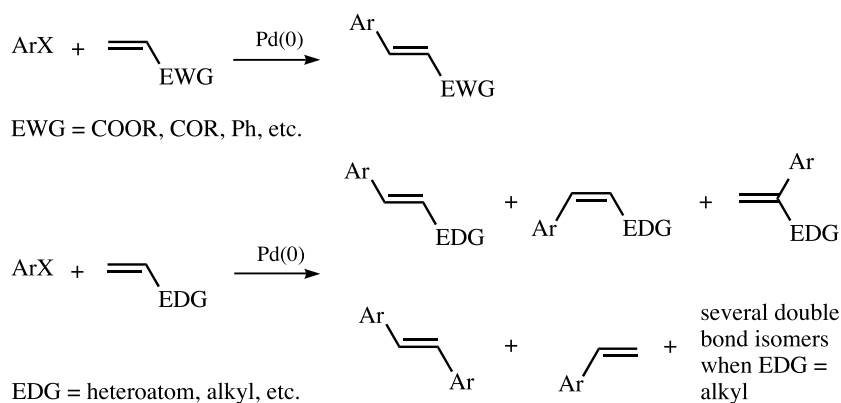


Scheme 1



Scheme 2

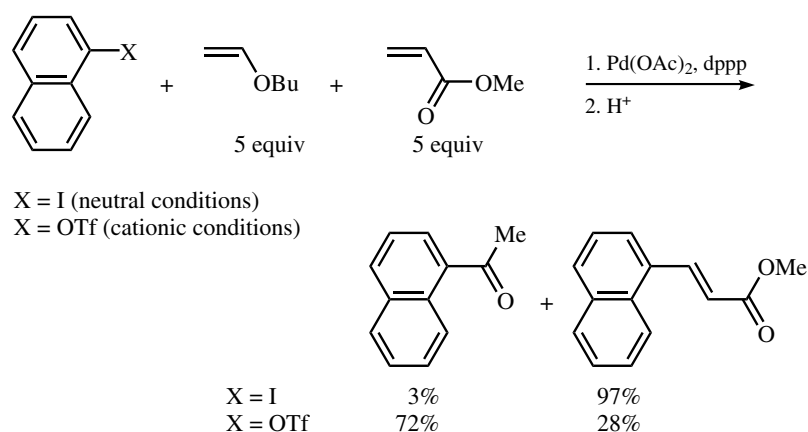
A large variety of functional groups are tolerated in the Heck reaction, a reaction that during the last thirty years has emerged as one of the most powerful reactions in organic synthesis. Traditional Heck couplings relied on aryl or vinyl iodides or bromides as the electrophilic partner. Later, triflates, carbonyl and sulfonyl chlorides, diazonium salts, iodonium salts, and various leaving groups encompassing diazo fragments were introduced.^[21] The Pd-catalyzed reactions proceeded smoothly in general with terminal alkenes substituted with electron-withdrawing groups, but electronically neutral alkenes or electron-rich alkenes were less suitable as substrates.^{[20],[29]} With the latter class of non-electron-poor alkenes, diarylated products, regioisomers, double bond isomers, mixtures of *cis*- and *trans*-isomers, products in which a heteroatom substituent bonded to the alkene had been eliminated, or sometimes even tar were encountered under the traditional conditions (**Scheme 3**).^[29]



Scheme 3

Today, efficient methods have been developed that also make possible regiocontrolled functionalizations of electron-rich alkenes,^{[30]–[36]} and frequently efficient double bond

migration control has been achieved with both cyclic and acyclic systems.^[23] Powerful catalytic systems have emerged after considerable experimentation with palladium salts, ligands, and solvents; very high turnover numbers^[37] and short reaction times have been accomplished.^{[38]–[40]} In addition, different reaction systems result in neutral or cationic mechanistic pathways,^{[20],[41]–[45]} and the reactivity in the Heck arylation depends both on the leaving group and on the charge density of the vinylic system. Competition experiments have shown that electron-poor methyl acrylate reacts faster than *n*-butyl vinyl ether with 1-naphthyl iodide under neutral conditions (**Scheme 4**).^[35] In contrast, following the cationic pathway, 1-naphthyl triflate was more reactive toward the electron-rich alkene.



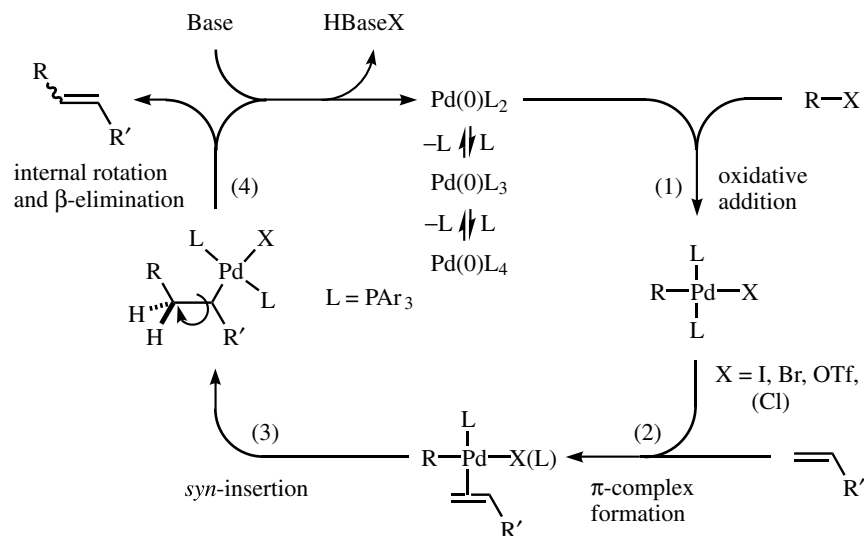
Scheme 4

B. MECHANISM

The basic feature of the catalysis mechanism, based on the Pd(0)/Pd(II) redox system proposed in the 1970s, is still generally accepted,^{[14],[15]} although the detailed structures of the catalytically active species in the reaction media, comprising various ligands and other additives, is still not fully understood.^[46] A quite different mechanistic rationale that takes Pd(IV) complexes into account as key intermediates in the catalytic cycle has been postulated recently (see **Sect. B.xii**).^[47]

B.i. Traditional Heck Mechanism: Pd(0) to Pd(II) Interconversions

The consecutive steps in the traditional Heck reaction are depicted in **Scheme 5**. The catalytic cycle involves four discrete reactions and several intermediates: Firstly, after generation of an active catalyst, an oxidative addition of an electrophilic substrate RX to palladium(0),^[48] affording the adduct RPdL_2X , takes place. Second, displacement of one ligand, L or X, and subsequent coordination to the alkene provides a π -complex, which can be either neutral or positively charged.^[20] Third, a *syn*-insertion process (carbopalladation),^[49] probably occurring via a concerted four-center transition state,^{[50],[51]} results in the generation of an unstable σ -organopalladium complex. The degree of the regioselectivity in a particular reaction is commonly determined by both



steric and electronic factors. Fourth, if a β -hydrogen is accessible that can be oriented by internal rotation in a *syn*-position, in relation to the metal, and provided there is a coordination vacancy on the palladium atom available, β -hydride elimination occurs and the Heck coupled product is eventually delivered. Finally, in order to close the catalytic cycle, a base is needed to regenerate the active Pd(0) species from the hydridopalladium complex.^{[52]–[54]}

The discrete steps and related processes of importance to the synthetic chemist, such as catalyst generation, decomposition of oxidative addition complexes, and the key aspects of regiocontrol with regard to insertion in particular, but also double bond migration and elimination, will be discussed in some detail below.

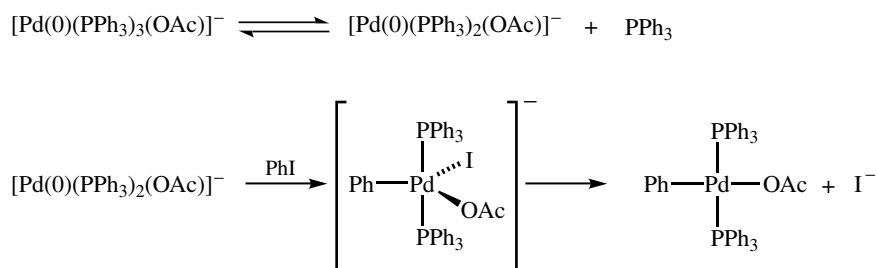
B.ii. Active Catalysts and Oxidative Addition Complexes

An active, electron-rich and nucleophilic 14-electron palladium(0) complex, Pd(0)L₂, with vacant coordination sites (often coordinated with weak donor ligands such as phosphines) participates in the oxidative addition process, whereby a square planar *trans*-RPdL₂X intermediate is formed, via the thermodynamically less stable *cis*-isomer.^{[55]–[58]} A σ -alkenyl- or a σ -arylpalladium complex is generated. Organyl iodides and, especially, diazonium salts are generally more reactive than the corresponding bromides and triflates.^[19] Aryl chlorides are reluctant to undergo Heck reactions as can be expected from high C—Cl bond dissociation energy as compared to the corresponding energies for C—Br and C—I bond dissociation. Organyl fluorides are not reactive. The Pd(0)L₂ complex is usually produced *in situ* from a Pd(II) salt such as Pd(OAc)₂ or PdCl₂ and 2–4 equiv of PPh₃ or alternatively from a Pd(0) complex. It has been established that the active Pd(0)(PPh₃)₂ complex is involved in fast equilibrium reactions with more highly ligated species^{[59]–[63]} and a large excess (sixfold or more) of the phosphine ligand over palladium is deleterious for the reaction.^[24] The Pd(II) salts act as Pd(0) precursors and are efficiently reduced to Pd(0) species in the reaction medium, a process probably

promoted by the alkene,^[64] a trialkylamine (the most common base),^[65] the solvent,^[66] or the phosphine ligand.^{[67]–[70]} The last of the above, for example, triphenylphosphine, often used in Heck reactions, is oxidized to the corresponding phosphine oxide.^{[68],[70]} However, there are also many examples in which phosphine free systems (palladium on charcoal and on other solid supports, palladium black, palladium clusters and colloids, etc.)^[71] serve as efficient catalysts.

Classical Heck reactions can also be conducted with polymer-bound palladium catalysts, for example, with diarylphosphinylated polystyrene.^[72]

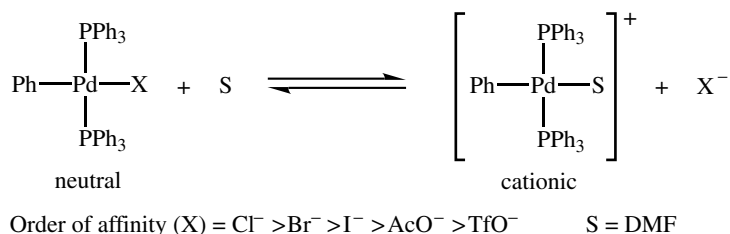
Recently, Amatore, Jutand, and colleagues have demonstrated that the highly nucleophilic, formally coordinately unsaturated and negatively charged $[\text{Pd}(0)(\text{PPh}_3)_2(\text{OAc})]^-$ complex was formed in DMF from $\text{Pd}(\text{OAc})_2$ and PPh_3 in a redox process.^[62] This 16-electron complex can deliver the oxidative addition product *trans*- $\text{PhPd}(\text{PPh}_3)_2(\text{OAc})$ via an anionic pentacoordinated arylpalladium species after reaction with iodobenzene according to the mechanism proposed in **Scheme 6**. Thus, it is important to realize that different palladium precatalysts may generate not only deviating active $\text{Pd}(0)$ complexes, but also different reaction intermediates.^[46]



Scheme 6

Neutral phenylpalladium(II) complexes $\text{PhPd}(\text{PPh}_3)_2\text{X}$ ($\text{X} = \text{I}, \text{Br}, \text{Cl}, \text{OAc}$) are involved in an equilibrium with the cationic $\text{PhPd}(\text{PPh}_3)_2\text{DMF}$ and the anion X^- .^[73] The affinity of X^- for $\text{PhPd}(\text{PPh}_3)_2\text{DMF}$ was found to be in the order $\text{Cl}^- > \text{Br}^- > \text{I}^- > \text{AcO}^-$. The contribution of the cationic complex should therefore be more important for acetate than for chloride anions. Although cationic $\text{PhPd}(\text{PPh}_3)_2^+$ was found to react more slowly than $\text{PhPd}(\text{PPh}_3)_2(\text{OAc})$ with styrene,^[62] suggesting that $\text{PhPd}(\text{PPh}_3)_2(\text{OAc})$ is a key intermediate in the Heck reaction, a number of cationic organopalladium(II) complexes have been reported to be more prone to insert than the corresponding neutral $\text{Ar}-\text{Pd}-\text{X}$ ($\text{X} = \text{halide}$) complexes.^{[74],[75]} Interestingly, the presence of a base in the Heck reaction mixture might be important not only for the recycling of the $\text{Pd}(0)$ catalyst, but to inhibit a shift in the equilibrium toward the less reactive cationic $\text{PhPd}(\text{PPh}_3)_2^+$ complex.^[46] In this context, we must also emphasize that the triflate anion is considered to be fully dissociated from $\text{Pd}(\text{II})$ in polar solvents (**Scheme 7**).

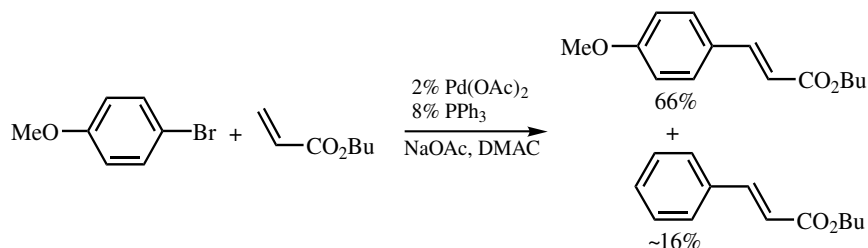
Arylation of butyl vinyl ether with an arylpalladium chloride complex predominantly delivers the terminally arylated product (as expected if a neutral oxidative addition complex is involved). Internal arylation of the highly polarized vinyl ether dominates with the corresponding iodide precursor, suggesting that in this case the cationic intermediate is more plausible as the key intermediate.^[76]



Scheme 7

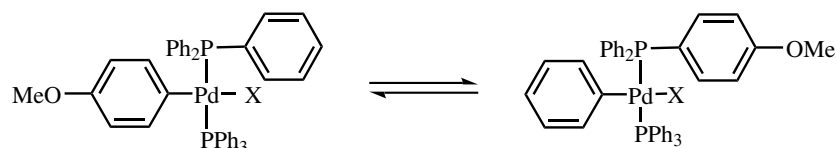
B.iii. Side Products from Aryl Migration in the Oxidative Addition Complex

Frequently, a considerable amount of side products, derived from facile aryl–aryl exchange in the oxidative addition complex, is formed in a Heck reaction executed in the presence of phosphine ligands.^{[77]–[81]} This process is particularly significant at higher reaction temperatures and with electron-rich aryl halides. Thus, a reaction of 4-bromoanisole with butyl acrylate with Pd(OAc)₂/PPh₃ as the catalyst system and sodium acetate furnish butyl *E*-cinnamate in addition to the expected coupling product (**Scheme 8**).^[24]



Scheme 8

An equilibrium reaction involving aryl group exchange, as depicted in **Scheme 9**, is responsible for the product pattern, and donor-substituted derivatives underwent particularly facile aryl–aryl exchange.

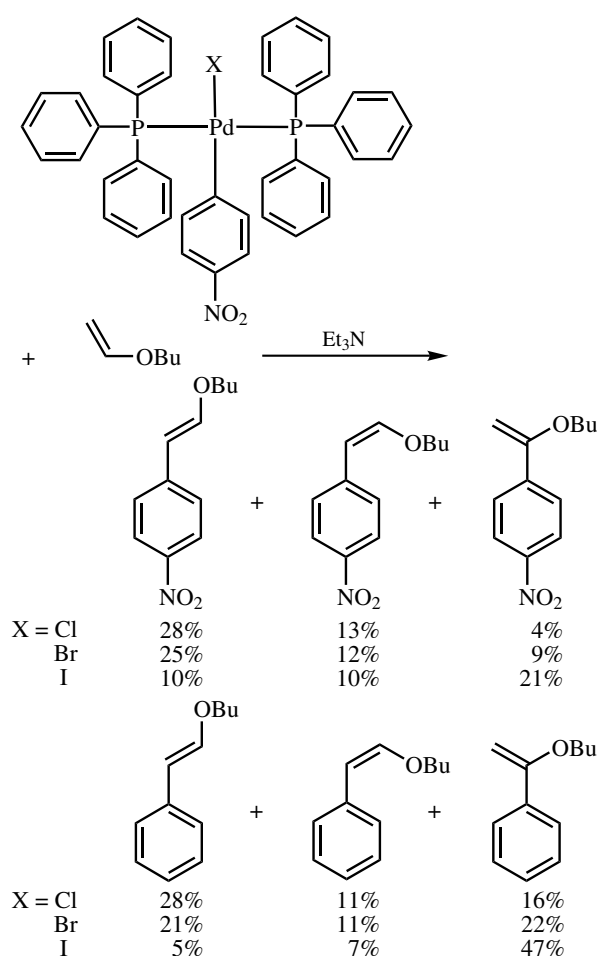


Scheme 9

Herrmann emphasized that aryl chlorides are unsuitable as arylating agents in Heck reactions primarily because P–C cleavage and loss of Pd(0)-stabilizing phosphines ultimately occur, leading to catalyst deactivation and palladium black formation, rather than resistance of aryl chlorides to oxidative addition.^[24]

Notably it was demonstrated in 1987 that oxidative addition complexes, substituted with strongly electron-withdrawing groups, O₂NPh(PPh₃)₂I, O₂NPh(PPh₃)₂Br, and

$\text{O}_2\text{NPh}(\text{PPh}_3)_2\text{Cl}$, in the presence of butyl vinyl ether as an alkene and 2 equiv of triethylamine in toluene at 100 °C, furnish arylated products in modest yields, almost equally divided between products derived from the 4-nitrophenyl group of the palladium reagents and phenylated products formed following rearrangement to the corresponding phenylpalladium species (**Scheme 10**).^[76] Product contamination in reactions in which triarylphosphines are employed is often a severe obstacle, and there is a strong need for more stable ligands that are less prone to undergo decomposition.

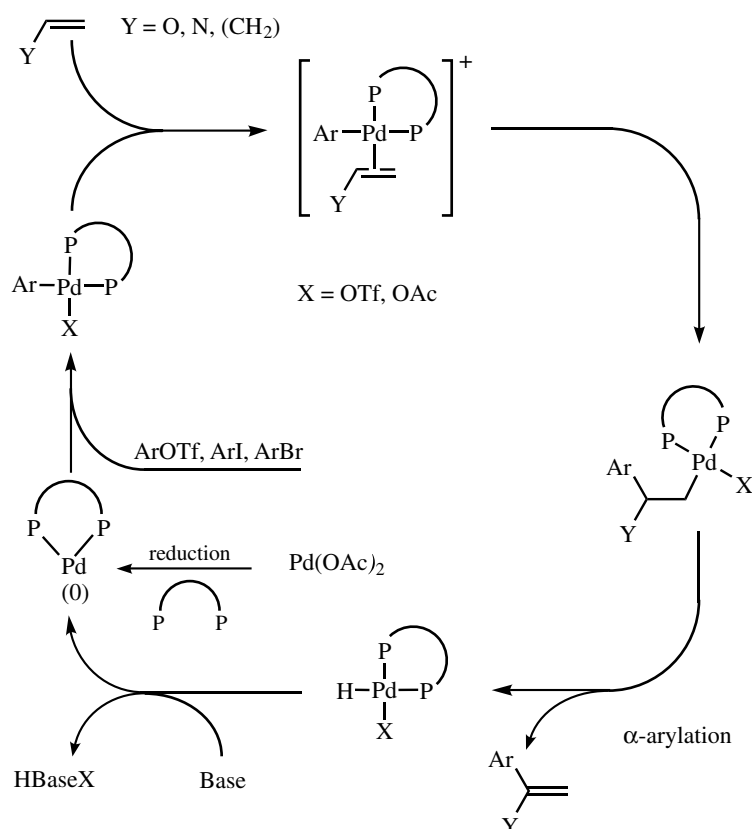


Scheme 10

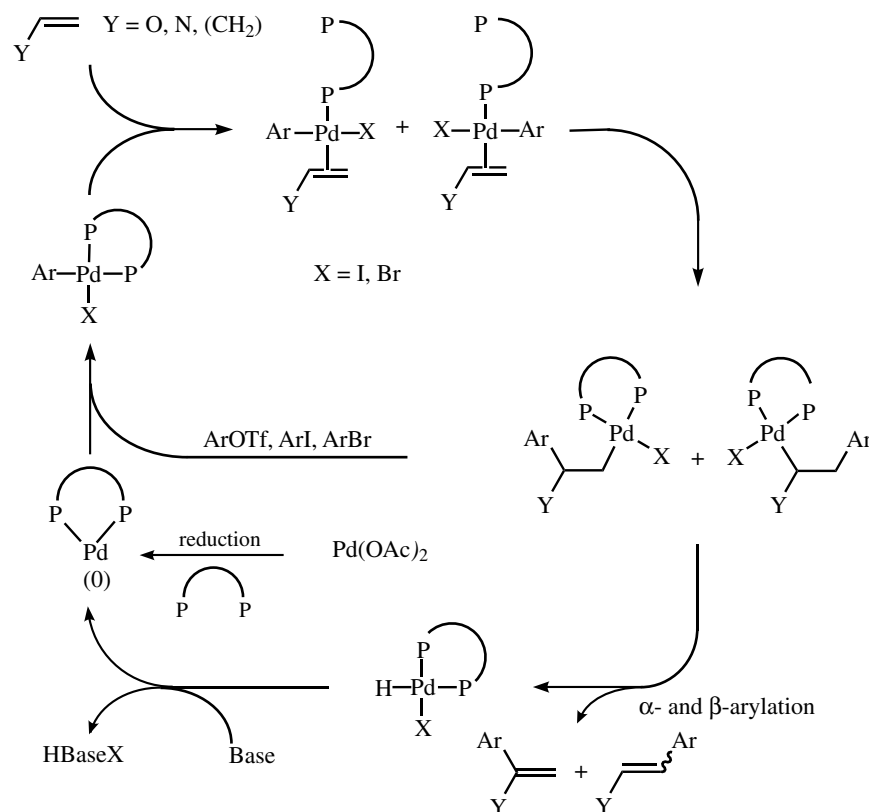
B.iv. Insertion and Regioselectivity

Given the many reports of Heck-type coupling reactions dating from the 1970s and 1980s, it is somewhat surprising that attempts to govern the insertion in either of the two possible directions are rare.^{[20],[29]} The major factors determining the regioselectivity of the aromatic and vinylic migratory insertion into the alkene are electronic and steric parameters, operating in a delicate balance.^{[14],[82]} Therefore, with alkenes carrying a

mesomerically electron-donating group, the regioselectivity is dictated by two mutually counteracting effects. The electronic effects correlate with the polarization of the R—Pd bond, and migration of the organic moiety, formally an anion, onto the internal carbon is expected as a consequence of the lower charge density experienced. In contrast, if the insertion is controlled by steric parameters, the organic group, acting as the larger moiety, attaches itself preferentially to the less substituted vinylic carbon. One might speculate, though, that alternatively the formation of terminal (β)-substituted acyclic vinyl ethers might be attributable to a strong driving force toward a stable palladium–oxygen coordinated internal σ -intermediate^[83] (a palladaoxacyclopropane) rather than entirely steric effects. Taking the arylation of alkyl vinyl ethers as an example, the regioselectivity is directed strongly by the electronic properties of the aromatic substrate, the counterion in the oxidative addition complex, the presence or absence of phosphine ligands, and the solvent.^{[76],[84]–[86]} Cabri and co-workers discovered that bidentate phosphine ligands promote internal (α)-arylations of heteroatom-substituted alkenes and allylic substrates with very high selectivity.^{[33]–[35]} For this observation Cabri and Candiani proposed a mechanistic rationale in which two different pathways for the coordination–insertion process were taken into account (**Schemes 11** and **12**).^[20] Ozawa, Hayashi, and colleagues, who extensively studied asymmetric arylation of 2,3-dihydrofuran, have made a similar mechanistic proposal.^{[41]–[45]}



Scheme 11



Scheme 12

B.v. Insertion Via Charged and Neutral π -Complexes

A cationic π -complex is formed when aryl triflates are employed with dppp,^[20] a strongly coordinating difunctional phosphine (**Scheme 11**). Thus, ionization occurs by dissociation of the weakly coordinating triflate counterion.^[58] Alternatively, a neutral π -complex is generated after phosphine dissociation of one of the arms of a bidentate ligand (**Scheme 12**).^[34]

The neutral intermediate predominates when aryl iodides or bromides are used as arylpalladium precursors. With electron-rich alkenes the cationic π -complex favors α -substitution, but the neutral intermediate is subject to both α - and β -substitution due to indecisive electronic control. The electronic requirements become more important when the reaction proceeds via the cationic route and an aryl group migration toward the internal electron-deficient carbon predominates. This argument is based on the higher polarization of the olefinic moiety in the charged π -complex.^[20] For selective internal arylation of vinyl ethers with aryl iodides or bromides for which cationic organopalladium intermediates are required as intermediates, thallium salts are utilized as additives.^[34] Although the role of the thallium additives^{[87]–[90]} (or silver additives)^{[91]–[96]} has not been fully elucidated, it is likely that these additives act as halide sequestering agents. Upon addition of thallium acetate, the halide ion in the oxidative addition complex is replaced by the acetate (X = OAc).^[34] The acetate anion can dissociate more easily^[97] and allows

coordination of the alkene in a cationic 16-electron π -complex, essential for the charged-controlled α -selectivity.

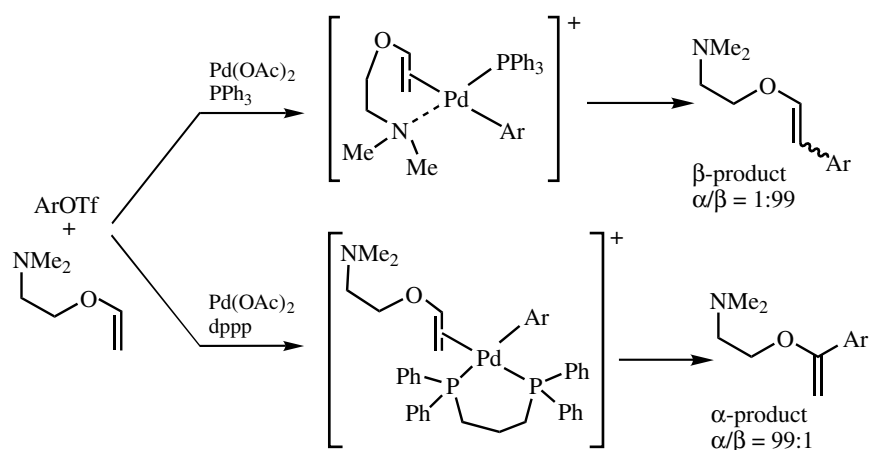
If the counterion (X) in the oxidative addition complex is iodide or bromide (and no thallium or silver salts are present) the dissociation of one of the phosphorus atoms in the bidentate ligand from the metal is probably attributed to the relatively high *trans* effect exerted by the halides.^[98] This reversible displacement facilitates formation of a neutral π -complex, in which the π -system of the electron-rich alkene is only weakly polarized. Therefore, after insertion and hydridopalladium halide elimination, a larger fraction of β -arylated product is formed, since steric factors always favor terminal arylation.

Importantly, the Cabri–Hayashi hypothesis also accounts for the mixture of regioisomers produced when less tightly coordinating monodentate ligands such as PPh_3 are used together with aryl halides. Overman, Poon, and colleagues have recently suggested a neutral-cationic hybrid reaction pathway.^{[99],[100]}

B.vi. Chelation-Controlled Insertion

Facile and regioselective chelation-controlled, but stoichiometric, palladations of allylic and homoallylic systems are well known.^[21] The directing effect of the heteroatoms in these substrates and the selective formation of the five- or six-membered chelate accounts for the good regiocontrol achieved. There are also examples of catalytic chelation-controlled insertions but such Heck reactions are more rare. The size and stability of the chelate ring control these reactions and the outcome can be manipulated by the addition of metal salts or ligands and the choice of other reaction parameters. A number of functional groups, such as tertiary amines, diarylphosphines, carbamates, and hydroxyl and sulfinyl groups are effective for chelation to Pd(II). For example, electron-rich alkenes are β -arylated or vinylylated with high regioselectivity through stabilization of key transition states (**Scheme 13**).^{[30]–[32],[101],[102]}

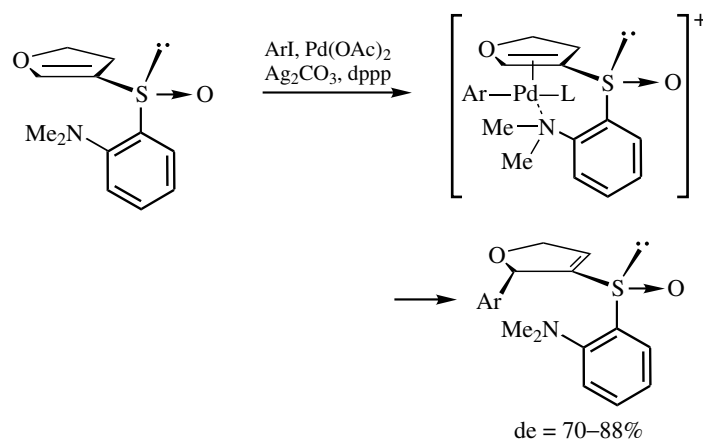
Formation of a chelated nitrogen palladium π -complex presumably directs the migratory insertion through steric control favoring the six-membered ring. Alternatively, insertion may be affected by electronic constraints, by which the electron density on the



Scheme 13

terminal carbon would be reduced by bending the oxygen out of plane (favoring the inductive effect at the expense of the mesomeric effect of the oxygen).^[30] In a control experiment an almost equimolar mixture of the linear β -product and branched α -product was formed after displacing the chelating vinyl ether with butyl vinyl ether.^{[30],[31]} The formation of π -complexes in which the palladium atom is coordinated to the dimethylamino group is supported by the early work of McCrindle and co-workers, who isolated a *cis*-PdCl₂ π -complex very similar to that proposed in **Scheme 13**.^[103] In the presence of a bidentate ligand the branched α -product is formed exclusively, reflecting the powerful influence of ligands on the outcome of the reaction.^[32]

One of the more fascinating applications of the chelating effect is the stereoselective synthesis of 2-aryl-3-sulfinyl-2,5-dihydrofurans (**Scheme 14**).^[104] The high stereocontrol is attributed to the Pd(II) coordination with the dimethylamino group and the subsequent selective presentation of the σ -adduct during the insertion step (de = 70–88%). Consistent with this scenario, Heck arylations of non-amino-containing 4-arylsulfinyl-2,3-dihydrofurans resulted predominantly in the opposite diastereomers (de = 34–56%).



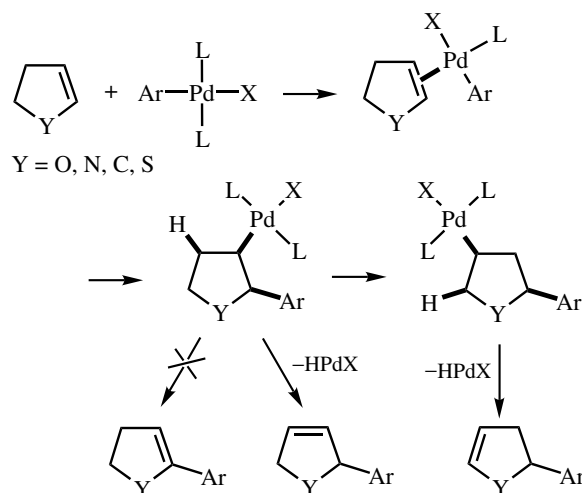
Scheme 14

In short, arylation of electron-deficient alkenes (good π -acceptors, poor σ -donors) are best conducted with monodentate ligands along the neutral pathway to deliver linear products. No procedures allowing the preparation of branched electron-poor alkenes are yet available. The arylation of electron-rich alkenes (poor π -acceptors, good σ -donors) works well with bidentate ligands according to the cationic pathway and yields branched products with high selectivity. To induce formation of linear products with electron-rich alkenes, strategies based on control by chelating auxiliaries have been most successful to date. It is noteworthy that there is no general and efficient methodology for regioselective arylation of unfunctionalized 1-alkenes.

B.vii. β -Elimination and Double Bond Migration

The development of the intermolecular cyclic version of the Heck reaction began in the late 1970s. It was immediately evident that the problem with reversible hydride eliminations complicated the use of endocyclic alkenes^{[82],[94],[105]–[107]} and long chain acyclic

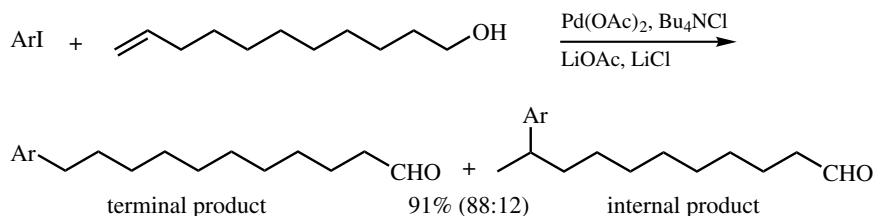
1-alkenes.^[16] Mixtures of isomers were obtained. An example of an isomerization process is shown in **Scheme 15**.



Scheme 15

The arylpalladium complex inserts in a 1,2-*syn* mode and a σ -complex is produced. After β -elimination, the allylic compound might be liberated. Alternatively, readdition of the hydridopalladium species in the reverse direction eventually leads to the arylated cyclic system with the double bond in conjugation with the heteroatom. Recently, a bisphosphine C-5- σ -alkylpalladium complex was fully characterized by Brown and co-workers, which suggests that the formation of the conjugated double bond isomer by β -elimination of the C-5-palladium σ -complex also has to be taken into account.^[83] The isomer with the double bond conjugated to the aromatic ring is not observed, as expected since formation of that isomer requires either *anti*-elimination or readdition of the hydridopalladium species at the opposite face of the ring system. A suitably positioned hydrogen, accessible for *syn*-elimination, is a prerequisite for the β -elimination to occur. The elimination of a hydrogen atom in an *anti* fashion to the palladium is very uncommon and the metal is postulated to be uninterruptedly coordinated to the same side of the cyclic alkene until irreversible elimination of HPdX occurs.^[14]

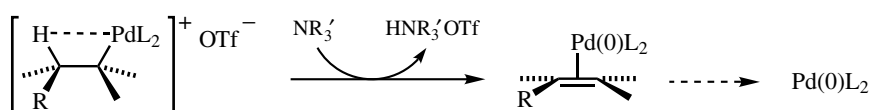
In an impressive acyclic case, 10-undecenyl alcohol reacts with iodobenzene to give thermodynamically favored 11-phenylundecanal as the major regioisomer (**Scheme 16**).^[108] The



Scheme 16

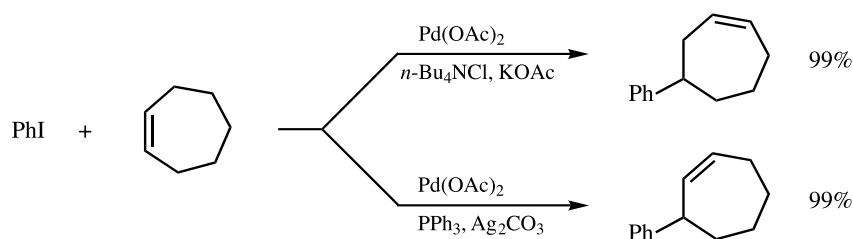
very efficient and repeated elimination of HPdX and subsequent readdition, regardless of the regioselectivity in the original ArPdX insertion, is a clear example of “living” HPdX species.

Recent Density Functional Theory (DFT) calculations reveal a substantial agostic interaction between the metal and the β -hydrogens in the σ -complex formed after the migratory insertion.^{[109]–[111]} Most importantly, since the calculations show that hydride complexes are not local minima intermediates, liberation of the product by classic β -elimination is not a likely outcome.^[110] The calculations instead support a base-promoted deprotonation of the agostic hydrogens.^[110] The suggested (revised) directly base-mediated proton transfer from the σ -bonded alkyl group is displayed in **Scheme 17**. Thus, the existence of the free hydridopalladium species depicted in **Schemes 11** and **12** and, consequently, the mechanism for the sequential arylation–double bond migration are under debate.



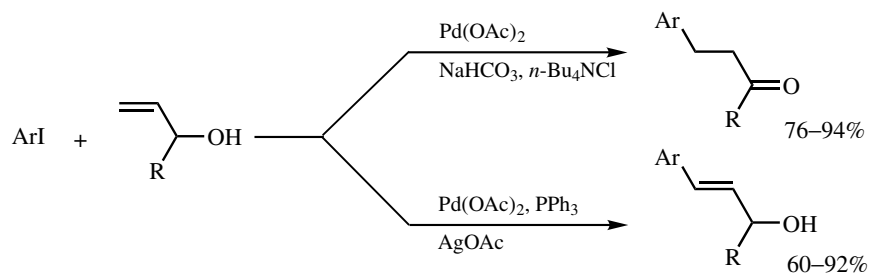
Scheme 17

Pd-catalyzed isomerizations are often efficiently suppressed by addition of thallium or silver salts (**Sect. B.v**). Moreover, additions of both acetate^{[112],[113]} or water^[114] are reported to suppress double bond migration in certain systems. Cyclic alkenes give different regioisomers and often product mixtures owing to double bond isomerizations after arylation. For example, in **Scheme 18**, arylation of cycloheptene gives entirely the homoallylic product.^[115] Addition of silver carbonate cleanly suppresses the double bond migration (**Scheme 18**).^[115]

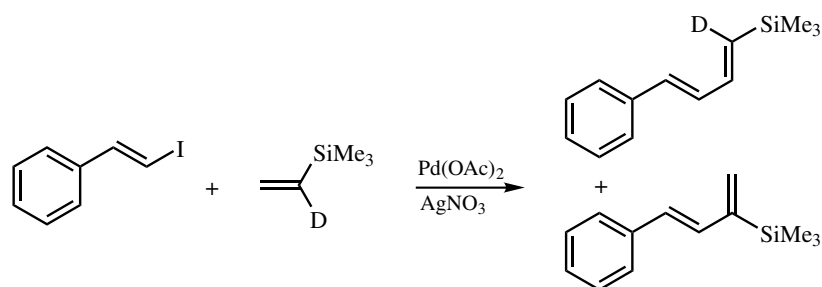


Scheme 18

As illustrated in **Scheme 19**, when allylic alcohols are used as an alkene component in the reaction with aryl halides under standard conditions, elimination of hydrogen occurs from the oxygen-bearing carbon and aldehydes or ketones are obtained rather than allylic alcohols.^{[82],[116]} However, the outcome of the Heck reaction in **Scheme 19** can be controlled by silver salt addition. Thus, either the terminally arylated carbonyl compounds or the terminally arylated allylic alcohols can be obtained selectively simply by alteration of the reaction conditions.^[116] This silver-mediating effect on double bond migration is attributed to the probable generation of positively charged hydridopalladium complexes that are less prone to undergo readdition. Support for an irreversible elimination of a hydridopalladium species in the presence of silver salts was obtained in an experiment with β -iodostyrene and (1-deuteriovinyl)trimethylsilane (**Scheme 20**).^[117]



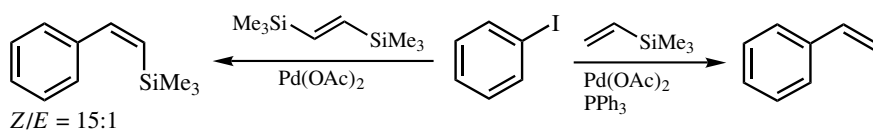
Scheme 19



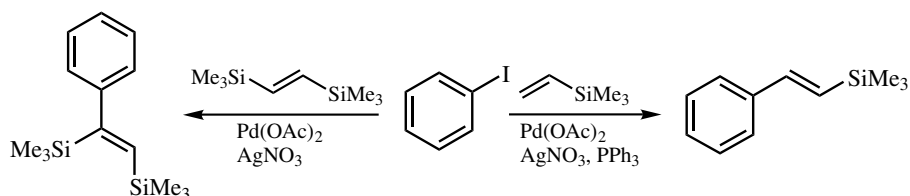
Scheme 20

This Heck vinylation provided both regioisomers and revealed that the deuterium atom is contained in the terminally vinylated compound, while it is lost in the internally vinylated derivative. Frequently, elimination of the heteroatom substituent bonded to the alkene is the predominant process. For example, vinylsilanes are prone to undergo palladium-mediated desilylation. Thus, arylation of vinyltrimethylsilane predominantly affords styrene,^[118] and employing *E*-1,2-bis(trimethylsilyl)ethylene as substrate leads to exclusive formation of the (*Z*)-product as a consequence of *syn* Me₃SiPd elimination (Scheme 21).^{[119],[120]}

This desilylation process is efficiently suppressed by addition of silver salts (Scheme 22).^{[92],[121]}

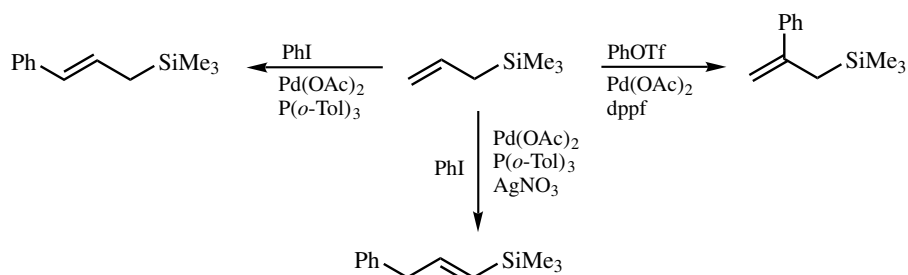


Scheme 21

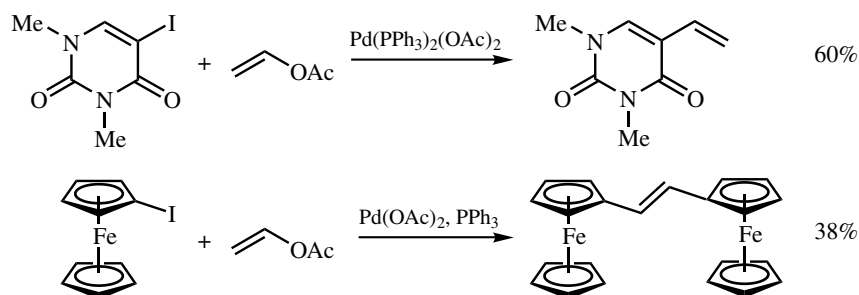


Scheme 22

In the case of arylation of allyltrimethylsilane with iodobenzene, addition of silver nitrate has a dramatic effect on the reaction (**Scheme 23**). The silver addition (i) enhances the reaction rate, (ii) changes the direction of β -hydrogen elimination, and (iii) suppresses competing desilylation.^[91] It is also worth comparing the different regioselectivities obtained with iodobenzene- $P(o\text{-Tol})_3$ (neutral conditions) and phenyl triflate-dppf (cationic conditions, internal/terminal = 95:5) in the arylation step.^[40] In **Scheme 24** two examples are given in which the acetate, as a good leaving group, has been eliminated rather than hydrogen.^{[122],[123]}



Scheme 23



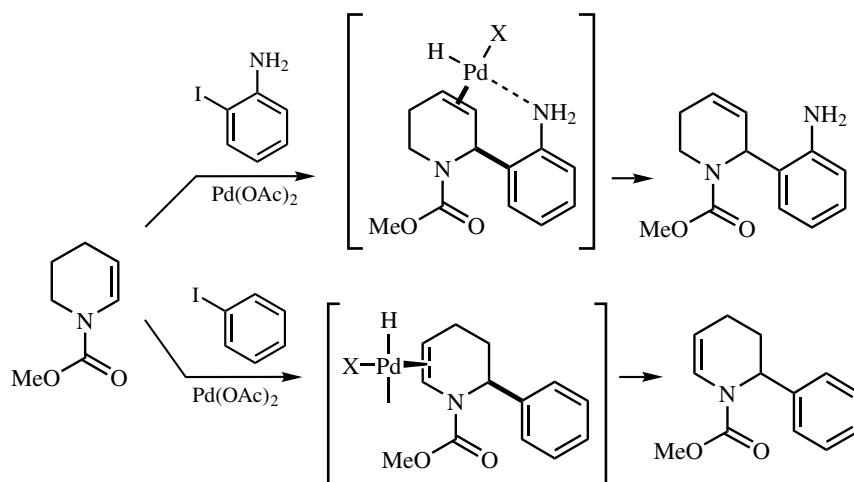
Scheme 24

B.viii. Chelation-Controlled β -Elimination

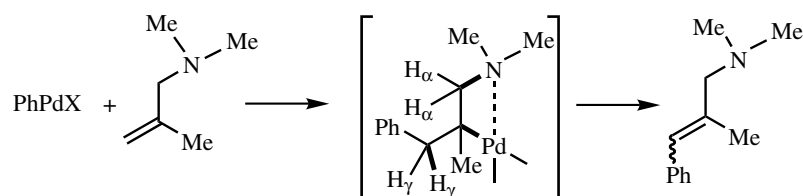
The powerful impact exerted by a chelating group on the insertion process has been demonstrated above (**Sect. B.vi**). Coordinating groups also affect the outcome of the β -elimination step. Thus, arylation of the cyclic enamide with 2-iodoaniline furnishes the allylic derivative, while using iodobenzene as arylating agent leads to double bond isomerization until conjugation with the enamide nitrogen on the opposite side of the ring is achieved (**Scheme 25**).^[124]

The involvement of nitrogen-coordinated intermediates has also been proposed with Pd-catalyzed arylations of tertiary allyl amines.^[125] *Syn* β -elimination of H _{α} PdX (which leads to enamides) is hindered by the chelating nitrogen group, provided the reaction is performed in a nonpolar solvent (**Scheme 26**). The short lifetime of the free hydridopalladium species in the presence of base prevents readdition/isomerization.

Tamaru and colleagues utilized O-substituted allyl alcohols to direct the coupling with aryl iodides, which caused formation of the cinnamyl product with high

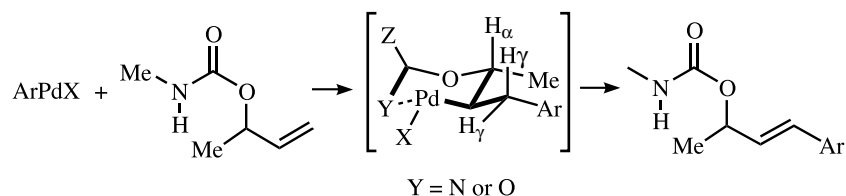


Scheme 25



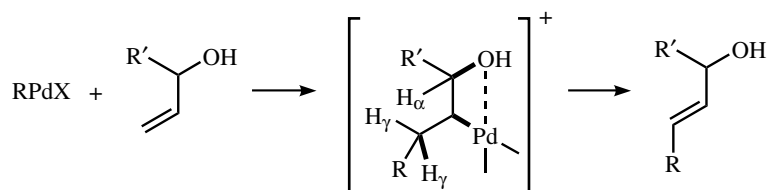
Scheme 26

selectivity.^[126] It is likely that Pd(II) coordinates to the carbamate group in the σ -adduct and that the hydrogen atom (H_α) on the carbamate-bearing carbon is located unfavorably for *syn* β -elimination with Pd(II). Consequently, only the H_γ hydrogens can undergo β -elimination (**Scheme 27**).



Scheme 27

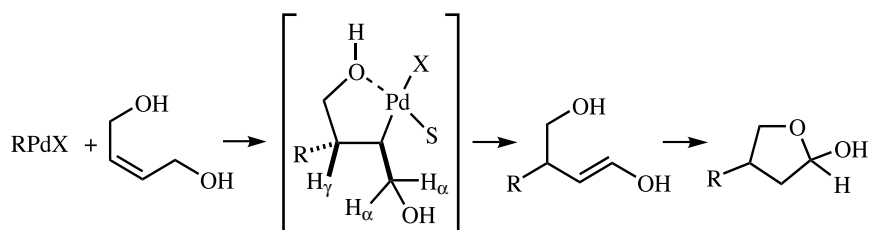
The selective formation of the arylated or vinylated allyl alcohol was rationalized by assuming a cationic four-membered intermediate, in which the hydrogen atom (H_α) on the hydroxyl-bearing carbon is located unfavorably for a *syn* palladium hydride elimination. The cationic intermediates were generated from organic triflates,^[127] iodonium salts,^[128] or organic iodide/thallium or silver salt combinations^[129] (**Scheme 28**).



Scheme 28

Heck reactions of allyl alcohols, with the involvement of neutral intermediates and more strongly coordinating leaving groups, alternatively provided aldehydes or ketones, as a result of H_α β -elimination or double bond migration by hydridopalladium readdition/elimination to give unstable enols (**Sect. B.vii**).

Hydroxyl coordination may also provide a plausible explanation for the very high selectivity observed in the *syn* β -elimination step with the Pd-catalyzed synthesis of β -substituted γ -butyrolactones by vinylation of 2-butene-1,4-diol (**Scheme 29**).^{[130],[131]}

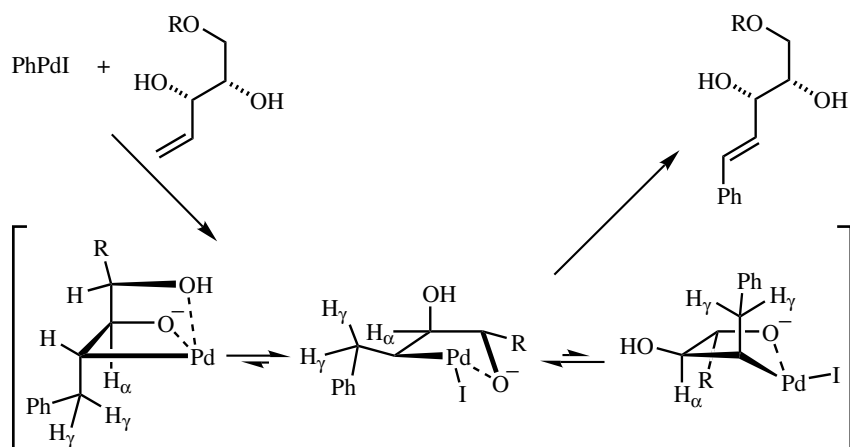


Scheme 29

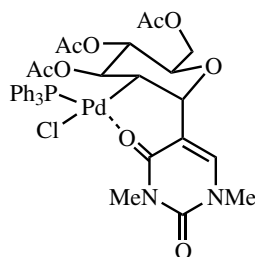
In the absence of phosphine ligands and amines, chelation of the allylic hydroxy group to Pd(II) may yield a five-membered cyclic σ -complex. This chelate ring makes it difficult to achieve the conformation required for elimination of H_γ and preferentially directs the elimination of the hydridopalladium species to give the enol.

Heck arylation of allylic diols, with iodobenzene in the presence of potassium carbonate, resulted in phenyl-substituted diols.^[132] A selective β -hydride elimination in a chelated ring intermediate may be responsible for this outcome (the authors suggest deprotonated σ -intermediates) (**Scheme 30**). Arylation of an allylic substrate lacking the homoallylic hydroxy group under otherwise identical conditions furnished a mixture of products, suggesting that the aforementioned hydroxy group has an impact on the hydride elimination.

Interception of the σ -adduct with an external hydride source, leading to an overall Michael-type addition is a synthetically useful variation of the Heck reaction (see **Sect. IV.2.5**). But there are also examples of σ -intermediates that are relatively stable toward elimination due to chelation. One such intermediate as reported by Cheng and Daves Jr. is shown in **Scheme 31**.^[133] This isolated complex underwent β -elimination of hydrogen, *anti*-alkoxide elimination, and replacement by hydrogen in addition to *anti*-elimination of acetate, depending on the conditions used.



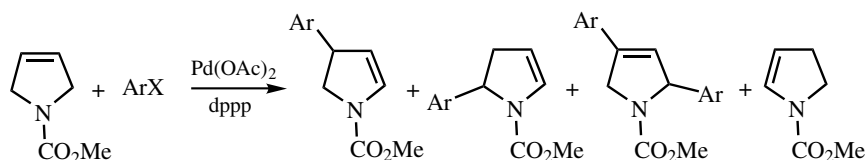
Scheme 30



Scheme 31

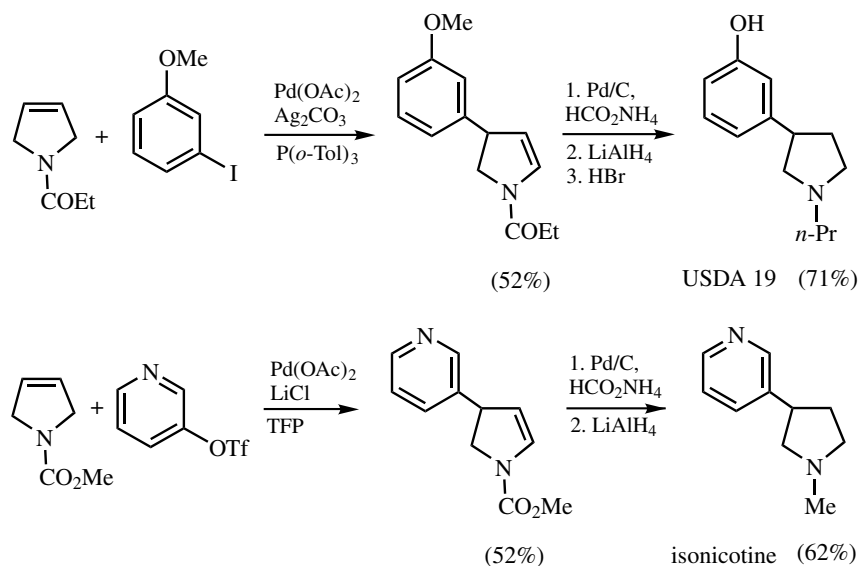
B.ix. Double Bond Migration Prior to Arylation

Palladium is a commonly used catalyst for double bond isomerization.^{[134]–[136]} It is therefore not surprising that double bond isomerization sometimes competes with arylation, in particular, in cases in which alkenes with allylic substituents are subjected to traditional Heck reaction conditions.^[137] The arylation of the cyclic allylamine derivative in **Scheme 32**, which is prone to undergo isomerization, constitutes an illustrative example in which a mixture of compounds is formed.^[138] The alkene undergoes two types of Pd-catalyzed reactions: (i) arylation to provide C-3 arylated derivatives and (ii) competing double bond isomerization. Addition of silver carbonate or thallium acetate fully suppresses this isomerization and good yields of 3-substituted compounds could be obtained. Alternatively, aryl triflates were useful as arylating agents, provided that tri(2-furyl)phosphine (TFP)^[139] was employed as ligand and lithium



Scheme 32

chloride^{[58],[97],[140]} was added to accelerate the C-3 arylation. Two examples are presented in **Scheme 33**.^[138]



Scheme 33

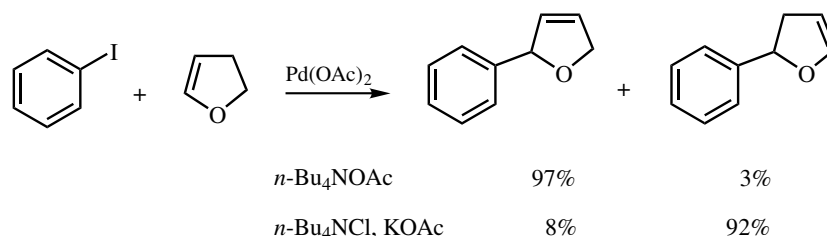
B.x. Tetraalkylammonium Salts, Jeffery Conditions

The introduction of phase transfer catalysts by Jeffery, in the mid-1980s, contributed significantly to extending the scope of the Heck reaction.^{[23],[141],[142]} Thus, arylations of methyl acrylate, vinyl methyl ketone, and acrolein were found to proceed smoothly at room temperature with a combination of tetra-*n*-butylammonium chloride and sodium hydrogencarbonate.^[141] The reaction rate increased linearly with the concentration of the phase transfer catalyst, up to the use of 1 equiv. In the absence of the phase transfer additive, at room temperature, no conversion took place. Since tetraalkylammonium chlorides appear to be more efficient than bromides, which in turn promote the reactions to a greater extent than hydrogensulfates, it is reasonable to assume that the phase transfer catalysts serve as halide donors. Anion exchange by tetraalkylammonium chloride could transform organopalladium iodides or bromides into organopalladium chlorides, thus leading to higher reactivity in the subsequent β -hydride elimination step.^[142] On the other hand, addition of alkali metal halides generally does not exert a significant rate-enhancing effect, suggesting that the tetraalkylammonium salts act as true solid-liquid phase transfer catalysts. Jeffery has demonstrated that water could be a determining factor for the efficiency of quaternary ammonium salts in the Heck coupling.^[142] Thus, while arylation of methyl acrylate in anhydrous acetonitrile with *n*-Bu₄NCl hydrate delivers a 97% yield of methyl cinnamate, the corresponding reaction with dry tetra-*n*-butylammonium chloride as additive provides a poor conversion of 10%.

Jeffery recently stated that tetraalkylammonium salts may have a multiple and complex role in Heck-type reactions.^{[23],[142]} Among all of the elementary steps in the

catalytic cycle that could be affected by tetraalkylammonium salts it is likely that solid–liquid phase transfer could play a very important role in the regeneration of Pd(0) from HPdX, in particular, when inorganic salts serve as bases. Thus, the accelerating effect of the tetraalkylammonium salt can be attributed to the salt assisting in the decomposition of the hydridopalladium species into the zerovalent palladium catalyst.

Furthermore, addition of tetra-*n*-butylammonium chloride improved the selectivity in certain reactions, such as in the arylation of allylic alcohols.^[116] Finally, an appropriate selection of tetraalkylammonium salt-based systems can be used to control the product pattern in certain Heck reactions (**Scheme 34**). In these examples, phase transfer agents have been shown to be an alternative to silver salts in directing the outcome of the reaction.^{[143],[144]}



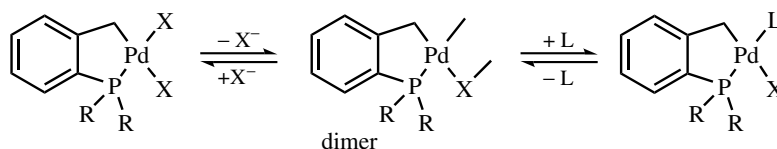
Scheme 34

B.xi. New Catalytic Systems

At higher reaction temperatures $\text{P}(o\text{-Tol})_3$ has often been preferred over PPh_3 , since the more bulky phosphine was assumed to minimize the undesired quaternization of the phosphorus atom by the aryl halide and also results in more stable 14-electron $\text{Pd}(\text{P}(o\text{-Tol})_3)_2$ complexes.^[14] It was discovered that upon reaction of $\text{Pd}(\text{OAc})_2$ with $\text{P}(o\text{-Tol})_3$ a dimeric palladacycle in equilibrium with monomers was formed (**Scheme 35**).^{[37],[145]–[147]}

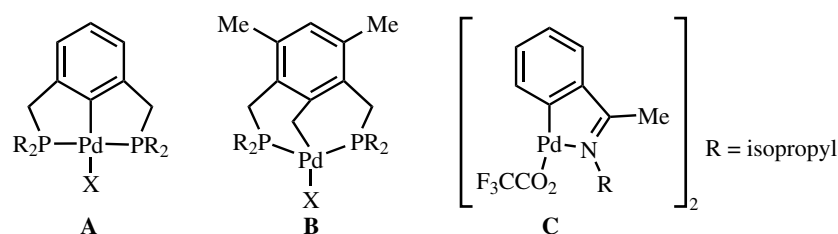
These palladacycles, created by Pd(II)-mediated C—H activation of the *ortho*-methyl group of the phosphine ligand, are excellent catalysts for both triflates and aryl bromides, although nonactivated aryl chlorides react only reluctantly.^{[148]–[150]} No aryl migration or ligand decomposition leading to precipitation of palladium metal occurs at 150 °C.^[37] The isolated pure palladacycle is recommended as a catalyst, since *in situ* preparation from a mixture of $\text{Pd}(\text{OAc})_2$ and $\text{P}(o\text{-Tol})_3$ delivers catalytic species that are less stable.^[149] Dimeric palladacycles are recovered unchanged and can be recycled with little loss of catalytic activity.^[37] Very high turnover numbers were encountered.^{[37],[151]}

In 1997 Milstein and co-workers disclosed a new type of cyclometallated catalysts that exhibited exceptionally high activity in the Heck reaction with aryl iodides and bromides



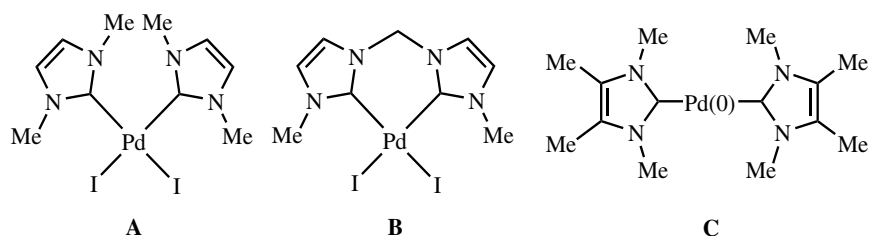
Scheme 35

(**Scheme 36, A and B**).^[152] Turnover numbers up to approximately 500,000 were reported for the reaction of iodobenzene with methyl acrylate and an impressive number (about 100,000) was also achieved with bromobenzene and 4-methoxy-bromobenzene. Characteristic features of these tridentate PCP catalysts are thermal stability and air stability. A competitive experiment, including 4-bromoiodobenzene, iodobenzene, 4-methyliodobenzene, and 4-methoxy-iodobenzene with methyl acrylate provided a linear correlation with Hammett σ -values, which, however, exhibited a low ρ value (1.39).^[152] It was concluded that nucleophilic aromatic substitution is not rate determining, but a subsequent step with different electronic requirements, such as alkene insertion, may account for this observation. Chlorobenzene could not be coupled with these catalyst. Very recently, Milstein's group reported new cyclopalladated, phosphine-free imine complexes as catalysts in the Heck arylation reaction (**Scheme 36, C**).^[153] The new dimeric imine complexes show extremely high activity, leading to more than a million turnovers.



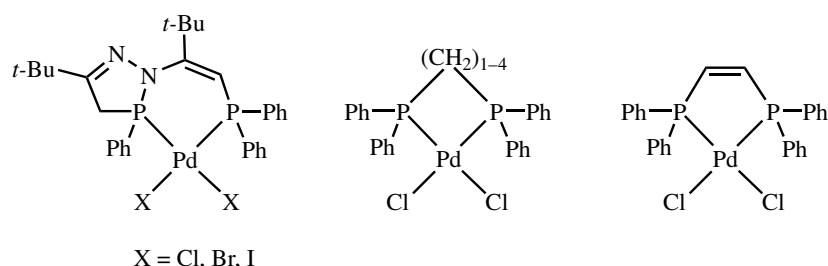
Scheme 36

Carbene-containing palladium complexes such as **A** and **B** in **Scheme 37** have been introduced as suitable catalysts in Heck couplings.^{[154],[155]} These catalysts, characterized by good σ - and π -donor and poor π -acceptor capacity are thermally extraordinarily stable and are not, as compared to phosphines, prone to undergo oxidation.^{[24],[37],[154],[156]} The nonchelating *N*-heterocyclic carbene catalysts **A** appear to be generally more active than the traditional palladium/phosphine systems but less active than the palladacycles.^[24] Mechanistic research by Cavell indicates that the catalytically active species is a 14-electron Pd(0)(carbene)₂ complex of type **C** (**Scheme 37**).^[157] Although these Pd(0)(carbene)₂ complexes may be regarded as having Pd(II) character, they endure oxidative additions typical of Pd(0). Thus, there are similarities to related phosphine complexes such as Pd(0)(PR₃)₂. One clear difference between carbene and phosphine ligands is, however, that carbene ligands are not involved in dissociation equilibria typical for phosphines.^[157]



Scheme 37

It has been reported that chelating diphosphine–palladium(II) dihalides, contrary to previously held views,^{[34],[158]} are outstandingly good catalysts for Heck reactions of aryl halides (**Scheme 38**).^[159] The catalysts are active over the temperature range 50–150 °C, and high yields and turnover numbers were observed. It was not advisable to prepare the active catalyst, [(L-L)PdX₂], *in situ*, since a Magnus-type salt, [M(L-L)₂](MX₄), with very low solubility is proposed to be formed from the diphosphine and the palladium.^[159] Thus, the catalyst should be preformed, and the chelating diphosphine ligand and the palladium species should not be added separately to the reaction medium.

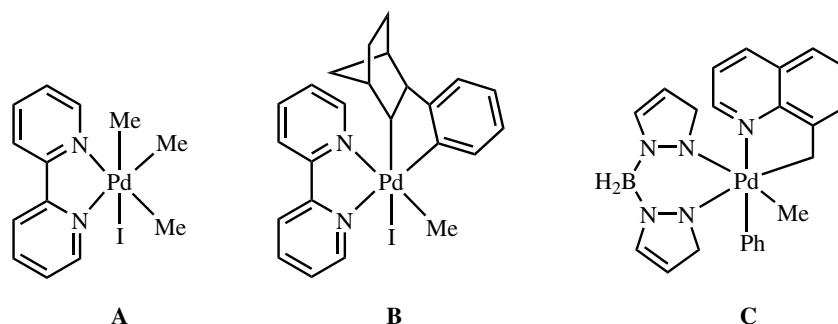


Scheme 38

Other transition metals than palladium have been reported to activate aryl halides for reactions with alkenes [e.g., Ni(0),^[160] Cu(I),^[161] Co(I),^[162] Rh(I) (Wilkinson's catalyst)^[162] and Ir(I) (Vaska's complex)].^[162]

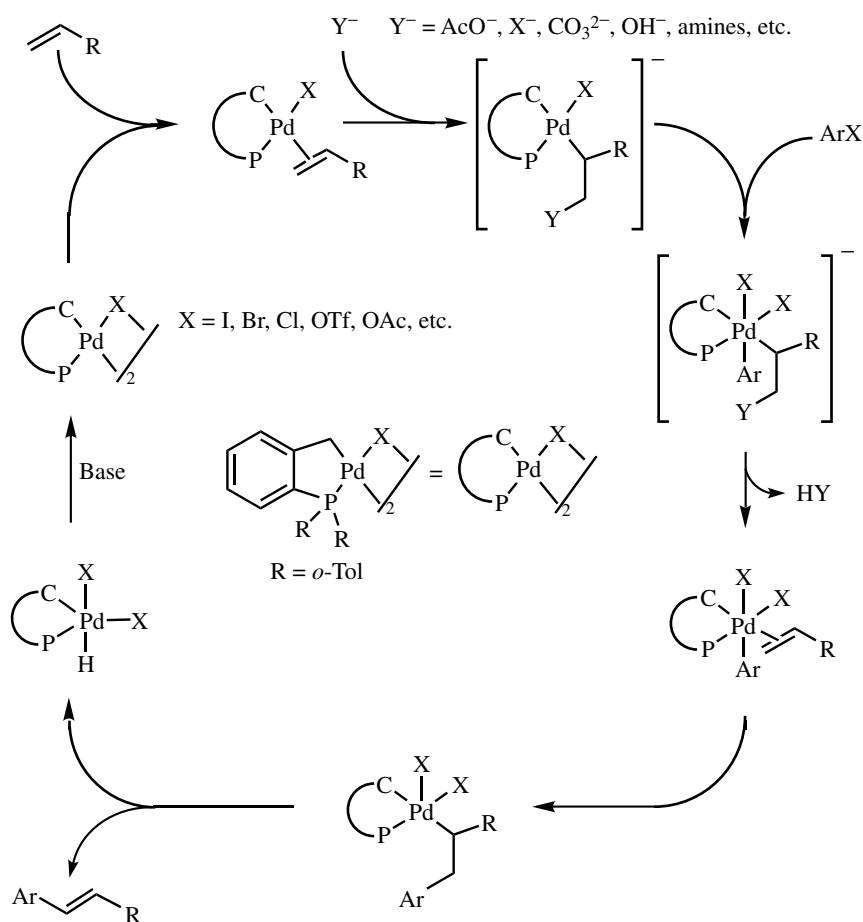
B.xii. Shaw Mechanism: Pd(II) to Pd(IV) Interconversions

The development of recovered palladacycles and related stable palladium(II) catalysts that showed no signs of being reduced to Pd(0) required that alternative mechanisms, other than the classical mechanism, which relies on the Pd(0)/Pd(II) interconversion, had to be considered.^[37] Redox cycling involving Pd(II)/Pd(IV) had to be taken into account. Alkylpalladium(IV) complexes do exist, although they are not very common, and can be formed from reactive aryl halides and Pd(II) complexes encompassing aryl or alkyl groups combined with strongly coordinating *N,N*-bidentate ligands (**Scheme 39**).^{[163],[164]}



Scheme 39

Shaw has proposed a mechanistic rationale that involves Pd(II) and Pd(IV) complexes (**Scheme 40**).^[47] In the first step, the metallacycle is coordinated to the alkene, which becomes susceptible to nucleophilic attack (e.g., by acetate, carbonate, halide, water, or amines) either at the terminal position as depicted in **Scheme 40**, or alternatively at the internal carbon. In this process an electron-rich palladium(II) complex, coordinating two alkyl groups, is created. This Pd(II) complex, as compared to monoalkyl (or aryl) σ -complexes, more readily undergoes oxidative addition with an organic halide, and a Pd(IV) complex is subsequently generated.

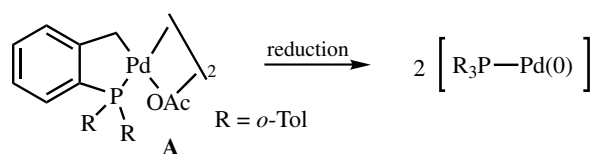


Scheme 40

Regeneration of an alkeneic π -complex is likely to occur smoothly at the high temperatures often employed with the palladacycles. Insertion into the alkene and a β -hydride elimination ultimately delivers the coupled product. The palladacycle is recovered after reaction with a base (e.g., acetate).^[47]

The mechanistic research and discussion concerning the palladacycle systems in Heck reactions is still ongoing. Recent investigations by Beller and Riermeier^[150] and

Herrmann et al.^[37] have indicated that the standard palladacycle *trans*-di(μ -acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]-dipalladium(II) (**A**) might be a catalyst precursor to active palladium(0) complexes (**Scheme 41**). In other words, the palladacycle may act as a thermally stable reservoir for the “real” catalytic species, which is released by heterolytic Pd—C bond cleavage and is activated by subsequent reduction. If this is the actual case a traditional catalytic cycle via Pd(0)/Pd(II) has to be postulated also with palladacycles. In addition, for cross-coupling and amination reactions there is strong evidence for the reduction mechanism of phosphapalladacycle **A** into a Pd(0) species.^{[38],[165]}

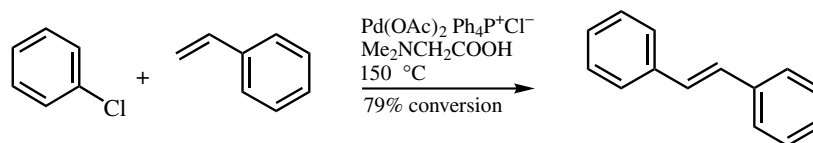


Scheme 41

B.xiii. Aryl Chlorides as Starting Materials

Aryl chlorides are attractive arylpalladium precursors since they are readily available and inexpensive compared to aryl bromides and aryl iodides.^{[166],[167]} In 1973, Julia and co-workers published a successful Heck coupling of styrene with chlorobenzene, catalyzed by palladium on charcoal.^[168] Activity in the area since then has been impressive. During the 1990s a series of Heck reactions with chlorobenzenes and electron-poor aryl chlorides were performed with the new catalytic systems developed, and frequently fair conversions were achieved.^[166] Activated alkenes such as styrene and alkyl acrylates were most often employed. To increase the reaction rates with aryl chlorides, nickel bromide/sodium iodide additives have been employed successfully.^[169] Furthermore, the use of basic ligands, which are anticipated to facilitate oxidative addition, has largely been successful.^{[54],[170]} Littke and Fu very recently devised a protocol that allows conversion of electron-rich aryl chlorides in the Heck reaction (**Table 2**, entry 13).^[171] Thus, Heck reaction of aryl chlorides with styrene or methyl acrylate with $Pd_2(dba)_3/P(t-Bu)_3$ as a catalytic system and with Cs_2CO_3 as a base delivered good yields of isolated products. Contamination as a result of aryl–alkyl exchange between the palladium(II) center and the coordinated phosphine was, as expected with this type of ligand, not encountered. A survey of solvents suggested dioxane to be most suitable. The choice of ligand appeared to be critical for activity, and the bulky, electron-rich $P(t-Bu)_3$ was uniquely effective among the phosphines that were examined.^[171] Thus, $P(n-Bu)_3$, PCy_3 , $Cy_2PCH_2CH_2PCy_2$, dppf, and $P(o-Tol)_3$ all delivered less than 2% yield.

Interestingly, Beller and Zapf have reported that electron-poor phosphites are useful ligands for the coupling of electron-deficient aryl chlorides.^[172] Reetz and co-workers discovered that palladium salts in the presence of tetraphenylphosphonium salts and dimethylglycine constitute a very active and selective catalyst system for the Heck arylation of styrene.^[173] Note that the system is more efficient than the palladacycles for converting nonactivated arylpalladium precursors such as chlorobenzene into products. High yields of coupled products are obtained at 150 °C and only minor amounts of *cis*-stilbene or 1,1-diphenylethene are encountered (**Scheme 42**).



Scheme 42

B.xiv. Novel Reaction Conditions and Heating Techniques

In the mid-1990s, several academic teams started to investigate alternative heating techniques and nonconventional reaction conditions for the Heck reaction. The heating technologies comprised new types of microwave reactors.^{[174]–[176]} The nonclassical reaction conditions included the use of aqueous media at high temperature, solid phase synthesis,^[177] and high-pressure methods. With these methods, reaction rate and productivity potentially could be enhanced, and the developments of at least laboratory-scale environmentally benign Heck reactions could be accelerated.^[178]

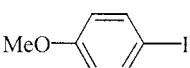
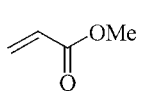
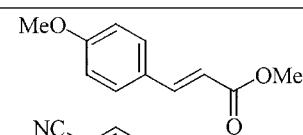
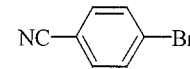
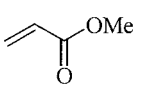
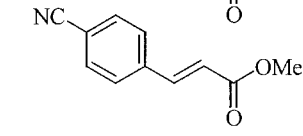
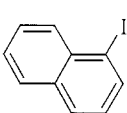

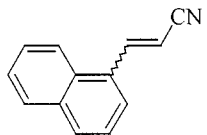
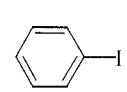
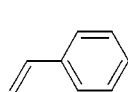
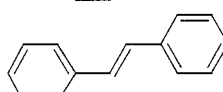
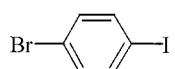
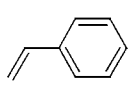
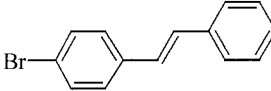
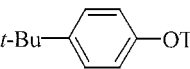
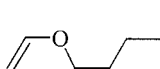
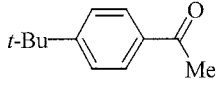
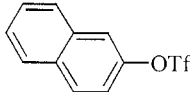
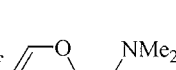
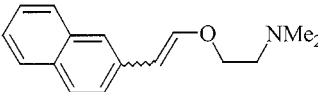
B.xiv.a. Microwave-Heated Heck Reactions. If microwave heating is regarded simply as an equivalent to conventional oven heating, then its importance and potential in organic synthesis is limited. However, the input of microwave energy into a chemical reaction mixture is quite different from conventional thermal heating. Microwaves can heat a reaction mixture very rapidly (flash heating), uniformly, and directly, without any problems of heat transfer through the walls of the reaction vessel (since the vessel is microwave transparent, it will be no hotter than its content).^{[179]–[181]}

Recently, a wide range of organic reactions have been promoted by microwave irradiation,^[182] but in the field of Heck chemistry only a limited number of papers have appeared.^{[38]–[40],[183]–[185]} Two types of microwave heating equipment have been used, a multimode reactor or a monomode reactor.^{[174],[179],[180]} The latter is more expensive but allows the placement of the reaction mixture at a fixed position of much higher continuous electric field strength than can be obtained in a multimode reactor.^[186] This is particularly important with Pd-catalyzed reactions since the reaction mixture must be heated to a high temperature in a reproducible and homogeneous fashion.

The examples in **Table 1** disclose that with an appropriate choice of microwave power and irradiation time, complete conversions and high yields can be obtained in a few minutes.^[38] It is surprising to find that the unstable organometallics, participating in product formation, are compatible with the high reaction temperatures achieved during microwave treatment. In general, the same high chemo- and regioselectivity as experienced in classical heating appears to apply to microwave-promoted Heck reactions.^[38] 4-Bromostilbene was conveniently synthesized in 4.8 min with high chemoselectivity, in full resemblance with the thermal literature procedure,^[187] provided a relatively low microwave power was employed (**Table 1**). Microwave-promoted Pd-catalyzed dppp-controlled arylation of butyl vinyl ether with 4-*tert*-butylphenyl triflate afforded a mixture of the branched arylation product and the corresponding methyl ketone, indicating a highly selective α -arylation.^[34]

Addition of water to the reaction mixture and conduction of the reaction for 2.8 min at 55 W smoothly produced 4-*tert*-butylacetophenone with an isolated yield of 77%. An equally high selectivity for terminal coupling was encountered by application

TABLE 1. Fast Intermolecular Heck Coupling Reactions Under Microwave Irradiation^a

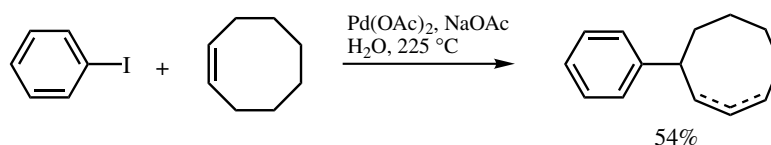
Aryl Halide or Aryl Triflate	Alkene	Time and Microwave Power ^b	Product	Isolated Yield %
		3.8 min 60 W Pd(OAc) ₂ , DMF		70
		3.8 min 60 W Pd(OAc) ₂ , DMF <i>o</i> -(Tol) ₃ P		94
		3.8 min 80 W Pd(OAc) ₂ , DMF		90
		2.8 min 90 W Pd(OAc) ₂ , DMF		87
		4.8 min 60 W Pd(OAc) ₂ , DMF		63
		2.8 min 55 W Pd(OAc) ₂ , dppp DMF, H ₂ O		77
		7.0 min 35 W Pd(OAc) ₂ , Ph ₃ P DMF		87

^aThe microwave reactions were performed on 1.0 mmol scale in sealed Pyrex tubes under nitrogen.^bContinuous irradiation (2450 MHz, monomode reactor Micro Well 10, Personal Chemistry AB).

of low-power microwave heating, permitting the isolation of 87% β -arylated product and corroborating the use of microwave-assisted chelation-controlled Heck reactions (Table 1).^[32] Attempts to shorten the reaction time by increasing the temperature by classical means (warmed up oil baths) were not comparably successful.^[38] Since kinetic investigations into specific microwave effects in homogeneous reactions have disclosed that no “magic” molecular activation occurs, the advantage of microwave heating presumably lies in rapid heating and the relative lack of temperature gradients and wall effects.^[180]

B.xiv.b. High-Temperature Water as Reaction Medium. In order to conduct Heck reactions in pure water, important solubility problems must be overcome. Two different types of modifications can be investigated: either the catalyst/substrates or the reaction environment. First, use of water-soluble phosphine ligands to solubilize the metal catalyst has been investigated extensively, although these ligands are rarely utilized in pure water.^[188] Alternatively, Beletskaya and colleagues in their pioneering

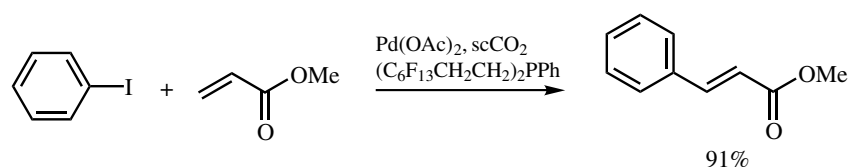
work have carefully matched the properties of the starting materials to the polar aqueous reaction environment.^[189] This methodology, unfortunately, demands hydrophilic starting materials. The second route to perform “truly” aqueous Heck reactions is based on increasing the water solubility of the reacting organic compounds. Importantly, water has a dielectric constant, which decreases from 78 at 25 °C to around 20 at 300 °C, this latter value being comparable with that of acetone at ambient temperature.^[178] Thus, by taking advantage of the change in polarity, water can behave as a “green” pseudo-organic solvent at elevated temperatures. This approach was investigated by Gron and Tinsley in the arylation of different cycloalkanes at 225 °C at 100 bar (**Scheme 43**).^[190]



Scheme 43

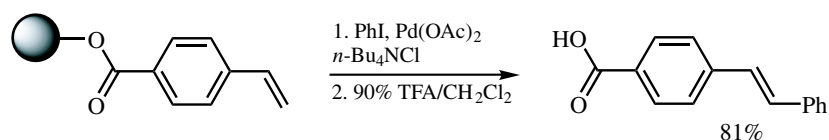
The products were surprisingly similar to those found in typical organic solvents, although the isolated yields were lower (17–54% based on conversion of the iodobenzene). A group at Clemson University have also reported aqueous Heck reactions at 260 °C and in supercritical water at 400 °C.^[191]

Another example of an environmentally benign solvent for Heck chemistry is supercritical carbon dioxide (**Scheme 44**).^{[192],[193]} Undoubtedly, the future need for cleaner chemical processing is great.



Scheme 44

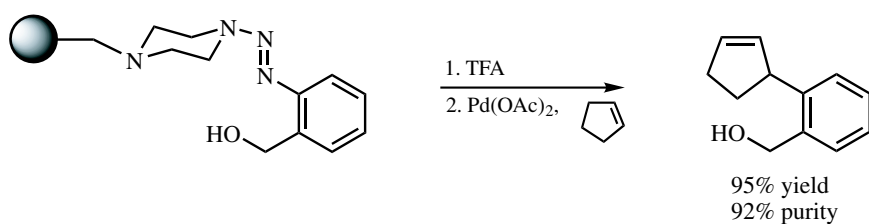
B.xiv.c. Intermolecular Heck Reactions on Polymeric Support. Combinatorial chemistry has initiated a reappraisal and consequent renaissance in synthesis of compounds attached to polymeric supports.^[194] Therefore, it comes as no surprise that Pd-catalyzed reactions are among the most widely explored reactions for the generation of combinatorial libraries on solid phase. The first example of the intermolecular Heck reaction on solid phase was reported in 1994.^[195] In this article, 4-vinylbenzoic acid was attached to Wang resin and coupled with aryl halides/triflates under catalysis with Pd(OAc)₂ (**Scheme 45**). Similar



Scheme 45

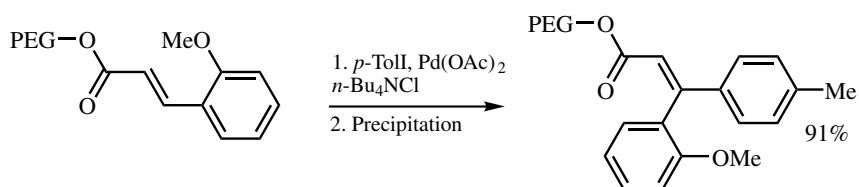
methodologies have thereafter been devised by other research groups and the scope of this chemistry is now approaching the current range of solution Heck chemistry, although naturally the number of examples is still limited.^{[196]–[198]}

Bräse and Schroen very recently developed a new cleavage–Heck coupling strategy for combinatorial applications (**Scheme 46**).^[199] Starting from Merrifield resin, an immobilized triazene was prepared in three steps. Acidic release of the diazonium compound and subsequent Pd-catalyzed *in situ* coupling with different alkenes furnished, after filtration and evaporation, the products in high purity and yield.



Scheme 46

Although highly successful, solid phase synthesis still has several shortcomings due to the nature of the heterogeneous reaction conditions. These problems in solid phase Heck couplings are now being addressed elegantly by the use of solution chemistry with selectively soluble polymers.^[200] Almost quantitative arylation, and excellent stereoselectivity, of the polyethylene glycol-bound (mPEG 5000-bound) 3-substituted acrylic acid was accomplished after purification by the ether precipitation method (**Scheme 47**).^[201] This methodology essentially avoids the difficulties of solid phase synthesis while preserving its positive aspects (easy purification and the possibility of using a large excess of a reagent).



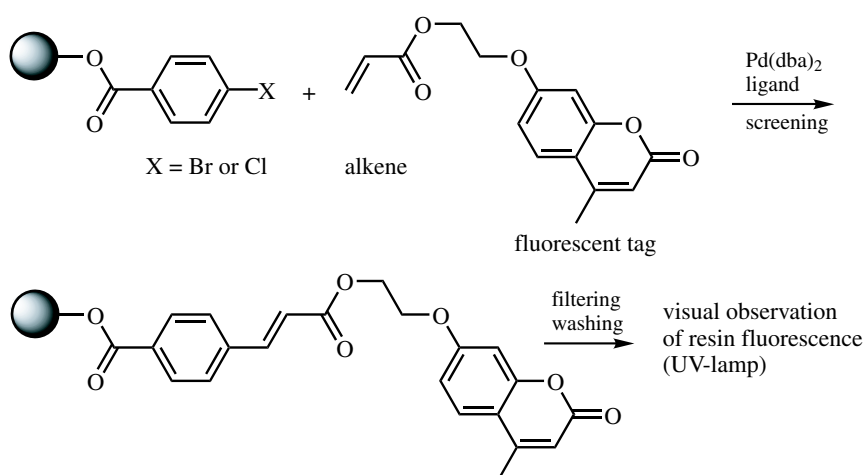
Scheme 47

In another series of Heck experiments, PEG was proposed to act as a solid–liquid phase transfer additive.^[202] The enhanced reaction rate was explained by a PEG-mediated solvation of the potassium cation (to transfer the insoluble inorganic base potassium carbonate to the acetonitrile solvent).

Much of the reported solid phase organic chemistry has so far described the synthesis of combinatorial libraries. But it should be remembered that the fundamentals of combinatorial chemistry apply also to other applications.

Recently, a fluorescence-based assay for high-throughput screening of a Heck reaction was described (**Scheme 48**).^[203] The assay involves coupling of an electron-deficient alkene, containing a tethered fluorophore, with an aryl halide attached to a Wang resin. A

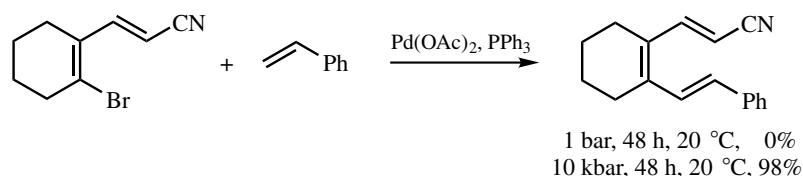
successful coupling process was identified by the fluorescence of the polymeric support. To evaluate the screening assay, a set of readily available monodentate phosphines was utilized. Comparison of the results from the assay with results from a series of solution phase reactions showed that the fluorescence-based technique accurately selected the most active ligands for the Heck coupling with aryl bromides $[P(t\text{-Bu})_3]$ and chlorides $[(t\text{-Bu})_2\text{PFc}]$. By employing this method, or analogous strategies, considerable time could be saved in optimizing reaction conditions.^[203]



Scheme 48

B.xiv.d. High-Pressure Conditions. A wide range of liquid phase organic reactions have been reported to be promoted under high pressure.^[204] Pressure can be expected to cause a rate enhancement when the activation volume, that is, the difference of the volume of the transition state and the starting materials, is less than zero. This can easily be understood to be the case in addition reactions. However, a Pd-catalyzed Heck process consists of a number of reaction steps and, consequently, to predict the net effect of pressure in such a reaction is much more difficult.^[205] Nevertheless, rate enhancements and increased lifetime of the catalyst have been reported.

According to the studies of de Meijere and colleagues (**Scheme 49**)^[206] and Sugihara et al.,^[207] high pressure can considerably increase the rate of typical Heck reactions under very mild conditions. Furthermore, de Meijere and Bräse recently discovered that the reaction rates of aryl bromides depend more strongly on the pressure than those of aryl iodides and hence can efficiently be accelerated by increased pressure.^[208] Interestingly,



Scheme 49

Sugihara and co-workers observed suppression of β -elimination at high pressure.^[207] In yet another investigation, the Pd-catalyzed arylation of 2,3-dihydrofuran, high pressure was found to greatly increase the lifetime of the catalyst.^[209] A logical extension of the Heck functionalization of 2,3-dihydrofuran was to carry out a more detailed kinetic study of this pressurized reaction. From this study, the activation volume in the reaction was determined to be negative ($-12 \pm 2 \text{ cm}^{-3}$), indicating the benefits of pressure in transition metal-catalyzed reactions.^[205]

C. SCOPE OF THE INTERMOLECULAR HECK REACTION

C.i. Arylation of Electron-Deficient Alkenes

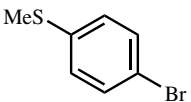
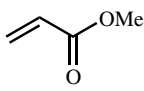
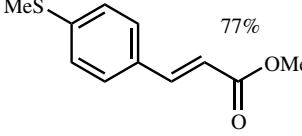
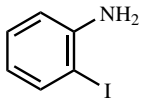
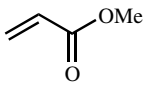
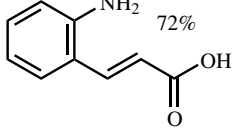
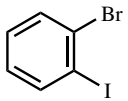
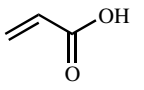
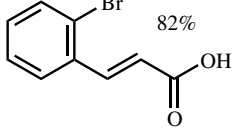
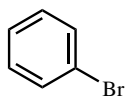
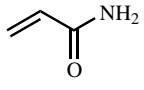
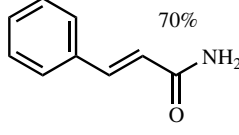
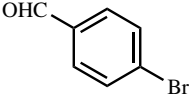
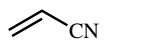
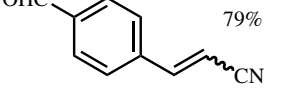
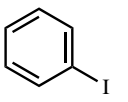
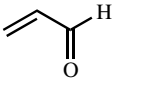
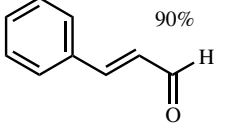
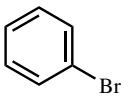
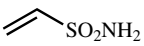
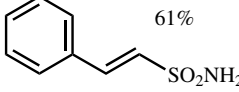
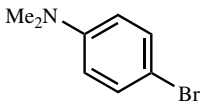
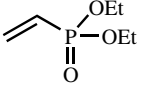
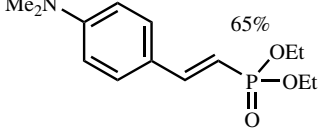
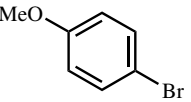
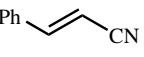
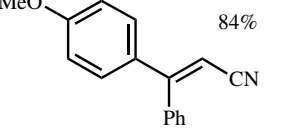
The order of reactivity of the alkenes is monosubstituted > disubstituted >> tri- and tetrasubstituted.^{[14],[22]} Tri- and tetrasubstituted alkenes do not normally undergo intermolecular arylations. The product pattern after arylations of 1,2-disubstituted alkenes is governed by both steric and electronic factors. Arylation of alkenes with one electron-withdrawing group is the most common Heck reaction. The reaction delivers β -arylated products often in high yields. The (*E*)-isomers are most often formed but with some alkenes, for example, acrylonitrile, mixtures of the (*E*)- and (*Z*)-isomers are obtained.

In **Table 2** several examples are given. The examples are selected to illustrate the scope of the reaction with focus on the variety of arylpalladium precursors and the catalytic systems that can be employed. Virtually all functional groups are tolerated. *p*-Methylthiobromobenzene, for example, provides a yield of 77%, entry 1,^[210] of coupled product (*p*-Cl, 93%; *p*-NH₂, 73%; *p*-Me₂N, 80%; *p*-AcNH, 83%, *p*-NO₂, 73%; *p*-CN, 98%; *p*-OMe, 54%; *p*-CHO, 72%; *p*-OH, 98%; *p*-CO₂Me, 81%; H, 88%)^[22] but high yields are also achieved with most *ortho*-substituted bromobenzenes, such as with 2-aminoiodobenzene, which affords the corresponding cinnamic acid in 72% yield, entry 2^[211] (*o*-NO₂, 83%; *o*-OH, 24%; *o*-CHO, 28%; *o*-COMe, 89%; *o*-OAc, 66%; *o*-CO₂Me, 69%).^[22] High yields and a highly regioselective β -arylation are achieved in reactions of aryl halides with acrylic acid,^[187] acrylamides,^[210] acrylonitrile,^[212] α,β -unsaturated carbonyl compounds,^[141] sulfonamides,^[213] and vinylphosphonates,^[214] and with 1,2-disubstituted alkenes^[215] as depicted in entries 3–9. The reactions are preferentially performed in polar nonprotic solvents such as acetonitrile or DMF, and frequently under phase transfer conditions. Thus, acrolein, an example of an easily polymerizable substrate, can be arylated at room temperature in the presence of sodium hydrogencarbonate or potassium carbonate and tetra-*n*-butylammonium chloride (entry 6).

The Heck reaction is compatible with water, and water-soluble catalysts have successfully been employed (entry 10).^[188] Alkali metal salts (NaHCO₃, K₂CO₃, and KOAc) are effective bases in the smooth reactions of acrylic acid with *o*-, *m*-, or *p*-iodobenzoic acid or *p*-iodophenol in which water-soluble salts are formed and very high yields are encountered (entry 11).^[189] Activated heteroaryl chlorides are good arylpalladium precursors (entry 12) while nonactivated aryl chlorides have to date been considered to be less useful in the Heck reaction.^[216] In entry 13, the recent protocol devised by Littke and Fu for arylation with nonactivated chlorobenzenes is shown.^[171]

Aryl triflates are suitable arylating agents and, in particular, in the presence of chloride ions.^[85] The fact that aryl triflates and other aryl fluoroalkanesulfonates readily take part

TABLE 2. Intermolecular Heck Coupling Reactions

Entry	Organic Halide or Pseudohalide	Alkene	Reaction Conditions	Product
1			$\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-Tol})_3$, Et_3N , 125 °C, 72 h	 77%
2			$\text{Pd}(\text{OAc})_2$, Et_3N , 100 °C, 80 h	 72%
3			$\text{Pd}(\text{OAc})_2$, Et_3N , 100 °C, 1 h MeCN	 82%
4			$\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-Tol})_3$, Et_3N , 100 °C, 1 h MeCN	 70%
5			$\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-Tol})_3$, NaOAc , 130 °C, 24 h MeCN	 79%
6			$\text{Pd}(\text{OAc})_2$, $n\text{-Bu}_4\text{NCl}$, NaHCO_3 , 20 °C, 60 h DMF	 90%
7			$\text{Pd}(\text{OAc})_2$, PPh_3 , Et_3N , 140 °C, 24 h DMF	 61%
8			$\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-Tol})_3$, Et_3N , 100 °C, 6 h MeCN	 65%
9			$\text{Pd}(\text{OAc})_2$, $n\text{-Bu}_4\text{NBr}$, KOAc , 80 °C, 72 h DMF	 84%

(Continued)

TABLE 2. (Continued)

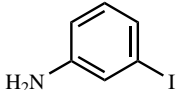
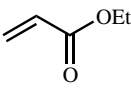
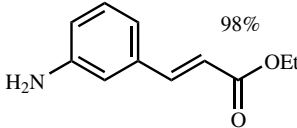
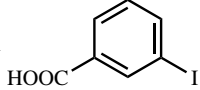
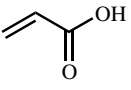
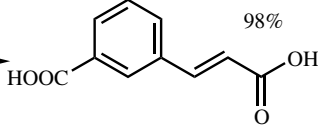
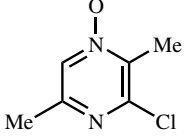
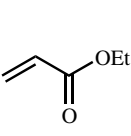
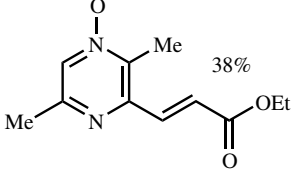
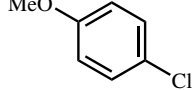
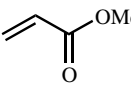
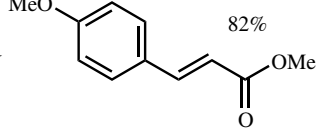
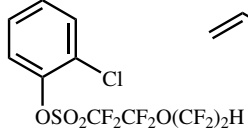
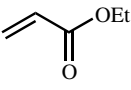
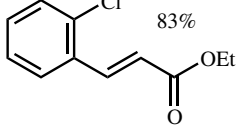
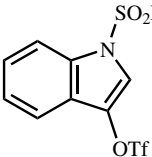

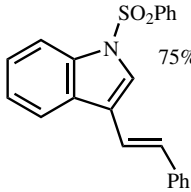
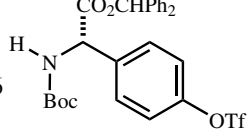
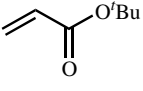
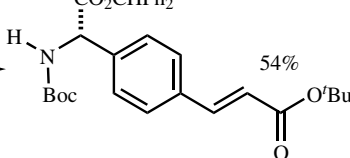
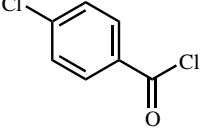
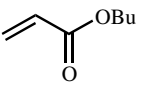
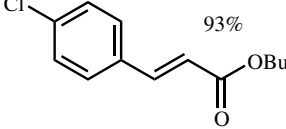
Entry	Organic Halide or Pseudohalide	Alkene	Reaction Conditions	Product
10			$\text{Pd}(\text{OAc})_2$, TPPTS Et_3N , 37 °C, 10 h, MeCN/H ₂ O TPPTS = $\text{P}(m\text{-PhSO}_3\text{Na})_3$	 98%
11			$\text{Pd}(\text{OAc})_2$, K_2CO_3 KOAc, 50 °C, 1 h H ₂ O	 98%
12			$\text{Pd}(\text{PPh}_3)_4$, KOAc 130–140 °C, 15 h DMA	 38%
13			$\text{Pd}_2(\text{dba})_3$, $\text{P}(t\text{-Bu})_3$ Cs_2CO_3 , 120 °C, 24 h dioxane	 82%
14			$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, Et_3N , 90 °C, 72 h, 13 DMF	 83%
15			$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ $i\text{-Pr}_2\text{NEt}$, 80 °C DMF	 75%
16			$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, Et_3N 90 °C, 24 h DMF	 54%
17			$\text{PdCl}_2(\text{PhCN})_2$, K_2CO_3 $\text{Bzl}(\text{Oct})_3\text{NCl}$, 140 °C, 4 h, <i>m</i> -xylene	 93%

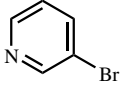
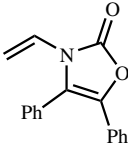
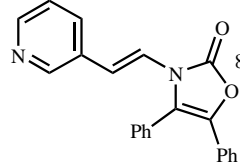
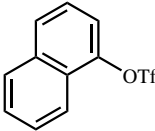
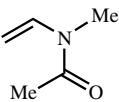
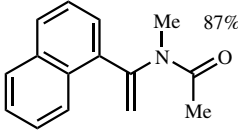
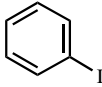
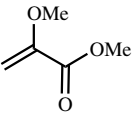
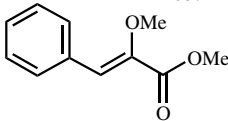
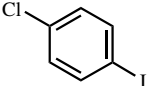
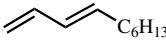
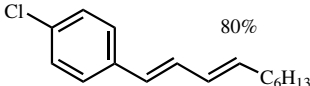
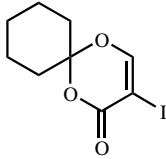
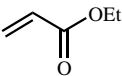
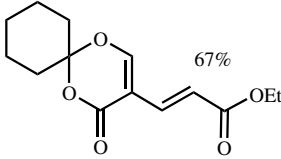
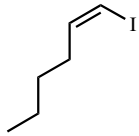

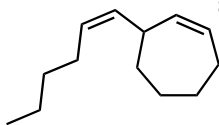
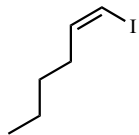
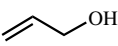
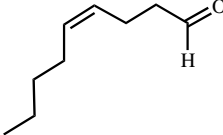
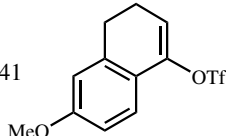
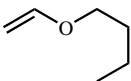
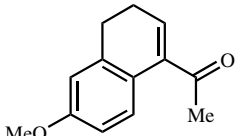
TABLE 2. (Continued)

Entry	Organic Halide or Pseudohalide	Alkene	Reaction Conditions	Product
18			$\text{PdCl}_2(\text{PhCN})_2$, K_2CO_3 $\text{Bzl}(\text{Oct})_3\text{NCl}$, 140°C 4 h, <i>m</i> -xylene	 89%
19			$\text{Pd}(\text{dba})_2$, NaOAc r.t., 2 h MeCN	 96%
20			$\text{Pd}(\text{dba})_2$, <i>t</i> -BuONO 140°C , 0.5 h AcOH	 79%
21	$(\text{PhCO})_2\text{O}$		PdCl_2 , NaBr 160°C , 1.5 h NMP	 77%
22			$\text{Pd}(\text{dppf})\text{Cl}_2$, <i>n</i> -Bu ₄ NI Et_3N , 40°C , ~16 h DMF/H ₂ O	 60%
23			$\text{Pd}(\text{OAc})_2$, PPh_3 CsCO_3 , 60°C , 21 h DMF	 47%
24			$\text{Pd}(\text{OAc})_2$, <i>n</i> -Bu ₄ NBr K_2CO_3 , 100°C , 7 h DMF	 56%
25			$\text{Pd}(\text{OAc})_2$, <i>n</i> -Bu ₄ NCl NaHCO_3 , 85°C , 16 h DMF	 52% (Continued)

TABLE 2. (Continued)

Entry	Organic Halide or Pseudohalide	Alkene	Reaction Conditions	Product
26			$\text{Pd}(\text{OAc})_2$ 80 °C EtOH	
27			$\text{Pd}(\text{OAc})_2$, NaHCO_3 $n\text{-Bu}_4\text{NCl}$, 100 °C DMF	 55%
28			$\text{Pd}(\text{OAc})_2$, $n\text{-Bu}_4\text{NCl}$ NaHCO_3 DMF	 36%
29			$\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-Tol})_3$ Et_3N , 100 °C, 18 h MeCN	 95%
30			$\text{Pd}(\text{PPh}_3)_2(\text{OAc})_2$ Et_3N , 100 °C, 3 h	 63%
31			1. $\text{Pd}(\text{OAc})_2$, dppp Et_3N , 80 °C, 0.5 h, DMF 2. HCl	 97%
32			1. $\text{Pd}(\text{OAc})_2$, dppp Et_3N , 80 °C, 24 h DMF 2. HAc	 76%
33			$\text{Pd}(\text{OAc})_2$, Et_3N 60 °C, 18 h	 69%
34			$\text{Pd}(\text{OAc})_2$, PPh_3 $i\text{-Pr}_2\text{NEt}$, 100 °C 16 h	 66%

TABLE 2. (Continued)

Entry	Organic Halide or Pseudohalide	Alkene	Reaction Conditions	Product
34			$\text{Pd}(\text{OAc})_2$, <i>n</i> -Bu ₄ NCl NaHCO ₃ , 120 °C, 24 h DMF	 89%
35			$\text{Pd}(\text{OAc})_2$, dppp Et ₃ N, 100 °C, 7 h DMF	 87%
36			$\text{Pd}(\text{OAc})_2$, <i>n</i> -Bu ₄ NCl NaHCO ₃ , 80 °C, 24 h MeCN	 68%
37			$\text{Pd}(\text{OAc})_2$, PPh ₃ TIOAc, 70 °C, ~16 h DMF	 80%
38			$\text{Pd}(\text{OAc})_2$, <i>n</i> -Bu ₄ NCl NaHCO ₃ , 60 °C DMF	 67%
39			$\text{Pd}(\text{OAc})_2$, PPh ₃ Ag ₂ CO ₃ , 80 °C, 24 h MeCN	 81%
40			$\text{Pd}(\text{OAc})_2$, <i>n</i> -Bu ₄ NHSO ₄ Ag ₂ CO ₃ , 70 °C, 24 h MeCN	 54%
41			1. $\text{Pd}(\text{OAc})_2$, Et ₃ N 65 °C, 3 h, DMSO 2. H ⁺	 48%

(Continued)

TABLE 2. (Continued)

Entry	Organic Halide or Pseudohalide	Alkene	Reaction Conditions	Product
42			$\text{Pd}(\text{OAc})_2$, <i>n</i> -Bu ₄ NOTf K ₂ CO ₃ , 55 °C, ~16 h DMF	 80%
43			$\text{Pd}(\text{OAc})_2$, NEt ₃ 80 °C, 1.5 h DMSO	 72%
44			$\text{Pd}(\text{OAc})_2$, NEt ₃ 80 °C, 1.5 h DMSO	 42%
45			$\text{Pd}(\text{OAc})_2$, K ₂ CO ₃ KOAc, 80 °C, 4 h DMF	 62%
46			1. C ₄ F ₉ SO ₂ F, <i>n</i> -Bu ₄ NF r.t., 16 h, THF 2. $\text{Pd}(\text{OAc})_2$, K ₂ CO ₃ KOAc, DMF, 85 °C, 1.5 h	 39%
47			$\text{Pd}(\text{OAc})_2$, NaHCO ₃ r.t., 2 h DMF	 73%
48			$\text{Pd}(\text{OAc})_2$, <i>n</i> -Bu ₄ NCl K ₂ CO ₃ , 20 °C, 6 h DMF	 54%
49			CuBr, K ₂ CO ₃ , NMP 150 °C, 24 h	 75%

in the Heck reaction has extended the scope of the reaction considerably (entries 14–16).^{[217]–[219]} There are a large number of phenols available that can be converted to triflates readily.

Although aryl halides and triflates are the most commonly used arylating agents, there are successful examples where both aryl chlorides^[220] and arylsulfonyl chlorides^[221] have been employed. Pd-catalyzed decarbonylations and desulfonylations and subsequent Heck couplings are often conducted with trialkylamines such as *N*-ethylmorpholine as a base, but improved yields are reported in cases in which the tertiary amine is replaced by a mixture of potassium carbonate and benzyltriethylammonium chloride. In **Table 2** two examples are given (entries 17 and 18).^[222]

Aryl halides are frequently prepared from the corresponding aryl diazonium salts by diazotation procedures. However, diazonium salts can be subjected directly to very mild Heck arylation conditions, which deliver coupled products (entry 19).^[223] Preferably, the reaction is executed in nonaqueous solvents such as acetonitrile, acetone, or methylene chloride with sodium acetate as base and with palladiumbis(dibenzylideneacetone) as catalyst. Alternatively, a combination of the amine and *t*-butyl nitrite, in a mixture of acetic acid and monochloroacetic acid, can provide the desired product directly, which makes the isolation of a diazonium salt unnecessary (entry 20).^[224] It is also possible to use aromatic acid anhydrides as oxidative addition precursors (entry 21).^[225] Clearly, anhydrides are very interesting starting materials for a number of Heck reactions due to price and absence of halide salt formation.

An example of a Heck reaction conducted with an activated alkene on a solid phase is depicted in entry 22 (**Table 2**).^[197] The arylating agent is attached to the resin by an ester linkage and very good yields are achieved in this reaction. Recently, Miura and co-workers reported their interesting observation that arylation of 2-substituted 2-alkenals and 3-substituted 2-cyclohexen- and 2-cyclopenten-1-ones proceeds at their ρ -position and not at the β -position as could be expected (entry 23).^[226] The Jeffery conditions have allowed for successful use of polyhalogenated arylating agents. Thus, arylation of styrene with 1,2,3-tribromobenzene delivers a 56% yield of tristyrylbenzene (entry 24).^[227] A selective twofold coupling of 4-bromoiodobenzene with 2-amidoacrylates is depicted in entry 25.^[228] The high reactivity of aryl diazonium salts is reflected in entry 26, where two consecutive selective Heck reactions have been accomplished.^[229]

C.ii. Arylation of Electron-Rich Alkenes

Heck reactions with allylic derivatives as substrates are presented in entries 27^[230] and 28.^[231] In the absence of Tl(I) or Ag(I) salts and under Jeffery conditions, arylation of allylic alcohols provides a useful highly regioselective direct route to arylethyl ketones.^[230]

Electron-rich alkenes are more prone to be attacked at the most electron-deficient carbon.^[29] Thus, Arai and Daves Jr. have demonstrated that cyclic vinyl ethers are attacked exclusively at the carbon adjacent to the oxygen atom (entry 29).^[106] As discussed earlier (**Sect. B.vi**), methods that result in regiocontrolled arylations of acyclic vinyl ethers have been developed, and a series of representative examples are given in entries 30–33. Heck arylation of methyl vinyl ether with 4-iodoanisole gives a fair yield of 4-acetylanisole but an electron-donating group was required for preparatively useful α -arylations to occur.^[29] The employment of bidentate ligands constituted a significant improvement with an exclusive internal arylation as a result (entry 30).^[33] Arylation of

an alkene with a palladium coordinating nitrogen atom in the presence of a bidentate ligand leads to internal arylation but in the absence of this ligand, terminal attack occurs as discussed in **Scheme 13**.^[32] Protected acetals are obtained in cases in which the chelating nitrogen is substituted with a hydroxyl group as depicted in entry 31.^[232] Aryl chlorides are generally good arylpalladium chloride precursors, but under certain conditions the migratory decarbonylation can be suppressed, and procedures that allow a very regioselective formation of semimasked 1,3-dicarbonyl compounds have been developed (entry 32).^[233]

The first example of a Heck arylation of a free enol is shown in entry 33.^[39] Enamides are suitable substrates in the Heck reaction and the regioselectivity depends on both electronic and steric factors. Terminal attack is observed both with vinylphthalimide and the cyclic carbamate in entry 34 (**Table 2**).^[234] As with the vinyl ethers, bidentate ligands can be utilized to afford a highly regioselective internal arylation (entry 35).^[35] Enol ethers of arylpyruvates can be prepared smoothly by terminal arylation of methyl π -methoxyacrylate under Jeffery conditions, entry 36.^[235] Entry 37 provides an example of arylation of a diene, which affords a good yield of the terminally arylated diene.^[236]

C.iii. Vinylation of Alkenes

Vinyl halides and triflates serve as good vinyllating agents (entries 38–48). Vinylation occurs in the β -position of electron-deficient alkenes, as in the case of the arylation reactions, and the same reaction profiles including double bond migrations are encountered (entries 38–40).^{[94],[95],[237]} However, the vinylation of electron-rich alkenes such as vinyl ethers tends to furnish considerably higher α -selectivity than that observed with corresponding arylation reactions under similar conditions (entry 41).^[238] In 1996, Crisp and Gebauer reported Heck couplings between protected 2-aminobut-3-en-1-ols and cyclohexenyl triflate.^[239] The reactions were carried out utilizing a “ligand-free” palladium catalyst, potassium carbonate, water, and tetra-*n*-butylammonium triflate (entry 42). The utility of vinyl triflates as starting materials is further substantiated by the reaction of 1-[(trimethylsilyl)ethynyl]-2,2-dimethylethenyl triflate with trimethylvinylsilane in entry 43 (**Table 2**).^[117]

Heck-type reactions with enol carboxylates (e.g., vinyl acetate) are generally complex. Most common are reactions in which vinyl acetate is employed as an ethylene equivalent (see **Scheme 24**). However, an example of a preparatively useful reaction with an intact acetate function is given in entry 44.^[240] The reaction of vinyl triflates with vinyl phosphonates affords the corresponding conjugate dienylphosphonates (entry 45).^[241] A new access to reactive nonaflates via a one-pot nonaflation–Heck reaction was recently reported (entry 46).^[242] This reaction sequence starts from silyl enol ethers and provides functionalized 1,3-dienes in a simple manner. Iodonium salts can be used as R_Pd precursors (entry 47).^[243] It is notable that the palladium(0) insertion preferentially occurs inbetween the iodonium ion and the vinylic, rather than the aryl sp²-hybridized carbon (entry 47). Some years ago, Jeffery used acetylenic halides to achieve (*E*)-enynoates and (*E*)-enynones in fair yields at room temperature (entry 48).^[244]

In recent years there have been a number of reports on the use of nonpalladium catalysts in the Heck-type reaction. An example of a Cu-catalyzed arylation of methyl acrylate is presented in entry 49.^[161]

D. SUMMARY

The strength and growing popularity of the Heck reaction are attributed primarily to the high generality of the reaction, the extreme tolerance of various functional groups, and the simplicity of the experimental procedures—attributes already recognized by Heck in the early 1970s. Today, numerous intermolecular chemoselective, regioselective, and stereoselective (to be discussed elsewhere) reactions can be accomplished successfully. Procedures for oligofold and multiple couplings have been devised. The proposed mechanism outlined by Heck is to a large extent still valid 30 years after the discovery of the reaction, but with regard to the individual organometallic transformation steps, there is much more to be learned. However, interest in the reaction among chemists devoted to detailed mechanistic studies will provide new insights and ensure that new attractive synthetic chemistry will be developed.

In the next ten years, fine-tuning of reaction conditions and catalytic systems, aided by a better mechanistic understanding, will extend the scope of the reaction further. It is foreseen by the authors that carefully designed protocols will be available, which enable prediction of the synthetic outcome from any combination of reactants, prior to synthesis.

At present there are relatively few industrial processes relying on the Heck reaction as key steps. The fast development in recent years of new catalysts with very high turnover numbers and the ongoing intense research activity aimed at finding new efficient catalytic systems will probably result in a larger number of large-scale industrial processes in the future. Heck reactions performed in water, frequently under high pressure, will be seen and new heating techniques e.g., focused microwave irradiation) will provide dramatic shortening of reaction times. The robust Heck reaction will be established further as a major carbon–carbon bond-forming reaction in combinatorial chemistry in solution and on solid support.

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