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Palladium-Catalysed Cross-Coupling and Related Processes: Some Interesting Observations That Have Been Exploited in Synthetic Chemistry

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Palladium-catalysed cross-coupling reactions are routinely used in the synthesis of important organic and organometallic compounds, including advanced materials and natural products. Industry and academia depend heavily on these ubiquitous transformations. Their success is quite remarkable, but not without their share of problematic and sometimes unusual observations, which continue to probe our fundamental understanding of these reactions. Through an identification of side-reactions, our train of thought of a well-known reaction can be challenged. In this review we identify exemplary processes and show how they have been exploited in synthetic chemistry. A deeper insight into well-established processes is provided, which alerts us to new synthetic transformations. On one hand, it is of significant interest to understand how to minimise unwanted reactions and their side-products, but on the other, one can seek to exploit such reaction pathways and develop new synthetic methodologies. Either way, synthetic chemists only stand to benefit from such findings, which, more often than not, stimulate further research into this ever-expanding field.

Introduction

Carbon–carbon bond formation by activation of a C–X bond is one of the most important transformations in synthetic organic chemistry.[1–6] Amongst the transition metals,palladium is without question most commonly utilised. Named reactions such as Kumada, Heck, Hiyama, Negishi, Suzuki/Miyaura, Stille, Sonogashira and others are not only well-known, but few total syntheses are completed without using at least one of these reactions.[7] Concerning these and related transformations, unexpected but interesting observations can be found scattered throughout the literature, although sometimes these go unreported. These, in the main, stem from poor catalytic turnover, unusual reactivity or selectivity, or the presence of unwanted side-products (e.g. homocoupling and hydrodehalogenation etc.). Our fundamental understanding of Pd-catalysed reaction systems is continually questioned by new transformations or unusual (often unwanted) side reactions. Furthermore, both

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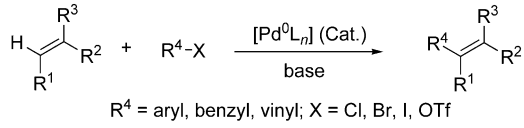
old and new catalyst systems probe our understanding of the origin of reactivity in catalytic cycles which can involve Pd^0, Pd^{II} and Pd^{IV} species. Pd^0 and Pd^{II} species can either be neutral or anionic, adding to the overall complexity of these reactions. $Pd_n(dba)_{n+1}$ [dba = (*E*,*E*)-dibenzylidene acetone; $n = 1$ or 2] is the most used precatalytic source of Pd^0. The behaviour of this precatalyst has proven complex, even prior to commencement of any formal cross-coupling process.[8–13] Additional donor ligands (e.g. phosphanes and N-heterocyclic carbenes), and varying concentrations of dba, addition of substituents to the aryl rings in dba-Z ligands etc., not only affects the intimate bonding interactions with Pd, but ultimately the overall catalytic efficacy.

As with the majority of Pd-catalysed cross-coupling processes, the lowest energy pathway will more often than not prevail, whether that is β-hydride elimination, heteroatom elimination or homolytic cleavage of the carbon–metal bond. It may also involve the formation of new species such as radicals, which display different propensities such as atom transfer, dimerisation or disproportionation. On identifying a *dead-end* or *side-reaction*, which appears difficult to overcome without significant effort, most synthetic chemists will look to alternative methodologies; the logical decision, and in many cases the correct one. However, in some cases, efforts have been made to either understand the full implications of the side-reaction, or at least to try and exploit it, expand the substrate scope and develop a new synthetic methodology.

This review is inherently subjective. It is important to state that although there are limited reports on side-reactions found in Stille cross-coupling,[2] and comments concerning hydrodehalogenation reactions,[14] to date there has been no comprehensive review broadly encompassing cross-coupling and related processes. The central purpose of this review is to collate exemplary reactions and processes. After a brief introduction to the various reactions, the main side-reactions are discussed, and where these have been exploited, representative examples are provided. Given the large body of literature reports in this vast field of study the review is not exhaustive, but we hope that the examples selected are broadly of interest to the synthetic chemistry community.

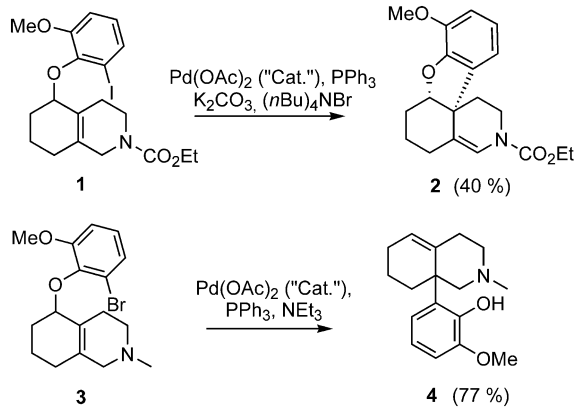
1. Heck Reactions

The Heck reaction can be regarded as the "father" of Pd-catalysed coupling processes.[15] Seven back-to-back papers published in the late 1960s not only revolutionized organic synthesis but laid the foundation for many of the well known named reactions reported since. It involves the reaction of an aryl or alkenyl halide or triflate with an alkene, resulting in a alkene product, whereby one of the C–H bonds has been substituted (Scheme 1);[16,17] formally, this represents a direct functionalisation reaction.



Scheme 1. The Heck reaction.

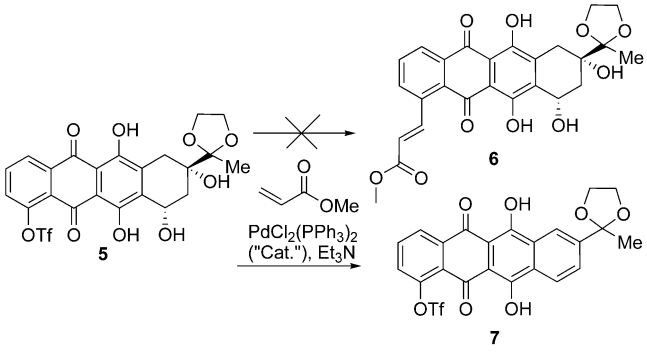
Double-bond isomerisation in the Heck reaction is a significant problem. However, various additives can alleviate this; for example, the use of silver[18–21] or thallium[22,23] salts or the "greener" supercritical CO_2.[24] Double arylation of the double bond (on both carbon atoms of the double bond and even diarylation on the terminal carbon) was observed in the attempted preparation of inflammatory Lewis-X peptidomimetics for example.[25] Often, if the Pd^{II}-alkenyl intermediate is unable to undergo β-hydride elimination then it can proceed to a termination cross-coupling reaction.[26–29] During the course of work directed toward the stereoselective synthesis of the ACNO core of morphine, it was found that carbamate **1** gave tetracyclic **2** in 41% yield in the presence of catalytic Pd (Scheme 2).[30] When the related bromide **3** was reacted under the same conditions, the Heck reaction did not occur and alcohol **4** was formed by an unusual Claisen rearrangement.



Scheme 2. Expected Heck product **2** and unexpected Claisen rearrangement **4** (cat. refers to catalyst and "cat." refers to precatalyst; used throughout the review).

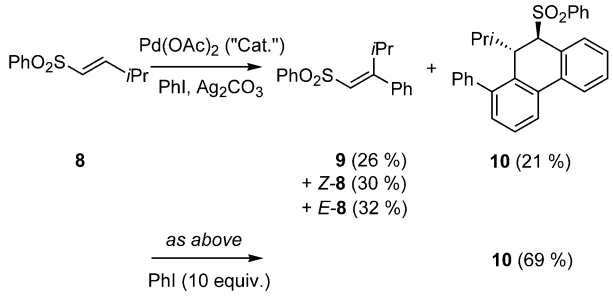
Cabri and co-workers expected C–C bond formation by a Heck coupling of ketal triflate **5** and highly volatile methyl acrylate.[31] The expected product **6** was not observed using standard catalytic conditions [$PdCl_2(PPh_3)_2$, DMF, 90 °C], instead loss of two of the hydroxy groups occurred, and aromatisation resulting in **7**, exclusively (Scheme 3).

Carretero and co-workers have developed a method for the synthesis of acyclic β,β′-disubstituted α,β-unsaturated sulfones.[32] Heck arylation of α,β-unsaturated sulfones with iodobenzene was expected to proceed via a simple *syn*-carbopalladation/*syn*-β-hydrogen elimination pathway. However, when **8** (R^1 = *i*Pr) was treated with iodobenzene (1 equiv.) and Ag_2CO_3 (2 equiv.) in DMF at 120 °C for 72 h a mixture of four compounds were obtained (Scheme 4): the starting vinyl sulfone (32%), the corresponding isomerised allyl sulfone (30%), the expected Heck product **9** (26%)



Scheme 3. Pd-mediated aromatisation.

and surprisingly, the dihydrophenanthrene **10** in 21% yield. When ten equivalents of iodobenzene were used, **10** could be isolated after recrystallisation in 69% yield.

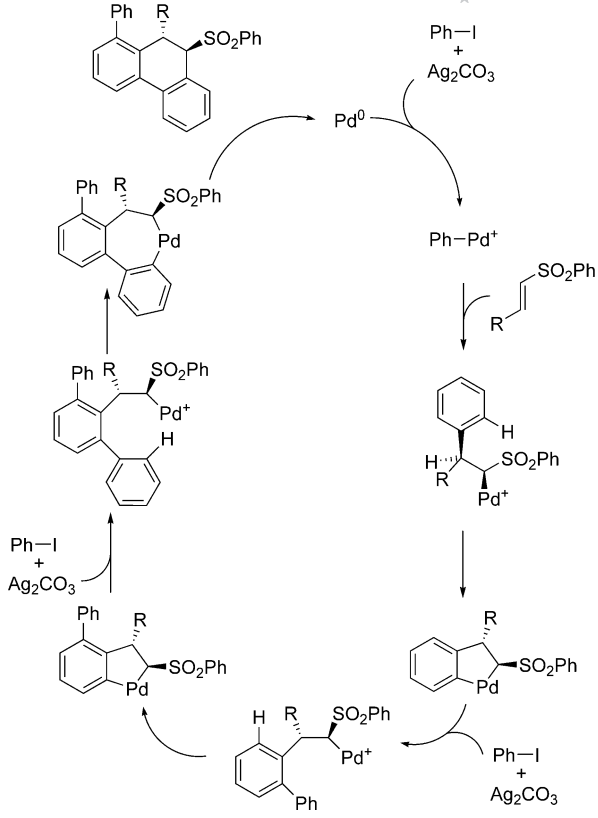


Scheme 4. Formation of dihydrophenanthrene **10**.

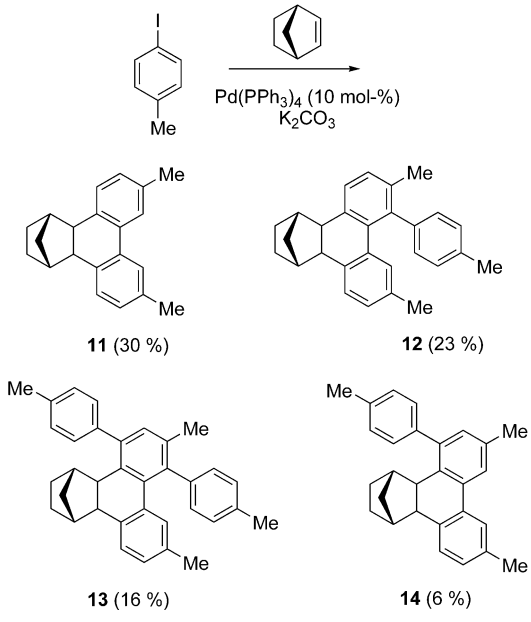
The initial step involves a fast Heck reaction to give the *trans*-disubstituted alkene intermediate. Oxidative addition is followed by formation of a cationic Pd species and *syn*-insertion. Aromatic C–H bond insertion is favoured over β-hydride elimination. A palladacycle is then formed and a second arylation takes place by another C–H functionalisation. Reductive elimination of a seven-membered palladacycle affords the product (Scheme 5).

Pd-catalysed coupling of unactivated norbornene with aryl halides[33–37] has also led to many interesting results. There are several reports from the Catellani group of unusual large multi-ringed systems arising through the reaction of norbornene with aryl halides. The example shown below (Scheme 6) occurs in the presence of catalytic $Pd(PPh_3)_4$, base and DMF at 105 °C affording multi-ringed systems (e.g. **11**, **12**, **13** and **14**).[38]

The proposed mechanism consists of a complex sequence of steps, most notably involving bicycloheptene insertion into Pd–aryl bonds and its expulsion when steric hindrance is encountered. It was also found that interesting Csp^2–Csp^3 couplings could be achieved by an intramolecular benzylic C–H activation.[39] A similar observation was made by de Meijere.[40,41] This methodology can be readily applied to the preparation of norbornene-free biaryls such as **15** in the presence of allylic alcohols, which is mediated by norbornene in excellent yields (Scheme 7).[42]

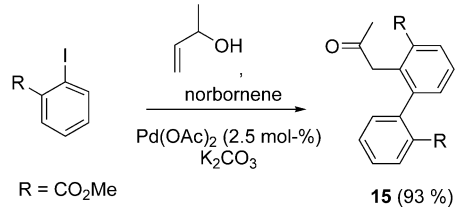


Scheme 5. Mechanism to account for dihydrophenanthrene **10** formation.



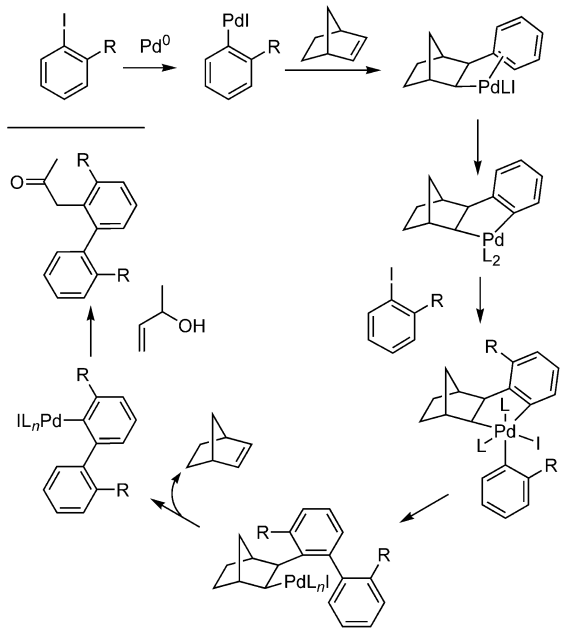
Scheme 6. Norbornene incorporation to give multi-ringed products.

The suggested mechanism involves formation of a Pd^{IV} intermediate which, due to the presence of *o*-substituents, undergoes a reductive elimination step to form an aryl–aryl bond. Norbornene is lost by retrocarbopalladation, and coupling with the allylic alcohol furnishes the final product



Scheme 7. Norbornene-mediated biaryl synthesis.

(Scheme 8). These reactions exhibit remarkable substrate scope with various coupling components, e.g. to alkenes,[43,44] acetylenes[45] arylboronic acids,[46] amongst others.[42,47,48]

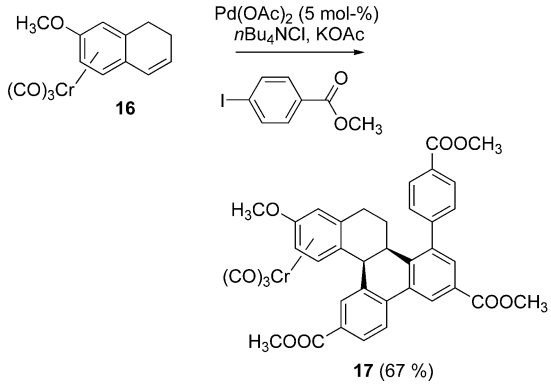


Scheme 8. Catalytic cycle involving a Pd^{IV} intermediate.

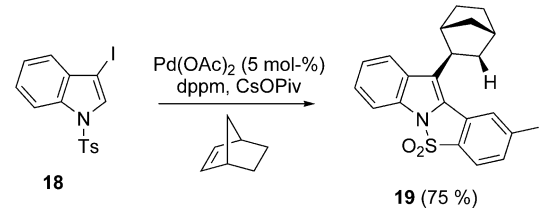
Thiemann prepared multi-ringed systems such as **17** from **16** by a triple arylation sequence involving a tricarbonylchromium complex (Scheme 9).[49] Some time ago Cheng noticed that a Pd-catalysed reaction of norbornadiene with aryl halides gave three-membered nortricyclenes.[50] More recently, Pd-catalysed alkylidenecyclopropropanation of norbornadiene with alkynes was found to produce interesting cycloadducts.[51]

Norbornene was again found responsible for the unusual coupling of 3-iodo-1-*p*-tosylindole **18**.[52] Oxidative addition and *syn*-addition of norbornene to Pd^{II}, is then followed by a 1,4-Pd shift to the 2-position of the indole. Final intramolecular cyclisation to the tosyl group affords the fused-ring system in **19** (Scheme 10).

Rawal observed some interesting results *en route* to the total synthesis of (±)-dehydrotubifoline (Scheme 11).[53,54] When R = CO_2Me, Jeffery conditions led to the unusual product **24** in 84% yield from **20**. Initially, this seems to arise from a standard 7-*endo*-cyclopalladation process. However, close inspection of the spectroscopic data revealed inversion of the *exo*-cyclic double bond. This is of course inconsistent with a simple 7-*endo* ring closure. The proposed mechanism consists of the initial expected 6-*endo* cyclisation with complexation from the carbamate moiety sustaining intermediate **21** long enough to allow a second cyclopalladation. Bond rotation in **22** followed by a Pd-shift gives Pd^{II} species **23**. Free of carbamate coordination **23** undergoes a β-hydride elimination affording **24** in 84% yield. When the free secondary amine is used the expected product dehydrotobifoline is formed in 79% yield (Scheme 11).



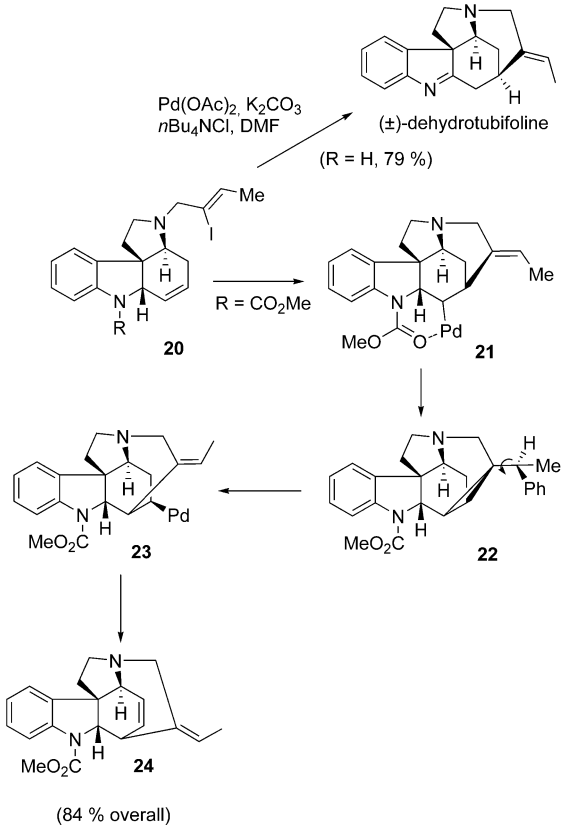
Scheme 9. A triple arylation sequence.



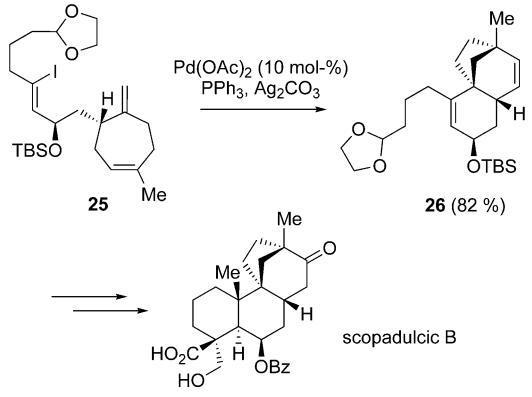
Scheme 10. Cyclisation of a tosyl group involving a 1,4-Pd shift.

Falling under the heading of unusual but fascinating Pd-catalysed reactions the recently reported "domino" and "zipper" polycyclisation reactions are among the most visually impressive.[55,56] Negishi[57] and Trost[58,59] have reported such cascade reactions. The Overman group also displayed artistic ingenuity in the total synthesis of scopadulcic acid B (Scheme 12). Intermediate **26** was formed in a single step from **25**. Remarkably, two new ring systems are formed with all the stereocentres correctly installed (in 82% yield).

The total synthesis of okaramine N includes some interesting findings.[60] Several complex mechanistic steps are suggested to account for the transformation of **27** to **28** (a precursor to natural product okaramine) in Scheme 13. This Heck-like transformation (oxidative palladation gives a "C–Pd–OAc" intermediate) employs an $AcOH/H_2O$ solvent combination. The first proposed step involves selective palladation at the 2-indole position. A 6-*exo*-*trig* 1,2-insertion followed by a heterolytic fragmentation and selective migration of the β-2-indolyl group results in ring expansion to give the eight-membered ring. Proton loss then reveals **28**. It is quite remarkable that no β-elimination occurs, de-



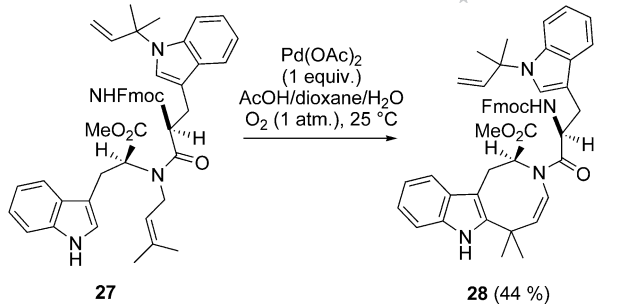
Scheme 11. 6-*endo* Cyclisation and carbamate (**21**) coordination allows a second palladation event.



Scheme 12. Domino-type polycyclisation reaction.

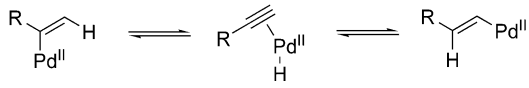
spite several opportunities to do so. In the absence of acetic acid no cyclisation occurred, whereas in the absence of water almost exclusive formation of seven-membered cyclisation products were observed. Fmoc cleavage/cyclisation, an ene reaction, photooxidation, reduction and an end-game thermolysis furnished okaramine N.

Recently Skrydstrup reviewed their own work in the context of serendipitous discoveries in Heck-like reactions.[61] β-Hydride elimination is a common occurrence in cross-coupling chemistry and can represent an unwanted pathway and thus reduces yields of the desired product. It usually



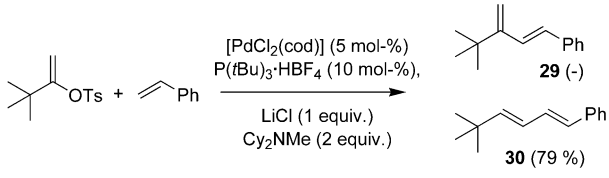
Scheme 13. AcOH/H_2O as a key solvent combination.

involves the movement of a hydride from the β-position of a ligand to the metal centre leading to the formation of a metal(II) hydride and an alkene. However, a similar process can occur with movement of a hydride from an alkenyl species, giving a Pd^{II} hydride species ligated by an alkyne (Scheme 14).



Scheme 14. β-hydride elimination in Pd^{II} alkene species.

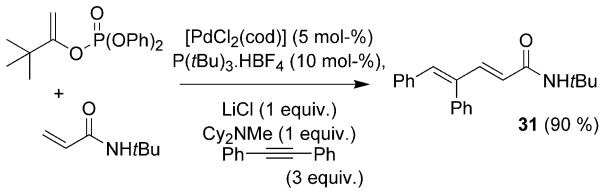
Skrydstrup and co-workers found that this could be applied to the formation of isomeric alkenes (Scheme 15). The mechanism involved oxidative addition, followed by β-hydride elimination of an Pd^{II} alkenyl species. The final isomeric Pd^{II} alkenyl species therefore occurs after a formal 1,2-hydride transfer allowing the proceeding steps (carbopalladation etc.) to ensue in the normal manner. If the three species in Scheme 14 are in equilibrium then the rate of the following reactions will determine the isomeric composition in the final product. In the reaction of 1-*tert*-butyl vinyl tosylate with styrene, for example the expected coupling product **29** was not formed, instead **30** was formed in 79% yield in DMF at 100 °C. A variety of alkenes gave similar yields and excellent *trans*-selectivity. The corresponding vinyl phosphates (far less expensive to prepare) also participated in a 1,2-migration.



Scheme 15. Utilisation of an Pd^{II}-alkynyl intermediate.

It is noteworthy that only vinyl tosylates and phosphates bearing substituents with a quaternary carbon connected to the C1 of the alkene were susceptible to 1,2-migration. Remarkably when a triflate was used in place of tosylate, reactions could be performed at room temperature. DFT calculations subsequently suggested that the product outcome is determined in the carbopalladation step, which occurs rapidly when the metal and bulky *t*Bu group are *trans* and slowly when the groups are *cis*. The likely existence of

an alkyne coordinated Pd^{II} complex also tempted the group to introduce a second alkyne into the reaction which could allow cross-over and incorporation of a second alkene into the final product (Scheme 16). Indeed this turned out to be the case with diphenylacetylene and *tert*-butyl vinyl phosphate coupling to give diene **31** in 90% yield.

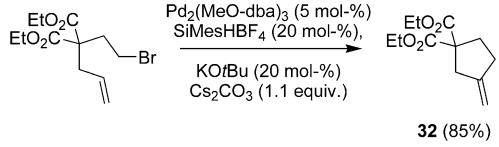


Scheme 16. Alkyne crossover-type reaction.

The group later showed that neither the base, the vinyl phosphate or the lithium chloride were needed for the reaction to take place. A mechanism involving a Pd^{II} hydride species was suggested. Evidence for this included the in situ preparation of the hydride species which in the presence of $Pd(dba)_2$ and $(tBu)_3P$ efficiently catalysed the coupling of a variety of alkynes to alkenes in a Heck reaction. Ultimately this serendipitous finding led to the development of two very useful methodologies: 1) that β-hydride elimination can occur efficiently with alkenyl metal compounds, furnishing isomeric products not easily accessible by other means; 2) the Pd^{II}-alkyne intermediate was also utilised in successful ene-yne coupling which represents an atom-efficient Heck reaction.

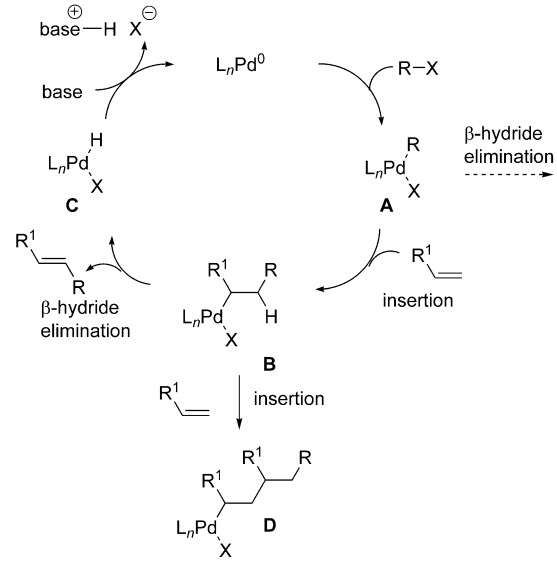
Hierso recently described the Pd-catalysed alkynylation of aryl bromides in an imidazolium ionic liquid.[62] Unexpected hydrogenation of the alkyne function was observed along with amine arylation reactions involving pyrrolidine (present as a base in the reactions) and the aryl bromide.

A recent communication from Fu outlines how, based on a Heck framework, unactivated β-hydrogen-containing intramolecular C–C bond formation can occur with alkyl bromides and chlorides (Scheme 17) giving five-membered rings such as **32**.[63] MeO-dba is a *key ligand*, which appears to hinder β-hydrogen elimination from the initial oxidative addition product.



Scheme 17. Alkyl-Heck reactions of unactivated alkyl bromides.

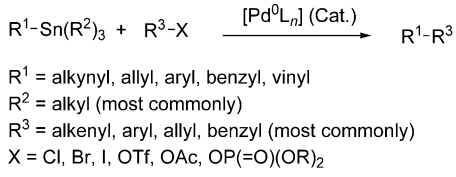
Minimising β-elimination in the first instance (**A** to **B**) and choice of β-elimination over intermolecular insertion (**B** to **C**) are crucial considerations (Scheme 18). Deuterium studies indicate that unlike similar reactions with other metals, the reaction described here is not radical-mediated.



Scheme 18. Mechanistic considerations for the alkyl-Heck reaction.

2. Stille Cross-Couplings

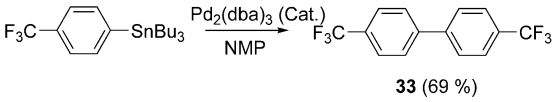
The Stille cross-coupling reaction is a powerful tool for C–C bond formation.[64] The transformation involves reaction of a $R^1Sn(R^2)_3$ moiety, whereby R^1 is the transferable group and usually an unsaturated moiety and R^3X, the "electrophile", which is usually a bromide, iodide or triflate (Scheme 19).



Scheme 19. The Stille reaction.

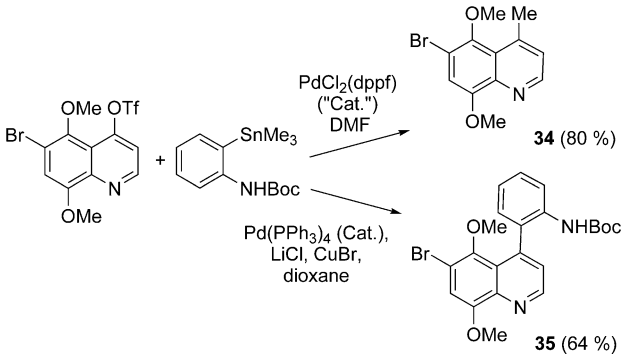
Side-reactions include homocoupling, transfer of "non-transferable" ligands (e.g. Me), destannylation, cine substitution and aryl migration. Side reactions of the Stille reaction were compiled in 1997,[2] therefore those reported before that time are only given brief mention here in relevant cases. Undoubtedly the most common side-products are those involving a homocoupling event.[2,65–70] Reaction of a Pd^{II} precatalyst with two equivalents of the organostannane mostly accounts for this observation. In other cases such as when preformed Pd^0 is used, the homocoupling products can be formed in the presence of air which could include insertion of the Pd^0 into the C–Sn bond.[2] This side-reaction can be taken advantage of if biaryls are needed.[2] In this case **33** was formed in 69% yield in the presence of a catalytic amount of Pd_2dba_3 and 1-methyl-2-pyrrolidinone (NMP) (Scheme 20).

Homocoupling of the electrophile is often observed.[71] An exchange of organic groups between tin and Pd is likely in Stille reactions,[72] as is unwanted alkyl transfer.[73–77] For example, when phenyltrimethylstannane is coupled with



Scheme 20. Homocoupling from arylstannanes.

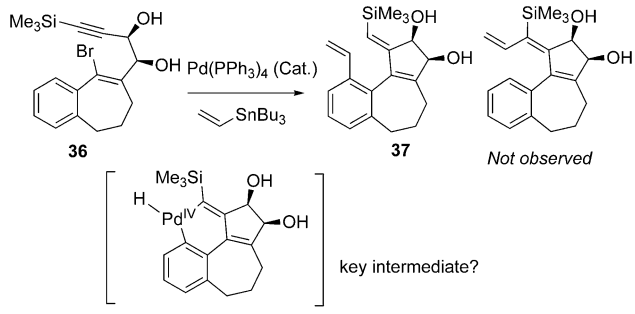
aryl triflates, the product reflects both transfer of the methyl and phenyl groups; the phenyl group transferring 5 times faster than the methyl group and 37 times faster than an *n*Bu group, suggesting the latter is the preferable "non-transferable" group. The use of Cu^{I} salts can help elevate this problem. It can improve selectivity in the transferability of butyl vs. alkenyl groups, for example.[2,78] In the interesting case shown in Scheme 21 methyl transfer is solely observed [without the use of copper(I) bromide] giving **34**, whereas the desired Boc-protected arylstannane is transferred in the presence of the copper salt (optimised conditions for each transformation are shown) to give **35**.[79]



Scheme 21. Unwanted alkyl transfer to give **34**.

When electron-rich aryl- or heteroarylstannanes are used, destannylation can be a problem;[80,81] however, usually the volatile side products can be removed during work-up. Some scattered examples of cine substitution have been reported in the case of 1-substituted 1-stannylethylenes.[82–84] A proposed mechanism involves insertion of the Pd^{II}–aryl species across the double bond of the alkene followed by β-elimination and protodestannylation. Direct transmetallation is hindered by the β-phenyl substituent on the stannane.[66] Correct regiochemistry can sometimes be restored by the use of copper(I) salts[2] or indeed silver carbonate.[83] Aryl migration can occasionally prove to be a problem, also with migration occurring between phosphorus and Pd giving the scrambled products.[83,85]

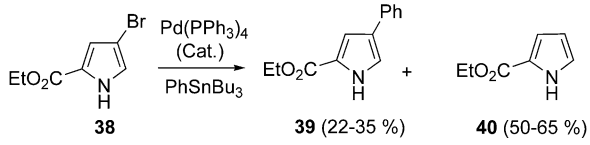
An interesting tandem process involves a Stille coupling, followed by a Diels–Alder reaction, affording the core of manzamine A.[86,87] Three new stereocentres were introduced in one step directed by a single stereocentre. Other tandem reactions have been reported where β-bromopropargylic-1,2 diols are reacted with alkenyl or alkynyl stannanes.[88] In contrast when vinyl bromide **36** was used with tributylvinyltin (Scheme 22) in the presence of catalytic $Pd(PPh_3)_4$, coupling of the vinyl moiety occurred with the phenyl ring rather than with the *exo*-cyclic double bond giving **37**.[89] A 1,5-vinyl-to-aryl shift of the metal moiety in the cyclocarbopalladation step is suggested based on theoretical studies.



Scheme 22. Vinyl coupling to a neighbouring aryl group.

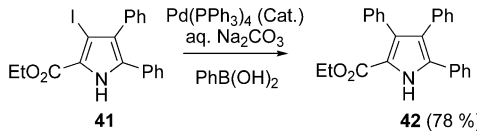
The vinyl Pd^{II} derivative formed after cyclopalladation undergoes an intramolecular oxidative addition of the phenyl C–H bond to Pd. The possible Pd^{IV} intermediate could then undergo a formal H/Pd exchange (reductive elimination). Stille coupling gives the observed product. DFT calculations suggest, however, that the 1,5-vinyl-to-aryl-Pd shift best corresponds to a proton transfer between two negatively charged carbon atoms that are bound to the Pd atom in the transition state. In this case Pd will remain in a +2 oxidation state throughout the catalytic cycle.

The attempted Stille coupling of 4-bromopyrrole-2-carboxylate **38** with tributylphenyltin under standard conditions led only to coupled product **39** in variable and poor yields (< 35%). Hydrodehalogenated product **40** was the major isolated product (ca. 50% yield) (Scheme 23).[90]



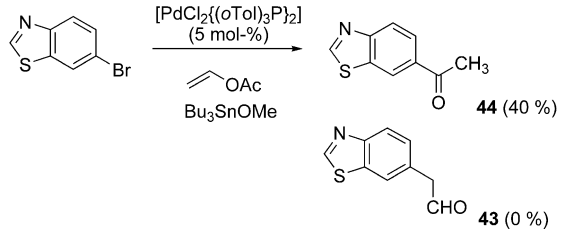
Scheme 23. Hydrodehalogenation in pyrroles.

The authors also attempted a Suzuki coupling of the pyrrole with phenylboronic acid (also see proceeding section). Significant hydrodehalogenation remained a problem (28–42%). However, when the amine moiety was protected with a Boc group not only was hydrodehalogenation prevented, but the protecting group was removed in one-pot. Interestingly, 4,5-dibromopyrrole ester exhibits selective C4 hydrodehalogenation. For 3-halopyrrole esters no such side-reactions are observed in fully substituted pyrrole **41** (Scheme 24), where the expected arylated compound **42** was formed in good yield.



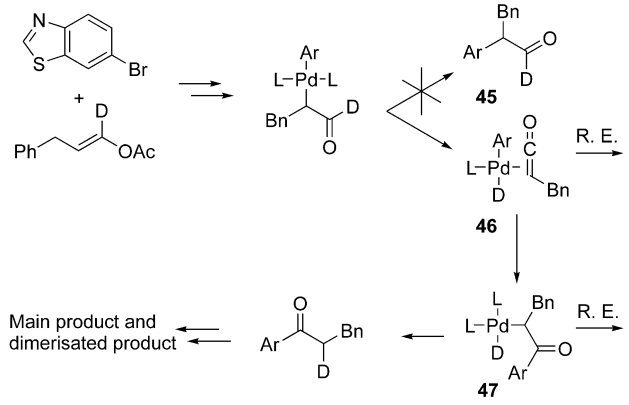
Scheme 24. An efficient Suzuki coupling in a system susceptible to hydrodehalogenation.

An attempted Pd-catalysed α-arylation of aldehydes was met with some difficulty.[91] None of the expected product **43** was observed. Instead acylation of the benzothiazole took place giving ketone **44** (Scheme 25). Exploitation of this side-reaction by using two equivalents of the tin coupling partner and a change of solvent from toluene to DMSO afforded a variety of ketones, in yields as high as 76%.



Scheme 25. Selective acylation.

The catalytic cycle illustrated in Scheme 26 is consistent with deuterium labelling experiments. Prior to the final reductive elimination step, deviation from the normal mechanistic route which would give **45**, gives Pd^{II} ketene species **46**. Insertion of the ketene into the Pd^{II}-aryl bond, followed by reductive elimination, gives the final product and regenerates the Pd catalyst. Reductive elimination (R. E.) products from both **46** and **47** are observed.

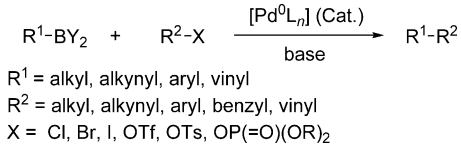


Scheme 26. α-Palladation processes.

Another side-reaction observed in some Stille couplings is electrophilic reduction.[2,73,92–95] Several examples of product isomerisation have also been reported.[2,64,83,96–103] Aryl triflates can be hydrolytically cleaved to the corresponding phenols.[74] The tributyltin halide intermediate formed in these reactions can reduce enones.[73] Reduction of quinine systems can also occur.[104,105] Interestingly, 1,1-dibromo olefins only undergo Stille coupling once; the second bromide eliminates.[106] Carbonylative homocoupling of the organo-stannane can also be observed in CO insertion reactions.[2] More general side-products derive from the homocoupling of either electrophilic or nucleophilic coupling components. Palladium-free "Stille" reactions have been reported[107] and even applied in total synthesis.[108]

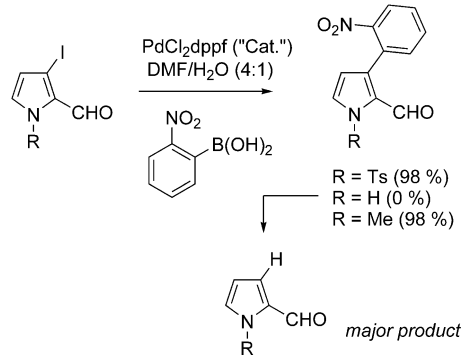
3. Suzuki–Miyaura Cross-Couplings

The Suzuki–Miyaura ("Suzuki") cross-coupling reaction is related to the previously described Stille reaction but an boron-containing group replaces the stannane group, and a base is required (Scheme 27).[109,110]



Scheme 27. The Suzuki–Miyaura reaction.

Ghosez and co-workers recorded substantial hydrodehalogenation in several reactions of unprotected 3-halogenated pyrroles (Scheme 28).[111] This might suggest that a Pd^{II} hydride species (where the hydrogen originates from the pyrrole-H) could be a key intermediate. However, for similar substrates deuterium incorporation at the 3-position was observed using $[D_8]$DMF as the reaction solvent.

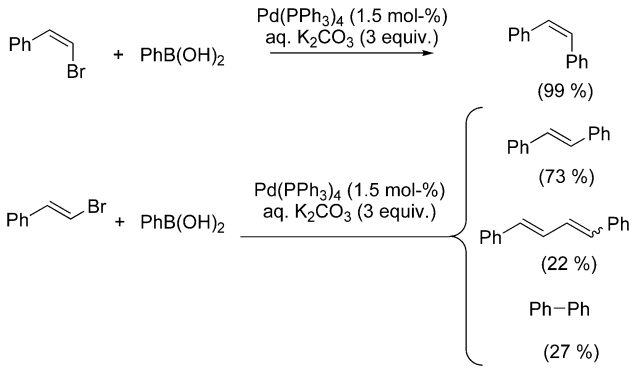


Scheme 28. Hydrodehalogenation using an unprotected pyrrole.

Interesting geometric requirements lead to unexpected reactivities in some Suzuki couplings. For example, calix[4]-arene triflates do not undergo Suzuki coupling, carbonylative coupling or deoxygenation under standard conditions.[112] It is suggested that steric congestion interferes with the formation of a square planar[113] Pd intermediate[114] in the initial oxidative addition step.[109] This geometry is thought to be necessary for the Pd^0–Pd^{II} cycle. Disproportionation involving the triflate or nonaflate groups occurs. The carbonylative reactions gave an unusual non-solvent-derived 1:1 clathrate whereas the deoxygenation reactions gave an *exo*-type 1:1 clathrate.[112] A very useful report by Espinet revealed that several organoboronic acids prepared in the literature contained noticeable amounts of HCl.[115] After the screening of several purification methods, column chromatography proved very effective. In these cases the purified organoboronic acids allowed coupling of sterically hindered partners which were otherwise inactive!

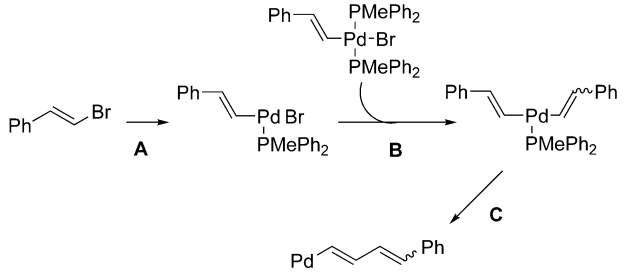
Ozawa found that reaction of (*Z*)-styryl bromide with $PhB(OH)_2$ in toluene in the presence of catalytic $Pd(PPh_3)_2$ in an aqueous solution of K_2CO_3 afforded (*Z*)-stilbene in 99% yield (Scheme 29).[116] Surprisingly, when the (*E*)-isomer was used in the reaction a considerable amount

of the homocoupled product was formed along with biphenyl. Because the cross-coupled product retains the (*E*)-stereochemistry in the homocoupled product it is likely that the *E*/*Z*-isomerisation takes place during the homocoupling process.



Scheme 29. Homocoupling using *E*-styryl bromide.

From a mechanistic point of view several deuterium labelling and kinetic experiments allowed a mechanism to be proposed (Scheme 30). In key step B intermolecular exchange of the styryl ligand and the bromide is followed by reductive elimination. In short, the isomerised ligand arises from an η^1/η^2-interconversion in step B.

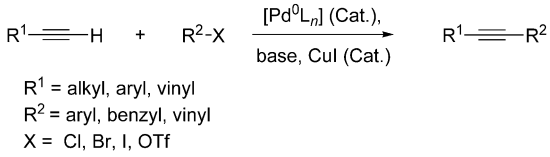


Scheme 30. η^1/η^2-Interconversion leads to isomerisation.

In 2003 Leadbeater and co-workers published a series of papers on "*Transition-Metal Free Suzuki-Type Coupling Reactions*".[117,118] The authors went to great lengths to avoid metal contamination, including the use of new glassware, apparatus and reagents. The crude product was analysed for Pd with none detected down to 0.1 ppm. The crude mixture was also screened for other metals and ultrapure water was used (purified to a specific resistance of >16 mΩcm). Even a SiO_2-coated needle (used to connect the pressure monitor to the vessel) was removed to avoid a possible contaminant. The biaryl products were still formed. Several sources of reaction starting materials were used, with no major deviation in results adding credence to the notion of metal-free reaction conditions. For example, 4-bromoacetophenone was coupled with phenylboronic acid in water in the presence of TBAB (1.0 equiv.) and Na_2CO_3 with microwave irradiation (100 W) in 98% yield. Two years later a reassessment of the methodology was reported.[119] As it turns out, trace Pd contaminants (ca. 50 ppb) found in commercially available Na_2CO_3 were responsible for the catalytic turnover.[119] Sub-ppm detection by ICP-MS revealed that aqueous solutions of Na_2CO_3 solutions in ultrapure water contained levels of Pd corresponding to 0.09 ppb. The ultra-low Pd loading of 0.0000008 mol-%, and turnover numbers of 1,250,000, are truly exceptional! In many ways this finding highlights that this type of substrate represents a poor test for new Pd catalysts. Follow-up papers report on the use of ultra-low Pd catalyst loadings.[120]

4. Sonogashira Reactions

The cross-coupling of terminal alkynes with aryl halides in the presence of a Pd as the catalyst, CuI as co-catalyst, and a suitable base is referred to as the Sonogashira reaction (Scheme 31).[27,121]

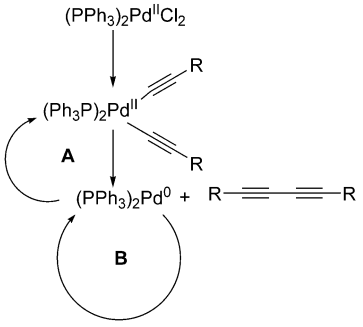


Scheme 31. The Sonogashira reaction.

The related "Cu-free" process is formally known as Heck alkynylation, but is sometimes referred to as the Cu-free Sonogashira cross-coupling, although there is still the question of whether some Pd sources are indeed completely Cu-free. The generally accepted mechanism put forward by Hagihara and co-workers can be divided into two parts: (i) catalyst initiation and (ii) the catalytic cycle.[121] Small amounts of 1,3-diyne formed in the reaction can be accounted for by the reaction of, for example, $PdCl_2(PPh_3)_2$ and alkynyl cuprate (2 equiv.) in the presence of base (e.g. Et_3N). The bis(triphenylphosphane) di(alkyne)palladium(II) intermediate can undergo reductive elimination to give "$Pd(PPh_3)_2$" and the 1,3-diyne. Pd is thus reduced (Pd^{II} to Pd^0). The formation of symmetrical 1,3-diynes are routinely reported;[83,122–124] however, the inconsistency concerning the amount of 1,3-diyne formed (ranging from 1 to 4 equiv. with respect to Pd catalyst loading), reported by Marder and co-workers, is confusing.[125] A series of experiments were designed to probe the origin of this observation.[32] These results indicated that oxidative homocoupling of terminal alkynes can take place to a certain extent, in the presence of Cu^I, Et_2NH and O_2. A Pd^{II} precatalyst containing two halogens, allows quantitative alkyne homocoupling based on the global Pd loading. Ultimately the reactions show that great care must be taken to avoid O_2 in these cross-coupling reactions. Ho and co-workers showed that in a reducing atmosphere (H_2 mix) oxidation could be greatly curtailed; however, such reactions are potentially hazardous.[126]

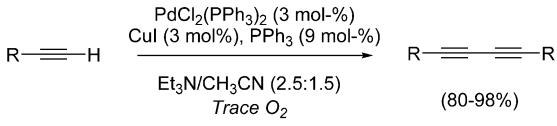
In 1988 Neenan and Whitesides reported the cross-coupling of aryl halides with ethynyltrimethylsilane.[127] While the isolated yields were good, in one particular case, namely bromopentafluorobenzene, the yield was unusually low (20%). Marder proposed that the poor isolated yield could be explained by a competing reaction.[125] In this case hydrogen donation from the terminal alkyne enabled re-

duction of the highly activated aryl halide in the presence of a catalytically active Pd species. Again carefully chosen experiments shed some light on these reactions. It was proposed that in the presence of an oxidising agent, Pd^{II} does not enter the cross-coupling catalytic cyclic B and undergo oxidative addition. Instead, it becomes repeatedly oxidised to Pd^{II} (path A) which allows for further addition of two alkyne units (Scheme 32).



Scheme 32. Mechanistic depiction of alkyne homocoupling in the presence of an oxidant.

Fairlamb and co-workers also reported significant alkyne homocoupling in the attempted synthesis of biologically active[128] electron-deficient 2-pyrones.[129] It was noted that 3-bromo- and 5-bromo-6-methoxy-2-pyrone did not couple efficiently with terminal alkynes and that a 1,3-diyne was formed. It was felt that, providing the 2-pyrone was not necessary for this process, the reaction conditions could prove a convenient method for the preparation of 1,3-diynes (Scheme 33).

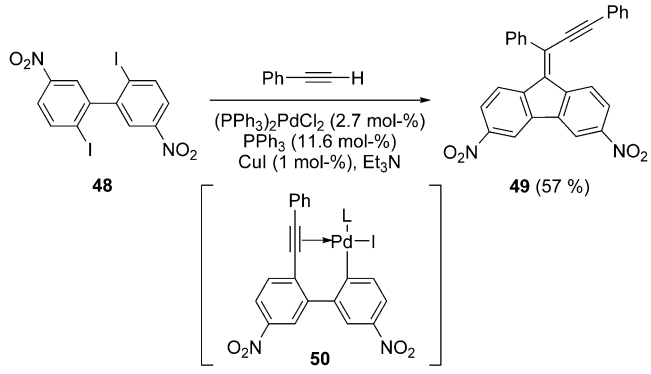


Scheme 33. Homocoupling of terminal alkynes to give 1,3-diynes.

By this method several Pd-containing catalysts were compared and a diverse series of alkynes were homocoupled,[130] which were formed at room temperature. The method is tolerant to a number of functional groups and the substrate scope is good. Further kinetic studies and theoretical calculations support the requirement for an oxidant in these reactions.[131] In its absence, H_2 would be formally produced (unless solvent was involved as a reactant and oxidant) which is demonstrated by B3LPY and CCSD(T) to be endothermic and thus unfavoured thermodynamically. It was shown that under rigorous inert conditions (levels $O_2 < 5$ ppm) substantially less 1,3-diyne was formed. In fact, the quantity of 1,3-diyne formed could be accounted for by initial reduction of Pd^{II} to Pd^0 and thus a stoichiometric quantity of air or added oxidant, such as I_2 or the "organohalide", is necessary for alkyne homocoupling. It is interesting to note that where organohalides act as the oxidant, they are usually electron-deficient, which perhaps reflects the ease of reaction of "Pd^{II}–R" with "Cu^{I}-alkyne" giving "Pd^{II}–alkyne" and "Cu^{I}–R". The latter Cu^{I} complex can be protonated by base·HX, revealing "RH" and "$Cu^{I}X$". It is fairly clear that further mechanistic studies are required to understand the origin of hydrodehalogenation in these and related coupling processes.

In terms of application, this type of "Sonogashira-type homocoupling" method has been used in the dimerisation of protected nucleosides, the products of which may serve as building blocks for the preparation of backbone-modified oligonucleotides for DNA repair or mutation in functional genomics.[132]

En route to polyaromatic compounds furnishing highly fused nuclei, Leung and co-workers coupled diiodide compound **48** with phenylacetylene (Scheme 34). It was found that unusual fluorenyl compounds such as **49**, were formed arising from key intermediate **50**.[133]



Scheme 34. Neighbouring alkynyl-Pd interactions.

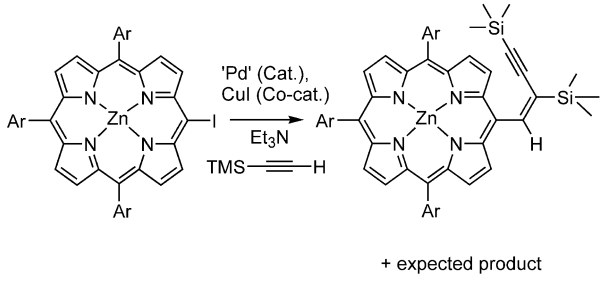
The selectivity is highly dependant on the amine solvent and the phosphane ligands used. The authors propose that **49** is formed by a fast hydrodeiodination, followed by Sonogashira phenylethynylation type reaction. When bidentate phosphane ligands were used, the lack of a vacant coordination site on the Pd prevents further reaction. However, monodentate bulky ligands such as P(*o*-tolyl)$_3$ favour dissociation, allowing a vacant coordination site on the Pd for further coordination and hydrogen incorporation. Results from deuterium labelling experiments indicate that the proton exchange occurs between the amine and acetylenic protons and that the proton in the hydrodeiodination side-product originates mainly from the acetylene.[133] Similar aromatic moieties were observed along with hydro-deiodo-phenylethynylation compounds by other groups.[134,135]

Recently the use of Pd/C has proven a surprisingly good catalyst in the Sonogashira coupling reaction of bromo-2-pyrones.[130] In fact this catalytic system is more efficient in a number of cases than more commonly used catalyst/precatalyst systems, e.g. $Pd(OAc)_2/PPh_3$.

Leadbeater reported the first examples of transition-metal free Sonogashira-type couplings.[120] It may be possible that in this case (as in that of the Suzuki couplings mentioned earlier) that trace Pd in the NaOH accounts for the coupling, although to the best of our knowledge this has not been addressed. Whether or not trace amounts of copper in reactants account for the "copper-free" Pd-cata-

lysed Sonogashira reactions has not, to the best of our knowledge, been addressed.[136]

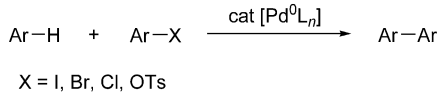
The unexpected formation of a porphyrinic enyne under Sonogashira conditions provided useful intermediates which were suitable for further transformation (Scheme 35).[137] For example, TMS deprotection and a second Sonogashira reaction. This unusual product was formed along with the expected Sonogashira product in varying ratios depending on the catalyst and added ligand employed.



Scheme 35. 1,3-Enyne formation in a Zn-porphyrin.

5. Direct Arylation Involving C–H Activation/Functionalisation Reactions

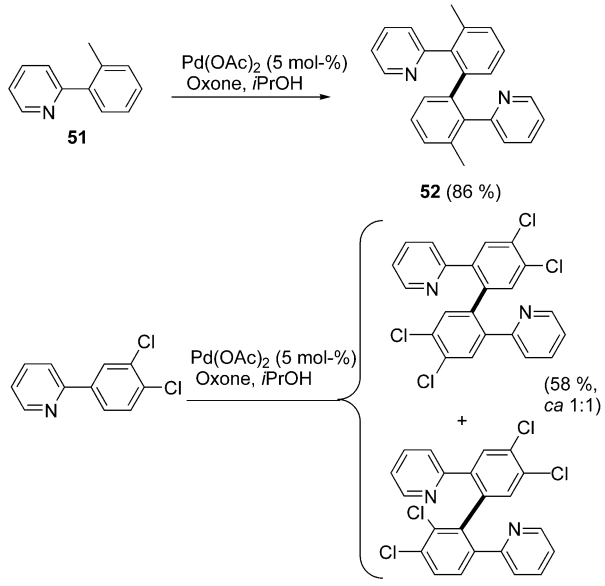
Aryl–aryl bond formation has been known for more than a century, in fact it was one of the first reactions to use a transition metal (copper, which is considered a transition metal in its higher oxidation states).[138] Since then Pd has stamped its authority in this area and has become popular in many aryl–aryl bond forming processes and annelation reactions, according to the general Scheme 36.[138,139]



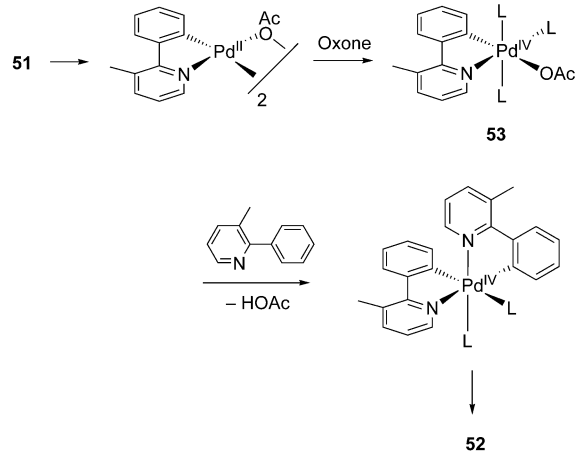
Scheme 36. Direct arylation by C–H activation/functionalisation.

For the purpose of this review we have selected reports whereby unusual/interesting outcomes have been noticed on the formation, or attempted formation, of an Ar–Ar bond. These processes can be inter- or intramolecular, directed or undirected. They all include activation of a C–H bond by Pd insertion.[26,138–141]

Sanford and co-workers reported some fascinating oxidative coupling reactions.[142] Pd-coupling of 2-*o*-tolylpyridine **51** was carried out at room temperature using Oxone™ as the terminal oxidant giving dimer **52** (Scheme 37, new bonds in bold). The fact that oxidants such as air, AgF, and AgOAc did not afford any of the dimer cast a doubt that a traditional $Pd^{II/0}$ switch was operative. The modest selectivity when *meta*-substituted aryl rings were used stands in marked contrast to previous studies where the less sterically hindered *ortho*-position is favoured in >20:1 selectivity.[143] Through carefully designed mechanistic investigations the origin of the "mixed" products was discerned. A mechanism involving a *bis*-cyclometallated Pd^{II} species was briefly entertained; however, an independently prepared sample failed to give any of the desired compound **52** on treatment with AcOH. The mechanism outlined in Scheme 38 was the only one consistent with all of Sanford's experiments. It involves two different C–H activation events – one at Pd^{II} and one at Pd^{IV}. A highly reactive Pd^{IV} intermediate **53** accounts for the poor selectivity in the second electrophilic C–H activation process.

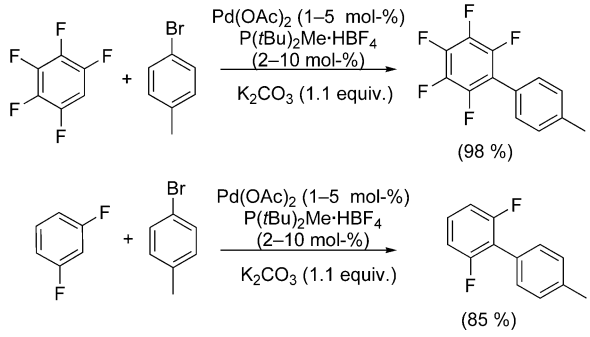


Scheme 37. Products formed by a Pd-catalysed oxidative process.



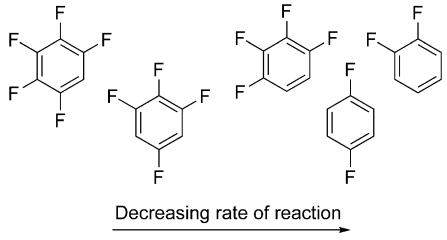
Scheme 38. Mechanism involving two separate C–H activation events.

Halogenated organic compounds are present in a number of natural products and biologically important organic molecules as isosteres;[144] perfluorobiphenyl compounds have found a variety of uses in medicinal[145] and in materials chemistry.[102,146–151] Recent emphasis has been placed on multi-halogenated aromatic systems. Fagnou showed that a novel mechanism was likely operative in the direct aryl coupling of electron deficient benzenes (Scheme 39).[152]



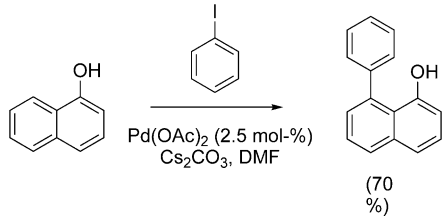
Scheme 39. Steric hindrance is not the main factor in determining the regioselectivity in C–H functionalisation of aryl fluorides.

Arylation at the most acidic site would not occur in reactions proceeding by a S_EAr-type mechanism. A reversal of reactivity compared to that seen in typical S_EAr-type mechanisms was determined (Scheme 40). While the mechanism is not understood fully it is likely that no catalyst-fluorine interactions take place and that C–H acidity is an important parameter to be considered in C–H arylation reactions. It was also the first report of a non-directed catalytic benzene arylation.



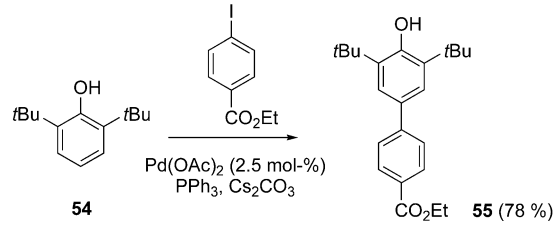
Scheme 40. Affect of C–F bonds on the relative rate of C–H functionalisation.

Miura reported the hydroxy-directed arylation of naphthol (Scheme 41). The reaction is proposed to proceed by a transmetallation of cesium naphthoxide with Pd, neighbouring C–H activation and Pd insertion as the key steps.[153] Under the same conditions coupling at the *p*-position is forced in 2,6-disubstituted phenol **54** giving **55** in good yield (Scheme 42).[154]

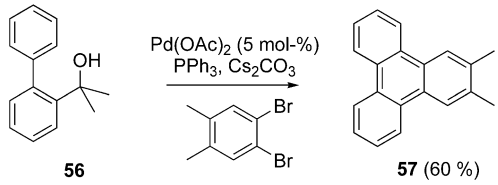


Scheme 41. Hydroxy-directed arylation.

Instead of using the hydroxy substituent as a directing group the Buchwald group designed sterically encumbered phosphane ligands to force the formation of a diaryl ether bond.[155] In this case $Pd(OAc)_2$, P-ligands, K_3PO_4 and toluene at 100 °C were used to couple various phenols with aryl bromides. Miura's group also noticed that 1,2-dibromo-4,5-dimethybenzene **56** underwent a competing reaction with hydroxy-directed aryl-coupling giving triphenylene **57** (Scheme 43).[156] The compound is proposed to arise by a Csp^2–Csp^3 cleavage, followed by loss of acetone and ultimately aryl coupling.

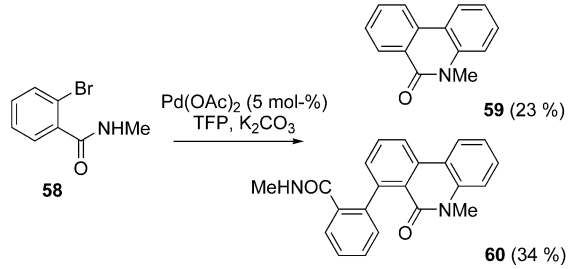


Scheme 42. *p*-Selective arylation forced by steric congestion.



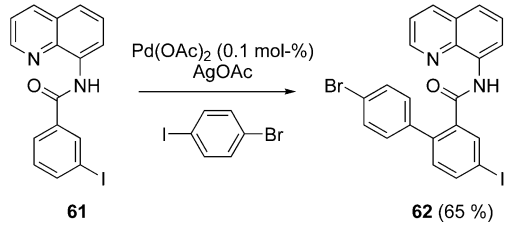
Scheme 43. Triphenylene formation leading to **57**.

Side-product **60** was isolated in 34% yield from the crude mixture along with expected arylation product **59** from **58** (Scheme 44).[157] A five-membered, amide-coordinated palladacyclic intermediate was proposed.



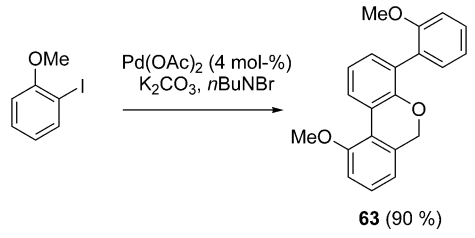
Scheme 44. Double amide-directed coupling leading to side-product **60**.

Regioselective arylation of amide **61** proceeds with very low catalyst loading and with iodine retention on the benzamide (Scheme 45).[158] The final arylated compound **62** was isolated in 65% yield.



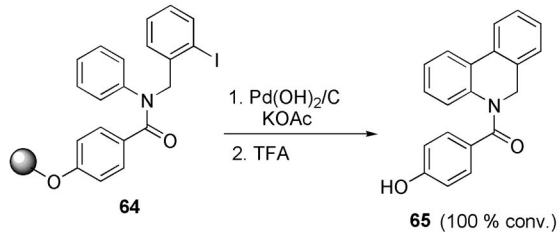
Scheme 45. Amide-directed C–H activation with the C–I bond remaining intact.

Dyker reported the unusual coupling of three molecules of 2-iodoanisole to form dibenzopyran **63** in 90% yield (Scheme 46).[159–161] A five-membered oxapalladacycle is a suggested intermediate.



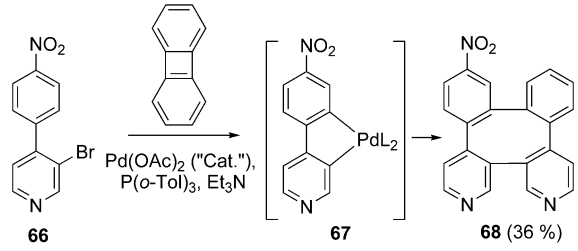
Scheme 46. Unusual multi-ringed product formation.

Fagnou has reported that a range of aryl bromides[162] and aryl chlorides[163] that undergo C–H activation and subsequent coupling. Pd(OH)/C with base and DMA at 140 °C was found to be a very effect catalytic system.[164] To discern the nature of the catalytically active species, a solid-supported amide **64** was used. The reaction gave **65** quantitatively (Scheme 47). This result suggests that a catalytically active homogeneous Pd species had leached from the heterogeneous catalyst (confirmed by other control tests).



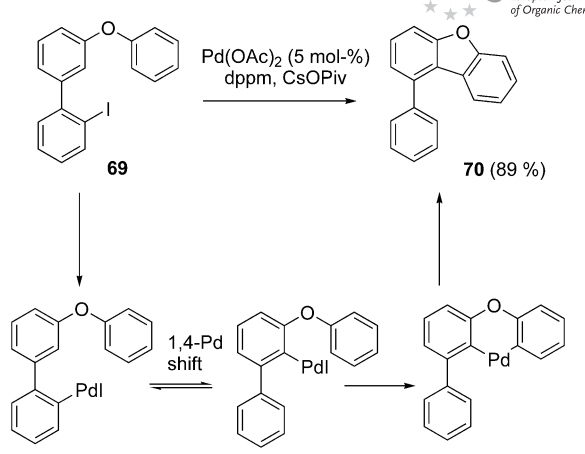
Scheme 47. Turnover indicates catalytically active Pd species in solution.

Gallagher and co-workers judiciously interrupted intermediate palladacycle **67** after reacting disubstituted pyridine **66** with biphenylene affording tetracycle **68** (Scheme 48).[165]



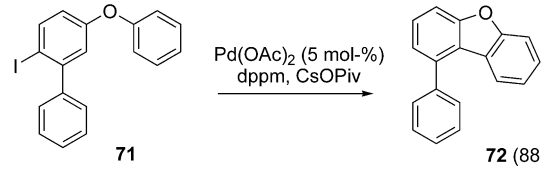
Scheme 48. Tetracycle formed by interruption of an intermediate palladacycle.

Several interesting examples of Pd migration appear in the context of direct arylation.[140] Larock capitalized on atypical observations and developed an elegant method for fused polycycle formation.[166,167] Oxidative addition of **69**, followed by a reversible 1,4-Pd shift to a Pd^{II} aryl species was proposed. Reductive elimination to give Pd^0 affords the dibenzofuran compound **70** (Scheme 49).



Scheme 49. 1,4-Palladium shift leads to unusual Ar–Ar bond formation.

A careful look at the ring formation outlined in Scheme 50 reveals a double 1,4-Pd shift carried out by the same group.[167] Initial oxidative addition of **71**, 1,4-shift bond rotation is followed by a further 1,4-shift. Finally, C–H activation and direct arylation affords **72**.

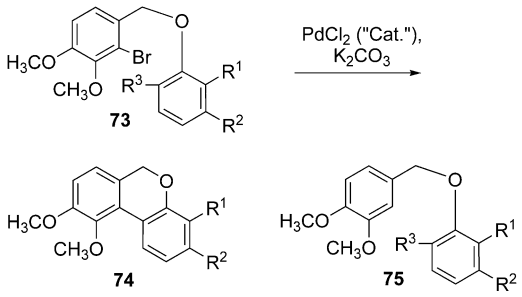


Scheme 50. A double 1,4-Pd shift revealing compound **72**.

The Larock group continues to report multi-component Pd-catalysed cross-coupling reactions.[168,169] One particular example appears to involve both a palladium migration mechanism and a C–H activation process via an organopalladium(IV) hydride intermediate.[170] These unusual, controlled, sequential coupling reactions merit a review in their own right.

In an example of semi-synthetic studies toward the morphine core by Schäfer, a model study of C–C aryl bond formation revealed hydrodehalogenation problems.[171] When the reaction conditions of $PdCl_2$, K_2CO_3, and DMF at 180 °C were applied to **73** (R^1, R^2 and R^3 = H) the desired cyclised product **74** was obtained along with the reduced product **75** in a ratio of 5:95, respectively (Scheme 51). However, a change in base to the more soluble sodium acetate and with substituents $R^1 = CH_3$, R^2 = OH and R^3 = H, a satisfactory yield of 56% of **74** was obtained.

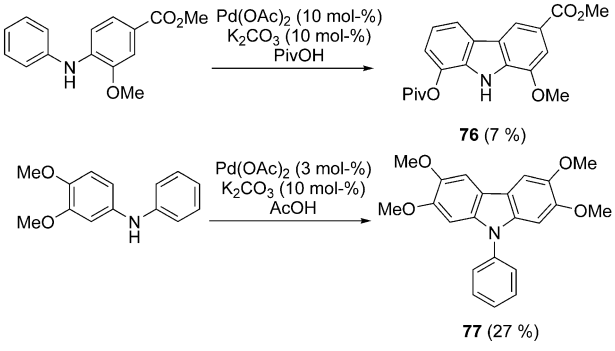
Stabilization of the Pd^0 species with PPh_3 increased this ratio to 69:31. Further improvement was observed by changing the base (up to 93:7 in favour of the desired product **74**). Under such conditions the reaction could tolerate a hydroxy group in the *meta*-position (R^2 = OH); however, when the coupling sites (R^1 and R^2) are substituted with methyl groups only the reduced product is observed. After further model studies the desired salutaridine derivative was eventually achieved in a yield of 17% along with an apor-



Scheme 51. Substituents and base affect hydrodehalogenation.

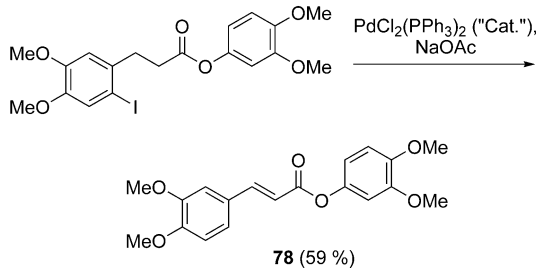
phine derivative (8%), non-cyclised bromide (4%) and the non-cyclised dehalogenated product (3%).

Fagnou and co-workers described the intramolecular Pd^{II}-catalysed oxidative biaryl synthesis under air (Scheme 52).[172] Initial investigations involved the oxidative ring-closing of diphenylamine in acetic acid using $Pd(OAc)_2$ and K_2CO_3. Yields were inconsistent ranging from 8 to 82% using identical substrates and conditions. Substituting AcOH with pivalic acid (PivOH) led to increased reactivity and reproducibility. However, side product **76** was isolated under standard reaction conditions. The formation of this new C–O bond may also occur when acetic acid is used as solvent; however, the arylacetoxy products may be unstable under the reaction conditions undergoing acetate deprotection and subsequent oxidative degradation. While the formation of oxidative products via a C–H activation event has been reported using stoichiometric quantities of iodine(III) oxidants, this example using air as the oxidant makes for a potentially powerful methodology. Other notable and unusual products described in this report include **77**. This oxidative C–N forming process certainly warrants further investigation given the importance of C–N formation in the pharmaceutical industry.



Scheme 52. Ar–Ar bond formation by the activation of two C–H bonds.

Ung and Pyne observed that a number of side products arose from a C–H activation event followed by α-deprotonation.[173] In an example (Scheme 53), β-hydride elimination eventually gives alkene **78** as the major product. An alternative mechanism could involve a Pd^{IV} intermediate. In similar compounds reductive elimination of the Pd^{II}-palladacycle intermediate prevails.



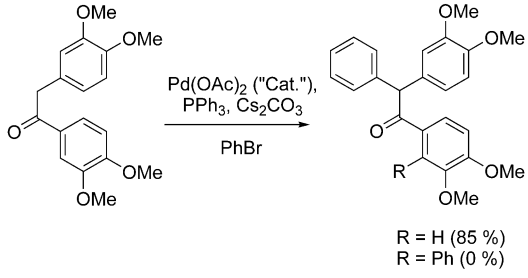
Scheme 53. β-hydride elimination leads to alkene formation.

As observed in other Pd-catalysed coupling reactions, hydrodehalogenation is also observed in direct functionalisation reactions vide supra.[162,167] In some of these cases we can gain mechanistic information. For example en route to the natural product rhazinilam, Trauner found it necessary to protect an amide group (MOM) in order to avoid hydrodehalogenation which is thus proposed to occur by the protonation of a palladacyclic intermediate.[174] Here the hydride most likely originates from the amide, thus *N*-protection is the obvious solution.

6. Others

a) α-Phenylation (Arylation)

Dominguez reported α-arylation of several ketones using Pd catalysis. Surprisingly α-arylation took place during the syntheses of 1,2,2-triarylethanones from deoxybenzoins (Scheme 54).[175] Furthermore, no dehalogenation of the aryl bromide was observed. This is in contrast to reported α-arylation events under very similar reaction conditions.[156,176]



Scheme 54. α-Arylation rather than *o*-arylation.

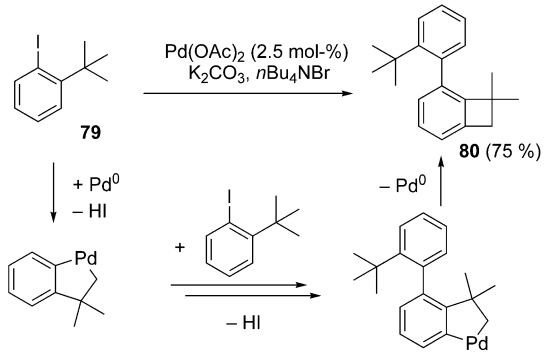
b) Buchwald-Hartwig Aminations

This amination reaction, in its most well-known form, involves the coupling of an aryl halide and an amine in the presence of base and a Pd catalyst creating a new C–N bond.[177–180] Meticulous kinetic studies concerning the oxidative addition step reveals some interesting anomolies.[181] Firstly, the overall amination reactions catalysed by $Pd(BINAP)_2$ exhibit rate constants that are zero order in aryl halide, amine, base and added ligand and first order in catalyst. This showed that the overall reaction was rate-

determining in the oxidative step, more specifically in ligand elimination. While deviation occurs when secondary amines were used this was shown to be due to catalyst decomposition in the way of P–C cleavage of the bisphosphane ligands. Perhaps surprisingly, the introduction of substituents on the "dba" ligands[182] had little affect on the Buchwald–Hartwig reaction rates.[129] However, when you consider that the amine, base or combination of both, in such reactions effectively removes the dba from interfering with the reaction (by a Michael-type addition to the enone moiety), this becomes a rationalised finding.

c) C–H Functionalisation at sp^3-Carbons

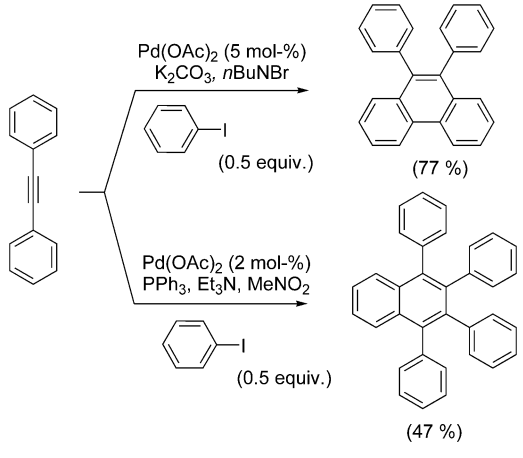
C–H activation of an sp^3 carbon occurred when benzocyclobutyl **80** was formed on treatment of *o*-substituted *tert*-butyl iodobenzene **79** with a catalytic amount of Pd(OAc)$_2$.[183] The proposed mechanism includes formation of a five-membered palladacycle (Scheme 55).



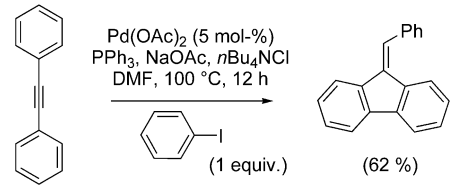
Scheme 55. C–H activation of an sp^3-carbon leading to cyclobutane formation.

d) Annelation Reactions

Some time ago the formation of phenanthrenes by a Pd-catalysed annelation of alkynes was reported by Dyker (Scheme 56).[184] In similar reactions Larock found that the nature of the base seemed to affect the product distribution (Scheme 57).[185] When NaOAc was used in place of K_2CO_3, for example 9-alkylidene-9*H*-fluorenes were formed under almost identical conditions.



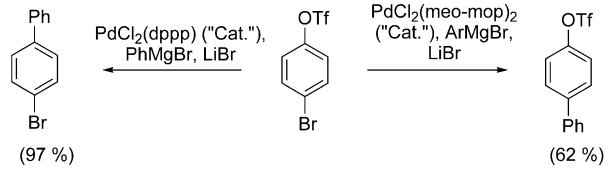
Scheme 56. Phenanthrene and naphthalene derivatives formed by annelation of alkynes.



Scheme 57. Affect of base on the annelation of alkynes (compare Scheme 56).

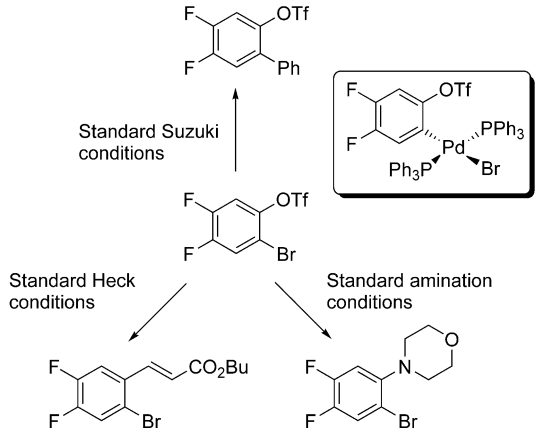
e) Kumada Reactions

In Kumada reactions where aliphatic halides or triflates are coupled with Grignard reagents in the presence of an in situ formed Pd^0 catalyst,[186] a mixture of the alkane and alkene products are often seen under standard conditions.[187–189] Homocoupled products can be obtained even with aromatic Grignard reagents. Reduction of the C–I bond is an occasional problem.[188] Hayashi reported surprising regioselectivity (Scheme 58) at both 0 °C and room temperature.[190]



Scheme 58. Selective substitution of a bromide or triflate group.

More recently, Brown's investigations showed that in Pd-catalysed amination, Kumada and Mizoroki-Heck reactions under typical conditions, the triflate rather than the bromide preferentially is the electrophilic leaving group (Scheme 59).[191] However, in Suzuki couplings, bromide displacement occurs, the pathway of which was deemed normal after isolation of the expected oxidative addition

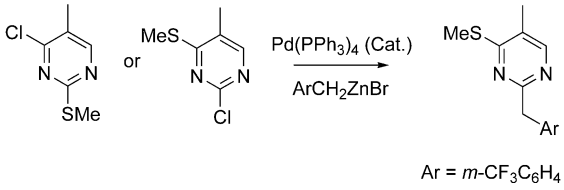


Scheme 59. A preference for bromide in Suzuki couplings.

product (see inset in Scheme 59). The observed chemoselectivity is better viewed as a preference for bromide displacement in Suzuki couplings rather than reluctance to displace triflate. The reason for this could lie in the affinity of organoboranes for bromides ions, or more likely coordination of a three- or four-coordinate boronate anion to Pd^{II} species providing a lower energy pathway for the transmetallation step.

f) Negishi Reactions

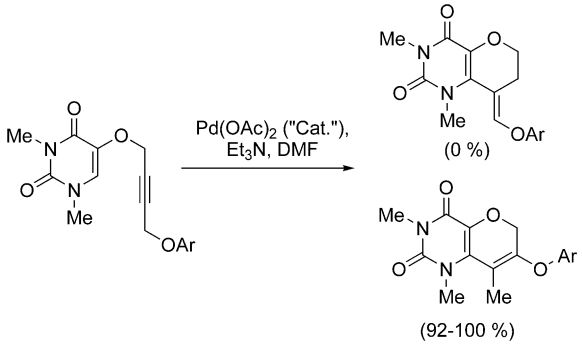
Casalnuovo and co-workers found that methylthio-substituted *N*-heterocycles were unusually reactive in the 2-position (usually the 4-position is more reactive) in Pd-catalysed cross-coupling reactions with organozinc reagents.[192] Both methylthio chlorides surprisingly gave the same product (Scheme 60).



Scheme 60. The same sulfide product is formed using different methylthio chloride starting materials.

g) Others

Polymerization of alkylthiophenes occurs in a highly regioselective manner,[193–195] which has been applied to the preparation of well-defined thiophenes tetramers.[196] Unusual regioselectivity is seen in the reaction of simple terminal alkenes with trichlorosilane in the presence of certain Pd catalysts.[190] An unusual intramolecular Pd-catalysed enolate driven cross-coupling reaction was used in the total synthesis of (–)-koumidine.[197] In one particular step the simple replacement of triphenylphosphane with tricyclohexylphosphane as the ligand for Pd allowed intramolecular cross-coupling to take place. Very recently, Majumdar found that uracil-annulated pyranoheterocycles are formed regioselectively in excellent yields by an unusual Pd-catalysed [1,3]-aryloxy shift, followed by 6-*endo-dig* cyclisation and [1,3]-prototropic shift (Scheme 61).[198] The mechanism is proposed to include a Pd^{II} allene species.



Scheme 61. Pd-catalysed [1,3]-aryloxy shift, followed by 6-*endo-dig* cyclisation and [1,3]-prototropic shift.

Conclusions

In this review, we have detailed a collection of interesting results encountered in exemplary Pd-catalysed cross-coupling reactions. The identification of side-products, observed regioselectivity, reactivity or lack of reactivity, should be viewed merely as a symptom of the underlying complicated mechanistic pathways involving Pd (and low energy barriers between many possible Pd^{II} intermediates). Although the processes leading to these side-products can be accounted for by mechanistic considerations involving traditional intermediates, on occasion one needs to consider and propose new Pd intermediates and mechanistic pathways to explain certain observations. For example, a radical pathway has been considered in the Pd/C and Zn co-catalysed coupling of pyridine and aryl halides.[199] It was found that when 5% (w/w) 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added, the conversion of the reaction decreased by two orders of magnitude – can this observation be exploited in tandem Pd-mediated radical processes?

The existence of Pd^{II}/Pd^{IV} catalytic cycles have been proposed over the years and hotly debated. In some cases C–H activation/oxidation reactions involve a Pd^{IV} intermediate.[200] There can be no doubt that future studies in this area are likely to emerge in the coming years.

Acknowledgments

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