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Solvent effects in palladium catalysed cross-coupling reactions

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Abstract

Palladium catalysed cross-couplings reactions have been a dominant method in synthetic chemistry for decades. Despite this, the role of the solvent is often taken for granted and poorly understood. Regulations affecting some the most frequently used solvents for cross-coupling reactions are accelerating current trends towards using new types of solvents. In this review, the fundamental interactions between solvent and catalyst are explained so that it may inform the rational selection of high performance and safe solvents. The popular cross-coupling methodologies are addressed (Suzuki, Stille, Kumada, Negishi, Hiyama, Heck, Sonogashira, and Buchwald-Hartwig reactions) and novel solvents introduced.

1. Introduction

The cross-coupling methodology has become indispensable for modern chemistry, including the synthesis of pharmaceuticals,[1] natural products,[2] and polymeric materials.[3,4] An extraordinary number of patented procedures and large scale manufacturing processes have cross-coupling chemistry at their core.[5] Palladium catalysed cross-coupling was acknowledged with the 2010 Nobel Prize for chemistry,[6] awarded to Richard Heck, Ei-ichi Negishi,[7] and Akira Suzuki.[8] While interest in other metals for cross-coupling procedures grows,[9,10] "*Pd remains, by far, the most effective metal for such reactions*".[11] Accordingly this review focuses on palladium catalysed procedures. While C–H bond activation remains in its infancy it is expected that conventional cross-coupling methods will dominate for decades to come.[12] The high reactivity and regioselectivity of cross-coupling reactions, along with their broad applicability to diverse reactants is still unrivalled.

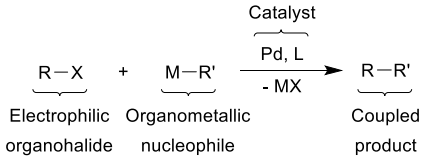
Many solvents can be used for cross-coupling reactions. The solvent is very important in palladium catalysed cross-couplings, as it is in most solution-based chemical transformations.[13] The solvent has a significant influence on the rate and selectivity of a reaction, as well as equilibria. Partitioning or precipitation of products can also be controlled by the solvent, either to remove by-products or cleanly separate the product. The stability of catalysts can be affected by coordinating solvents competing with ligands and the function of acids and bases can be suppressed by a complementary functionality on the solvent (due to hydrogen bond accepting or donating groups). Conversely, by choosing the correct solvent the lifetime of the catalyst and activity of acids and bases can be enhanced. The solvent provides process benefits too, acting as a heat sink to safely regulate the temperature of reactions and permitting substances to be pumped as solutions.

The purpose of this review is to build the basis for future reaction development. To correctly develop synergetic solvent-catalyst systems, the role of the solvent must be understood. This understanding is now even more important because tightening regulations are phasing out or discouraging the use of the conventional cross-coupling reaction solvents (Section 1.3), and

inventive solutions to find replacements are needed to stop some cross-coupling protocols becoming redundant.

1.1 The cross-coupling methodology

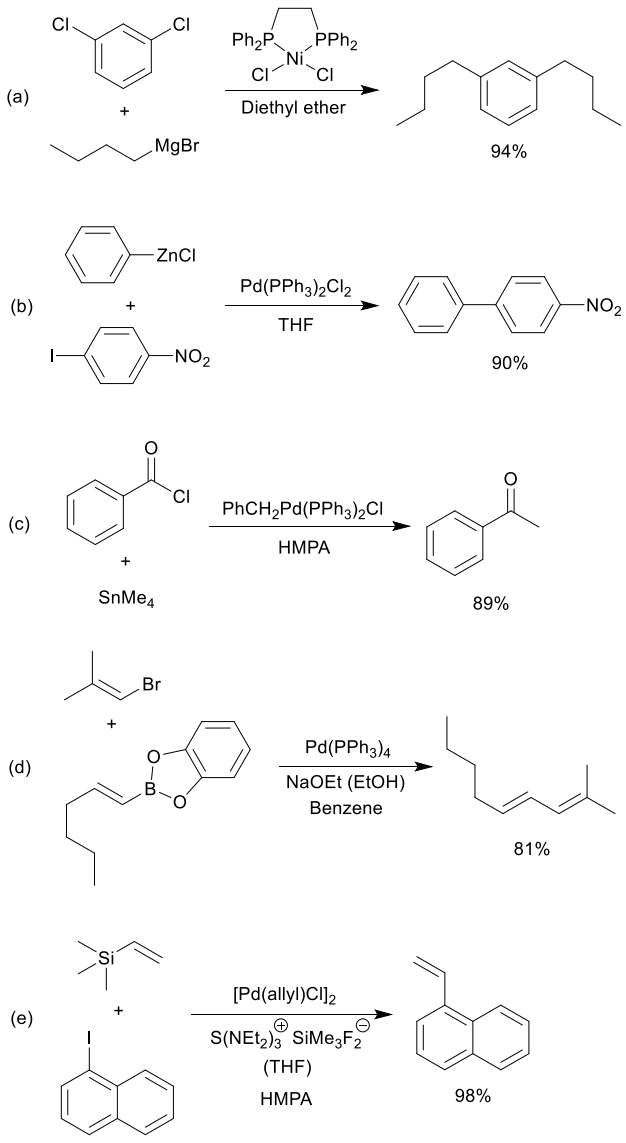
The reaction of organohalides and organometallic compounds can be accomplished by using a catalytic source of Pd(0), with additional ligands, base and solvent as required. The principle of the reaction is deceptively simple (Scheme 1), but there are many possible mechanistic pathways and competing reactions. Throughout this review, common abbreviations have been adopted. A neutral ligand added specifically to the reaction mixture to coordinate to palladium is designated as L. It can be assumed that this is a monodentate phosphine unless stated otherwise. X denotes a halide or pseudohalide (e.g. triflate) which may be present as an anionic ligand to palladium. Metal containing functional groups within organometallic compounds are written as M (e.g. $–SnBu_3$). This designation is also broadened to include boron and silicon containing functional groups in generic schemes. Solvent molecules coordinating to palladium are indicated by an S. The use of R– (and R'–, *etc.*) to indicate various sp, sp^2, sp^3 hybridised organic groups and Ar– to signify aryl groups follows convention.



Scheme 1. A general reaction scheme for a cross-coupling.

Once the concept was proven, a wide variety of cross-coupling reactions were discovered in relatively quick succession (Scheme 2). Early protocols were established firstly by Kumada,[14] and Corriu,[15] for the coupling of Grignard reagents (first published 1972) with nickel catalysts. They were followed by Negishi (oranozincs, 1977),[16] Stille (stannanes, 1978),[17] and Suzuki (organoboranes,

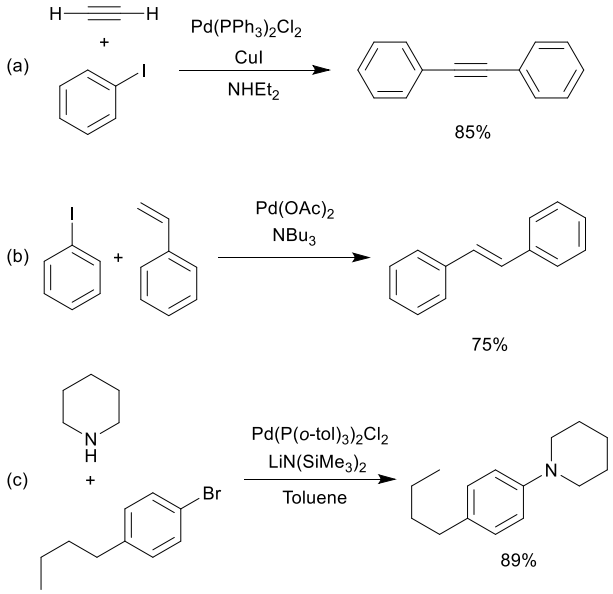
1979).[18,19] The Hiyama coupling of organosilicon compounds came later in 1988.[20] The Stille and Suzuki variants of cross-coupling are considered the most generally applicable.[5] The cross-coupling reactions of other organometallics are not addressed in this review due to a lack of data regarding solvent effects.



Scheme 2. The original cross-coupling methodologies. (a) Kumada reaction, (b) Negishi reaction, (c) Stille reaction, (d) Suzuki reaction, (e) Hiyama reaction.

There are related transformations that employ nucleophilic coupling partners, where a bond to a hydrogen atom is replaced with a new carbon bond (Scheme 3). These reactions are also

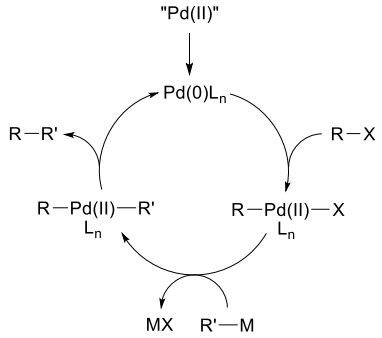
covered in this review. The Sonogashira coupling (alkynes, 1975) can employ an additional copper catalyst, so in fact under these conditions the nucleophile is an *in situ* organocopper compound and analogous to the aforementioned cross-coupling protocols.[21,22] The Heck reaction (alkenes, 1971-1972) lacks a transmetalation as the alkene reacts directly with the catalyst.[23,24] The original Sonogashira reaction conditions used excess amine as solvent, while the first publication by Richard Heck on the coupling between alkenes and aryl halides requires a single molar equivalent of amine base and no additional solvent (Scheme 3). The final protocol to be addressed in this review is the Buchwald-Hartwig coupling of amines, first demonstrated for aminostannanes in 1994,[25,26] then published in its currently recognised form a year later.[27,28] Although the Buchwald-Hartwig reaction also lacks a transmetalation, and a carbon-nitrogen bond is formed instead of a carbon-carbon bond, it shares many parallels with other examples of cross-coupling reactions.



Scheme 3. First reports of complementary synthetic methods sharing characteristics with true cross-coupling reactions. (a) Sonogashira reaction, (b) Heck reaction, (c) Buchwald-Hartwig reaction.

The different cross-coupling protocols are broadly similar in terms of the sequence of steps in the mechanism, but a complete understanding of all the specific nuances is not known.[29] The basic

mechanism (Scheme 4) involves three major steps: (1) oxidative addition of an electrophilic halide or pseudohalide compound to a zerovalent palladium catalyst; (2) transmetalation of an organometallic reactant with the palladium complex formed in the previous step; (3) reductive elimination to create a new carbon-carbon bond and regenerate the catalyst. Additional isomerisations and ligand substitutions can occur and bases are needed for some protocols. Specific catalytic cycles for the Sonogashira, Heck, and Buchwald-Hartwig protocols (for which Scheme 4 does not apply) are presented at relevant points in the text.



Scheme 4. A simplified catalytic cycle for a generic cross-coupling reaction including a Pd(II) pre-cursor to the active catalyst.

1.2 Types of solvent

It is important to be able to describe solvent interactions in order to understand how they influence cross-coupling reactions. Of the intermolecular forces exhibited by solvents, the most abundant but weakest are spontaneously induced dipoles (dispersion forces), present in all solvents as a result of the polarisability of organic molecules. Solvents that are strongly polarisable, such as aromatic and chlorinated solvents, can stabilise the induced and permanent dipoles of other molecules. Toluene, which has these characteristics, is not an uncommon choice of solvent for certain cross-coupling reactions. Solvents featuring a strong permanent dipole are referred to as polar or dipolar. A cyclic solvent is more polar than an equivalent acyclic compound by virtue of its

restricted conformation only permitting geometries with higher dipole moments (e.g. tetrahydrofuran (THF) is more polar than diethyl ether). Hydrogen bonding is a strong intermolecular force with specific directionality, and solvents can be hydrogen bond donors (such as alcohols) and/or hydrogen bond acceptors (including ethers). Non-hydrogen donors are commonly referred to as aprotic.

A cross-coupling reaction involves quite dissimilar substances and that poses a challenge for the solvent. The reaction medium needs to dissolve a full range of solute types: lipophilic reactants, organometallics, inorganic metal complexes, and sometimes salts (e.g. bases and other additives). The obvious choice of solvent for this role is a dipolar aprotic solvent. *N*,*N*-Dimethyl formamide (DMF) is the classic example of a highly polar and aprotic solvent. It is a cheap commodity amide capable of coordinating as a ligand in metal complexes. It will dissolve most organic compounds as well as many inorganic salts to some degree. The boiling point of DMF is 153 °C; sufficiently high to enhance reaction rates but also capable of being recovered by distillation. The Heck reaction is often conducted in DMF.

Dipolar aprotic solvents share a characteristic with some less polar solvents, specifically ethers, and that is the ability to coordinate to a solute in a specific orientation.[30] Coordinating solvents act as Lewis bases, usually donating electrons through an electronegative atom. Halogenated solvents interact differently due to the unique electrostatic potential distribution of organohalides.[31] The stability of the more reactive organometallics is greatly helped by the electron donation of ether solvents, which is particularly relevant to the Kumada and Negishi reactions.

The final intermolecular force to consider is ion-pair interactions, which applies to ionic liquids, deep eutectic solvents, and dissociating solvents (i.e. acids and bases). The presence of ionic species has implications for the solubility of salts and the formation and stabilisation of charged intermediates (including species in the catalytic cycle) and palladium nanoparticles.

The aforementioned solvent-solute interactions make the immediate solvation sheath of a dissolved molecule or ion (called the cybotactic region) more ordered than the bulk medium. This is

especially true of electron donating, coordinating solvents or hydrogen bonding solvents. These specific close range interactions can create an entropic penalty in chemical processes that counteracts the favourable enthalpy of solution.

As an illustration of solvent polarity, solvent donor number has been plotted against relative permittivity (dielectric constant) (Figure 1),[32] and solvatochromic parameters,[33] representing dipolarity (π*),[34] and hydrogen bond accepting ability (β),[35] are given in Figure 2.[13,36,37,38,39] Electron donor and hydrogen bond acceptor are broadly transposable descriptions unless steric hinderance prevents a hydrogen bond acceptor from being an effective electron donor in other circumstances. There is also some commonality between dielectric constant and π* although the former is a bulk medium property and the latter a measure of the strength of solvent-solute interactions. The solvents included in Figure 1 and Figure 2 have relevance to cross-coupling methods, or are included for reference.

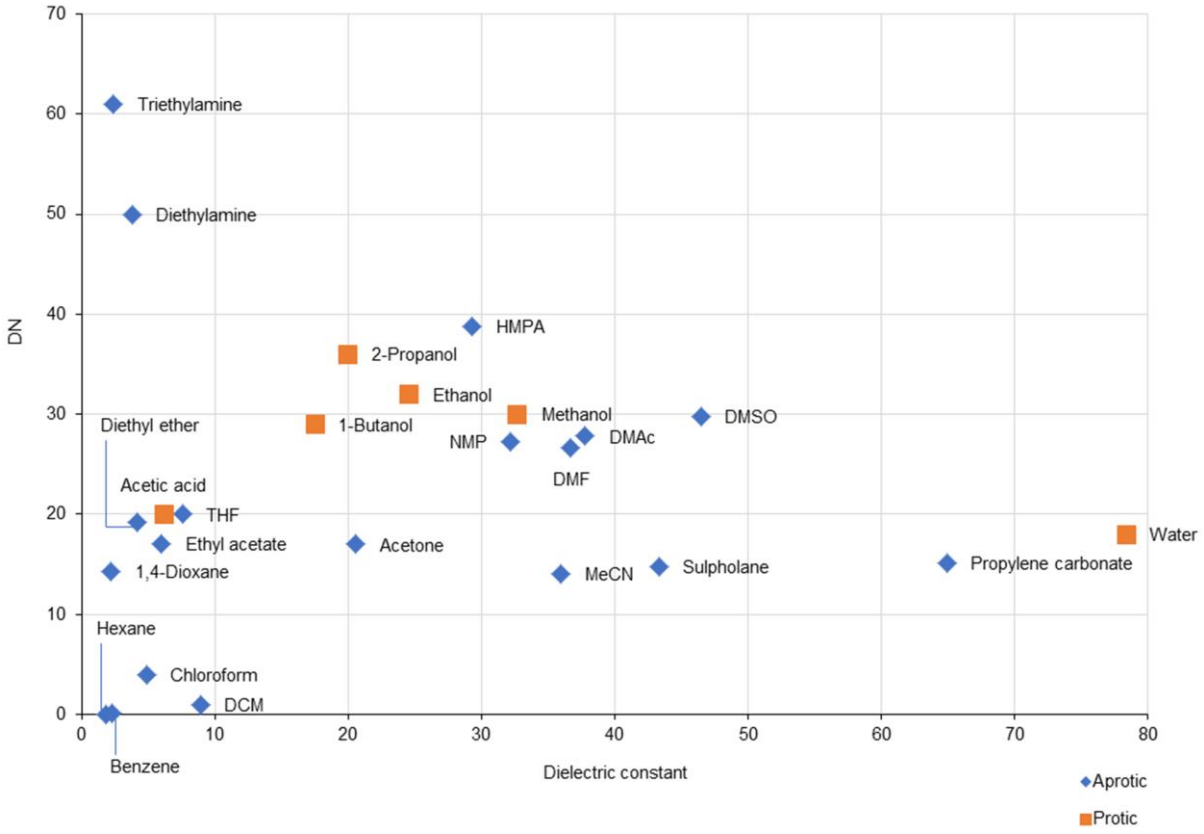


Figure 1. A polarity map displaying relative permittivity and electron donor number (DN) of relevant solvents.

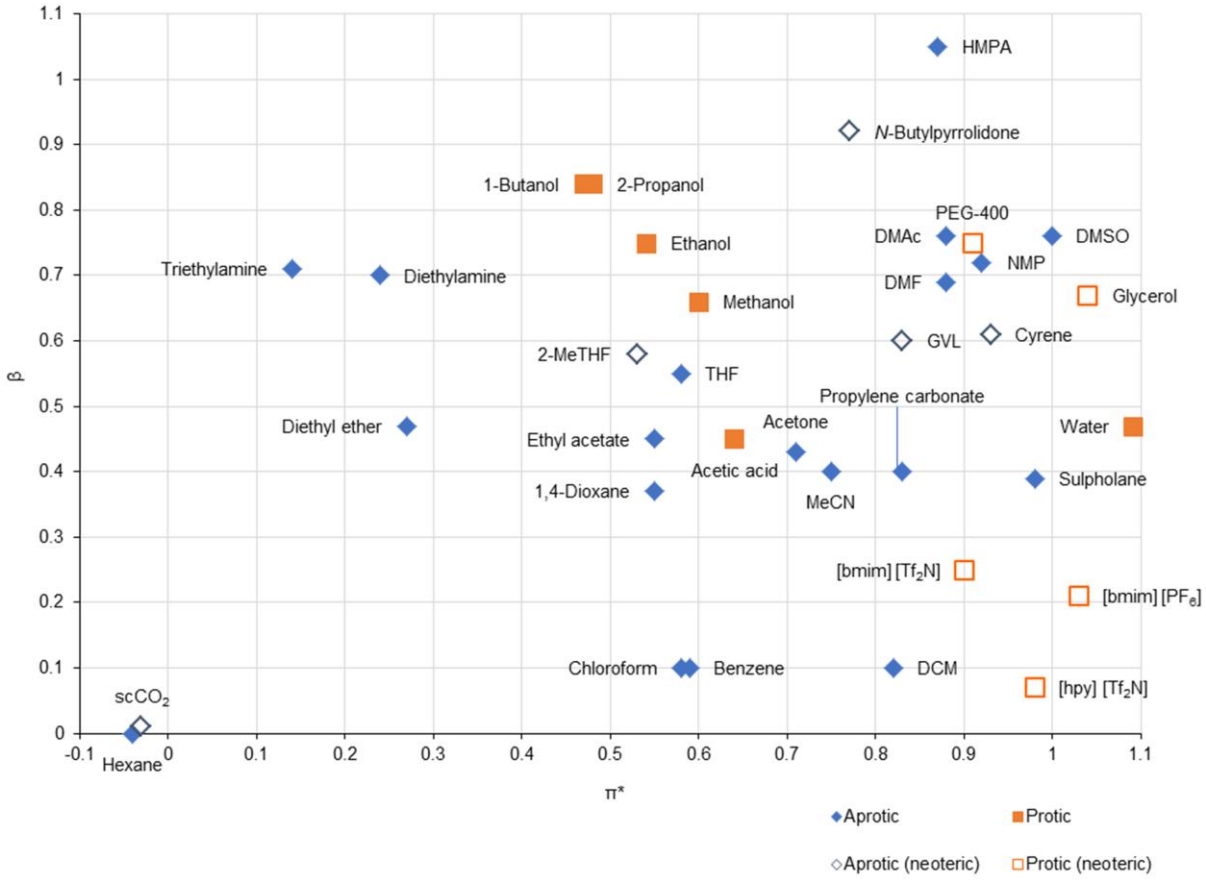


Figure 2. A polarity map of solvatochromic parameters, including newly introduced 'neoteric' solvents.

1.3 Solvent issues

Contemporary chemists still enjoy near-unrestricted use of solvents in R&D and university facilities. Operating at larger scales, there is most definitely not a free choice of solvent. The economics of solvent use, from purchasing to disposal or recovery becomes more relevant. The need for safety equipment is more pertinent, and regulations are more restrictive towards toxic and environmentally damaging substances. Scrutiny of solvent selection has intensified in recent decades, and with it tools to assist solvent replacement have blossomed.[40] A solvent selection guide created by GSK categorises solvents on the basis of waste, health, safety, environment and life cycle analysis impacts.[41] Another tool developed by a partnership of pharmaceutical companies allows the user to add new solvents to the assessment as they become available.[42] The types of laws that tend

to affect solvent users generally relate to good practice (health and safety), waste disposal, industrial emissions, and environmental protection.[43] Those working in specific industries will also know certain solvents are not permitted in some products or processes (usually relating to food, cosmetics, and other consumer products). Solvent hazards can be severe, and present themselves during the reaction, and after: as the waste from the process, and as contamination in the final product. As the major component of a reaction (by mass),[44] any solvent hazards make a considerable contribution to the overall risk and life cycle impacts of a process.[45]

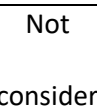
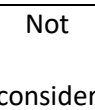
A new wave of chemical legislation is placing restrictions on how toxic and environmentally damaging solvents can be used, and demanding permits are required for others to be used at all. Legislation is frequently revised and therefore a thorough discussion is not appropriate here. However it is wise to appreciate some of the overarching principles of worldwide chemical regulations and the direction in which they are moving.[46] In the USA, the 'Toxic Substances Control Act' (TSCA) was recently updated.[47] A more proactive agenda begins with an initial round of investigations into ten chemicals,[48] setting the tone for more expansive work to come. The results of these risk evaluations will define control measures (if found necessary) to limit the use of these substances and therefore reduce human exposure and environmental pollution. Seven of the first ten chemicals are solvents, including 1,4-dioxane and *N*-methyl pyrrolidone (NMP) which are frequently used as the reaction medium for cross-couplings.

In Europe, the 'Registration, Evaluation, Authorisation and Restriction of Chemicals' (REACH) regulation is the most broad and impactful chemical legislation ever put into practice by the European Commission.[49] In short, chemicals (including solvents) can be taken out of routine use should they be proven to be carcinogenic, mutagenic, reprotoxic, or environmentally damaging (persistent, bio-accumulative, and eco-toxic). Chemical substances can be either restricted (banned from certain applications),[50] or require authorisation before use.[51] In the latter case a full ban is put in place unless a company applies for a permit, which is extremely costly and time limited. Authorisations are now needed to use two chlorinated solvents (trichloroethylene, 1,2-

dichloroethane),[52] and diglyme (*bis*(2-methoxyethyl) ether). The amide polar aprotic solvents (DMF, *N*,*N*-dimethyl acetamide (DMAc), NMP) favoured for many cross-couplings are reprotoxic and are already banned from consumer products in Europe. Industrial restrictions are in preparation.[53] As of 9th May 2020, NMP will not be allowed in applications where the concentration of solvent vapour emitted exceeds a value of 14.4 mg/m^3.[54]

The hazards associated with solvents used in cross-coupling reactions are well known (Table 1). The Globally Harmonized System of Classification and Labelling of Chemicals (GHS) makes the reporting and communication of hazards unambiguous. All the solvents in Table 1 are irritants, which is a minor hazard and can be controlled easily. Most organic solvents are flammable. Diethyl ether is considered extremely flammable (H224), while THF and 1,4-dioxane are highly flammable (H225). Conversely the dipolar aprotic solvents have high flash points. This means DMF is considered flammable (H226) but DMAc and NMP are not because they have flash points above 60 °C. Despite being safer to handle these dipolar aprotic solvents are reprotoxic. Traces of acrylonitrile in acetonitrile (MeCN), with which it is co-produced,[55] have meant additional acute toxicity and chronic toxicity hazards have been associated with acetonitrile.[56] Toluene presents a number of chronic toxicity hazards. The least hazardous solvent in Table 1 is ethanol, which is sometimes used alongside water as a co-solvent for Suzuki reactions in particular.

Table 1. The hazards of solvents popular in cross-coupling reactions.

MeCN	DMF	DMAc	NMP	Diethyl ether	THF	1,4-Dioxane	Ethanol	Toluene
								
H302 H312 H319 H332	H312 H319 H332	H312 H319 H332	H315 H319 H335	H302 H336	H302 H319 H335	H319 H335	H319	H315 H336
								
H225	H226	Not considered flammable	Not considered flammable	H224	H225	H225	H225	H225
No chronic toxicity hazard	 H360D	 H360D	 H360D	No chronic toxicity hazard	 H351	 H351	No chronic toxicity hazard	 H304 H361D H373

H224: Extremely flammable liquid and vapour; H225: Highly flammable liquid and vapour; H226: Flammable liquid and vapour; H302: Harmful if swallowed; H304: May be fatal if swallowed and enters airways; H312: Harmful in contact with skin; H315: Causes skin irritation; H319: Causes serious eye irritation; H332: Harmful if inhaled; H335: May cause respiratory irritation; H336: May cause drowsiness or dizziness; H351: Suspected of causing cancer; H360D: May damage the unborn child; H361D: Suspected of damaging the unborn child; H373: May cause damage to organs through prolonged or repeated exposure.

2. Solvent effects in cross-coupling reactions

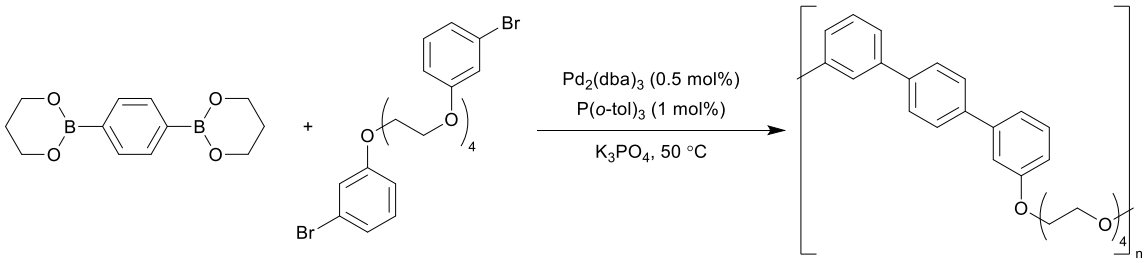
The different cross-coupling protocols have their own nuances and a number of experimental variables to explore. With this comes profound changes to reaction rates, product selectivity and yields.[57] The solvent is a straightforward and rewarding variable to investigate. The common choice of solvent in different cross-coupling reactions utilising extremely low catalyst loadings has been surveyed by Roy and Uozumi,[58] who found no difference to cross-coupling protocols as a whole which is summarised in general terms below.

Some cross-coupling protocols often rely on high temperature conditions, and the Heck reaction, although not exclusively, is a prime example.[59] Therefore the choice of solvent is important to define the maximum operating temperature (that being the solvent's boiling point). The role of bases in cross-coupling reactions (where they are needed) varies between protocols with different solvent requirements. For higher solubility, water or a dipolar aprotic solvent enables homogeneity with inorganic bases.[60,61] As can be seen in Scheme 2, hexamethylphosphoramide (HMPA) was once a popular dipolar aprotic solvent. Now rarely used, the highly toxic and moisture sensitive HMPA has since been replaced by DMF and other similar amide solvents. The combination of amine bases and less polar solvents (e.g. toluene) is applicable to the Heck reaction, which is convenient to provide a homogeneous solution that is compatible with flow chemistry, and also non-miscible with water to allow partitioning of products and by-products to help with extraction and purification of the product.[59] Sometimes limited base solubility is better to provide a thermodynamic impetus to achieve a charge neutralisation, and for this reason aromatic hydrocarbons and 1,4-dioxane are routinely used in the Buchwald-Hartwig reaction in combination with alkoxide bases.[62]

Sometimes the solubility and stability of the reactants is more important than other considerations and the solvent is chosen for this reason. Ethers are used to synthesise and stabilise the more reactive organometallics, including Grignard (organomagnesium) and Reformatsky (organozinc) reagents, as well as more exotic organoindium coupling partners.[63] Adamo *et al.* found

the choice of solvents available to them for a Suzuki reaction was limited by the solubility of 4-cyanophenylboronic acid (which is soluble in DMF).[64] Protic solvents (e.g. alcohols) are avoided in some cross-coupling protocols because of their reactivity.[65] However, in methods employing less reactive organometallics, alcohol solvents can be beneficial. Alcohols will also reduce Pd(II) pre-catalysts in some circumstances, instead of sacrificing other reaction components (ligands, bases, organometallics) as reducing agents.[66]

Rarely is the choice of solvent decided by the solubility of the product in a cross-coupling reaction, but this is more frequently the case in polymer synthesis. The solubility of the polymer overrides other demands on the solvent, because to obtain the necessary molecular weight the product must stay in solution and hence remain reactive. The regular choice of solvent (DMF) for a Suzuki reaction between a diboronic ester and an organodibromide was found to result in product precipitation before the polymer molecular weight reached sufficiently high values (Scheme 5).[67] Dichloromethane (DCM) was used instead to increase the number average polymer molecular weight by an order of magnitude (Table 2). In other situations, precipitation of the product can be helpful for separation purposes which of course is also controlled by the polarity of the solvent.



Scheme 5. A polymerisation reaction between *bis*-functionalised bromide and boronic ester reactants.

Table 2. A solvent screen in a cross-coupling polymerisation.

Solvent	M_n	M_w
DCM	63,600	178,000
THF	51,900	124,000
Dimethoxyethane	44,200	117,000
Toluene	39,600	92,300
1,4-Dioxane	39,600	84,300
DMF	6,290	9,140

Where the role of the solvent has been investigated in literature studies, the following descriptions of oxidative addition (Section 2.3), transmetalation (Section 2.4), and reductive elimination (Section 2.6) will attempt to provide a complete overview of our contemporary understanding of solvent effects in cross-coupling reactions. A simplified mechanism highlighting these different steps was provided in Scheme 4. The transmetalation step is specific to each organometallic reagent and as such are treated separately in this work. Reactions with no formal transmetalation step, as in the Heck, Sonogashira, and Buchwald-Hartwig reactions, are addressed in Section 2.5.

2.1 Catalyst activation

2.1.1 Reduction of Pd(II) pre-catalysts

The palladium species added to the reaction is not necessarily the active catalyst. In fact it is common to use stable and commercially available Pd(II) compounds as a pre-catalyst, with an active Pd(0) species generated *in situ*. In many catalytic cycles the reduction of the pre-catalyst is abbreviated or excluded so as not to distract from the cross-coupling reaction itself. In recognition of this very important phase of any cross-coupling reaction using a Pd(II) pre-catalyst, a detailed

examination of the reduction to Pd(0) is provided here, highlighting the role of solvent alongside reactants, ligands, water, and bases.

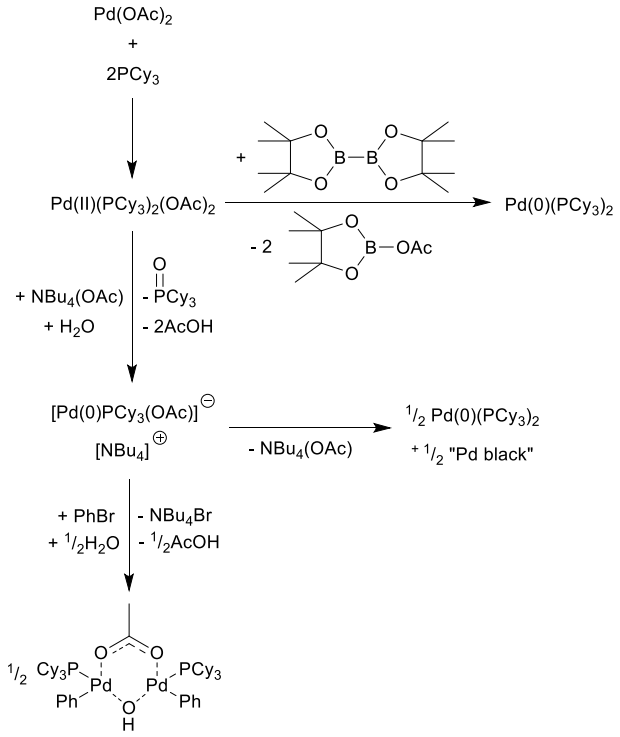
Palladium acetate is a frequently used pre-catalyst. It is a trimer in the solid state, but solvents assist its dissociation into a monomeric form that is more susceptible to reduction. Extended X-ray Absorption Fine Structure (EXAFS) makes it possible to study the structure of catalysts in solution. It has been found that the amount of $Pd(OAc)_2$ monomer liberated is proportional to the dipole moment of the solvent (Table 3).[68] On top of the thermodynamic preference established by the solvent, the addition of water will accelerate the breakdown of trimeric palladium acetate, releasing the desired monomer.

Table 3. The distribution of palladium acetate forms in solvents of different polarity.

Solvent	Dipole moment	Trimer	Monomer	Other
Toluene	0.3 D	71%	21%	8%
DMF	3.8 D	56%	42%	2%
NMP	4.1 D	0%	100%	0%

In a case study of a borylation, the reaction used to produce boronic esters for Suzuki reactions (also see Section 2.2), Wei *et al.* found palladium acetate in the presence of PCy_3 was reduced to zerovalent $Pd(PCy_3)_2$ by bis(pinacolato)diboron in toluene (Scheme 6).[69] Boronic acids can also act in this role of reducing agent in Suzuki reactions.[70] The presence of base (tetrabutylammonium acetate introduced with 1 equivalent of water) only led to 50% conversion to $Pd(PCy_3)_2$. This is due to the oxidation of one equivalent of ligand, resulting in a monophosphine complex that thermodynamically prefers disproportionation into $Pd(PCy_3)_2$ and palladium black. Toluene is not a polar enough solvent to offer sufficient stabilisation to a monophosphine complex.

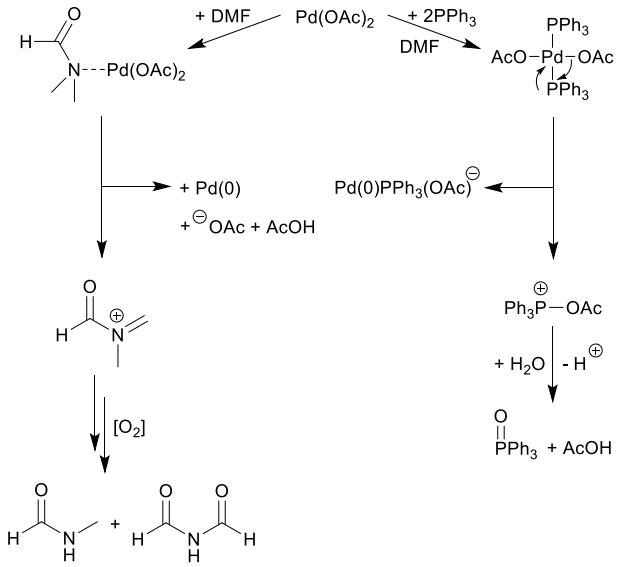
Yet with the addition of bromobenzene, rapid oxidative addition will trap the monophosphine complex as a dipalladium complex with bridging acetate and hydroxide ligands.



Scheme 6. Reduction routes for palladium acetate in non-polar solvents where bis(pinacolato)diboron or tricyclohexylphosphine are oxidised.

Whereas less polar solvents are appropriate for borylations, cross-coupling reactions are frequently performed in more polar solvents better suited to stabilising charge. Jutand *et al.* found ancillary phosphine ligands are also capable of reducing palladium in DMF.[71] If palladium acetate is being used as the pre-catalyst then the acetate counter-ion retains a role by forming an anionic Pd(0) species (Scheme 7). Amide dipolar aprotic solvents (such as DMF) can themselves be oxidised by Pd(II) species,[72] ultimately producing an imide by-product (Scheme 7). Cyclohexanone, 1,4-dioxane and 1,2-dimethoxyethane (DME) will also participate in redox reactions to yield Pd(0).[72] Thus the solvent itself can have a direct role in the formation of active catalysts. As the solvent is used in vast excess it is still practical and convenient to consider it as inert, but this is further

evidence that the choice of solvent has a crucial impact on all aspects of cross-coupling reactions, even the less obvious and subtle aspects. Reduction of Pd(II) salts is also the principal way in which palladium nanoparticles are synthesised.[73,74] Palladium nanoparticles are effective catalysts for many cross-coupling reactions (Section 2.1.3). Following the left pathway in Scheme 7, the reduced palladium is logically in the form of nanoparticles to provide an active catalyst.



Scheme 7. Reduction of palladium(II) by triphenylphosphine in DMF (right-hand side pathway) and DMF itself (left side).

2.1.2 Active form of homogeneous catalysts in solution

Often the active catalyst is represented as a simplified 14 electron $Pd(0)L_2$ species, with L indicating a ligand. However the coordination sphere around the palladium is sensitive to the conditions and there is an energetic motivation to attract more ligands to bolster the complex electron count. If salts are present in solution, anionic active catalyst species have been proposed which will be stabilised in the more polar solvents.[22,75] The interaction between countercations and dipolar aprotic solvents is sufficient to liberate an active anionic catalyst from an otherwise less reactive state caused by shielding ionic pairs.[65] Non-polar solvents disfavour the formation of ionic

species, and they might not be expected to exist at all. This also means the nature of the pre-catalyst has a role in determining the optimal solvent, as summarised by Miyaura and Suzuki in their review of palladium catalysed cross-coupling reactions of organoboron compounds (the Suzuki reaction).[76] They have stated less polar solvents (aromatic solvents, 1,4-dioxane) complement $Pd(PPh_3)_4$ while an ionic pre-catalyst (prone to forming an anionic active species) is suited to highly polar solvents.

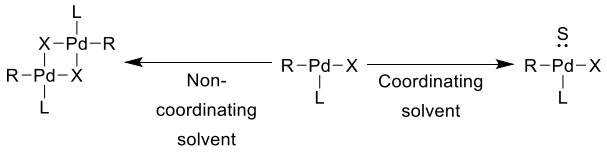
The active catalyst is not necessarily the major palladium species found in solution. If a minor species is much more reactive, the product will be formed mostly through this intermediate. Anionic complexes, or those with fewer ligands have been found to be more reactive than neutral and 18 electron complexes (Table 4).[75] Where a ligand has dissociated a solvent molecule will likely take its place, especially in the absence of anions. This equilibrium is enhanced by the massive excess of solvent molecules that will be present, compensating for the weaker ligand behaviour of a typical solvent molecule compared to a phosphine molecule for example.

Table 4. The difference between the thermodynamic (major) and reactive (minor) palladium complexes produced by the transformation of selected pre-catalysts. Dibenzylideneacetone is represented as dba, and *n* is used to denote an unspecified number of ligands.

Precursor	Major species	Reactive species
$Pd(0)L_4$	$Pd(0)L_3$	$Pd(0)L_2(S)$
$Pd(0)(dba)_2$ + *n*L	$Pd(0)(dba)L_2$	$Pd(0)L_2(S)$
$Pd(II)Cl_2L_2$	$Pd(0)L_2Cl^-$	$Pd(0)L_2Cl^-$
$Pd(II)(OAc)_2$ + *n*L	$Pd(0)L_2(OAc)^-$	$Pd(0)L_2(OAc)^-$

In the literature there are frequent references to T-shaped 14-electron Pd(II) complexes active in the catalytic cycle of cross-coupling reactions.[57] The implication is of a square planar geometry with a vacant position due to the loss of a ligand. As described in detail by Casares *et al.*,[77] a 14-electron complex will not exist when there is any possibility that a molecule of the solvent can

act as the fourth ligand. A coordinating solvent can fill the vacant position of a square planar complex in an otherwise T-shaped complex (Scheme 8).[78] In non-coordinating solvents, 16-electron Pd(II) complexes are formed by dimerisation. Such is the reticence of palladium to drop to low coordination numbers, it is believed that ligand substitutions on a Pd(II) complex, including those where the solvent displaces a formal ligand, always occur through an associative mechanism (and temporarily a higher coordination number) in preference to a dissociative pathway where a transient vacant ligand site is created.[57]



Scheme 8. The nature of so-called T-shaped Pd(II) complexes in solution, as shown after oxidative addition.

Some studies clearly show a single ancillary ligand (e.g. a phosphine) is bound to palladium in the catalytic cycle. Single ligand palladium species are less stable but therefore more reactive.[79,80,81,82] To maximise the concentration of monophosphine complexes the ligand is typically bulky and electron rich like tri-*tert*-butylphosphine and tricyclohexylphosphine.[83] Very little if any of a Pd(0)L species would favourably exist in solution due to its low coordination number, promoting rapid oxidative addition. Crystal structures of mono-phosphine palladium compounds formed after the oxidative addition of bromobenzene (of the general form shown in Scheme 8) actually show a square planar geometry with the vacant ligand position trans- to the phenyl ligand being stabilised by a weak agostic interaction arriving from the ligand (e.g. P^tBu_3).[84] These complexes are prepared by a solvent-free oxidative addition and crystallised from pentane, which is a non-polar, non-coordinating solvent. In a solution of coordinating solvent, an agostic bond, with a typical bond

strength of 10 kJmol^{-1},[85] is vulnerable to the superior enthalpy of solvent coordination (~20 kJmol^{-1} for ethers, ~25-30 kJmol^{-1} for amides, as derived from the donor number,[13] DN, of these solvents).

It is also known that many examples of cross-coupling do not require the addition of a specific ligand at all. The Heck reaction is often catalysed by palladium acetate or palladium nanoparticles alone. Pd(0) must be stabilised (in part at least) by the excess solvent in the solution phase. To do this the solvent must be coordinating, and DMF is the conventional choice.[65] It is also possible to perform Suzuki reactions without ligands and this is particularly true in protic solvents, be it alcohols or aqueous dipolar aprotics.[68,86,87] We will return to this topic in the following section on heterogeneous catalysts (Section 2.1.3). The role of the solvent is amplified when ligands are absent as it is now the solvent that is key to tuning the electronics of the catalyst as well as stabilising activated complexes and thus ensuring the reaction proceeds. A fast oxidative addition step is helpful in this situation as it supplies two ligands once palladium has inserted into the organohalide C–X bond, the rate of which is solvent dependent (Section 2.3).

2.1.3 The role of solvent in heterogeneously catalysed cross-coupling reactions

In heterogeneous catalysis the solvent remains an important component of the reaction. The reasons for favouring heterogenous catalysts centre on the reuse of the palladium. As well as economic benefits the potential for lower Pd contamination in products is welcome, especially for the synthesis of pharmaceuticals where strict metal residue limits apply,[88,89] and also organic materials for electronic components. When a palladium complex is tethered to a solid support *via* modified ligands the solvent retains the same responsibilities as in homogeneous catalysis.[90] Another form of heterogeneous palladium is a surface or encapsulated catalyst, typically palladium nanoparticles. Note that the popular palladium on carbon (Pd/C) is an ill-specified mixture of palladium oxides and hydroxides on a carbon support.[91] When using a heterogeneous source of palladium to catalyse cross-coupling reactions, the solvent must ensure mass transfer limitations are overcome whilst continuing to participate in the reaction as the solvation sheath (cybotactic region)

of the reaction intermediates.[92] As summarised in Figure 3, for purely heterogeneous catalysis to occur, the reactants must diffuse through the medium (in this case a solvent) to approach the catalyst. In porous heterogeneous catalysts the reactants must then further diffuse into the material. Then the reactant is available to absorb onto the catalytic site, firstly by physical absorption (physisorption) and then chemically interact (chemisorption). Some solvent molecules are expected to be displaced from the cybotactic region in the process. Any charge generated on the surface of the catalyst particles can be expected to change its affinity towards solvent molecules and any ions in solution, creating a double layer which the reactants will exchange into. Now the reaction can occur in an analogous fashion to a homogeneous cross-coupling reaction (Scheme 4). The product will then desorb from the catalyst and be taken up into solution with the assistance of the solvent. Kinetic descriptions of heterogeneous catalysis are dependent on the concentrations of reactants in the rate determining step, mass transfer coefficients between phases, and diffusivity into porous catalysts.[93] The viscosity of the solvent is a crucial parameter to consider in this regard.[94] Most organic solvents are reasonably similar in terms of their viscosity, but some neoteric solvents have much higher values (see glycerol and dihydrolevoglucosenone in Section 3.1).

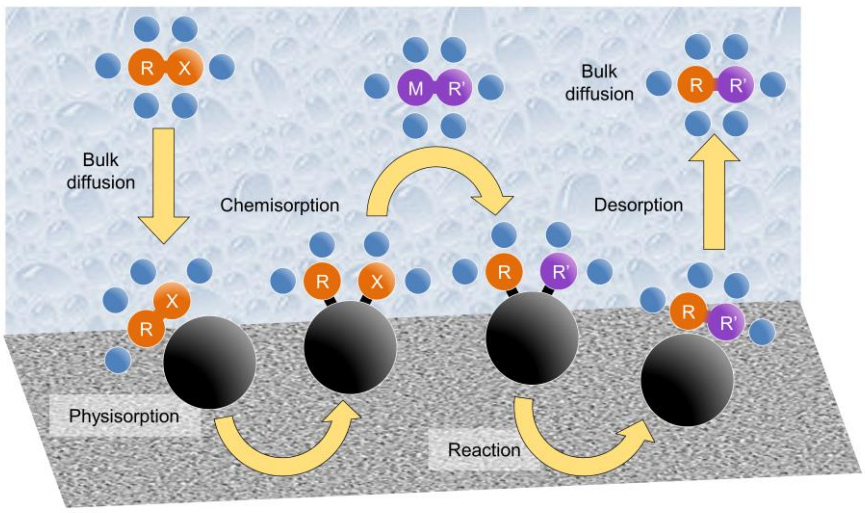
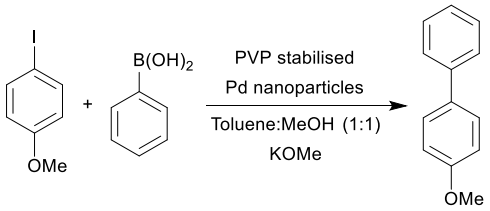


Figure 3. A presumed catalytic pathway of heterogeneous catalysis with palladium nanoparticles. Key: large black circles represent a catalyst; small blue circles represent coordinating solvent molecules; reactants (R–X and R'–M) and product (R–R') are labelled by group.

Most studies into the action of solid palladium catalysts conclude the true catalyst is in fact homogeneous, and not heterogeneous.[88,95] Leaching of palladium as Pd(II) is reported as being relatively slow, which is why many cross-couplings have a kinetic induction period characteristic of homogeneous catalysis from a heterogenous source.[88] In these instances the solvent must be encouraging leaching and diffusion of palladium into solution. As a consequence Ostwald ripening is regularly observed in palladium nanoparticles when Suzuki reactions are conducted for long durations under reflux conditions (e.g. in acetonitrile).[96] In an example of a Heck reaction, palladium nanoparticles were found to have increased in diameter by an order of magnitude (average size of 2.4 nm prior to reaction, but 23 nm after reaction).[97] These observations are consistent with the dissolution of palladium and a homogeneous mechanism of catalysis. In this instance the reaction was conducted with prolonged heating (140 °C, 20 hours) in DMAc. Some solvents are suited to the extraction of heterogeneous palladium nanoparticles into solution,[98] particularly the dipolar aprotic amides.[99]

True heterogenous nanoparticle catalysis does occur under the right conditions, and a variety of tests are available to discern when this type of activity is present.[100] A medium polarity solvent system at no more than modestly elevated temperatures can eliminate the palladium leaching observed in dipolar aprotic solvents.[101] For this purpose a mixed toluene-methanol solvent has successfully been applied as the medium for truly heterogeneous catalysis of a Suzuki reaction (Scheme 9).[102] Reaction monitoring by EXAFS demonstrated that polyvinylpyrrolidone (PVP) stabilised palladium nanoparticles do not leach palladium into solution. This was verified by various analyses, and no induction period was observed. The rate of reaction was related to the availability of palladium atoms at defect sites on the nanoparticle, which is dependent on its size.

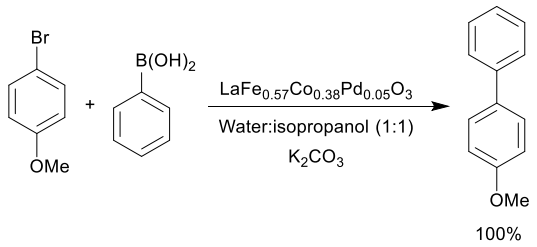


Scheme 9. Palladium nanoparticle catalysis of a heterogeneous Suzuki reaction.

Encapsulation of palladium is a satisfactory way of regulating the concentration of palladium that is leached into solution to promote cross-couplings. The effectiveness of this approach depends on the ability of the solvent to swell the encapsulating polymer. Palladium acetate encapsulated in a polyurea matrix (Pd EnCat™) is a popular variety of this style of catalyst.[103] Broadwater and McQuade found that aprotic solvents (DMF, and toluene to a lesser degree) swell the Pd EnCat™ polymer matrix significantly more than protic solvents (i.e. isopropanol) and thus more palladium escapes into solution.[104] However, the rate of a Heck reaction between butyl acrylate and 4-bromoacetophenone is not enhanced by the extra solution-based palladium in aprotic solvents. Instead the reaction is slower, indicating the higher concentration of palladium results in faster deactivation, perhaps as palladium black. Therefore alcohols are the most appropriate solvents for cross-couplings catalysed by this particular type of polyurea encapsulated palladium. More generally the compatibility of different solvents with polymers can be evaluated with the Hansen solubility parameters (dispersion forces, δ_D; dipolarity, δ_P; and hydrogen bonding, δ_H).[105] The more similar all three Hansen solubility parameters are between a polymer and a solvent the more likely that swelling or dissolution will occur. In this case the encapsulating polymer will have a relatively low δ_H value whereas alcohols like isopropanol have high values of δ_H.

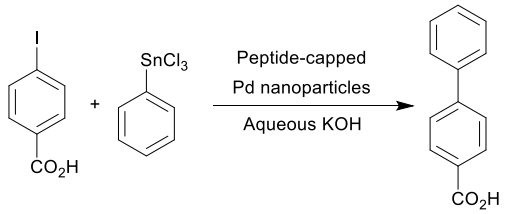
A solvent that will dissolve palladium as well as reduce it to Pd(0) is necessary for ligand-less homogeneous Suzuki reactions catalysed by Pd/C and other heterogeneous sources of palladium in high oxidation states. Aqueous DMAc has been used for this purpose, reducing the palladium oxides and hydroxides found in Pd/C to Pd(0).[106] Other Suzuki reactions using the Pd(III) contained in

perovskite materials (e.g. $LaFe_{0.57}Co_{0.38}Pd_{0.05}O_3$) as a source of catalytic palladium also operate by a homogenous mechanism (Scheme 10).[107] Here, aqueous isopropanol was able to dissolve and reduce the palladium. This is unsurprising given isopropanol is known for its ability in hydrogen transfer reactions to reduce substrates (oxidising to acetone as it donates hydrogen).



Scheme 10. A Suzuki reaction catalysed by a palladium-containing perovskite.

It is now widely recognised that through leaching, detachment, and aggregation there can be several forms of potentially catalytic palladium present in a reaction at the same time.[108] To take an example of the Stille reaction (Scheme 11), EXAFS shows the leaching mechanism by which palladium nanoparticles in water yield single palladium atoms.[109] Oxidative addition with an aryl halide on the nanoparticle surface makes this possible. The process stabilises the nanoparticles because the more reactive palladium atoms situated in disordered surface sites (defects) are favoured for reaction, rendering the remaining nanoparticle less reactive. After passing through one catalytic cycle, the palladium atoms in solution are likely to remain the most reactive species towards the Stille coupling reactants unless they aggregate into amorphous and inactive palladium black, or indeed deposit back onto the parent nanoparticles. There is a fine line between this instance where individual palladium atoms are levered from the nanoparticle by oxidative addition,[109] and where they remain associated to the nanoparticle (Scheme 9).[102] One difference is the polymer used to stabilise the catalyst, and the other is the solvent (water versus toluene-methanol).

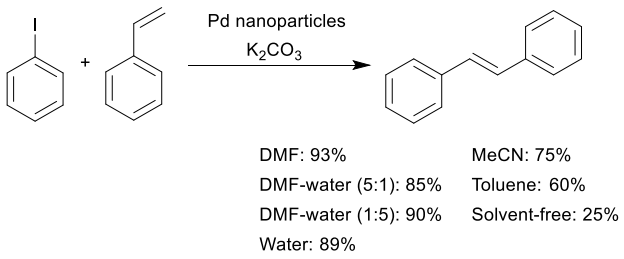


Scheme 11. An aqueous Stille reaction catalysed by single atom palladium.

In-between single atoms and nanoparticles are palladium clusters of approximately 1 nm in size.[110] Metal clusters consist of only a few atoms and are highly reactive.[111] Leyva-Pérez *et al.* found that the fastest rates of cross-coupling reactions are only achieved when palladium clusters of just three and four atoms are formed in solution.[112] The catalyst precursor was irrelevant, for heating in a solution of NMP created the palladium clusters regardless of their source ($Pd(OAc)_2$, $Pd_2(dba)_3$, or dimeric complexes). Concurring with other observations, an aryl halide was needed to cause leaching due to an oxidative addition reaction. The presence of water stabilised the palladium clusters, and under anhydrous conditions the quantity of leached palladium from Pd/C was much reduced. The nucleophilicity of water is believed to be the reason behind its stabilising effect. To prove this, Leyva-Pérez *et al.* also applied nucleophilic amines as a stabiliser for palladium clusters, to find a greater degree of leached palladium in solution.[112] As expected, the Heck reaction which utilises amine bases benefits greatly from this effect.

An additional role for water (as a solvent or co-solvent) occurs in Heck reactions where hydrophilic heterogeneous catalyst supports are used. The obvious explanation is the natural affinity between the solid phase and the liquid phase, reducing any mass transfer barrier. For instance, a flow chemistry procedure for the reaction between aryl iodides and alkenes has been optimised in an azeotropic blend of water and acetonitrile (84 wt% MeCN, boiling point 77 °C).[113] The catalyst consists of palladium nanoparticles immobilised on a hydrophilic ionic liquid-like polymer phase which itself is supported on silica. The solvent could be 95% recovered by distillation. In other work, a solvent screen for the reaction of iodobenzene and styrene catalysed by palladium nanoparticles

on a starch-derived support was high yielding in DMF, aqueous DMF, and water after 24 hours (Scheme 12).[114]



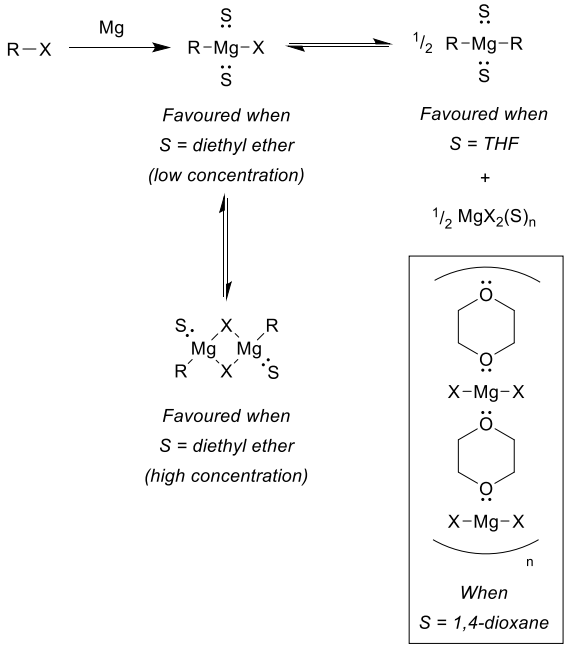
Scheme 12. A solvent screen for a Heck reaction catalysed by starch supported palladium nanoparticles.

2.2 Organometallic reactant preparation

The choice of organometallic reactant and its preparation can dictate solvent selection. The less stable options for nucleophilic partners in cross-coupling reactions obviously have the advantage of being more reactive. The disadvantage is that these substrates typically need to be prepared at the time they are needed. Grignard (organomagnesium) and Reformatsky (organozinc) reagents in Kumada and Negishi couplings are usually synthesised in ether solvents, which are typically used directly as a solution in the subsequent coupling. On occasion the medium for the cross-coupling is tuned by adding a co-solvent.

Ethers possess significant electron donating ability, and it is known than the oxygen donor atom of an ether will form a complex with a Grignard reagent of the form $RMgXS_2$ (S is a coordinating solvent molecule). This complex stabilises the magnesium, but it is sensitive to the choice of ether solvent. The Schlenk equilibrium describes the formation of dialkyl magnesium (and therefore also MgX_2) from a Grignard reagent. Diethyl ether favours the Grignard reagent, while THF promotes MgR_2 (Scheme 13).[115,116] In the diether 1,4-dioxane, the MgX_2 complex is polymeric, which can precipitate and break the equilibrium that otherwise limits the formation of dialkylmagensium.[117] It should be apparent from this observation that the ether solvents are not

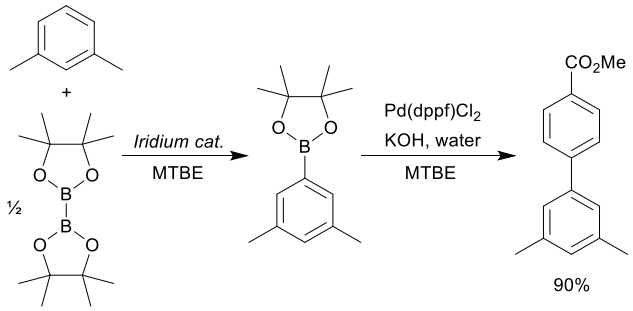
interchangeable, for their molecular structure determines how polar and electron donating they are. This in turn impacts the stability of organometallic reactants. Acyclic monoethers (e.g. diethyl ether) are apolar, while cyclic ethers are more polar (THF is on a par with ethyl acetate in this respect), but not to the extent of an amide. 1,4-Dioxane has the potential to chelate and bridge molecules as a coordinating solvent, as might glyme solvents when circumstances allow.



Scheme 13. The Schlenk equilibrium, and the favoured position indicated according to solvent choice.

The organoboron and organotin reactants of the Suzuki and Stille cross-couplings are less reactive than Grignard and Reformatsky reagents and are characterised by a less polar C–M bond. As such the stability of organoboron and organotin compounds is satisfactory in many different solvents, and are commercially available in neat preparations rather than in solution. The classical method of producing boronic acids and stannane compounds is from a more reactive organometallic compound such as a Grignard reagent. Alternatively, C–H activated arenes can undergo borylation to

form boron compounds needed for a Suzuki type cross-coupling. Iridium catalysed borylation is hindered by the coordinating solvents favoured for cross-coupling. Therefore to establish a one-pot protocol (borylation-cross coupling), a compromise is provided by sterically hindered ethers. Methyl *t*-butyl ether (MTBE) has been shown to be tolerated in the borylation, and then water and the cross-coupling components (including a 1,1′-bis(diphenylphosphino)ferrocene (dppf) functionalised palladium catalyst) can be added to conduct the Suzuki reaction (Scheme 14).[118]



Scheme 14. A one-pot borylation and cross-coupling in methyl *t*-butyl ether.

2.3 Oxidative addition

The oxidative addition (and the mechanistically opposite reductive elimination) of homogeneous molecular systems are fairly well understood through experimental and computational studies. The former describes low valent metals reacting with organohalides in a two electron reduction of the reactant. Catalysis is required because organohalides cannot react directly with organometals and therefore oxidative addition is a necessary prelude to cross-coupling. The oxidative addition process is common to all the cross-couplings discussed in this work as it does not involve the organometallic reactant.[119] The rate of oxidative addition is greater in polar solvents, which has been appreciated since the inception of the cross-coupling methods and led to the adoption of dipolar aprotic solvents.[120] Oxidative addition is also assisted by strongly electron donating ligands, but a balance is required because electronic considerations favouring oxidative

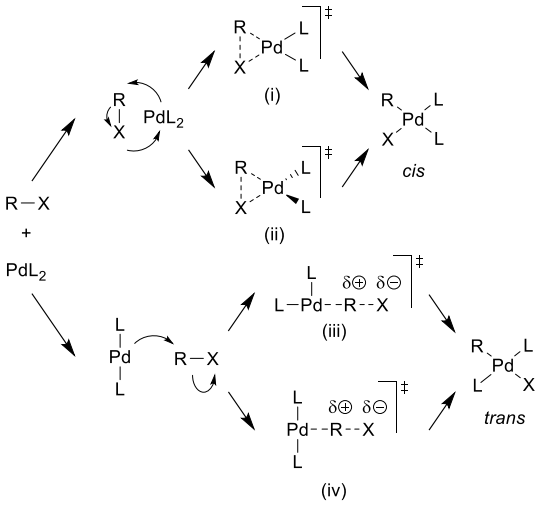
addition will hinder reductive elimination.[121] It is for this reason that phosphine ligands are often associated with cross-couplings, given their intermediate strength of electron donation.

Coordinating solvents (acetonitrile or THF but particularly amides) provide stabilisation to activated complexes. This effect is stronger when weaker AsR_3 arsine ligands are used in place of phosphines.[122] Regardless of the ligands used, the solvent will influence the energy of activation and the energy of reaction to some degree. Thus the solvent determines whether oxidative addition is rate determining or not, and whether it is effectively reversible or not.

The reaction of zerovalent palladium with electrophilic organohalides can be a concerted process progressing through a 3-membered cyclic activated complex. Or a mechanism analogous to a nucleophilic substitution could be in operation. Oxidative addition, say of an aryl halide to $Pd(0)L_2$, results in a 16 electron, square planar $Ar–Pd(II)L_2–X$ complex. Note that triflates are a valuable alternative to organohalides, and fit into the order of reactivity as follows: I > OTf > Br > Cl.[59] The delocalised triflate anion is labile in solution and does not coordinate strongly to the palladium after oxidative addition. If the solvent is sufficiently polar to permit dissociation of the triflate the resultant complex will be a cationic palladium species,[123] assuming that no added salts are present.

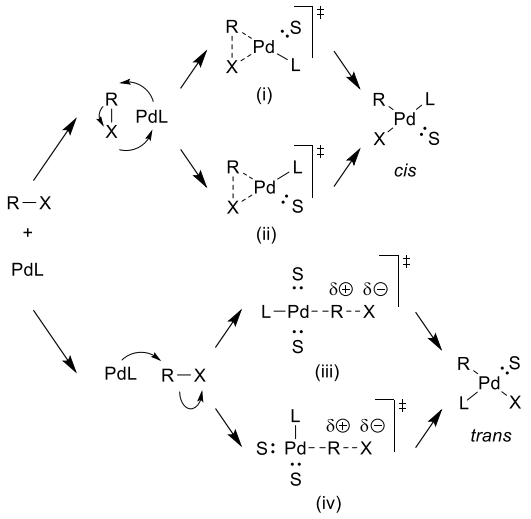
Considering the two possible mechanisms, eight possible activated complexes have been proposed.[79] Each depends on the number of (phosphine) ligands, and their orientation relative to the organohalide. Density functional theory (DFT) modelling has been used to study the possible transition states for a model oxidative addition of bromomethane. Solvation effects were included in this study using the polarisable continuum model (PCM), an implicit solvent model. The choice of ligand and solvent dictated which mechanism was in operation and how the ligands re-orientate to accommodate the oxidative addition. With two phosphine ligands in place (Scheme 15), trans-geometries (with respect to the ligands) are energetically preferred. Crystal structures of diphosphine palladium complexes show linear P–Pd–P bonds and so this is calculated to remain the favoured geometry after oxidative addition occurs.[124,125] The concerted 3-membered mechanism (Scheme 15, route (ii)) is only preferred when the activated complex of the rival S_N2 mechanism

(Scheme 15, route (iv)) is highly distorted. This was found using DFT calculations modelling the gas phase, THF and DMF.[79] The PF_3 ligand was the most supportive of the concerted 3-membered mechanism (preferred in the gas phase and THF) because of the unfavourable configuration adopted during a nucleophilic substitution. DMF is polar enough to support the charge generating S_N2 mechanism despite the conformational difficulties. Traditional PPh_3 ligands always favoured the S_N2 mechanism in any medium, as do bulkier ligands in these calculations.



Scheme 15. A 3-membered concerted oxidative addition process (top) and a nucleophilic substitution version (bottom) with a two-ligand palladium catalyst.

If a monophosphine catalyst is active (Scheme 16), Pd-C bond formation is favoured in a cis-configuration to the phosphine.[79] The S_N2 mechanism (Scheme 16, route (iv)) was calculated to proceed at a greater rate than the concerted 3-membered mechanism (Scheme 16, route (ii)) in DMF. In THF a 3-membered concerted mechanism was also unfavourable while the S_N2 was calculated to be exothermic and barrierless.[126] Based on the results of gas-phase calculations, only by using non-polar solvents might the 3-membered concerted mechanism become viable, if only because the greater charge stabilisation in the S_N2 mechanism is no longer supported by the solvent.

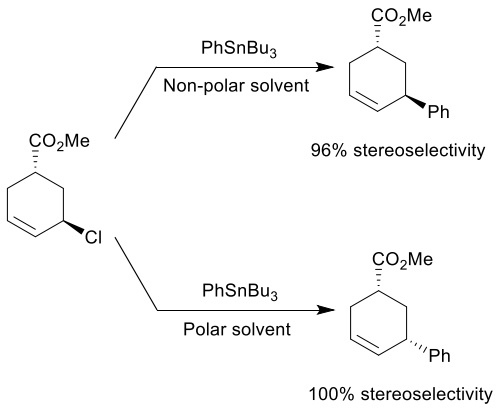


Scheme 16. A 3-membered concerted oxidative addition process (top) and a nucleophilic substitution version (bottom) with a single-ligand palladium catalyst.

Other work suggests the 3-membered concerted mechanism is more favourable than suggested thus far. Alternative DFT calculations found a concerted 3-membered activated complex is preferred as the first step in Suzuki reactions.[80] Lyngvi *et al.* used DFT approaches with both implicit and explicit solvent models to show that a concerted oxidative addition mechanism is favoured by a Pd(P^tBu_3) catalyst (KF base) regardless of whether aryl chlorides or aryl triflates are used as reactants.[127] The explicit solvent model included six molecules of solvent (acetonitrile), but due to lack of specific solvent-solute interactions the explicit solvent modelling did not result in different conclusions when compared to implicit solvent models. This can be ascribed to a lack of solvent-catalyst hydrogen bonding or other specific solvation effects. The authors point out that the calculations suggest $[Pd(P^tBu_3)F]^-$ is the active catalyst in polar solvents such as acetonitrile and DMF.[127] The existence of anionic catalysts was also suggested by the experiments of Proutiere *et al.*, who showed with indirect evidence that a Pd(0)L type active catalyst must exist with an additional electron donating participant.[128,129]

Experimental observations agree with computational studies, indicating the solvent does indeed control the mechanism of oxidative addition,[130] as do the ligands.[131] This is important for

some cross-couplings because stereochemistry is preserved in the cyclic oxidative addition mechanism and inverted by the S_N2 mechanism.[121] When sp^2 hybridised vinyl halides or sp^3 hybridised alkyl halides with a stereocentre are the reactant, the final product will depend on the mechanism of the oxidative addition. To take the example of 5-chlorocyclohex-3-ene-1-carboxylic acid methyl ester, stereochemistry was inverted in acetonitrile and dimethyl sulphoxide (DMSO) as part of a Stille reaction.[132] The stereochemistry of the allyl group is retained in benzene, DCM, THF, and acetone (Scheme 17).[132,133] This work showed it is possible to select the desired reaction pathway through a judicious choice of solvent. Swapping selectivity towards the concerted 3-membered transition state instead of the S_N2 mechanism appears easier to achieve through solvent selection than suggested by the DFT calculations reviewed previously. There is a clear division between the solvents with high dielectric constants that favour the S_N2 mechanism and those that promote the cyclic concerted mechanism (all with low dielectric constants).



Scheme 17. Solvent dependent stereoselective Stille reactions.

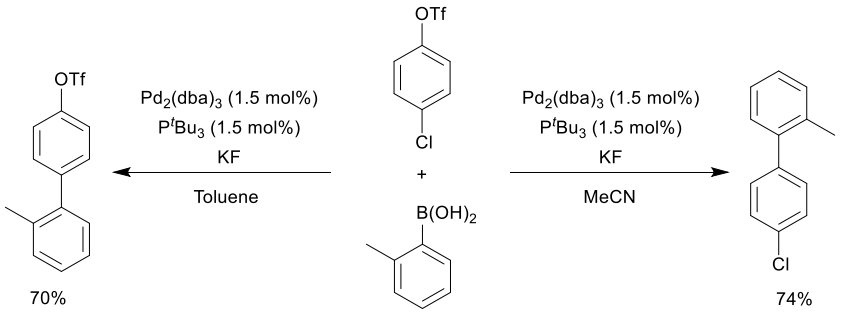
Hammett plots have indicated electron withdrawing groups on an aryl iodide reactant increases the rate of oxidative addition (in toluene or THF).[134,135] This indicates a negative charge forms on the aromatic ring instead of the halide, which is inconsistent with the S_N2 mechanism that occurs in more polar solvents. Thus the classic Hammett plot proves itself to be a useful technique to differentiate the two possible reaction pathways.[59]

Examples where oxidative addition is rate determining are not uncommon.[136,137,138] This can be the case with organochlorides. To activate aryl chlorides towards oxidative addition in Suzuki reactions (where alcohol solvents are generally tolerated) refluxing butanol is an option.[139] The beneficial role of a protic solvent system in Suzuki reactions can be exaggerated by the use of photochemically activated procedures. Palladium nanoparticles formed on WS_2 nanosheets are more catalytically active if they receive electrons to accelerate the rate determining oxidative addition step of a Suzuki reaction.[140] Raza *et al.* showed WS_2 electron holes are accepted by protic solvent molecules, with aqueous ethanol preferred. Other aqueous alcohols were also suitable solvents, but water alone is not. Aqueous DMF and aqueous DMSO also failed to facilitate the reaction in this instance.

Given the high reactivity of organozinc and organomagnesium reagents towards transmetalation it is conceivable that Negishi and Kumada couplings will have a rate determining oxidative addition. The choice of solvent is not as flexible as with other cross-coupling methods and so other variables need to be looked at. Given this is the case, sometimes a nickel catalyst is superior to palladium because they excel at oxidative addition.[141,142] The necessary trade-off is that a relatively electropositive metal such as nickel is not very effective at reductive elimination. It is also possible to use platinum catalysts for oxidative addition,[143] but more commonly the active catalyst is zerovalent palladium.

Chemoselectivity is also possible for substrates with more than one halide or pseudohalide functionality.[128] In the Suzuki reaction of a bifunctional chloroaryl triflate, oxidative addition at the chloro-position is helped by a lower polarity medium and a low ligand concentration. A bulky monophosphine catalyst ($Pd(P^tBu)_3$) enhances chloro-position selectivity, so much so that in toluene total selectivity is achievable. In THF the selectivity can be switched to favour triflate reactivity with a neutral bis-ligated $Pd(PCy_3)_2$ catalytic species. A change of solvent also provides the required effect, and acetonitrile or DMF will permit reaction of the triflate without changing the catalyst or base (Scheme 18). The (non-coordinating) triflate is more reactive in polar, coordinating solvents and with

higher ligand concentrations. In a polar solvent an anionic catalyst is formed from the base (KF) or the deprotonated boronic acid. Conversely a non-coordinating base will revert chemoselectivity in highly polar DMF back towards activating the C-Cl bond, as it also does in its reaction with a stannane in a Stille reaction.

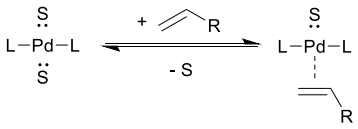


Scheme 18. Solvent determined chemoselectivity at the oxidative addition step of a Suzuki reaction.

The role of the solvent system can be tuned by the addition of salts. The conditions and choice of salt determine whether subsequent effects are due to a non-specific polarity increase of the medium or the active participation of ions in the reaction. Solvation of a cation by aprotic electron donating solvents liberates the anion,[144] and in particular the DMAc-LiCl system is known to produce freely interacting chloride anions where other solvent-salt combinations do not.[145] Furthermore, lithium chloride is significantly more soluble in organic solvents than similar compounds such as NaCl,[146] due to the higher affinity of solvents for the small and less electropositive lithium cation.[147] Accordingly LiCl has been used to modify the rate of oxidative addition undergone by organotriflates in THF.[137] A proposal has been made that salts help oxidative addition in THF (with arsine ligands on the catalyst) simply because it increases the polarity of the medium.[148,149] A non-specific salt effect would explain why it does not occur in solvents that are already highly polar. When an arsine ligand is used to form the catalyst the oxidative addition is slow due to their weak electron donating ability. Alternatively a chloride ion may replace an arsine ligand and make an anionic complex which is more nucleophilic and hence more amenable to oxidative

addition. With phosphine ligands the catalyst is inherently more nucleophilic anyway, and oxidative addition is not as likely to be rate determining. In this case salts slow the reaction because coordinating anions neutralise the active cationic palladium formed after oxidative addition of an organotriflate (triflate being non-coordinating). Further work on the Suzuki reaction catalysed by ligand-less Pd/C in toluene shows insoluble inorganic salts increase the rate of reaction (including sodium sulphate and potassium chloride).[150] Under the presumption of a rate determining oxidative addition, X-ray photoelectron spectroscopy (XPS) indicated electron donation from salt to palladium occurred which would promote cross coupling. Salts can also play a role in modifying the organometallic reactant, as is discussed later for the transmetalation step of the Negishi reaction (Section 2.4.3).

Unsaturated organometallic reactants can interfere with oxidative addition, before they are formally required in the catalytic cycle. The coordination of alkynes to palladium slows oxidative addition. A solvent molecule is displaced from the coordination sphere to accommodate the unwanted ligand, and even the strongest electron donating solvents cannot fend off a degree of coordination by alkenes or alkynes (Scheme 19).[151] Slow addition of alkynes in a Sonogashira reaction can supress this behaviour.



Scheme 19. The exchange of solvent for an alkene in the palladium coordination sphere.

Finally there is an alternative coupling mechanism that bypasses oxidative addition and indeed foregoes the need for a transition metal catalyst. This is the radical $S_{RN}1$ pathway.[152] The coupling of aryl halides with Grignard reagents has been shown to occur in this way. In THF (the solvent used to prepare the Grignard reagent) homocoupling of the intermediate [Ar·] occurred before reaction with the aryl magnesium bromide. This side-reaction was supressed when toluene

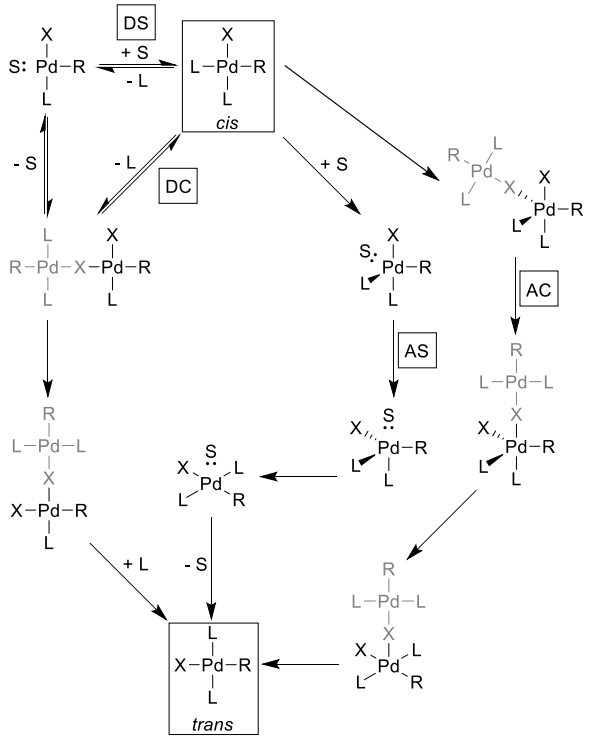
was used as the solvent instead of an ether.[152] Although excess THF was removed, stoichiometric amounts remained in a complex with the organometal and this was crucial for the success of the intended reaction.

2.3.1 Isomerisation

The cyclic 3-membered oxidative addition mechanism creates a Pd(II) product with *cis*-geometry. This would be satisfactory for the catalytic cycle as reductive elimination requires the leaving groups to adopt the same adjacent proximity to provide the final product. However, experimentally it is the *trans*-isomer that is almost always isolated. This could be preferred as a consequence of the S_N2 mechanism, as the halide can approach the complex without constraint once displaced by palladium. The observed *trans*-isomer does not rule out the cyclic mechanism because isomerisation is possible. The *trans*-isomer is the thermodynamic product due to a steric clash between ligands that occurs in the *cis*-geometry,[153] and isomerisation is very fast.[122]

This *cis*-*trans* isomerisation of square planar palladium complexes can occur by any of 4 processes (Scheme 20), which can be competing. These have been monitored using NMR spectroscopy where THF was the solvent.[154] Two pathways are autocatalytic, and two are solvent assisted. One of each type is sensitive to excess ligand (progressing through a dissociative mechanism) and the other type is associative. The dissociation mechanisms are made possible because a solvent molecule or another palladium complex displaces the ligand rather than leaving an empty coordination position (Scheme 8). In a coordinating solvent such as THF, the ligand dissociation-solvent assisted mechanism prevails (responsible for 67% of isomerisation).[154] A computational (DFT) study contradicts this experimental observation and concludes an associative mechanism has the lowest energy barrier (in the gas phase and in polar solvents).[80] Should autocatalytic isomerisation be favourable the solvent still has a (subtle) role to play because this process is concentration dependent, and the volume of solvent controls the concentration of the palladium complex. In non-coordinating solvents the autocatalytic routes may make a more

important contribution to the overall isomerisation. Ultimately *cis-trans* isomerisation is much faster than the other steps in the cross-coupling catalytic cycle and so does not limit the reaction in practice.



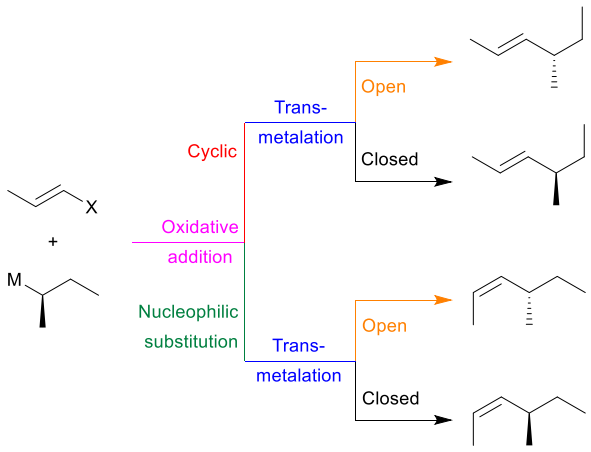
Scheme 20. The four pathways of cis-trans isomerisation. Key: DS, dissociative solvent assisted mechanism; DC, dissociative autocatalytic mechanism; AS, associative solvent assisted mechanism; AC, associative autocatalytic mechanism.

2.4 Transmetalation

Transmetalation is the least understood stage of a cross-coupling, and the unique step in each cross-coupling methodology. The transmetalation introduces the second moiety of the coupling reaction onto the palladium. Transmetalation is often rate determining, which is important because the solvent effects in the rate determining step dictate the rate of reaction. It has been said "*solvents exert a very important influence on the transmetalation and can displace both neutral and*

anionic ligands, including halides. This behaviour has very important stereochemical consequences".[57]

The process of transmetalation can occur *via* an open or a closed (cyclic) mechanism.[119] The defining difference is a bridging halide bond between palladium and the metal of the organometallic reactant. The open and closed mechanism have been extensively studied for Stille reactions, but have also been reported for others (e.g. the Hiyama reaction). The stereochemistry of the product depends on whether the activated complex is open or closed (Scheme 21). Thus in the final coupled product stereocentres in both organic moieties are controlled by oxidative addition and transmetalation.



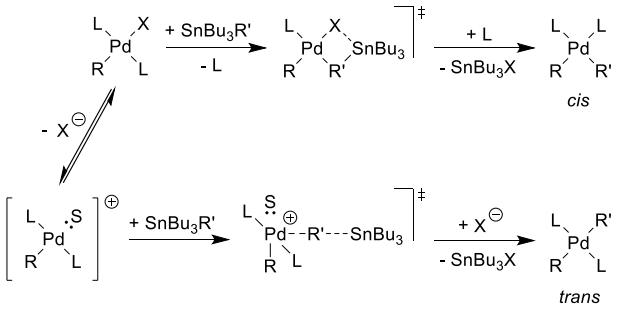
Scheme 21. A demonstration of the stereoselectivity in a generic cross-coupling caused by the different mechanisms of oxidative addition and transmetalation.

To explore transmetalation in more detail we need to consider the different organometallic reactants separately. The five major true cross-coupling methods are reviewed below, with specific discussions based on the findings of experimental and computational research.

2.4.1 Stille reaction transmetalation

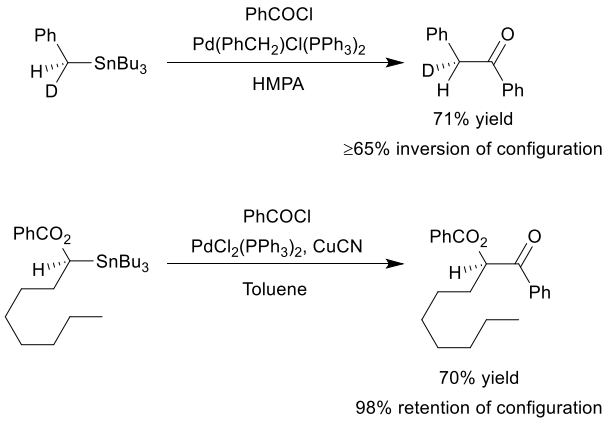
The proposed mechanism of transmetalation in a Stille reaction put forward by John Stille himself satisfied chemists for many years.[155] It is now known the processes behind the reaction are more complex.[57] The C–Sn bond is not as highly polarised as the carbon-metal bond of most other organometallics, which has implications for how the solvent interacts with reaction intermediates.[122] The stability of stannane reactants means transmetalation is usually rate determining in a Stille reaction.[122] Verification of this is obtained with the commonly isolated *trans*-oxidative addition intermediate, accumulating at the bottleneck of the reaction.[57] More conclusively, the definitive kinetic studies of Farina show an absence of the organohalide in the rate equation, and an inverse dependency on the concentration of ligand.[156] As such there is a benefit from using weaker electron donor ligands such as arsines.[156,157] Where ligand exchange is integral to the progress of Stille reaction transmetalation, the electron donating ability of the solvent will be influential on the rate of reaction. The Stille reaction is generally faster in amide solvents (DMF and NMP) than it is in ethers (1,4,-dioxane and THF).[156]

Modelling suggests the Stille reaction open mechanism of transmetalation (with inversion of stereochemistry) occurs with complexes retaining two phosphine (or equivalent) ligands, but the closed mechanism (retention of stereochemistry) occurs with one ligand dissociating (Scheme 22).[119,158] Therefore it is logical that bulky ligands favour the closed mechanism, while weaker (pseudo)halide ligands encourage the open mechanism in polar solvents. The triflate anion is a good leaving group in this circumstance.[130] A polar solvent will stabilise the cationic complex that results from the oxidative addition of an organotriflate.



Scheme 22. The open (lower route) and closed (upper route) mechanisms of transmetalation in a Stille reaction.

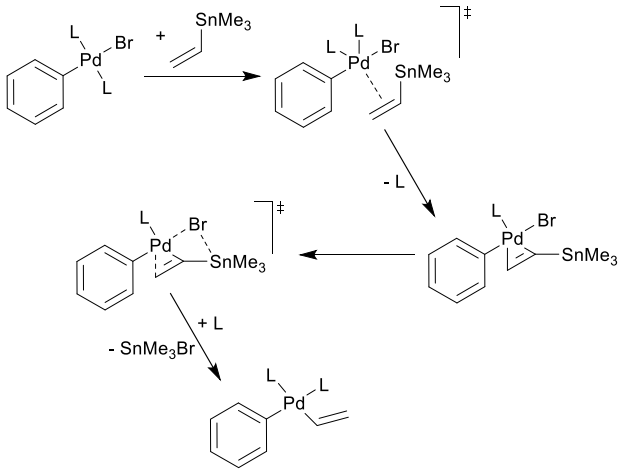
Most Stille reactions are believed to occur *via* the open transmetalation route,[57] but this is a consequence of the justified favouritism towards rate-accelerating highly polar solvents. In non-polar solvents (*e.g.* toluene) the less polar activated complex of the closed mechanism can occur.[159] This can be confirmed with retention of stereochemistry (Scheme 23). Usually the dipolar solvents normally employed in Stille reactions (classically HMPA) will give rise to an open transmetalation and hence inverted stereochemistry.[160] Thus if the retention of stereochemistry is desirable the solvent must be less polar to discourage the polarised open transmetalation activated complex.



Scheme 23. Solvent controlled stereochemistry in similar Stille reactions.

Modelling of the Stille transmetalation step was undertaken by Nova *et al.* on trans-(Ph)PdL_2(Br) and vinyl trimethylstannane.[119] The ligand (L) was represented by either PH_3 or AsH_3 (to

reduce computation time). The dissociative ligand pathways were found to be higher in energy than the associative mechanisms and so the former were discounted. However, some care should be taken in comparing these results to experiment, as the reduced size of the ligand models used in the computational work compared to experiment, will likely affect the competition between associative and dissociative mechanisms. Firstly the alkene group of the stannane coordinates (π-interaction) to the palladium to form a 5-coordinate complex. The rate determining step is a closed mechanism transmetalation of the η^2-coordinated alkene (Scheme 24). The addition of an explicit solvent into the model increased the energy barrier of the rate determining step relative to the gas phase, indicating ligand exchange is unfavourable.

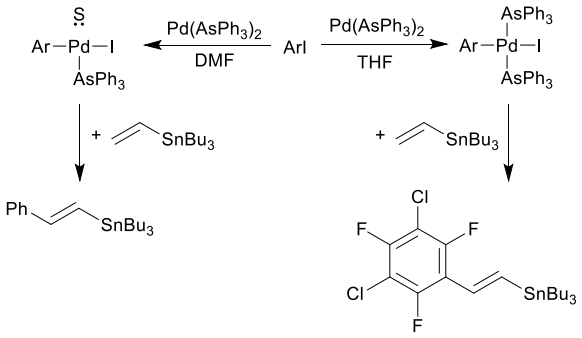


Scheme 24. The transmetalation of vinyl trimethylstannane with intermediates suggested by computer modelling.

With a triflate instead of a halide, the palladium complex is more electrophilic and coordinating solvents can interact and more easily displace weaker ligands.[119] For the open mechanism to occur, the halide is displaced from the palladium complex, creating a cationic species as a result. This is not energetically favourable for bromides, but can occur with a triflate. A coordinating solvent (e.g. THF) can take the place of the (pseudo)halide but the free phosphine or arsine ligand is preferred from an energetic viewpoint according to the DFT calculations. In the

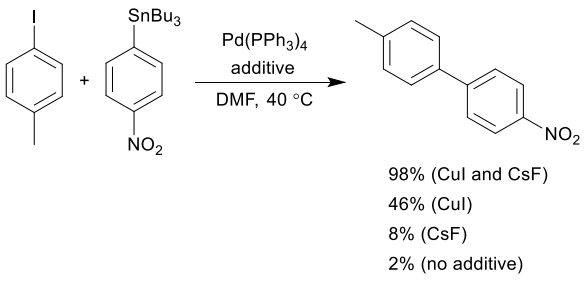
absence of excess ligand, $[(Ph)PdL_2(S)]^+$ becomes a relevant active species. A cationic complex is more reactive to transmetalation, but presumably requires a polar solvent to stabilise it and the subsequent transition state. Stannane coordination (through its alkene group) rather than the actual transmetalation has been suggested to be rate determining, and again the introduction of a solvent to the model raised the energy barrier compared to an idealised gas phase.[119] Upon completion of the transmetalation (occurring through the open mechanism), the palladium complex slightly favours a cis-geometry with respect to the organic moieties that later form the cross-coupling product.[119] The closed mechanism only produces a cis-complex, which eliminates the need for a trans-cis isomerisation before reductive elimination.

Experimentally consistent work with arsine ligands concurs with an associative transmetalation pathway through a 5-coordinate activated complex.[161] Activation parameters ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) were determined for a Stille reaction with a rate determining transmetalation in both chlorobenzene and THF. The two solvents are equally polar (on the π^* scale) but THF is an electron donor and chlorobenzene is at best weakly coordinating. In both cases $\Delta H^{\ddagger}$ is positive and $\Delta S^{\ddagger}$ is negative. The activated complex must be more ordered compared to the preceding reaction intermediate. The oxidative addition of PhX to $Pd(AsPh_3)_2$ results in a 4 coordinate complex. From here the stannane reactant approaches and a closed transition state has been proposed to produce a cis-complex as the product prior to reductive elimination.[161] In the associative mechanism, the departing ligand is replaced by coordination of the stannane. Somewhat surprisingly it was found that THF did not displace the labile triphenylarsine ligands from palladium (Scheme 25). However if DMF is used as the solvent instead, a molecule of solvent will replace a ligand in the active catalyst prior to transmetalation, even if additional triphenylarsine ligand is added. For example, the reaction of vinylstannane with iodobenzene in the presence of $Pd(dba)_2$ and 2 equivalents of $AsPh_3$ occurs *via* $(Ph)Pd(AsPh_3)I(DMF)$.[162] A kinetic analysis attributes no more than 10% of the transmetalation process as occurring through $(Ph)Pd(ArPh_3)_2I$, despite coexisting in solution alongside the active form of the catalyst in greater amounts.



Scheme 25. Different active catalysts depending on the coordinating ability of the solvent. Key: ArI is either 3,5-dichloro-2,4,6-trifluoroiodobenzene or iodobenzene.

The addition of CuI to a Stille reaction accelerates the rate of transmetalation due to its ability to interact with free ligands, thus deactivating them, if the solvent is an ether (THF or 1,4-dioxane).[156,163] If relatively weak ligands are employed, in highly dipolar solvents the Cu(I) can transmetalate as a substitute for tin, and the organocopper compound that results is more reactive towards transmetalation with palladium.[156,164,165] The combination of CuI and CsF promotes the Stille transmetalation to a greater degree than either on its own (Scheme 26). In this system DMF was the preferred solvent but DMSO and NMP are also effective.[166] The addition of fluoride separates the waste formed during transmetalation (in this example it is Bu_3SnX) as the insoluble organotinfluoride (X = F). As an aside, a version of the Stille reaction that is catalytic in tin as well as palladium can be conducted in ether solvents so that tin waste is reduced to a minimum.[167]



Scheme 26. Synergetic additive effects in a Stille reaction.

In the reaction of triflates, the addition of lithium chloride assists the transmetalation through the provision of a coordinating anion, as if it had been an organochloride reacting with palladium.[168] In this work the catalyst was sensitive to decomposition if LiCl was not present (the pre-catalyst was $Pd(Ph_3)_4$ and palladium black was observed). Furthermore, the choice of solvent was important in order to dissolve the LiCl. Non-coordinating solvents unable to dissolve LiCl also led to catalyst decomposition. To achieve the necessary concentration of LiCl, one of DMF, DMSO, HMPA, or *N*,*N*'-dimethyl propyleneurea (DMPU) was needed. Acetonitrile and chloroform were not capable of dissolving sufficient quantities of the salt. This can be attributed to the lesser electron donating ability of these solvents to solvate the lithium cation. Ethers (less dipolar than the amides and DMSO) could afford the same high yields but with slower reaction rates.[168]

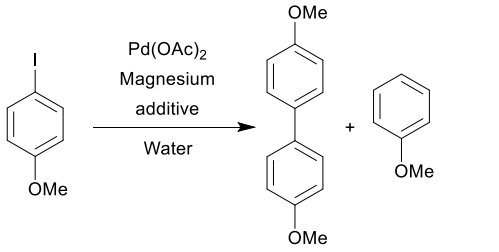
2.4.2 Kumada reaction transmetalation

The extensive use of highly polar aprotic solvents in Stille type cross-couplings is not the case in the Kumada reaction where the stability of the Grignard reagent is paramount.[141] Organomagnesium compounds are synthesised and stored as ethereal solutions, usually diethyl ether or THF, or sometimes the polyethers 1,4-dioxane or diglyme. The coordination of the ether oxygen to the magnesium atom is the origin of the stability imparted by the solvent (see Section 2.2). Anisole can also be used as a solvent, its reduced basicity compared to dialkyl ethers thought to promote reactivity.[169]

Given that Grignard reagents are highly reactive, the need for the solvent to promote reactivity in cross-coupling is diminished in a Kumada reaction. Still, is it not uncommon for the ether solvent that is dissolving the organometallic reactant to be supplemented by addition of a more dipolar co-solvent. Equally, when Grignard reagents are added as a diethyl ether solution to the other reaction components in a toluene solution, the Kumada reaction will proceed under mild conditions.[170] Under similar circumstances in an example of a nickel catalysed Kumada coupling,

toluene was also used as the solvent but in this case to both prepare the Grignard reagents and perform the reaction.[171] Two equivalents of THF are added to the reaction to stabilise the Grignard reagent as $RMgX(THF)_2$. The yield decreases in the presence of the radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), suggesting the mechanism may involve radical intermediates, as observed elsewhere for Kumada-type couplings.[152]

Addition of magnesium and palladium acetate to aqueous formaldehyde allowed a Kumada-type homocoupling of aryl iodides in the presence of water.[172] Other combinations of water and π-acidic, back-bonding ligands resulted in significant hydrodehalogenation (Scheme 27). It was also possible to make asymmetrical products from mixtures of electron rich and electron poor substrates. Magnesium insertion is likely to preferentially occur on the more electron deficient iodoarene for kinetic reasons, therefore limiting homocoupling.

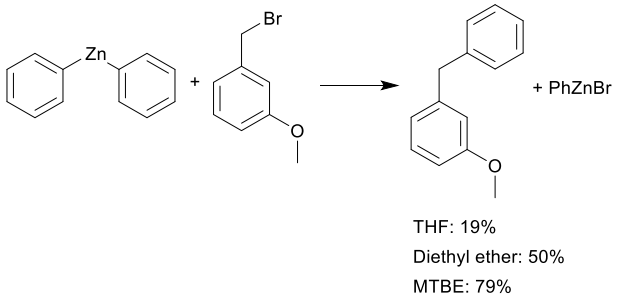


Scheme 27. The homocoupling of 4-iodoanisole, with the product distribution indicated in the form homocoupling/hydrodehalogenation (all reactions underwent full conversion).

2.4.3 Negishi reaction transmetalation

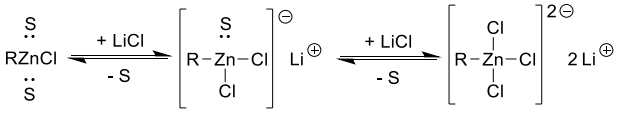
The Negishi reaction is the most similar to the Kumada reaction of all the common cross-couplings. Due to the high reactivity of the organometallic (organozinc), the primary need of the solvent is to stabilise the reactant. A $RZnX(S)_2$ species with two supporting solvent molecules has been proven to exist (S = THF) and is presumed to be the active organometallic species (Reformatsky

reagent).[173] Dialkylzinc reagents are also applicable to Negishi reactions. For direct radical reactions without catalyst (e.g. diarylzincs with benzylbromide), ethers actually hinder the reactivity of the organometal due to their coordination.[174] The order of nucleophilicity (THF > diethyl ether > MTBE) is inversely proportional to the yields obtained (Scheme 28). A different form of organozinc can be made as the pivalate salt, which are stable for handling as solids.[175,176] This helpful approach could be used to provide more flexibility with respect to solvent choice in future Negishi reactions.



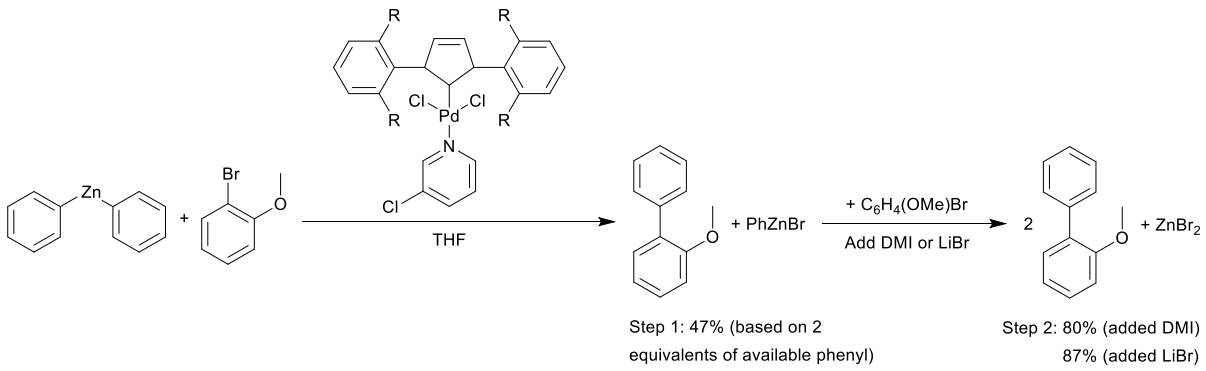
Scheme 28. The effect of ether nucleophilicity on Negishi reaction yields.

Observations indicate that LiCl accelerates the formation of organozinc compounds and improves their reactivity.[177] This is due to an equilibrium leading to zincate ions that are active towards transmetalation in a Negishi reaction.[177,178] In these circumstances it was believed that $RZnX_2^-$ was formed, yet after re-evaluation it appears that actually $RZnX_3^{2-}$ is the active species in transmetalation (Scheme 29).[177] Solvent molecules are excluded from the primary coordination sphere by chloride ions, but this does not change the type of solvent suited to this chemistry (THF is still appropriate).



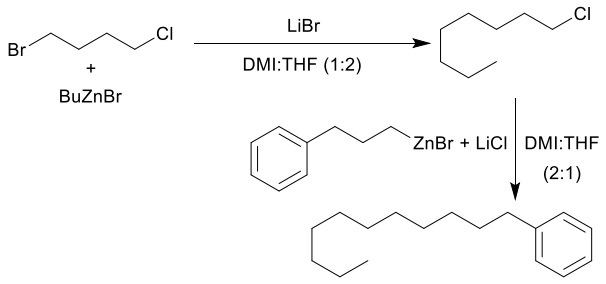
Scheme 29. The formation of higher zincates by the addition of salts.

Without LiCl, the use of polar solvents can provide an environment to accelerate the reaction, and NMP or the less common solvent dimethyl-2-imidazolidinone (DMI) can be added to THF as a co-solvent to achieve this.[178] Satisfactory results arylating the first of two equivalents of an organohalide with $ZnPh_2$ are obtained in THF. However, to react the remaining aryl group (now in the form ArZnX) with a second equivalent of organohalide the addition of salt or a more polar medium is required (Scheme 30).[177]



Scheme 30. The two-step Negishi reaction of diphenyl zinc. R = 3-pentyl.

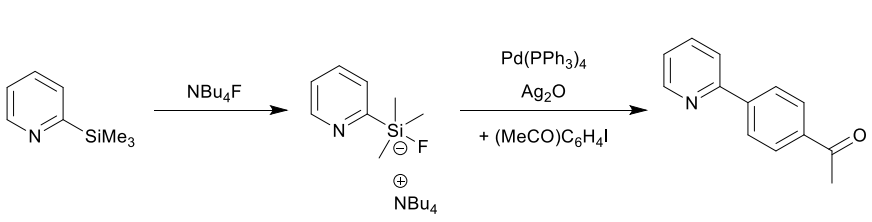
Chemoselective control can also be imparted to the Negishi reaction by tuning the solvent polarity with a binary solvent blend (Scheme 31, where the catalyst is the same as that in shown in Scheme 30 except R = isopropyl).[179] A bromochloroalkane can be reacted with an organozinc compound in DMI-THF (1:2) to convert the more reactive bromo group, then a different organozinc can then be added along with enough DMI to modify the final solvent system into a more polar DMI-THF (2:1) mixture. The use of DMI is proven to benefit Negishi reactions because less polar solvents can lead to β-hydride elimination instead of the desired cross-coupling.[180]



Scheme 31. Polarity driven activation of alkylhalides in a Negishi reaction.

2.4.4 Hiyama reaction transmetalation

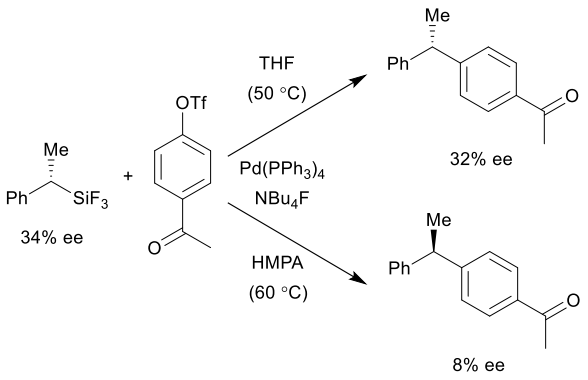
A base is necessary to conduct a Hiyama reaction, which increases the nucleophilicity of the silane reactant by virtue of creating a pentavalent silicon anion.[181] An alternative mode of base action postulated for Suzuki cross-couplings, the displacement of a halide ligand, does not appear to be necessary in a Hiyama reaction. The base can be fluoride, hydroxide or carbonate. The preferred solvent for high performance Hiyama reactions is DMF.[182] A solvent screen of a Hiyama reaction revealed the yield is enhanced in dipolar aprotic solvents (DMF and NMP), but minimal yields were obtained in other types of solvents, including toluene, ethers, DCM and acetonitrile (Scheme 32).[183] The solvent effect was not conclusively revealed, but the electron donating, highly dipolar solvents are clearly superior to solvents that lack one or both of this properties. If the solvent cannot dissolve the base or stabilise the pentavalent silicon intermediate the progress of the reaction will be limited.



NMP: 43%
DMF: 42%
THF: 18%
DCM: 7%
MeCN: 4%
1,4-Dioxane: 4%
Di-*n*-butyl ether: 0%
Toluene: 0%

Scheme 32. A solvent screen for a Hiyama reaction.

The choice of solvent and reaction temperature is very important for stereoselectivity.[184] The Hiyama transmetalation retains stereochemistry in low temperature reactions performed in THF. By elevating the temperature or by using a more polar solvent the stereochemical preference of the reaction is inversion (Scheme 33). The choice of catalyst and base does not need to be changed. As with other transmetalations, the closed activated complex provides retention of stereochemistry. The greater dipole moment of the open transition state (compared to a closed activated complex) requires the stabilisation of a polar solvent. Higher temperatures will increase the entropic penalty incurred by cyclising into the closed activated complex and encourage the open transition state.

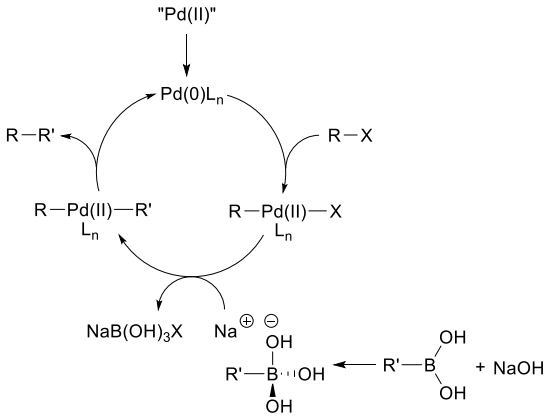


Scheme 33. Solvent-dependent stereochemistry in a Hiyama reaction.

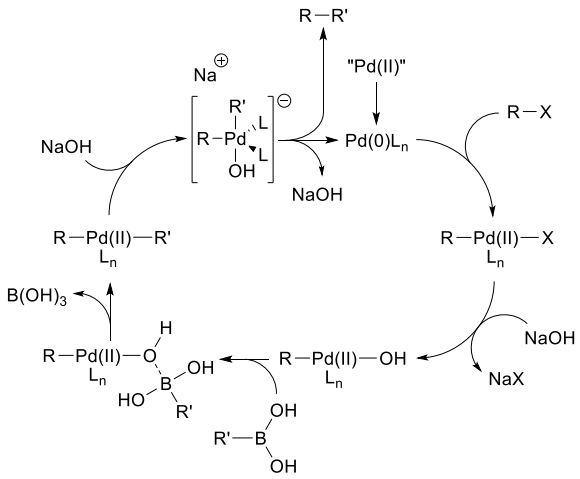
2.4.5 Suzuki reaction transmetalation

The Suzuki reaction has become the most frequently practiced palladium catalysed cross-coupling methodology.[185] The choice of solvent is very flexible compared to other cross-couplings. Alcohols, dipolar aprotic solvents, ethers, and toluene are all regularly used for the Suzuki reaction. Alcohol solvents appear to promote the action of the base, even allowing weaker bases (e.g. amines, acetate salts) to be successful in certain circumstances.[186] In the presence of strong bases alcohols can be problematic, causing hydrodehalogenation of organohalides (see Section 2.7). Water is frequently used as a co-solvent or even the sole solvent. Organoboron compounds are generally

tolerant of water, and the inorganic bases most often used in Suzuki reactions have higher solubilities in aqueous solvents. The amount of hydrophilic boronate ($R'B(OH)_3^-$) species will increase with higher quantities of water present,[187] which leads us to the long standing dispute over the role of the base in the Suzuki reaction. Either the action of the base is analogous to a Hiyama reaction (converting the organometal into an anion) (Scheme 34), or alternatively the base exchanges with the halide ligand on the palladium complex created after oxidative addition (Scheme 35). The precise reaction pathway was unclear for a number of decades, with a number of studies falling on the boronate side of the debate,[29,130,188,189,190,191] but also a substantial number in support of the ligand role of the base.[192,193,194,195] It is now generally accepted that the latter is more representative of the reaction mechanism.

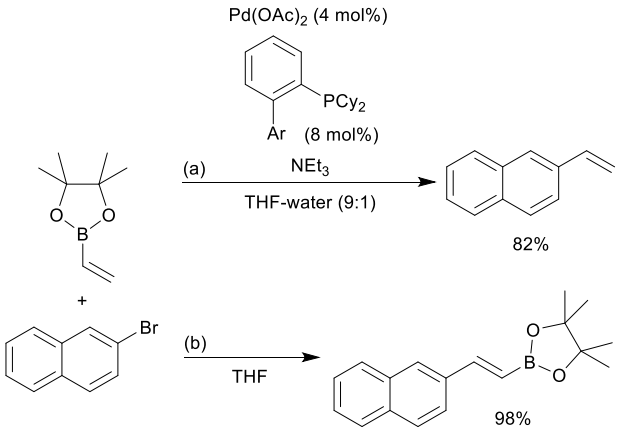


Scheme 34. The proposal for an active boronate reactant in the Suzuki reaction catalytic cycle, where the base is sodium hydroxide.



Scheme 35. The accepted Suzuki reaction catalytic cycle, where the base is sodium hydroxide.

The necessity of a palladium hydroxide catalytic intermediate was elegantly proven by Molloy *et al*.[196] In THF, vinylboronic acid pinacol ester exclusively forms Suzuki reaction products with aryl palladium(II) hydroxides (e.g. $[(Ph_3P)(Ar)Pd(\mu\text{-}OH)]_2$) and the Heck reaction product from aryl palladium(II) bromides. A solvent switch allowed the same catalytic system (made from palladium acetate and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl) to perform either a Suzuki reaction (aqueous THF) or a Heck reaction (anhydrous THF) (Scheme 36). The use of triethylamine as the base in anhydrous conditions cannot participate in the Scheme 35, but in the presence of water generates the hydroxide anion. The transmetalation of boronic acids and boronic esters proceeds through a Pd–O–B complex, but any specific solvent effect has not yet been studied at a molecular level.[197,198,199] This does imply a closed transmetalation transition state would be favoured. There is a lesser dependence on the dipolarity of the solvent compared to the open transmetalation mechanism,[200] and this is consistent with the compatibility of different types of solvents with the Suzuki reaction. However, inversion of stereochemistry (synonymous with an open mechanism of transmetalation) is observed in some Suzuki reactions, for instance when the oxophilic boron compound features a functional group (*e.g.* an amide) to which it will preferentially coordinate instead of forming the expected Pd–O–B complex.[201]



Scheme 36. Chemoselective couplings of vinylboronic acid pinacol ester instigated by addition of water. The catalyst and base are the same for both reactions. Ar = 2,6-dimethoxyphenyl.

Amatore *et al.* used electrochemical reaction monitoring to study a Suzuki reaction with a rate limiting transmetalation.[195] The solvent was DMF, with a tetrabutylammonium hydroxide base added as a methanol solution. The major palladium species (but not a reactive one, see Table 4) was identified as $Pd(PPh_3)_3$. Excess boronic acid appeared to retard the rate of reaction due to quenching of the base as the boronate. The boronate is in a virtually barrier-less equilibrium with the free base and boronic acid.[29] The beneficial role of the base as a substitute for the halide ligand on palladium was confirmed, but also a surprising second positive effect was observed where a 5-membered intermediate encourages reductive elimination, forming the product (Scheme 35). This was deduced from the absence of $Pd(R)(R')(PPh_3)_2$ in voltammetry experiments. Carbonate bases require the generation of hydroxide with water to operate, and as with all bases, the counterion can retard the rate of transmetalation by coordinating to hydroxide once bonded to palladium.[202] The use of dipolar aprotic solvents with a high affinity for cations does not completely eliminate this effect. Fluoride bases perform the same role as hydroxides.[203]

It is possible to use borane reactants with no Lewis acidity in Suzuki reactions that will not form a boronate. Suzuki reactions of boranes still require a base, again implying the base is actually needed as a ligand. The work of Matos *et al.* found boronic acids undergo Suzuki reactions with a

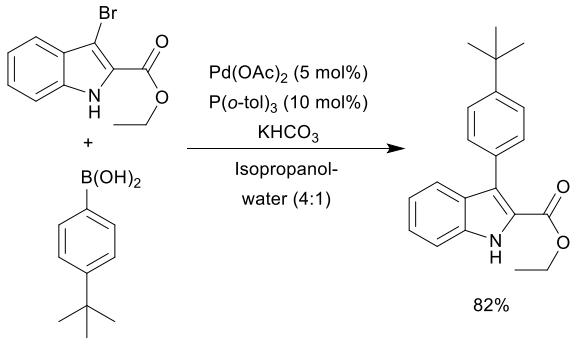
rate determining oxidative addition, while a non-acidic borane reacts with a rate of reaction dependent on the concentration of the base.[204] The solvent in this case was benzene, with water also present due to the hydroxide base having been added as an aqueous solution. The low polarity medium made have influenced these observations. The transmetalation was reported to retain the stereochemistry of alkylboranes, which indicates a closed mechanism (as is possible in a low polarity solvent).

Unstable boronic acids can be protected as a *N*-methyliminodiacetic acid (MIDA) boronic ester,[205] or converted to the corresponding potassium trifluoroborate,[206] to permit higher yielding Suzuki reactions without competing hydrodeboronation. The long shelf life of these derivatives has made vinyl, cyclopropyl, and 2-heterocyclic boron compounds practical substrates for commercial applications. Slow hydrolysis to the parent boronic acid maintains a selective cross-coupling reaction.[207] Aqueous THF has emerged as a favourable medium for the Suzuki reaction of these substrates although they do not require special treatment with regards to the choice of solvent.

The widespread use of aqueous-organic solvent systems for Suzuki reactions raises the question whether the reaction mixture is homogeneous or heterogeneous. As little as 20 equivalents of water is known to create a separate phase in Suzuki reactions performed in ether solvents.[208] A biphasic system introduces limitations by partitioning the reaction components,[187] separating the base and any boronate from the organohalide, boronic acid, and catalyst, but may actually assist the progress of the reaction overall. It has been proposed that the major reason water is useful in Suzuki reactions as solvent or co-solvent is because it solvates the halide by-product, reducing its ability to interfere with the progress of the reaction.[209]

To take an industrially relevant example of a Suzuki reaction, a 'design-of-experiment' (DoE) approach has been used to optimise the solvent-ligand-base combination.[210] The procedure was originally a 20 litre scale aqueous DMAc process catalysed by a palladium catalyst featuring the dppf ligand. Evaluating the reaction revealed that an aqueous solvent, either DMAc or 1-butanol, was optimal in combination with a mild base. The reason for these two very different types of organic

solvent prevailing was not revealed, because the DoE approach is designed to optimise conditions but not explain the underlying mechanistic reasoning. What is clear is that like all cross-coupling procedures, the optimum reaction solvent reflects the choice of other variables. In DMAc, potassium bicarbonate (base) and dppf (a bidentate ligand) were needed for >80% yield. Virtually the same yield in 1-butanol required P(*o*-tol)$_3$ as ligand and triethylamine as base. Not all solvent-base-ligand combinations were initially tested, with the model predicting further improvement with potassium bicarbonate instead of triethylamine in butanol, resulting in 94% yield when put into practice. Ultimately aqueous isopropanol was chosen as the solvent (Scheme 37), because although the performance was slightly inferior to 1-butanol, the work-up was easier with a water miscible solvent, and reduced the level of residual palladium in the isolated product.[210]



Scheme 37. A kilogram scale Suzuki reaction with optimised reaction variables.

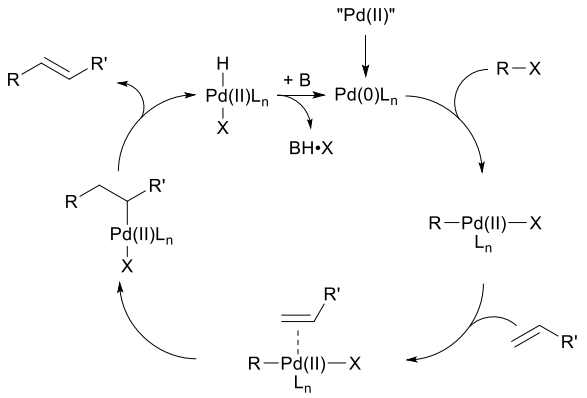
2.5 Alternative mechanisms to transmetalation

Where the organometallic reactant (R'–M) is replaced by a compound with a sp^2-hybridised carbon-hydrogen bond (Heck reaction), a sp-hybridised carbon-hydrogen bond (Sonogashira reaction), or an amine (Buchwald-Hartwig reaction), the cross-coupling follows a different path to the general mechanism. These special cases are described in this section.

2.5.1 Heck reaction

The Heck reaction involves an alkene rather than an organometallic reactant. The origin of the Heck reaction was the arylation of alkenes with aryl-mercury compounds.[211,212] Later, Heck,[24] and Mizoroki,[23] found aryl halides worked in place of the organomercury reagents. Unsurprisingly, "*the catalytic activity in the Heck reaction is susceptible to the solvent and additive effects*".[213] The types of catalysts applicable to Heck reactions are broadly equivalent to the other reactions covered in this review.

After the oxidative addition, a Heck reaction proceeds *via* π-coordination of the olefin reactant, then a migratory insertion of the alkene into the Pd-C bond previously formed during oxidative addition of the organohalide (Scheme 38). Olefin coordination and migratory insertion is then followed by β-hydride elimination. The product may be interacting with palladium through π-coordination before dissociating and the (assumed) $PdH(L)_2X$ complex that results is reduced to the Pd(0) catalyst by a base (*via* reductive elimination). A mild amine base is used in the Heck reaction to abstract HX from the palladium, resulting in a salt by-product. The role of the base is widely accepted, and is markedly different to the role of the base in a Suzuki or Hiyama reaction.



Scheme 38. The basic catalytic cycle of a Heck reaction. The base is represented as B.

The rate determining step of the Heck reaction depends on the proportion of ligand added.[214] Generally speaking, in excess phosphine olefin coordination is rate determining, but with

equimolar amounts of ligand it is the migratory insertion.[215] Non-coordinating solvents that cannot exchange with the ligands will exacerbate competition in the coordination sphere in excess ligand conditions. The work of Zhao (Figure 4 and Figure 5) on the reaction between methyl acrylate and iodobenzene tested combinations of several solvents with different quantities of ligand (triphenyl phosphine).[216] In non-polar solvents (octane and toluene) and nitriles (acetonitrile (MeCN) and propionitrile (EtCN)) two equivalents of ligand (relative to Pd) is superior to no ligand or 4 equivalents, but the rate of reaction in hydrocarbon solvents remains slow and therefore the yield after 1 hour is poor. In more polar solvents the Heck reaction is faster (Figure 4) and higher yielding (Figure 5). Four equivalents of ligand gave poorer results in amide solvents and no reaction in nitrile solvents, ethanol, or octane. Yet good yields were still obtained in amide solvents when excess ligand was present (albeit a lower yield than under other conditions). It is possible that the amides are competitive with triphenyl phosphine and some lower coordinated palladium ($Pd(PPh_3)_2S_2$) is generated in solution alongside free ligand and inactive $Pd(PPh_3)_4$. Ultimately it is preferable to have lower ligand concentrations in amide solvents as the rate of reaction is inversely proportional to ligand concentration, with ligand-free conditions providing the best results. Coordinating dipolar aprotic solvents are frequently applied as the solvent in Heck reactions.[217] In the absence of ligands β-hydride elimination has been found to be rate determining.[218,219] Overall it appears that conditions that discourage olefin coordination (e.g. 4 equivalents of ligand) hinder or even stop the Heck reaction. Nitrile solvents excel under conditions where migratory insertion may possibly be rate limiting rather than olefin coordination, while amides facilitate ligand-free cross-coupling. In the absence of ligands specific solvent-catalyst interactions are vitally important, as evidenced by the large variation of reaction rates in these conditions (Figure 4).

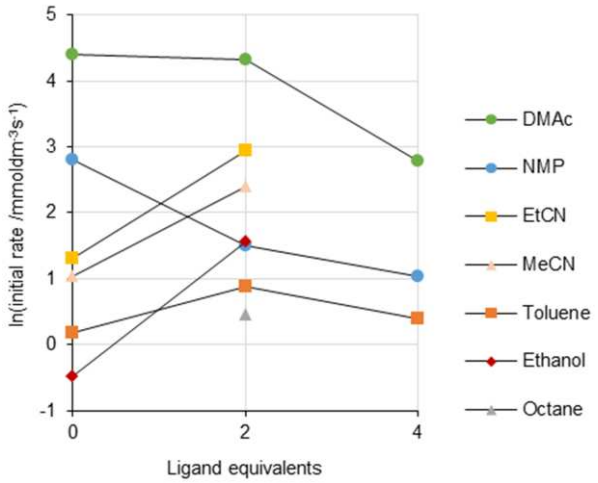


Figure 4. The ligand and solvent effects on the rate of a model Heck reaction.

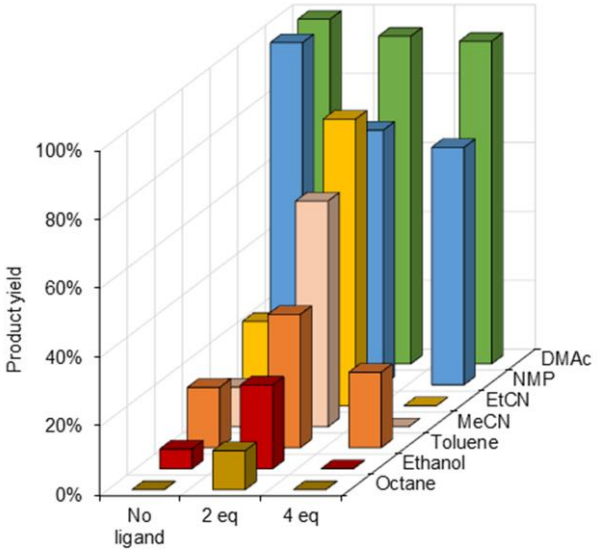


Figure 5. The ligand and solvent effects on the yield of a model Heck reaction.

One study of solvent effects designed to reveal the optimum properties of the reaction medium investigated the kinetics of a ligand free Heck reaction.[220] Parker *et al.* found a correlation between the initial rate of reaction (between iodobenzene and methyl acrylate) and the dipolarity of the solvent. This meant the reaction was slow in hydrocarbon solvents and fast in dipolar aprotic solvents. Equivalent results to DMSO and NMP were obtained by using the cyclic carbonate solvents ethylene carbonate and propylene carbonate. Cyclic carbonates have very large dielectric constants

(Figure 1). Propylene carbonate is the more versatile (but less polar) of the two because ethylene carbonate is a solid at room temperature. The scale of dipolarity used in the study of Parker *et al.* is the π* solvatochromic parameter devised by Kamlet and Taft.[220] Interestingly, the reaction in DMF proceeds at a much greater rate than expected from its dipolarity alone (Figure 6). This may be due to the well-known coordinating behaviour of DMF. Coordination of the solvent to a metal is not represented by the π* scale. The solvent set did not include any protic solvents, because a trial experiment with *t*-butanol yielded less than 10% product after several days, a far slower reaction rate than achieved in any aprotic solvent. From this we might infer a hydrogen bond donating solvent will retard the rate of this Heck reaction, but the boiling point of *t*-butanol (83 °C) at which the reaction was conducted is significantly lower than the 100 °C reaction temperatures used in the other solvents. The kinetics of Heck reactions are known for a steep temperature dependence,[59] and so this is the likely reason for this observation. The Heck reaction is certainly compatible with alcohol solvents under appropriate conditions, with other procedures catalysed by palladium nanoparticles utilising aqueous ethanol for instance.[221,222]

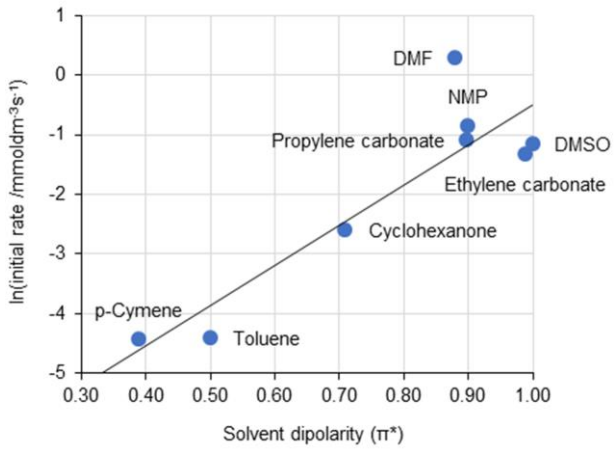
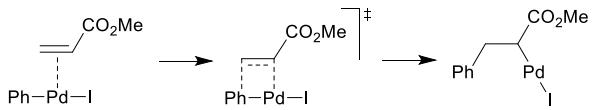
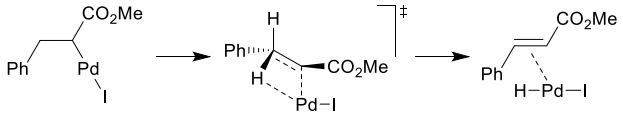


Figure 6. A linear solvation energy relationship correlating the rate of a Heck reaction with solvent polarity.

The original article reporting the findings presented in Figure 6 explains the role of the solvent as lowering the energy of the transition state resulting from the alkene insertion by palladium (Scheme 39).[220] The bond polarisation occurring in this activated complex will be stabilised by solvents with high π* values. However, ligand-free Heck reactions tend to have a slow and thus rate determining β-hydride elimination.[218,219] This would mean the solvent effect described by the linear solvation energy relationship in Figure 6 is a consequence of β-hydride elimination requiring stabilisation from a dipolar solvent. The activated complex that occurs during a β-hydride elimination exhibits some charge separation as bonds form and break, which like migratory insertion is consistent with the observation that dipolar solvents accelerate the reaction (Scheme 40).[223,224,225]



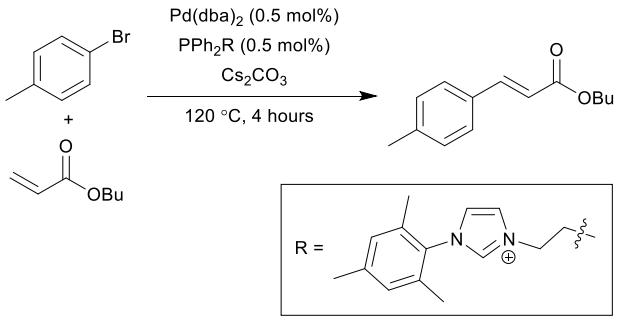
Scheme 39. The activated complex formed during migratory insertion in a Heck reaction assuming a neutral complex. Ancillary ligands or coordinating solvents not drawn.



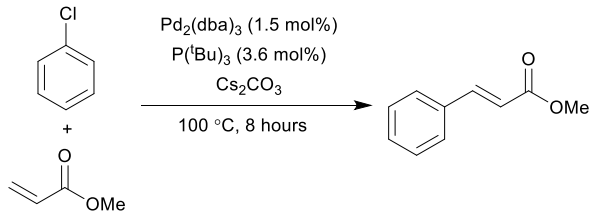
Scheme 40. The activated complex formed during β-hydride elimination in a Heck reaction assuming a neutral complex. Ancillary ligands or coordinating solvents not drawn.

Burello *et al.* attempted to model solvent-ligand synergy to define the ideal reaction conditions for different Heck reactions.[217] A principle component analysis (PCA) revealed eight defining variables that dictate the performance of the reaction. These included the temperature, reaction duration, ligand to catalyst ratio, *etc*. A universal model could not be developed, with the solvent optimisation arriving at a different conclusion in each case study. Of all the possible variables, the solvent dipolarity and solvent basicity were the most relevant in describing the

reaction efficiency within each model. Conventionally, high polarity solvents are favoured in Heck reactions (Scheme 41).[226] However, on some occasions less polar electron donors give superior yields, e.g. ethers (Scheme 42).[227] The consequence of the different solvent effects are indicated by the resulting yields shown in Figure 7. The contradiction could be due to a change of rate determining step. The more conventional solvent effect controlling the reaction in Scheme 41, and the use of equimolar pre-catalyst and ligand, implies migratory insertion is rate determining as the solvent stabilises the charge polarisation at the transition state. The yield of the reaction in Scheme 42 in 1,4-dioxane (the most effective solvent) can be doubled if the concentration of ligand is increased and the reaction extended to 2 days (from 39% to 76%), which suggests olefin coordination may become rate determining with the acceleration of other stages in the reaction under these optimised conditions. These conditions where reaction rates and yields in dipolar aprotic solvents are at their poorest (so much so that ethers are superior solvents in this instance) would also support the proposal of a rate limiting olefin coordination. It is also worth considering that with an aryl chloride reactant oxidative addition to palladium is likely to be slow, but in this case assisted by electron donating P^tBu_3 ligands.



Scheme 41. An example of a Heck reaction enhanced by dipolar aprotic solvents.



Scheme 42. An example of a Heck reaction enhanced by less polar and electron donating solvents.

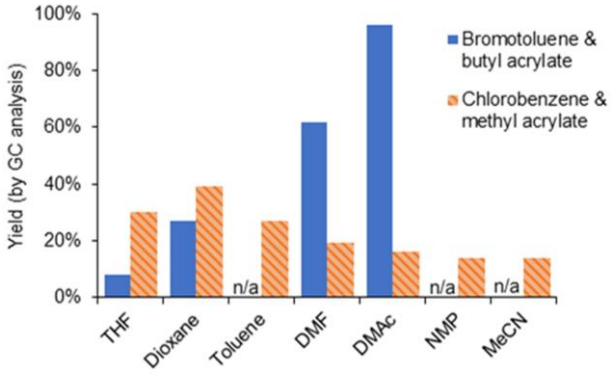
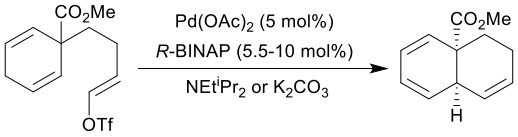


Figure 7. Yields of Heck reaction products (no data bar means the reaction was not attempted).

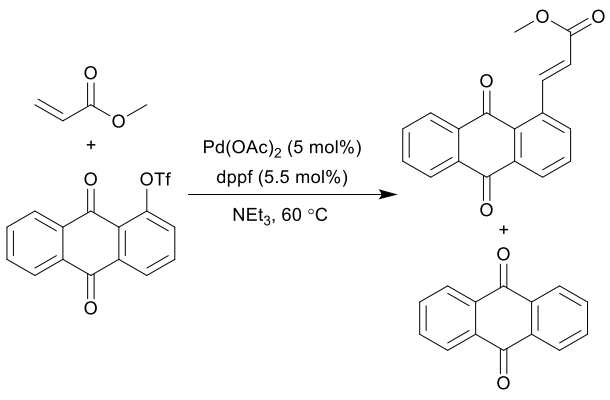
While dipolar aprotic solvents are effective solvents for the coupling of iodides, when the organohalide is a triflate they can lead to poor enantioselectivity and low yields (Scheme 43). Using palladium acetate as the pre-catalyst and (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) (BINAP) as a ligand, higher optical purities of *cis*-decalin derivatives were obtained in toluene, THF, and 1,2-dichloroethane.[228] Toluene and 1,2-dichloroethane provided the highest enantioselectivity but the reaction was much slower in the latter, to the extent that half the starting material was recovered. 1,2-Dichloroethane has been reported as oxidising Pd(0) to PdL_nCl_2 which will deactivate the catalyst.[228] This could be prevented with the addition of *tert*-butanol or pinacol, improving the yield to become comparable to that achieved in toluene. The reason for dipolar aprotic solvents inhibiting the reaction yield and enantioselectivity imparted by the bidentate ligand may be due to competitive coordination by the solvent, thus breaking the chelate ligand arrangement.



DMSO: 29% yield, 3% ee
MeCN: 9% yield, 10% ee
NMP: 15% yield, 43% ee
THF: 33% yield, 82% ee
Toluene: 54% yield, 91% ee
DCE: 13% yield, 87% ee
DCE and *t*-BuOH: 17% yield, 87% ee
DCE and pinacol: 51% yield, 92% ee

Scheme 43. Yields and enantioselectivities of an intramolecular Heck reaction in different solvents.

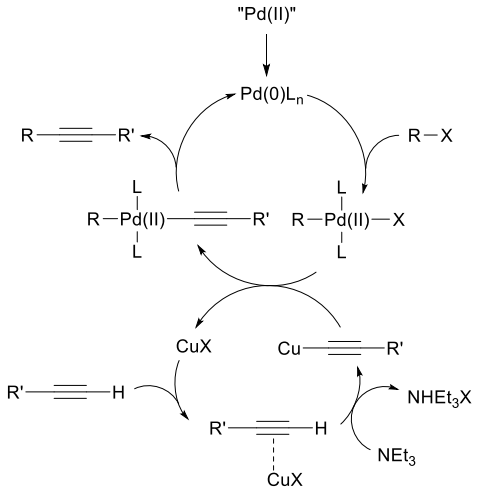
In other instances a labile bidentate ligand with reversible chelation has been shown to be useful. In the specific example of a Heck reaction between anthraquinoyl triflate and methyl acrylate, oxidative addition was facile but the reaction faltered at the transmetalation step (Scheme 44).[229] The use of a bidentate ligand opened up the possibility of one phosphine atom departing from the palladium centre to create a vacancy for olefin coordination. Alternatively, due to the use of a organotriflate reactant, the pseudohalide ligand could dissociate to create a low-coordination cationic palladium species after oxidative addition. Toluene was superior to 1,4-dioxane, but the reaction slower than in DMF. However, hydro(pseudo)dehalogenation was observed in DMF (and slightly in 1,4-dioxane) to produce an arene rather than the desired reaction. This prevalence of this side-reaction increased with decreasing excess of alkene. Hydrodehalogenation tends to be an issue only in solvents that can oxidise under the reaction conditions (see Section 2.7 for a full discussion). Based on toluene's lower polarity it would seem plausible that the ligand substitution route is preferred, whereas in DMF a charged palladium complex would also be feasible.



Scheme 44. The Heck reaction between anthraquinoyl triflate and methyl acrylate with a competing reduction of the triflate to anthraquinone.

2.5.2 Sonogashira reaction

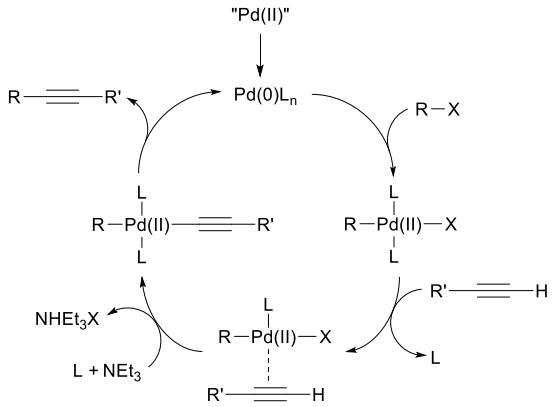
Sonogashira found that the addition of CuI assisted the palladium catalysed coupling of alkynes to organohalides, allowing these reactions to proceed at room temperature.[21] Prior to Sonogashira's invention, the coupling of alkynes required excess amine to be used as the solvent.[230,231] This made the procedure difficult to scale up as amines are corrosive and cause severe skin, eye, and respiratory irritation. The copper generates an organometallic reactant *in situ*, and the copper is recycled in catalytic amounts. This makes it analogous to the true cross-coupling reactions with the addition of a second catalytic cycle to account for the role of copper (Scheme 45).[232] Transmetalation (of the *in situ* alkynyl copper reactant) is usually the rate determining step,[22] while a carbopalladation mechanism has been ruled out.[233]



Scheme 45. The simplified copper co-catalysed Sonogashira reaction catalytic cycle, where triethylamine is the base and n = 2.

The regular choice of solvent in a copper assisted Sonogashira reaction is DMF,[234] and it has been reported that 41% of Sonogashira reactions use DMF as a reaction solvent.[235] Other reported solvent options are DMSO, 1,4-dioxane, toluene, DME, and also aqueous systems.[22] Yet sometimes less polar solvents are preferred. Toluene provided better yields (70%) than DMF (20%) in a (copper-free) Sonogashira reaction of β-bromoporphyrin.[236] The authors indicated that DMF may have slowed the reaction by displacing the $AsPh_3$ ligands from the active palladium complex.

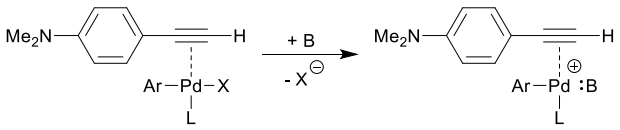
Issues with copper favouring alkyne homocoupling in the presence of oxygen has meant copper-free protocols are generally now preferred (Scheme 46).[232] All the examples of Sonogashira reactions subsequently described in this work are copper-free methods. After oxidative addition, without an organometallic reactant there can be no transmetalation, but instead coordination of the alkyne to palladium. η^2-Coordination of the alkyne occurs at the expense of one ligand. Bringing the reaction pathway back in line with the copper catalysed Sonogashira reaction, the base deprotonates the alkyne to form an alkynide ligand amenable to reductive elimination. This mechanism relies on metal coordination increasing the acidity of the alkyne (phenylacetylene pK_a = 19), which would otherwise not be adequately deprotonated by amine bases. Kinetic isotope effect studies using deuterated methanol compared to conventional methanol have confirmed the influence of the deprotonation on the reaction rate.[237]



Scheme 46. A generally accepted version of the copper-free Sonogashira catalytic cycle, where triethylamine is the base and n = 2 for the active catalyst.

It has been shown that the amine base can assume the role of a ligand. Tougerti *et al.* used secondary amines as the solvent in copper-free Sonogashira reactions.[238] After oxidative addition a ligand can be replaced by piperidine, but the equilibrium is not favourable unless PPh_3 is substituted for $AsPh_3$. If arsine ligands are employed, the oxidative addition product, $PdR(AsPh_3)_2X$, is converted into $Pd(amine)R(AsPh_3)X$, and the alkyne competes with free amine to remove the final arsine ligand. The alkyne must coordinate to palladium to allow deprotonation, but this needs to occur after oxidative addition because (as covered earlier in Scheme 19) alkyne η^2-coordination to the catalyst inhibits oxidative addition.[71,151] The rate determining step in the absence of copper is the reversible coordination of the alkyne.[238]

The mechanism of the Sonogashira reaction is changed by electron rich alkynes.[233] In methanol as the solvent, electron rich alkynes undergo the Sonogashira reaction *via* a cationic complex (Scheme 47), in which the base replaces the halide ligand only after alkyne coordination, and then abstracts the proton from the alkyne. Hence what is often the role of the solvent is now undertaken by the base: coordinating to palladium and defining the active form of the catalyst. The historical use of amines as the solvent is therefore logical, if unpleasant from a health and safety perspective.



Scheme 47. An example of a cationic intermediate palladium complex.

A DoE study found that the temperature of a Sonogashira reaction is more influential in determining the yield than the choice of solvent or base.[239] In this instance a highly active homogeneous palladium catalyst with a NCP pincer ligand was applied. A tailored catalyst may diminish the influence of the solvent by virtue of a high turnover frequency that curtails the impact

of any solvent effects. Furthermore a tridentate ligand may well shield the palladium centre from intrusive solvent molecules, meaning the choice of medium is fairly redundant in this example. Another approach is to eliminate the catalyst entirely, as is possible by conducting a cross-coupling of radicals formed from an alkyne and cyclohexane instead of an organohalide.[240] Benzene and chlorobenzene are the favoured solvents, drawing parallels with a radical Kumada-type reaction reliant on toluene as the solvent instead of electron donating solvents.[152]

A solvent screen for the Sonogashira reaction between phenylacetylene and iodobenzene (all at 80 °C for 6 hours) revealed that alcohols (methanol and ethanol) were as effective as DMF and DMAc, with high yields obtained (89-96%) (Figure 8).[241] A supported palladium catalyst immobilised on silica with chelating amine ligands meant the reaction would still progress in acetonitrile, THF, or 1,4-dioxane, but not in benzene or toluene. The lack of reaction in aromatic solvents was ascribed to the negligible solubility of the base (which was potassium carbonate rather than the usual amine). It would appear that the commonality of strong electron donating ability between alcohols and amide solvents is responsible for the greater yields compared to the medium strength basicity of ethers and nitriles. With alkyne deprotonation being an important stage of the reaction, possibly rate determining, the ability of the solvent to dissolve the base, and liberate the carbonate anion from its potassium counterions might be important. Ethanol has also been used as the solvent in a Sonogashira reaction catalysed by single atom palladium supported on titanium dioxide.[242] The energy barrier of the reaction was very low, with the rate determining step identified as the oxidative addition of iodobenzene in this special case.

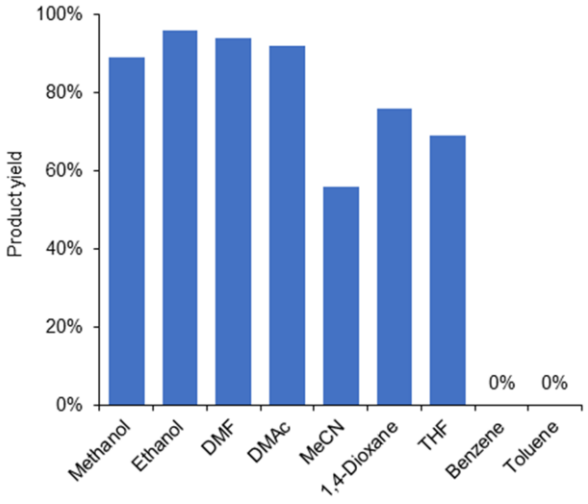
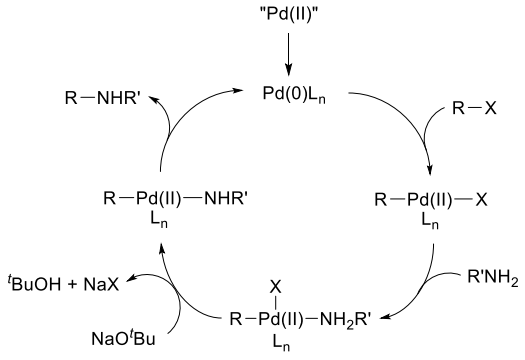


Figure 8. Yields of a model Sonogashira reaction catalysed by palladium tethered to a solid support through chelating amine ligands.

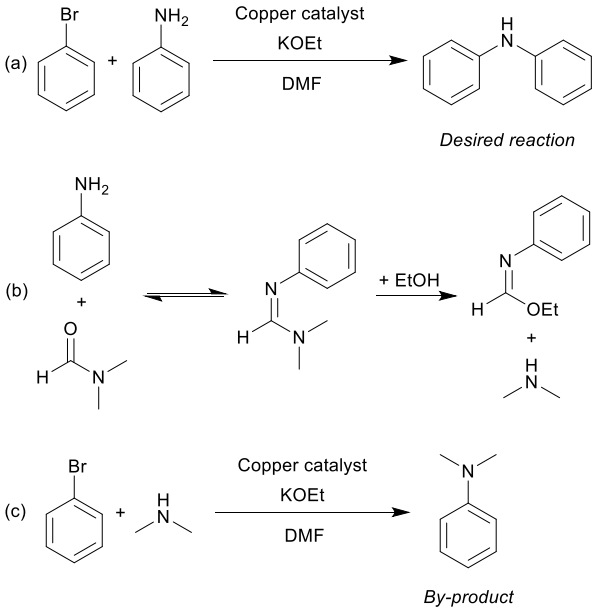
2.5.3 Buchwald-Hartwig reaction

The Buchwald-Hartwig reaction requires the coordination and deprotonation of an amine reactant to palladium instead of the transmetalation of an organometallic species (Scheme 48).[243,244] A strong base is introduced to deprotonate the amine which sets the Buchwald-Hartwig reaction apart from the Sonogashira reaction.[245] The product of a Buchwald-Hartwig reaction is the *N*-substituted amine.



Scheme 48. A general catalytic cycle for the Buchwald-Hartwig reaction using sodium *tert*-butoxide as a base.

The Buchwald-Hartwig reaction will occur in hydrocarbon solvents, with alkanes and aromatic solvents (most frequently toluene) both applicable. 1,4-Dioxane is the other common solvent for Buchwald-Hartwig reactions. In heterogeneous copper catalysed variants of the Buchwald-Hartwig reaction it has been observed that catalyst performance is inversely proportional to the dielectric constant of the solvent.[246] This behaviour is unique to the Buchwald-Hartwig reaction, for other cross-coupling methods are often successful in DMF and other highly polar and/or electron rich solvents. Tirsoaga *et al.* suggest this may be due to competitive coordination to active sites.[246] Additionally, the same work reports that DMF, a poor solvent, participates in transamidation with the amine reactant (Scheme 49). This means dimethylamine is now liberated as the free amine in solution, and that is reflected in the observed product distribution.

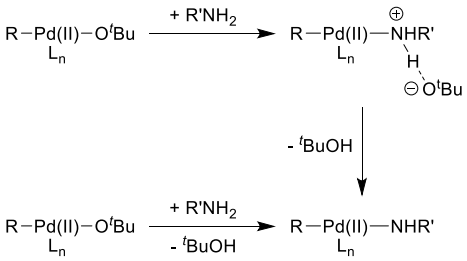


Scheme 49. An illustration of competing aminations in Buchwald-Hartwig reactions when amide solvents are used: (a) intended reaction; (b) interference of solvent; (c) side-reaction.

Competitive palladium coordination during Buchwald-Hartwig reactions has been investigated, leading to the use of chelating ligands such as BINAP.[247] Bidentate ligands help supress

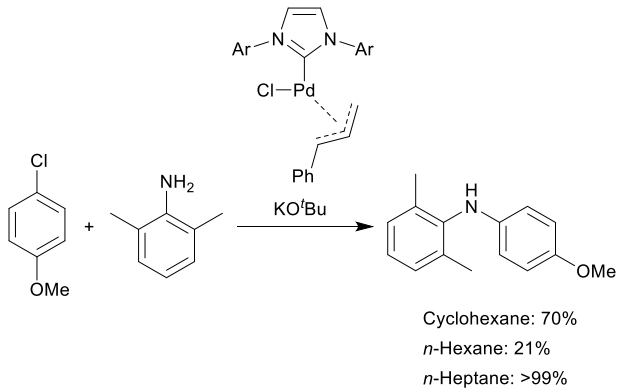
β-hydride elimination, and exclude halides from the coordination sphere. Contrary to many observations in other types of cross-coupling, the addition of salts inhibits the Buchwald-Hartwig reaction.[248] Buchwald and co-workers rationalised the rate-slowing effect of halide salts with the competitive formation of anionic palladium complexes, inhibiting coordination of the amine reactant or slowing reductive elimination.[249] In this respect the lower solubility of bromide salts compared to iodides in toluene is consistent with the observation that aryl bromides react more readily than aryl iodides. Salt solubility is higher in ether solvents compared to toluene, producing yet slower reaction rates.

Computational mechanistic examinations indicate charge neutralising reactions between base and catalyst are important to understanding the salt effect that controls Buchwald-Hartwig reactions.[250] In a non-polar or low polarity solvent, oxidative addition was assumed to produce a T-shaped complex from a monophosphine catalyst, but dimeric catalysts with bridging halide ligands are also known.[27] Comparing the performance of toluene and DMF using DFT calculations, in the less polar of the two solvents an alkoxide base substitutes the halide ligand first, and then deprotonates the amine as it approaches the palladium to avoid generating charge. The result is a neutral palladium complex stable in toluene (Scheme 50).[250] Participation of the base as a ligand is possible when it is sodium *tert*-butoxide, but not when caesium carbonate is used for instance. In DMF, which will support the charged intermediates avoided in toluene, halide dissociation from the palladium after oxidative addition to give a cationic complex is possible, but ion pairing with the base then deactivates the catalyst. Should the base become a formal ligand, further ion pairing during the ligand substitution with the amine reactant stalls the reaction (Scheme 50). A neutral base is not appropriate for Buchwald-Hartwig reactions because a charge would be generated that is not adequately stabilised.[250]



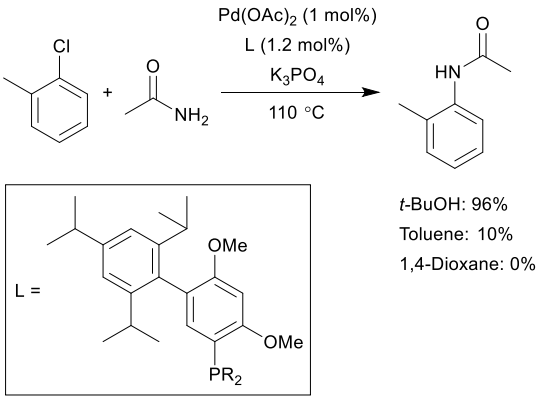
Scheme 50. A metal amine complex formed in DMF (top pathway) and toluene (bottom pathway).

Alkane solvents are applicable to the Buchwald-Hartwig reaction.[251] Hydrocarbon solvents are valued in some solvent selection protocols because their calorific value can be used to offset the energy demand of their production.[252] This is not to say they are safe or non-toxic, but simply benefit from incentivised waste disposal. In the work of Marelli *et al.*,[251] they emphasise this benefit of alkane solvents and test *n*-hexane, cyclohexane, and *n*-heptane in combination with potassium *tert*-butoxide at a target temperature of 80 °C (Scheme 51). The reason for the high performance of alkane solvents is certainly the same as for toluene and 1,4-dioxane, that being the driving force to neutralise the key reaction components is greatest in the solvents poorest at stabilising ions. Despite the reactions being carried out in sealed vessels, *n*-hexane has a boiling point below 80 °C and so may explain the poorer performance compared to the excellent conversions in the other alkane solvents. The Kamlet-Taft π* parameter and relative permittivity (dielectric constant) measurements concur that *n*-hexane is the least polar of the three alkanes, and cyclohexane the most polar, although the difference is very small. Therefore the lower boiling point of *n*-hexane is a logical explanation as to why the yields do not follow this trend.



Scheme 51. The Buchwald-Hartwig reaction in alkane solvents. The Ar– group of the ligand is a 2,6-di(5-nonyl)phenyl group.

There are examples of tertiary alcohols being used as a solvent for the Buchwald-Hartwig reaction.[253] The use of metal hydroxide or ammonium hydroxide bases necessitated the change to a protic solvent so that a suspension of the base could be formed. Viable solvents are 2-methoxyethanol, ethylene glycol, and *tert*-butanol. *Tert*-butanol was also preferred to 1,4-dioxane and toluene to maximise yields in another example of the Buchwald-Hartwig reaction (Scheme 52).[254] In this case the productivity of the Buchwald-Hartwig reaction is linked to the water-activated formation of the catalyst, which requires a compatible (water-miscible) solvent. The application of alcohol solvents is very appealing for the scale up of these procedures. Caille and co-workers made 12 kilograms of a Buchwald-Hartwig coupling product using 2-propanol as the solvent, sodium *tert*-butoxide as base, and a catalyst formed from palladium acetate and an equivalent ligand to that shown in Scheme 52 (R = cyclohexyl).[255]



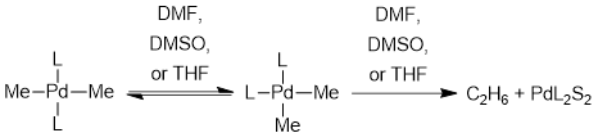
Scheme 52. A Buchwald-Hartwig reaction with an amide reactant conducted in *tert*-butanol. R = *t*-Bu.

2.6 Reductive elimination

Reductive elimination is a common process in transition metal chemistry and well understood.[256,257] It is usually a very facile step in the cross-coupling mechanism,[121] and for that reason it is not prioritised as a topic for mechanistic studies. Having said that, occasionally reductive elimination is rate determining in Stille,[258] and Kumada reactions.[259] The Heck reaction is different in that there is no reductive elimination of the product, but instead a β-hydride elimination. The resulting palladium hydride complex does undergo reductive elimination with the help of a base to return the oxidation state of palladium to zero with the loss of HX (Scheme 38).

The reductive elimination process is essentially the reverse of oxidative addition. To study reductive elimination, different *cis*- and *trans*-dimethyl palladium complexes have been prepared (Scheme 53).[260] This work, published in 1980 by Stille, confirmed two principles of cross-coupling reactions that have been taken for granted ever since: reductive elimination is intramolecular; and *trans*-complexes need to isomerise to the *cis*- form before elimination. The *trans*-isomer is the thermodynamically more stable complex, and so solvent stabilisation of the required *cis*-isomer is needed. The solvent has a role to play along with the ligands when facilitating the isomerisation and reductive elimination phase of a cross-coupling reaction. The dimethyl palladium complexes are stable at room temperature, meaning reductive elimination to give ethane can be temperature

controlled. Polar coordinating solvents allowed the isomerisation from *trans*- to *cis*- at 50 °C, and reductive elimination occurred at 100 °C. This indicates the isomerisation has a lower energy barrier than the reductive elimination, but even so no isomerisation occurred in benzene or tetrachloroethane (both low polarity solvents). Reductive elimination studies of complexes more representative of the intermediates found in a cross-coupling reaction concur that low polarity solvents hinder the process.[261] The addition of extra quantities of ligand (or use of more electron rich ligands) retards the rate of reductive elimination.

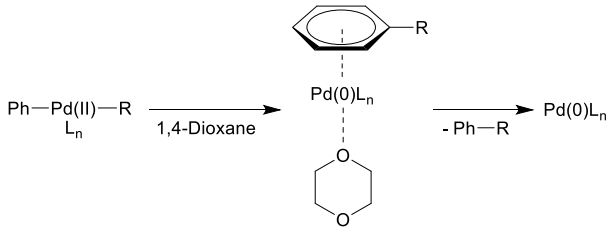


Scheme 53. The reductive elimination of a model compound. Various phosphine ligands were applied.

Only if reductive elimination is the rate determining step of a cross-coupling will these findings be of practical significance to inform solvent selection, but regardless of the rate of reductive elimination it does have a bearing on the structure of the product. Retention of stereochemistry has been reported after reductive elimination,[262] indicating a concerted process *via* a three-membered activated complex.

The mechanism of reductive elimination is being revisited as a research topic in the context of C–H activation. Highlights include DFT calculations investigating the energy lowering benefit supplied by solvent molecules, even in an outer solvation sphere (with ligands occupying the innermost coordination sphere).[263] In jointly experimental and computational studies, 1,4-dioxane was shown to support reductive elimination (where toluene and 1,2-dichloroethane, solvents of a similar dielectric constant, did not) due to solvent assisted dissociation of the product.[264] After reductive elimination, an aromatic product may interact with palladium as a π-bonding ligand.

Electron donating solvents can replace this interaction and displace the product, freeing the catalyst to participate in another catalytic cycle (Scheme 54). In both of these studies, it was necessary to include both implicit solvation models and explicit solvent molecules in order to begin to understand solvent effects in these systems.

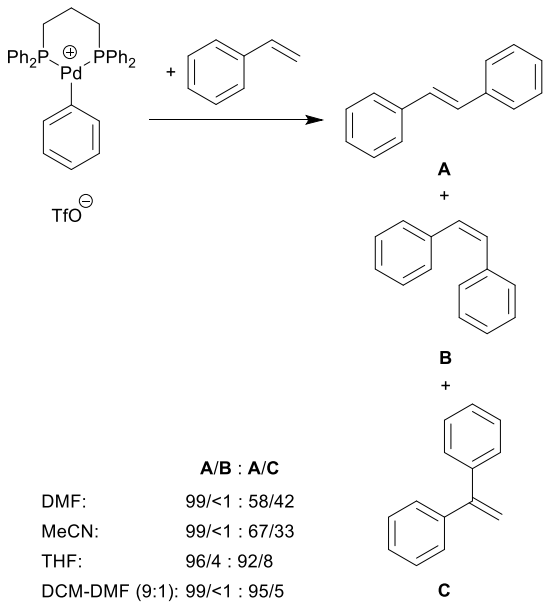


Scheme 54. Solvent assisted dissociation of a generic cross-coupling product.

2.7 Cross-coupling selectivity and side-reactions

Having now covered the principle mechanistic aspects of popular cross-coupling methods, it is important to review developments that address the competing reactions in more detail. This section will also present more advanced applications of cross-coupling reactions, such as enantioselective transformations.

The Heck reaction is regarded with high esteem for its high *trans*-selectivity. However there are possible alternative products. The *cis*-product could be formed instead, or α-hydride elimination would lead to a 1,1-substitution pattern instead of the 1,2-*trans*-product expected from β-hydride elimination. If oxidative addition occurs on an organotriflate substrate, the resulting palladium complex may be cationic (with a dissociated triflate counterion). This species has a lower selectivity for β-hydride elimination than a neutral palladium complex with a true halide ligand.[265] Replacing a DMF solvent system (which is polar enough to support ionic catalytic intermediates) with a DCM-DMF (9:1) mixture will return β-elimination selectivity to Heck reaction products made from organotriflate reactants (Scheme 55). The same is true of THF, but the *cis*-product is then also formed to a small extent.[265]

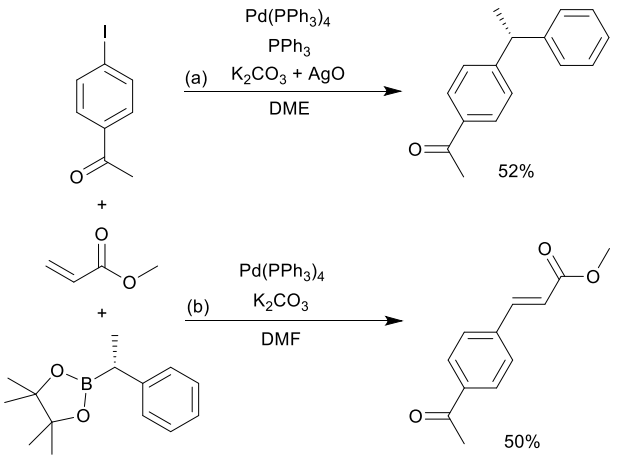


Scheme 55. Heck reaction regioselectivity controlled by the solvent using a preformed arylpalladium complex.

In an experiment using a bifunctional vinyl alkoxysilane as a substitute for a more conventional organometallic reactant, a Heck coupling or a Hiyama coupling is possible depending on the prevailing chemoselectivity.[266] The selectivity of this reaction is solvent dependent. In water a Heck reaction occurs, and in THF the Hiyama reaction is observed. The reason is due to how the solvent interacts with the base (sodium hydroxide). Water reduces the basicity of the hydroxide due to solvation.[266] This prevents the silicon anion formation but will neutralise HX as part of the Heck reaction. Therefore the choice of a protic or aprotic solvent is crucial for chemoselectivity because the role of the base is fundamentally different in a Heck reaction compared to a Hiyama reaction.

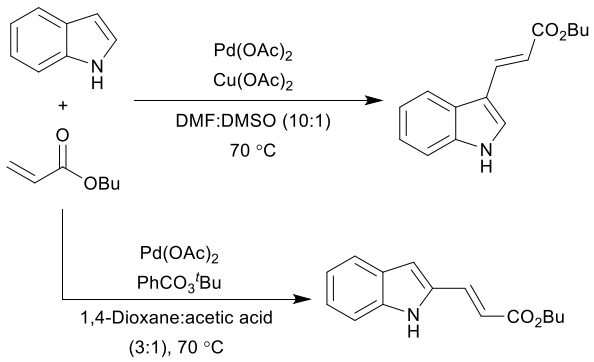
Switchable chemoselectivity between boronic esters (Suzuki reaction) and alkenes (Heck reaction) was found by changing the solvent and introducing silver oxide as an additional base.[267] In DMF, potassium carbonate permits a Heck reaction to occur. In DME, with excess ligand and silver oxide at lower temperatures, alkenes are unreactive in the presence of a boronic acid pinacol ester (Scheme 56). The same effect was achieved by adding water to THF for the bifunctional vinylboronic

acid pinacol ester substrate (see Section 2.4.5).[196] The Suzuki coupling retains stereochemistry during the transmetalation meaning a closed transition state is expected.



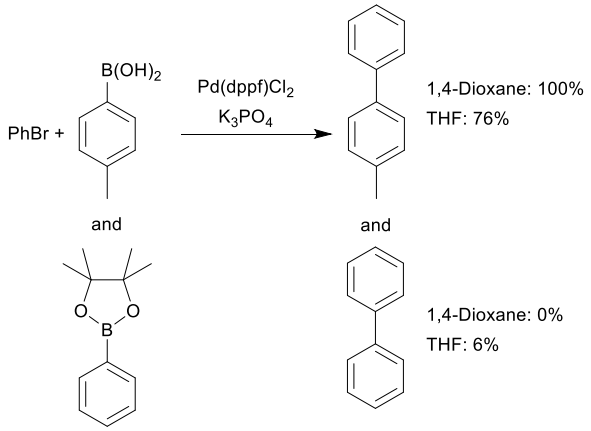
Scheme 56. A solvent and temperature switch of chemoselectivity between a Suzuki reaction and a Heck reaction.

Looking to new advances in carbon-hydrogen bond activation, oxidative Heck reactions operate on C–H bonds rather than C–X bonds. The issue to resolve here is how to obtain the selectivity the halide bond defines in its absence. The choice of solvent has been found to dictate regioselectivity for the oxidative Heck coupling of indoles to acrylates.[268] Substitution at the C2 position (7:1 selectivity) was achieved using a mixture of 1,4-dioxane and acetic acid with *tert*-butyl benzoyl peroxide as the oxidant, while a blend of DMF and DMSO redirected the alkenation to the C3 position with 95% selectivity ($Cu(II)OAc_2$ was the oxidant) (Scheme 57). The change of oxidant was due to solubility issues. Inorganic oxidants such as copper(II) acetate are insoluble in 1,4-dioxane, hence the use of *tert*-butyl benzoyl peroxide. Acidic conditions were found to promote reactivity at the C2 position, and so the optimum solvent was 25% acetic acid in 1,4-dioxane (by volume). The addition to DMSO to DMF (1:10) helped stabilise the Pd(0) oxidation state. This is a glimpse into how fine-tuning reactions with judicious solvent selection will only become more important as synthetic coupling methodologies evolve.



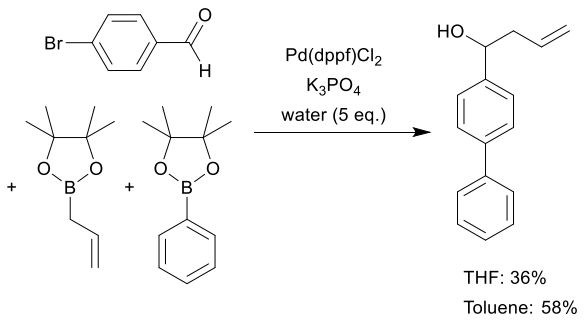
Scheme 57. Regioselectivity in an oxidative Heck reaction controlled by solvent polarity and acidity.

A chemoselective Suzuki reaction in the presence of arylboronic acids and their pinacol esters was made possible once the authors recognised that "*the choice of reaction medium was crucial to both efficiency and selectivity*".[208] A boronic acid is more reactive than its pinacol ester. In 1,4-dioxane the selectivity was absolute, but in THF a mixture of products was formed (Scheme 58). By extension, 1,4-dioxane maximised selectivity in the reaction of mixed boronic acid and boronic pinacol ester with dihaloarenes such as 4-bromochlorobenzene. Tetrahydrofuran is a stronger hydrogen bond acceptor and electron donor compared to 1,4-dioxane, and this is likely to activate the catalyst and make the reaction of the less reactive pinacol ester competitive.



Scheme 58. Solvent controlled competitive Suzuki reactions.

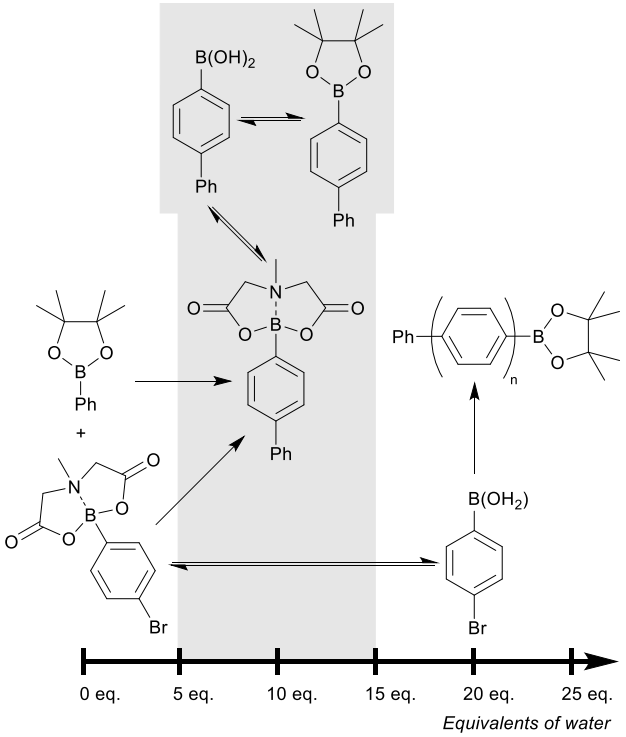
The reaction of 4-bromobenzaldehye with allylboronic pinacol ester can result in allylboration as well as a cross coupling (Suzuki reaction).[269] In order to selectively conduct the allylboronation in the same pot as a less reactive aryl boronic ester, the correct choice of solvent is needed to mediate the relative rates of reaction. Allylboronation,[270] as with carbonyl additions generally,[271] occur faster in low basicity (β) solvents. Therefore to minimise undesirable cross-coupling toluene was employed as a solvent, replacing THF (Scheme 59). The aryl boronic ester can then participate in a Suzuki reaction to further functionalise the substrate. A yield of 58% was increased to more than 80% (both in toluene) by optimising other parameters (catalyst loading, ratio of boronic esters).



Scheme 59. Chemoselective one-pot allylation and cross-coupling.

N-Methyliminodiacetic acid (MIDA) boronic esters are less reactive than their pinacol counterparts, and water is critical to achieving a chemoselective reaction in the presence of both types of boronic ester. Fyfe *et al.* have extensively investigated boron speciation in aqueous THF.[272,273] It was shown that 5-15 equivalents of water permitted the desired cross-coupling (where the pinacol ester acts as the organometallic reaction partner) and subsequently hydrolysed the MIDA ester replacing it with a pinacol ester (Scheme 60). Pinacol is available in the reaction after being hydrolysed from the boric acid ester formed after the intended Suzuki reaction occurs. A potassium phosphate hydrate regulated the rate of hydrolysis to prevent premature formation of a reactive boronic acid. This tactic has seen use elsewhere to protect unstable boronic acids from

hydrodeboronation.[274,275] When larger quantities of water were used, approaching co-solvent proportions, oligomers of the bifunctional bromophenylboronic acid MIDA ester formed. In the absence of added water the original reactants were mostly present. This study has been extended to react the intended (non-polymeric) pinacol ester product with an additional organochloride (20 equivalents of water in THF), using the difference in reactivity between aryl chlorides and bromides to introduce another level of selectivity.[276] Li *et al.* have shown the same chemoselectivity operates when triethylamine is used as the base and as the solvent.[277]



Scheme 60. A simplified equilibrium of mixed boronic esters undergoing Suzuki reactions, with species approximately positioned according to the water content of the reaction at which they are observed. Optimal water content is 5-15 equivalents (grey shaded area).

The choice of solvent can be crucial in helping ligands impart enantioselectivity. A helical poly(quinoxaline-2,3-diyl)-based ligand has been functionalised with pendant $-PAr_2$ groups for the purpose of asymmetric Suzuki reactions.[278] When the polymeric ligand (L = (*P*)-(*R*)-PQXphos) is

prepared in chloroform, it is 'right handed'. Surprisingly, when heated in a mixture of 1,1,2-trichloroethane (TCE) and THF the polymer inverts into the opposite stereoisomer, (*M*)-(*R*)-PQXphos. Then the remaining coupling reaction components can be introduced to the (*M*)-ligand to achieve the desired product (Figure 9). The origin of this subtle solvent effect has been investigated but the exact mechanism remains elusive.[279,280] The current proposal is that the conformational preference of the two (*R*)-2-butoxy groups on the non-phosphine-bearing monomer within the polymeric ligand is solvent dependent, and the helix that provides the most stability changes accordingly from solvent to solvent. There is no general trend: ethers, DCM and 1-butanol join chloroform in favouring the right-handed form of the helical ligand, while nitriles, 1,2-dichloroethane and 2-butanol stabilise the left-handed helix.[280]

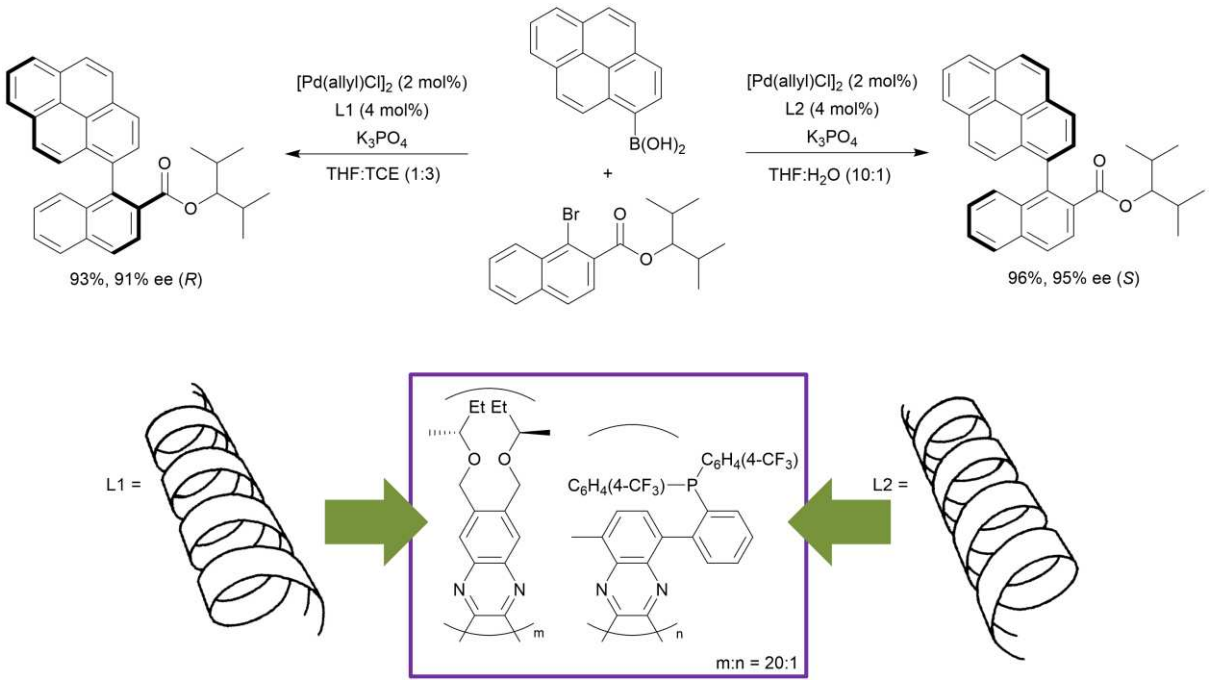
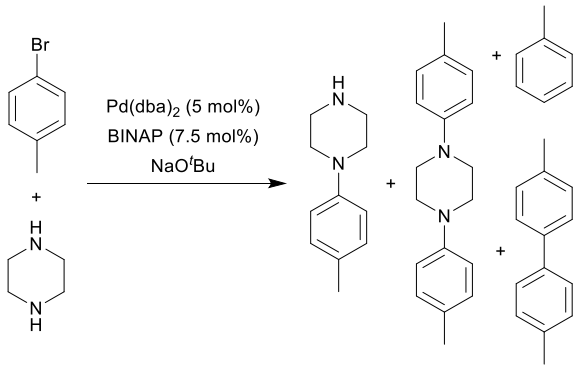


Figure 9. Invertible ligand (bottom) to control the stereochemistry of a Suzuki reaction (top).

The selectivity of a Buchwald-Hartwig reaction can be diminished by homocoupling of the aryl halide, hydrodehalogenation, and in the case of diamine reactants, a mixture of mono and di-arylated amine products. An example of the Buchwald-Hartwig reaction has been studied in an

attempt to create a viable flow chemistry set-up (Scheme 61).[62] The usual combination of non-polar solvent and inorganic base is not suited to flow chemistry due to the low solubility of the base in this system. For this reason NMP and DMAc were investigated as solvents and compared to *m*-xylene and 1,4-dioxane. The rate of conversion appears to be proportional to the polarity of the solvent, in line with base solubility. However, side products are formed more rapidly as well which limits the yield and confirmed the well-known preference for low polarity solvents in the Buchwald-Hartwig reaction. In NMP for example, hydrodehalogenation yields matched that of the intended product. The reason may be due to longer lived catalytic intermediates (not achieving steady-state kinetics) making β-hydride elimination of the amine reactant more competitive.[281] This side-reaction places a hydride on the palladium and so reductive elimination results in an arene rather than the intended coupling product. In a non-coordinating solvent this issue is resolved. Overall the best yield was obtained in 1,4-dioxane with higher excesses of amine (Figure 10).[62]



Scheme 61. A Buchwald-Hartwig reaction with several possible by-products.

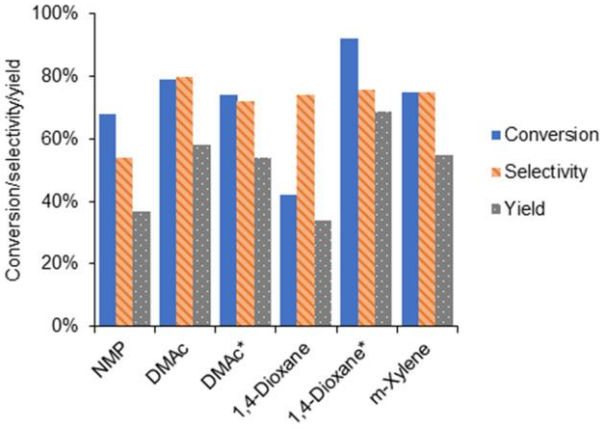
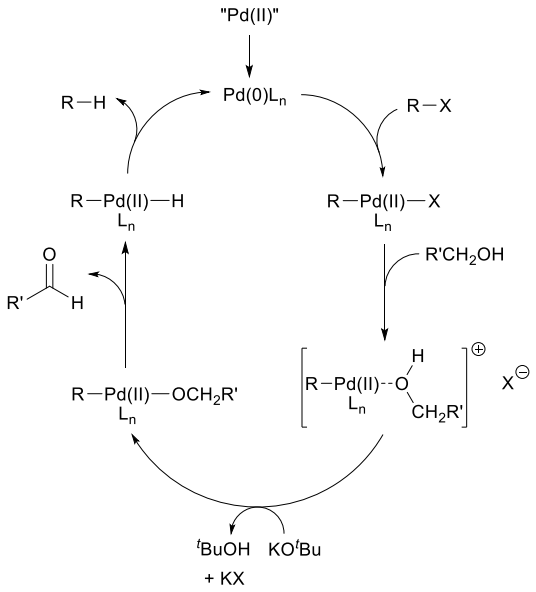


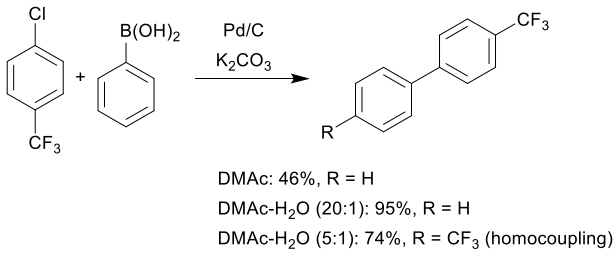
Figure 10. The performance of a Buchwald-Hartwig reaction in different solvents, reported as conversion, selectivity, and yield. *Quantity of base doubled to 2.2 equivalents.

The hydrodehalogenation observed in the previous case study can occur on the organohalide reactant common to all cross-coupling reactions. However it is the presence of strong bases that tends to promote this unwanted side-reaction. Alcohol solvents are thought to be deprotonated in these circumstances and can act as alkoxide ligands. [282] The solvent is ultimately oxidised to an aldehyde or ketone in a β-hydride elimination that precedes reductive elimination of the hydrodehalogenated product (Scheme 62). This catalytic cycle has been suggested after analysis by mass spectrometry and kinetic isotope experiments (methanol vs. CH_3OD and CD_3OD).[283]



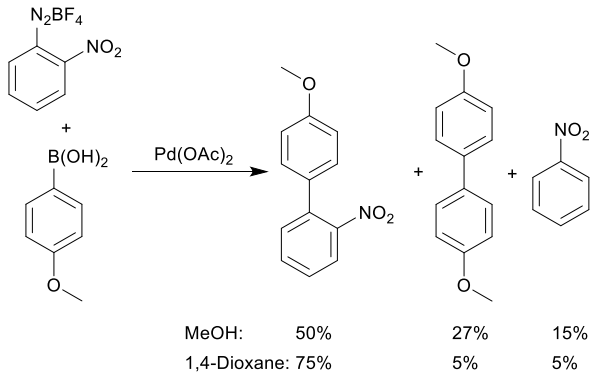
Scheme 62. The catalytic cycle of hydrodehalogenation caused by oxidising solvents (a primary alcohol solvent is represented as R'CH_2OH).

Solvent effects can also promote or impede homocoupling, another unwanted side-reaction. The Suzuki reaction of benzoyl chlorides, catalysed by palladium on carbon (ligand-free) is effective in aqueous acetone, with superior yields to reactions conducted in other aqueous solvent mixtures or undiluted organic solvents.[284] A ratio of 3 parts acetone to 1 part water eliminated the homocoupling that was observed with greater proportions of water. Higher proportions of water in an aqueous-organic mixture can also inhibit the dispersion of Pd/C.[285] Suzuki reactions performed in DMAc are also assisted by the addition of water, but again too much water resulted in homocoupling (Scheme 63).[286] The ability of DMAc to reduce Pd(II) (as in Scheme 7) was suggested as contributing to the performance of this particular solvent.



Scheme 63. The formation of Suzuki reaction products or homocoupling products in different solvent systems.

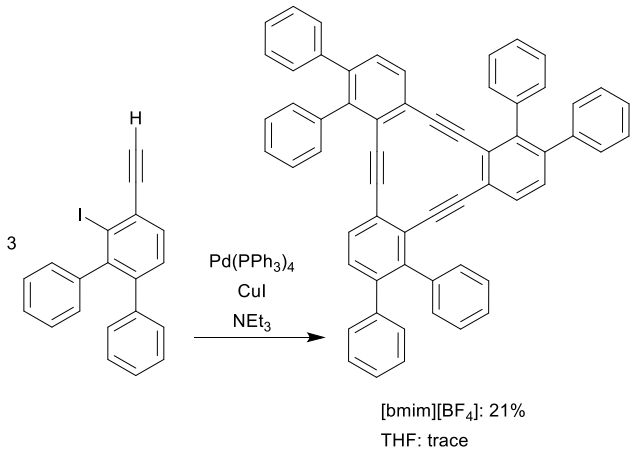
Methanol and 1,4-dioxane have been used as solvents for the Suzuki reaction of arenediazonium tetrafluoroborate salts (Scheme 64).[287] In methanol, N_2 evolution was observed and palladium black forms rapidly. Arene and homocoupling by-products were observed, with a yield of the intended product only 50%. Reactions conducted in 1,4-dioxane were superior, which was attributed to ether solvents being less potent reducing agents.[287] Other studies have shown 1,4-dioxane can be oxidised after coordinating to palladium in a β-hydride elimination,[72] which may explain the 5% selectivity for hydrode(psuedo)halogenation.



Scheme 64. Suzuki reaction selectivity in protic and aprotic solvents.

The Sonogashira reaction of multifunctional 2-iodophenylacetylenes to create cyclic products works well in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) but not in organic solvents (DMF, THF) under the same conditions (Scheme 65).[288] Copper(I) iodide

was used to assist the coupling but was responsible for undesirable homocoupling becoming the major reaction pathway in organic solvents, even under an inert atmosphere. The ionic liquid permitted much reduced quantities of CuI to be used (1 mol%), thus improving the selectivity of the reaction.



Scheme 65. The use of a Sonogashira reaction to create trimeric products.

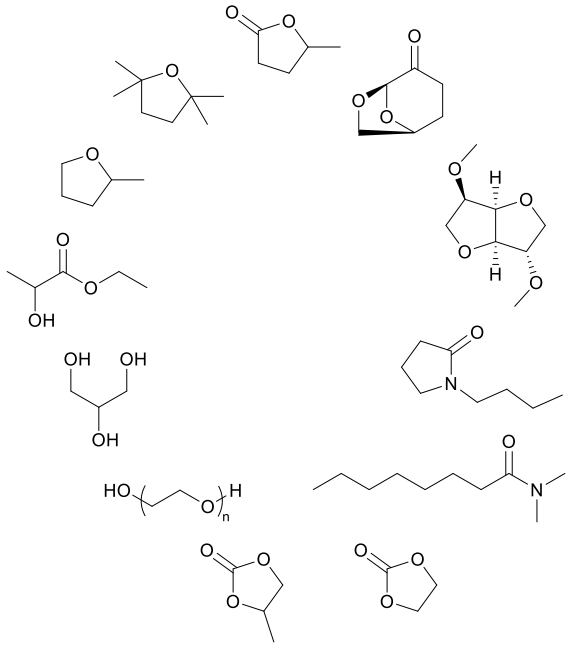
3. Solvent substitutions in cross-coupling reactions

Recent reviews addressing solvent substitution provide a wealth of examples where desirable solvents have been implemented in cross-coupling reactions.[289,290,291,292] The purpose of this review is different, using a mechanistic understanding (as put forward in the previous sections) to create a rationale for solvent optimisation. To conclude this exercise, it is helpful to look at prominent examples of recent solvent substitutions and interpret them in terms of how the replacement solvent promotes the reaction, and what allowances need to be made to accommodate an unconventional reaction medium.

3.1 Alternative organic solvents

A number of new, 'neoteric' solvents have recently been developed to provide different benefits over conventional solvents. Novel dipolar aprotic solvents have been designed to be non-

toxic or renewable alternatives to the conventional amides. There are also speciality ether and alcohol functionalised solvents that have specific uses as cross-coupling solvents. The molecular structures of some of these solvents can be found in Scheme 66.



Scheme 66. The structures of neoteric solvents used in cross-coupling reactions (clockwise from top): γ-Valerolactone (GVL), Cyrene™, dimethyl isosorbide, *N*-butyl pyrrolidone (NBP), *N*,*N*-dimethyl octanamide, ethylene carbonate, propylene carbonate, polyethylene glycol (PEG), glycerol, ethyl lactate, 2-methyltetrahydrofuran (2-MeTHF), and 2,2,5,5-tetramethyloxolane.

3.1.1 γ-Valerolactone

γ-Valerolactone (GVL) is a bio-based ester which as a cyclic molecule has greater dipolarity than acyclic esters. This makes it comparable in many respects to conventional dipolar aprotic solvents. The primary benefit that GVL provides in cross-coupling reactions is the low leaching of palladium, with significantly less palladium contaminating the product than what results from the use of an amide solvent. Figure 11 shows the yield of a Pd/C catalysed Sonogashira reaction between phenylacetylene and iodobenzene compared to the amount of palladium contamination in the

isolated product.[234] The difference is remarkable but logical. The coordination of dipolar aprotic solvents to palladium is responsible for faster reactions and simultaneously greater losses of palladium because leached palladium is the active catalyst. The weaker coordination of GVL provides a satisfactory balance, sacrificing reaction rate for lower palladium leeching. After 4 hours the eventual yield of the reaction in GVL is comparable to other solvents.

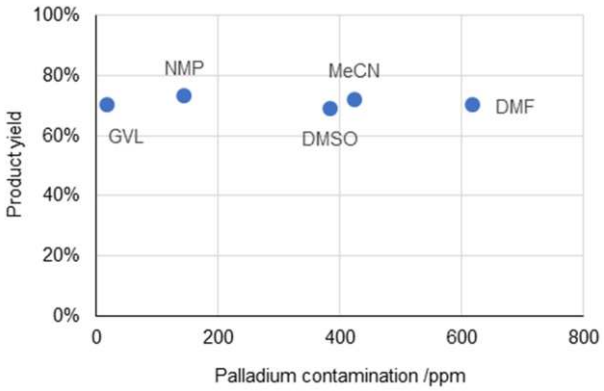
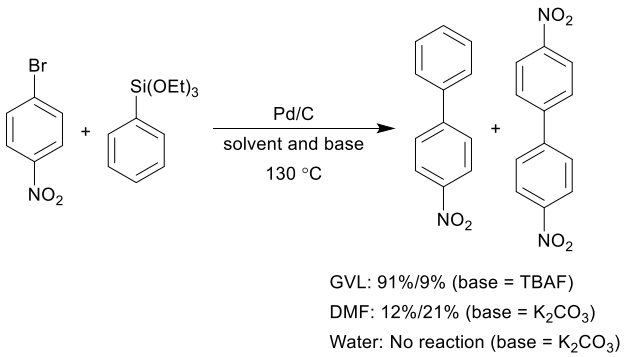


Figure 11. Yields and palladium contamination in a Sonogashira coupling product.

The benefits of low palladium contamination provided by GVL in polymeric cross-coupling products has also been realised.[293] An organic semiconducting material, poly(2,5-dihexyloxyphenylenedivinylene-*alt*-1,4-phenylenevinylene), was produced in NMP and GVL by means of a Heck reaction. Palladium contamination was 2 orders of magnitude lower within the polymer formed in GVL, However the number average molar mass was double in the NMP sample. To see if this had an impact on the applications of the polymer, solar cells and transistors were fabricated and performance tested. The lower molecular weight polymers were not as effective, but were considerably worse if they were doped with palladium to replicate the level of contamination resulting from NMP use in their synthesis. The difference in polymer size is probably due to the point when the product molecular mass is sufficient to cause precipitation, thus halting the reaction.

γ-Valerolactone is also appropriate as a solvent for the Hiyama reaction.[182] Tetrabutylammonium fluoride (TBAF) was needed for solubility reasons, whereas in DMF potassium

carbonate is applicable. GVL significantly outperforms DMF, with much greater yields and homocoupling restricted below 10%, while in water no reaction occurred (Scheme 67).



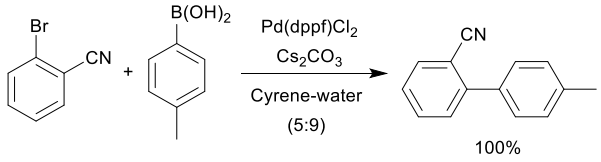
Scheme 67. The product distribution (yields) of a Hiyama reaction in GVL, DMF, and water.

3.1.2 Dihydrolevoglucosenone

Similar to GVL, dihydrolevoglucosenone (Cyrene™) is a bio-based, oxygenated solvent that shares some of the physical properties of conventional dipolar aprotic solvents but with no known chronic toxicity hazards.[38] Both GVL and Cyrene™ have a comparable dipolarity to DMF and the other amide solvents, but lesser electron donating ability (which also equates to weaker hydrogen bond accepting ability). Nevertheless Cyrene™ has been applied in different examples of cross-coupling. An investigation of the Sonogashira reaction in Cyrene™ was successful after addressing the choice of base.[235] Cyrene™ is sensitive to the vast majority of inorganic bases, and also amines if heated. Under these conditions dihydrolevoglucosenone undergoes an aldol addition which can cause the reaction mixture to solidify. The use of triethylamine at 30 °C is appropriate, and a large screening exercise demonstrated the broad utility of this reaction system.

The reactivity of Cyrene™ towards bases is also a stumbling block in the Suzuki reaction.[294] With amines generally ineffective bases for the Suzuki reaction, aqueous caesium carbonate was chosen as the least damaging inorganic base, preventing the solidification of the reaction and allowing the procedure to be scaled up to gram-quantities with a quantitative coupling yield

(Scheme 68). The kinetics of a Heck reaction (assisted by triethylamine) have been measured in different solvents, showing Cyrene™ to afford marginally slower formation of methyl cinnamate compared to GVL, but both solvents were some way behind the rapid reaction in DMF.[295]



Scheme 68. A gram-scale Suzuki reaction in Cyrene™-water mixed solvent.

3.1.3 Dimethyl isosorbide

Dimethyl isosorbide was developed as a non-toxic, bio-based solvent for formulation science, but has now been applied in cross coupling reactions. Suzuki, Heck, and Sonogashira reactions are all successful in dimethyl isosorbide.[296] The Heck reaction of aryl bromides required higher temperatures (115 °C) than the analogous iodides (80 °C) which is understandable given their relative reactivities. The removal of dimethyl isosorbide from the product is achieved by washing with water, as is true of conventional dipolar aprotic solvents given their high boiling points.

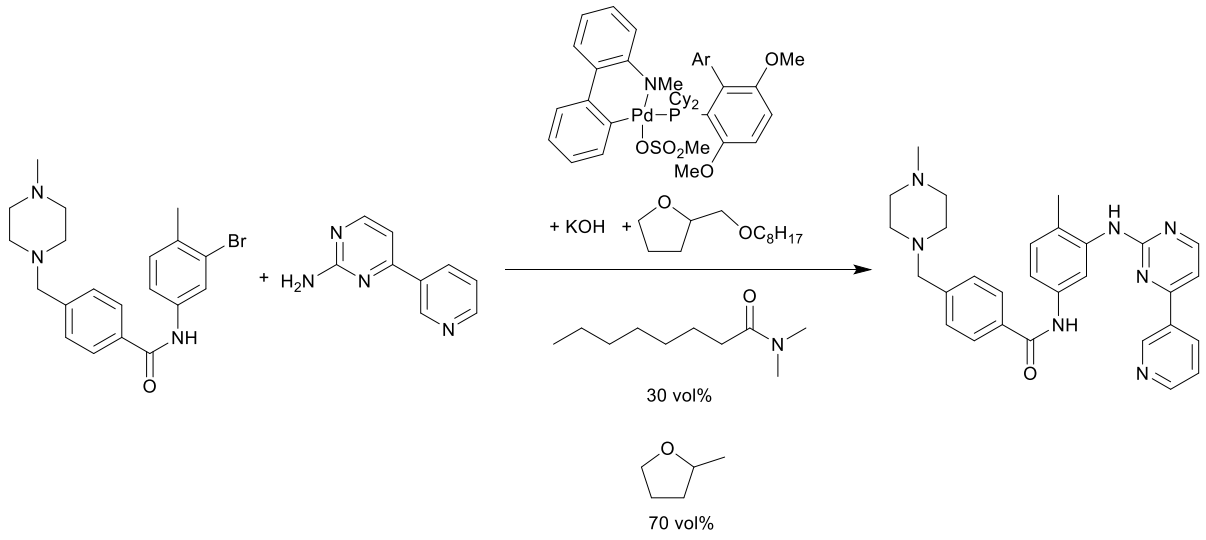
3.1.4 N-Butyl pyrrolidone

N-Butyl pyrrolidone (NBP) was designed as a drop-in replacement for NMP.[39] It is not reprotoxic like NMP and DMF, as confirmed by thorough toxicological testing. *N*-Butyl pyrrolidone has been evaluated in the Heck reaction,[220] and is equivalent to NMP and DMSO in terms of the rate of reaction obtained, but some way behind DMF. In a Heck reaction substrate screening yields in NMP and NBP were broadly equivalent, but for Suzuki reactions yields in the less polar NBP were generally 10% lower. This may be due to the lesser solubility of salts in NBP leading to halide by-products associating with the catalyst and causing deactivation. By-products and side-reactions were not investigated. The use of NBP with water as a co-solvent has not been investigated but may

potentially improve yields. The one other reported use of NBP in cross-coupling reactions is as a co-solvent with THF for the preparation of Grignard reagents, which were used directly in a Kumada reaction.[297]

3.1.5 N,N-Dimethyl octanamide

Another speciality amide has been described as a "catalytic solvent".[298] *N*,*N*-Dimethyl octanamide is a commercially available amphiphilic molecule.[43] Applied as a 10% solution in toluene *N*,*N*-dimethyl octanamide facilitated the progress of a Buchwald-Hartwig reaction. It was also possible to conduct a multi-step reaction in flow whereby *N*,*N*-dimethyl octanamide was added to 2-MeTHF to modify the reaction medium prior to a final cross-coupling step, resulting in the production of the cancer treatment drug Imatinib in 56% yield (Scheme 69).[298] The advantage of an amphiphilic solvent is the increased base (potassium hydroxide) solubility for flow chemistry, while maintaining an (overall) low polarity environment that suits the Buchwald-Hartwig reaction.



Scheme 69. The final step in the flow synthesis of Imatinib.

3.1.6 Ethylene carbonate and propylene carbonate

Cyclic carbonates offer a low toxicity and high performance option for the substitution of amide solvents.[41] Ethylene carbonate and propylene carbonate are widely available but not utilised to their full potential despite obvious advantages.[299,300] The application of cyclic carbonate solvents in the Heck reaction has been successful.[220] Carbonylative Suzuki-type cross-coupling is possible in propylene carbonate.[301]

3.1.7 Polyethylene glycol

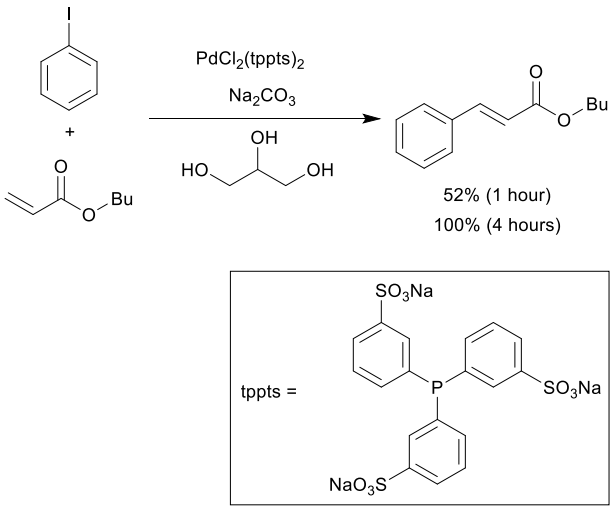
Polyethylene glycol (PEG) is an alternative cross-coupling medium, as demonstrated for Stille, Suzuki, and Heck reactions,[302] and Sonogashira reactions.[303] A variety of relatively low molecular weight PEG oligomers are applicable as a solvent for cross-coupling reactions, and the higher molecular weight polymers can be used as additives and catalyst supports.[304,305] When Nobre *et al*. used a mixed PEG-methanol reaction solvent for Suzuki reactions, immiscible non-polar solvents could be used to extract the product, avoiding an aqueous-organic separation.[306] Heptane was used as the extraction solvent, and minimised leaching of palladium into the product. Diethyl ether is also an applicable extraction solvent due to its low solubility in cold PEG.[307,308] The catalyst-containing PEG phase can then be reused.

3.1.8 Glycerol

Uses of glycerol in cross-coupling reactions have recently been reviewed by Vaccaro and co-workers.[291,309] The advantages of glycerol as a reaction solvent are numerous. It is non-toxic and renewable, and crude glycerol is cheap.[310] For cross-coupling reactions that require a base, glycerol can dissolve inorganic bases and is immiscible with non-polar extraction solvents. A solvent screen for the Suzuki reaction between 2-bromothiophene and phenylboronic acid showed glycerol outperformed a wide variety of conventional and alternative organic solvents in terms of the conversions obtained at 100 °C.[311] It is interesting to note that in this example the catalyst was

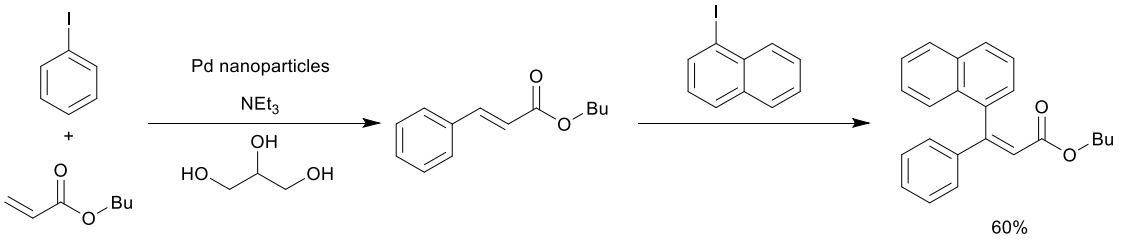
prepared by the hyperaccumulation of Pd(II) salts in the roots of common water hyacinth. A disadvantage of glycerol at lower temperatures is its very high viscosity. When this becomes an issue, ultrasonic irradiation can improve mass transfer, as has been applied for the Suzuki reaction.[312,313]

Nanoparticles, formed from palladium complexes or by the reduction of palladium salts under hydrogen, can be successfully dispersed in glycerol with appropriate stabilisers.[314] These colloidal solutions of catalyst can be recycled and reused, for example in the multi-step synthesis of heteroaromatic compounds.[315] The high polarity and viscosity of glycerol probably plays a role in defining this character. To stabilise palladium in glycerol solution, the anionic trisodium triphenylphosphine-3,3',3''-trisulphonate (tppts) ligand that was designed for use in aqueous systems,[316] can be advantageous.[317] Four hours is sufficient for complete transformation of butyl acrylate and iodobenzene at 80 °C with sodium carbonate as the base and a $PdCl_2(tppts)_2$ catalyst pre-cursor (Scheme 70).[317] It has also proved possible to use crude glycerol from vegetable oil transesterification directly as a solvent in the same Heck reaction.[318] In fact, the residual sodium hydroxide in crude glycerol can be put to use as the base with marginally lower yields than if additional sodium hydroxide is purposely added. It is yet to be seen if glycerol obtained from the industrial processing of mixed triglyceride-containing wastes is also suitable rather than a relatively clean form generated directly from refined vegetable oil.



Scheme 70. An example of a Heck reaction in glycerol.

Delample *et al.* used supercritical carbon dioxide to extract the product of a Heck reaction from a glycerol reaction medium, which was catalysed by palladium nanoparticles stabilised by a sugar derived surfactant.[319] The methodology was extended to diarylations (Scheme 71). The extraction efficiency is dependent on the duration of the extraction, the flow rate of CO_2, and its density. The use of supercritical carbon dioxide to extract products has the benefit of leaving no solvent residue in the product. However, longer extractions began to extract some glycerol along with the product.



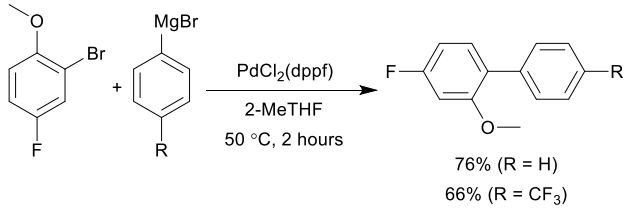
Scheme 71. A two-step double Heck reaction in glycerol.

3.1.9 Ethyl lactate

Ethyl lactate is an appealing solvent given its synthesis occurs from the industrial fermentation products ethanol and lactic acid.[320] However this alcohol-ester bifunctional solvent reduces palladium to palladium black, as can happen with other alcohols. A melamine ligand can prevent this unwanted catalyst deactivation and allow ethyl lactate to be applied successfully in Suzuki reactions.[321] Efforts to prevent the homocoupling of alkynes in the Sonogashira reaction are undertaken by excluding air, but the Glaser reaction is useful in its own right. Ethyl lactate has been shown to be a suitable solvent for the Glaser reaction.[322]

3.1.10 2-Methyltetrahydrofuran

The recent availability of neoteric ethers makes alternative solvent systems for Kumada reactions and Negishi reactions an interesting possibility. 2-Methyltetrahydrofuran (2-MeTHF) is a bio-based ether, likened to THF as a solvent due to the obvious structural similarity.[323,324] The comparison is treated in detail by Aycock in his 2007 paper introducing 2-MeTHF as a viable renewable solvent.[325] The high solubility of Grignard reagents made from organobromides in 2-MeTHF means that Kumada couplings can be conducted in less solvent whilst also promoting the reaction (Scheme 72).[326] It was also possible to produce the catalyst from a phosphinoferrocene ligand and a palladium salt in 2-MeTHF. The high solubility of aryl magnesium bromides in 2-MeTHF is useful in continuous flow reactors to prevent clogging the system with solids.[327] Conversely, organomagnesium chlorides are less soluble in 2-MeTHF than THF.[325]



Scheme 72. Examples of Kumada couplings performed in 2-MeTHF.

Process chemists are rapidly implementing 2-MeTHF as a neoteric alternative to THF.[328] For example, the coupling of boron compounds is successful in the production of bio-active compounds,[329] and for aerobic boron-Heck reactions.[330] An attempt to use 2-MeTHF in the Buchwald-Hartwig reaction was less productive than the conventional (and less dipolar) toluene and 1,4-dioxane,[246] but is suitable in combination with *N*,*N*-dimethyl octanamide for the synthesis of Imatinib, as described in Section 3.1.5. At present the number of examples where 2-MeTHF is being applied in C-C and C-N coupling reactions is fairly low,[331,332,333] but the benefits of a water-immiscible alternative to THF should be valued more highly.

3.1.11 2,2,5,5-Tetramethyloxolane

The formation of peroxides from 2-MeTHF remains a concern and this solvent should not be perceived as completely benign.[325] The inability of 2,2,5,5-tetramethyloxolane to form peroxides by α-proton abstraction makes it an obvious candidate for a superior ether solvent, but due to the sterically hindered ether oxygen atom it is unable to facilitate the preparation of organomagnesium compounds or their reactions.[334] It is however a useful solvent for some carbon-hydrogen bond activation chemistries because its bulky structure limits homocoupling and β-hydride elimination.[335]

3.2 Ionic liquids and deep eutectic solvents

Ionic liquids created an explosion of academic interest at the turn of the century,[336] which is now slowly filtering into industrial applications.[337,338] There have been many reviews covering the various applications of ionic liquids and deep eutectic solvents, and these satisfactorily address cross-coupling reactions.[339,340,341,342] This attention elsewhere in the literature does not warrant excessive repetition here. Instead a small sample of cross-couplings in ionic liquids and deep eutectic solvents are presented which display some aspects of how these solvents interact with catalysts and

the other reaction components. In addition, some recent contributions of particular interest in terms of sustainable chemistry are highlighted.

The Stille reaction of iodobenzene and tributylvinylstannane using a Pd_2dba_3 pre-catalyst and 2 equivalents of $AsPh_3$ was studied by Chiappe *et al.* in ten different ionic liquid solvents (Figure 12).[343] Generally, an anion with a more delocalised charge improved the yield, and for this reason $[Tf_2N]^-$ (*bis*(trifluoromethanesulphonyl) imide) was a good choice. More nucleophilic anions were expected to coordinate to palladium and tin species during the reaction. The authors ascribe the solvent effect to a weak but beneficial coordination of anions to assist the transmetalation.[344] If this coordination is too strong the stannane may be deactivated,[345] or if an active cationic palladium species is formed the anion component of the solvent may coordinate to neutralise and thus deactivate it. The cation of the ionic liquid also plays a role through its interaction with its partner anion. Stronger ion-pairing was less favourable for this reaction. This could be linked to the viscosity of the ionic liquid, or the balance of ion-ion to ion-substrate interactions in the system. In a related study, the yield of the Suzuki coupling between iodobenzene and phenylboronic acid has been found to be inversely proportional to the viscosity of the ionic liquid solvent.[344]

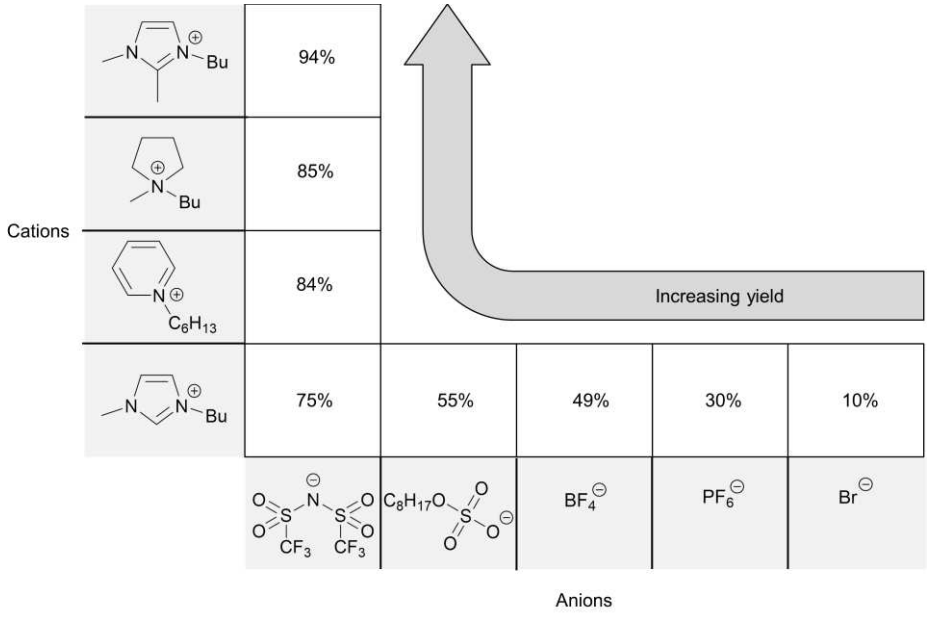
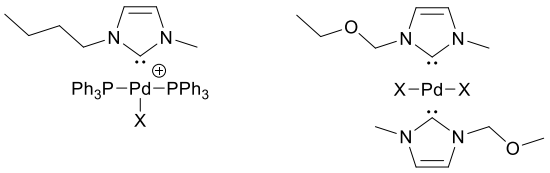


Figure 12. The yields of styrene produced by the Stille reaction in different ionic liquids.

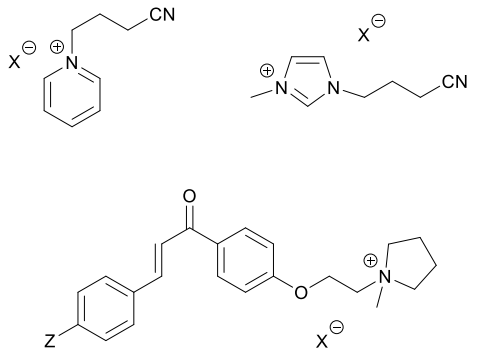
The cation can also have a role in the coordination and stabilisation of palladium. Ionic liquids featuring imidazolium cations can be activated by palladium pre-catalysts to form a *N*-heterocyclic carbene complex *in situ*. Isolation of $[Pd(II)(PPh_3)_2(bmim)X]^+$ species is possible, and have been implicated as crucial in the catalytic cycle (Scheme 73).[346] In related work, Dyson and co-workers made a *bis*-imidazolylidene complex of palladium which turned out to be ineffective in the catalysis of Suzuki reactions. They commented that "*it is probable that strong interactions between the ionic liquid and palladium catalyst (i.e. species with carbenoid centres derived from the ionic liquid) inhibit catalysis*".[347] The result is a palladium complex too stable to react further. Thus, it seems that activation of the ionic liquid cation by palladium may be advantageous for catalysis in some cases, but detrimental in others.



Scheme 73. Reactive (left) and unreactive (right) palladium complexes formed by the reaction of palladium pre-catalysts and ionic liquids.

One of the most desirable aspects of ionic liquid solvents is the potential to draw on the near-endless number of potential cations and anions to design bespoke solvents to enhance specific applications.[348] A wide range of task-specific ionic liquids have been designed with palladium catalysis in mind. For example, early work by Dyson and co-workers prepared nitrile-functionalised ionic liquids based on pyridinium and imidazolium cations and used these as reaction media for Suzuki and Stille reactions (Scheme 74).[349,350] In most cases, functionalisation of the ionic liquid cation did not affect the yield or rate of reaction compared to non-functionalised ions. However, recyclability of the ionic liquid-catalyst mixture was excellent compared to conventional ionic liquids.

An analysis of palladium nanoparticles formed during the reaction showed that these were more aggregated in the conventional ionic liquids. Thus, it was suggested that nitrile functionalization resulted in reduced aggregation of the nanoparticles, which behaved as heterogeneous catalysts or reservoirs for homogeneous palladium to enter the reaction. This in turn allowed the catalyst to remain active during repeated re-use of the combined ionic liquid-catalyst system.

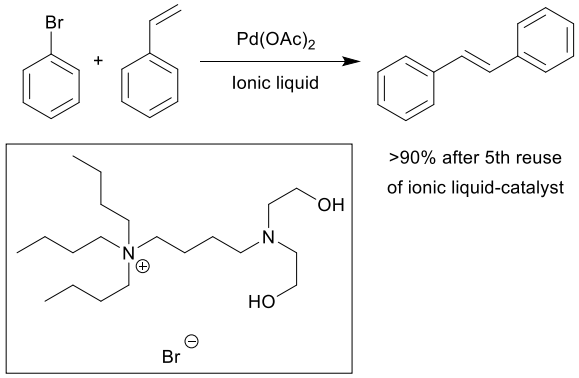


Scheme 74. Ionic liquids with nitrile (top) and chalcone (bottom) functionalised cations. Key: X is chloride, tetrafluoroborate, *etc.*; Z is –H, –OMe, or $–NO_2$.

An example of Hiyama-type coupling in ionic liquids utilised alkene-functionalised task-specific ionic liquids based on ion-tagged chalcone ligands (Scheme 74).[351] For this reaction, it proved essential to have alkenyl functionality present in the solvent in order to allow the reaction to proceed. Thus, doping ion-tagged chalcone ligands into conventional ionic liquids produced reaction media that allowed quantitative conversions to be achieved, whereas only trace amounts of product were detected in the absence of the chalcone. The electronic properties of the alkenyl ligand were modified by changing the Z substituent (as drawn in Scheme 74), which strongly influenced the reaction outcome. This was linked to the size of palladium nanoparticles formed during the reaction, with smaller particles (1-3 nm) being formed, and consequently higher product yields seen with a methoxy substituent. The advantage of using an ionic alkenyl ligand, immobilised within an ionic liquid, is that the product of the reaction can be separated from the ligand easily (by simple solvent

extraction or distillation from the essentially non-volatile ionic liquid). In conventional solvents such as THF, separation of product and alkenyl ligand can be complicated by their similar polarities, requiring time consuming and solvent-intensive chromatographic separation.

In a final example, 4-di(hydroxyethyl)aminobutyltributylammonium bromide has been developed as a recyclable solvent for Heck reactions acting as base, ligand, and solvent (Scheme 75).[352] Thus, only the reactants and the palladium acetate pre-catalyst need to be added. The product could be easily extracted with diethyl ether which is immiscible with the ionic liquid. The ionic liquid-catalyst system could be re-used six times with little reduction in yield. As in the examples above, palladium nanoparticles of around 4 nm in diameter were observed to form in this system. Transmission electron microscopy showed these to be well dispersed, suggesting that coordination by the solvent prevented aggregation.

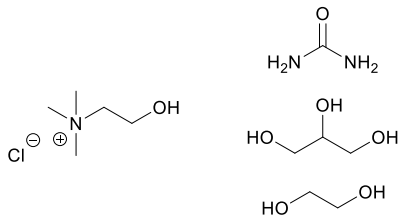


Scheme 75. A task-specific ionic liquid (inset box) used as a recyclable medium for the Heck reaction.

Recently, significant attention has turned to the use of deep eutectic solvents as low-cost, low-toxicity alternatives to ionic liquids. Compared to ionic liquids, there are relatively few reports of the use of deep eutectic solvents as reaction media for palladium-catalysed cross coupling reactions. However, the number of papers has increased of late and this area looks set to grow. In early work, low-temperature melts prepared by combining sugars, sugar alcohols or citric acid with urea and inorganic salts, such as NH_4Cl or NaCl or betaines such as *L*-carnitine, were used as reaction media

for various palladium-catalysed cross coupling reactions including Suzuki, Heck and Sonogashira reactions.[353,354] Suzuki reactions of phenyboronic acid and aryl bromides, with palladium acetate and no additional ligand, proceeded smoothly in all melts giving essentially quantitative conversions. The Heck cross-coupling of iodobenzene and *n*-butyl acrylate was tested in a range of melts, with different sources of palladium, and the product yields compared to solvents such as DMF and ionic liquids. Although the catalysts used were not directly comparable in all cases it appears that the melts promoted the reaction in some cases, allowing shorter reaction times compared to reactions taking place in the ionic liquid.

More recently, cross coupling reactions have been reported in deep eutectic solvents based on choline chloride (Scheme 76).[355] Marset *et al*. used cationic phosphines as supporting ligands in Suzuki, Heck, and Sonogashira coupling reactions to overcome the poor solubility of neutral phosphines in the polar medium.[356] Choline chloride-glycerol (1:2 molar ratio) was identified as the most suitable deep eutectic solvent for the Suzuki and Heck reactions, as it allowed very good product yields to be achieved and has advantages in terms of sustainability: both choline chloride and glycerol are cheap and non-toxic. For the Sonogashira coupling of aryl halides and phenylacetylene, an alternative deep eutectic solvent based on PPh_3MeBr-glycerol (1:2) was found to be optimal. As with many ionic liquid systems, the deep eutectic solvent-catalyst mixtures in this work could be re-used several times whilst maintaining significant catalyst activity.



Scheme 76. Choline chloride (left) and commonly encountered hydrogen-bond donors (right) that are used to form deep eutectic solvents.

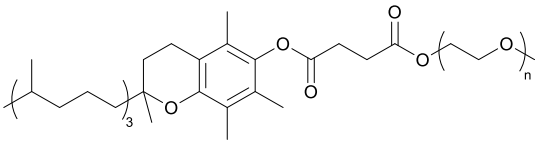
Although cationic phosphine ligands were advantageous for the cross coupling reactions studied by Marset *et al.*,[356] Dilauro *et al.* have recently shown that Suzuki couplings of aryl boronic acids or trifluoroborate salts with a wide range of aryl halides are possible in deep eutectic solvents without additional ligands added.[357] The success of these reactions appears to be strongly solvent dependent, with even structurally similar deep eutectic solvents giving different results. For example, choline chloride-ethylene glycol (1:3) led to no biphenyl production upon combination of iodobenzene and phenylboronic acid, whereas choline chloride-glycerol 1:2) resulted in essentially quantitative conversion. Clearly there is much work to do to fully understand the basis for solvent effects in these systems. Surprisingly, it has been recently reported that the direct coupling of *n*-BuLi and 1-bromonaphthalene, using $Pd(P^tBu_3)_2$ as the catalyst, is possible in choline chloride-based deep eutectic solvents, even in the presence of protic functionality and water in the solvent.[358] While significant amounts of naphthalene, the product of a competing dehalogenation reaction, were formed in all the deep eutectic solvents studied, this reaction could be optimised to take place in (or more appropriately on) water containing sodium chloride. This is an exciting finding and offers significant potential for organometallic catalysis in sustainable solvent systems.

3.3 Surfactant-based systems

Synthetic carbon-carbon bond forming reactions in water are not uncommon.[359,360] Increasing regulatory controls and concerns over the sustainability of solvent-based processes have generated an interest in chemistry that does not need organic solvents.[361] Unlike virtually all organic solvents, water is safe and non-toxic. It is also is widely available and cheaper than organic solvents. Water is used in industry on a massive scale, and as a resource for chemical processes must be managed responsibly.[362] It is important to consider that during many reactions, palladium catalysed cross coupling included, there is significant potential for water to become contaminated with organic or metal-containing impurities. Purification of aqueous solvent systems after their use, prior

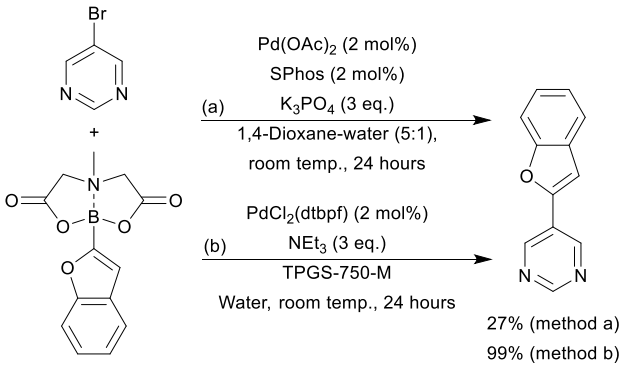
to reuse or release into the environment, is an important factor to consider when designing processes.

The body of work produced by Bruce Lipshutz on the topic of micellar cross-coupling is an elegant riposte to conventional synthetic chemistry in organic solvents.[363] Micelles create a suitable reaction environment for the hydrophobic (and often water-sensitive) reactants. Many palladium catalysts have limited water solubility, and so with the exception of an inorganic base (where needed) all the reaction components congregate within the micelles. An important surfactant for room temperature cross-coupling reactions in water is TPGS-750-M. This amphiphile is constructed from hydrophobic α-tocopherol (vitamin E), a monomethyl-capped PEG-750 chain, and linked together by one succinic acid moiety (Scheme 77).[364] An earlier generation surfactant utilised a 1,10-diacid linker (known as PTS).



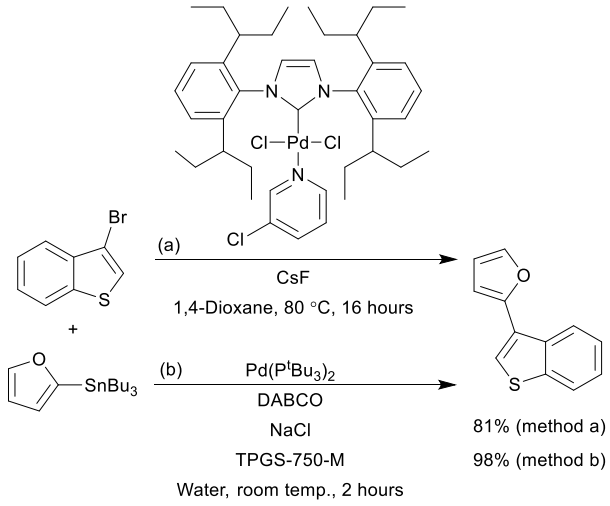
Scheme 77. The structure of the TPGS-750-M surfactant.

The room temperature Suzuki reaction of MIDA boronic esters is successful in aqueous TPGS-750-M (Scheme 78).[365] Yields were vastly improved over those in a traditional aqueous 1,4-dioxane solvent. The solvent (surfactant plus water) is recoverable and reusable. The advantages of the TPGS-750-M water reaction medium also translate into large scale cross-couplings, as illustrated by recent work on developing a Suzuki reaction free of organic solvents at a kilogram scale.[366] In order to use oxygen sensitive catalysts, Mattiello *et al.* used the emulsifying agent Kolliphor EL to stablise $Pd(PPh_3)_4$ for use in micellar Suzuki reactions.[367] Again, the catalyst solution was demonstrated to be recyclable, although this caused the yield of a coupling reaction between 3-bromoisoquinoline and 3-thiopheneboronic acid to fall from 90% to 70%.



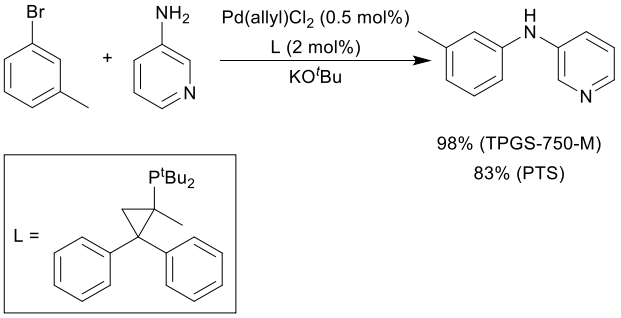
Scheme 78. A Suzuki reaction in (a) aqueous 1,4,-dioxane and (b) TPGS-750-M aqueous solution. The SPhos ligand is drawn in Scheme 36; dtbpf is 1,1'-*bis*(di-*tert*-butylphosphino)ferrocene.

The Stille reaction can be catalysed by $Pd(P^tBu_3)_2$ at room temperature with the addition of aqueous TPGS-750-M (Scheme 79).[368] For the reaction between 2,6-dimethylbromobenzene and tributyl phenylethynyltin, the solvent system can be reused to conduct at least 5 reactions without an appreciable drop in yields. The catalyst loading is topped up before each reuse, in a reversal of the more common approach to recycling in chemical reactions where the more valuable catalyst is reclaimed and the solvent disposed of each time.

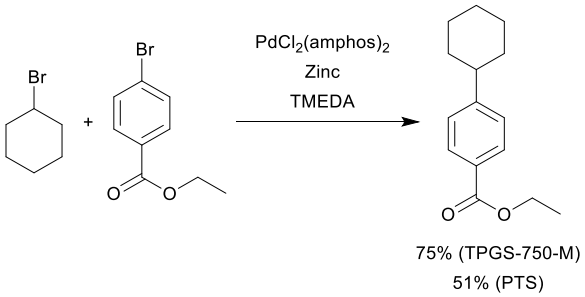


Scheme 79. A comparison between conventional and micellar Stille reaction protocols. DABCO is 1,4-diazabicyclo[2.2.2]octane.

The Buchwald-Hartwig reaction between bromoarenes and anilines will also occur in aqueous PTS or TPGS-750-M in the presence of potassium *tert*-butoxide (Scheme 80).[364] Even more surprisingly Negishi couplings are also compatible to this approach. Zinc powder was added to an organohalide in aqueous solution, with TMEDA to stabilise the resulting organozinc compound. The Reformatsky reagent formed *in situ* will react with ethyl 4-bromobenzoate when catalysed by *bis*-(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium ($Pd(amphos)_2Cl_2$) with the assistance of either PTS or TPGS-750-M micelles (Scheme 81).[364] Room temperature Sonogashira reactions of aryl bromides with PTS in water,[364,369] or at 45 °C with TPGS-750-M in water,[370] were also broadly successful.



Scheme 80. A Buchwald-Hartwig reaction performed in an aqueous micellar environment.

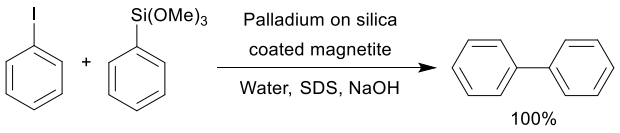


Scheme 81. A Negishi reaction performed in an aqueous micellar environment.

The importance of micelle size was highlighted in another investigation of the Negishi reaction under equivalent conditions to that above.[371] A screening of different surfactants revealed the yield of the cross-coupling is greatest in larger micelles. It was suggested that the zinc powder will be attracted to the polar surface of the micelle, and the organohalide will reside inside the micelle, associated with the hydrophobic region of the surfactant. Upon formation of the organozinc compound a larger micelle is said to offer more protection to intermediates because of the greater separation possible between the hydrophobic centre of the micelles and the bulk water medium.

The aforementioned surfactant-assisted aqueous protocols all utilise a homogeneous source of catalyst, but other forms of catalyst are also compatible with the methodology. Aqueous TPGS-750-M solutions have been used to disperse iron nanoparticles. Traces of palladium in parts-per-million quantities,[372] is sufficient to catalyse a Suzuki reaction.[11] Addition of a ligand is crucial, indicating that the mode of catalysis is ultimately homogeneous.

An example of a Hiyama reaction catalysed by palladium anchored to a modified magnetite support works best in water when sodium dodecyl sulphate (SDS) is added (Scheme 82).[373] This surfactant is known to act as a reducing agent and will also stabilise palladium nanoparticles. The yield falls sharply as the concentration of SDS is reduced, and alternative conditions with organic solvents resulted in poor yields.

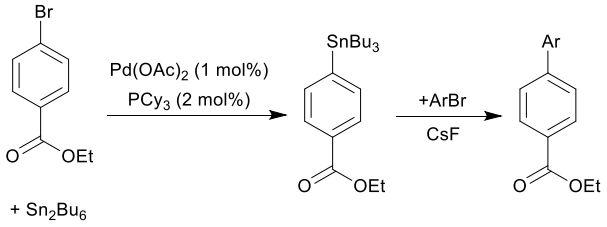


Scheme 82. An example of a model Hiyama reaction optimised in an aqueous micellar environment.

3.4 Solvent-free procedures

It is important to consider not using any solvent in an effort to reduce waste and exposure to harmful substances.[374] The concept of a solvent-free reaction is somewhat ambiguous as often one

or more reactants are liquid and moisture can wet the surfaces of solid reactants,[375] but a solvent-free reaction can be taken to mean no auxiliary solvent, in addition to the reagents themselves, has been added. Mechanochemistry describes the discipline of grinding solid reactants together, typically in a ball mill, to facilitate a reaction. Safety and simplicity are amongst the benefits of mechanochemistry.[374] However, these solvent-free processes have been criticised for "*slow reaction rates, high capital costs* [of equipment]*, and low energy efficiencies*".[290] Nevertheless, Buchwald-Hartwig reactions,[376] Suzuki reactions,[377] Sonogashira reactions,[378] Heck reactions,[379] and Hiyama reactions,[380] are all possible without solvent. Not until 2018 was a solvent-free Stille reaction reported (Scheme 83).[381] Mechanochemical Buchwald-Hartwig reactions can be improved by the addition of a 0.2 mL per gram dose of olefins (*e.g.* 1-hexene and 1,5-cyclooctadiene).[382] Cyclohexane and toluene improved yields but not to the same extent, which suggests more than a simple solvent effect was in operation. The authors conclude these additives either act as dispersants to maintain small palladium nanoparticles, or in combination with the phosphine ligand stabilise the leaching of active Pd(0). The synthesis of heterocycle appended ferrocenyl complexes by the Suzuki reaction of ferrocene-1,1'-diboronic acid is improved by replacing extended refluxing conditions with a shorter solid phase protocol.[383]



Scheme 83. A solvent-free method of stannylation followed by a Stille-type cross-coupling.

Some protocols, such as the Kumada reaction and the Negishi reaction, are inherently poorly suited to solvent-free conditions. This is due to the stability of the organometallic reagent being highly dependent on the complex formed with an ether solvent (Section 2.2). Nevertheless, Cao *et*

al. have managed to synthesise organozinc compounds from zinc metal in different forms (wire, powder, foil, *etc.*) using mechanochemistry and successfully couple them with aryl halides.[384]

4. Future trends and prospects

It has been more than 40 years since the first palladium catalysed cross-coupling methods were developed. We have arrived at a point where this innovation has been rewarded with a Nobel Prize and is routinely used to make valuable products, yet there are still many challenges to overcome, not least of all legislation restricting access to toxic solvents. The lessons learned through years of research into cross-coupling chemistry is more valuable than ever as established synthetic protocols are now being re-evaluated to eliminate solvents such as DMF.

The role of the metal and ligand components of the catalyst is usually given the credit for how the reaction transpires, but equally the choice of solvent makes the difference between no reaction and a successful one. The solvent can have a profound effect on the pathway of any step in the reaction, changing the mechanism or the rate determining step. If the medium is optimised in tandem with the other reaction components, a true maximum efficiency can be reached. This is acknowledged in the literature but rarely put into practice.[309] The current level of dedication to solvent selection in catalysis has been described as receiving merely "cursory attention".[65] However some scientists do undertake comprehensive screenings of different solvent-catalyst pairings in order to design the most effective conditions.[385] More efficient approaches to accelerate the optimisation of reaction conditions should also be encouraged, including principle component analysis (PCA) and design of experiment (DoE) techniques. Rarely are cross-coupling methods optimised with these tools.

Computational modelling has uncovered many important details regarding cross-coupling reactions. Density functional theory (DFT) calculations are now commonly used to understand reaction mechanisms in this area. However, some caution must be exerted when devising computational studies and interpreting their results. Indeed, this is also true of experimental studies.

Solvent effects in particular need careful consideration, as they can have a pronounced impact on speciation in solution and on many mechanistic details. For example, the formation of low valent palladium species with dissociated ligands is extremely solvent dependent. Solvents can play a direct role in key steps such as deprotonation or protonation, and the solubility of some components is important in determining their concentrations under catalytic conditions. Studying these effects computationally requires careful consideration of the most appropriate model for the system. Implicit solvent models are simple to apply, but neglect specific solvent-solute interactions. Mixed explicit-implicit solvent models may improve accuracy, but configurational space is complex and the appropriate placement of explicit solvent molecules may not be straightforward. It has been noted that "*subtle solvation effects cannot accurately be reproduced with computational means*".[128] Thus different calculations can give very different results.[80] Further development of computational methodologies and models, in particular for solvation, will be needed in order to address concerns such as this as the field moves forward.

Going forward, the development of entirely new solvents is expected to become more important and widespread. Safer, non-toxic solvents with unfamiliar functionalities, and combinations of different functionalities, will become more commonplace as structurally complex biomass is used as a feedstock for chemicals in the growing bio-based economy. The solvent sector is an important market for renewable products given the volumes of solvent used worldwide and their ubiquitous nature in the chemical industry.[55] New solvents must be introduced in a positive way, with data and experience accumulated to best understand the stability and compatibility of these solvents with different catalysts, bases, and in reactions conducted at elevated temperatures.[13,325,386,387,388] Subtle solvent effects such as the reducing power of solvents (*i.e.* to convert Pd(II) pre-catalysts to Pd(0), Scheme 7) and their ability to leech heterogeneous sources of palladium into solution also need to be studied to fully explain experimental observations. This may differentiate otherwise seemingly equivalent solvents (e.g. NMP, GVL, and Cyrene™). What we have discovered about solvent complexes with active catalytic species, the role of the solvent in stabilising

intermediates, and how solvents permit ligand substitution and dictate product selectivity must be used to progress new chemistry without causing undue harm to people or the planet.

5. References

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