
# Exploring New Avenues in C-C Coupling:

# Broadening Application of the Heck Reaction via *in-situ* Formation of Olefins

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy

by

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## Acknowledgements

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## Abstract

Since its discovery, the Heck reaction has received great attention from academic research. As a result, many advances have been made, making the Heck reaction one of the most widely adopted methods for the construction of carbon-carbon bonds in modern organic chemistry. Chapter 1 presents a brief history of the Heck reaction, from its initial discovery to current day applications. This is followed by a brief overview of the different classes of cross-coupling reactions catalysed by palladium.

Chapter 2 describes the synthesis of alkyl aryl ketones from aryl chlorides and aldehydes by the development of a novel Heck-type acylation reaction. The aldehyde first condenses with pyrrolidine to form an enamine intermediate, which acts as an electron-rich olefin and undergoes a regioselective Heck coupling with the aryl chloride. Additional experiments such as *in-situ* IR spectroscopy were carried out in order to probe the reaction mechanism.

Chapter 3 is an extension of Chapter 2. The scope of the newly developed acylation reaction is extended beyond commercially available aliphatic aldehydes. The palladium catalysed Heck arylation-isomerisation reaction of aryl bromides and allyl alcohol leads to the generation of aldehydes which, by intervention of pyrrolidine and the same palladium catalyst, undergo the acylation reaction with a second aryl bromide. This leads to the one-pot synthesis of functionalised dihydrochalcones from readily available starting materials.

Chapter 4 presents the development of a second one-pot methodology, based on the same principle of design, whereby the reactive C=C double bond is generated *in situ*. A Keggin-type heteropolyacid is employed to catalyse the formation of styrenes from secondary aryl alcohols which, following addition of palladium, base and an aryl bromide, undergo regioselective Heck arylation. Interesting stilbene products are obtained in good to excellent yields.

## Publications

- **Feeding the Heck Reaction with Alcohol: One-Pot Synthesis of Stilbenes from Aryl Alcohols and Bromides**

  Colbon, P.; Barnard, J. H.; Purdie, M.; Mulholland, K.; Kozhevnikov, I. V.; Xiao, J. *Adv. Synth. Catal.* **2012**, *354*, 1395-1400.

- **Double Arylation of Allyl Alcohol via a One-Pot Heck Arylation-Isomerisation-Acylation Cascade**

  Colbon, P.; Ruan, J.; Purdie, M.; Mulholland, K.; Xiao, J. *Org. Lett.* **2011**, *13*, 5456-5459.

- **Direct Acylation of Aryl Chlorides with Aldehydes by Palladium-Pyrrolidine Co-catalysis***

  Colbon, P.; Ruan, J.; Purdie, M.; Xiao, J. *Org. Lett.* **2010**, *12*, 3670-3673.

  * This paper was one of the top 3 most accessed articles in Organic Letters within Q3 of 2010.

## Definitions and Abbreviations

| | |
|---|---|
| **MeCN** | acetonitrile |
| **Ac** | acetyl |
| **α** | alpha |
| **Å** | amstrong |
| **Ar** | aryl |
| **β** | beta |
| **$Pd(dba)_2$** | bis(dibenzylideneacetone)palladium(0) |
| **dppp** | 1,3-bis(diphenylphosphino)propane |
| **$[bmin][BF_4]$** | 1-butyl-3-methylimidazolium tetrafluoroborate |
| **δ** | chemical shift |
| **$CuCl_2$** | copper(II) chloride |
| **°C** | degrees Celsius |
| **DHR** | dehydrogenative heck reaction |
| **dba** | dibenzylacetone |
| **DHC's** | dihydrochalcones |
| **DMSO** | dimethylsulfoxide |
| **DBS** | dodecylbenzenesulfonate |
| **EG** | ethylene glycol |
| **γ** | gamma |
| **g** | gram(s) |
| **HPA** | heteropolyacid |

| | |
|---|---|
| **[hmin]Br** | 1-hexyl-3-methyl-1H-imidazol-3-ium bromide |
| **HRMS** | high resolution mass spectrometry |
| **h** | hour(s) |
| **HBD** | hydrogen bond donor |
| **β** | hydrogen bonding acceptor ability of solvent |
| **IR** | infra-red |
| **Kg** | kilogram(s) |
| **Me** | methyl |
| **min** | minute(s) |
| **MS** | molecular sieves |
| **DMA** | *N,N*-dimethylacetamide |
| **DMF** | *N,N*-dimethylformamide |
| **NMR** | nuclear magnetic resonance |
| **$Pd(OAc)_2$** | palladium(II) acetate |
| **Ph** | phenyl |
| **π** | pi |
| **S/C ratio** | substrate to catalyst molar ratio |
| **TBHP** | *tert*-butyl hydroperoxide |
| **$Pd(PPh_3)_4$** | tetrakis(triphenylphosphine)palladium(0) |
| **TMS** | tetramethylsilane |
| **TlOAc** | thallium acetate |
| **TLC** | thin layer chromatography |

| | |
|---|---|
| **OTf** | triflate |
| **$[P_{666,14}]X$** | trihexyl(tetradecyl)phosphonium ionic liquids |
| **$PPh_3$** | triphenylphosphine |
| **P(*o*-tol)$_3$** | tri(*o*-tolyl)phosphine |
| **P(*t*-Bu)$_3$** | tri-*tert*-butylphosphine |
| **P(*t*-Bu)$_3$.$HBF_4$** | tri-*tert*-butylphosphonium tetrafluoroborate |
| **$Pd_2(dba)_3$** | tris(dibenzylideneacetone)dipalladium(0) |
| **TON** | turnover number |
| **TOV** | turnover value |

## Contents

# Chapter 1

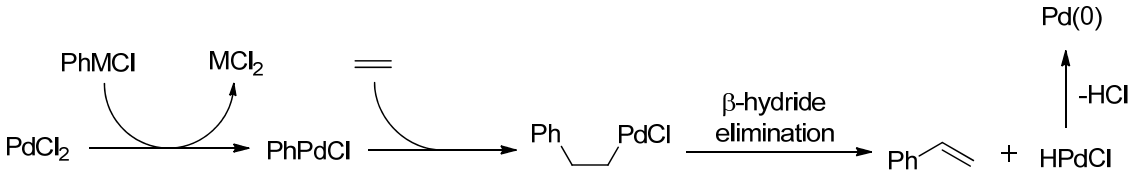
## Introduction

### 1.1 Mizoroki-Heck Reaction

#### 1.1.1 Discovery

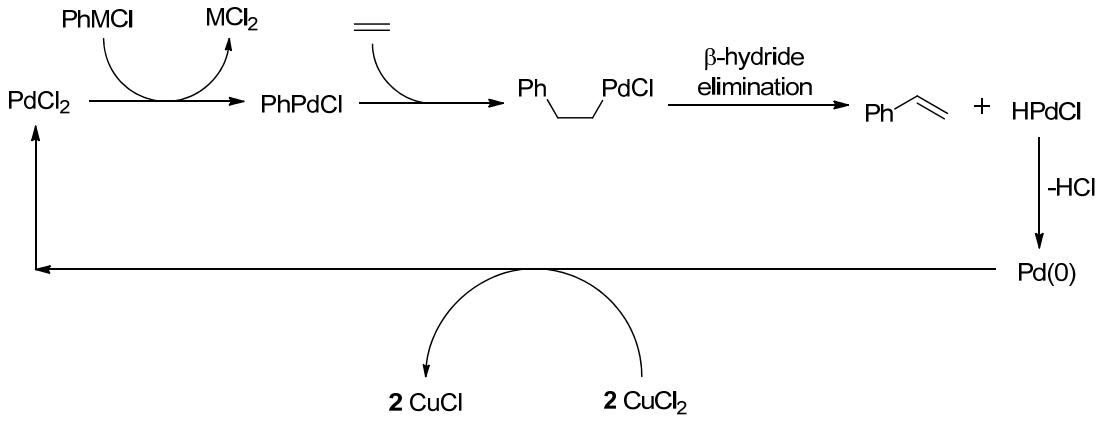
Carbon-carbon bonds provide the framework upon which organic molecules are constructed. Therefore, the development of methods for the selective synthesis of carbon-carbon bonds is of central importance to synthetic organic chemistry. Such importance is reflected in the fact that the Nobel Prize in Chemistry has been awarded several times in this area; the Grignard reaction (1912),[1] the Diels-Alder reaction (1950),[2] the Wittig reaction (1979),[3] olefin metathesis (2005),[4] and most recently to palladium catalysed C-C coupling in organic synthesis (2010).[5]

At the heart of the discovery of palladium catalysed C-C coupling lies the Mizoroki-Heck reaction.[6] In three independent reports by Mizoroki,[7] Julia[8] and Heck,[9] the palladium mediated coupling of an aryl halide with an alkene afforded the corresponding arylalkene. In prior reports from Heck it was disclosed that *in situ* generated arylpalladium halides are added to olefins at room temperature;[10] transmetallation between an organomercury, -lead or -tin compound, RMX, and a palladium(II) salt gives rise to the arylpalladium halide. For example, the addition of phenylpalladium chloride to ethylene followed by elimination of palladium gave styrene (Scheme 1.1).



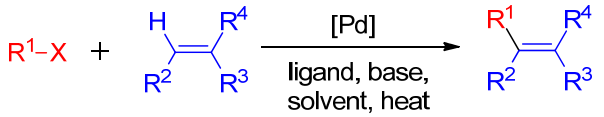

**Scheme 1.1**: Pd-mediated coupling of chlorobenzene and ethylene.

Heck first made the reaction catalytic by employing $CuCl_2$ as a stoichiometric reoxidant for the oxidation of Pd(0) to Pd(II), thus forming a complete catalytic cycle (Scheme 1.2).[10d]




**Scheme 1.2**: Pd(II) catalysed coupling of chlorobenzene and ethylene.

Heck then realised that if Ar-X was to undergo an oxidative addition reaction with Pd(0), this would eliminate the need for stoichiometric metals such as mercury to be employed for the generation of arylpalladium halides. Such oxidative additions to Pd(0) had been previously reported by Fitton,[11] who in 1968 found that aryl halides reacted with Pd(0) to give arylpalladium halides. Heck was aware of Fitton's work and used it to generate the organopalladium complex required for the coupling reaction. Thus, with this new modification, arylation of an olefin was achieved from the reaction of an aryl halide and an olefin in the presence of a palladium catalyst. The overall reaction is shown in Scheme 1.3:



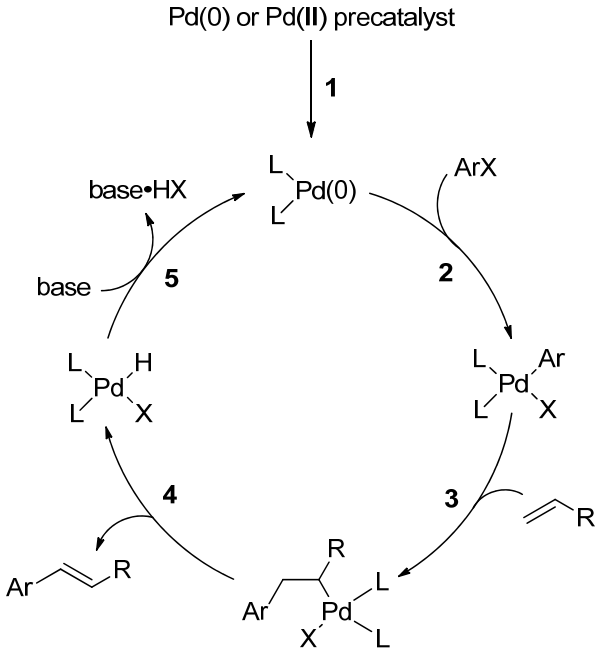

$R^1$ = aryl, benzyl, vinyl (alkenyl), alkyl (no β hydrogen)

X = Cl, Br, I, OTf, OTs, $N_2^+$

**Scheme 1.3**: The modern day Heck reaction

### 1.1.2 Mechanism[12]

The basic mechanism of the Heck reaction is shown below (Scheme 1.4):

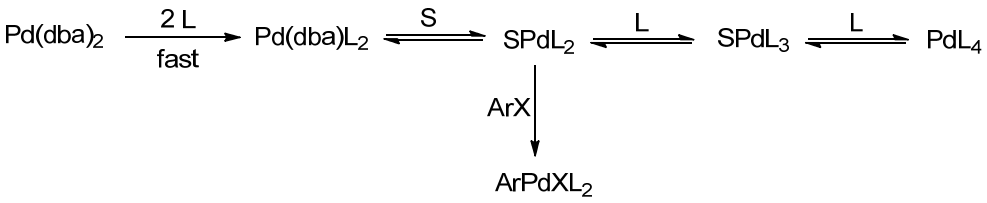



**Scheme 1.4**: Basic mechanism of the Heck reaction.

#### 1.1.2.1. Preactivation step (Step 1 in Scheme 1.4)

It is normally convenient to form the active catalyst *in situ*. If a stable Pd(0) precatalyst is used such as $Pd_2(dba)_3$, addition of a ligand (such as $PPh_3$) will result in ligand substitution at palladium and the active catalyst is formed. If a stable Pd(II) precatalyst is employed such as $Pd(OAc)_2$, a sacrificial reductant is required in order to access the catalytically active Pd(0) complex. Depending on the reaction conditions, this sacrificial reductant can be the phosphine ligand, amine base or the substrate olefin.[13]

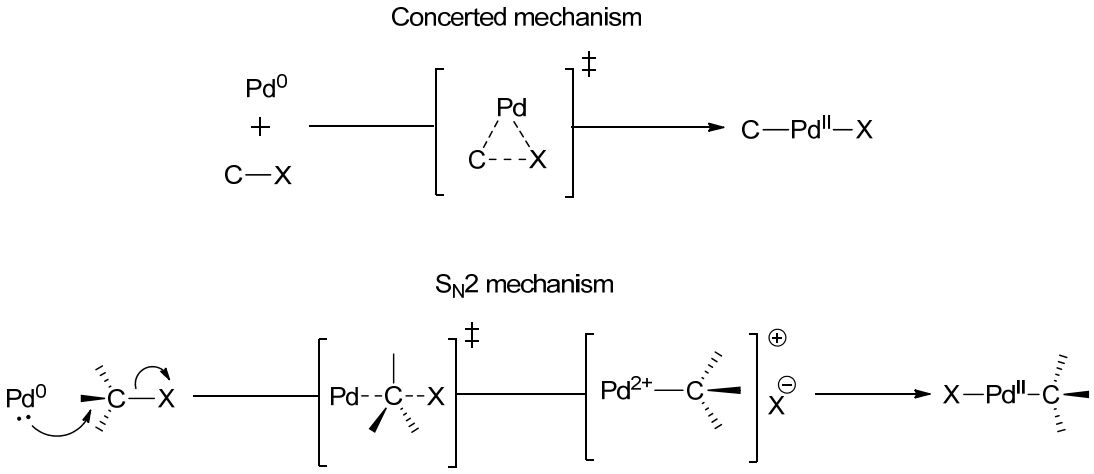
At first, one may think that it is simpler to employ a Pd(0) precatalyst instead of Pd(II) so that no reduction step is necessary. In reality, however, the situation is a little more complicated. For example, if $Pd(dba)_2$ is employed as precatalyst and $PPh_3$ as ligand, the concentration of desired complex $Pd(PPh_3)_2$ is in fact rather low. This is because the binding strength of dba is comparable to, if not greater than, $PPh_3$.[14]




**Scheme 1.5**: Ligand substitution

Full displacement of dba (Scheme 1.5) takes much more that four equivalents of phosphine; thus, the catalyst based on $Pd(dba)_2$ plus several equivalents of phosphine might happen to be inferior in reactivity than $PdL_4$ complex. The presence of dba can have a strong negative effect on the rate of oxidative addition to less reactive electrophiles e.g. aryl triflates.[15]

### 1.1.2.2. Oxidative addition (Step 2 in Scheme 1.4)




**Scheme 1.6**: Schematic representations of concerted and $S_N2$ type mechanisms of oxidative addition of C-X bonds by Pd(0).

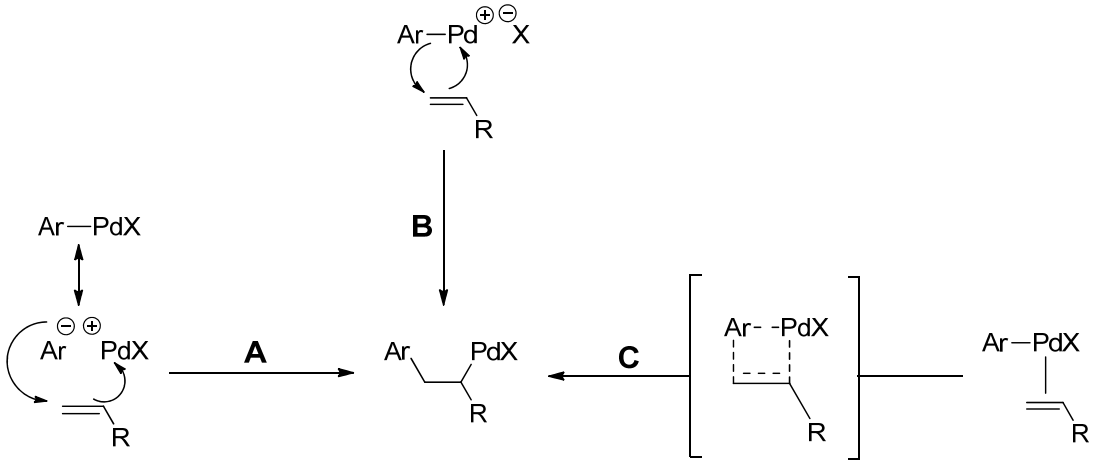
Oxidative addition of a polar bond by a transition metal centre can occur by a variety of mechanisms, including $S_N2$, radical and concerted pathways (Scheme 1.6). Fortunately for the traditional organic chemist, it is possible to investigate the mechanism of oxidative addition using core principles of organic reactivity. For example, an $S_N2$ type mechanism for the oxidative addition of an alkyl halide by a transition metal centre is supported by experimental data such as increased reaction rate in more polar solvents,[16] inversion of configuration at the electrophilic carbon,[17] overall second order reaction kinetics and decreased reaction rate going from 1° to 2° to 3° carbon centres.[18]

Oxidative addition of Ar-X by Pd(0) is generally considered to occur via a concerted three-centered transition state, in which C-X bond breakage and M-C and M-X bond formation occur simultaneously (Scheme 1.6).[19] As a general rule, the rate of oxidative addition follows the order of I >> OTf > Br >> Cl.[20] Until the turn of the century, aryl chlorides were rarely employed in Heck reactions due to their unwillingness to undergo oxidative addition. This

problem was overcome by the discovery that bulky, electron rich trialkylphosphine ligands form Pd complexes that readily undergo oxidative addition into the Ar-Cl bond, even at room temperature in certain cases (refer to section 1.1.3.2).

### 1.1.2.3. Migratory insertion (Step 3 in Scheme 1.4)

Of all the mechanistic steps that occur during the Heck catalytic cycle, migratory insertion should be considered the most significant, as this is the step in which the new carbon-carbon bond is formed. Therefore, a good understanding of migratory insertion may give the synthetic chemist control over the chemo, regio and stereoselectivity of the Heck reaction.

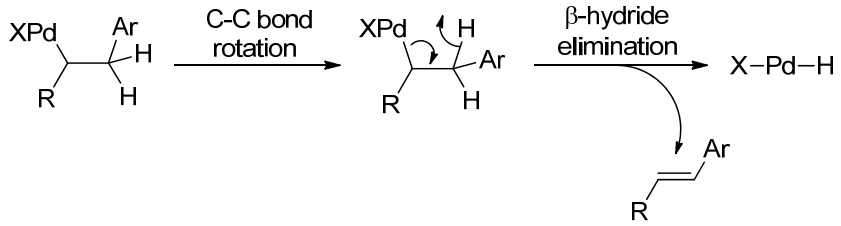



**Scheme 1.7**: Proposed mechanisms of migratory insertion

It is possible to imagine three distinct pathways in which migratory insertion can occur (Scheme 1.7). Firstly, we can think of ArPdX as any Grignard reagent that acts as a carbanion and undergoes nucleophilic addition into the alkene (pathway **A**).[21] This mode of action is only supported by the fact that Michael acceptor olefinic substrates (such as acrylates and acrylonitrile) are highly active in the Heck reaction. Secondly, we can consider palladium to be an electrophilic centre that undergoes electrophilic addition into the alkene (pathway **B**). This mechanism is particularly likely in the case of $ArPd^+$ intermediates. Thirdly, ArPdX and $ArPd^+$ intermediates may add to the double bond of the alkene in a concerted process (pathway **C**). The variable transition state of this mechanism is adaptable to the electronic demands of the involved species, just as in the classical concerted mechanism of $S_N2$ reactions. The adaptability of concerted mechanisms to electronic factors puts forward steric factors as a main source of all types of selectivity.

*N.B.* The nature of the arylpalladium intermediate (i.e. ArPdX vs. $ArPd^+$) will be discussed in length as we reflect on the development of the Heck reaction over the last few decades (section 1.1.3.1).

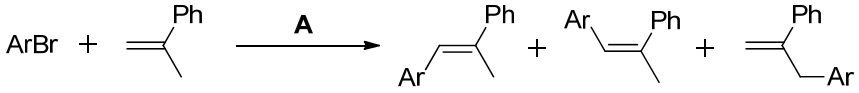
### 1.1.2.4. β-hydride elimination (Step 4 in Scheme 1.4)




**Scheme 1.8**: β-hydride elimination through *syn*-elimination

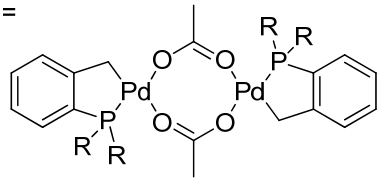
β-Hydride elimination can occur by one of two possible mechanisms. The first possibility is that of *syn*-elimination, which is the opposite of Pd-H insertion into the double bond (Scheme 1.8). *Syn*-elimination controls the stereoselectivity of the Heck reaction and generally obeys the Curtin-Hammett kinetic control principle.[22] The high stereoselectivity generally observed in the Heck reaction is a major advantage over alternative methods of olefin formation/functionalisation, such as the Wittig reaction.

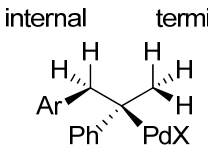
It is also possible for an E2-type elimination of Pd-H to occur if assisted by a suitable base. Such a mechanism is supported by experimental evidence in the Heck reaction of disubstituted olefins (Scheme 1.9).[23] When the inorganic base NaOAc was used, the reaction produced a mixture of internal and terminal olefins. However, use of the organic base $(i\text{Pr})_2\text{NEt}$ yielded the internal olefin almost exclusively. This may suggest base-assisted E2 elimination in which the amine base is selective towards the more acidic hydrogen atoms situated on the benzylic carbon.




**A**: [Pd] (0.1 mol %), base, DMA, 140 °C.

[Pd] =



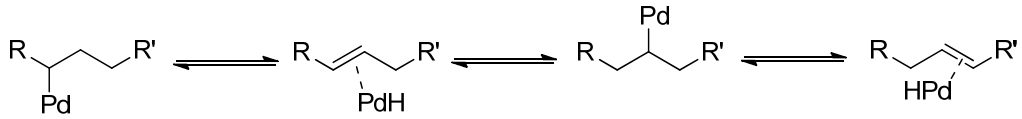




| base | internal/terminal | internal E/Z |
|---|---|---|
| NaOAc | 39/61 | 17 |
| $(i\text{Pr})_2\text{NEt}$ | 95/5 | 2.5 |

**Scheme 1.9**: Experimental evidence for base-assisted β-hydride elimination

### 1.1.2.5. Reductive elimination (Step 5 in Scheme 1.4)

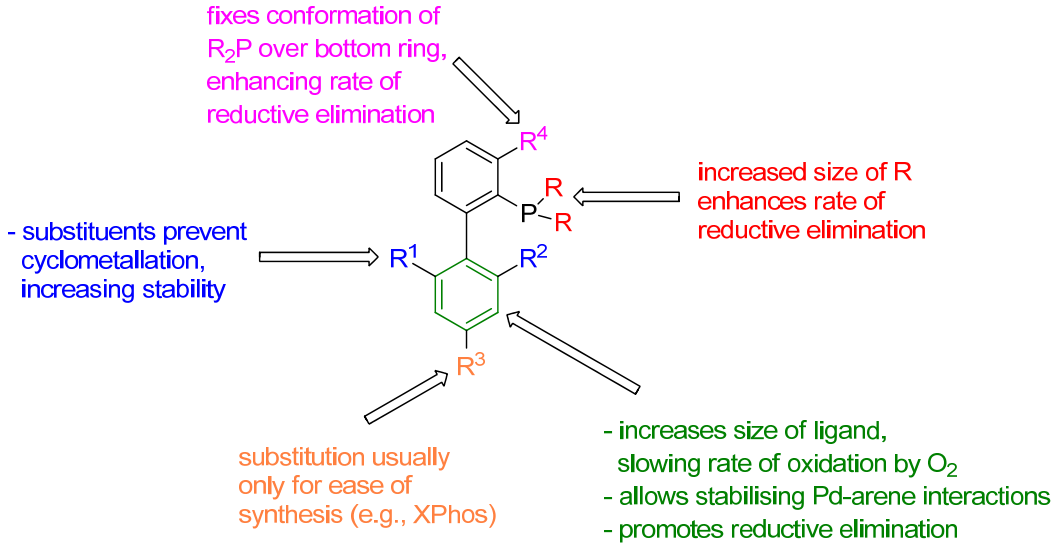
After β-hydride elimination, the X-Pd-H produced remains coordinated to the alkene product. If a suitable base is present, HX will be scavenged in the process of reductive elimination, which regenerates Pd(0) and so completes the catalytic cycle.[24] If reductive elimination is sluggish, Pd-H may insert itself into either end of the double bond, resulting in scrambling of the olefin (Scheme 1.10).




**Scheme 1.10**: Olefin scrambling by Pd-H

The rate of reductive elimination at Pd(II) is usually fastest when σ-donation from the ligands to the metal centre is weak, thus encouraging reduction of Pd. However, there is a compromise to be made, as oxidative addition of Pd(0) into the Ar-X bond is enhanced by strongly electron donating ligands that increase the electron density of the metal centre.

The rate of reductive elimination may also be increased by the use of ligands with a high steric bulk, which encourages the resulting reduction in coordination number of the Pd centre. One example of such ligands is the Buchwald ligand family. In 2008, Buchwald published his rationale for the various effects that the individual components of the ligands have on the individual steps of the Suzuki reaction (Scheme 1.11):[25]

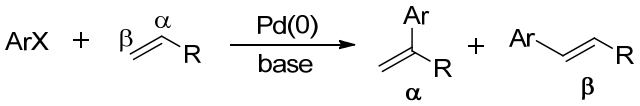



**Scheme 1.11**: Substituent effects of dialkylbiarylphosphine ligands, particularly towards enhanced rate of reductive elimination

### 1.1.3 Selected areas of development

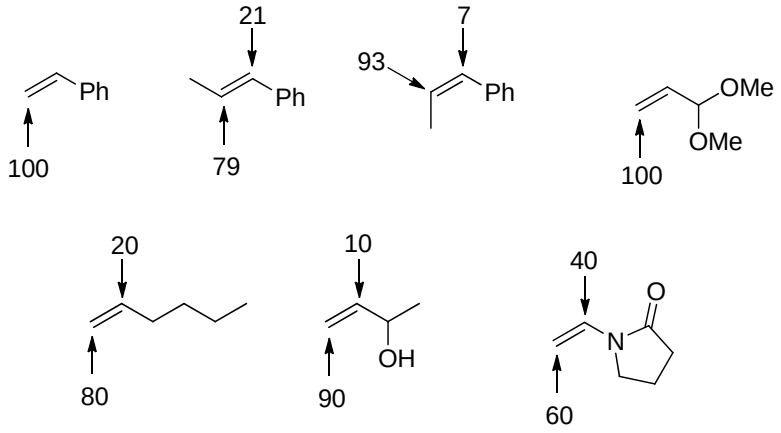
#### 1.1.3.1 Regiocontrol

As previously mentioned, the Heck reaction is widely adopted in chemical synthesis for the construction of C-C bonds. This is due to the fact that the modern day Heck reaction works for a wide range of substrates and can tolerate high levels of functionality, as well as being highly regio and stereospecific in most cases.



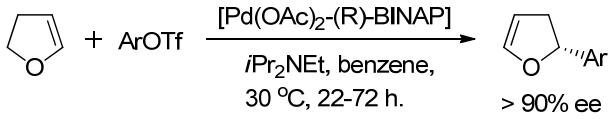

**Scheme 1.12**: Regioisomeric products of the Heck reaction

In its early years, however, the Heck reaction was regioselective for only a few classes of olefin substrates. When electron-deficient olefins were employed, such as acrylates and acrylonitriles, the linear β-arylated products were formed almost exclusively. The use of electron-rich olefins, such as acyclic enol ethers and enamides, usually resulted in a mixture of α- and β-arylated products. In his study of the arylation, Heck noted that "Double bonds substituted with electron-donating substituents tend to produce significant amounts of 2-aryl adducts in addition to the major 1-aryl isomers."[26] In a 1979 account, Heck summarised the orientation of PhBr addition to various olefins (Scheme 1.13).[27]



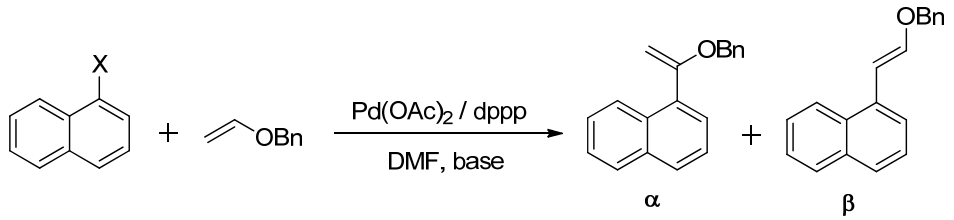

**Scheme 1.13**: Orientation of addition of PhBr to olefins prior to 1979

If the Heck reaction was to become a widely adopted methodology, solutions to the problem of regiocontrol when employing electron-neutral and electron-rich olefins would be a critical progression. It was to this end that Cabri[28] and Hayashi[29] independently made significant developments. Hayashi found that the coupling of aryl triflates with the electron-rich olefin, 2,3-dihydrofuran, was highly regioselective towards the α-carbon when the Pd catalyst was ligated by a bisphosphine ligand. In fact, the reaction was also highly enantioselective due to the use of the chiral bisphosphine ligand, (*R*)-BINAP (Scheme 1.14).




**Scheme 1.14:** First report of the arylation of an electron-rich olefin to proceed with high regioselectivity and enantioselectivity.

Cabri also realised that by using aryl triflates instead of aryl halides, and bidentate ligands instead of monodentate, the Heck reaction becomes strongly regioselective to the α-carbon of electron-rich olefins. Alternatively, aryl halides could be made to give rise to the same regioselectivity if stoichiometric silver or thallium salts were added (Scheme 1.15).[30]

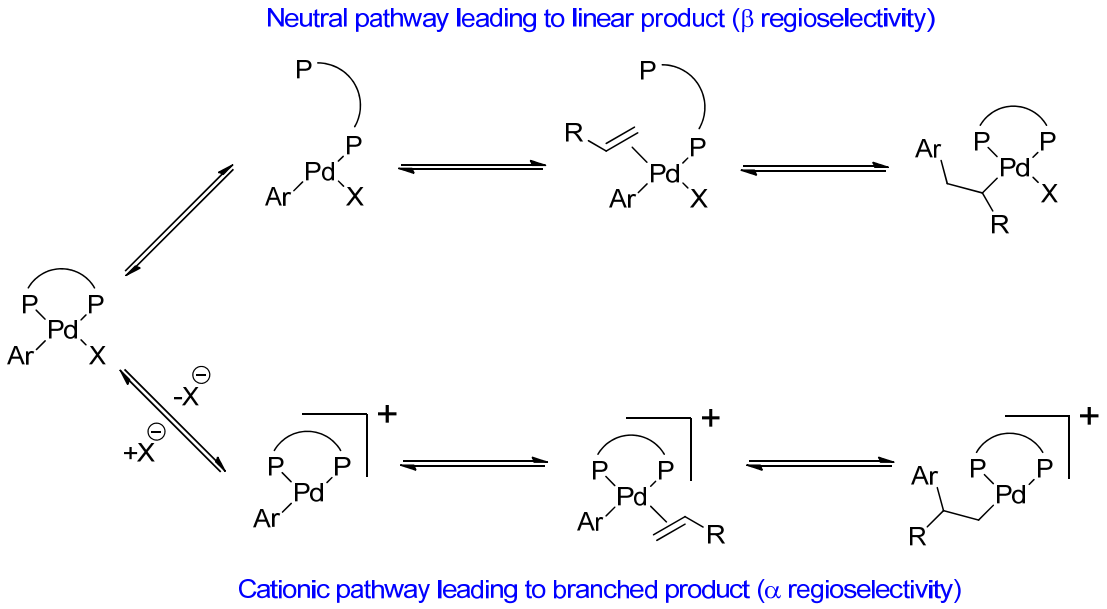



| X | base | conditions | α/β | % yield |
|---|---|---|---|---|
| OTf | $Et_3N$ | 60 °C, 0.5 h | >99/1 | 97 |
| Br | $Et_3N$ | 100 °C, 18 h | 61/39 | 54 |
| Br | TlOAc | 80 °C, 0.7 h | >99/1 | 97 |

**Scheme 1.15**: First general method for regioselective Heck arylation of electron-rich olefins

Based on these observations, it was proposed that two distinct mechanistic pathways exist and compete with each other during the Heck reaction (Scheme 1.16). The neutral pathway proceeds via dissociation of a phosphine ligand, creating a vacant site to which the olefin can coordinate. This neutral complex results in migratory insertion with arylation on the terminal olefinic carbon to yield the linear product. The cationic pathway proceeds via dissociation of the leaving group ($X^-$) to give a cationic complex to which the olefin coordinates and aryl insertion occurs on the internal olefinic carbon, leading to the branched product. This relatively simple mechanism can account for most of the developments made towards regioselective Heck arylation of electron-rich olefins over the past few decades. By employing aryl triflates, Hayashi and Cabri were encouraging the arylation reaction to proceed via the cationic pathway, as the $^-$OTf anion can dissociate from Pd much more readily than a halide anion. The use of BINAP and dppp as ligands also

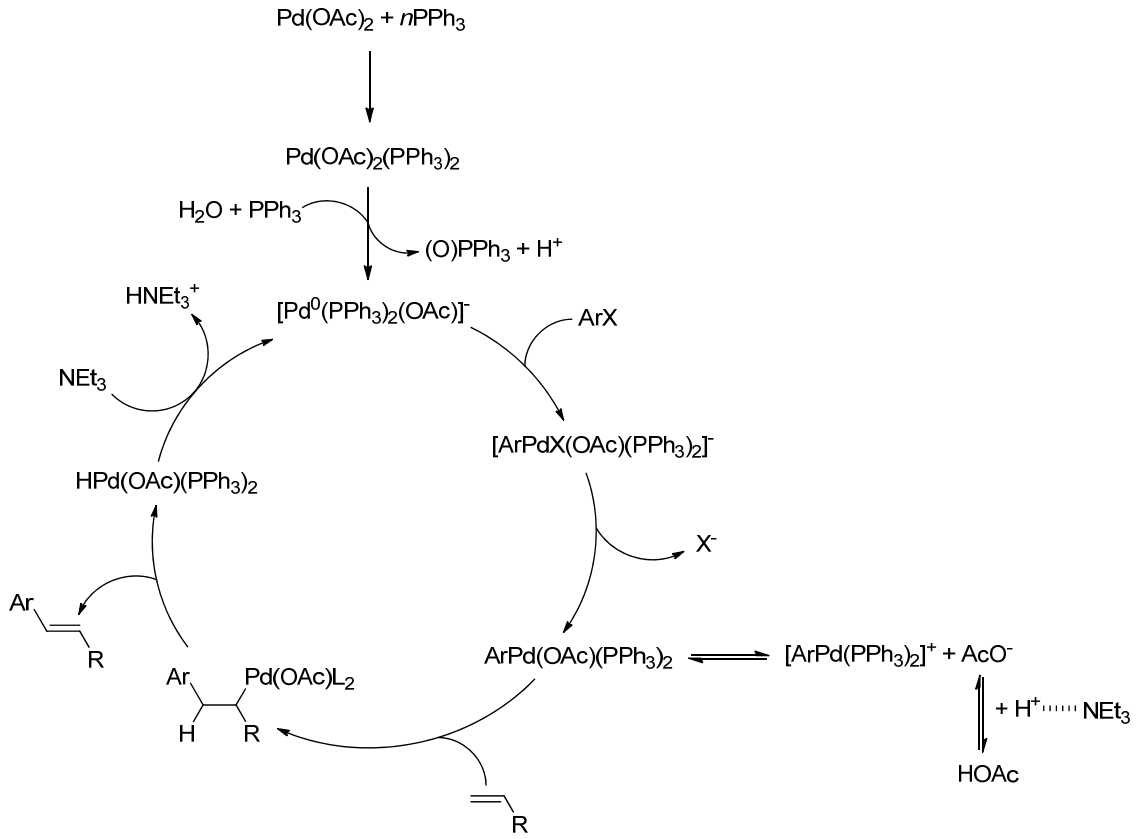
favours the cationic pathway as the bidentate bisphosphines are tightly bound to Pd and are therefore unlikely to dissociate from the metal centre. Dissociation of $^{-}$OTf whilst the chiral bisphosphine ligand remains tightly bound to the Pd centre, maintaining a rigid chiral environment, is thought to be key to the high enantioselectivity achieved by Hayashi (Scheme 1.14). Cabri was again encouraging the cationic pathway to proceed during the Heck reaction of aryl halides by employing thallium salts, which can pull the halide anion away from Pd and so produce the required cationic Pd complex.




**Scheme 1.16**: Two competing pathways in the Heck reaction

Several years after the reports of Cabri and Hayashi, an alternative 'anionic' mechanism was proposed by Amatore and Jutand (scheme 1.17).[31] Experimental evidence revealed that the choice of Pd(II) precursor was very important, as the anions of the precatalyst can effect the structure of the active catalyst that is formed. When consulting a textbook, one usually sees a 14e$^{-}$ species in the form of $Pd^0L_2$ depicted as the active catalyst. However, Amatore and Jutand found that tricoordinated anionic complexes such as $Pd^0L_2(OAc)^-$ and $Pd^0L_2Cl^-$ can be active catalysts when starting from the Pd(II) precursors $Pd(OAc)_2$ and $PdCl_2$, respectively. More significantly, the ligated anion was found to affect the rate of oxidative addition of ArI with the anionic complex. Protons released in the reduction of Pd(II) (Scheme 1.17) interact with the acetate of $Pd^0(PPh_3)_2(OAc)^-$ to afford a more "naked" and thus more reactive complex, being closer to $Pd^0(PPh_3)_2$. Interestingly, the intermediate complexes formed from oxidative addition of ArI with the anionic complexes were found to be the pentacoordinate anionic complexes, $ArPdI(OAc)L_2^-$ and $ArPdI(Cl)L_2^-$.[32] These high energy intermediates were then found to lose the halide ion ($I^-$) to yield *trans*-$ArPd(OAc)L_2$ and *trans*-$ArPd(Cl)L_2$. When compared to $ArPdIL_2$, the commonly postulated intermediate following oxidative addition, $ArPd(OAc)L_2$ was found to show increased reactivity with the olefin substrate. This was

attributed to the bidentate nature of the acetate ligand, which may assist in phosphine release to open a coordination site for the olefin.

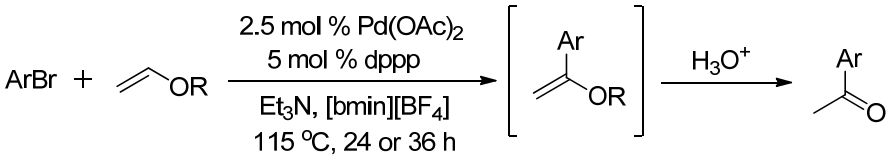



**Scheme 1.17**: Anionic mechanism proposed by Amatore and Jutand

The use of aryl triflates is very effective, but is not desirable due to the fact that aryl triflates are generally commercially unavailable, as well as being base sensitive and thermally labile. Employing silver or thallium salts as additives for the reaction with aryl halides is also problematic, as stoichiometric silver is expensive and thallium is highly toxic. Therefore, if an alternative method could be developed that promotes the cationic pathway and so results in regioselective Heck arylation, without any of the problems associated with aryl triflates or silver/thallium additives, it would be very useful indeed.

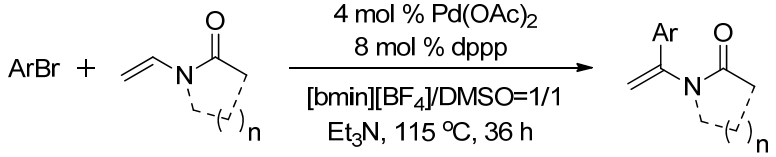
Xiao made a significant contribution to the development of the regioselective Heck reaction of electron-rich olefins.[33] This was achieved based on understanding of the cationic pathway proposed by Hayashi and Cabri. The first major breakthrough to this end came by employing ionic liquid as the solvent medium for the Heck reaction of electron-rich olefins.[34] Xiao proposed that the ionic nature of ionic liquids could provide an ideal medium for the stabilisation of ionic intermediates, thereby encouraging the Heck reaction to proceed via the cationic pathway. Indeed, the arylation of vinyl ethers with aryl bromides proceeded with >99:1 regioselectivity towards the branched α-product when the imidazolium salt [bmin][$BF_4$] was used as solvent (Scheme 1.18). The reaction was successful for a wide range

of ArBr and the regioselectivity was excellent for both electron-rich and electron-deficient halides. In addition, aryl iodides could be employed with equal success.



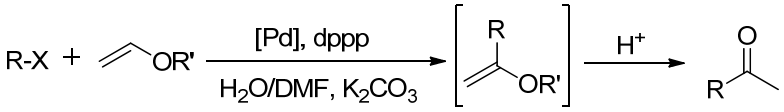

**Scheme 1.18**: Internal arylation of vinyl ethers with aryl bromides in [bmin][$BF_4$]

The electron-rich olefin allyltrimethylsilane could also be arylated with excellent regioselectivity under the newly developed conditions.[34b] Unfortunately, arylation of enamides was unsuccessful. This may be attributed to the effect of the nitrogen lone pair that is in conjugation with the carbonyl group. This problem was surprisingly overcome by the addition of DMSO as a co-solvent to the ionic liquid, which led to the regioselective arylation of a range of enamides (Scheme 1.19).[34b]




**Scheme 1.19**: Internal arylation of enamides in DMSO/[bmin][$BF_4$]

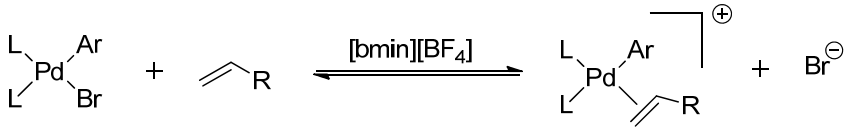
The regioselective internal arylation of electron-rich olefins with aryl halides was reported by Hallberg soon after (Scheme 1.20).[35] Hallberg realised that addition of water to the reaction medium should increase the polarity of the reaction environment, thus facilitating the formation of ionic intermediates and promote the cationic pathway, leading to regioselective arylation.




**Scheme 1.20**: $H_20$/DMF polar medium as a substitute for Tl and Ag additives

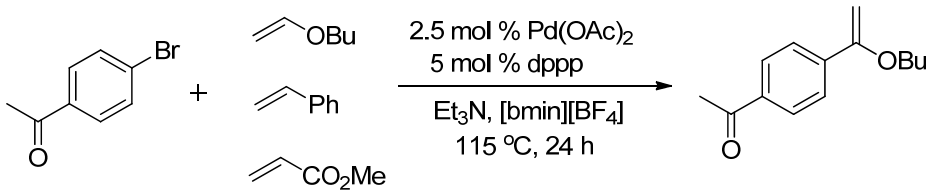
Xiao and Hallberg proposed that formation of the cationic Pd(II)-olefin species, which is key to α-arylation, is favoured in polar mediums such as ionic liquids and DMF/$H_20$. This view has been supported by Amatore and Jutand who showed that a high ionic strength favours α-arylation.[36] Also, an earlier study by Milstein *et al* revealed that olefin insertion into the Pd-Ar bond in [$L_2$Pd(Ar)X] is greatly facilitated in a polar solvent.[37]

Xiao obtained experimental evidence to support the importance of the $[L_2ArPd]^+Br^-$ intermediate.[34b] Addition of halide anions in the form of $Bu_4NBr$ significantly slowed the reaction rate for the arylation of butyl vinyl ether with 4-bromoacetophenone. As the amount of halide additive was increased, the rate of reaction continued to decrease. This can be explained by considering the equilibrium shown below (Scheme 1.21):



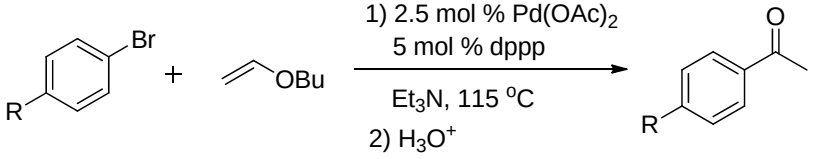

**Scheme 1.21**: Dissociation of $Br^-$ from $Pd^{II}$

Le Chatelier's principle tells us that the position of equilibrium will shift to oppose the change. Therefore, addition of halide anion will cause the equilibrium to shift to the left, thus decreasing the concentration of $[Pd]^+$ and so inhibiting the cationic pathway. Further evidence was obtained to support the ionic pathway by carrying out competition experiments (Scheme 1.22). The Heck reaction of 4-bromoacetophenone was carried out in the presence of the three different olefins. When the reaction was run in $[bmin][BF_4]$, only the electron-rich vinyl ether reacted. This is a result of preferential coordination of an electron-deficient $Pd^{II}$ cation to an electron-rich olefin. By way of contrast, when run in DMF, the reaction of 1-napthyl iodide with a mixture of butyl vinyl ether and methyl acrylate gave the opposite chemoselectivity, due to preferential coordination of the electron-poor acrylate to a neutral $Pd^{II}$ complex.

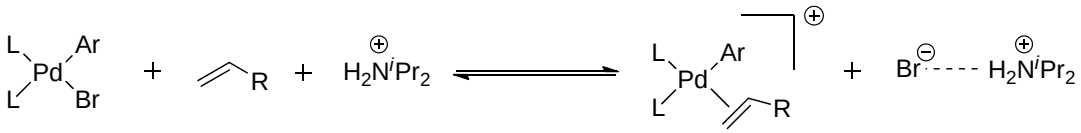



**Scheme 1.22:** Competition experiment for the Heck arylation of various olefins

The use of an ionic liquid proved to be an excellent advancement in the regioselective Heck arylation of electron-rich olefins. Xiao and coworkers next sought further ways of encouraging the cationic pathway to dominate in the Heck reaction. It was proposed that the introduction of hydrogen bond donors (HBD's) should enhance the reaction rate by scavenging halide anions in a similar manner to the thallium and silver salts originally employed by Cabri. To their delight, this indeed proved to be the case.[38] Scheme 1.23 clearly shows that use of the HBD salt $[H_2N^iPr_2][BF_4]$ leads to a dramatic rate enhancement. This is again attributed to an increase in concentration of the cationic $Pd^{II}$ intermediate that rapidly reacts with electron-rich olefins in a regioselective manner.

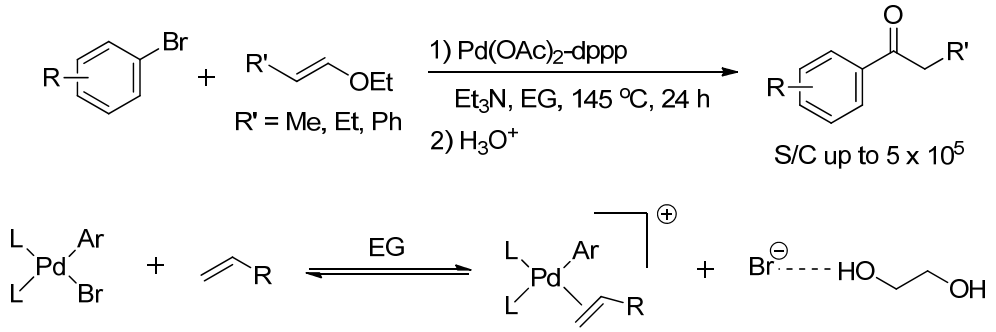



| R | solvent | additive (1.5 equiv.) | time (h) | yield (%) |
|---|---|---|---|---|
| H | [bmin][$BF_4$] | - | 24-36 | 97 |
| H | DMF | [$H_2N^iPr_2$][$BF_4$] | <4 | 91 |
| COMe | [bmin][$BF_4$] | - | 24-36 | 92 |
| COMe | DMF | [$H_2N^iPr_2$][$BF_4$] | <4 | 90 |
| OMe | [bmin][$BF_4$] | - | 24-36 | 81 |
| OMe | DMF | [$H_2N^iPr_2$][$BF_4$] | <4 | 82 |



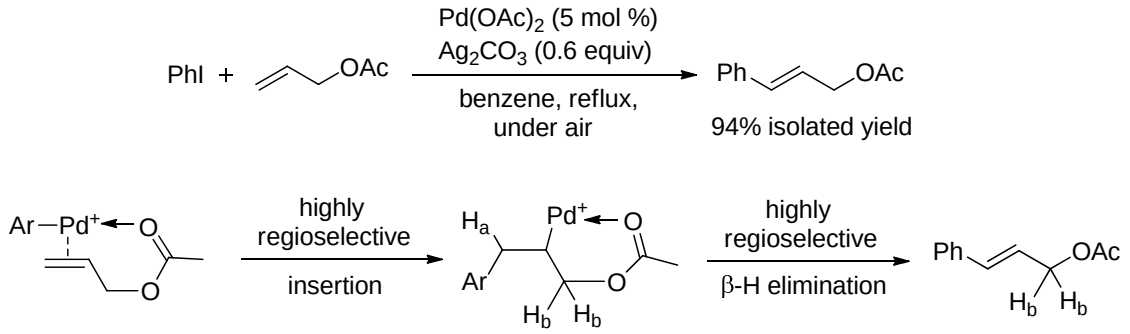

**Scheme 1.23**: HBD effect on Heck arylation of butyl vinyl ether

The *pièce de résistance* of the group's development towards the regioselective Heck arylation of electron-rich olefins was yet to come. Indeed, no one could disagree with the fact that HBD salts such as [$H_2N^iPr_2$][$BF_4$] are much more desirable additives to use than thallium or silver salts. However, they raised the question of whether an even simpler HBD could be found. Alcohols are known to act as receptors for halide anions, and in particular ethylene glycol (EG) is a good HBD as judged by its high $E_T^N$ value of 0.790.[39] Therefore, the Heck arylation of butyl vinyl ether with 4-bromoacetophenone was carried out in a range of alcohol solvents. Gratifyingly, the arylation in alcohols such as EG proceeded rapidly and with excellent α-regioselectivity.[40] A further study revealed remarkably high activity (TOF up to 15,625 $h^{-1}$) and productivity (TON up to 3.75 x $10^5$) in the arylation of vinyl ethers, with the substrate-to-catalyst (S/C) ratio reaching 5 x $10^5$.[41] These numbers far surpass those observed in ionic liquids or when using ammonium HBD's, representing actually the highest values ever reported for the Heck reaction of electron-rich olefins. In particular, sterically demanding vinyl ethers also reacted under these conditions, leading to interesting alkyl aryl ketones (Scheme 1.24).



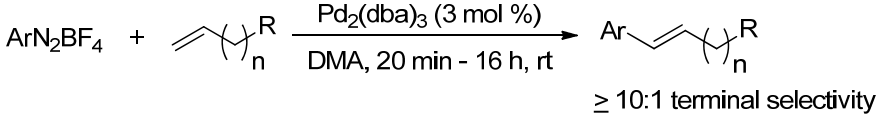

**Scheme 1.24**: EG solvent for HBD promoted Heck arylation of vinyl ethers

Unfortunately, the regioselective Heck reaction of electron-neutral aliphatic olefins still remained a challenge. High levels of terminal selectivity can be achieved for substrates that possess a suitably positioned chelating group, as proposed for the Heck reaction of ArI with allyl acetate in the presence of $Ag_2CO_3$ (Scheme 1.25).[42] High levels of terminal selectivity can also be achieved for the arylation of protected allylic/homoallylic alcohols.[43] The chelation strategy has also been implemented in oxidative[44] and decarboxylative[45] Heck reactions to achieve high terminal regioselectivity.




**Scheme 1.25**: Chelation-controlled terminal arylation of allyl acetate

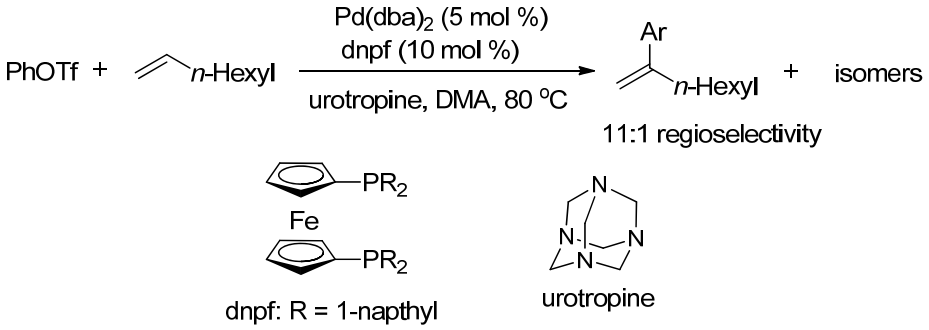
It was not until 2011, when a report by Sigman and Werner showed it was possible to achieve high terminal selectivity for electron-neutral aliphatic olefins that are without chelating groups (Scheme 1.26).[46] The use of aryl diazonium salts allows the reaction to proceed under extremely mild conditions.




**Scheme 1.26**: Terminal arylation of electron-neutral olefins that lack a chelating group

Selective internal Heck arylation of electron-neutral olefins is also difficult to achieve. Allylic alcohols can be made to undergo internal arylation when bidentate ligands are used.[47,48] However, this is partly due to the electronic bias caused by the inductive effect of the hydroxyl group, which decreases the electron density of the internal olefinic carbon. Consequently, the selectivity drops when homoallylic alcohols are employed. A report by Xiao showed that ionic liquids are again useful for promoting internal selectivity of Heck arylation, allowing aryl halides to be employed instead of aryl triflates for the first time with excellent regiocontrol.[49]

Earlier this year, Zhou *et al* published the first report for the highly selective internal arylation of electron-neutral, terminal aliphatic olefins that lack any directing group (scheme 1.27).[50] Computational experiments suggest that the large steric bulk of the ferrocene ligands inhibit the minor pathway of terminal insertion.

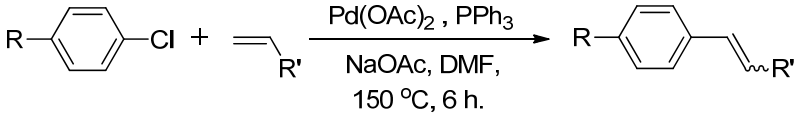



**Scheme 1.27**: Highly selective internal arylation of terminal aliphatic olefins

### 1.1.3.2 Activation of aryl chlorides[51]

As the Heck reaction continued to develop, it quickly became apparent that some aryl electrophiles were more reactive than others. The efficiency of the Heck reaction followed the trend that ArI >> ArOTf > ArBr >> ArCl, with ArCl being particularly ineffective if not completely inert.[52] It is generally accepted that this is a result of the strong C-Cl bond, which is difficult to activate with Pd(0) through oxidative addition. As we will see, this problem was most successfully overcome by increasing the electron density at Pd by the use of strongly electron-donating ligands, thus facilitating oxidation of the metal centre. This approach was first realised in other Pd-catalysed cross-coupling reactions such as Suzuki and Stille couplings, which will be covered in section 1.2.

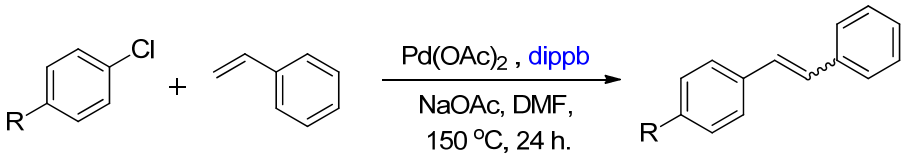
The first notable report of the Heck reaction employing aryl chlorides was disclosed by Spencer in 1984.[53] Spencer examined the arylation of activated alkenes with aryl chlorides homogeneously catalysed by $Pd(OAc)_2$ in the presence of $PPh_3$ or P(*o*-tol)$_3$ at elevated temperature. At 150°C the Heck product could be obtained in moderate yields as a mixture of E/Z isomers (Scheme 1.28). Electron-withdrawing substituents on ArCl were necessary for successful reaction, most likely in order to activate the C-Cl bond towards oxidative addition.



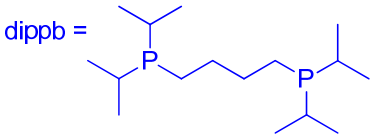

| R | R' | Yield (%) |
|---|---|---|
| CHO | $CO_2Et$ | 39 |
| CHO | $CONEt_2$ | 45 |
| CHO | CN | 23 |
| CHO | $C_6H_5$ | 37 |
| $NO_2$ | $CO_2Et$ | 21 |
| CN | $CO_2Et$ | 32 |
| COMe | $CO_2Et$ | 26 |
| $CO_2Me$ | $CO_2Et$ | 51 |
| H | $CO_2Et$ | 4 |

**Scheme 1.28**: First detailed study on the Heck reaction of aryl chlorides

The first report showing the effectiveness of electron-rich trialkylphosphine ligands in promoting the Heck reaction of ArCl was that of Milstein in 1992.[54] In contrast to the system developed by Spencer, the bidentate ligand dippb formed a Pd catalyst capable of activating electron-neutral ArCl such as chlorobenzene, as well as challenging electron-rich ArCl's such as chloroanisole, albeit with a slower reaction rate (Scheme 1.29).

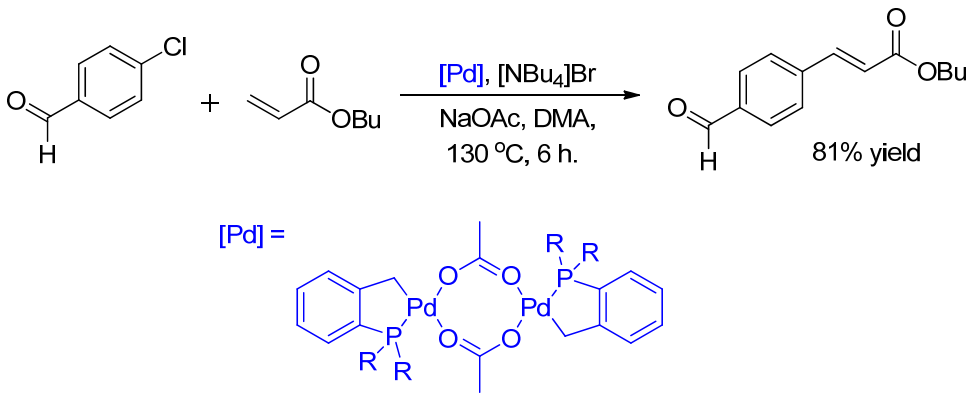



| R | amount of ArCl (%) | amount of ArCH=CHPh (%) | |
|---|---|---|---|
| | | cis | trans |
| H | 15.6 | 4.4 | 80 |
| Me | 45 | 5 | 50 |
| OMe | 78.8 | 2.2 | 19 |
| CHO | 5 | 5 | 90 |
| PhCO | 0 | 3 | 97 |




**Scheme 1.29**: First report of Heck reaction employing electron-rich ArCl

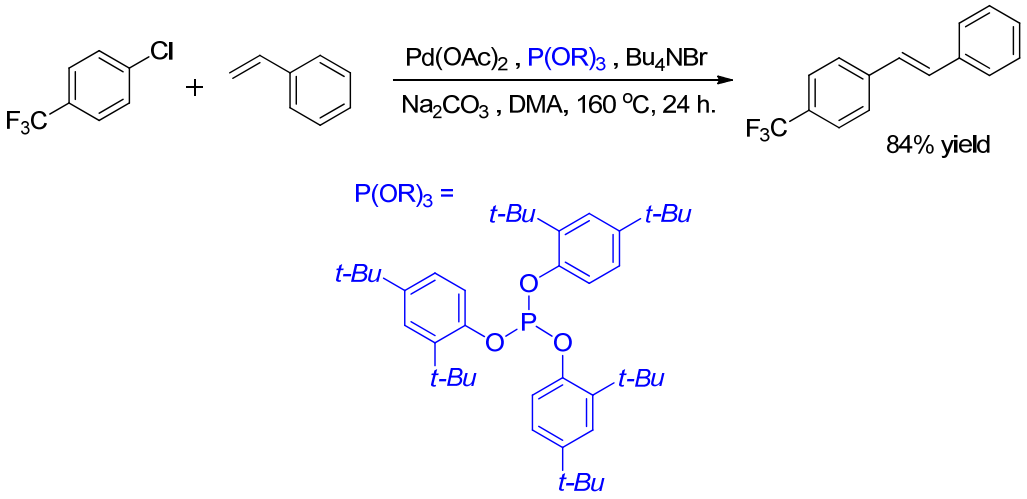
It was later presented by Herrmann that it is not possible for the $Pd/PAr_3$ system to sustain high catalytic activity at such high temperatures, as above 120°C cleavage of P-C bonds in $ArPd^{II}XL_n$ intermediates becomes a significant process.[55] As a result, the stabilising phosphine ligands are destroyed and Pd quickly aggregates to form inactive Pd metal. In solution to this problem, Herrmann developed a palladacyclic catalyst that he thought to be inert to such degradation pathways and so could sustain high activity under extreme heating. For the Heck arylation of ArCl, the addition of a bromide salt was necessary to further stabilise the catalyst, resulting in a system that can achieve TON of 600-800 (Scheme 1.30).[55] However, later studies have suggested that Hermann's palladacycle was in fact a precursor to Pd nanoparticles, which were the active catalyst.[56] This is supported by the fact that tetrabutylammonium salts are known to stabilise Pd nanoparticles that are able to activate aryl halide substrates.[57]




**Scheme 1.30**: Herrmann's Palladacycle used for the Heck reaction of ArCl

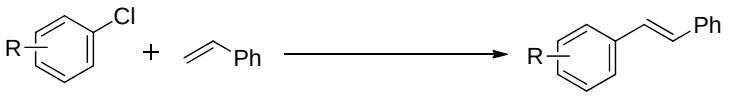
Herrmann also pioneered the use of another class of cyclometallated Pd(II) complexes derived from stable N-heterocyclic carbenes.[58] Others have later utilised Pd-carbene catalysts for the Heck reaction of ArCl,[59] but, as with Herrmann's catalyst, they are only capable of activating electron-deficient ArCl at elevated temperatures.

At the beginning of his independent research career, Beller (a former student of Herrmann) investigated the effectiveness of phosphite ligands in the Heck reaction of ArCl.[60] Due to the poor electron-donating capability of the phosphite ligands relative to phosphines, a large excess of the ligand was required in order to stabilise Pd. However, the Pd-$P(OR)_3$ system was capable of producing an effective system for the arylation of electron-deficient ArCl at 140-160°C (Scheme 1.31). As in Herrmann's system, the presence of the bromide salt $Bu_4NBr$ was necessary to achieve high TONs.

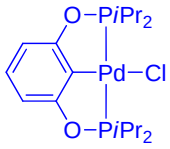



**Scheme 1.31**: First use of phosphite ligands in Heck reaction

Soonafter the studies of Beller, another class of phosphite ligands was developed by Jensen (Scheme 1.32).[61] These PCP ligands form pincer complexes with Pd that are non-sensitive to air or moisture and are thermally stable. When utilised as catalysts for the Heck reaction of ArCl, elevated temperatures and prolonged reaction times allow electron-rich ArCl to be successfully coupled to olefins in excellent yields.[62] Jensen proposed that the reaction proceeded via Pd(II)/Pd(IV) intermediates. Thus, oxidative addition of a vinyl C-H bond is followed by reductive elimination of H-Cl, oxidative addition of Ar-Cl, and finally reductive elimination of the coupled product.

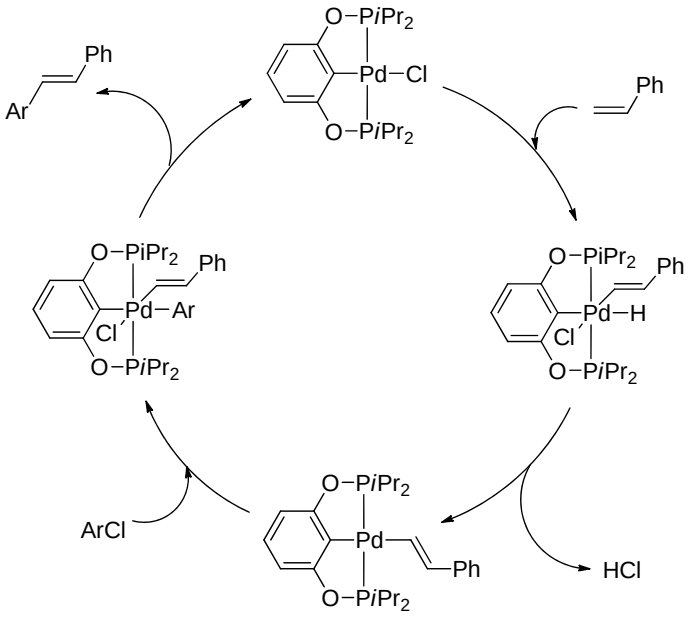



| Entry | R | Yield (%) |
|---|---|---|
| 1 | 4-MeCO | >99 |
| 2 | H | >99 |
| 3 | 4-OMe | 88 |
| 4 | 2-OMe | 85 |




**PCP**

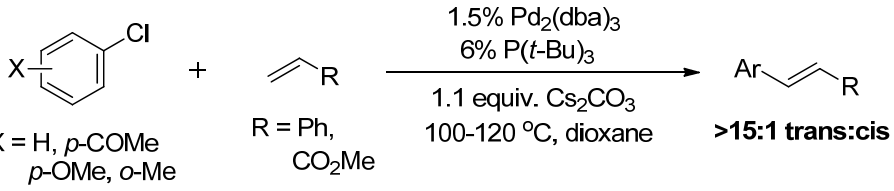
Conditions: ArCl (1 equiv.), styrene (2 equiv.), **PCP** (0.67 mol%), CsOAc (1.1 equiv.), dioxane, 120 °C (120 h), or 180 °C (24 h).




**Scheme 1.32**: Activity of Jensen's PCP complexes and propsed Pd(II)/Pd(IV) mechanism.

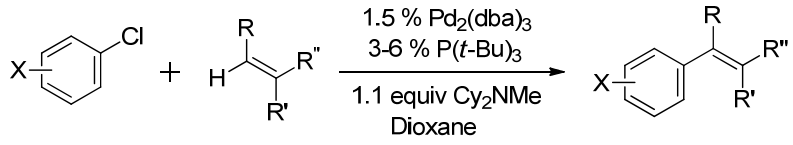
At this stage, all current methodologies for the Heck reaction of ArCl had significant limitations. The reaction only worked well for 'activated' olefins such as styrene and acrylic acid derivatives, was highly inefficient for electron-rich and sterically hindered ArCl, and sufficient activity could only be achieved at elevated temperatures $\geq$ 120°C. These drawbacks started to be overcome in 1998/1999 when the three independent research groups of DeVries,[63] Hartwig[64] and Fu[65] utilised P(*t*-Bu)$_3$ as a ligand, which allowed sterically

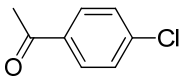
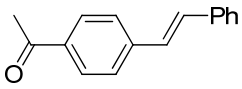
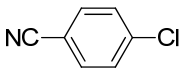
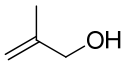
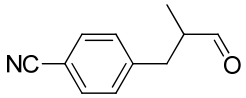
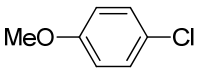
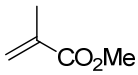
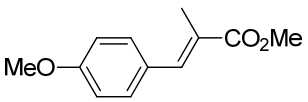
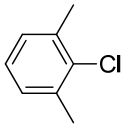
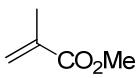
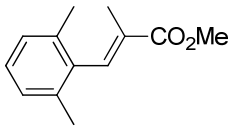
demanding and electron-rich ArCl to be coupled to olefins at 100-120°C. Fu's initial conditions are shown in Scheme 1.33 below:




**Scheme 1.33**: Fu's initial conditions for the Heck reaction of ArCl

Stimulated by an investigation of his colleague, Buchwald,[66] Fu subsequently discovered that the use of $Cy_2NMe$ (rather than $Cs_2CO_3$) as the Brønsted base allows Pd/P(*t*-Bu)$_3$-catalysed Heck reactions to proceed under even milder conditions.[67] Remarkably, the Pd/P(*t*-Bu)$_3$/$Cy_2NMe$ system allows the Heck arylation of electron-deficient ArCl with mono- and disubstituted olefins to occur *at room temperature* with good *E/Z* selectivity (Scheme 1.34). Reactions of unactivated ArCl require heating, but challenging substrates can be employed as coupling partners, such as highly electron-rich and di-*ortho*-substituted ArCl. To this day, the conditions developed by Fu remain the most mild and efficient way to couple a wide range of aryl chlorides with olefins in the Heck reaction.

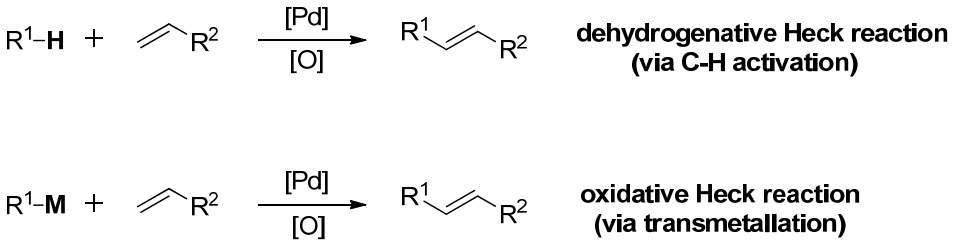



| aryl chloride | olefin | temperature | product | yield (%) |
|---|---|---|---|---|
|  |  | r.t. |  | 78 |
|  |  | r.t. |  | 79 |
|  |  | 120 °C |  | 72 |
|  |  | 120 °C |  | 80 |

**Scheme 1.34**: Fu's optimal conditions for mild and versatile Heck reactions.

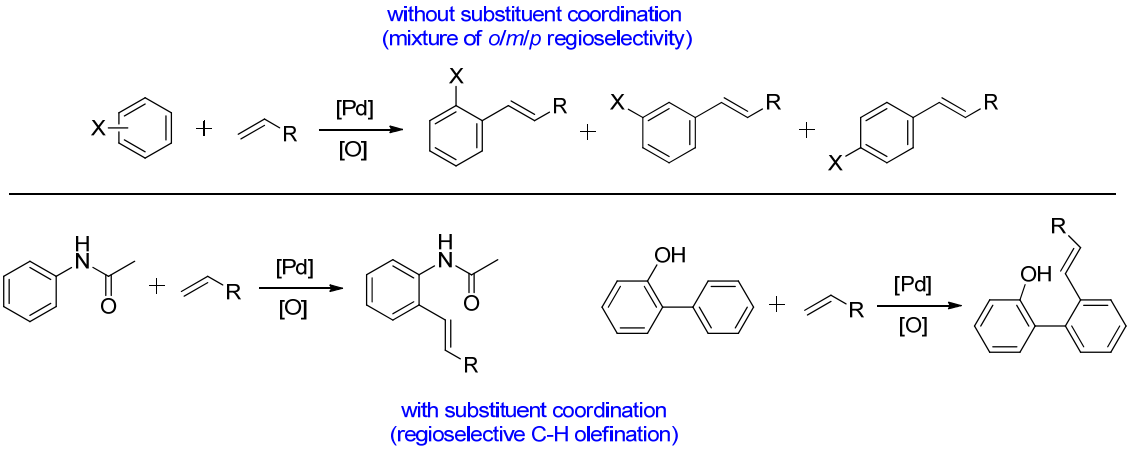
### 1.1.3.3 Oxidative/Dehydrogenative Heck reaction

In recent years, research into the Heck reaction has focused on the oxidative coupling of olefins with organometallic compounds such as organoboranes, organosilanols and aryl stannanes, as well as the dehydrogenative coupling with arenes (Scheme 1.35).



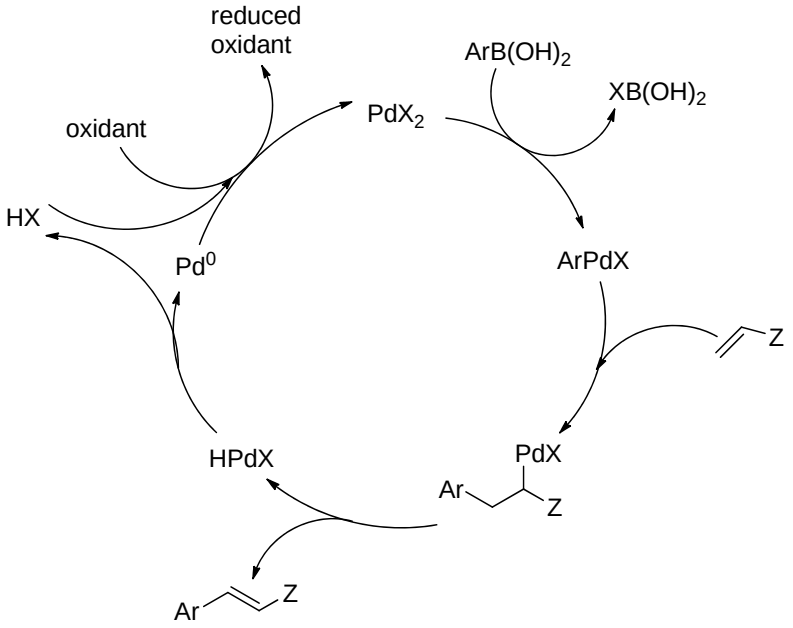

**Scheme 1.35**: Outline of the dehydrogenative and oxidative Heck reactions

The dehydrogenative Heck reaction (DHR)[68] is particularly appealing, as it eliminates the need for prefunctionalisation of the arene. The major drawback to olefination of arene C-H bonds is the inherent lack of regiocontrol that is observed in many cases where multiple C-H bonds exist in the substrate molecule. However, this problem can be overcome in substrates that possess a functional group capable of coordinating to the Pd catalyst and aid C-H activation at a particular position (Scheme 1.36). The DHR was recently reviewed in great detail.[68]




**Scheme 1.36**: Issues of regiocontrol in DHRs

The Oxidative Heck reaction[69] is also complimentary to the traditional coupling of aryl halides and olefins, as halogenated substrates can easily be tolerated without any reaction at the C-X bond. This is due to the fact that under oxidative conditions, Pd exists in its +2 oxidation state and so is unlikely to undergo oxidative addition into the C-X bond. For example, the oxidative coupling of arylboronic acids and olefins is proposed to occur by the following mechanism (Scheme 1.37). The arylpalladium(II) complex is formed by transmetallation with the arylboronic acid. After π-coordination of the olefin, migratory insertion followed by β-hydride elimination yields the coupled product. The resultant Pd(II) hydride undergoes reductive elimination to form Pd(0), which is oxidised by the stoichiometric oxidant that makes the process catalytic with respect to Pd.



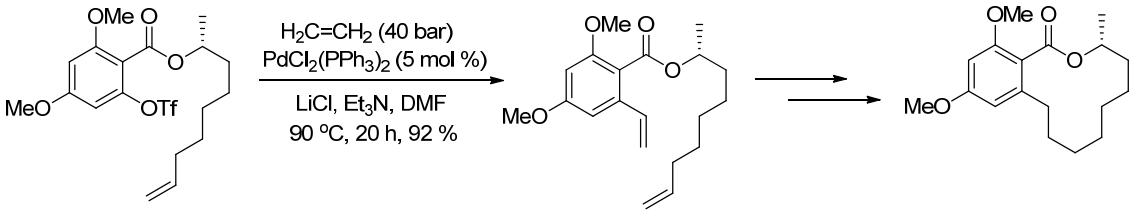

**Scheme 1.37**: Mechanism of the oxidative Heck reaction.

### 1.1.4 Applications in synthetic chemistry

In recent decades, the Heck reaction has been widely adopted throughout synthetic chemistry, including in the areas of total synthesis and medicinal chemistry.[70] This is due to the fact that the methodology tolerates a wide range of functionality, and continued development has made the reaction highly efficient and selective for a wide variety of substrates. Several specific applications of the Heck reaction are presented below in order to give some idea of its synthetic value.

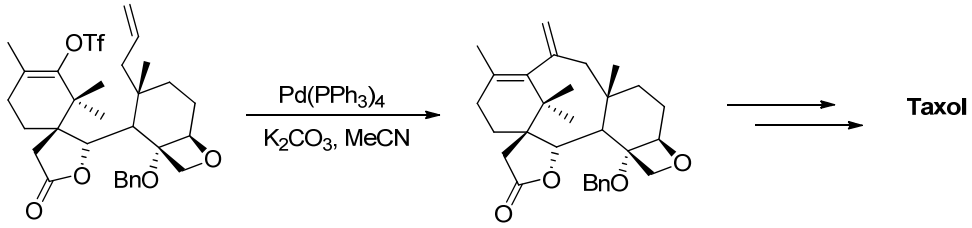
Total Synthesis examples

The total synthesis of the potent anticancer macrocyclic natural product lasiodiplodin was achieved in the laboratory of Fürstner. The styrenyl moiety was introduced by the Heck reaction of an aryl triflate with ethylene gas (Scheme 1.38).[71]




**Scheme 1.38**: Total synthesis of lasiodiplodin

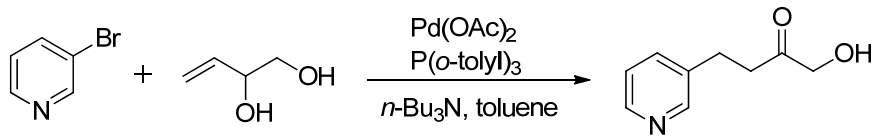
In the total synthesis of taxol, the eight-membered ring can be constructed by an intramolecular Heck reaction (Scheme 1.39).[72]




**Scheme 1.39**: Total synthesis of taxol

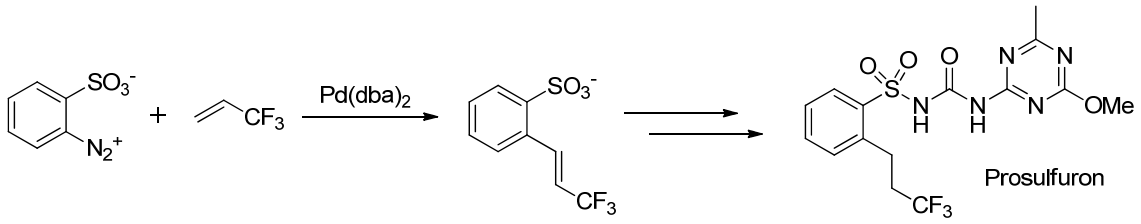
Medicinal Chemistry examples

In 2002, AstraZeneca published a synthetic route to a key intermediate, which was achieved by the Heck coupling of 3-bromopyridine and 3-butene-1,2-diol (Scheme 1.40), in which Pd-catalysed isomerisation also occurred.[73] Even though the reaction yield was modest (33% on 3 kg scale), this was a significant advancement on the previous route that involved five steps, including aldol and Wittig chemistry.




**Scheme 1.40**: AstraZeneca's route to a key intermediate

Prosulforon is a sulfonyl urea herbicide produced on a multi-tonne scale. The initial synthetic route developed by Ciba-Geigy included a Heck reaction as one of the key steps (Scheme 1.41).[74]

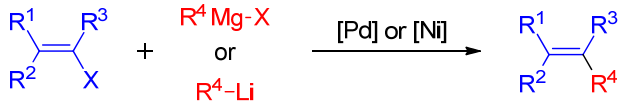



**Scheme 1.41**: Ciba-Geigy's route to prosulforon

### 1.2 Further cross-coupling reactions catalysed by palladium

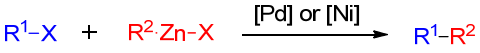
The Heck reaction is just one of many coupling reactions catalysed by palladium. Over the past decades, several classes of Pd-catalysed reactions have been developed, which are classified by the type of substrates that participate in the reaction. They include:

Kumada cross-coupling[75]



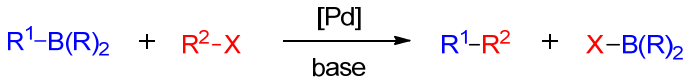

$R^{1-3}$ = H, alkyl, aryl, alkenyl; X = F, Cl, Br, I, OTf; $R^4$ = alkyl, aryl, alkenyl; X = Br, I

Negishi cross-coupling[76]



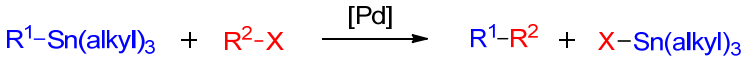

$R^1$ = aryl, alkenyl, acyl; X = Cl, Br, I, OTf, OAc; $R^2$ = aryl, alkenyl, allyl, benzyl, homoallyl, homopropargyl; X = Cl, Br, I

Suzuki cross-coupling[77]



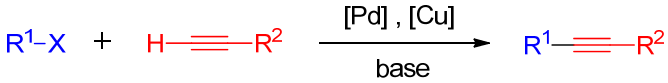

$R^1$ = alkyl, allyl, alkenyl, aryl; R = alkyl, OH, O-alkyl; $R^2$ = alkenyl, aryl, alkyl; X = Cl, Br, I, OTf

Stille cross-coupling[78]



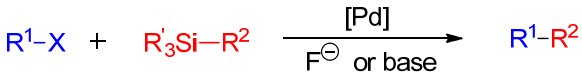

$R^1$ = allyl, alkenyl, aryl; $R^2$ = alkenyl, aryl, acyl; X = Cl, Br, I, OTf, $OPO(OR)_2$

Sonogashira cross-coupling[79]




$R^1$ = aryl, alkenyl, heteroaryl; X = Cl, Br, I, OTf; $R^2$ = H, alkyl, aryl, alkenyl, $SiR_3$

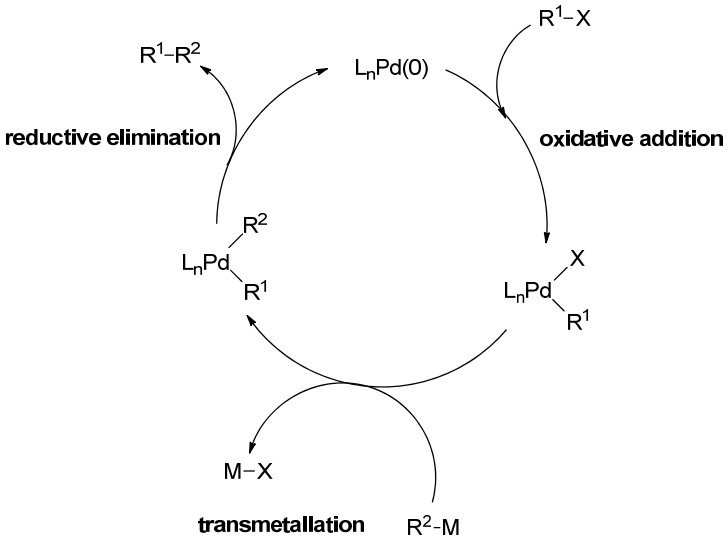
Hiyama cross-coupling[80]




$R^1$ = aryl, alkenyl, alkyl; X = Cl, Br, I, OTf; $R^2$ = aryl, alkenyl, alkyl; R' = RO, $Me_{(3-n)}F_n$

**Scheme 1.42**: Various classes of Pd catalysed cross-coupling reactions

All of the above reactions are based upon three key mechanistic steps, as summarised in Scheme 1.43 below:




**Scheme 1.43**: General mechanism of the Pd catalysed cross-coupling reactions

Pd(0) is oxidised to Pd(II) as it adds across the C-X bond. The resulting intermediate is capable of participating in a transmetallation reaction with the organometallic reagent $R^2$-M. Once the two coupling partners are ligated to the same Pd complex, the coupled product is released by a reductive elimination reaction in which Pd(II) is reduced back to Pd(0), thus forming a complete catalytic cycle.

Various substrates that undergo Pd catalysed cross-coupling reactions require some kind of activation before undergoing transmetallation. In a Sonogashira coupling, catalytic Cu is required in order to activate the alkyne and in doing so produce an intermediate species capable of undergoing transmetallation with Pd(II).[81] In a Hiyama coupling, a stoichiometric source of fluoride is usually employed, which favourably coordinates to Si, thus forming a pentacoordinate silicate intermediate that can more readily undergo transmetallation with Pd(II).[82] In a Suziki coupling, oxygen bases are usually employed, which coordinate to the boron atom of the boronic acid, forming an ate complex that is more susceptible towards transmetallation.[83]

Due to the importance of C-C bond formation in organic synthesis, each of the coupling reactions named above are now vast research areas in their own right. Consequently, the reader is urged to refer to the references given, which are relevent reviews and book chapters.

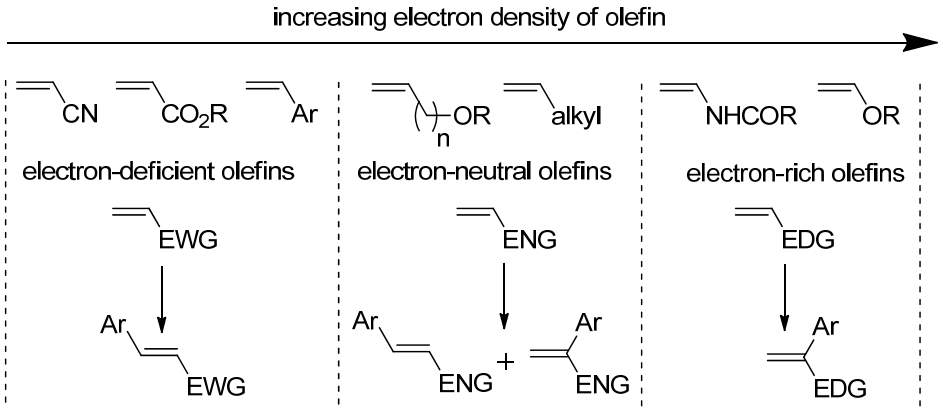
## 1.2 Research aims

This introduction clearly shows the significance of the Heck reaction in synthetic chemistry. Ever since its discovery in the early 1970's, the reaction has received considerable attention from both the academic and industrial scientific communities, which has led to great advancement of the methodology. A deepened understanding of the reaction has broadened its application to a wide range of aryl halides and triflates, as well as controllable regioselectivity with electron-deficient, electron-neutral and electron-rich olefins (Scheme 1.44). Recent advances have also enabled the direct alkenylation of arenes and arylboronic acids, in the dehydrogenative and oxidative variants, respectively. However, the range of olefins commercially available is by no means exhaustive, and sometimes the desired olefin lacks sufficient stability to be conveniently stored. It is, therefore, the aim of this research investigation to further widen the scope of the Heck reaction by developing methods that allow the *in situ* formation of substrate olefins.

Chapter 2 investigates the *in situ* formation of C=C double bonds by the condensation of aliphatic aldehydes with the secondary amine, pyrrolidine, which acts as both organocatalyst and base. The resultant enamine may then undergo regioselective Heck arylation with an aryl chloride catalysed by a Pd-phosphine complex also formed *in situ*. Hydrolysis of the coupled product gives rise to alkyl aryl ketones.

Chapter 3 is an extension of Chapter 2, in which the aliphatic aldehydes are formed by the Pd catalysed Heck-isomerisation reaction of aryl bromides with allyl alcohol, before undergoing the recently developed acylation reaction catalysed by pyrrolidine and the same Pd catalyst, all of which is carried out in the same reaction vessel as a two step process.

Chapter 4 investigates the *in situ* formation of C=C double bonds by the dehydration of secondary aryl alcohols catalysed by the Keggin-type heteropolyacid, $H_3PW_{12}O_{40}$. On addition of a base, aryl bromide, Pd catalyst and a ligand, the resultant styrenes may undergo regioselective Heck arylation to provide one-pot access to functionalised stilbenes.




**Scheme 1.44:** Range of olefins typically employed and selectivity observed in Heck reaction.

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# Chapter 2

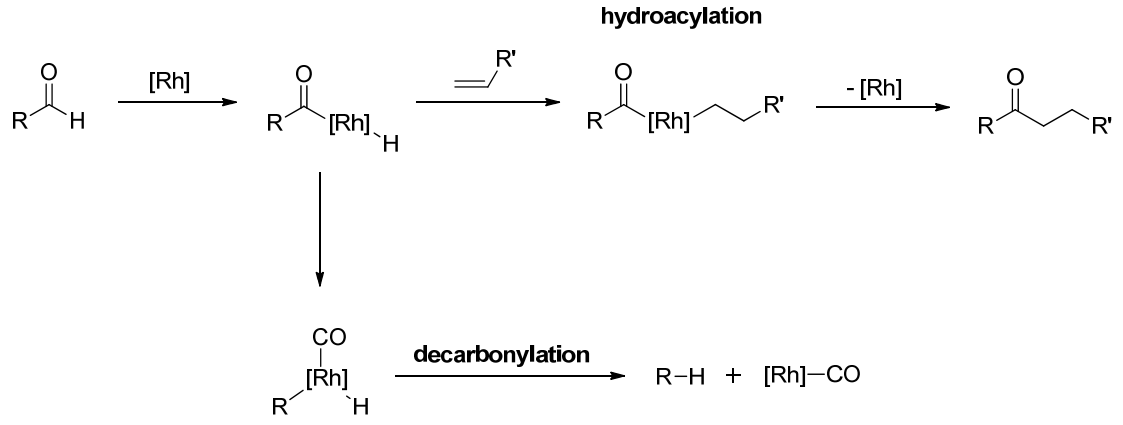
## Direct Acylation of Aryl Chlorides with Aldehydes

## by Palladium-Pyrrolidine Co-catalysis

### 2.1 Introduction

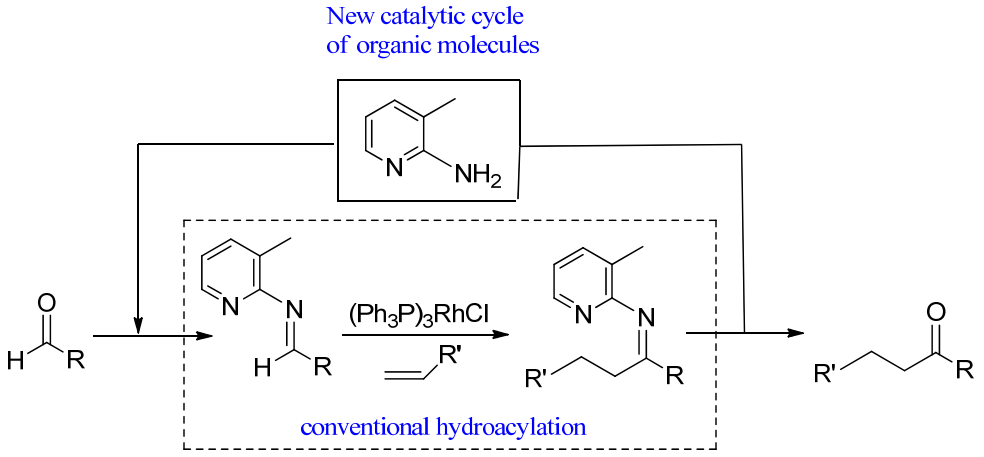
Alkyl aryl ketones are a class of organic compounds found in pharmaceutical agents, agrochemicals, dyes and fragrances.[1] Since its discovery in 1877, the Friedel-Crafts acylation reaction made these compounds widely accessible to the synthetic chemist.[2] The reaction involves the introduction of a keto group into an aromatic or aliphatic substrate by using an acyl halide or anhydride in the presence of a Lewis acid catalyst. The reaction works well for electron-rich aromatics, but aromatic substrates with strongly electron-withdrawing substituents fail to undergo the acylation reaction, as do electron-deficient heteroaromatic systems. There is, however, an alternative reaction method known as the Minisci reaction, which is capable of acylating protonated heteroaromatic compounds with nucleophilic carbon-centred radicals.[3] The carbon radical can attack the protonated ring, after which the presence of a suitable oxidant causes rearomatisation of the radical adduct. Both of these methods are extremely useful, but require the handling of hazardous reagents and produce stoichiometric toxic metal waste.

Alkyl aryl ketones may also be prepared by hydroacylation of olefins with aldehydes.[4] This reaction is usually achieved by employing a rhodium catalyst that can activate the aldehyde C-H bond. However, a major shortfall arises when the aldehyde substrate lacks the presence of a strong coordinating group, which is required to suppress decarbonylation (Scheme 2.1).



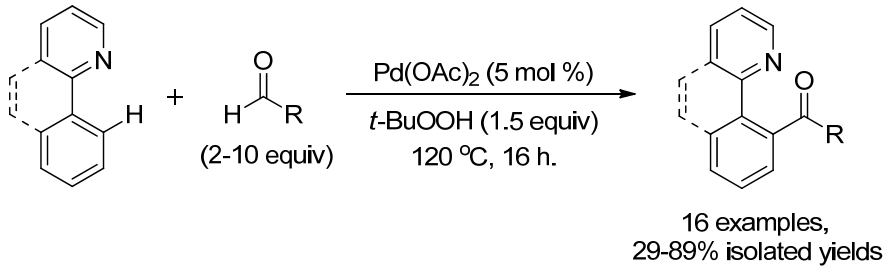

**Scheme 2.1**: Hydroacylation and decarbonylation pathways

Recent work by Jun *et al*[4a] has provided an excellent way of overcoming this problem by adopting a chelation-assisted protocol in which the coordinating group is not bound to the initial aldehyde substrate. Instead, 2-amino-3-picoline condenses with the aldehyde to form the corresponding imine, in which the pyridine nitrogen can act as the coordinating group necessary to suppress decarbonylation. Therefore, this modification allows the successful hydroacylation of a much wider range of aldehydes (Scheme 2.2).



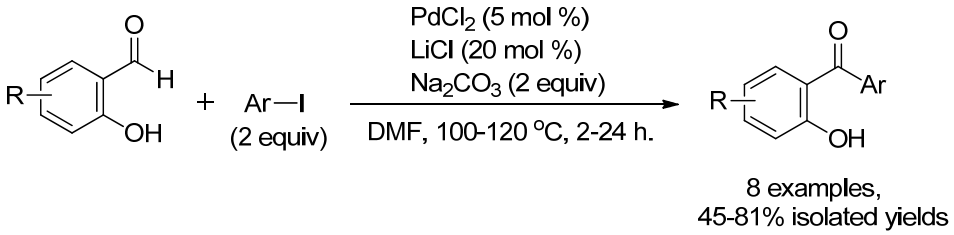

**Scheme 2.2**: Chelation-assisted hydroacylation

Another modern approach to alkyl aryl ketones made possible by transition metal catalysis is the direct acylation of arene C-H bonds with aldehydes.[5] For example, Li *et al* showed that with the aid of a directing group on the arene substrate, regioselective acylation with aldehydes is catalysed by $Pd(OAc)_2$ under an air atmosphere, with *tert*-butyl hydroperoxide (TBHP) as the stoichiometric oxidant (Scheme 2.3).[5a] This approach is particularly attractive due to the fact no prefunctionalisation of either substrate is required.




**Scheme 2.3**: Direct acylation of arenes with aldehydes

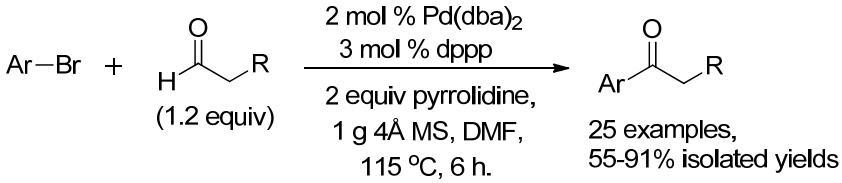
Another attractive approach to the synthesis of alkyl aryl ketones is the acylation of aryl halides with aldehydes. This transformation was first achieved for aryl iodides and salicylaldehydes.[6] Unfortunately, the presence of the chelating auxiliary on the aldehyde was critical to the success of the reaction, and therefore the methodology was limited to salicylaldehydes (Scheme 2.4).




**Scheme 2.4**: Initial report for the direct acylation of ArI with salicylaldehydes

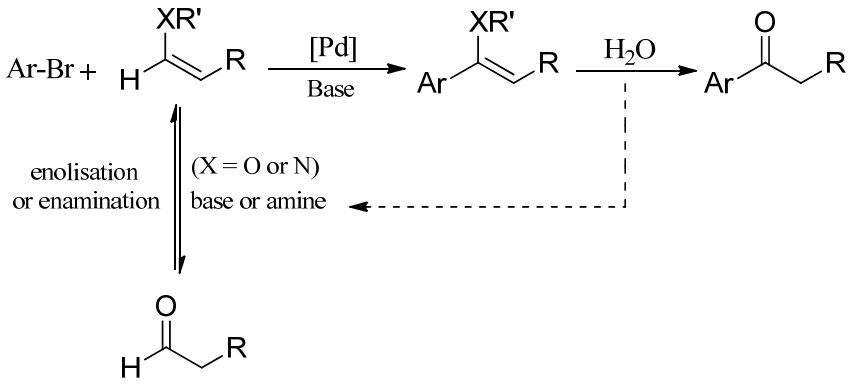
Similar methodologies were later reported, although these were also limited to aryl iodides in substrate scope and required bimetallic systems and a chelating auxiliary on the aldehydes.[7] In related studies, aryl boronate salts have been acylated with aldehydes to give diaryl ketones,[8] which could also be obtained by coupling of aryl iodides with *N*-pyrazyl aldimines or *N*-tert-butylhydrazones followed by hydrolysis.[9,10]

Our group recently reported an efficient protocol for the direct acylation of aryl bromides with aldehydes, which uses palladium-amine cooperative catalysis, allowing a variety of alkyl aryl ketones to be readily synthesised (Scheme 2.5).[11,12]




**Scheme 2.5**: Direct acylation of ArBr with aldehydes

Given our experience in the regioselective Heck reaction of electron-rich olefins, it was initially proposed that *in-situ* enolisation or enamination of aliphatic aldehydes would lead to the electron-rich double bonds of enolates or enamines, which could undergo regioselective arylation with ArBr. Hydrolysis of the coupled product would yield the desired alkyl aryl ketone (Scheme 2.6).




**Scheme 2.6**: Proposed reaction pathway for the acylation

In the initial screening of conditions it was revealed that the presence of a secondary amine and molecular sieves were critical to the acylation reaction.[11] Therefore, we proposed that the reaction was likely to proceed via Heck arylation of an enamine intermediate formed by the condensation of the secondary amine with the aldehyde, encouraged by the presence of molecular sieves by the absorption of the water released.

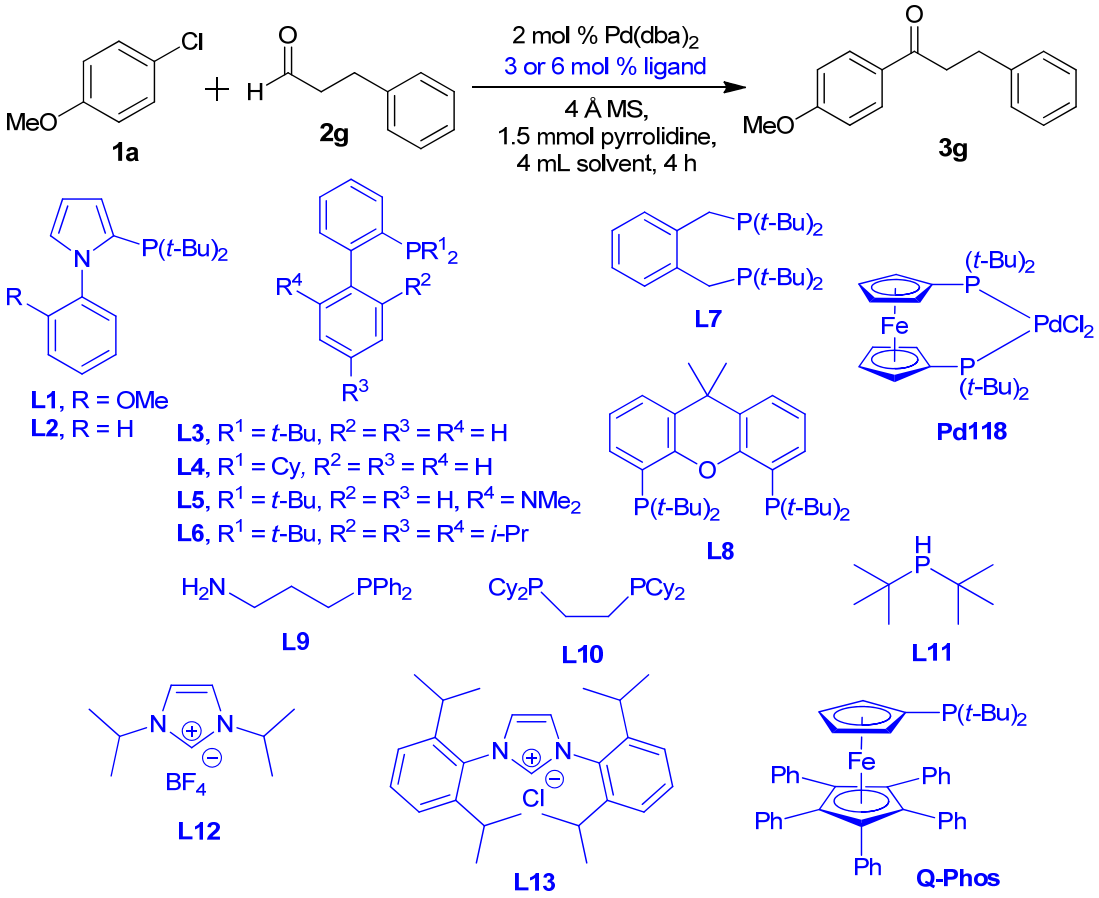
This methodology would be of even greater appeal if it were applicable to aryl chlorides, as they are cheaper and more widely available than their bromide or iodide counterparts. Unfortunately, aryl chlorides proved to be essentially inactive when subjected to the Pd-dppp catalysis we had developed for aryl bromides.[11] Research from a number of pioneering groups has led to the discovery of palladium catalysts bearing bulky and electron-rich phosphine or carbene ligands that exhibit much enhanced activity towards aryl chlorides (chapter 1.1.3.2).[13] We thought that by ligating palladium with such a ligand we might be able to force aryl chlorides to enter the acylation reaction.

## 2.2 Results and Discussion

### 2.2.1 Optimisation of reaction conditions

We set out to examine the acylation of 4-chloroanisole **1a** with 3-phenylpropanal **2g** by combining $Pd(dba)_2$ with various ligands under conditions previously developed for ArBr.[11] The results are summarized in Table 1. After screening several bidentate and monodentate ligands in DMF, we were delighted to find that the bulky, electron-rich monophosphine **L1** (entry 10) led to the formation of the desired product in 19% isolated yield. The yield was increased to 53% by raising the reaction temperature to 140 °C (entry 11). A wider range of ligands were then tested at the increased reaction temperature in order to find the optimal catalyst system. Surprisingly, all other monophosphine ligands, except the structurally similar **L2** (entry 12), gave poor results, regardless of their steric and electronic characteristics. Likewise, all of the diphosphine ligands tested, including the previously successful dppp,[11] failed to yield any of the desired product. When investigating the use of ligands as their stable salts (entries 18, 25 and 26), a small amount of a strong base was added in the hope to release the free ligand *in-situ*. Unfortunately, these ligands were also unable to catalyse the desired acylation reaction.

**Table 1**: Optimising conditions for the acylation of **1a** with **2g**[a]

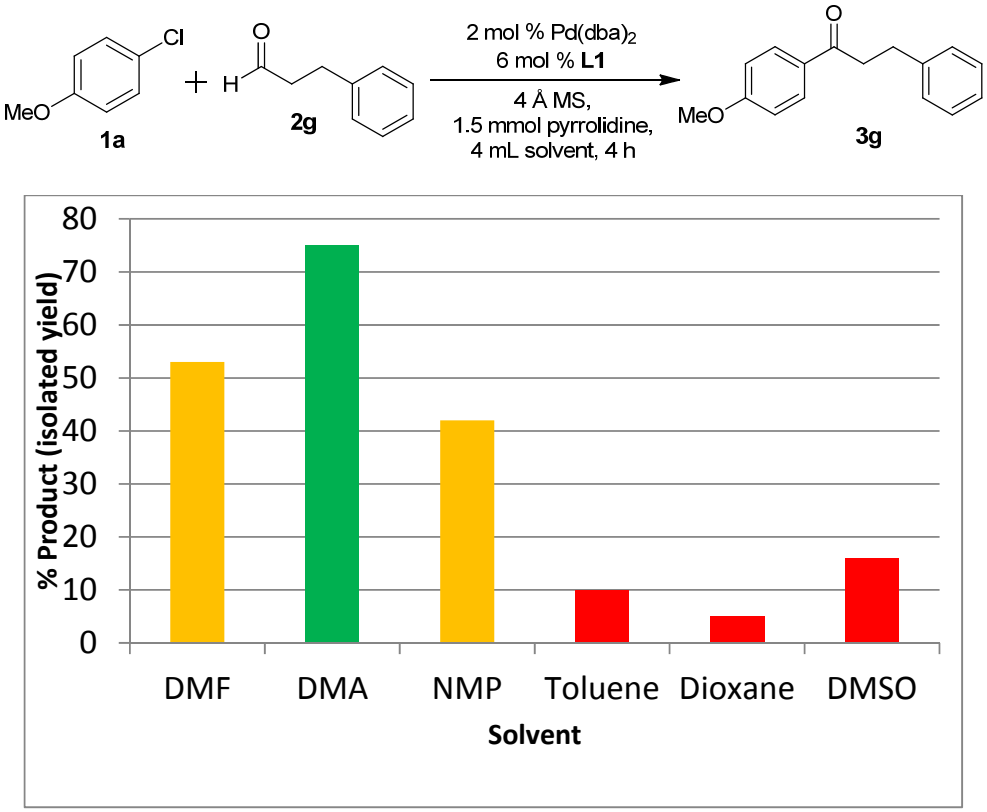


| entry | ligand | solvent | temp ($^{o}$C) | yield (%)[b] |
|---|---|---|---|---|
| 1 | - | DMF | 115 | 0 |
| 2 | dppp[c] | DMF | 115 | 0 |
| 3 | dppm[c] | DMF | 115 | 0 |
| 4 | dppe[c] | DMF | 115 | 0 |
| 5 | **L9** | DMF | 115 | 0 |
| 6 | **L10**[c] | DMF | 115 | 0 |
| 7 | **L11** | DMF | 115 | 0 |
| 8 | $PCy_3$ | DMF | 115 | 0 |
| 9 | $PPh_3$ | DMF | 115 | 0 |
| 10 | **L1** | DMF | 115 | 19 |
| 11 | **L1** | DMF | 140 | 53 |
| 12 | **L2** | DMF | 140 | 50 |
| 13 | **L3** | DMF | 140 | 8 |
| 14 | **L4** | DMF | 140 | 0 |
| 15 | **L5** | DMF | 140 | <5 |
| 16 | **L6** | DMF | 140 | <5 |
| 17 | Q-Phos | DMF | 140 | 24 |
| 18 | P(*t*-Bu)$_3$·HBF$_4$[d] | DMF | 140 | 18 |
| 19 | dppf[c] | DMF | 140 | 0 |
| 20 | Binap[c] | DMF | 140 | 0 |
| 21 | 4-OMe-dppp[e] | DMF | 140 | 0 |
| 22 | 4-$CF_3$-dppp[f] | DMF | 140 | 0 |
| 23 | **L7**[c] | DMF | 140 | 0 |
| 24 | **L8**[c] | DMF | 140 | 0 |

| | | | | |
|---|---|---|---|---|
| 25 | **L12**[d,g] | DMF | 140 | 0 |
| 26 | **L13**[d,g] | DMF | 140 | 0 |
| 27[h] | **Pd118** | DMF | 140 | 13 |
| 28 | **L1** | DMA | 140 | 75 |
| 29 | **L1** | NMP | 140 | 42 |
| 30 | **L1** | Toluene | 140 | 10 |
| 31 | **L1** | Dioxane | 140 | <5 |
| 32 | **L1** | DMSO | 140 | 16 |

[a] All the reactions were carried out with **1a** (1.0 mmol), **2g** (2.0 mmol), pyrrolidine (1.5 mmol), $Pd(dba)_2$ (2 mol %), ligand (6 mol %), and 4 Å MS (1 g) in 4 mL solvent. [b] Isolated yields of ketone; zero indicates no or trace **3g** in the crude $^1H$ NMR spectrum. [c] 3 mol % of ligand was used. [d] 3 mol % *t*-BuOK was added. [e] $(4\text{-}OMePh)_2PCH_2CH_2CH_2P(4\text{-}OMePh)_2$. [f] $(4\text{-}CF_3Ph)_2PCH_2CH_2CH_2P(4\text{-}CF_3Ph)_2$. [g] 2 mol % of ligand was used. [h] 2 mol % **Pd118** was used as palladium source.

Changing the solvent from DMF to DMA (entry 28) further enhanced the acylation rate with Pd-**L1**, resulting in a 75% isolated yield of the desired ketone **3g**. The choice of solvent proved to be a significant parameter, as shown in Scheme 2.7 below.



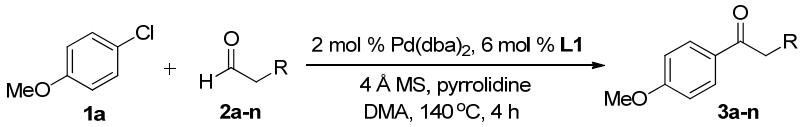

**Scheme 2.7**: Importance of solvent choice for acylation reaction

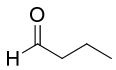
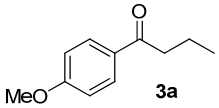
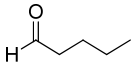
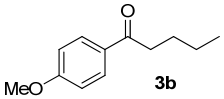
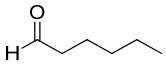
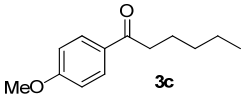
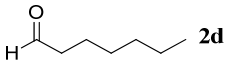
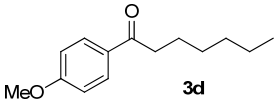
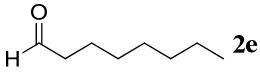
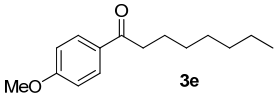
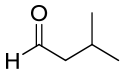
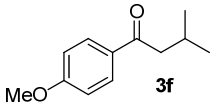
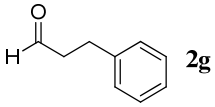
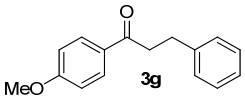
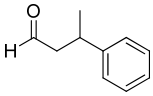
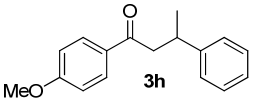
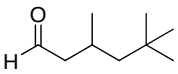
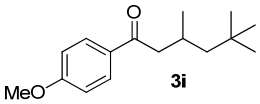
It was found that two equivalents of the aldehyde component were required in order to achieve full conversion of **1a**. This is due to the competing pathway of aldol condensation, as well as the limited stability of the aldehyde under the reaction conditions. Further increase in the amount of aldehyde used did not increase the product yield. As in the case of ArBr,[11] the presence of the pyrrolidine and 4 Å MS was critical; no desired reaction occurred in the absence of either additive.

### 2.2.2 Substrate scope

With the optimised conditions in hand, we then tested the acylation of **1a** with various aldehydes **2a-n**. As can be seen in Table 2, the reactions afforded moderate to good yields of ketones **3** when subjected to the Pd-**L1** catalysis in the presence of pyrrolidine and 4 Å MS. As in the case of ArBr, the reaction proved to be tolerant of functionalities on the aldehyde component (entries 10-13). The substrate scope was limited, however, to aldehydes without substitution on the $\alpha$ carbon, although $\beta$ substitution did not pose a problem (e.g. entries 8 and 9). Thus, acylation of **1a** with 2-methylhexanal under the optimised conditions failed to yield any of the desired ketone (entry 15).

**Table 2.** Acylation of **1a** with aldehydes **2a-n**[a]




| entry | aldehyde | product | yield (%)[b] |
|---|---|---|---|
| 1 |  2a |  3a | 60 |
| 2 |  2b |  3b | 68 |
| 3 |  2c |  3c | 67 |
| 4 |  2d |  3d | 74 |
| 5 |  2e |  3e | 61 |
| 6 |  2f |  3f | 55 |
| 7 |  2g |  3g | 75 |
| 8 |  2h |  3h | 78 |
| 9 |  2i |  3i | 73 |

| | | | |
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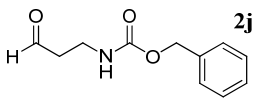
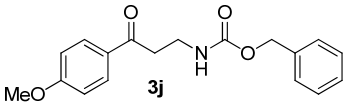
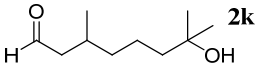
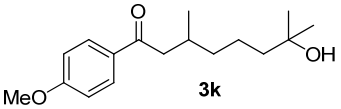
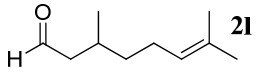
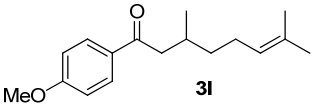
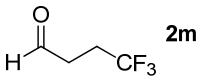
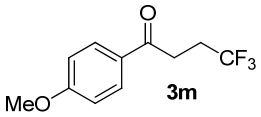
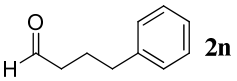
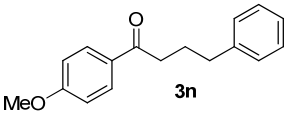
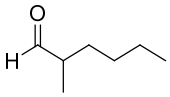
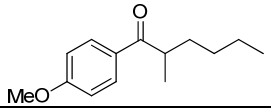
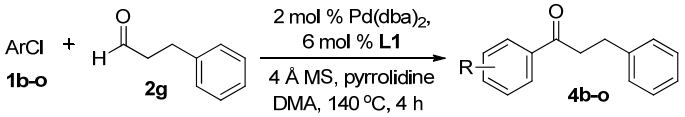
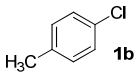
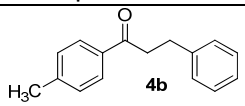
| 10 |  **2j** |  **3j** | 74[c] |
| 11 |  **2k** |  **3k** | 72[c] |
| 12 |  **2l** |  **3l** | 40 |
| 13 |  **2m** |  **3m** | 54 |
| 14 |  **2n** |  **3n** | 60 |
| 15 |  |  | 0 |

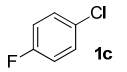
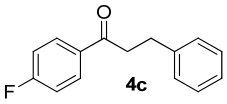
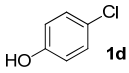
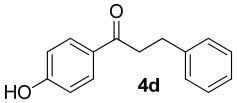
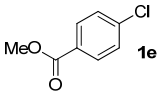
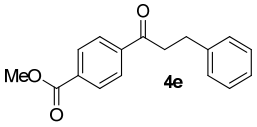
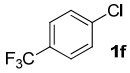
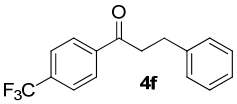
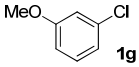
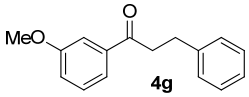
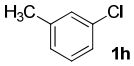
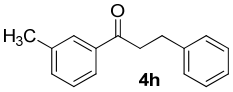
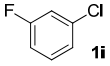
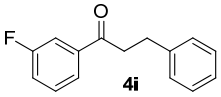
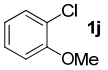
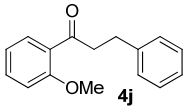
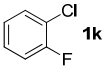
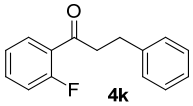
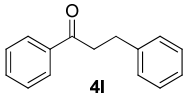
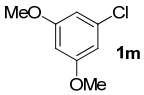
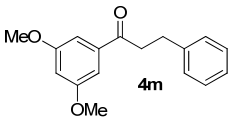
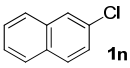
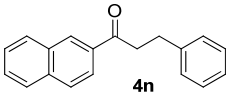
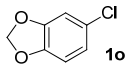
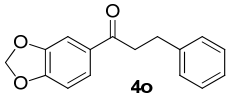
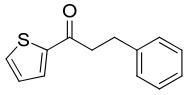
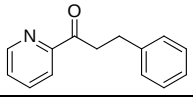
[a] Reactions were carried out with **1a** (1.0 mmol), **2a-n** (2.0 mmol), pyrrolidine (1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (2 mol %), and **L1** (6 mol %) in 4 ml DMA at 140 °C for 4 h. [b] Isolated yields. [c] 4 mol % $Pd(dba)_2$ and 12 mol % **L1** were used.

We next extended the acylation to a series of aryl chlorides **1b-o** coupling with the aldehyde **2g**. As summarized in Table 3, the reaction afforded moderate to good yields of ketones **4**, particularly when electron-rich aryl chlorides were used. However, as previously found for ArBr,[11] the presence of *ortho* (entries 9 and 10) or electron-withdrawing substituents (entries 4 and 5) on the aryl ring resulted in lower yields. It should be noted that the moderate success of the electron-deficient substrates **1e** and **1f** is a significant improvement, as the equivalent ArBr were completely inactive under the previously reported Pd-dppp catalysis.[11] Unfortunately, acylation of heterocyclic chlorides, such as 2-chlorothiophene and 2-chloropyridine, did not occur under the same conditions (entries 15 and 16).

**Table 3.** Acylation of aryl chlorides **1b-o** with **2g**[a]



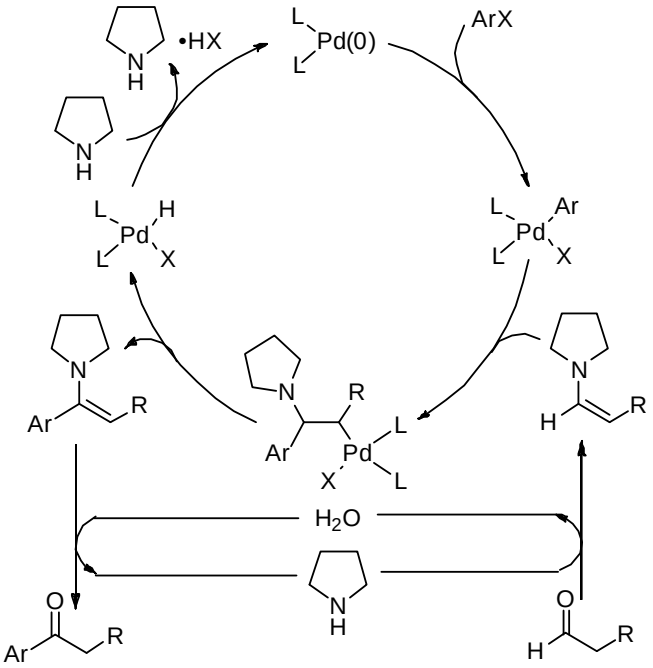

| entry | ArCl | product | yield (%)[b] |
|---|---|---|---|
| 1 |  **1b** |  **4b** | 64 |

| | | | |
|---|---|---|---|
| 2 |  **1c** |  **4c** | 61 |
| 3 |  **1d** |  **4d** | 50[c] |
| 4 |  **1e** |  **4e** | 44 |
| 5 |  **1f** |  **4f** | 43 |
| 6 |  **1g** |  **4g** | 73 |
| 7 |  **1h** |  **4h** | 61 |
| 8 |  **1i** |  **4i** | 55 |
| 9 |  **1j** |  **4j** | 39 |
| 10 |  **1k** |  **4k** | 37 |
| 11 |  **1l** |  **4l** | 73 |
| 12 |  **1m** |  **4m** | 50 |
| 13 |  **1n** |  **4n** | 74 |
| 14 |  **1o** |  **4o** | 59 |
| 15 |  |  | 0 |
| 16 |  |  | 0 |

[a] The conditions were the same as in Table 2. No **4a**, which would be the same as **3g**. [b] Isolated yields. [c] 4 mol % $Pd(dba)_2$ and 12 mol % **L1** was used.

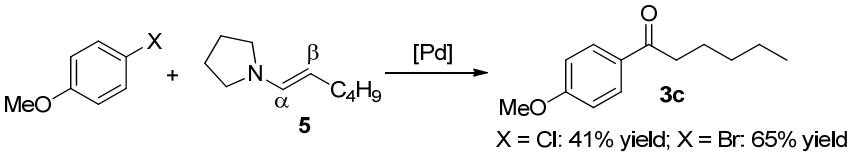
**- 2.2.3 Mechanistic investigations**

We previously suggested that the acylation may take place via a Heck-type pathway. A possible catalytic cycle is depicted in Scheme 2.8 below.



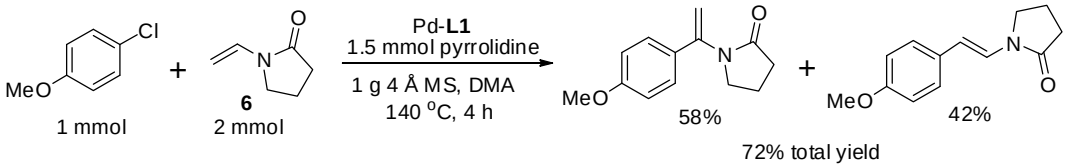

**Scheme 2.8**: proposed mechanism for acylation reaction

Pyrrolidine plays two roles in the reaction: one is to form an enamine in a catalytic fashion and the other is to neutralize the acid HX. The *in situ* formation of the enamine from the aldehyde is a key element of the catalytic cycle. If instead pyrrolidine deprotonated the aldehyde, $\alpha$ arylation might result.[14] To determine if the enamine is involved in the acylation, we carried out a reaction starting from a preformed enamine **5**. Under the conditions established (Table 2), the ketone **3c** was indeed formed (Scheme 2.9), thus supporting the intermediacy of enamine. A higher yield was obtained when using bromoanisole under the previously developed conditions.[11] As with the acylation of ArBr, the coupling of ArCl with aldehydes becomes catalytic in pyrrolidine in the presence of an additional base. Thus, the ketone **3g** could be obtained by reacting **1a** with **2g** using 20 mol % pyrrolidine and 1 equiv KF under otherwise identical conditions to those above (Table 2); this resulted in a 51% isolated yield of **3g**.[15]




**Scheme 2.9**: arylation of preformed enamine **5**

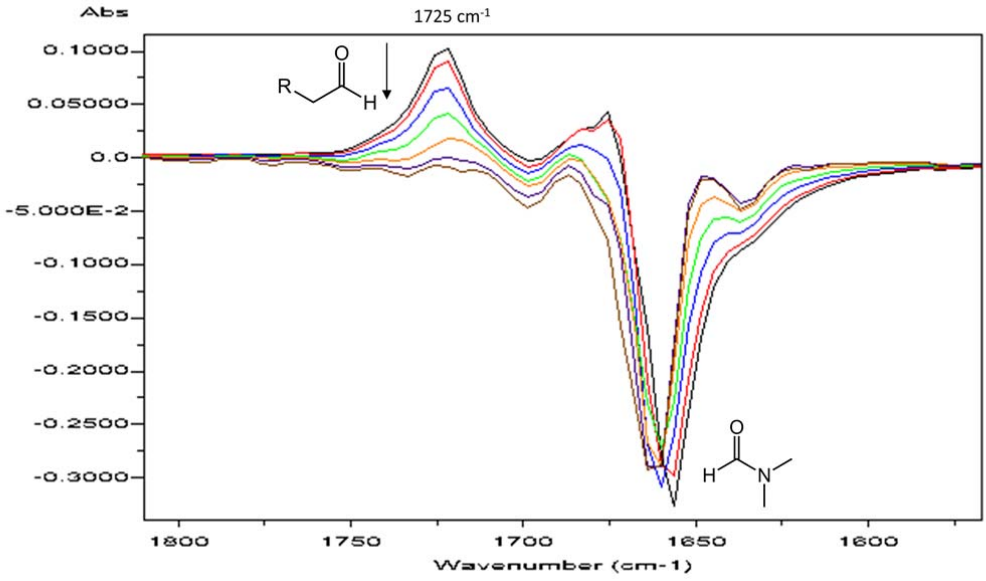
The pyrrolidinyl moiety of the enamine is critical for the desired acylation. It polarises the C=C double bond, which facilitates the β carbon coordination to Pd(II) and the migration of the aryl group to the α carbon, thereby furnishing the α arylated product.[16] In line with this view, the arylation of **6** led to a mixture of α and β arylated enamides (Scheme 2.10). The formation of these relatively stable regioisomers is most likely a result of the electron-withdrawing effect of the carbonyl group, which renders the C=C double bond less polarised. When using a bidentate ligand under ionising conditions, however, the α product can be exclusively obtained from **6**.[17]




**Scheme 2.10**: Arylation of enamide **6**

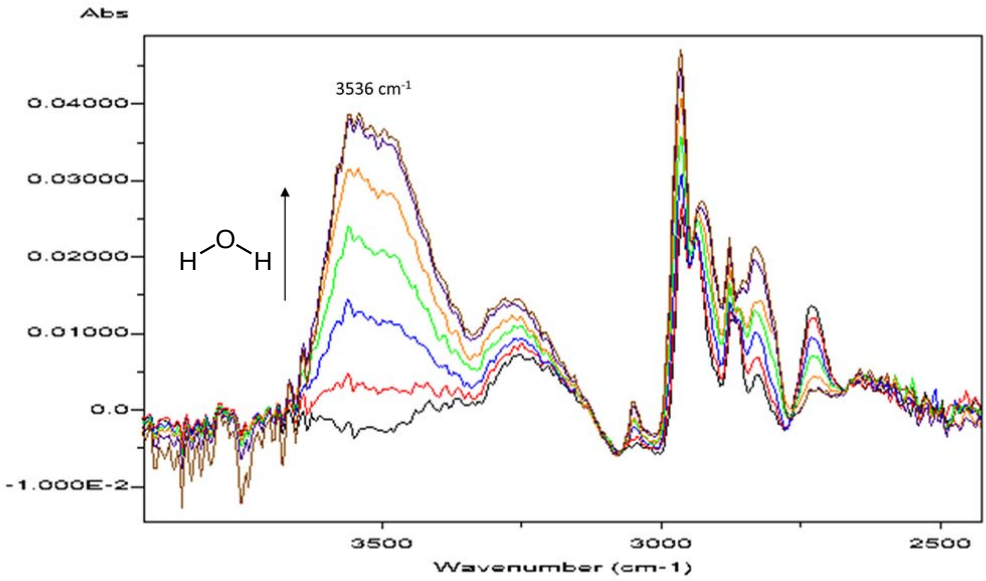
Eager to gain as much insight into the reaction as possible, we next carried out some *in situ* IR spectroscopy experiments. This allowed us to investigate the position of equilibrium between the aldehyde and enamine at the reaction temperature, as well as the effect of the molecular sieves, if any, on this equilibrium. In addition, we can analyse the stability of the enamine at the reaction temperature over time.

When a DMF solution of hexanal was stirred at room temperature, an absorption peak at 1725 $cm^{-1}$ was observed in the IR spectrum, corresponding to the C=O stretch of the aldehyde (Scheme 2.11).



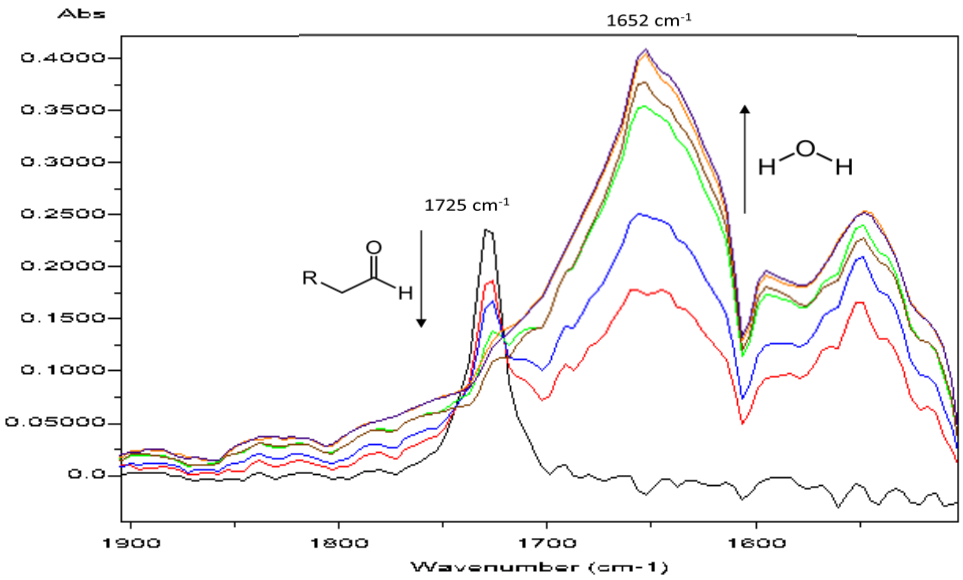

**Scheme 2.11**: Effect of pyrrolidine addition on aldehyde C=O stretch

Unfortunately, auto-correction of the solvent peak led to a large negative absorbance at 1660 $cm^{-1}$ which would pose problematic to the analysis of other important peaks. Therefore, it was decided to repeat the experiment in toluene. A mixture of hexanal was stirred in toluene at room temperature and the C=O stretch was again observed, with the solvent peaks now coming at different wavelengths that would not affect future peaks of interest to the experiment. Next, pyrrolidine was slowly added to the mixture and as the addition proceeded, the C=O stretch disappeared and new peaks emerged. A broad absorbance at 3536 $cm^{-1}$ was a result of the water released by the condensation of the aldehyde and amine (Scheme 2.12).



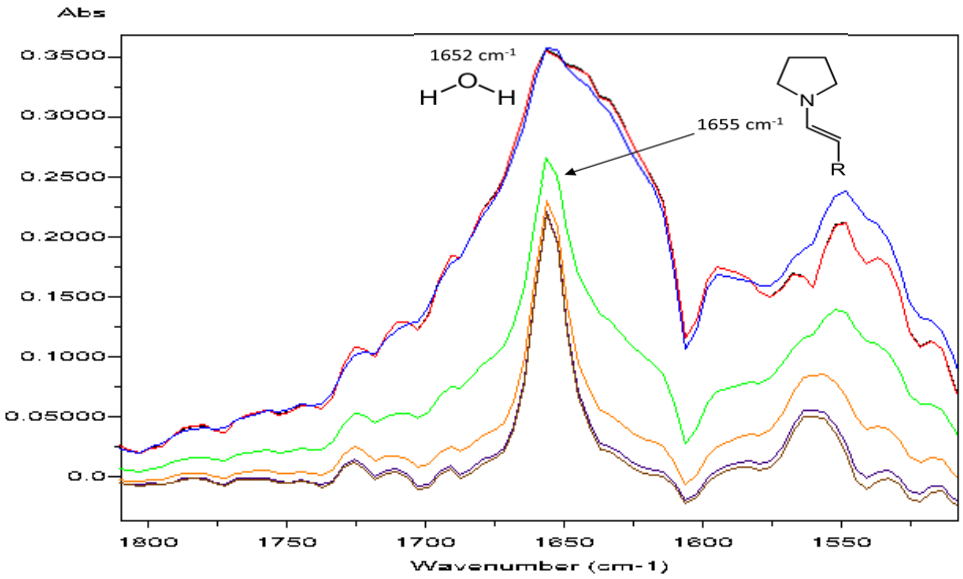

**Scheme 2.12**: Water released from condensation reaction

We next searched for an absorbance peak referring to the C=C double bond of the enamine, which was reported to appear at 1655 $cm^{-1}$.[18] A peak at 1652 $cm^{-1}$ was observed (Scheme 2.13) but it appeared to be unusually broad for a C=C double bond absorbance. To our surprise, this peak corresponded to a H-O-H bending mode corresponding to the water released by the condensation reaction.[19] This particular absorbance peak of water is often overlooked.



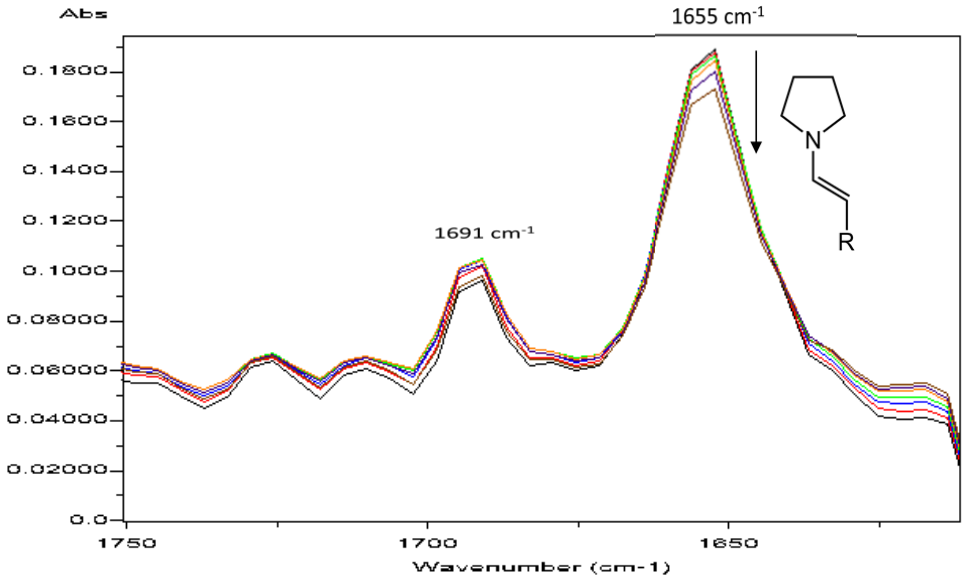

**Scheme 2.13**: Enamine C=C stretch hidden by H-O-H bending mode

If we were to observe the enamine C=C stretch, we would need to absorb the water released by the condensation. At this point, the molecular sieves were added and the peaks at 3536 $cm^{-1}$ and 1652 $cm^{-1}$ quickly disappeared. This shows that the molecular sieves can efficiently absorb the water released from the condensation reaction. To our delight, as the water was absorbed and the corresponding peaks were removed, a sharp peak at 1655 $cm^{-1}$ was revealed, thus providing direct evidence for the presence of enamine (Scheme 2.14). It was found that 4 g of activated 4 Å MS were required to absorb 28 mmol of water.



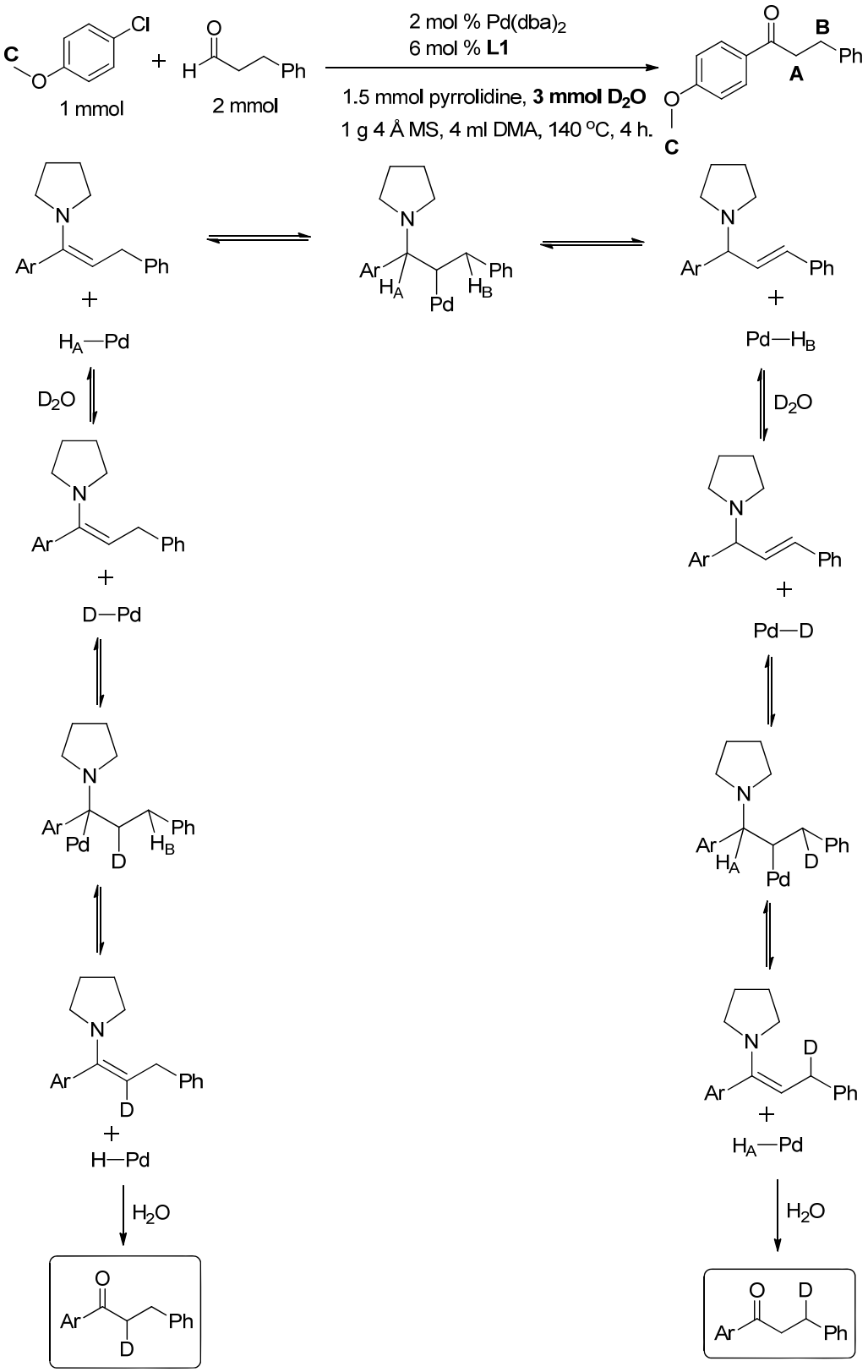

**Scheme 2.14**: Water absorbed by addition of molecular sieves

At this point, we had shown that the position of equilibrium between aldehyde and enamine lies heavily to the right at room temperature, as well as the fact that the water released is efficiently absorbed by the molecular sieves. We next wanted to investigate the stability of the enamine at the reaction temperature. Therefore, the solution was heated to 110 °C and held for 90 mins. Scheme 2.15 shows that the enamine was slowly decomposing at the elevated temperature, but had sufficient stability to be a viable reaction intermediate. This is especially true if one considers that the aldehyde is used in excess for the acylation reaction.



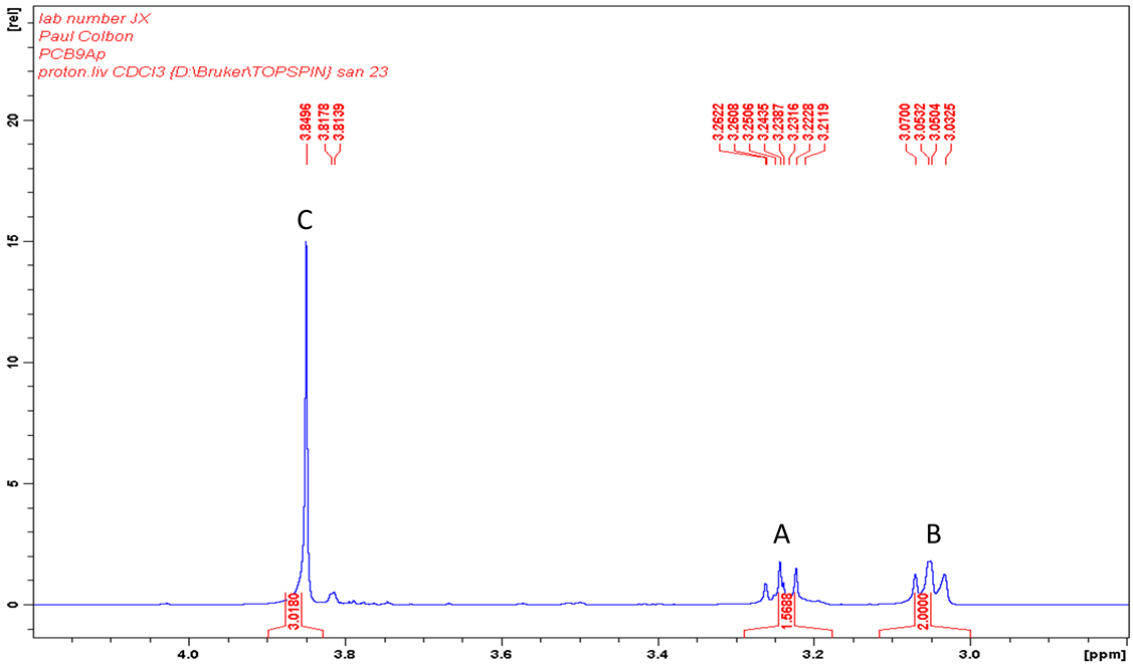

**Scheme 2.15**: Enamine held at 110°C for 90 minutes

During the publication of this research work, it was suggested by a referee that deuteration experiments may shed some more light onto the reaction mechanism. It is possible that β-hydride elimination may occur at either $C_A$ or $C_B$ (Scheme 2.16). If β-hydride elimination does occur at $C_B$ and the reaction was carried out in the presence of $D_2O$, deuterium exchange with the Pd-H species (followed by insertion of Pd-D) would lead to deuterium incorporation at $C_B$.




**Scheme 2.16**: Deuteration experiment to probe the possible pathways of β-hydride elimination

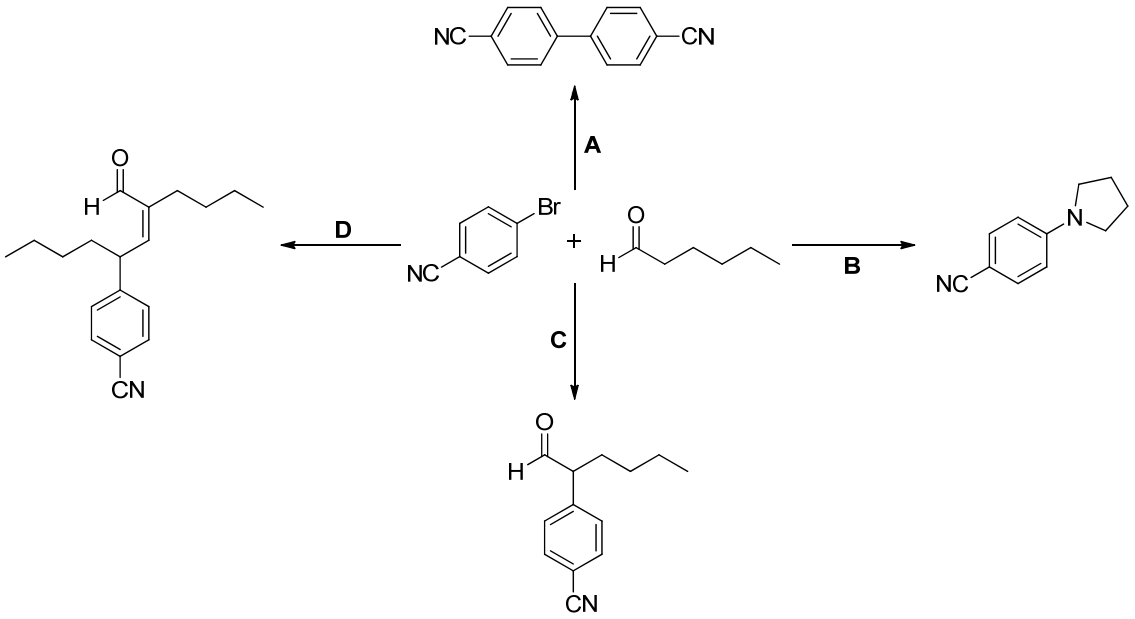
$^{1}$H NMR analysis of the isolated ketone product showed no deuteration at $C_B$ but only at $C_A$ (Scheme 2.17).[20] This suggests that β-hydride elimination preferentially occurs with $H_A$ over $H_B$, which is likely to be more acidic due to the high electronegativity of the pyrrolidinyl nitrogen.




**Scheme 2.17**: $^{1}$H NMR with integrals to show deuterium incorporation

### 2.2.4 Notable observations

During optimisation of the acylation reaction (Table 1), we attempted to account for the loss of yield by isolating any impurities visible by TLC. For the reaction of 4-bromobenzonitrile and hexanal catalysed by palladium and pyrrolidine (Scheme 2.18), the following impurities were isolated and tentatively assigned based upon $^{1}H$ and $^{13}C$ NMR analysis:

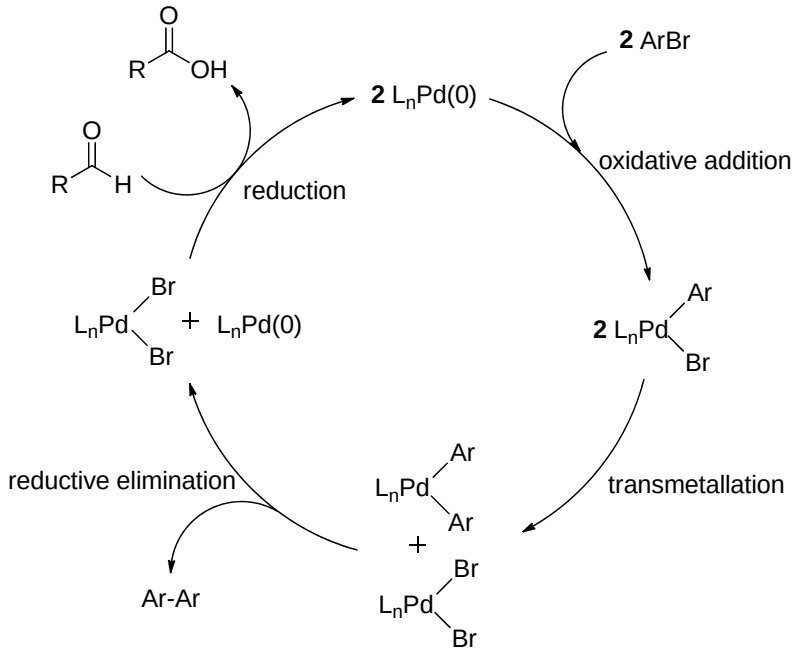



**Scheme 2.18**: Side products isolated during optimisation of the acylation reaction

The rate of the acylation reaction of electron-deficient aryl halides is slower than that of electron-rich ArX. As a result, alternative reaction pathways catalysed by palladium can outcompete the desired acylation, thus proving to be highly detrimental to the reaction yield.

**A** - Homocoupling

Palladium catalysed homocoupling of aryl halides is a well known process.[21] However, it was somewhat surprising to observe this impurity as the reaction requires a reductant in order to be catalytic with respect to palladium. One possibility is that in the presence of water released by the condensation reaction, the excess aldehyde may be oxidised to the corresponding carboxylic acid, thereby reducing Pd(II) back to Pd(0) and completing the catalytic cycle (Scheme 2.19).

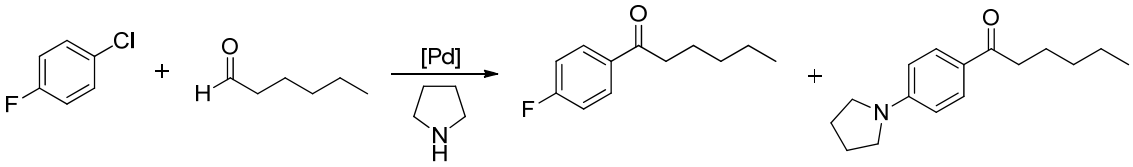



**Scheme 2.19**: Proposed mechanism for homocoupling of ArBr

**B** - C-N coupling

Due to the research of Buchwald and Hartwig,[22] the Pd catalysed amination of aryl halides is a well known and efficient process. Therefore, it was not very surprising to observe the aryl amine impurity. On the contrary, we are always surprised that the acylation reaction is able to dominate over the C-N coupling. From our *in-situ* IR studies we have attributed this to the fact that the amine/enamine equilibrium lies heavily to the right and so there is only ever a very small concentration of the free amine available to undergo C-N coupling.

An unexpected cascade reaction occurred when subjecting 1-chloro-4-fluorobenzene to the acylation reaction with hexanal (Scheme 2.20), with amination of the C-F bond occurring after acylation of the C-Cl bond. The presence of the electron-withdrawing ketone group activates the C-F bond towards the $S_NAr$ reaction with pyrrolidine.[23]




**Scheme 2.20**: $S_NAr$ substitution reaction of electron-deficient Ar-F with pyrrolidine

**C** - α-Arylation

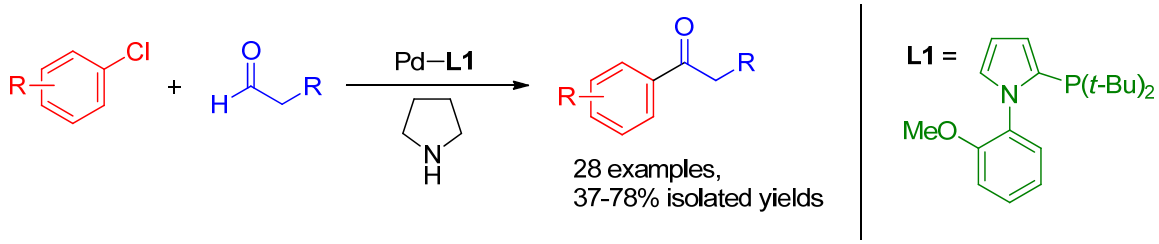
α-Arylation of the aldehyde was an unexpected side reaction. Although the α-Arylation of ketones has been known for some time,[24] it is only in recent years that this catalytic transformation has been reported for aldehyde substrates.[14] It is thought to proceed via formation of an enolate intermediate which reacts with the Ar-Pd-X intermediate formed by oxidative addition of Pd(0) into the C-X bond. During the acylation reaction, small amounts of enolate formation might be possible as pyrrolidine may deprotonate the aldehyde at the elevated reaction temperature.

**D** - γ arylation

The acylation reaction requires an excess of the aldehyde due to the competing pathway of aldol condensation, which is catalysed by pyrrolidine. Unexpectedly, a small amount of the α,β-unsaturated aldehyde produced by aldol condensation underwent selective γ-arylation. This reaction was also observed by Buchwald when developing the α-arylation of aldehydes[14a] and has previously been reported in the literature.[25]

## 2.3 Conclusions and future work

The direct acylation of a wide range of aryl chlorides with aliphatic aldehydes has been successfully developed (Scheme 2.21). The choice of ligand was critical, with a bulky, electron-rich monophosphine ligand **L1** proving to be the most effective. The solvent is also a critical reaction parameter, with the polar aprotic solvent DMA effecting the most efficient catalysis. The reaction proceeded smoothly when employing electron-rich ArCl with *meta* and/or *para* substitution. Unfortunately, ArCl that are electron-deficient or have *ortho* substitution were problematic substrates. In terms of the aldehyde component, various functional groups can be incorporated along the alkyl chain, but α-substitution was completely inhibitive towards the acylation reaction.




**Scheme 2.21**: Summary of the direct acylation of aryl chlorides

We had previously proposed that the reaction proceeds via a Heck-type arylation of an enamine intermediate formed by the condensation of the aldehyde with pyrrolidine. The information obtained by additional experiments and *in situ* IR spectroscopy was supportive of this mechanistic pathway.

The development of the acylation chemistry from ArBr to ArCl is of industrial significance, as many ArCl are cheaper and more widely available than their bromo or iodo counterparts. Future investigations may focus on the development of a catalyst system capable of efficient acylation at a lower reaction temperature, as well as the reaction of strongly electron-deficient aryl chlorides.

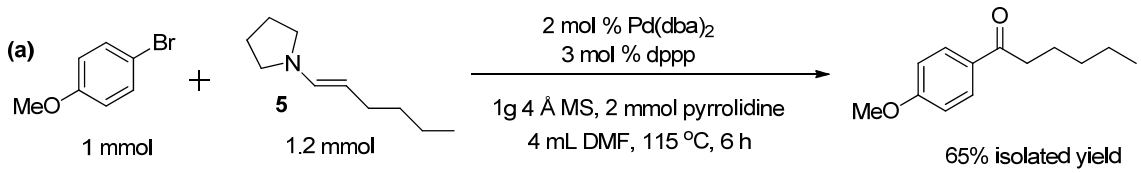
## 2.4 Experimental

**Materials:** All the reactions were carried out under a nitrogen atmosphere with dried solvents. Silica gel plates (GF254) were used for TLC monitoring and silica gel (230-400 mesh) was used for flash column chromatography. The following chemicals were purchased from Aldrich, Lancaster, or Strem, and used as received: all the aryl chlorides, aldehydes, phosphine ligands, $Pd(dba)_2$, 1-vinyl-2-pyrrolidinone and pyrrolidine. The 4 Å molecular sieves (4 Å MS) were purchased from Aldrich, and were activated by drying in oven at 100 °C for more than 24 h before use. Aldehyde **2n** was synthesised by known procedure.[26] The $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker DRX-400 spectrometer with TMS as the internal standard, and infrared spectra on a JASCO FT/IR-4100 spectrometer. The mass spectra were obtained by electrospray ionization (EI).

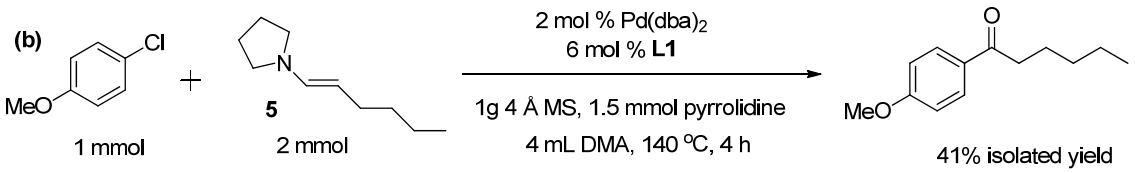
**General procedure for the acylation:** An oven-dried carousel reaction tube containing a stirrer bar was charged with an aryl chloride (**1a**-**o**) (1.0 mmol), $Pd(dba)_2$ (0.02 mmol), **L1** (0.06 mmol), and 4 Å MS (1 g). After degassing three times with nitrogen, *N*,*N*-dimethylacetamide (DMA) (4 mL), an aldehyde (**2a**-**n**) (2.0 mmol), and pyrrolidine (1.5 mmol) were injected sequentially. The reaction mixture was stirred at 140 °C for 4 h. After cooling down to room temperature, 15 mL EtOAc was added and the mixture was washed with $H_2O$ (3 x 5 mL) to remove the DMA, dried over $Na_2SO_4$, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel using a mixture of ethyl acetate and hexane (1/99 to 30/70) as eluant. The desired ketone products **3a**-**n** and **4b-o** were obtained in 37-78% yields (Tables 2 and 3).

**Preparation of enamine 5:** A 100 mL round bottomed flask containing a magnetic stirrer bar was placed into an ice bath and charged with $K_2CO_3$ (0.15 mol) and pyrrolidine (0.3 mol). Hexanal (0.15 mol) was added dropwise to the stirring mixture, after which the ice bath was removed and the reaction mixture left to stir at room temperature overnight. The reaction mixture was diluted with toluene, filtered and then concentrated *in vacuo*. The filtrate was then subjected to vacuum distillation to give exclusively the *trans* enamine product as judged by $^{1}H$ NMR (68% isolated yield).

**Acylation reactions with preformed enamine 5**




The general procedure for the acylation was employed, using 4-bromoanisole (0.13 mL, 1 mmol), **5** (184 mg, 1.2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (3% EtOAc/hexane) yielded 134 mg (65%) of the product shown.

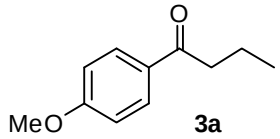



The general procedure for the acylation was employed, using 4-chloroanisole (0.12 mL, 1 mmol), **5** (307 mg, 2.0 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (3% EtOAc/hexane) yielded 85 mg (41%) of the product shown.

**Acylation employing a catalytic amount of pyrrolidine:** An oven-dried carousel reaction tube containing a stirrer bar was charged with 4-chloroanisole (0.12 mL, 1.0 mmol), KF (58.1 mg, 1 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and 4 Å MS (1 g). After degassing three times with nitrogen, *N*,*N*-dimethylacetamide (DMA) (4 mL), hydrocinnamaldehyde (0.26 mL, 2.0 mmol), and pyrrolidine (0.02 mL, 0.20 mmol) were injected sequentially. The reaction mixture was stirred at 140 °C for 4 h. After cooling down to room temperature, 15 mL EtOAc was added and the mixture was washed with $H_2O$ (3 x 5 mL) to remove the DMA, dried over $Na_2SO_4$, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel using a mixture of ethyl acetate and hexane (3/97) as eluant. The desired ketone product **3g** was obtained in 51% yield.

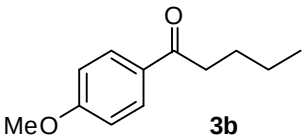
**2.5 Analytical data**

*All analytical data is in agreement with that previously reported in the literature, which is referenced accordingly.*



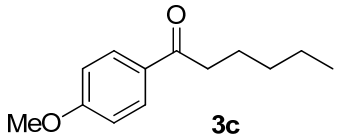

**3a**

**1-(4-Methoxyphenyl)propan-1-one (3a).**[28] The general procedure for the acylation was employed, using 4-chloroanisole (0.12 mL, 1 mmol), 1-butanal (0.18 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (1% EtOAc/hexane) yielded 107 mg (60%) of the title compound as a pale yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H), 2.90 (t, *J* = 7.4 Hz, 2H), 1.81-1.71 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.5, 163.7, 130.7, 130.6, 114.1, 55.9, 40.6, 18.4, 14.4; Anal. calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.28; H, 7.91; HRMS for $C_{11}H_{14}NaO_2$ $[M + Na]^+$: m/z Calcd: 201.0886; Found: 201.0888; IR (neat, $cm^{-1}$): 1676 (s).



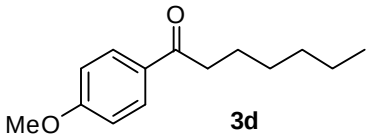

**3b**

**1-(4-Methoxyphenyl)pentan-1-one (3b).**[28] The general procedure for the acylation was employed, using 4-chloroanisole (0.12 mL, 1 mmol), 1-pentanal (0.21 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (1% EtOAc/hexane) yielded 131 mg (68%) of the title compound as a colourless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.87 (s, 3H), 2.91(t, *J* = 7.5 Hz, 2H), 1.75-1.67 (m, 2H), 1.45-1.36 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.7, 163.7, 130.7, 130.6, 114.1, 55.9, 38.4, 27.2, 23.0, 14.4; Anal. calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.63; H, 8.35; HRMS for $C_{12}H_{17}O_2$ $[M + H]^+$: m/z Calcd: 193.1223; Found: 193.1221; IR (neat, $cm^{-1}$): 1676 (s).



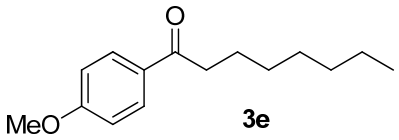

**3c**

**1-(4-Methoxyphenyl)hexan-1-one (3c).**[28] The general procedure for the acylation was employed, using 4-chloroanisole (0.12 mL, 1 mmol), 1-hexanal (0.24 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (1% EtOAc/hexane) yielded 138 mg (67%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.87 (s, 3H), 2.91(t, *J* = 7.5 Hz, 2H), 1.76-1.71 (m, 2H), 1.38-1.34 (m, 4H), 0.93-0.89 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.7, 163.7, 130.7, 130.6, 114.1, 55.8, 38.7, 32.0, 24.7, 23.0, 14.4; Anal. calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.17; H, 8.79; HRMS for $C_{13}H_{19}O_2$ $[M + H]^+$: m/z Calcd: 207.1380; Found: 207.1381; IR (neat, $cm^{-1}$): 1670 (s). Melting point: 35-37 °C.



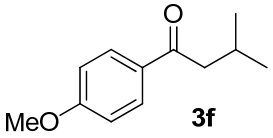

**3d**

**1-(4-Methoxyphenyl)heptan-1-one (3d).**[28] The general procedure for the acylation was employed, using 4-chloroanisole (0.12 mL, 1 mmol), 1-heptanal (0.28 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (1% EtOAc/hexane) yielded 163 mg (74%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz), 3.87 (s, 3H), 2.91 (t, *J* = 7.4 Hz, 2H), 1.72 (m, 2H), 1.41-1.29 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.7, 163.7, 130.7, 130.6, 114.1, 55.9, 38.7, 32.1, 29.5, 25.0, 23.0, 14.5; Anal. calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.30; H, 9.21; HRMS for $C_{14}H_{21}O_2$ $[M + H]^+$: m/z Calcd: 221.1536; Found: 221.1533; IR (neat, $cm^{-1}$): 1670 (s). Melting point: 39-41 °C.



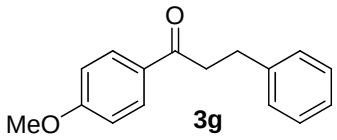

**3e**

**1-(4-Methoxyphenyl)octan-1-one (3e).**[28] The general procedure for the acylation was employed, using 4-chloroanisole (0.12 mL, 1 mmol), 1-octanal (0.31 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (1% EtOAc/hexane) yielded 143 mg (61%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H), 2.91 (t, *J* = 7.4 Hz, 2H), 1.76-1.68 (m, 2H), 1.37-1.27 (m, 8H), 0.88 (t, *J* = 6.7 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.7, 163.7, 130.7, 130.6, 114.1, 55.9, 38.7, 32.1, 29.8, 29.6, 25.1, 23.0, 14.5; Anal. calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.44; H, 9.59; HRMS for $C_{15}H_{22}NaO_2$ $[M + Na]^+$: m/z Calcd: 257.1512; Found: 257.1513; IR (neat, $cm^{-1}$): 1668 (s). Melting point: 45-48 °C.



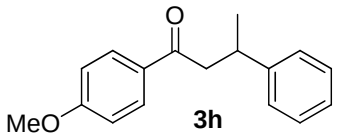

**3f**

**1-(4-Methoxyphenyl)-3-methylbutan-1-one (3f).**[28] The general procedure for the acylation was employed, using 4-chloroanisole (0.12 mL, 1 mmol), 3-methylbutanal (0.22 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (1% EtOAc/hexane) yielded 106 mg (55%) of the title compound as a pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.87 (s, 3H), 2.78 (d, *J* = 6.9 Hz, 2H), 2.33-2.23 (m, 1H), 0.99 (d, *J* = 6.7 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.3, 163.7, 130.9, 130.8, 114.1, 55.9, 47.6, 25.8, 23.2; Anal. calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.73; H, 8.37; HRMS for $C_{12}H_{16}NaO_2$ $[M + Na]^+$: m/z Calcd: 215.1043; Found: 215.1046; IR (neat, $cm^{-1}$): 1674 (s).



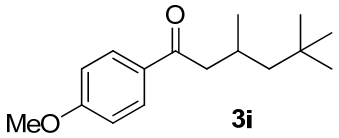

**3g**

**1-(4-Methoxyphenyl)-3-phenylpropan-1-one (3g).**[28] The general procedure for the acylation was employed, using 4-chloroanisole (0.12 mL, 1 mmol), hydrocinnamaldehyde (0.26 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (2% EtOAc/hexane) yielded 180 mg (75%) of the title compound as a pale yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.8 Hz, 2H), 7.31-7.18 (m, 5H), 6.92 (d, *J* = 8.9 Hz, 2H), 3.85 (s, 3H), 3.25 (t, *J* = 7.7 Hz, 2H), 3.05 (t, *J* = 7.7 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 198.2, 163.9, 141.9, 130.7, 130.4, 128.9, 128.9, 126.5, 114.1, 55.9, 40.5, 30.7; Anal. calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.70; H, 6.69; HRMS for $C_{16}H_{16}NaO_2$ [M + Na]$^+$: m/z Calcd: 263.1043; Found: 263.1038; IR (neat, cm$^{-1}$): 1670 (s). Melting point: 88-91 °C.



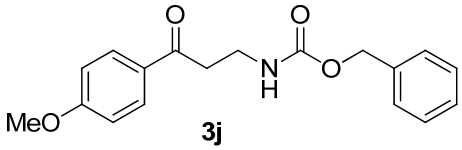

**3h**

**1-(4-Methoxyphenyl)-3-phenylbutan-1-one (3h).**[29] The general procedure for the acylation was employed, using 4-chloroanisole (0.12 mL, 1 mmol), 3-phenylbutyraldehyde (0.30 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (2% EtOAc/hexane) yielded 198 mg (78%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.9 Hz, 2H), 7.32-7.26 (m, 4H), 7.21-7.17 (m, 1H), 6.91 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H), 3.53-3.45 (m, 1H), 3.24 (dd, *J* = 16.2, 5.7 Hz, 1H), 3.13 (dd, *J* = 16.2, 8.4 Hz, 1H), 1.33 (d, *J* = 7.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 198.1, 163.8, 147.1, 130.8, 130.7, 128.9, 127.3, 126.6, 114.1, 55.9, 47.1, 36.2, 22.3; Anal. calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.06; H, 7.13; HRMS for $C_{17}H_{18}NaO_2$ [M + Na]$^+$: m/z Calcd: 277.1199; Found: 277.1201; IR (neat, cm$^{-1}$): 1668 (s). Melting point: 86-88 °C.



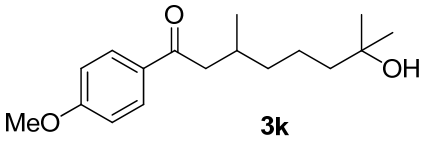

**3i**

**1-(4-Methoxyphenyl)-3,5,5-trimethylhexan-1-one (3i).** The general procedure for the acylation was employed, using 4-chloroanisole (0.12 mL, 1 mmol), 3,5,5-trimethylhexanal (0.35 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (1% EtOAc/hexane) yielded 181 mg (73%) of the title compound as a colourless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.87 (s, 3H), 2.86 (dd, *J* = 15.5, 5.7 Hz, 1H), 2.79-2.73 (dd, *J* = 15.5, 8.1 Hz, 1H), 2.29-2.20 (m, 1H), 1.32 (dd, *J* = 14.0, 3.9 Hz, 1H), 1.17 (dd, *J* = 14.0, 6.5 Hz, 1H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.3, 163.7, 131.0, 130.8, 114.1, 55.9, 51.5, 48.3, 31.6, 30.4, 27.1, 23.4; Anal. calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.36; H, 9.74; HRMS for $C_{16}H_{24}NaO_2$ $[M + Na]^+$: m/z Calcd: 271.1669; Found: 271.1673; IR (neat, $cm^{-1}$): 1676 (s).



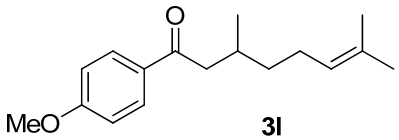

**3j**

**Benzyl (3-(4-methoxyphenyl)-3-oxopropyl)carbamate (3j).**[28] The general procedure for the acylation was employed, using 4-chloroanisole (0.12 mL, 1 mmol), 3-[(Benzyloxycarbonyl)amino]propionaldehyde (0.41 g, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (23.0 mg, 0.04 mmol), **L1** (38.1 mg, 0.12 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (15% EtOAc/hexane) yielded 232 mg (74%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.8 Hz, 2H), 7.37-7.29 (m, 5H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.42 (br, 1H), 5.08 (s, 2H), 3.86 (s, 3H), 3.63-3.58 (m, 2H), 3.17 (t, *J* = 5.6 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) 198.0, 164.2, 156.8, 137.0, 130.7, 130.1, 128.9, 128.5, 128.4, 114.2, 67.0, 55.9, 38.5, 36.5; Anal. calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.94; H, 6.13; N, 4.73; HRMS for $C_{18}H_{19}NNaO_4$ $[M + Na]^+$: m/z Calcd: 336.1206; Found: 336.1208; IR (neat, $cm^{-1}$): 3352 (m), 1716 (s), 1651 (m). Melting point: 65-66 °C.



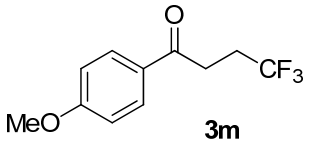

**3k**

**7-Hydroxy-1-(4-methoxyphenyl)-3,7-dimethyloctan-1-one (3k).**[30] The general procedure for the acylation was employed, using 4-chloroanisole (0.12 mL, 1 mmol), hydroxycitronellal (0.37 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (23.0 mg, 0.04 mmol), **L1** (38.1 mg, 0.12 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (10% EtOAc/hexane) yielded 200 mg (72%) of the title compound as a colourless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H), 2.89 (dd, *J* = 15.5, 5.9 Hz, 1H), 2.72 (dd, *J* = 15.5, 7.9 Hz, 1H), 2.21-2.13 (m, 1H), 1.47-1.34 (m, 6H), 1.21 (s, 6H), 0.96 (d, *J* = 6.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.4, 163.7, 130.9, 130.8, 114.1, 71.3, 55.8, 46.0, 44.3, 38.0, 30.4, 29.7, 29.6, 22.1, 20.4; Anal. calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.44; H, 9.48; HRMS for $C_{17}H_{26}NaO_3$ $[M + Na]^+$: m/z Calcd: 301.1774; Found: 301.1780; IR (neat, $cm^{-1}$): 3442 (br, m), 1670 (m).



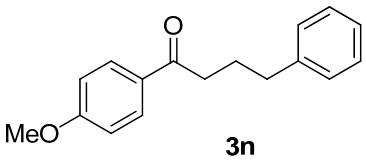

**3l**

**1-(4-Methoxyphenyl)-3,7-dimethyloct-6-en-1-one (3l).**[30] The general procedure for the acylation was employed, using 4-chloroanisole (0.12 mL, 1 mmol), (±)-citronellal (0.36 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (2% EtOAc/hexane) yielded 104 mg (40%) of the title compound as a colourless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 5.12-5.08 (m, 1H), 3.87 (s, 3H), 2.91 (dd, *J* = 15.4, 5.5 Hz, 1H), 2.69 (dd, *J* = 15.4, 8.1 Hz, 1H), 2.20-1.94 (m, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.46-1.23 (m, 2H), 0.95 (d, *J* = 6.7 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.4, 163.7, 131.8, 131.0, 130.8, 124.9, 114.0, 55.8, 46.0, 37.7, 30.2, 26.1, 26.0, 20.3, 18.1; Anal. calcd for $C_{17}H_{24}O_2$: C, 74.13; H, 7.92. Found: C, 74.28; H, 7.91; Anal. calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.93; H, 9.39; HRMS for $C_{17}H_{24}NaO_2$ $[M + Na]^+$: m/z Calcd: 283.1669; Found: 283.1661; IR (neat, $cm^{-1}$): 1676 (s).



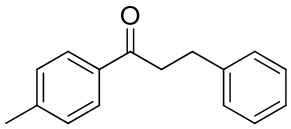

**3m**

**4,4,4-Trifluoro-1-(4-methoxyphenyl)butan-1-one (3m).** The general procedure for the acylation was employed, using 4-chloroanisole (0.12 mL, 1 mmol), 4,4,4-trifluorobutanal (232 mg, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (2% EtOAc/hexane) yielded 125 mg (54%) of the title compound as a pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 3.88 (s, 3H), 3.21 (t, *J* = 7.8 Hz, 2H), 2.64-2.52 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 195.2, 164.3, 130.7, 129.6, 127.7 (q, $J_{CF}$ = 275.0 Hz), 114.3, 55.9, 31.2 (q, $J_{CF}$ = 2.5 Hz), 28.8 (q, $J_{CF}$ = 29.6 Hz). HRMS for $C_{11}H_{11}F_3NaO_2$ $[M + Na]^+$: m/z Calcd: 255.0603; Found: 255.0613 IR (neat, $cm^{-1}$): 1676 (s).



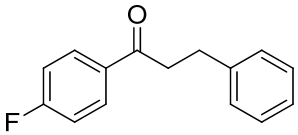

**3n**

**1-(4-Methoxyphenyl)-4-phenylbutan-1-one (3n).**[31] The general procedure for the acylation was employed, using 4-chloroanisole (0.12 mL, 1 mmol), (254 mg, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (2% EtOAc/hexane) yielded 153 mg (60%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.9 Hz, 2H), 7.31-7.19 (m, 5H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 2.93 (t, *J* = 7.3 Hz, 2H), 2.71 (t, *J* = 7.6 Hz, 2H), 2.11-2.03 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.1, 163.8, 142.2, 130.7, 130.5, 128.9, 128.8, 126.3, 114.1, 55.9, 37.8, 35.7, 26.3; Anal. calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.08; H, 7.13; HRMS for $C_{17}H_{18}NaO_2$ $[M + Na]^+$: m/z Calcd: 277.1199; Found: 277.1203; IR (neat, $cm^{-1}$): 1674 (s). Melting point: 53-55 °C.



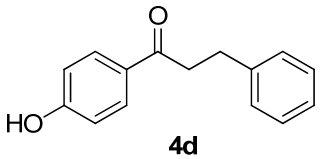
**4b**

**3-Phenyl-1-(p-tolyl)propan-1-one (4b).**[32] The general procedure for the acylation was employed, using 4-chlorotoluene (0.12 mL, 1 mmol), hydrocinnamaldehyde (0.26 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (2% EtOAc/hexane) yielded 144 mg (64%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.32-7.20 (m, 7H), 3.27 (t, *J* = 7.7 Hz, 2H), 3.05 (t, *J* = 7.7 Hz, 2H), 2.40 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.3, 144.3, 141.8, 134.8, 129.7, 128.9, 128.9, 128.6, 126.5, 40.8, 30.6, 22.1; Anal. calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.63; H, 7.22; HRMS for $C_{16}H_{17}O$ $[M + H]^+$: m/z Calcd: 225.1274; Found: 225.1275; IR (neat, $cm^{-1}$): 1674 (s). Melting point: 68-70 °C.



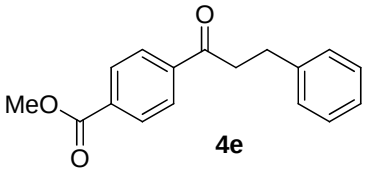
**4c**

**1-(4-Fluorophenyl)-3-phenylpropan-1-one (4c).**[28] The general procedure for the acylation was employed, using 1-chloro-4-fluorobenzene (0.11 mL, 1 mmol), hydrocinnamaldehyde (0.26 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (2% EtOAc/hexane) yielded 139 mg (61%) of the title compound as a pale yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.99-7.96 (m, 2H), 7.32-7.28 (m, 5H), 7.13-7.09 (m, 2H), 3.27 (t, *J* = 7.6 Hz, 2H), 3.06 (t, *J* = 7.7 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 198.0, 166.1 (d, $J_{CF}$ = 254.7 Hz), 141.6, 133.7 (d, $J_{CF}$ = 3.0 Hz), 131.8 (d, $J_{CF}$ = 9.3 Hz), 129.0, 128.9, 126.6, 116.2 (d, $J_{CF}$ = 21.4 Hz), 40.8, 30.5; Anal. calcd for $C_{15}H_{13}FO$: C, 78.93; H, 5.74. Found: C, 79.15; H, 5.75; HRMS for $C_{15}H_{13}FNaO$ $[M + Na]^+$: m/z Calcd: 251.0843; Found: 251.0847; IR (neat, $cm^{-1}$): 1680 (s). Melting point: 37-40 °C.



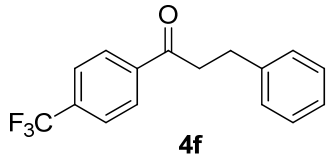
**4d**

**1-(4-Hydroxyphenyl)-3-phenylpropan-1-one (4d).**[33] The general procedure for the acylation was employed, using 4-chlorophenol (0.10 mL, 1 mmol), hydrocinnamaldehyde (0.26 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (23.0 mg, 0.04 mmol), **L1** (38.1 mg, 0.12 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (10% EtOAc/hexane) yielded 113 mg (50%) of the title compound as a pale orange solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.8 Hz, 2H), 7.31-7.19 (m, 5H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.28 (br, 1H), 3.26 (t, *J* = 7.8 Hz, 2H), 3.05 (t, *J* = 7.7 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.0, 160.8, 141.7, 131.2, 130.2, 128.9, 128.8, 126.6, 115.8, 40.6, 30.8; Anal. calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.47; H, 6.57; HRMS for $C_{15}H_{14}NaO_2$ $[M + Na]^+$: m/z Calcd: 249.0886; Found: 249.0881; IR (neat, $cm^{-1}$): 1655 (s). Melting point: 85-88 °C.



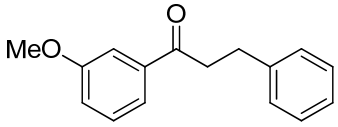
**4e**

**Methyl 4-(3-phenylpropanoyl)benzoate (4e).**[34] The general procedure for the acylation was employed, using methyl 4-chlorobenzoate (171 mg, 1 mmol), hydrocinnamaldehyde (0.26 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (10% EtOAc/hexane) yielded 118 mg (44%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.6 Hz, 2H), 7.99 (d, *J* = 8.6 Hz, 2H), 7.32-7.19 (m, 5H), 3.94 (s, 3H), 3.32 (t, *J* = 7.6 Hz, 2H), 3.07 (t, *J* = 7.6 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.1, 166.6, 141.4, 140.4, 134.3, 130.3, 129.0, 128.8, 128.4, 126.7, 52.9, 41.2, 30.4; Anal. calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.05; H, 6.07; HRMS for $C_{17}H_{16}NaO_3$ $[M + Na]^+$: m/z Calcd: 291.0992; Found: 291.0990; IR (neat, $cm^{-1}$): 1722 (s), 1674 (m). Melting point: 84-87 °C.



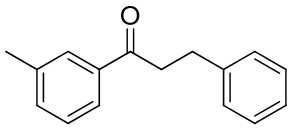
**4f**

**3-Phenyl-1-(4-(trifluoromethyl)phenyl)propan-1-one (4f).**[35] The general procedure for the acylation was employed, using 4-chlorobenzotrifluoride (0.13 mL, 1 mmol), hydrocinnamaldehyde (0.26 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (5% EtOAc/hexane) yielded 120 mg (43%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.2 Hz, 2H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.32-7.21 (m, 5H), 3.32 (t, *J* = 7.6 Hz, 2H), 3.08 (t, *J* = 7.6 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ ; 198.6, 141.3, 139.9, 134.8 (q, $J_{CF}$ = 32.7 Hz), 129.0, 128.8, 128.8, 126.7, 126.1 (q, $J_{CF}$ = 3.7 Hz), 124.0 (q, $J_{CF}$ = 274.2 Hz), 41.2, 30.3; Anal. calcd for $C_{16}H_{13}F_3O$: C, 69.06; H, 4.71. Found: C, 69.42; H, 4.95; HRMS for $C_{16}H_{13}F_3NaO$ $[M + Na]^+$: m/z Calcd: 301.0811; Found: 301.0821; IR (neat, $cm^{-1}$): 1685 (m). Melting point: 46-48 °C.



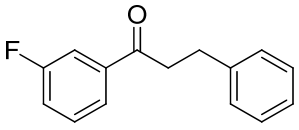
**4g**

**1-(3-Methoxyphenyl)-3-phenylpropan-1-one (4g).**[36] The general procedure for the acylation was employed, using 3-chloroanisole (0.12 mL, 1 mmol), hydrocinnamaldehyde (0.26 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (3% EtOAc/hexane) yielded 175 mg (73%) of the title compound as a colourless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.6 Hz, 1H), 7.48 (s, 1H), 7.36-7.18 (m, 6H), 7.10-7.08 (m, 1H), 3.83 (s, 3H), 3.28 (t, *J* = 7.6 Hz, 2H), 3.06 (t, *J* = 7.7 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.5, 160.3, 141.7, 138.6, 130.0, 129.0, 128.9, 126.6, 121.1, 120.0, 112.6, 55.9, 41.0, 30.6; Anal. calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.71; H, 6.71; HRMS for $C_{16}H_{16}NaO_2$ $[M + Na]^+$: m/z Calcd: 263.1043; Found: 263.1046; IR (neat, $cm^{-1}$): 1684 (s).



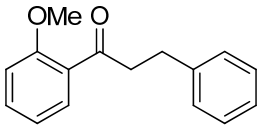
**4h**

**3-Phenyl-1-(m-tolyl)propan-1-one (4h).**[32] The general procedure for the acylation was employed, using 3-chlorotoluene (0.12 mL, 1 mmol), hydrocinnamaldehyde (0.26 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (2% EtOAc/hexane) yielded 137 mg (61%) of the title compound as a colourless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.77-7.74 (m, 2H), 7.37-7.19 (m, 7H), 3.29 (t, *J* = 7.7 Hz, 2H), 3.06 (t, *J* = 7.7 Hz, 2H), 2.40 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.9, 141.8, 138.8, 137.3, 134.3, 129.0, 128.9, 128.9, 128.9, 126.5, 125.7, 41.0, 30.6, 21.8; HRMS for $C_{16}H_{16}NaO$ $[M + Na]^+$: m/z Calcd: 247.1093; Found: 247.1100; IR (neat, $cm^{-1}$): 1684 (s).



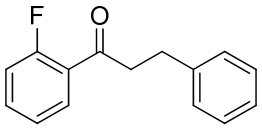
**4i**

**1-(3-Fluorophenyl)-3-phenylpropan-1-one (4i).**[37] The general procedure for the acylation was employed, using 1-chloro-3-fluorobenzene (0.11 mL, 1 mmol), hydrocinnamaldehyde (0.26 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (2% EtOAc/hexane) yielded 126 mg (55%) of the title compound as a pale yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.7 Hz, 1H), 7.65-7.61 (m, 1H), 7.45-7.39 (m, 2H), 7.32-7.19 (m, 5H), 3.28 (t, *J* = 7.6 Hz, 2H), 3.06 (t, *J* = 7.6 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 198.3 (d, $J_{CF}$ = 2.0 Hz), 163.3 (d, $J_{CF}$ = 248.0 Hz), 141.4, 139.3 (d, $J_{CF}$ = 6.1 Hz), 130.7 (d, $J_{CF}$ = 7.7 Hz), 129.0, 128.9, 126.7, 124.2 (d, $J_{CF}$ = 3.0 Hz), 120.5 (d, $J_{CF}$ = 21.5 Hz), 115.2 (d, $J_{CF}$ = 22.2 Hz), 41.0, 30.4; Anal. calcd for $C_{15}H_{13}FO$: C, 78.93; H, 5.74. Found: C, 79.43; H, 5.87; HRMS for $C_{15}H_{17}FNO$ $[M + NH_4]^+$: m/z Calcd: 246.1289; Found: 246.1287; IR (neat, $cm^{-1}$): 1689 (s). Melting point: 42-44 °C.



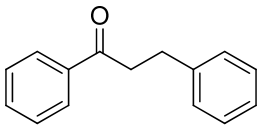

**4j**

**1-(2-Methoxyphenyl)-3-phenylpropan-1-one (4j).**[38] The general procedure for the acylation was employed, using 2-chloroanisole (0.13 mL, 1 mmol), hydrocinnamaldehyde (0.26 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (3% EtOAc/hexane) yielded 94 mg (39%) of the title compound as a colourless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.7 Hz, 1H), 7.47-7.43 (m, 1H), 7.31-7.17 (m, 5H), 7.01-6.94 (m, 2H), 3.87 (s, 3H), 3.30 (t, *J* = 7.8 Hz, 2H), 3.02 (t, *J* = 7.8 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 202.1, 159.0, 142.1, 133.9, 130.8, 128.9, 128.8, 128.7, 126.3, 121.1, 111.9, 55.9, 45.9, 30.9; Anal. calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.17; H, 6.74; HRMS for $C_{16}H_{16}NaO_2$ $[M + Na]^+$: m/z Calcd: 263.1043; Found: 263.1049; IR (neat, $cm^{-1}$): 1672 (s).



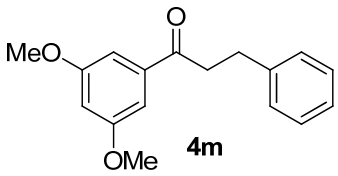

**4k**

**1-(2-Fluorophenyl)-3-phenylpropan-1-one (4k).** The general procedure for the acylation was employed, using 1-chloro-2-fluorobenzene (0.11 mL, 1 mmol), hydrocinnamaldehyde (0.26 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (2% EtOAc/hexane) yielded 84 mg (37%) of the title compound as a pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.89-7.85 (m, 1H), 7.53-7.48 (m, 2H), 7.31-7.09 (m, 6H), 3.34-3.29 (m, 2H), 3.05 (t, *J* = 7.6 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 198.0 (d, $J_{CF}$ = 4.1 Hz), 162.4 (d, $J_{CF}$ = 254.4 Hz), 141.6, 134.9 (d, $J_{CF}$ = 9.1 Hz), 131.1 (d, $J_{CF}$ = 2.6 Hz), 129.4, 128.9, 126.5, 126.0 (d, $J_{CF}$ = 12.9 Hz), 124.9 (d, $J_{CF}$ = 3.4 Hz), 117.1 (d, $J_{CF}$ = 23.8 Hz), 45.7 (d, $J_{CF}$ = 7.4 Hz), 30.4 (d, $J_{CF}$ = 1.9 Hz); HRMS for $C_{15}H_{13}FNaO$ $[M + Na]^+$: m/z Calcd: 251.0843; Found: 251.0851; IR (neat, $cm^{-1}$): 1685 (s).



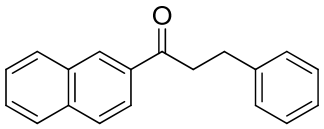
**4l**

**1,3-Diphenylpropan-1-one (4l).**[39] The general procedure for the acylation was employed, using chlorobenzene (0.10 mL, 1 mmol), hydrocinnamaldehyde (0.26 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (2% EtOAc/hexane) yielded 154 mg (73%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.96-7.94 (m, 2H), 7.56-7.52 (m, 1H), 7.46-7.42 (m, 2H), 7.32-7.18 (m, 5H), 3.30 (t, *J* = 7.7 Hz, 2H), 3.06 (t, *J* = 7.7 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.6, 141.7, 137.2, 133.5, 129.0, 129.0, 128.9, 128.5, 126.6, 40.9, 30.5; HRMS for $C_{15}H_{15}O$ $[M + H]^+$: m/z Calcd: 211.1117; Found: 211.1120; IR (neat, $cm^{-1}$): 1682 (s). Melting point: 64-68 °C.



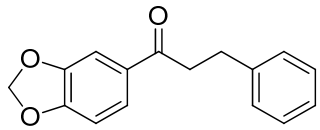
**4m**

**1-(3,5-Dimethoxyphenyl)-3-phenylpropan-1-one (4m).** The general procedure for the acylation was employed, using 5-chloro-1,3-dimethoxybenzene (173 mg, 1 mmol), hydrocinnamaldehyde (0.26 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (5% EtOAc/hexane) yielded 135 mg (50%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.31-7.18 (m, 5H), 7.08 (s, 2H), 6.63 (s, 1H), 3.80 (s, 6H), 3.25 (t, *J* = 7.7 Hz, 2H), 3.04 (t, *J* = 7.7 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.3, 161.3, 141.7, 139.2, 129.0, 128.9, 126.6, 106.2, 105.8, 56.0, 41.0, 30.6; Anal. calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.41; H, 6.71; HRMS for $C_{17}H_{18}NaO_3$ $[M + Na]^+$: m/z Calcd: 293.1148; Found: 293.1156; IR (neat, $cm^{-1}$): 1680 (s). Melting point: 84-87 °C.



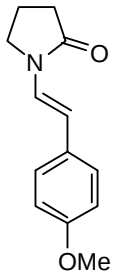
**4n**

**1-(Naphthalen-2-yl)-3-phenylpropan-1-one (4n).**[40] The general procedure for the acylation was employed, using 2-chloronapthalene (163 mg, 1 mmol), hydrocinnamaldehyde (0.26 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (3% EtOAc/hexane) yielded 193 mg (74%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.84-7.80 (m, 2H), 7.56-7.47 (m, 2H), 7.32-7.26 (m, 4H), 7.22-7.18 (m, 1H), 3.38 (t, *J* = 7.7 Hz, 2H), 3.10 (t, *J* = 7.7 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.5, 141.8, 136.0, 134.6, 133.0, 130.2, 130.0, 129.0, 129.0, 128.9, 128.2, 127.2, 126.6, 124.3, 41.0, 30.7; Anal. calcd for $C_{19}H_{16}O$: C, 87.66; H, 6.19. Found: C, 87.23; H, 6.20; HRMS for $C_{19}H_{16}NaO$ $[M + Na]^+$: m/z Calcd: 283.1093; Found: 283.1095; IR (neat, $cm^{-1}$): 1678 (s). Melting point: 90-94 °C.

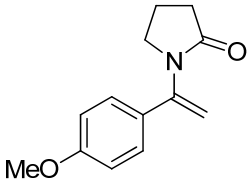


**4o**

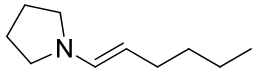
**1-(Benzo[d][1,3]dioxol-5-yl)-3-phenylpropan-1-one (4o).**[41] The general procedure for the acylation was employed, using 5-chloro-1,3-benzodioxole (0.12 mL, 1 mmol), hydrocinnamaldehyde (0.26 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (5% EtOAc/hexane) yielded 150 mg (59%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.2 Hz, 1H), 7.43 (s, 1H), 7.31-7.18 (m, 5H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.02 (s, 2H), 3.21 (t, *J* = 7.6 Hz, 2H), 3.04 (t, *J* = 7.7 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.7, 152.1, 148.6, 141.8, 132.1, 128.9, 128.8, 126.5, 124.7, 108.3, 102.3, 40.6, 30.8; Anal. calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.76; H, 5.58; HRMS for $C_{16}H_{14}NaO_3$ $[M + Na]^+$: m/z Calcd: 277.0835; Found: 277.0838; IR (neat, $cm^{-1}$): 1662 (s). Melting point: 60-64 °C.




**(E)-1-(4-Methoxystyryl)pyrrolidin-2-one.** The general procedure for the acylation was employed, using 4-chloroanisole (0.12 mL, 1 mmol), 1-vinyl-2-pyrrolidinone (0.21 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (15% EtOAc/hexane) yielded 65 mg (30%) of the title compound as a pale orange solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 14.9 Hz, 1H), 7.29 (d, *J* = 8.7Hz, 2H), 6.84 (*J* = 8.8 Hz, 2H), 5.85 (d, *J* = 14.8Hz, 1H), 3.80 (s, 3H), 3.64 (t, *J* = 7.2 Hz, 2H), 2.54 (t, *J* = 8.1 Hz, 2H), 2.19-2.11 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.6, 158.9, 129.4, 127.2, 122.5, 114.6, 111.9, 55.7, 45.7, 31.7, 17.9, 3.4; HRMS for $C_{13}H_{15}NO_2$ $[M + H]^+$: m/z Calcd: 218.1176; Found: 218.1173; IR (neat, $cm^{-1}$): 1685 (s), 1643 (m). Melting point: 113-116 °C.




**1-(1-(4-Methoxyphenyl)vinyl)pyrrolidin-2-one.**[42] The general procedure for the acylation was employed, using 4-chloroanisole (0.12 mL, 1 mmol), 1-vinyl-2-pyrrolidinone (0.21 mL, 2 mmol), pyrrolidine (0.13 mL, 1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L1** (19.0 mg, 0.06 mmol), and DMA (4 mL). After 4 h at 140 °C, workup and column chromatography (15% EtOAc/hexane) yielded 91 mg (42%) of the title compound as a colourless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.32 (s, 1H), 5.18 (s, 1H), 3.81 (s, 3H), 3.54 (t, *J* = 7.0 Hz, 2H), 2.55 (t, *J* = 8.0 Hz, 2H), 2.14-2.07 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 175.0, 160.3, 143.5, 129.0, 128.0, 114.2, 108.4, 55.7, 50.1, 32.4, 19.0; HRMS for $C_{13}H_{15}NO_2$ $[M + Na]^+$: m/z Calcd: 240.0995; Found: 240.0999; IR (neat, $cm^{-1}$): 1691 (s), 1670 (s).




**5**

**(E)-1-(Hex-1-en-1-yl)pyrrolidine.** $^1$H NMR (400 MHz, $CDCl_3$) δ 6.17 (d, *J* = 13.7 Hz, 1H), 4.13 (m, 1H), 2.97-2.94 (m, 4H), 1.99-1.94 (m, 2H), 1.86-1.81 (m, 4H), 1.34-1.29 (m, 4H), 0.91-0.86 (m, 3H).

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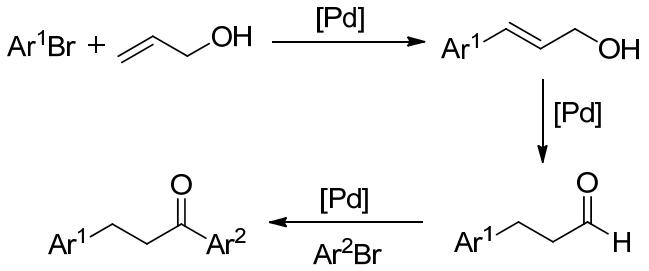
# Chapter 3

## Double Arylation of Aryl Alcohol via a

## One-Pot Heck Arylation-Isomerisation-Acylation Cascade

### 3.1 Introduction

During the acylation reaction of aryl chlorides (Chapter 2), aldehyde **2n** was synthesised by a palladium catalysed Heck arylation-isomerisation reaction of iodobenzene with 3-buten-1-ol.[1,2] We therefore proposed that it might be possible to develop a single palladium catalyst that is capable of generating aldehydes from aryl halides and allylic/homoallylic alcohols, and in the same reaction vessel, catalyses the acylation of a second aryl halide (Scheme 3.1). This would broaden the scope of the acylation reaction beyond commercially available aldehydes, while circumventing the need for intermittent isolation and purification. When employing allyl alcohol, the products of this one-pot reaction would be substituted dihydrochalcones (DHCs),[3] which have been reported to demonstrate antioxidant properties[4] and have received considerable attention as food sweeteners.[5]

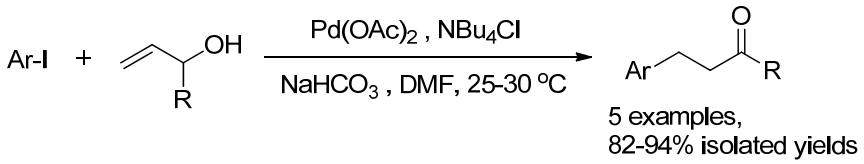



**Scheme 3.1**: Proposed one-pot pathway to DHC's

The acylation reaction necessitates a set of specific conditions (Chapter 2). We reasoned that, if the Heck arylation-isomerisation sequence could be catalysed under conditions suitable for the acylation, the one-pot process should be feasible.

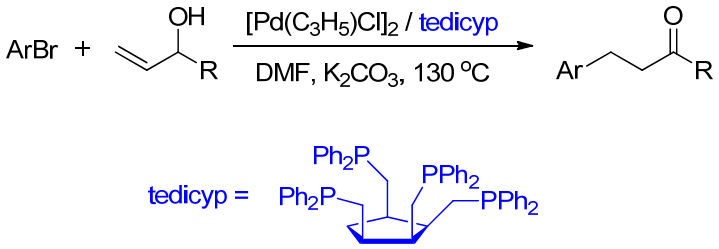
### 3.1.1 Background to Heck arylation-isomerisation reaction of allylic/homoallylic alcohols

For aryl iodides, the Heck arylation-isomerisation reaction of allylic/homoallylic alcohols is most commonly catalysed by $Pd(OAc)_2$ in the presence of tetraalkylammonium salts.[6] Often referred to as Jeffrey's conditions, such systems are particularly selective towards formation of the carbonyl product due to the high levels of isomerisation generally observed, but are generally inefficient when employing aryl bromides. For example, in Jeffrey's original report in 1984, aryl iodides were reacted with allylic alcohols at or near room temperature to yield the corresponding carbonyl products (Scheme 3.2).



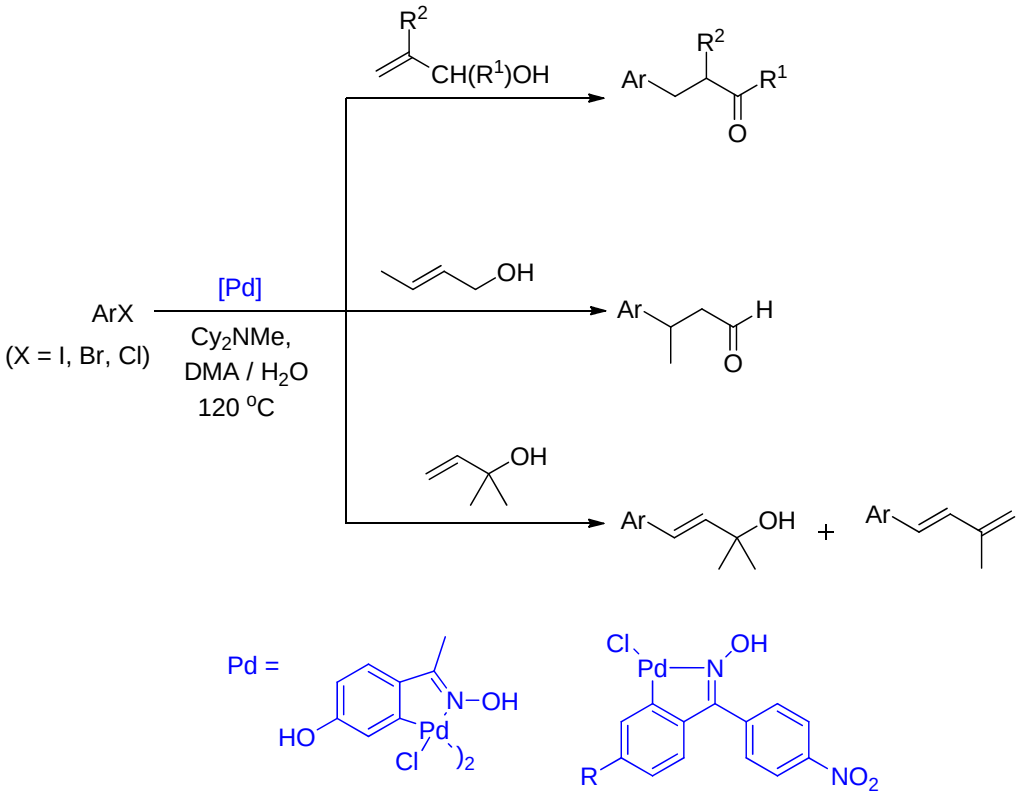

**Scheme 3.2**: Jeffrey's conditions for the Heck reaction of allylic alcohols

While the presence of a phosphine ligand can promote the arylation-isomerisation reaction of ArBr, high temperatures are often required to achieve sufficient activity.[7] For example, the tetraphosphine ligand tedicyp efficiently catalyses the Heck reaction of ArBr with alk-1-en-3-ol derivatives at 130 °C to yield the corresponding ketones (Scheme 3.3).




**Scheme 3.3**: Pd-phosphine catalysed reactions of ArBr and allylic alcohols

More recent and advanced catalyst systems employ oxime-derived palladacycles, which have proven to be highly active and selective catalysts for the arylation of aryl halides with a variety of allylic alcohols (Scheme 3.4).[1b] However, the catalysis takes place in aqueous/organic media, which would be incompatible with the molecular sieves needed for the acylation reaction.




**Scheme 3.4**: Palladacyclic catalysts for Heck reaction of allylic alcohols

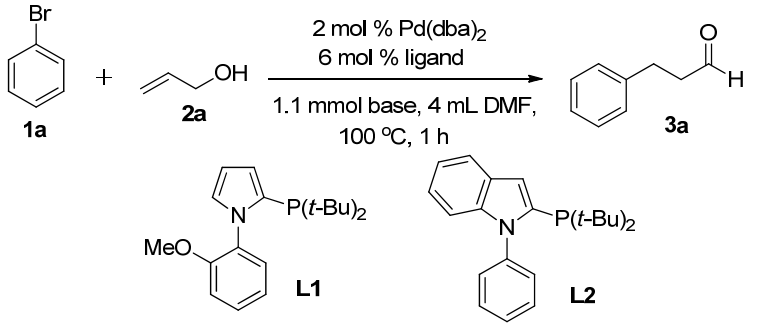
## 3.2 Results and Discussion

### 3.2.1 Optimisation of aldehyde formation and substrate scope

Table 1 shows our attempt for the formation of hydrocinnamaldehyde **3a** from a model arylation-isomerisation reaction of bromobenzene **1a** and allyl alcohol **2a**. Commonly employed phosphine ligands such as triphenylphosphine and dppp resulted in poor conversion, as did the ligand-free condition (entries 1-3). Use of P(*t*-Bu)$_3$.HBF$_4$ resulted in selective arylation at the terminal carbon of allyl alcohol, but the yield of aldehyde was low due to incomplete isomerisation (entry 4). Large amounts of (*E*)-3-Phenylprop-2-en-1-ol were observed in the crude $^1$H NMR of the reaction mixture. The use of bulky, electron-rich monophosphine ligands **L1** and **L2**[8] led to selective formation of the desired aldehyde product, with full conversion achieved in just one hour (entries 5 and 6). **L1** was previously demonstrated to be effective in promoting the acylation of aryl chlorides (Chapter 2). The reaction conditions were further optimised by changing the base (entries 7 to 9). It was hoped that pyrrolidine would be a suitable base for the reaction, as its presence is critical to the acylation step that follows in the overall one-pot process. Unfortunately, use of pyrrolidine as the base yielded very little of the aldehyde product (entry 7). Whilst the inorganic base potassium carbonate led to some success (entry 9), the tertiary amine Cy$_2$NMe afforded the best result, with **3a** being isolated in 74% yield (entry 8).

To test the utility of the newly developed reaction conditions, we examined the Heck-isomerisation reaction of a range of aryl bromides with allylic/homoallylic alcohols (Table 2). Functional groups on the aryl bromides were easily tolerated, posing no signifcant effect on the isolated yield of the aldehyde products (entries 2-4). Internal substitution of the double bond of the allylic alcohol was also tolerated (entry 5); however, the reaction became sluggish and non-selective when terminally substituted allylic alcohols were employed. Secondary allylic alcohol **2c** was also a very effective substrate, giving access to the corresponding ketone in high yield (entry 6). In contrast, the homoallyic alcohol **2d** furnished a lower yield, due to incomplete isomerisation (entry 7).[9]

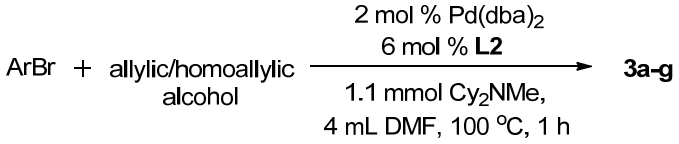
**Table 1.** Optimizing Conditions for Heck Arylation-Isomerisation Reaction of **1a** with **2a**[a]

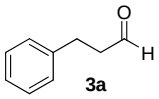
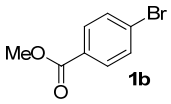
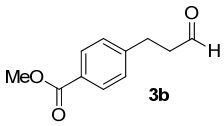
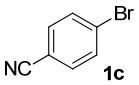
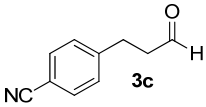
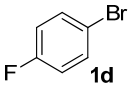
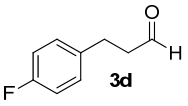
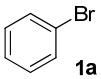
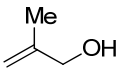
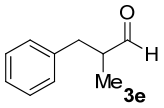
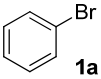
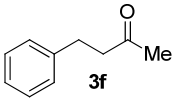
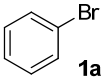
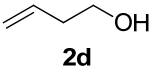
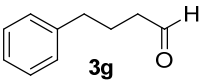



| entry | ligand | base | conversion (%)[b] | yield (%)[c] |
|---|---|---|---|---|
| 1 | - | $Et_3N$ | <2 | - |
| 2 | $PPh_3$ | $Et_3N$ | <5 | - |
| 3 | dppp[d] | $Et_3N$ | <2 | - |
| 4 | P(*t*-Bu)$_3$.$HBF_4$ | $Et_3N$ | 100 | 37 |
| 5 | **L1** | $Et_3N$ | 100 | 59 |
| 6 | **L2** | $Et_3N$ | 100 | 62 |
| 7 | **L2** | Pyrrolidine | <2 | - |
| 8 | **L2** | $Cy_2NMe$ | 100 | 74 |
| 9 | **L2** | $K_2CO_3$ | 100 | 22 |

[a] All reactions were carried out with **1a** (1.0 mmol), **2a** (1.1 mmol), base (1.1 mmol), $Pd(dba)_2$ (0.02 mmol) and ligand (0.06 mmol) in 4 mL of DMF at 100 °C for 1 h. [b] Conversion based on **1a**. [c] Isolated yields. [d] 3 mol % of ligand was used.

**Table 2.** Arylation-Isomerisation Reaction of Aryl Bromides with Allylic Alcohols[a]



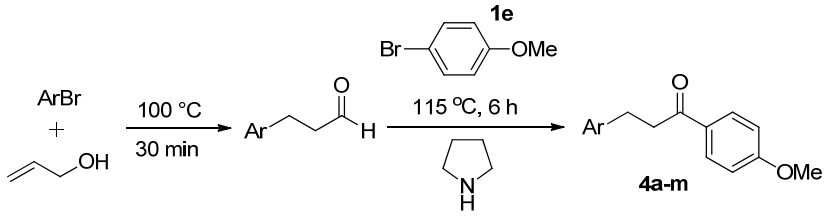

| entry | ArBr | allylic/homo-allylic alcohol | product | yield (%)[b] |
|---|---|---|---|---|
| 1 |  **1a** | **2a** |  **3a** | 74 |
| 2 |  **1b** | **2a** |  **3b** | 68 |
| 3 |  **1c** | **2a** |  **3c** | 67 |
| 4 |  **1d** | **2a** |  **3d** | 71 |
| 5 |  **1a** |  **2b** |  **3e** | 66[c] |
| 6 |  **1a** |  **2c** |  **3f** | 81 |
| 7 |  **1a** |  **2d** |  **3g** | 43 |

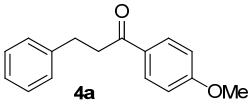
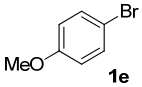
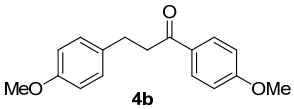
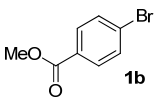
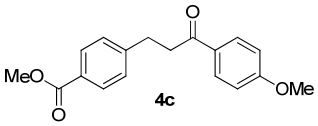
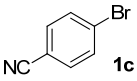
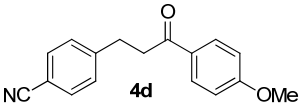
[a] Reactions were carried out with **1a-d** (1.0 mmol), **2a-d** (1.1 mmol), $Cy_2NMe$ (1.1 mmol), $Pd(dba)_2$ (0.02 mmol) and **L2** (0.06 mmol) in 4 mL of DMF at 100 °C for 1 h. [b] Isolated yields. [c] The reaction time was increased to 2 h.

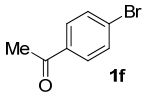
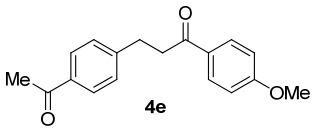
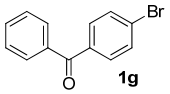
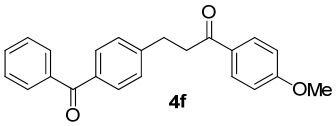
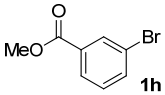
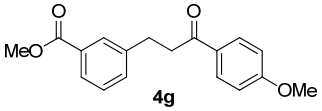
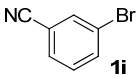
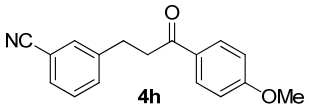
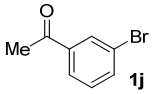
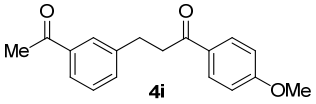
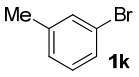
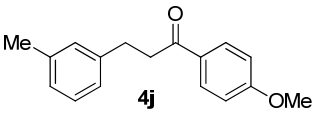
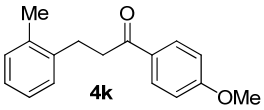
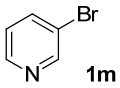
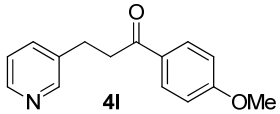
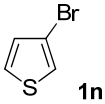
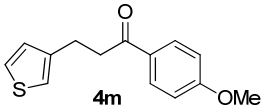
### 3.2.2 One-pot synthesis of dihydrochalcones

Armed with conditions that enable the facile formation of aldehydes from aryl bromides and allyl alcohol, we turned our attention to the one-pot synthesis of DHCs. Bearing in mind that pyrrolidine is necessary for the acylation but inhibits the arylation-isomerisation reaction, an aryl bromide was first allowed to react with one equivalent of allyl alcohol at 100 °C for 30 min, at which point a second aryl bromide was added together with pyrrolidine and the reaction temperature was raised to 115 °C for 6 h. The molecular sieves, another critical additive for the acylation reaction, were present from the beginning and did not impact on the initial aldehyde formation. It was also found that the presence of potassium carbonate as an additional base accelerates the acylation reaction, giving cleaner products and higher yields. As can be seen in Table 3, the one-pot reaction proved capable of forming a variety of DHCs in moderate to good isolated yields. In particular, functional groups on the initial aryl bromides, such as ester, ether, nitrile and ketone, were tolerated by the multi-step catalysis (entries 2-10). In steric terms, *meta* and *para* substitution did not pose any problem, but unfortunately *ortho* substitution with any group of steric bulk greater than that of methyl (entry 11) dramatically inhibited the initial Heck coupling. Furthermore, some heterocyclic aryl bromides were successfully employed (entries 12 and 13).

**Table 3.** One-pot Arylation, Isomerisation and Acylation Reactions Varying the Initial Aryl Bromides[a]



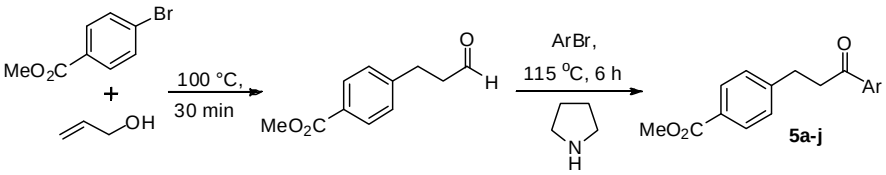

| entry | ArBr | product | yield (%)[b] |
|---|---|---|---|
| 1 |  1a |  4a | 64 |
| 2 |  1e |  4b | 43 |
| 3 |  1b |  4c | 66 |
| 4 |  1c |  4d | 58 |

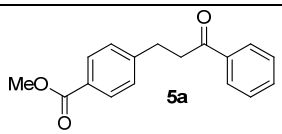
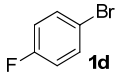
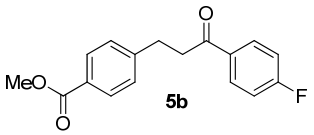
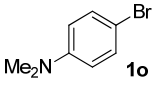
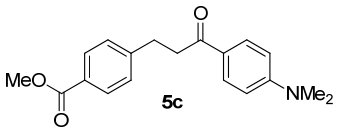
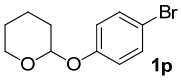
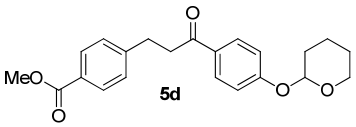
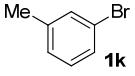
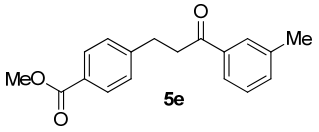
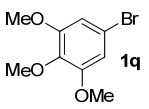
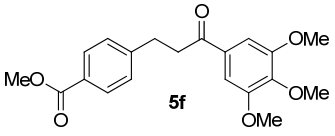
| | | | |
|---|---|---|---|
| 5 |  **1f** |  **4e** | 63 |
| 6 |  **1g** |  **4f** | 52 |
| 7 |  **1h** |  **4g** | 55 |
| 8 |  **1i** |  **4h** | 57 |
| 9 |  **1j** |  **4i** | 54 |
| 10 |  **1k** |  **4j** | 56 |
| 11 |  **1l** |  **4k** | 51 |
| 12 |  **1m** |  **4l** | 51[c] |
| 13 |  **1n** |  **4m** | 48[c] |

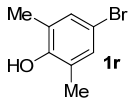
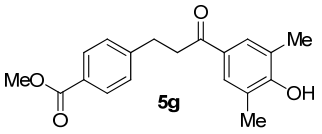
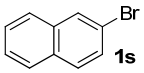
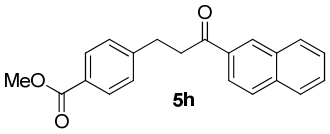
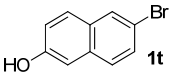
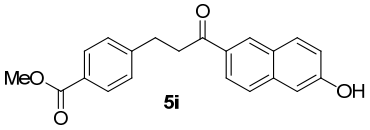
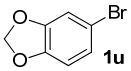
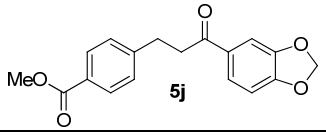
[a] Reactions were carried out with **1a-c, e-n** (2.0 mmol), **2a** (2.0 mmol), $Cy_2NMe$ (2.0 mmol), $K_2CO_3$ (1.0 mmol), 4 Å MS (1g), $Pd(dba)_2$ (0.02 mmol) and **L2** (0.06 mmol) in 4 mL of DMF at 100 °C for 30 min, followed by addition of **1e** (1.0 mmol) and pyrrolidine (1.0 mmol) at 115 °C for 6 h. [b] Isolated yields based on **1e**. [c] 0.04 mmol of $Pd(dba)_2$ and 0.12 mmol of **L2** were used.

We next examined the efficiency of the one-pot process by varying the second aryl bromide, which undergoes the acylation reaction. The results are seen in Table 4. We were happy to observe that the acylation step in the one-pot process appears to behave in the same way as it does in isolation. As such, the aryl bromide can be broadly functionalised in the *meta* and *para* positions and the reaction runs smoothly, affording the DHCs in moderate yields.
As a general trend, the arylation step appears to favour aryl bromides bearing electron-withdrawing substituents, whilst the acylation reaction works better with those having electron-donating groups (Tables 3 and 4). This is probably because the oxidative addition in the arylation and the insertion step in the acylation are facilitated by these electron-withdrawing and donating groups, respectively. In addition, when allyl alcohol was replaced with the substituted allylic alcohol **2b**, the one-pot reaction was unsuccessful due to the failure of the acylation with α-substituted aldehydes. Similarly, replacement of allyl alcohol with homoallylic alcohol **2d** gave poor results as a result of incomplete isomerisation.

**Table 4.** One-pot Arylation, Isomerization, and Acylation Reactions Varying the Second Aryl Bromides[a]



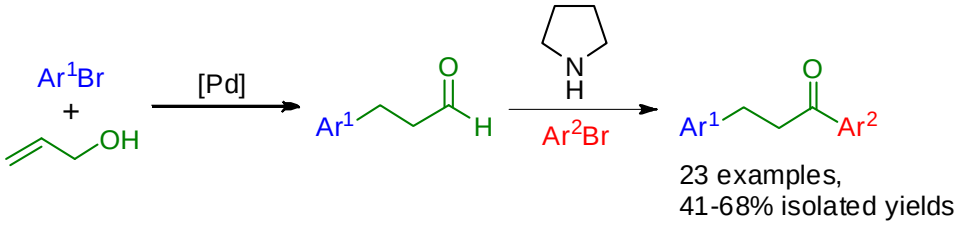

| entry | ArBr | product | yield (%)[b] |
|---|---|---|---|
| 1 |  **1a** |  **5a** | 53 |
| 2 |  **1d** |  **5b** | 52 |
| 3 |  **1o** |  **5c** | 50 |
| 4 |  **1p** |  **5d** | 57 |
| 5 |  **1k** |  **5e** | 55 |
| 6 |  **1q** |  **5f** | 57 |

| | | | |
|---|---|---|---|
| 7 |  **1r** |  **5g** | 61[c] |
| 8 |  **1s** |  **5h** | 41 |
| 9 |  **1t** |  **5i** | 66[c] |
| 10 |  **1u** |  **5j** | 68 |

[a] Reactions were carried out with **1b** (2.0 mmol), **2a** (2.0 mmol), $Cy_2NMe$ (2.0 mmol), $K_2CO_3$ (1.0 mmol), 4 Å MS (1g), $Pd(dba)_2$ (0.02 mmol) and **L2** (0.06 mmol) in 4 mL of DMF at 100 °C for 30 min, followed by addition of **1a, d, k, o-u** (1.0 mmol) and pyrrolidine (1.0 mmol) at 115 °C for 6 h. [b] Isolated yields based on ArBr. [c] 0.04 mmol of $Pd(dba)_2$ and 0.12 mmol of **L2** were used.

### 3.3 Conclusions and future work

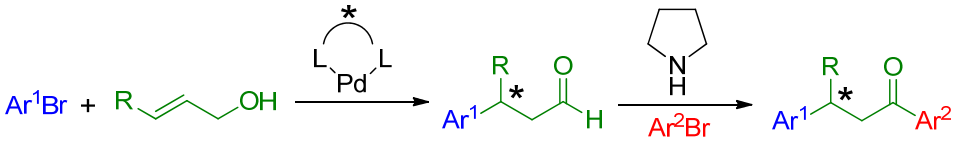
A one-pot protocol has been developed, which allows highly functionalized DHCs to be easily synthesised from readily available substrates. The palladium catalyzed Heck arylation-isomerisation reaction of aryl bromides and allyl alcohol first leads to the formation of aldehydes which, under the intervention of pyrrolidine and the same palladium catalyst, undergo an acylation reaction with an additional aryl bromide, affording the DHCs (Scheme 3.5). As a result, a wider range of aldehydes become accessible, derived from the commercial building blocks of aryl bromides and allyl alcohol.




**Scheme 3.5**: Two step, one-pot process for the formation of DHC's

As expected for a Heck coupling, the initial reaction between the aryl bromide and allyl alcohol works best for electron-deficient ArBr. In contrast to this, the acylation reaction is more amenable to electron-rich ArBr, possibly due to the unusual electronic demands of the insertion step of $L_nPd$-Ar into the highly electron-rich C=C double bond of the enamine intermediate.

Future extension of the methodology may include investigation into various substituted allylic alcohols (Scheme 3.6), thus leading to chiral products. If a chiral ligand is employed, enantiomerically enriched molecules may be formed:[10]




**Scheme 3.6**: Possible future work

### 3.4 Experimental

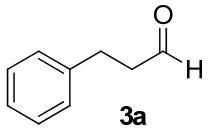
**Materials:** All the reactions were carried out under a nitrogen atmosphere with dried solvents. Silica gel plates (GF254) were used for TLC monitoring and silica gel (230-400 mesh) was used for flash column chromatography. The following chemicals were purchased from Alpha Aesar or Sigma Aldrich and used as received: all the aryl bromides, all the allylic/homoallylic alcohols, all the phosphine ligands, $Pd(dba)_2$, potassium carbonate, N-methyldicyclohexylamine and pyrrolidine. The 4 Å molecular sieves (4 Å MS) were purchased from Fluka, and were activated by drying in oven at 300 °C for 15 h before use. The $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker DRX-400 spectrometer with TMS as the internal standard, and infrared spectra on a JASCO FT/IR-4100 spectrometer. The mass spectra were obtained by electrospray ionization (EI).

**General procedure for aldehyde formation:** An oven-dried carousel reaction tube containing a stirrer bar was charged with an aryl bromide (**1a**-**d**) (1.0 mmol), $Pd(dba)_2$ (0.02 mmol), and **L2** (0.06 mmol). After degassing three times with nitrogen, an allylic/homoallylic alcohol (**2a**-**d**) (1.1 mmol), N-methyldicyclohexylamine (1.1 mmol) and *N*,*N*-dimethylformamide (DMF) (4 mL) were injected sequentially. The reaction mixture was stirred at 100 °C for 1 h. After cooling down to room temperature, 15 mL EtOAc was added and the mixture was washed with $H_2O$ (3 x 5 mL) to remove the DMF, dried over $Na_2SO_4$, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel using a mixture of ethyl acetate and hexane (1/99 to 5/95) as eluant. The desired aldehyde products **3a-g** were obtained in 43-81% yields (Table 2).

**General procedure for DHC formation:** An oven-dried carousel reaction tube containing a stirrer bar was charged with an aryl bromide (**1a**-**c, e-n**) (2.0 mmol), $Pd(dba)_2$ (0.02 mmol), **L2** (0.06 mmol), potassium carbonate (1.0 mmol) and 4 Å MS (1 g). After degassing three times with nitrogen, an allyl alcohol (**2a**) (2.0 mmol), N-methyldicyclohexylamine (2.0 mmol) and *N*,*N*-dimethylformamide (DMF) (4 mL) were injected sequentially. The reaction mixture was stirred at 100 °C for 30 mins, after which a second aryl bromide (**1a, d, e, k, o-u)** (1.0 mmol) and pyrrolidine (1.0 mmol) were injected and the reaction temperature was raised to 115 °C for 6 h. After cooling down to room temperature, 15 mL EtOAc was added and the mixture was washed with $H_2O$ (3 x 5 mL) to remove the DMF, dried over $Na_2SO_4$, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel using a mixture of ethyl acetate and hexane (1/99 to 25/75) as eluant. The desired ketone products **4a-m, 5a-j** were obtained in 41-68% yields (Table 2).

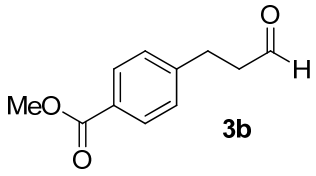
### 3.5 Analytical data

*All analytical data is in agreement with that previously reported in the literature, which is referenced accordingly.*



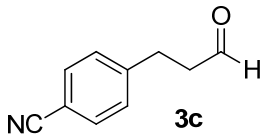
**3a**

**3-Phenylpropanal (3a).**[11] The general procedure for aldehyde formation was employed, using bromobenzene (0.11 mL, 1 mmol), allyl alcohol (0.07 mL, 1.1 mmol), N-methyldicyclohexylamine (0.24 mL, 1.1 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After 1 h at 100 °C, workup and column chromatography (1% EtOAc/hexane) yielded 99 mg (74%) of the title compound as a colourless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.31-7.18 (m, 5H), 2.96 (t, J = 7.5 Hz, 2H), 2.78 (t, J = 7.6 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 202.1, 140.8, 129.0, 128.7, 126.7, 45.7, 28.5; HRMS for $C_9H_{14}NO$ $[M + NH_4]^+$: m/z Calcd: 152.1070; Found: 152.1072; IR (neat, $cm^{-1}$): 1711 (s).



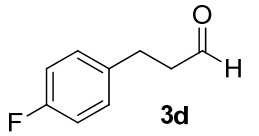
**3b**

**Methyl 4-(3-oxopropyl)benzoate (3b).**[12] The general procedure for aldehyde formation was employed, using methyl 4-bromobenzoate (215 mg, 1 mmol), allyl alcohol (0.07 mL, 1.1 mmol), N-methyldicyclohexylamine (0.24 mL, 1.1 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After 1 h at 100 °C, workup and column chromatography (3% EtOAc/hexane) yielded 131 mg (68%) of the title compound as a pale yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 3.90 (s, 3H), 3.01 (t, J = 7.5 Hz, 2H), 2.82 (t, J = 7.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 201.3, 167.4, 146.2, 130.3, 128.8, 128.7, 52.5, 45.2, 28.4; HRMS for $C_{11}H_{12}O_3$ $[M]^+$: m/z Calcd: 192.0781; Found: 192.0781; IR (neat, $cm^{-1}$): 1720 (s), 1284 (s). Melting point: 55-60 °C.



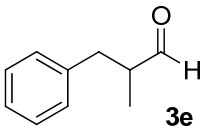

3c

**4-(3-Oxopropyl)benzonitrile (3c).**[12] The general procedure for aldehyde formation was employed, using 4-bromobenzonitrile (182 mg, 1 mmol), allyl alcohol (0.07 mL, 1.1 mmol), N-methyldicyclohexylamine (0.24 mL, 1.1 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After 1 h at 100 °C, workup and column chromatography (2% EtOAc/hexane) yielded 107 mg (67%) of the title compound as a pale brown solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 3.02 (t, J = 7.3 Hz, 2H), 2.84 (t, J = 7.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 200.7, 146.5, 132.8, 129.6, 119.3, 110.7, 44.9, 28.4; HRMS for $C_{10}H_{13}N_2O$ $[M + NH_4]^+$: m/z Calcd: 177.1028; Found: 177.1022; IR (neat, $cm^{-1}$): 2227 (m), 1714 (s). Melting point: 79-83 °C.



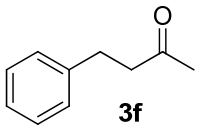

3d

**3-(4-Fluorophenyl)propanal (3d).**[13] The general procedure for aldehyde formation was employed, using 1-bromo-4-fluorobenzene (0.11 mL, 1 mmol), allyl alcohol (0.07 mL, 1.1 mmol), N-methyldicyclohexylamine (0.24 mL, 1.1 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After 1 h at 100 °C, workup and column chromatography (1% EtOAc/hexane) yielded 108 mg (71%) of the title compound as a creamy-white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.17-7.12 (m, 2H), 7.00-6.94 (m, 2H), 2.93 (t, J = 7.5 Hz, 2H), 2.77 (t, J = 7.5 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 201.6, 161.9 (d, $J_{CF}$ = 244.1 Hz), 136.4 (d, $J_{CF}$ = 3.2 Hz), 130.1 (d, $J_{CF}$ = 7.9 Hz), 115.8 (d, $J_{CF}$ = 21.3 Hz), 45.8, 27.7; HRMS for $C_9H_{13}FNO$ $[M + NH_4]^+$: m/z Calcd: 170.0976; Found: 170.0978; IR (neat, $cm^{-1}$): 1705 (s), 1215 (s).



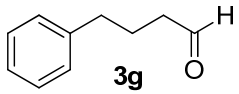
**3e**

**2-Methyl-3-phenylpropanal (3e).**[14] The general procedure for aldehyde formation was employed, using bromobenzene (0.11 mL, 1 mmol), 2-methyl-2-propen-1-ol (0.09 mL, 1.1 mmol), N-methyldicyclohexylamine (0.24 mL, 1.1 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After 2 h at 100 °C, workup and column chromatography (1% EtOAc/hexane) yielded 98 mg (66%) of the title compound as a colourless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.32-7.16 (m, 5H), 3.09 (dd, J = 13.3, 5.6 Hz, 1H), 2.72-2.58 (m, 2H), 1.09 (d, J = 6.9 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 204.8, 139.2, 129.4, 128.9, 126.8, 48.5, 37.1, 13.6; HRMS for $C_{10}H_{16}NO$ $[M + NH_4]^+$: m/z Calcd: 166.1226; Found: 166.1227; IR (neat, $cm^{-1}$): 1722 (s).



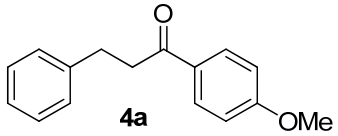
**3f**

**4-Phenylbutan-2-one (3f).**[15] The general procedure for aldehyde formation was employed, using bromobenzene (0.11 mL, 1 mmol), 3-buten-2-ol (0.10 mL, 1.1 mmol), N-methyldicyclohexylamine (0.24 mL, 1.1 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After 1 h at 100 °C, workup and column chromatography (1% EtOAc/hexane) yielded 120 mg (81%) of the title compound as a colourless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2H), 7.21-7.17 (m, 3H), 2.90 (t, J = 7.6 Hz, 2H), 2.76 (t, J = 7.4 Hz, 2H), 2.14 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 208.4, 141.4, 128.9, 128.7, 126.5, 45.6, 30.5, 30.1; HRMS for $C_{10}H_{16}NO$ $[M + NH_4]^+$: m/z Calcd: 166.1226; Found: 166.1223; IR (neat, $cm^{-1}$): 1716 (s).



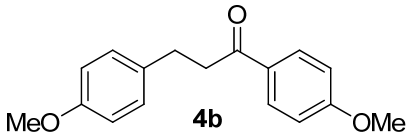

3g

**4-Phenylbutanal (3g).**[16] The general procedure for aldehyde formation was employed, using bromobenzene (0.11 mL, 1 mmol), 3-buten-1-ol (0.09 mL, 1.1 mmol), N-methyldicyclohexylamine (0.24 mL, 1.1 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After 1 h at 100 °C, workup and column chromatography (1% EtOAc/hexane) yielded 64 mg (43%) of the title compound as a colourless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.31-7.27 (m, 2H), 7.23-7.16 (m, 3H), 2.66 (t, J = 7.6 Hz, 2H), 2.45 (td, J = 7.3, 1.5 Hz, 2H), 1.96 (p, J = 7.5 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 202.7, 141.6, 128.9, 126.5, 43.6, 35.4, 24.1; HRMS for $C_{10}H_{16}NO$ $[M + NH_4]^+$: m/z Calcd: 166.1226; Found: 166.1225; IR (neat, $cm^{-1}$): 1722 (s).



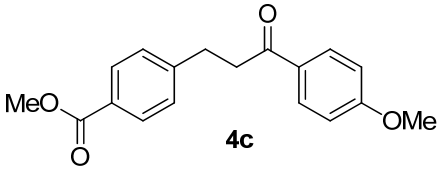

4a

**1-(4-Methoxyphenyl)-3-phenylpropan-1-one (4a).**[17] The general procedure for ketone formation was employed, using bromobenzene (0.21 mL, 2 mmol), 4-bromoanisole (0.13 mL, 1 mmol) allyl alcohol (0.14 mL, 2.0 mmol), N-methyldicyclohexylamine (0.43 mL, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), pyrrolidine (0.08 mL, 1 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After heating, workup and column chromatography (2% EtOAc/hexane) yielded 154 mg (64%) of the title compound as a pale yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 9.0 Hz, 2H), 7.32-7.18 (m, 5H), 6.92 (d, J = 9.0 Hz, 2H), 3.86 (s, 3H), 3.27-3.23 (m, 2H), 3.06 (t, J = 7.8 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 198.2, 163.6, 141.9, 130.7, 130.4, 128.9, 128.8, 126.5, 114.1, 55.9, 40.5, 30.7; HRMS for $C_{16}H_{17}O_2$ $[M + H]^+$: m/z Calcd: 241.1223; Found: 241.1219; IR (neat, $cm^{-1}$): 1670 (s). Melting point: 86-90 °C.



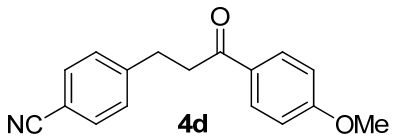
**4b**

**1,3-Bis(4-methoxyphenyl)propan-1-one (4b).**[17] The general procedure for ketone formation was employed, using 4-bromoanisole (0.25 mL, 2 mmol), 4-bromoanisole (0.13 mL, 1 mmol) allyl alcohol (0.14 mL, 2.0 mmol), N-methyldicyclohexylamine (0.43 mL, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), pyrrolidine (0.08 mL, 1 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After heating, workup and column chromatography (3% EtOAc/hexane) yielded 116 mg (43%) of the title compound as a pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 9.0 Hz, 2H), 7.17 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 3.86 (s, 3H), 3.78 (s, 3H), 3.21 (t, J = 7.7 Hz, 2H), 3.00 (t, J = 7.7 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 198.0, 163.4, 158.0, 133.5, 130.3, 130.0, 129.4, 113.9, 113.7, 55.5, 55.3, 40.4, 29.5; HRMS for $C_{17}H_{19}O_3$ $[M + Na]^+$: m/z Calcd: 293.1148; Found: 293.1157 ; IR (neat, $cm^{-1}$): 1674 (m), 1250 (s).



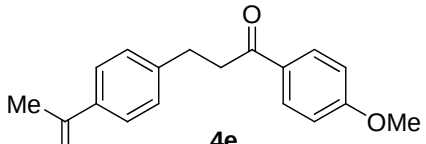
**4c**

**Methyl 4-(3-(4-methoxyphenyl)-3-oxopropyl)benzoate (4c).** The general procedure for ketone formation was employed, using methyl 4-bromobenzoate (430 mg, 2 mmol), 4-bromoanisole (0.13 mL, 1 mmol) allyl alcohol (0.14 mL, 2.0 mmol), N-methyldicyclohexylamine (0.43 mL, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), pyrrolidine (0.08 mL, 1 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After heating, workup and column chromatography (4% EtOAc/hexane) yielded 197 mg (66%) of the title compound as a pale yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.4 Hz, 2H), 7.93 (d, J = 8.9 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.9 Hz, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 3.26 (m, 2H), 3.10 (t, J = 7.5 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.6, 167.4, 163.9, 147.4, 130.7, 130.2, 130.2, 128.9, 128.5, 114.2, 55.9, 52.4, 39.8, 30.6; HRMS for $C_{18}H_{18}O_4$ $[M + Na]^+$: m/z Calcd: 321.1097; Found: 321.1107; IR (neat, $cm^{-1}$): 1714 (s), 1672 (m). Melting point: 99-105 °C.



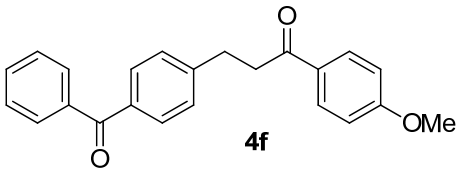

**4d**

**4-(3-(4-Methoxyphenyl)-3-oxopropyl)benzonitrile (4d).** The general procedure for ketone formation was employed, using 4-bromobenzonitrile (364 mg, 2 mmol), 4-bromoanisole (0.13 mL, 1 mmol) allyl alcohol (0.14 mL, 2.0 mmol), N-methyldicyclohexylamine (0.43 mL, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), pyrrolidine (0.08 mL, 1 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After heating, workup and column chromatography (4% EtOAc/hexane) yielded 154 mg (58%) of the title compound as a yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.9 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 3.86 (s, 3H), 3.27 (t, J = 7.3 Hz, 2H), 3.12 (t, J = 7.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.2, 164.0, 147.6, 132.7, 130.7, 130.0, 129.8, 119.4, 114.2, 110.3, 55.9, 39.4, 30.6; HRMS for $C_{17}H_{15}NO_2$ $[M + Na]^+$: m/z Calcd: 288.0995; Found: 288.0999; IR (neat, $cm^{-1}$): 2229 (w), 1668 (s). Melting point: 98-104 °C.



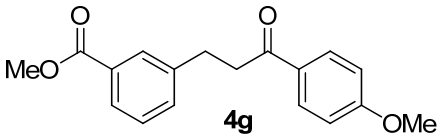

**4e**

**3-(4-Acetylphenyl)-1-(4-methoxyphenyl)propan-1-one (4e).** The general procedure for ketone formation was employed, using 4-bromoacetophenone (398 mg, 2 mmol), 4-bromoanisole (0.13 mL, 1 mmol) allyl alcohol (0.14 mL, 2.0 mmol), N-methyldicyclohexylamine (0.43 mL, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), pyrrolidine (0.08 mL, 1 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After heating, workup and column chromatography (6% EtOAc/hexane) yielded 178 mg (63%) of the title compound as a pale yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 9.0 Hz, 2H), 7.89 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 3.86 (s, 3H), 3.27 (t, J = 7.5 Hz, 2H), 3.11 (t, J = 7.5 Hz, 2H), 2.57 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 198.2, 197.6, 164.0, 147.7, 135.6, 130.7, 130.2, 129.1, 129.1, 114.2, 55.9, 39.8, 30.5, 27.0; HRMS for $C_{18}H_{18}O_3$ $[M + Na]^+$: m/z Calcd: 305.1148; Found: 305.1148; IR (neat, $cm^{-1}$): 1674 (s), 1603 (m). Melting point: 98-104 °C.



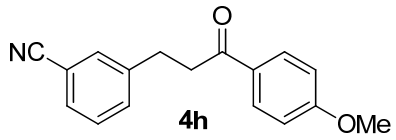

**4f**

**3-(4-Benzoylphenyl)-1-(4-methoxyphenyl)propan-1-one (4f).** The general procedure for ketone formation was employed, using 4-bromobenzophenone (522 mg, 2 mmol), 4-bromoanisole (0.13 mL, 1 mmol) allyl alcohol (0.14 mL, 2.0 mmol), N-methyldicyclohexylamine (0.43 mL, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), pyrrolidine (0.08 mL, 1 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After heating, workup and column chromatography (5% EtOAc/hexane) yielded 179 mg (52%) of the title compound as a pale yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.9 Hz, 2H), 7.79-7.73 (m, 4H), 7.57 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 3.85 (s, 3H), 3.30 (t, J = 7.5 Hz, 2H), 3.14 (t, J = 7.5 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.7, 196.8, 164.0, 147.1, 138.2, 135.9, 132.7, 130.9, 130.7, 130.4, 130.2, 128.9, 128.7, 114.2, 55.9, 39.9, 30.6; HRMS for $C_{23}H_{20}O_3$ $[M + Na]^+$: m/z Calcd: 367.1305; Found: 367.1326; IR (neat, $cm^{-1}$): 1649 (s), 1599 (s). Melting point: 88-95 °C.



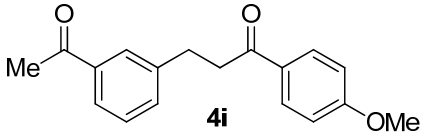

**4g**

**Methyl 3-(3-(4-methoxyphenyl)-3-oxopropyl)benzoate (4g).** The general procedure for ketone formation was employed, using methyl 3-bromobenzoate (430 mg, 2 mmol), 4-bromoanisole (0.13 mL, 1 mmol) allyl alcohol (0.14 mL, 2.0 mmol), N-methyldicyclohexylamine (0.43 mL, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), pyrrolidine (0.08 mL, 1 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After heating, workup and column chromatography (4% EtOAc/hexane) yielded 164 mg (55%) of the title compound as a yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.96-7.93 (m, 3H), 7.88 (dt, J = 7.7, 1.4 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 6.93 (d, J = 9.0 Hz, 2H), 3.92 (s, 3H), 3.87 (s, 3H), 3.28 (t, J = 7.6 Hz, 2H), 3.11 (t, J = 7.7 Hz, 2H),; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.8, 167.6, 163.9, 142.2, 133.7, 130.7, 130.2, 129.9, 129.0, 127.8, 114.2, 55.9, 52.5, 40.2, 30.4; HRMS for $C_{18}H_{18}O_4$ $[M + Na]^+$: m/z Calcd: 321.1097; Found: 321.1106; IR (neat, $cm^{-1}$): 1710 (s), 1664 (s). Melting point: 51-56 °C.



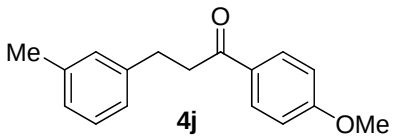

**4h**

**3-(3-(4-Methoxyphenyl)-3-oxopropyl)benzonitrile (4h).** The general procedure for ketone formation was employed, using 3-bromobenzonitrile (364 mg, 2 mmol), 4-bromoanisole (0.13 mL, 1 mmol) allyl alcohol (0.14 mL, 2.0 mmol), N-methyldicyclohexylamine (0.43 mL, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), pyrrolidine (0.08 mL, 1 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After heating, workup and column chromatography (4% EtOAc/hexane) yielded 151 mg (57%) of the title compound as a yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.9 Hz, 2H), 7.55 (s, 1H), 7.52-7.48 (m, 2H), 7.39 (t, J = 7.7 Hz, 1H), 6.93 (d, J = 8.9 Hz, 2H), 3.87 (s, 3H), 3.27 (t, J = 7.3 Hz, 2H), 3.10 (t, J = 7.3 Hz, 2H), ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.2, 164.0, 143.3, 133.6, 132.4, 130.7, 130.3, 130.0, 129.7, 119.4, 114.2, 112.9, 55.9, 39.6, 30.0; HRMS for $C_{17}H_{15}NO_2$ $[M + Na]^+$: m/z Calcd: 288.0995; Found: 288.1003; IR (neat, $cm^{-1}$): 2229, (w), 1670 (s). Melting point: 76-78 °C.



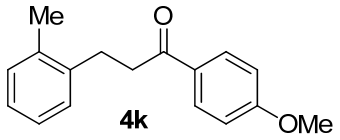

**4i**

**3-(3-Acetylphenyl)-1-(4-methoxyphenyl)propan-1-one (4i).** The general procedure for ketone formation was employed, using 3-bromoacetophenone (0.26 mL, 2 mmol), 4-bromoanisole (0.13 mL, 1 mmol) allyl alcohol (0.14 mL, 2.0 mmol), N-methyldicyclohexylamine (0.43 mL, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), pyrrolidine (0.08 mL, 1 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After heating, workup and column chromatography (6% EtOAc/hexane) yielded 152 mg (54%) of the title compound as a pale yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 9.0 Hz, 2H), 7.86 (s, 1H), 7.79 (d, J = 7.7 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 8.9 Hz, 2H), 3.85 (s, 3H), 3.28 (t, J = 7.6 Hz, 2H), 3.11 (t, J = 7.5 Hz, 2H), 2.59 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 198.7, 197.8, 163.9, 142.4, 137.7, 133.8, 130.7, 130.2, 129.1, 128.5, 126.7, 114.2, 55.9, 40.1, 30.4, 27.1; HRMS for $C_{18}H_{18}O_3$ $[M + Na]^+$: m/z Calcd: 305.1148; Found: 305.1159; IR (neat, $cm^{-1}$): 1672 (s). Melting point: 74-78 °C.



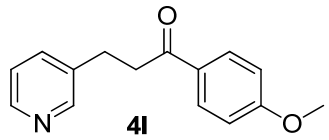
**4j**

**1-(4-Methoxyphenyl)-3-(m-tolyl)propan-1-one (4j).** The general procedure for ketone formation was employed, using 3-bromotoluene (0.24 mL, 2 mmol), 4-bromoanisole (0.13 mL, 1 mmol) allyl alcohol (0.14 mL, 2.0 mmol), N-methyldicyclohexylamine (0.43 mL, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), pyrrolidine (0.08 mL, 1 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After heating, workup and column chromatography (2% EtOAc/hexane) yielded 142 mg (56%) of the title compound as a pale yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 9.0 Hz, 2H), 7.19 (t, J = 7.5 Hz, 1H), 7.07-6.98 (m, 3H), 6.92 (d, J = 9.0 Hz, 2H), 3.86 (s, 3H), 3.24 (t, J = 7.8 Hz, 2H), 3.01 (t, J = 7.3 Hz, 2H), 2.34 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 198.3, 163.8, 141.8, 138.5, 130.7, 130.4, 129.7, 128.8, 127.2, 125.8, 114.1, 55.9, 40.6, 30.7, 21.8; HRMS for $C_{17}H_{18}O_2$ [M + Na]$^+$: m/z Calcd: 277.1199; Found: 277.1208; IR (neat, cm$^{-1}$): 1668 (s). Melting point: 40-45 °C.



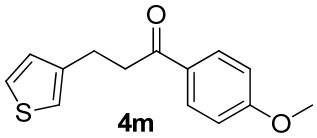
**4k**

**1-(4-Methoxyphenyl)-3-(o-tolyl)propan-1-one (4k).** The general procedure for ketone formation was employed, using 2-bromotoluene (0.24 mL, 2 mmol), 4-bromoanisole (0.13 mL, 1 mmol), allyl alcohol (0.14 mL, 2.0 mmol), N-methyldicyclohexylamine (0.43 mL, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), pyrrolidine (0.08 mL, 1 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After heating, workup and column chromatography (2% EtOAc/hexane) yielded 130 mg (51%) of the title compound pale yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.9 Hz, 2H), 7.19-7.11 (m, 4H), 6.91 (d, J = 8.9 Hz, 2H), 3.84 (s, 3H), 3.19 (t, J = 7.8 Hz, 2H), 3.03 (t, J = 7.8 Hz, 2H), 2.34 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 198.4, 163.9, 140.0, 136.4, 130.8, 130.7, 130.4, 129.2, 126.7, 126.6, 114.2, 55.9, 39.2, 28.1, 19.8; HRMS for $C_{17}H_{18}O_2$ [M + Na]$^+$: m/z Calcd: 277.1199; Found: 277.1204; IR (neat, cm$^{-1}$): 1670 (s). Melting point: 76-79 °C.



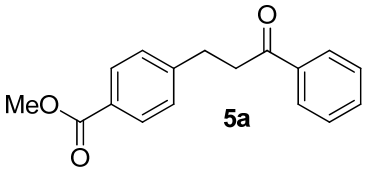
**4l**

**1-(4-Methoxyphenyl)-3-(pyridin-3-yl)propan-1-one (4l).** The general procedure for ketone formation was employed, using 3-bromopyridine (mL, 2 mmol), 4-bromoanisole (0.13 mL, 1 mmol), allyl alcohol (0.14 mL, 2.0 mmol), N-methyldicyclohexylamine (0.43 mL, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), pyrrolidine (0.08 mL, 1 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (23.0 mg, 0.02 mmol), **L2** (40.4 mg, 0.06 mmol), and DMF (4 mL). After heating, workup and column chromatography (15% EtOAc/hexane) yielded 123 mg (51%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 1.9 Hz, 1H), 8.46 (dd, J = 4.8, 1.6 Hz, 1H), 7.94 (d, J = 9.0 Hz, 2H), 7.60-7.57 (m, 1H), 7.22 (ddd, J = 7.8, 4.8, 0.7 Hz, 1H), 6.93 (d, J = 9.0 Hz, 2H), 3.87 (s, 3H), 3.27 (t, J = 7.5 Hz, 2H), 3.07 (t, J = 7.5 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.5, 164.0, 150.4, 148.0, 137.2, 136.5, 130.7, 130.1, 123.8, 114.2, 55.9, 39.8, 27.7; HRMS for $C_{15}H_{16}NO_2$ $[M + H]^+$: Calcd: 242.1176; Found: 242.1177; IR (neat, $cm^{-1}$): 1668 (s). Melting point: 74-76 °C.



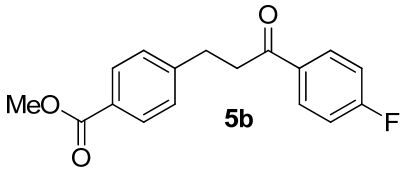
**4m**

**1-(4-Methoxyphenyl)-3-(thiophen-3-yl)propan-1-one (4m).** The general procedure for ketone formation was employed, using 3-bromothiophene (mL, 2 mmol), 4-bromoanisole (0.13 mL, 1 mmol), allyl alcohol (0.14 mL, 2.0 mmol), N-methyldicyclohexylamine (0.43 mL, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), pyrrolidine (0.08 mL, 1 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (23.0 mg, 0.02 mmol), **L2** (40.4 mg, 0.06 mmol), and DMF (4 mL). After heating, workup and column chromatography (4% EtOAc/hexane) yielded 118 mg (48%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.9 Hz, 2H), 7.27-7.25 (m, 1H), 7.01-6.98 (m, 2H), 6.93 (d, J = 8.9 Hz, 2H), 3.87 (s, 3H), 3.25 (t, J = 7.6 Hz, 2H), 3.08 (t, J = 7.5 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 198.2, 163.9, 142.1, 130.7, 130.4, 128.6, 125.9, 120.9, 114.1, 55.9, 39.6, 25.2; HRMS for $C_{14}H_{14}O_2S$ $[M + Na]^+$: m/z Calcd: 269.0607; Found: 269.0610; IR (neat, $cm^{-1}$): 1670 (s), 1255 (s).



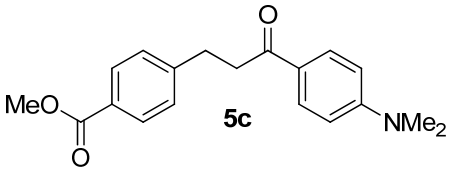

**5a**

**Methyl 4-(3-oxo-3-phenylpropyl)benzoate (5a).**[18] The general procedure for ketone formation was employed, using methyl 4-bromobenzoate (430 mg, 2 mmol), bromobenzene (0.11 mL, 1 mmol) allyl alcohol (0.14 mL, 2.0 mmol), N-methyldicyclohexylamine (0.43 mL, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), pyrrolidine (0.08 mL, 1 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After heating, workup and column chromatography (4% EtOAc/hexane) yielded 142 mg (53%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.98-7.94 (m, 4H), 7.56 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 3.90 (s, 3H), 3.33 (t, J = 7.5 Hz, 2H), 3.13 (t, J = 7.5 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.1, 167.5, 147.2, 137.1, 133.6, 130.3, 129.1, 128.9, 128.5, 128.4, 52.5, 40.2, 30.4; HRMS for $[M + Na]^+$: m/z Calcd: 291.0992; Found: 291.0999; IR (neat, $cm^{-1}$): 1714 (s), 1682 (m). Melting point: 85-87 °C.



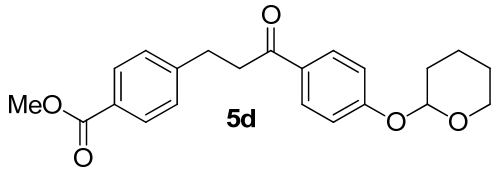

**5b**

**Methyl 4-(3-(4-fluorophenyl)-3-oxopropyl)benzoate (5b).** The general procedure for ketone formation was employed, using methyl 4-bromobenzoate (430 mg, 2 mmol), 1-bromo-4-fluorobenzene (0.11 mL, 1 mmol) allyl alcohol (0.14 mL, 2.0 mmol), N-methyldicyclohexylamine (0.43 mL, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), pyrrolidine (0.08 mL, 1 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After heating, workup and column chromatography (3% EtOAc/hexane) yielded 149 mg (52%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.00-7.96 (m, 4H), 7.32 (d, J = 8.3 Hz, 2H), 7.12 (m, 2H), 3.90 (s, 3H), 3.30 (t, J = 7.4 Hz, 2H), 3.12 (t, J = 7.5 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.5, 167.4, 166.2 (d, $J_{CF}$ = 255.1 Hz), 147.0, 133.5 (d, $J_{CF}$ = 3.0 Hz), 131.1 (d, $J_{CF}$ = 9.3 Hz), 130.3, 128.9, 128.6, 116.2 (d, $J_{CF}$ = 21.9 Hz), 52.4, 40.1, 30.4; HRMS for $C_{17}H_{15}FO_3$ $[M + Na]^+$: m/z Calcd: 309.0897; Found: 309.0895; IR (neat, $cm^{-1}$): 1720 (s), 1678 (m). Melting point: 72-74 °C.



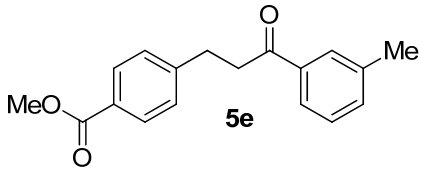
5c

**Methyl 4-(3-(4-(dimethylamino)phenyl)-3-oxopropyl)benzoate (5c).** The general procedure for ketone formation was employed, using methyl 4-bromobenzoate (430 mg, 2 mmol), 4-bromo-N,N-dimethylaniline (200 mg, 1 mmol) allyl alcohol (0.14 mL, 2.0 mmol), N-methyldicyclohexylamine (0.43 mL, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), pyrrolidine (0.08 mL, 1 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After heating, workup and column chromatography (15% EtOAc/hexane) yielded 156 mg (50%) of the title compound as a yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.2 Hz, 2H), 7.86 (d, J = 9.0 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 6.63 (d, J = 9.1 Hz, 2H), 3.89 (s, 3H), 3.23-3.19 (m, 2H), 3.10 (t, J = 7.4 Hz, 2H), 3.04 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.2, 167.5, 153.8, 147.9, 130.6, 130.2, 128.9, 128.3, 125.1, 111.1, 52.4, 40.4, 39.4, 31.0; HRMS for $C_{19}H_{21}NO_3$ $[M + Na]^+$: m/z Calcd: 334.1414; Found: 334.1415; IR (neat, $cm^{-1}$): 1711 (s), 1647 (m), 1603 (s). Melting point: 86-89 °C.



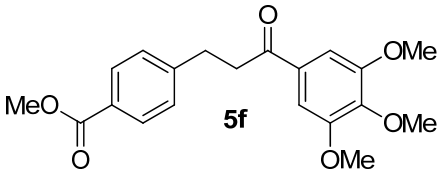
5d

**Methyl 4-(3-oxo-3-(4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)propyl)benzoate (5d).** The general procedure for ketone formation was employed, using methyl 4-bromobenzoate (430 mg, 2 mmol), 2-(4-bromophenoxy)tetrahydro-2H-pyran (514 mg, 1 mmol) allyl alcohol (0.14 mL, 2.0 mmol), N-methyldicyclohexylamine (0.43 mL, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), pyrrolidine (0.08 mL, 1 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After heating, workup and column chromatography (10% EtOAc/hexane) yielded 210 mg (57%) of the title compound as a pale yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.3 Hz, 2H), 7.92 (d, J = 8.9 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 7.07 (d, J = 8.9 Hz, 2H), 5.51 (t, J = 3.1 Hz, 1H), 3.89 (s, 3H), 3.86-3.80 (m, 1H), 3.63-3.59 (m, 1H), 3.26 (t, J = 7.6 Hz, 2H), 3.10 (t, J = 7.6 Hz, 2H), 2.02-1.94 (m, 1H), 1.89-1.85 (m, 2H), 1.75-1.56 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.7, 167.4, 161.5, 147.4, 130.7, 130.5, 130.2, 128.9, 128.4, 116.4, 96.4, 62.4, 52.4, 39.8, 30.6, 30.5, 25.4, 18.9; HRMS for $C_{22}H_{24}O_5$ $[M + Na]^+$: m/z Calcd: 391.1516; Found: 391.1514; IR (neat, $cm^{-1}$): 1718 (s), 1670 (m). Melting point: 97-102 °C.



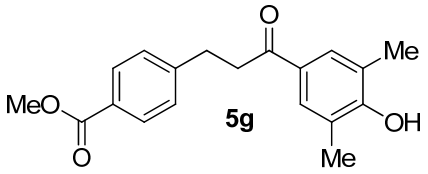
**5e**

**Methyl 4-(3-oxo-3-(m-tolyl)propyl)benzoate (5e).** The general procedure for ketone formation was employed, using methyl 4-bromobenzoate (430 mg, 2 mmol), 3-bromotoluene (0.12 mL, 1 mmol) allyl alcohol (0.14 mL, 2.0 mmol), N-methyldicyclohexylamine (0.43 mL, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), pyrrolidine (0.08 mL, 1 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After heating, workup and column chromatography (3% EtOAc/hexane) yielded 155 mg (55%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.3 Hz, 2H), 7.76-7.74 (m, 2H), 7.38-7.35 (m, 2H), 7.32 (d, J = 8.4 Hz, 2H), 3.90 (s, 3H), 3.31 (t, J = 7.5 Hz, 2H), 3.12 (t, J = 7.6 Hz, 2H), 2.40 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.3, 167.5, 147.3, 138.9, 137.1, 134.4, 130.3, 129.0, 128.9, 128.5, 125.6, 52.4, 40.3, 30.4, 21.8; HRMS for $[M + Na]^+$: m/z Calcd: 305.1148; Found: 305.1163; IR (neat, $cm^{-1}$): 1711 (s), 1676 (m). Melting point: 79-83 °C.



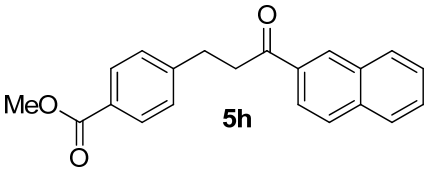
**5f**

**Methyl 4-(3-oxo-3-(3,4,5-trimethoxyphenyl)propyl)benzoate (5f).** The general procedure for ketone formation was employed, using methyl 4-bromobenzoate (430 mg, 2 mmol), 5-bromo-1,2,3-trimethoxybenzene (247 mg, 1 mmol) allyl alcohol (0.14 mL, 2.0 mmol), N-methyldicyclohexylamine (0.43 mL, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), pyrrolidine (0.08 mL, 1 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After heating, workup and column chromatography (8% EtOAc/hexane) yielded 204 mg (57%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.20 (s, 2H), 3.91 (s, 3H), 3.90 (s, 3H), 3.90 (s, 6H), 3.28 (t, J = 7.4 Hz, 2H), 3.12 (t, J = 7.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.8, 167.4, 153.5, 147.2, 143.2, 132.4, 130.3, 128.9, 128.6, 106.0, 61.3, 56.7, 52.4, 40.1, 30.6; HRMS for $C_{20}H_{22}O_6$ $[M + Na]^+$: m/z Calcd: 381.1309; Found: 381.1330; IR (neat, $cm^{-1}$): 1720 (s), 1676 (m). Melting point: 110-112 °C.



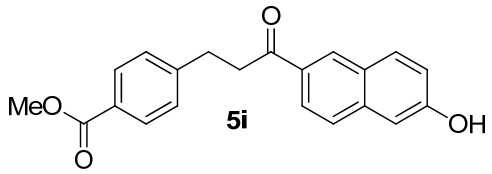
**5g**

**Methyl 4-(3-(4-hydroxy-3,5-dimethylphenyl)-3-oxopropyl)benzoate (5g).** The general procedure for ketone formation was employed, using methyl 4-bromobenzoate (430 mg, 2 mmol), 4-bromo-2,6-xylenol (201 mg, 1 mmol) allyl alcohol (0.14 mL, 2.0 mmol), N-methyldicyclohexylamine (0.43 mL, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), pyrrolidine (0.08 mL, 1 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After heating, workup and column chromatography (10% EtOAc/hexane) yielded 191 mg (61%) of the title compound as a white solid. $^1$H NMR (400 MHz, Acetone-$d_6$) δ 7.92 (d, J = 8.4 Hz, 2H), 7.68 (s, 2H), 7.43 (d, J = 8.4 Hz, 2H), 3.86 (s, 3H), 3.31 (t, J = 7.5 Hz, 2H), 3.01 (t, J = 7.5 Hz, 2H), 2.27 (s, 6H); $^{13}$C NMR (100 MHz, Acetone-$d_6$) δ 197.9, 167.6, 159.1, 149.1, 130.7, 130.3, 130.0, 129.3, 125.0, 52.6, 40.1, 31.3, 17.0; HRMS for $C_{19}H_{20}O_4$ $[M + Na]^+$: m/z Calcd: 335.1254; Found: 335.1265; IR (neat, $cm^{-1}$): 3809 (br, w), 1718 (m), 1670 (m). Melting point: 137-139 °C.

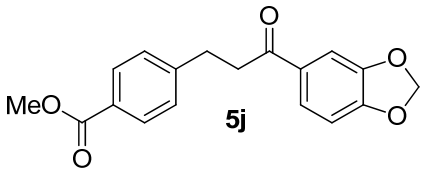


**5h**

**Methyl 4-(3-(naphthalen-2-yl)-3-oxopropyl)benzoate (5h).** The general procedure for ketone formation was employed, using methyl 4-bromobenzoate (430 mg, 2 mmol), 2-bromonaphthalene (207 mg, 1 mmol) allyl alcohol (0.14 mL, 2.0 mmol), N-methyldicyclohexylamine (0.43 mL, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), pyrrolidine (0.08 mL, 1 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After heating, workup and column chromatography (4% EtOAc/hexane) yielded 131 mg (41%) of the title compound as a pale yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.01 (dd, J = 8.7, 1.7 Hz, 1H), 7.98 (d, J = 8.2 Hz, 2H), 7.92 (d, J = 8.0 Hz, 1H), 7.86 (t, J = 7.8 Hz, 2H), 7.60-7.51 (m, 2H), 7.35 (d, J = 8.1 Hz, 2H), 3.89 (s, 3H), 3.44 (t, J = 7.6 Hz, 2H), 3.17 (t, J = 7.6 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.0, 167.4, 147.3, 136.0, 134.4, 132.9, 130.3, 130.1, 130.0, 129.0, 128.9, 128.6, 128.2, 127.2, 124.2, 52.4, 40.3, 30.6; HRMS for $C_{21}H_{18}O_3$ $[M + Na]^+$: m/z Calcd: 341.1148; Found: 341.1165; IR (neat, $cm^{-1}$): 1716 (s), 1672 (m). Melting point: 79-83 °C.




**Methyl 4-(3-(6-hydroxynaphthalen-2-yl)-3-oxopropyl)benzoate (5i).** The general procedure for ketone formation was employed, using methyl 4-bromobenzoate (430 mg, 2 mmol), 6-bromo-2-naphthol (223 mg, 1 mmol) allyl alcohol (0.14 mL, 2.0 mmol), N-methyldicyclohexylamine (0.43 mL, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), pyrrolidine (0.08 mL, 1 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After heating, workup and column chromatography (10% EtOAc/hexane) yielded 221 mg (66%) of the title compound as a white solid. $^1$H NMR (400 MHz, Acetone-$d_6$) δ 8.57 (s, 1H), 7.98-7.93 (m, 4H), 7.75 (d, J = 8.7 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.27-7.22 (m, 2H), 3.86 (s, 3H), 3.52 (t, J = 7.5 Hz, 2H), 3.15 (t, J = 7.5 Hz, 2H); $^{13}$C NMR (100 MHz, Acetone-$d_6$) δ 198.9, 167.6, 159.0, 148.9, 138.9, 133.2, 132.8, 131.2, 130.7, 130.0, 129.4, 128.7, 127.7, 125.4, 120.5, 110.3, 52.6, 40.4, 31.2; HRMS for $C_{21}H_{18}O_4$ [M + Na]$^+$: m/z Calcd: 357.1097; Found: 357.1118; IR (neat, cm$^{-1}$): 3313 (br, w), 1718 (m), 1651 (m). Melting point: 163-165 °C.




**Methyl 4-(3-(benzo[d][1,3]dioxol-5-yl)-3-oxopropyl)benzoate.** The general procedure for ketone formation was employed, using methyl 4-bromobenzoate (430 mg, 2 mmol), 1-bromo-3,4-(methylenedioxy)benzene (0.12 mL, 1 mmol) allyl alcohol (0.14 mL, 2.0 mmol), N-methyldicyclohexylamine (0.43 mL, 2.0 mmol), potassium carbonate (138 mg, 1.0 mmol), pyrrolidine (0.08 mL, 1 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), **L2** (20.2 mg, 0.06 mmol), and DMF (4 mL). After heating, workup and column chromatography (6% EtOAc/hexane) yielded 212 mg (68%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.3 Hz, 2H), 7.54 (dd, J = 8.2, 1.7 Hz, 1H), 7.43 (d, J = 1.7 Hz, 1H), 7.31 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.2 Hz, 1H), 6.03 (s, 2H), 3.90 (s, 3H), 3.25-3.22 (m, 2H), 3.10 (t, J = 7.5 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.1, 167.4, 152.2, 148.6, 147.2, 132.0, 130.3, 128.9, 128.5, 124.6, 108.3, 108.2, 102.3, 52.4, 39.9, 30.6; HRMS for $C_{18}H_{16}O_5$ [M + Na]$^+$: m/z Calcd: 335.0890; Found: 335.0901; IR (neat, cm$^{-1}$): 1711 (s), 1676 (m). Melting point: 94-96 °C.

### 3.6 References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10. (a) Yonehara, K.; Mori, K.; Hashizume, T.; Chung, K.-G.; Ohe, K.; Uemura, S. *J. Organomet. Chem.* **2000**, *603*, 40. (b) Tanaka, K.; Qiao, S.; Tobisu, M.; Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 9870.
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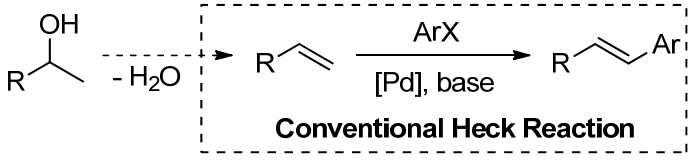
# Chapter 4

## Feeding the Heck Reaction with Alcohol: One-Pot synthesis of Stilbenes from Aryl Alcohols and Bromides

### 4.1 Introduction

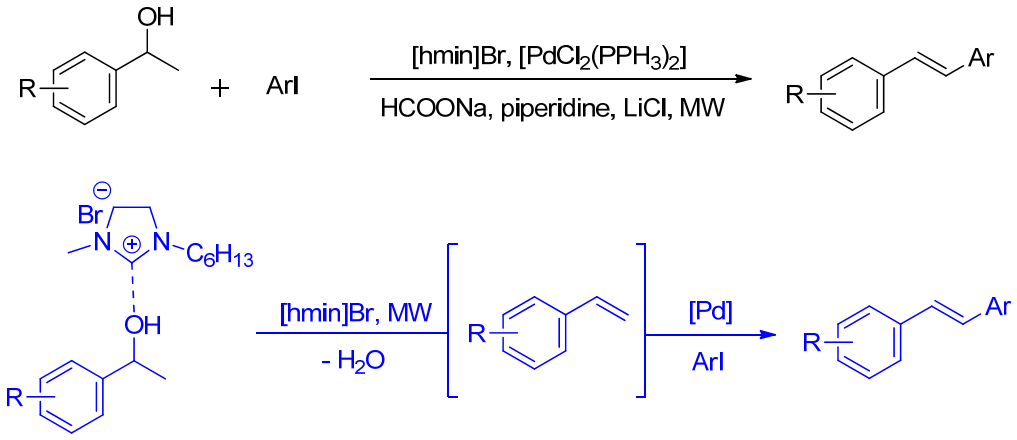
The acylation reaction (Chapters 2 and 3) is based on the principle that C=C double bonds can be formed in-situ by condensation of aliphatic aldehydes and the secondary amine, pyrrolidine. This allows us to carry out the Heck arylation of enamine substrates that would otherwise be difficult to prepare, isolate and store. It was then wondered if this same principle of generating olefins by loss of $H_2O$ could be applied to another class of substrates i.e. alcohols.

In a typical Heck reaction, an aryl halide couples with an olefin in the presence of a palladium catalyst and base, furnishing an arylated olefin (Scheme 4.1). In recent years, much effort has been focused on the dehydrogenative Heck reaction, which allows arene C-H bonds to be directly coupled to olefins, obviating the need for halogenation steps.[1] *The scope of the Heck reaction could be further widened if olefins could be easily generated, e.g. in-situ*, as demonstrated in Chapters 2 and 3. This is particularly the case for olefins that are not commercially available and may have poor stability.[2] For example, styrenes, which lead to stilbenes in the Heck reaction, are not commercially available in most cases and those that are available need to be stored at low temperatures to prevent self-polymerisation. Consequently, only a few styrenes have appeared in the Heck reaction ever since the reaction was invented, although stilbenes are found in many natural sources, show a number of pharmacological activities and are widely used as industrial dyes.[3] Realising that secondary aryl alcohols can be dehydrated to give styrenes, we thought it might be possibe to replace the latter with the former in the Heck reaction (Scheme 4.1).




**Scheme 4.1**: Alcohols as pseudo olefins for the Heck reaction.

This chapter demonstrates that one-pot Heck coupling of aryl alcohols with ArBr is indeed possible, affording various stilbenes, in which the alcohol is *in-situ* dehydrated by a green, solid acid catalyst. While this work was in progress, a similar approach using aryl iodides was reported by Sinha and coworkers (Scheme 4.2).[4]

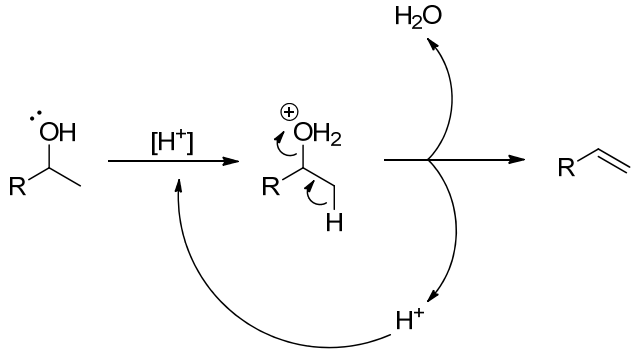



**Scheme 4.2**: First report of dehydrative Heck coupling of aryl alcohols and ArI (with proposed mechanism)

The reaction is thought to proceed via a styrenyl intermediate, which is formed by the [hmin]Br catalysed dehydration of the aryl alcohol. This transformation deserves conceptual acknowledgement as the dehydration of aryl alcohols usually requires acidic conditions, which opposes the basic conditions required for the catalytic Heck reaction. A drawback of this interesting method is the need for heating (150 °C) under microwave irradiation and the use of specific ionic liquid as solvent, in addition to limited substrate scope regarding the aryl alcohols.

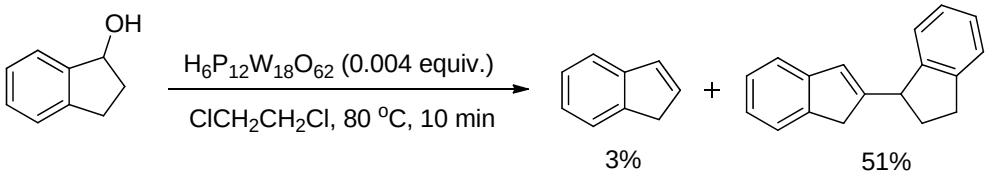
### 4.1.1 Background literature regarding the dehydration of secondary aryl alcohols to styrenes.

Strong Bronsted acids, such as sulfuric acid and *p*-toluenesulfonic acid, are the most commonly employed catalysts for the dehydration of alcohols.[5] The reaction proceeds by protonation of the hydroxyl group, which activates the alcohol towards loss of water and regeneration of the Bronsted acid catalyst (Scheme 4.3). Unfortunately, the reaction suffers from poor selectivity and low functional group tolerance.[6] The major competing reaction pathways are that of ether formation, olefin formation and dimerisation of the resultant olefins.



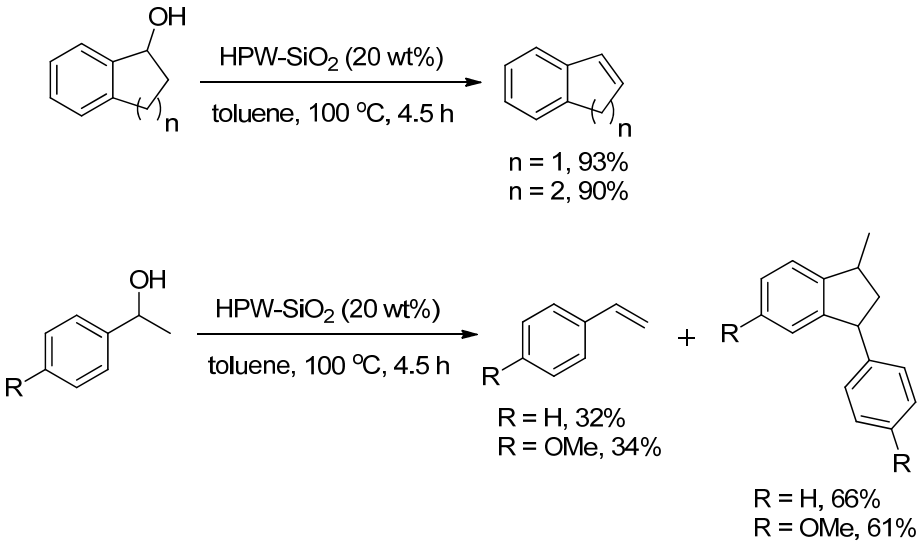

**Scheme 4.3**: Bronsted acid catalysed dehydration of alcohols

Another class of Bronsted acids sometimes employed for the dehydration of alcohols is heteropolyacids (HPAs). HPAs, safe, easy-to-handle and economic solid catalysts,[7] have proven to be excellent in terms of activity; but dimerisation of the product olefin is a major drawback to their use.[8] For example, in 2006 Muzart *et al* reported the HPA catalysed dehydration of 1-indanol (Scheme 4.4).[8a] The reaction rate was very fast and completed in just 10 minutes. However, the major product was not the expected styrene, but the corresponding dimer instead.



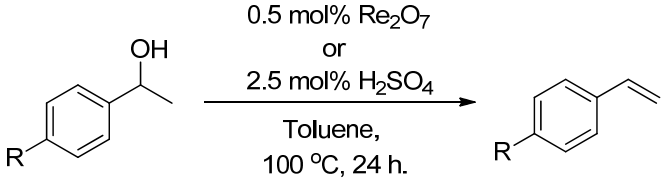

**Scheme 4.4**: HPA catalysed dehydration/dimerisation of 1-indanol

More recently in 2011, Jayaram *et al* observed very little dimerisation when carrying out the dehydration of 1-indanol and 1,2,3,4-tetrahydronapthol in the presence of silica supported HPA (Scheme 4.5).[9] However, when sterically unhindered aryl alcohols were employed, cyclodimerisation became the major reaction pathway, resulting in poor yields of the desired styrenes.




**Scheme 4.5**: Silica supported HPA catalysed dehydration/cyclodimerisation of aryl alcohols

A recent investigation by Gebbink *et al* showed the effectiveness of a transition metal catalyst, $Re_2O_7$, for the dehydration of aryl alcohols, giving direct comparison of its activity relative to $H_2SO_4$ as the benchmark catalyst (Scheme 4.6).[10]



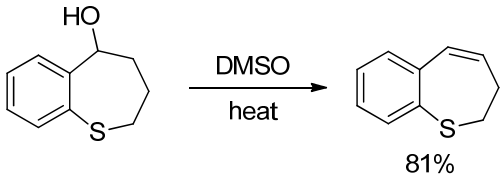

| R | $Re_2O_7$ conversion[b] [%] | Olefin yield[b] [%] | TOF[c] [$h^{-1}$] | $H_2SO_4$ conversion[b] [%] | Olefin yield[b] [%] | TOF[c] [$h^{-1}$] |
|---|---|---|---|---|---|---|
| OMe | >99 | 77 | 792 | >99 | 11 | 151 |
| H | >99 | 97 | 392 | >99[d] | 42[d] | 52 |
| Cl | >99 | 67 | 101 | >99 | 58 | 28 |
| CN | 0 | 0 | 0 | 0 | 0 | 0 |
| $NO_2$ | 0 | 0 | 0 | 92 | 42 | 5 |

[b] GC conversion or yield after 24 h.
[c] based on the consumption of starting material in the first 15 min.
[d] after 6 h.

**Scheme 4.6**: $Re_2O_7$ vs. $H_2SO_4$ as catalysts for dehydration of aryl alcohols

The results in scheme 4.6 show that for electron rich/neutral aryl alcohols (R = OMe, H, Cl) the activity is high for both catalysts, although $Re_2O_7$ is significantly more selective towards the olefin product. Unfortunately, when electron deficient aryl alcohols are employed (R = CN, $NO_2$), $Re_2O_7$ is completely ineffective as a dehydration catalyst. $H_2SO_4$ also fails to catalyse the reaction when R = CN, but manages to effect reasonable levels of alcohol dehydration to the corresponding styrene when R = $NO_2$.

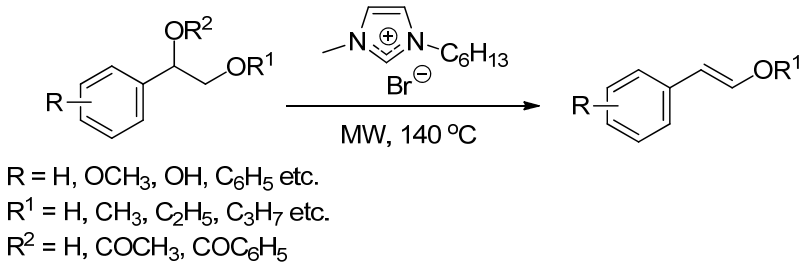
In 1958, Searles and Hays observed that heating a benzylic alcohol in DMSO unexpectedly resulted in selective dehydration to the corresponding styrene (scheme 4.7).[11]




**Scheme 4.7**: Unexpected dehydration of a benzylic alcohol promoted by DMSO

This observation was more thoroughly investigated by Livingston *et al* who subjected a wide range of alcohols to thermal heating in DMSO.[12] They found that, in general, 2° and 3° benzylic alcohols, as well as 3° aliphatic alcohols can be selectively dehydrated to the corresponding olefins, whereas 1° and 2° aliphatic alcohols were inert to the dehydration reaction. Temperatures of 160-185 °C for 9-16 h were required to reach reaction completion. The mode of action remains unclear, but one can rule out simple thermal activation alone, as the alcohols did not dehydrate in the absence of DMSO. The solvent was purified by fractional distillation before use, as well as being treated with NaOH to rule out acidic contamination. However, small levels of DMSO decomposition at the elevated temperatures makes it difficult to rule out the effects of trace impurities.

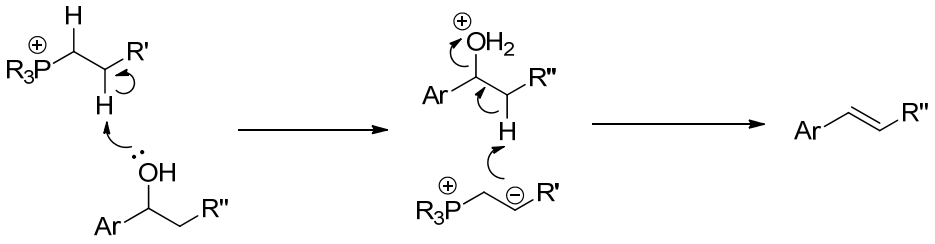
The concept of dehydration catalysed under neutral conditions (such as in DMSO) has great appeal due to the fact that molecules containing acid-sensitive groups are able to tolerate the reaction conditions.[13] In line with this view, Sinha *et al* discovered that benzylic, allylic and 3° aliphatic alcohols can be selectively dehydrated to the corresponding olefins when subjected to microwave irradiation in ionic liquids (Scheme 4.8).[14]




**Scheme 4.8**: Dehydration of alcohols promoted by imidazolium ionic liquid

The reaction works best with substrates bearing methoxy substitution on the aromatic ring. Unfortunately, electron-deficient aryl alcohols were again inert to the dehydration reaction, with only trace levels of olefin detected when 1-(4-nitrophenyl)ethanol was employed. Another advantage to this protocol is that the solvent can be recycled and successfully reused with minimal loss of activity over a few runs.

The dehydration of benzylic alcohols was also recently achieved in the phosphonium ionic liquids $[P_{666,14}]X$ (where X = Br, Cl or DBS) when subjected to microwave irradiation.[15] The acidity of the alkyl protons in close proximity to the phosphonium ion is sufficient to be abstracted by the hydroxyl group of the alcohol, thereby promoting the dehydration reaction (Scheme 4.9). Kerton proposed that the protons on the β carbon are abstracted by the alcohol, however, one may argue that the α protons are more acidic. The ionic liquids are recycled through vacuum distillation of the reaction mixtures. In terms of substrate scope, only a limited number of examples were presented, none of which were electron-deficient aryl alcohols.

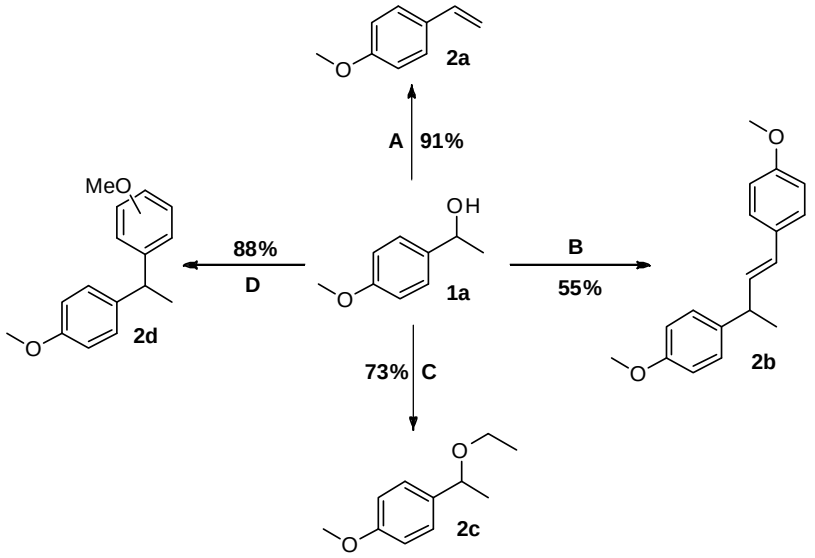



**Scheme 4.9**: Dehydration of alcohols promoted by phosphonium ionic liquids

## 4.2 Results and Discussion

### - 4.2.1 Optimisation of styrene formation

Given the benign features of HPAs, we set out to find conditions for their use as highly selective catalysts for the dehydration of aryl alcohols. As it has already been reported that the solvent plays a key role in the product distribution of the HPA-catalysed dimerisation of α-methylstyrene,[16] examining the effect of solvents seemed to be a good starting point. We began by subjecting 1-(4-methoxyphenyl)ethanol **1a** to thermal activation in the presence of a catalytic amount of the Keggin type HPA, $H_3PW_{12}O_{40}$, in a wide variety of solvents (Scheme 4.10).




**Scheme 4.10**: Effect of solvent on the product distribution of HPA-catalysed reactions of 1-(4-Methoxyphenyl)ethanol **1a**. Reactions were carried out on a 1.0 mmol scale in 2 mL solvent using 1 mol % $H_3PW_{12}O_{40}$ as catalyst. **A** = DMSO, 100 °C, 1 h. **B** = diglyme, 100 °C, 1 h. **C** = ethanol, 100 °C, 1 h. **D** = anisole, 130 °C, 1 h.

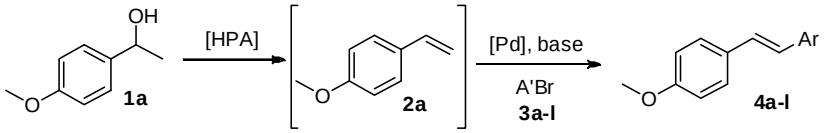
It was observed that both the catalytic activity and product selectivity were strongly affected by the solvent. In the solvents DMF, DMA and MeCN, no reaction was observed. The reactions in hexane and sulfolane were rapid but non-selective, resulting in a complex mixture of products that was impossible to interpret by crude $^1$H NMR. The reaction in ethanol led to an ether product **2c** in 73% isolated yield, which most likely results from nucleophilic interception of a cationic intermediate formed by protonation of the benzylic alcohol by the acid catalyst (Scheme 4.10, **C**).[17] In a similar way, a Friedel-Crafts type reaction occured when anisole was used as the solvent (Scheme 4.2, **D**, 88% isolated yield of **2d**; 10:1 *para*/*ortho* regioselectivity).[18] When diglyme was used as the solvent, the desired dehydration occured; however, the resultant styrene had been completely dimerised, leading to a 55% isolated yield of (*E*)-4,4'-(but-1-ene-1,3-diyl)bis(methoxybenzene) (**2b**)

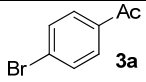
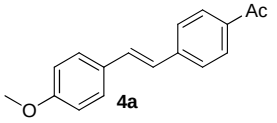
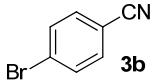
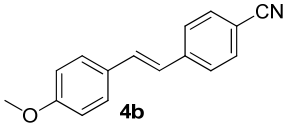
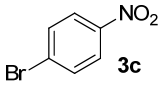
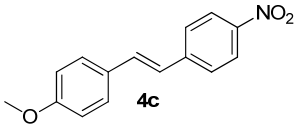
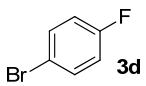
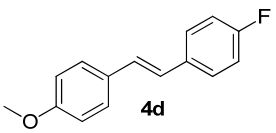
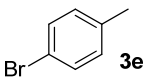
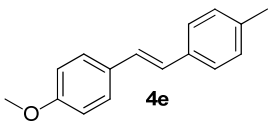
(Scheme 4.10, **B**). Remarkably, the dimerisation was completely suppressed when the reaction was carried out in DMSO, yielding the desired styrene **2a** in 91% isolated yield (Scheme 4.10, **A**). It must be noted that no reaction occurred in DMSO without the presence of the HPA

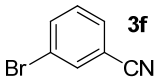
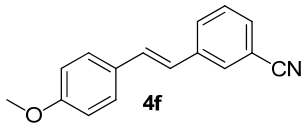
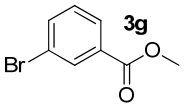
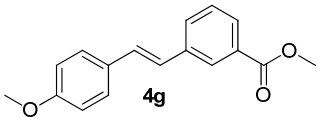
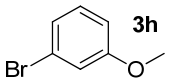
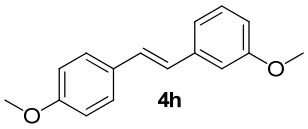
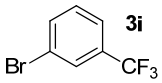
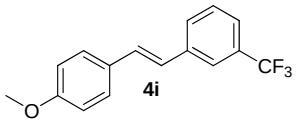
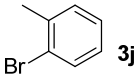
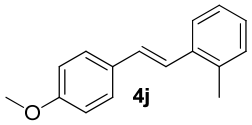
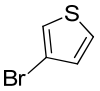
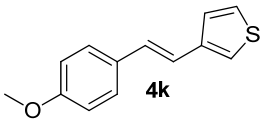
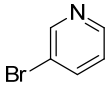
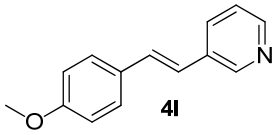
**- 4.2.2 One-pot synthesis of stilbenes**

Having found suitable conditions for the desired dehydration reaction, we turned our attention to the development of a one-pot dehydration-Heck procedure for the synthesis of stilbenes. Our initial attempts to have the HPA and components necessary for the Heck reaction in one-pot at the same time were unsuccessful, as the presence of a base needed for the Heck arylation neutralised the HPA, inhibiting the dehydration reaction. We therefore decided to develop a one-pot, two-step procedure consisting of initial dehydration of the secondary aryl alcohol in the presence of the HPA, followed by addition of a base, palladium catalyst and an aryl bromide coupling partner. A mixture of **1a** and HPA in DMSO was stirred at 100 °C for 1 h, at which point a mixture of aryl bromide **3a**, $NEt_3$, $Pd(dba)_2$ and $P(t\text{-}Bu)_3.HBF_4$[19] in DMF was added and the resultant mixture was stirred for a further 4 h. To our delight, this resulted in efficient formation of the desired stilbene product **4a**, with an isolated yield of 82% (Table 1). A number of aryl bromides were then examined. As can be seen from Table 1, this cascade reaction sequence proved tolerant of a wide range of functionality incorporated on the aryl bromide, yielding functionalised stilbenes in good yields. Both electron-rich and electron-deficient aryl bromides were successful, with substitution at the *ortho*, *meta* and *para* positions posing no problem. Furthermore, heterocyclic substrates were also shown to be viable (entries 11 and 12).

**Table 1**: Dehydration-Heck arylation of benzylic alcohol **1a** with aryl bromides **3a-l**.[a]




| entry | ArBr | product | Yield (%)[b] |
|---|---|---|---|
| 1 |  **3a** |  **4a** | 82 |
| 2 |  **3b** |  **4b** | 74 |
| 3 |  **3c** |  **4c** | 76 |
| 4 |  **3d** |  **4d** | 85 |
| 5 |  **3e** |  **4e** | 69 |

| | | | |
|---|---|---|---|
| 6 |  **3f** |  **4f** | 66 |
| 7 |  **3g** |  **4g** | 71 |
| 8 |  **3h** |  **4h** | 83 |
| 9 |  **3i** |  **4i** | 71 |
| 10 |  **3j** |  **4j** | 80 |
| 11 |  **3k** |  **4k** | 74 |
| 12 |  **3l** |  **4l** | 72 |

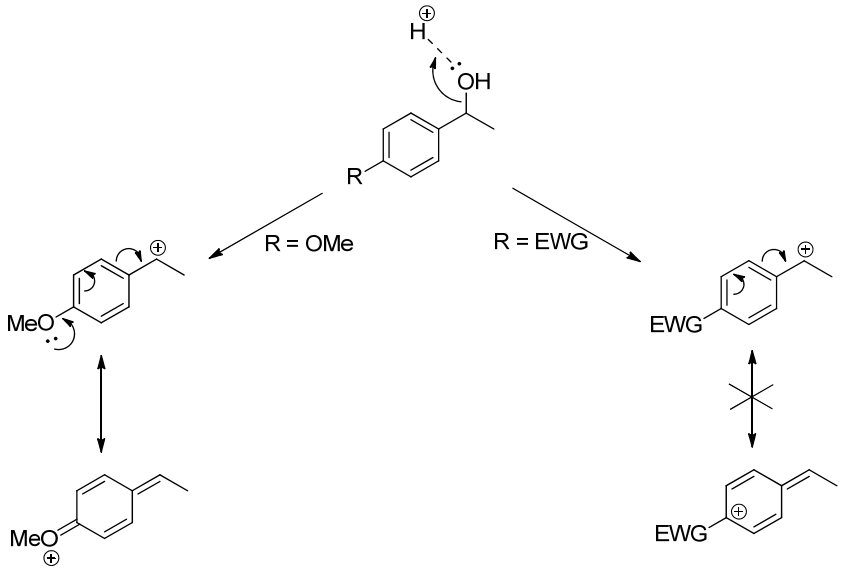
[a] General conditions: reactions carried out with **1a** (3 mmol) and $H_3PW_{12}O_{40}$ (50 mg) in 3 mL of DMSO at 100 °C for 1 h, followed by addition of $Et_3N$ (3 mmol), aryl bromide **3** (2 mmol), $Pd(dba)_2$ (0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (0.12 mmol) and DMF (3 mL) at 100 °C for 4 h. [b] Yield of isolated product.

If this newly developed protocol is truly general, it must work for a variety of secondary aryl alcohols. Therefore, we subjected a wide range of secondary aryl alcohols to the dehydration-Heck arylation sequence (Table 2). After attempting a small number of aryl alcohol substrates with varying electronic properties, it quickly became apparent that the current dehydration conditions were only suitable to electron rich aryl alcohols. For electron neutral aryl alcohols, a change of solvent from DMSO to diglyme was necessary, which allowed the alcohols to dehydrate to the corresponding styrene, with only small levels of the undesired dimerisation reaction.[20] In the case of the electron deficient aryl alcohol **1c**, use of 1,2-dichloroethane as solvent allowed successful dehydration to occur. It thus appears that solvent basicity plays an important role, with lower basicity needed for the generation of less stable carbocations. This rationale is expressed in Scheme 4.11 below. When the aryl possesses an electron donating substituent such as a methoxy group, the cationic carbon is stabilised by the extended conjugation. However, when the aryl possesses

an electron withdrawing group, the electron density of the π-system is reduced and therefore less able to stabilise the benzylic cation (*vida infra)*.

Careful solvent selection meant that a wide range of aryl alcohol substrates could be successfully employed, affording good to excellent yields of stilbenes (Table 2). Of particular note is that electron-rich heterocyclic aryl alcohols proved to be excellent substrates, giving access to interesting stilbene products (entries 10-12). In addition, non-terminal olefin intermediates could also be generated and were able to undergo the Heck arylation reaction, with very good isolated yields of the product stilbenes (entries 7 and 8).

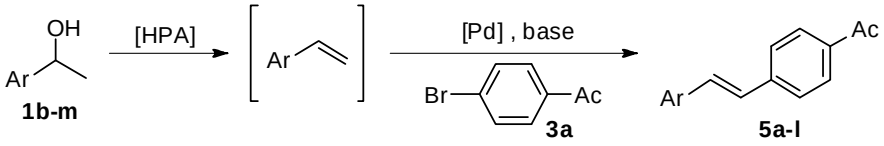
It is important to note that it is not possible to simply select the most active system (i.e. in 1,2-dichloroethane) for each aryl alcohol substrate, as this may lead to dimerisation of the product styrene. For example, dehydration of alcohol **1a** in 1,2-dichloroethane leads exclusively to the dimer **2b**. Therefore, in order to be selective towards styrenes, the dehydration conditions need to be optimised so that the system is sufficiently acidic to protonate the alcohol substrate, but unable to protonate the styrene produced, so that dimerisation cannot occur.

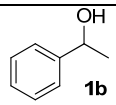
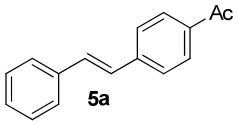
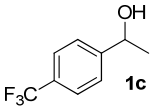
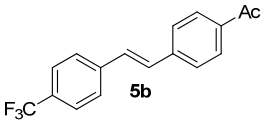
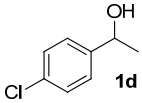
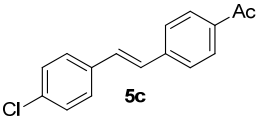
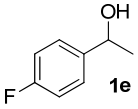
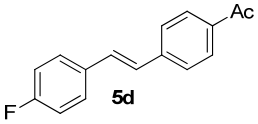
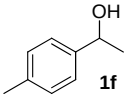
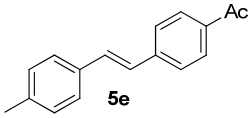
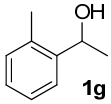
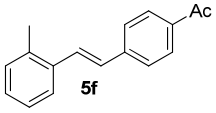
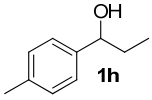
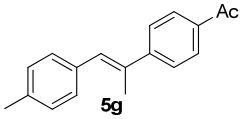
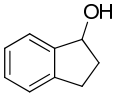
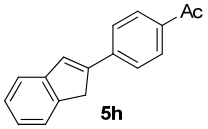
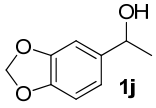
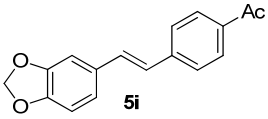
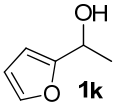
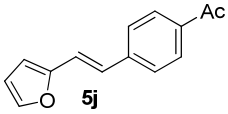
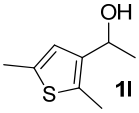
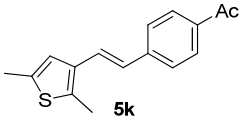


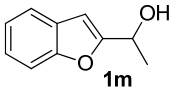
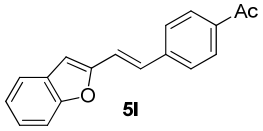

**Scheme 4.11**: Degree of stabilisation of cationic intermediates by neighbouring π-system

This cascade dehydration-arylation protocol tolerates the chloride substituent in **1** in the coupling with 4-bromoacetophenone **3a**, producing the chloride-substituted stilbene **5c** in 80% isolated yield; however, aryl chlorides can be used to couple with **1** as well. Thus, **5i** was also obtained when **3a** was replaced with 4-chloroacetophenone, albeit in a lower yield of 82% and a longer time of 18 h. Disappointingly, strongly electron-deficient aryl alcohols, such as 1-(4-nitrophenyl)ethanol, failed to undergo the desired dehydration reaction.

**Table 2**: Dehydration-Heck arylation of alcohols **1b-m** with 4-bromoacetophenone **3a**.[a]



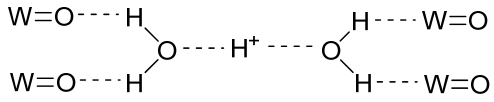

| entry | aryl alcohol | product | Yield (%)[b] |
|---|---|---|---|
| 1 |  1b |  5a | 70[c,d] |
| 2 |  1c |  5b | 51[e] |
| 3 |  1d |  5c | 80[c,d,f] |
| 4 |  1e |  5d | 51[c,d,f] |
| 5 |  1f |  5e | 68[g] |
| 6 |  1g |  5f | 76[c] |
| 7 |  1h |  5g | 72[c,f] |
| 8 |  1i |  5h | 89[c,f,h] |
| 9 |  1j |  5i | 91 |
| 10 |  1k |  5j | 66 |
| 11 |  1l |  5k | 74 |

| | | | |
|---|---|---|---|
| 12 |   |   | 68[i] |

[a] General conditions: reactions were carried out with alcohol **1b-m** (3 mmol) and $H_3PW_{12}O_{40}$ (50 mg) in 3 mL of DMSO at 100 °C for 1 h, followed by addition of $Et_3N$ (3 mmol), **3a** (2 mmol), $Pd(dba)_2$ (0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (0.12 mmol) and DMF (3 mL) at 100 °C for 4 h. [b] Yield of isolated product. [c] Diglyme as initial solvent. [d] 4 mmol of alcohol was used. [e] 1,2-Dichloroethane as initial solvent. [f] 18 h for arylation. [g] Dehydration at 130 °C for 2 h. [h] 10 min. for dehydration. [i] 2 h for dehydration.

### 4.2.3 Solvation controlled acidity of HPA

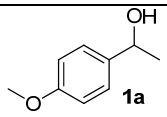
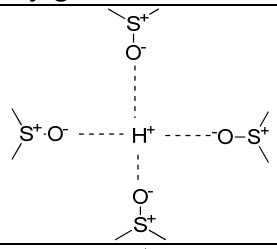
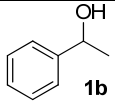
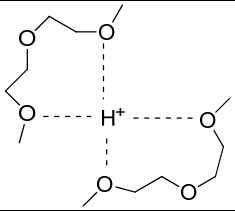
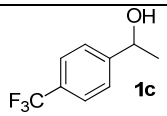
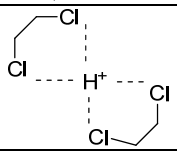
The effect of solvent choice on the reactivity and selectivity of the dehydration reactions was quite remarkable. In search of some basic explanation, we considered the effects solvation may have on the Brønsted acidity of the HPA. If one considers the structure of the HPA in question, $H_3PW_{12}O_{40}.nH_2O$, it is reasonable to predict that strong solvation of $H^+$ is likely to occur (Scheme 4.12).[7a]



**Scheme 4.12**: Schematic structure of bulk proton sites in $H_3PW_{12}O_{40}.6H_2O$

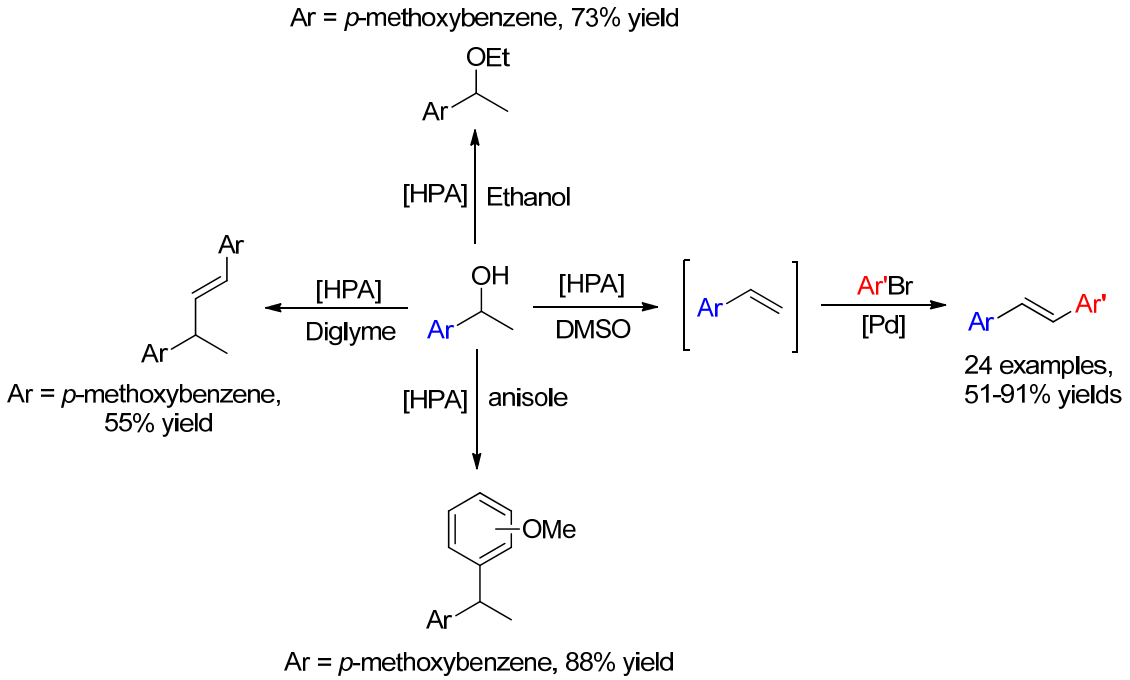
In the hydrated form of HPA, the protons are held by hydrogen bonding to water molecules, forming diaquahydrogen ions, $H_5O_2^+$, which are themselves hydrogen bonded to the heteropolyanions. When the HPA is dissolved in the reaction solvent, the protons are likely to be solvated by the excess of solvent molecules. As a result, one may predict that as the hydrogen bonding acceptor ability (β) of the solvent medium increases, the Brønsted acidity of the HPA will decrease, i.e. the HPA will exhibit a higher relative pKa. This may be compared to the levelling effect of pKa in water.[21] In line with this view, the β values of the three successful solvents used for the dehydration reaction of aryl alcohols correlate well with the observed reactivity for the different substrates (Table 3).[22] As the electron density of the aryl ring decreases, the substrates become less reactive and so higher Bronsted acidity is required in order to promote the dehydration reaction.

**Table 3**: Effect of solvation upon relative acidity of HPA

| Substrate | Reaction Solvent | β | Conjugate acid of solvent |
|---|---|---|---|
|  **1a** | DMSO | 0.76 |  |
|  **1b** | Diglyme | ~ 0.47 |  |
|  **1c** | 1,2-Dichloroethane | ~ 0.10 |  |

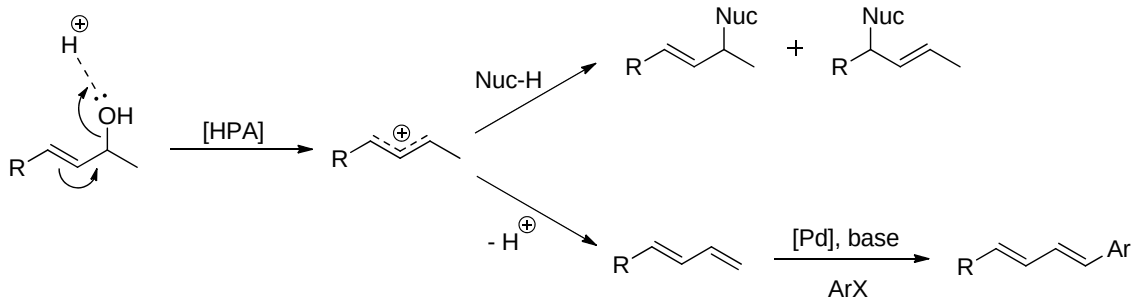
### 4.3 Conclusions and future work

The selective dehydration of secondary aryl alcohols to the corresponding styrenes has been successfully developed by use of a Keggin type HPA catalyst, $H_3PW_{12}O_{40}$. The activity of the acid catalyst was controlled by careful selection of the solvent medium. When electron-rich aryl alcohols were employed, the slightly basic medium of DMSO proved effective. When electron-neutral and electron-deficient aryl alcohols were used, a less basic medium of an ether solvent or halogenated solvent, respectively, yielded a more active catalyst that is capable of overcoming the loss of stabilisation of the benzylic cation by the aromatic π-system (Scheme 4.11). We have also demonstrated that with careful choice of solvent, HPA catalysis allows a range of useful products, including styrenes, to be selectively produced from aryl alcohols (Scheme 4.12).




**Scheme 4.12**: Summary of HPA catalysed reactions of secondary aryl alcohols

Development of a single catalyst system that is effective for a wider range of aryl alcohols, particularly those that are electron-deficient, as well as extension of the methods into other alcohols will be of interest to future work. For example, allylic alcohols may be suitably active substrates for the dehydration reactions, due to the comparable stabilisation of possible cationic intermediates to that of aryl alcohols (Scheme 4.13).




**Scheme 4.13**: Extension of methodology towards allylic alcohols

## 4.4 Experimental

**Materials:** All the reactions were carried out under a nitrogen atmosphere with dried solvents. Silica gel plates (GF254) were used for TLC monitoring and silica gel (230-400 mesh) was used for flash column chromatography. The following chemicals were purchased from Aldrich, Apollo Scientific or Alpha Aesar, and used as received: aryl bromides **3a-l**, aryl alcohols **1a-g**, $Pd(dba)_2$, $P(t\text{-}Bu)_3.HBF_4$, $H_3PW_{12}O_{40}.xH_2O$, $Et_3N$, DMSO, diglyme, 1,2-dichloroethane and *N,N*-dimethylformamide. Alcohols **1h-m** were synthesised by reduction of the parent ketone using $NaBH_4$ in MeOH (room temperature for thirty minutes). The $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker DRX-400 spectrometer with TMS as the internal standard. The mass spectra were obtained by electrospray ionisation (ES) or by chemical ionisation (CI).

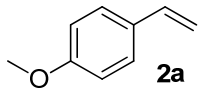
**Reactions of 1-(4-methoxyphenyl)ethanol in different solvents:** An oven-dried carousel tube containing a stirrer bar was charged with $H_3PW_{12}O_{40}.xH_2O$ (17 mg). After degassing three times with nitrogen, 1-(4-methoxyphenyl)ethanol (0.14 mL, 1.0 mmol) and solvent (2 mL) were injected and the reaction mixture was stirred at 100-130 °C for 1 h. After cooling down to room temperature, a saturated solution of $NaHCO_{3(aq)}$ (25 mL) was added and the product was extracted with Hexane/EtOAc (3:1, 3 x 20 mL). The organic washes were combined and concentrated *in vacuo* to yield the crude product, which was purified by column chromatography (1% EtOAc/Hexane). Products **2a-d** were obtained in 55-91% yields (Figure 1).

**General procedure for the dehydration-Heck arylation sequence:** An oven-dried carousel tube containing a stirrer bar was charged with $H_3PW_{12}O_{40}.xH_2O$ (50 mg). After degassing three times with nitrogen, an alcohol (**1a-m)** (3.0 mmol) and solvent (3 mL) were injected and the reaction mixture was stirred at 100 °C for 1h. $Et_3N$ (3 mmol) was injected before injection of a preformed mixture of aryl bromide (**3a-l**) (2 mmol), $Pd(dba)_2$ (0.04 mmol), $P(t\text{-}Bu)_3.HBF_4$ (0.12 mmol) and DMF (3 mmol), and the resultant mixture was stirred at 100 °C for 4 h. After cooling down to room temperature, a saturated solution of $NaHCO_{3(aq)}$ (150 mL) was added and the product was extracted with toluene (5 x 20 mL). The organic washes were combined and concentrated *in vacuo* to yield the crude product, which was purified by recrystallisation in hexane/EtOAc. The desired stilbene products **4a-l** and **5a-l** were obtained in 51-91% yields (Tables 1 and 2).

**Preparation of secondary aryl alcohol substrates (1h-m):** A mixture of ketone (5 mmol) and $NaBH_4$ (10 mmol) in anhydrous MeOH (50 mL) was stirred at room temperature for 30 minutes. Saturated $NaHCO_{3(aq)}$ (50 mL) and $CH_2Cl_2$ (100 mL) were added, and the mixture was stirred at room temperature for 10 minutes. The organic layer was removed, and the aqueous layer was extracted with $CH_2Cl_2$ (50 mL). The combined organic extracts were dried over anhydrous $Na_2SO_4$ and concentrated to give the alcohol.

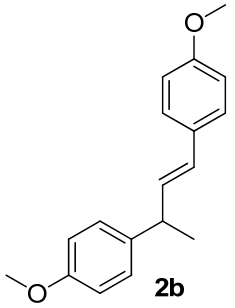
**4.5 Analytical data**

*All analytical data is in agreement with that previously reported in the literature, which is referenced accordingly.*



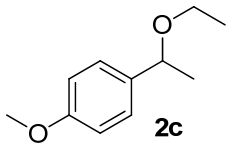

**2a**

**1-Methoxy-4-vinylbenzene (2a).**[23] 1-(4-Methoxyphenyl)ethanol was reacted with $H_3PW_{12}O_{40}.xH_2O$ (17 mg) in DMSO (2 mL) at 100 °C for 1 h. Work-up and column chromatography (1% EtOAc/hexane) yielded 122 mg (91%) of the title compound as a colourless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.66 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.60 (dd, *J* = 17.6, 1.0 Hz, 1H), 5.12 (dd, *J* = 10.9, 0.9 Hz, 1H), 3.80 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.8, 136.6, 130.9, 127.8, 114.3, 112.0, 55.7; MS (CI, *m/z*) 135 $[M + H]^+$; Anal. calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.95; H, 7.61.



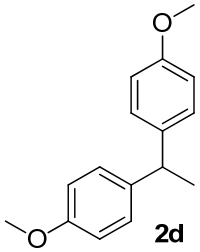

**2b**

**(*E*)-4,4'-(But-1-ene-1,3-diyl)bis(methoxybenzene) (2b).**[24] 1-(4-Methoxy phenyl)ethanol was reacted with $H_3PW_{12}O_{40}.xH_2O$ (17 mg) in diglyme (2 mL) at 100 °C for 1 h. Work-up and column chromatography (1% EtOAc/hexane) yielded 148 mg (55%) of the title compound as a creamy-white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.32 (d, *J* = 16.0 Hz, 1H), 6.21 (dd, *J* = 15.9, 6.6 Hz, 1H), 3.78 (s, 3H), 3.78 (s, 3H), 3.56 (m, 1H), 1.42 (d, *J* = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.2, 158.4, 138.4, 134.0, 130.9, 128.6, 128.0, 127.6, 114.3, 114.3, 55.7, 42.1, 21.9; MS (CI, *m/z*) 269 $[M + H]^+$ ; Anal. calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.95; H, 7.56. Melting point: 32-36 °C.



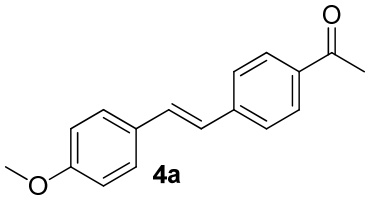
**2c**

**1-(1-Ethoxyethyl)-4-methoxybenzene (2c).**[25] 1-(4-Methoxyphenyl)ethanol was reacted with $H_3PW_{12}O_{40}.xH_2O$ (17 mg) in EtOH (2 mL) at 100 °C for 1 h. Work-up and column chromatography (1% EtOAc/hexane) yielded 132 mg (73%) of the title compound as a colourless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.5 Hz, 2H), 6,87 (d, *J* = 8.7 Hz, 2H), 4.35 (q, *J* = 6.5 Hz, 1H), 3.80 (s, 3H), 3.33 (q, *J* = 7.0 Hz, 2H), 1.42 (d, *J* = 6.5 Hz, 3H), 1.17 (t, *J* = 7.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.3, 136.7, 127.7, 114.2, 64.0, 55.6, 24.6, 15.8; MS (CI, *m/z*) 135 $[M - OEt]^+$ ; Anal. calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 74.01; H, 9.26.



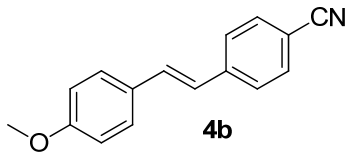
**2d**

**4,4'-(Ethane-1,1-diyl)bis(methoxybenzene) (2d).**[26] 1-(4-Methoxyphenyl) ethanol was reacted with $H_3PW_{12}O_{40}.xH_2O$ (17 mg) in anisole (2 mL) at 100 °C for 1 h. Work-up and column chromatography (1% EtOAc/hexane) yielded 213 mg (88%) of the title compound as a creamy-white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.5 Hz, 4H), 6.81 (d, *J* = 8.8 Hz, 4H), 4.05 (q, *J* = 7.2 Hz, 1H), 3.76 (s, 6H), 1.58 (d, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 158.2, 139.4, 128.8, 114.1, 55.6, 43.5, 22.7; MS (CI, *m/z*) 260 $[M + NH_3 + H]^+$ ; Anal. calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.07; H, 7.61. Melting point: 43-46 °C.



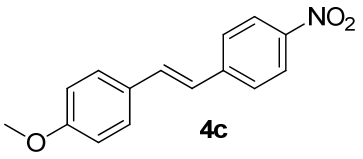
**4a**

**(*E*)-1-(4-(4-Methoxystyryl)phenyl)ethanone (4a).**[27] The general procedure for the dehydrative Heck arylation was employed by reacting 1-(4-methoxyphenyl)ethanol (0.42 mL, 3.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in DMSO (3 mL) at 100 °C for 1 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 4-bromoacetophenone (398 mg, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 4 h at 100 °C, work-up and recrystallisation in hexane/EtOAc yielded 414 mg (82%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 16.3 Hz, 1H), 6.98 (d, *J* = 16.3 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H), 2.59 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.8, 160.3, 142.8, 136.0, 131.4, 129.9, 129.3, 128.5, 126.6, 125.7, 114.7, 55.7, 26.9; HRMS for $C_{17}H_{16}NaO_2$ $[M + Na]^+$ : *m/z* Calcd: 275.1043; Found: 275.1051 ; Anal. calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.55; H, 6.36. Melting point: 169-172 °C.



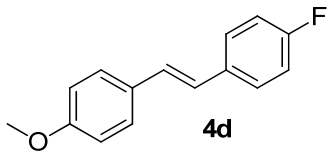
**4b**

**(*E*)-4-(4-Methoxystyryl)benzonitrile (4b).**[28] The general procedure for the dehydrative Heck arylation was employed by reacting 1-(4-methoxyphenyl)ethanol (0.42 mL, 3.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in DMSO (3 mL) at 100 °C for 1 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 4-bromobenzonitrile (364 mg, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 4 h at 100 °C, work-up and recrystallisation in hexane/EtOAc yielded 348 mg (74%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.16 (d, *J* = 16.3 Hz, 1H), 6.94 (d, *J* = 16.1 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.5, 142.6, 132.8, 132.4, 129.5, 128.7, 127.0, 125.0, 119.5, 114.7, 110.5, 55.8; MS (CI, *m/z*) 253 $[M + NH_3 + H]^+$ ; Anal. calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.43; H, 5.51; N, 5.82. Melting point: 139-144 °C.



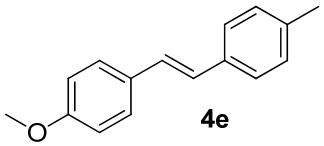

**4c**

**(*E*)-1-Methoxy-4-(4-nitrostyryl)benzene (4c).**[28] The general procedure for the dehydrative Heck arylation was employed by reacting 1-(4-methoxyphenyl)ethanol (0.42 mL, 3.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in DMSO (3 mL) at 100 °C for 1 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 1-bromo-4-nitrobenzene (404 mg, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 4 h at 100 °C, work-up and recrystallisation in hexane/EtOAc yielded 388 mg (76%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.9 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.21 (d, *J* = 16.3 Hz, 1H), 6.99 (d, *J* = 16.3 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.7, 146.8, 144.7, 133.3, 129.4, 128.8, 126.9, 124.5, 124.5, 114.8, 55.8; HRMS for $C_{15}H_{13}NNaO_3$ $[M + Na]^+$ : *m/z* Calcd: 278.0788; Found: 278.0797 ; Anal. calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.29; H, 5.02; N, 5.33. Melting point: 128-130 °C.



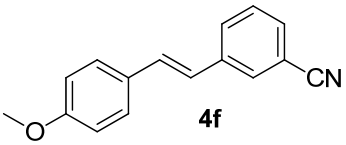

**4d**

**(*E*)-1-Fluoro-4-(4-methoxystyryl)benzene (4d).**[29] The general procedure for the dehydrative Heck arylation was employed by reacting 1-(4-methoxyphenyl)ethanol (0.42 mL, 3.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in DMSO (3 mL) at 100 °C for 1 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 1-bromo-4-fluorobenzene (0.22 mL, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 4 h at 100 °C, work-up and recrystallisation in hexane/EtOAc yielded 388 mg (85%) of the title compound. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.45-7.41 (m, 4H), 7.02 (t, *J* = 8.7 Hz, 2H), 6.97 (d, *J* = 16.3 Hz, 1H), 6.91 (d, *J* = 16.3 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H); *$^{13}$C NMR (100 MHz, $CDCl_3$) δ* 162.5 (d, $J_{CF}$ = 246.6 Hz), 159.8, 134.3 (d, $J_{CF}$ = 3.3 Hz), 130.4, 128.4 (d, $J_{CF}$ = 2.3 Hz), 128.1 (d, $J_{CF}$ = 7.8 Hz), 128.1, 128.0, 125.8, 116.0 (d, $J_{CF}$ = 21.6 Hz), 114.6, 55.7; MS (CI, *m/z*) 229 $[M + H]^+$ ; Anal. calcd for $C_{15}H_{13}FO$: C, 78.93; H, 5.74. Found: C, 78.80; H, 5.73. Melting point: 143-145 °C.



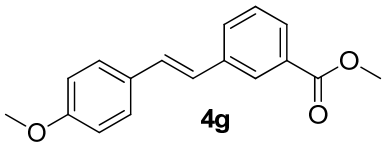
**4e**

**(*E*)-1-Methoxy-4-(4-methylstyryl)benzene (4e).**[30] The general procedure for the dehydrative Heck arylation was employed by reacting 1-(4-methoxyphenyl)ethanol (0.42 mL, 3.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in DMSO (3 mL) at 100 °C for 1 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 4-bromotoluene (342 mg, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 4 h at 100 °C, work-up and recrystallisation in hexane/EtOAc yielded 310 mg (69%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.7 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 7.02 (d, *J* = 16.3 Hz, 1H), 6.94 (d, *J* = 16.3 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 2.35 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.6, 137.4, 135.3, 130.8, 129.8, 128.0, 127.6, 127.0, 126.6, 114.5, 55.7, 21.6; MS (CI, *m/z*) 225 $[M + H]^+$ ; Anal. calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.64; H, 7.22. Melting point: 163-164 °C.



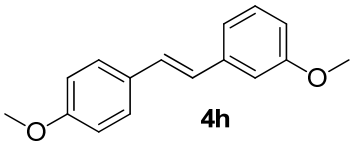
**4f**

**(*E*)-3-(4-Methoxystyryl)benzonitrile (4f).**[31] The general procedure for the dehydrative Heck arylation was employed by reacting 1-(4-methoxyphenyl)ethanol (0.42 mL, 3.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in DMSO (3 mL) at 100 °C for 1 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 3-bromobenzonitrile (364 mg, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 4 h at 100 °C, work-up and recrystallisation in hexane/EtOAc yielded 311 mg (66%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.48-7.39 (m, 4H), 7.08 (d, *J* = 16.3 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 16.4 Hz, 1H), 3.82 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.3, 139.4, 131.2, 130.7, 130.6, 130.0, 129.8, 129.6, 128.5, 124.4, 119.3, 114.7, 113.3, 55.8; MS (CI, *m/z*) 253 $[M + NH_3 + H]^+$ ; Anal. calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.72; H, 5.50; N, 6.14. Melting point: 110-113 °C.



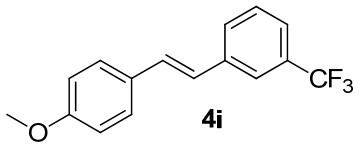
**4g**

**(*E*)-Methyl 3-(4-methoxystyryl)benzoate (4g).** The general procedure for the dehydrative Heck arylation was employed by reacting 1-(4-methoxyphenyl)ethanol (0.42 mL, 3.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in DMSO (3 mL) at 100 °C for 1 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), Methyl 3-bromobenzoate (430 mg, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 4 h at 100 °C, work-up and recrystallisation in hexane/EtOAc yielded 381 mg (71%) of the title compound. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.88 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.12 (d, *J* = 16.3 Hz, 1H), 6.97 (d, *J* = 16.3 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 3.93 (s, 3H), 3.82 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 167.5, 160.0, 138.4, 131.0, 131.0, 130.2, 129.9, 129.1, 128.5, 128.3, 127.6, 125.9, 114.6, 55.7, 52.5; MS (CI, *m/z*) 269 $[M + H]^+$ ; Anal. calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.17; H, 5.95. Melting point: 111-114 °C.



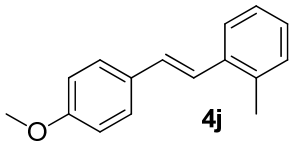
**4h**

**(*E*)-1-Methoxy-3-(4-methoxystyryl)benzene (4h).**[32] The general procedure for the dehydrative Heck arylation was employed by reacting 1-(4-methoxyphenyl)ethanol (0.42 mL, 3.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in DMSO (3 mL) at 100 °C for 1 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 3-bromoanisole (0.25 mL, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 4 h at 100 °C, work-up and recrystallisation in hexane/EtOAc yielded 399 mg (83%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.09-7.01 (m, 3H), 6.93 (d, *J* = 16.3 Hz, 1H), 6.89 9d, *J* = 8.8 Hz, 2H), 6.79 (ddd, *J* = 8.2, 2.5, 0.7 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.3, 159.8, 139.6, 130.5, 130.0, 129.0, 128.2, 126.9, 119.4, 114.6, 113.3, 112.0, 55.7, 55.7; MS (CI, *m/z*) 241 $[M + H]^+$ ; Anal. calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.92; H, 6.70. Melting point: 104-108 °C.



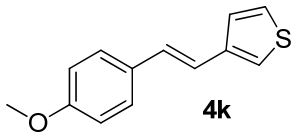

**4i**

**(*E*)-1-(4-Methoxystyryl)-3-(trifluoromethyl)benzene (4i).**[33] The general procedure for the dehydrative Heck arylation was employed by reacting 1-(4-methoxyphenyl)ethanol (0.42 mL, 3.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in DMSO (3 mL) at 100 °C for 1 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 1-bromo-3-(trifluoromethyl)benzene (0.28 mL, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 4 h at 100 °C, work-up and column chromatography (2% EtOAc/hexane) yielded 395 mg (71%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.46-7.39 (m, 4H), 7.09 (d, *J* = 16.3 Hz, 1H), 6.95 (d, *J* = 16.3 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.2, 138.9, 131.5 (q, $J_{CF}$ = 32.0 Hz), 130.5, 129.9, 129.7, 129.5, 128.4, 125.4, 124.6 (q, $J_{CF}$ = 272.6 Hz), 124.0 (q, $J_{CF}$ = 3.8 Hz), 123.2 (q, $J_{CF}$ = 3.8 Hz), 114.7, 55.7; MS (CI, *m/z*) 279 $[M + H]^+$; HRMS for $C_{16}H_{14}F_3O$ $[M + H]^+$ : *m/z* Calcd: 279.0991; Found: 279.0992. Melting point: 77-79 °C.



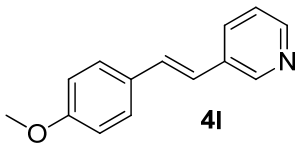

**4j**

**(*E*)-1-(4-Methoxystyryl)-2-methylbenzene (4j).**[34] The general procedure for the dehydrative Heck arylation was employed by reacting 1-(4-methoxyphenyl)ethanol (0.42 mL, 3.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in DMSO (3 mL) at 100 °C for 1 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 2-bromotoluene (0.24 mL, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 4 h at 100 °C, work-up and recrystallisation in hexane/EtOAc yielded 359 mg (80%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.4 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.20-7.12 (m, 4H), 6.94 (d, *J* = 16.2, 1H), 6.89 (d, *J* = 8.8 Hz), 3.80 (s, 3H), 2.40 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.8, 137.1, 136.0, 131.0, 130.8, 130.0, 128.2, 127.6, 126.6, 125.6, 124.9, 114.6, 55.8, 20.4; MS (CI, *m/z*) 225 $[M + H]^+$ ; Anal. calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.62; H, 7.27. Melting point: 74-76 °C.



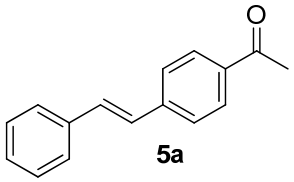
**4k**

**(*E*)-3-(4-Methoxystyryl)thiophene (4k).**[35] The general procedure for the dehydrative Heck arylation was employed by reacting 1-(4-methoxyphenyl)ethanol (0.42 mL, 3.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in DMSO (3 mL) at 100 °C for 1 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 3-bromothiophene (0.19 mL, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 4 h at 100 °C, work-up and recrystallisation in hexane/EtOAc yielded 320 mg (74%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.6 Hz, 2H), 7.33-7.28 (m, 2H), 7.20 (dd, *J* = 2.8, 1.3 Hz, 1H), 6.99 (d, *J* = 16.3 Hz, 1H), 6.92-6.97 (m, 3H), 3.81 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.6, 140.8, 130.6, 128.7, 127.9, 126.4, 125.3, 121.9, 121.4, 114.6, 55.7; MS (CI, *m/z*) 217 $[M + H]^+$ ; Anal. calcd for $C_{13}H_{12}OS$: C, 72.19; H, 5.59. Found: C, 71.52; H, 5.43. Melting point: 148-152 °C.



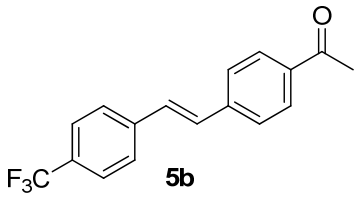
**4l**

**(*E*)-3-(4-methoxystyryl)pyridine (4l).**[36] The general procedure for the dehydrative Heck arylation was employed by reacting 1-(4-methoxyphenyl)ethanol (0.42 mL, 3.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in DMSO (3 mL) at 100 °C for 1 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 3-bromopyridine (0.19 mL, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 4 h at 100 °C, work-up and recrystallisation in hexane/EtOAc yielded 304 mg (72%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 2.1 Hz, 1H), 8.45 (dd, *J* = 4.8, 1.6, 1H), 7.78 (dt, *J* = 8.0, 1.9 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.25 (dd, *J* = 8.0, 4.7 Hz, 1H), 7.10 (d, *J* = 16.4 Hz, 1H), 6.94-6.89 (m, 3H), 3.82 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.2, 148.7, 148.6, 133.7, 132.8, 130.7, 129.9, 128.3, 123.9, 123.1, 114.6, 55.7; MS (CI, *m/z*) 212 $[M + H]^+$ ; Anal. calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N; 6.63. Found: C, 79.34; H, 6.17; N, 6.60. Melting point: 98-101 °C.



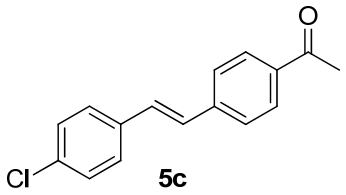
**5a**

**(*E*)-1-(4-Styrylphenyl)ethanone (5a).**[37] The general procedure for the dehydrative Heck arylation was employed by reacting 1-phenylethanol (0.49 mL, 4.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in diglyme (3 mL) at 100 °C for 1 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 4-bromoacetophenone (398 mg, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 4 h at 100 °C, work-up and column chromatography (2% EtOAc/hexane) yielded 311 mg (70%) of the title compound. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.54-7.51 (m, 2H), 7.39-7.35 (m, 2H), 7.31-7.27 (m, 1H), 7.21 (d, *J* = 16.3 Hz, 1H), 7.11 (d, *J* = 16.3 Hz, 1H), 2.59 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.8, 142.4, 137.1, 136.4, 131.9, 129.3, 129.2, 128.7, 127.9, 127.2, 126.9, 27.0; MS (CI, *m/z*) 240 $[M + NH_3 + H]^+$ ; Anal. calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.47; H, 6.37.



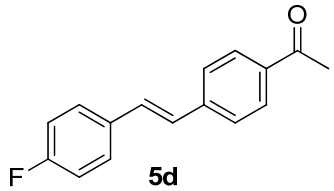
**5b**

**(*E*)-1-(4-(4-(Trifluoromethyl)styryl)phenyl)ethanone (5b).**[38] The general procedure for the dehydrative Heck arylation was employed by reacting 1-(4-(trifluoromethyl)phenyl)ethanol (570 mg, 3.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in 1,2-dichloroethane (3 mL) at 100 °C for 1 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 4-bromoacetophenone (398 mg, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 18 h at 100 °C, work-up and recrystallisation from hot EtOAc/hexane (1:10) yielded 296 mg (51%) of the title compound as a white powder. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.5 Hz, 1H), 7.26-7.22 (m, 6H), 6.90 – 6.83 (m, 2H), 2.25 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ; 197.52, 141.34, 140.30, 136.65, 130.09, 129.92, 129.07, 127.04, 126.95, 125.95, 125.91, 125.87, 125.83, 26.75; $^{19}$F {$^{13}$C} NMR (376 MHz, $CDCl_3$) δ -62.97; MS (CI, m/z) 313 $[M + Na]^+$; HRMS for $C_{17}H_{13}OF_3Na$ $[M + Na]^+$ : *m/z* calcd: 313.0816; Found: 313.0803. Melting point: 131-133 °C.



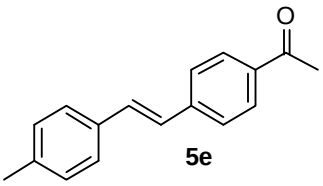

**5c**

**(*E*)-1-(4-(4-(Chlororomethyl)styryl)phenyl)ethanone (5c).** The general procedure for the dehydrative Heck arylation was employed by reacting 1-(4-chlorophenyl)ethanol (624 mg, 4.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in diglyme (3 mL) at 100 °C for 1 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 4-bromoacetophenone (398 mg, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 18 h at 100 °C, work-up and recrystallisation from hot EtOAc/hexane (1:10) yielded 410 mg (80%) of the title compound as an off white powder. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 16.3 Hz, 1H), 7.10 (d, *J* = 16.3 Hz, 1H), 2.61 (s, 3H); $^{13}$C {$^1$H} NMR (101 MHz, $CDCl_3$) δ 197.55, 141.77, 136.31, 135.37, 134.11, 130.23, 129.14, 129.05, 128.21, 128.10, 126.70, 26.74; MS (CI, m/z) 257.3 $[M + H]^+$; Anal. calcd for $C_{16}H_{13}ClO$: C, 74.85; H, 5.10. Found: C, 74.79; H, 5.15. Melting point: 136-139 °C.



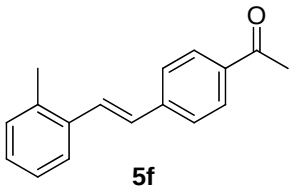

**5d**

**(*E*)-1-(4-(4-(Fluororomethyl)styryl)phenyl)ethanone (5d).**[39] The general procedure for the dehydrative Heck arylation was employed by reacting 1-(4-fluorophenyl)ethanol (560 mg, 4.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in diglyme (3 mL) at 100 °C for 1 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 4-bromoacetophenone (398 mg, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 18 h at 100 °C, work-up and purification by column chromatography (10% EtOAc/hexane, r.f. 0.3) yielded 245 mg (51%) of the title compound as a white powder. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.50 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.18 (d, *J* = 16.4 Hz, 1H), 7.10 – 6.99 (m, 2H + 1H), 2.60 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.53, 164.08, 161.61, 141.95, 136.13, 133.06, 133.03, 130.32, 129.02, 128.54, 128.46, 127.39, 127.36, 126.55, 116.03, 115.81, 26.69; $^{19}$F {$^{13}$C} NMR (376 MHz, $CDCl_3$) δ -133.41; MS ($ES^+$, m/z) 263 $[M + Na]^+$; HRMS for $C_{16}H_{13}NONa$ $[M + Na]^+$ : *m/z* calcd: 263.0848; Found: 263.0851. Melting point: 117-120 °C.



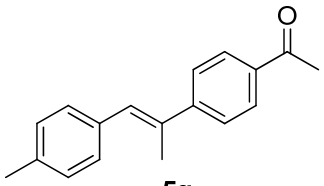
**5e**

**(*E*)-1-(4-(4-Methylstyryl)phenyl)ethanone.**[28] The general procedure for the dehydrative Heck arylation was employed by reacting 1-(*p*-tolyl)ethanol (0.41 mL, 3.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in DMSO (3 mL) at 130 °C for 2 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 4-bromoacetophenone (398 mg, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 4 h at 100 °C, work-up and recrystallisation in hexane/EtOAc yielded 321 mg (68%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.22-7.18 (m, 3H), 7.07 (d, *J* = 16.3 Hz, 1H), 2.60 (s, 3H), 2.37 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.9, 142.7, 138.8, 136.2, 134.4, 131.8, 129.9, 129.3, 127.2, 126.9, 126.8, 27.0, 21.7; MS (CI, *m/z*) 237 $[M + H]^+$ ; Anal. calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.82. Found: C, 85.78; H, 6.80. Melting point: 169-172 °C.



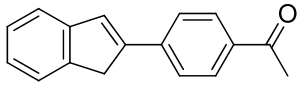
**5f**

**(*E*)-1-(4-(2-(Methyl)styryl)phenyl)ethanone (5f).** The general procedure for the dehydrative Heck arylation was employed by reacting 1-(*o*-tolyl)ethanol (409 mg, 3.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in diglyme (3 mL) at 100 °C for 1 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 4-bromoacetophenone (398 mg, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 18 h at 100 °C, work-up and and recrystallisation from hot EtOAc/hexane (1:10) yielded 359 mg (76%) of the title compound as a white powder. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 2H), 7.60 (m, *3H*), 7.47 (d, *J* = 16.2 Hz, 1H), 7.22 (m, 3H), 7.03 (d, *J* = 16.2 Hz, 1H), 2.62 (s, 3H), 2.46 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.60, 142.47, 136.30, 136.09, 135.90, 130.70, 129.39, 129.01, 128.89, 128.33, 126.68, 126.44, 125.63, 26.73, 20.04; MS (CI, m/z) 237.3 $[M + H]^+$; Anal. calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.82. Found: C, 85.72; H, 6.79.



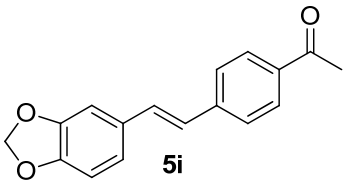
**5g**

**(*E*)-1-(4-(1-(*p*-Tolyl)prop-1-en-2-yl)phenyl)ethanone (5g).** The general procedure for the dehydrative Heck arylation was employed by reacting 1-(*p*-tolyl)propan-1-ol (450 mg, 3.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in diglyme (3 mL) at 100 °C for 1 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 4-bromoacetophenone (398 mg, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 18 h at 100 °C, work-up and purification by column chromatography (10% EtOAc/hexane, r.f. 0.3) yielded 360 mg (72%) of the title compound as a white powder. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 6.91 (s, 1H), 2.62 (s, 3H), 2.38 (s, 3H), 2.30 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ; 197.77, 148.92, 136.87, 135.78, 135.02, 129.79, 129.26, 129.12, 128.70, 128.63, 126.16, 26.74, 21.38, 17.43; MS (CI, m/z) 251 $[M + H]^+$; Anal. calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 85.91; H, 6.66. Melting point: 98-104 °C.



**5h**

**(1-(4-(1*H*-Inden-2-yl)phenyl)ethanone (5h).**[40] The general procedure for the dehydrative Heck arylation was employed by reacting indanol (402 mg, 3.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in diglyme (3 mL) at 100 °C for 10 min, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 4-bromoacetophenone (398 mg, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 18 h at 100 °C, work-up and and recrystallisation from hot EtOAc/hexane (1:10) yielded 417 mg (89%) of the title compound as a white powder. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.38 (s, 1H), 7.33 – 7.28 (m, 1H), 7.23 (td, *J* = 7.5, 1.1 Hz, 1H), 3.82 (s, 2H), 2.62 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.54, 145.18, 145.00, 143.55, 140.60, 135.92, 129.44, 129.04, 126.99, 125.71, 123.96, 121.70 (two aromatic peaks are overlapped), 39.09, 26.72; MS (CI, m/z) 235 $[M + H]^+$. Melting point: 157-162 °C.



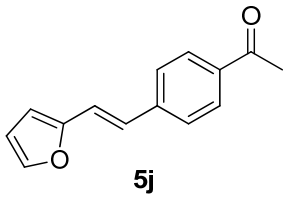
**5i**

**(*E*)-1-(4-(2-(benzo[d][1,3]dioxol-5-yl)vinyl)phenyl)ethanone (5i).**[41]

**From aryl bromide**; The general procedure for the dehydrative Heck arylation was employed by reacting 1-(benzo[d][1,3]dioxol-5-yl)ethanol (498 mg, 3.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in DMSO (3 mL) at 100 °C for 1 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 4-bromoacetophenone (398 mg, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 4 h at 100 °C, work-up and recrystallisation from hot EtOAc/hexane (1:10) yielded 484 mg (91%) of the title compound as a pale yellow powder.

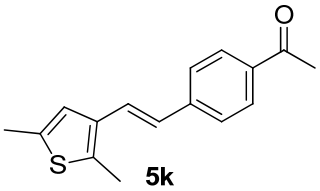
**From aryl chloride;** The general procedure for the dehydrative Heck arylation was employed by reacting 1-(benzo[d][1,3]dioxol-5-yl)ethanol (498 mg, 3.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in DMSO (3 mL) at 100 °C for 1 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 4-chloroacetophenone (309 mg, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.06 mmol) and DMF (3 mmol). After a further 18 h at 100 °C, work-up and recrystallisation from hot EtOAc/hexane (1:10) yielded 436 mg (82%) of the title compound as a pale yellow powder.

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 16.3 Hz, 1H), 7.09 (d, *J* = 1.7 Hz, 1H), 7.00 – 6.91 (m, 2H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.00 (s, 2H), 2.60 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.55, 148.45, 148.09, 142.31, 135.90, 131.42, 131.30, 129.03, 126.41, 125.89, 122.30, 108.67, 105.83, 101.43, 26.70; MS (CI, m/z) 267 $[M + H]^+$. Melting point: 149-152 °C.



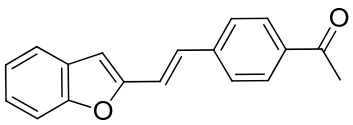
**5j**

**(*E*)-1-(4-(2-(furan-2-yl)vinyl)phenyl)ethanone (5j).**[42] The general procedure for the dehydrative Heck arylation was employed by reacting 1-(2-(furan-2-yl)ethanol (336 mg, 3.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in DMSO (3 mL) at 100 °C for 1 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 4-bromoacetophenone (398 mg, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 4 h at 100 °C, work-up and purification by column chromatography (r.f. 0.15) yielded 280 mg (66%) of the title compound as a white powder. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.44 (s, 1H), 7.06 (d, *J* = 16.3 Hz, 1H), 7.00 (d, *J* = 16.3 Hz, 1H), 6.49 – 6.40 (m, 2H), 2.60 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.50, 152.92, 142.98, 141.89, 136.01, 129.02, 126.40, 126.27, 125.89, 119.06, 112.03, 110.25, 26.70; MS (CI, m/z) 213 $[M + H]^+$; Anal. calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 78.36; H, 5.71. Melting point: 110-112 °C.



**5k**

**(*E*)-1-(4-(2-(2,5-dimethylthiophen-3-yl)vinyl)phenyl)ethanone (5k).** The general procedure for the dehydrative Heck arylation was employed by reacting 1-(2,5-dimethylthiophen-3-yl)ethanol (468 mg, 3.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in DMSO (3 mL) at 100 °C for 1 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 4-bromoacetophenone (398 mg, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 4 h at 100 °C, work-up and and recrystallisation from hot EtOAc/hexane (1:10) yielded 379 mg (74%) of the title compound as a white powder. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J* = 16.0 Hz, 1H), 6.91 (s, 1H), 6.81 (d, *J* = 16.0 Hz, 1H), 2.59 (s, 2H), 2.47 (s, 2H), 2.43 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.54, 142.84, 136.51, 135.74, 135.67, 134.68, 128.98, 126.40, 126.19, 124.05, 122.91, 26.67, 15.36, 13.22; MS (CI, m/z) 257 $[M + H]^+$; Anal. calcd for $C_{16}H_{16}OS$: C, 74.96; H, 6.29. Found: C, 74.05; H, 6.22. Melting point: 136-138 °C.



**5l**

**(*E*)-1-(4-(2-(Benzofuran-2-yl)vinyl)phenyl)ethanone (5l).** The general procedure for the dehydrative Heck arylation was employed by reacting 1-(benzofuran-2-yl)ethanol (486 mg, 3.0 mmol) with $H_3PW_{12}O_{40}.xH_2O$ (50 mg) in DMSO (3 mL) at 100 °C for 2 h, followed by injection of $Et_3N$ (0.42 mL, 3 mmol), 4-bromoacetophenone (398 mg, 2 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), P(*t*-Bu)$_3$.$HBF_4$ (35 mg, 0.12 mmol) and DMF (3 mmol). After a further 4 h at 100 °C, work-up and purification by column chromatography (10% EtOAc/hexane, r.f. 0.2) yielded 356 mg (68%) of the title compound as a white powder. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.56 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.49 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.39 – 7.27 (m, 2H), 7.23 (td, *J* = 7.5, 1.0 Hz, 1H), 7.12 (d, *J* = 16.1 Hz, 1H), 6.76 (s, 1H), 2.62 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ; 197.51, 155.22, 154.59, 141.35, 136.44, 129.09, 129.06, 128.93, 126.82, 125.30, 123.21, 121.24, 119.04, 111.14, 106.83, 26.74; MS (CI, m/z) 263 $[M + H]^+$. Melting point: 144-147 °C.

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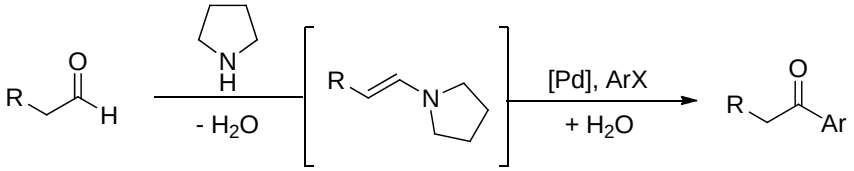
# Chapter 5

## Conclusions and Perspectives

Our group has previously made contributions towards the development and understanding of the Heck reaction of electron-rich olefins (Chapter 1). This knowledge was successfully applied to the development of a conceptionally new methodology, on which Chapters 2 and 3 are based. The direct acylation of aryl halides with aldehydes occurs via an enamine intermediate which acts as an electron-rich olefin that undergoes regioselective Heck arylation (Scheme 5.1). This proposed reaction pathway is supported by additional experimental evidence.

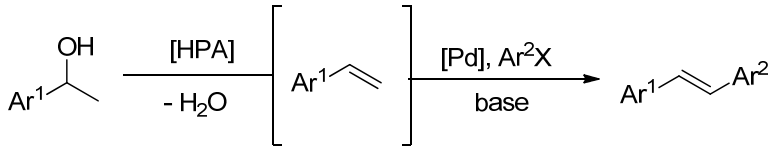



**Scheme 5.1**: Pathway for direct acylation of aryl halides with aldehydes

In Chapter 2, we showed that by use of a bulky, electron-rich monophosphine ligand, aryl chlorides could be activated and thus enter the acylation reaction. A wide range of functionalised alkyl aryl ketones could be synthesised in a single step from commercially available starting materials.

In Chapter 3, the aldehydes required for the acylation reaction were prepared by the Heck-isomerisation reaction of aryl bromides with allyl alcohol. A single palladium catalyst was capable of forming the aldehydes, and in the same vessel, catalyses the acylation reaction with another aryl bromide. Multi-substituted dihydrochalcones can be prepared in a two-step, one-pot process.

In Chapter 4, olefins are again formed *in-situ* by the development of a catalytic protocol for the selective dehydration of secondary aryl alcohols. The activity of the Keggin type HPA catalyst, $H_3PW_{12}O_{40}$, can be tuned simply by switching the solvent. The resultant styrene derivatives then undergo regioselective Heck arylation upon addition of a base, Pd catalyst and aryl bromide (Scheme 5.2). This provides facile access to some interesting and useful stilbene products.




**Scheme 5.2**: Pathway for the dehydrative coupling of alcohols with aryl bromides

It is reasonable to propose that this same principle (i.e. *in-situ* formation of olefins) could be applied to other classes of substrate molecules. As just one example, transition metal catalysed hydroamination of alkynes would also yield enamine intermediates that could undergo further catalytic transformations. Such catalytic methodologies provide direct access to target compounds, thus reducing waste and the associated costs. If the same transformations could be catalysed by cheaper metals that exist in greater abundance on our planet, such methodologies would be more widely adopted in industrial processes.